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Chapter 1

General introduction, aim and outline of this thesis

Introduction

Improved medical care for people with an intellectual disability in combination with advances in clinical genetic testing have resulted in an increased number of adults known to have a genetic neurodevelopmental disorder (GND). In the past, most studies focused on children with a GND, leaving a knowledge gap regarding conditions that are present at adult age.[1] The studies described in this thesis were conducted to characterize GNDs, with a focus on 22q11.2 deletion syndrome (22q11.2DS), at adult age. Study topics included parkinsonism and Parkinson's disease, otolaryngology, ophthalmology, and trauma-related disorders. In addition, the retina was examined for potential biomarkers for age-related disorders in 22q11.2DS. The following paragraphs will give an introduction to the study topics included in this thesis.

Genetic neurodevelopmental disorders

In the absence of one generally accepted definition, the following criteria for a GND were used, in line with the definition for "neurodevelopmental abnormality" developed by the Human Phenotype Ontology (https://hpo.jax.org/); 1) a deviation from the normal of the neurological development of a child, including any or all aspects of the development of personal, social, motor, and cognitive abilities, 2) in the presence of a disease-causing genetic variant.

A well-known example of a GND is Down syndrome, that has an estimated prevalence of 1:794 live births.[2] Rare GNDs, meaning less than 2000 individuals in the general population are affected,[3] include for example 22q11.2DS and Rett syndrome. [4, 5] Although individually rare, the prevalence of these GNDs as a group is about 3% of the population.[6] Most GNDs are associated with intellectual disabilities,[7] which is characterized by significant limitations in cognitive and adaptive skills.[8] Therefore, and because of limited studies in GNDs, prevalence rates and characteristics of conditions in adults with 22q11.2DS in this thesis are often compared to results of adults with an intellectual disability, in addition to adults from the general population.

From neurodevelopment to neurodegeneration

An interesting aspect of GNDs is that their phenotype is often associated with precocious aging.[9] For example, individuals with Down syndrome have an increased risk of developing early-onset Alzheimer's disease and presbycusis (age-related hearing loss) that, on averages, occurs about 30 years earlier compared to individuals in the general population.[10, 11] Another example is found in women with Turner syndrome, who show hearing loss comparable to what is seen in women from the general population aged 20-25 years older.[12] Likewise, while Parkinson's disease in the general population is rare under the age of 50 years,[13] individuals with 22q11.2DS are known to have an increased risk of early-onset Parkinson's disease with motor onset at a mean age of 40 years.[14] However, the prevalence of Parkinson's disease in individuals with 22q11.2DS is still unclear.

This co-existence of neurodevelopmental and early-onset neurodegenerative disorders, may indicate shared cellular and molecular mechanisms caused by the same genetic susceptibility.[9] Abnormal development of neurons may partly be responsible for an increased vulnerability to neurodegenerative disorders.[9] Approaching these neurodevelopmental and neurodegenerative disorders as a continuum, with origins early in life that can be influenced across the life span, stresses the importance of natural history studies in GNDs.[9]

22q11.2 deletion syndrome

22q11.2DS is a recurrent GND that is relatively common within the group of rare diseases,[3] with an estimated prevalence of 1:2148 live births.[4] It is a multisystem disorder with variable expression of associated manifestations including, but not limited to, congenital heart disease, intellectual disability, palatal defects and psychiatric disorders such as schizophrenia (Figure 1).[15] 22q11.2DS was previously also known as DiGeorge syndrome, Shprintzen syndrome, velocardiofacial syndrome and conotruncal anomaly face syndrome,[15] named after clinicians who recognized it as an entity, and after clusters of the clinical manifestations.

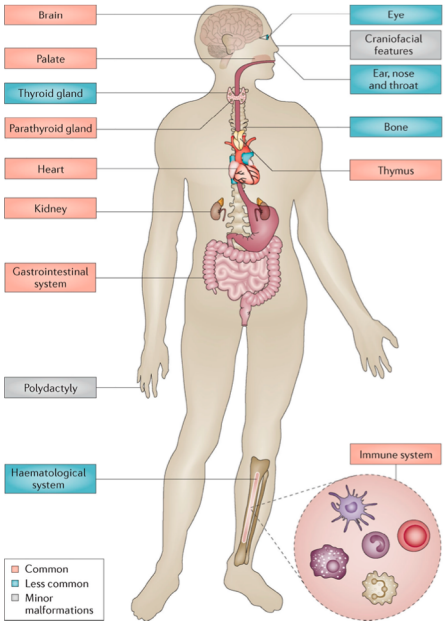

Figure 1. Body systems that may be affected in individuals with 22q11.2 microdeletion (McDonald-mcGinn et al.[15])

22q11.2DS is associated with recurrent hemizygous microdeletions on the long arm (q) of chromosome 22 (Figure 2). Most individuals (90-95%) have a *de novo* 22q11.2 deletion, meaning that it is not inherited from one of the parents.[16] In 85-90% of individuals the deleted region spans from low copy repeat (LCR) A to D. These LCRs are highly similar regions of DNA and susceptible for errors during meiosis.[17] The majority of clinical features result from a deletion of the "critical" 22q11.2 region between LCRA-LCRB.[18] The typically deleted region, LCRA-LCRD, involves ~100 genes of which more than 45 are protein-coding.[18] Many genes, that often have multiple functions, have been described to contribute to the 22q11.2DS phenotype including, but not limited to, *TBX1*, *CRKL, DGCR8*, *PRODH, COMT* and (other) genes involved in mitochondrial functioning.[18, 19] *TBX1* is considered crucial for the 22q11.2DS somatic phenotype, since it is involved in the development of the thymus, thyroid gland, parathyroid glands, cardiac and vascular system.[20] *CRKL* is important for the development of the kidneys and urinary tract, cardiac system, thymus and parathyroid glands, and may act via the same genetic pathways as *TBX1*.[21] *COMT* encodes for an enzyme

that is important for catecholamine degradation, including dopamine, and *PRODH* for proline degradation.[22] Some evidence, from mice and human studies, indicate a role for *COMT* and *PRODH* in the development of the neuropsychiatric phenotype of 22q11.2DS.[22-24] In addition, mitochondrial dysfunction, resulting from deletion of at least six mitochondrial genes in the 22q11.2 region,[25] may play a role in the cardiac, endocrinologic, neurologic and psychiatric phenotype of 22q11.2DS.[23, 25-27] *DGCR8* was found to be involved in the development of the cardiac, immune and central nervous system,[28] and in the biogenesis of mircoRNAs.[29] Non-coding regulatory genes such as microRNAs may be important for the etiology of 22q11.2DS, and have been implicated in fundamental cellular processes such as proliferation and apoptosis.[21, 30]

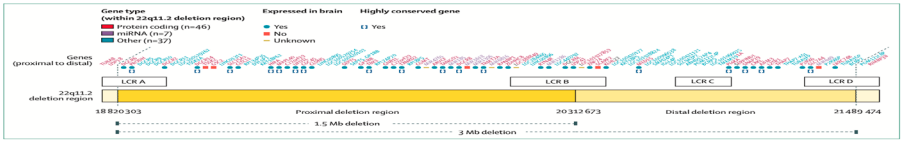

Figure 2. 22q11.2 deletion region and genes located in this region (Zinkstok et al.,[23] reproduced from Guna et al.[31])

Adults with 22q11.2 deletion syndrome

Research in adults with 22q11.2DS is important because studies in adults are much more scarce compared to studies in children, and manifestations differ from those in children.[32, 33] Differences include, for example, an increased risk of developing certain psychiatric disorders such as schizophrenia at adolescent and adult age, [32] whereas in children the emphasis is on the detection and treatment of congenital anomalies and developmental disabilities.[34] In order to improve genetic counseling and treatment for adults with 22q11.2DS, it is important to have a good understanding of the natural history, including prevalence estimates of conditions associated with the adult phenotype.[35] In addition, knowledge of the influence of age, sex or co-morbidities may facilitate personalized screening and treatment in subgroups that are at increased risk of a certain condition and may prevent overly screening in those who are not. Clinically relevant features at adult age include, but are not limited to, impairments in cognitive and adaptive functioning, anxiety and psychotic disorders,

hypothyroidism, obesity, disrupted sleep patterns, gastro-intestinal problems, scoliosis, and dental caries.[36] In addition, multimorbidity and polypharmacy are prevalent and require special attention.[36, 37] Studies on mortality are limited to one adult 22q11.2DS cohort, reporting a median age of death of 46.4 (range 18.1 – 68.6) years in those who had died, with higher survival probabilities for individuals without a congenital heart disease.[38] Cause of death was mostly related to cardiovascular disease.[38] Findings of studies on prevalence rates, trajectory and treatment outcomes of conditions associated with 22q11.2DS are incorporated in the international clinical practice recommendations for individuals with 22q11.2DS,[34, 36] and contribute to the improvement of multidisciplinary care across the life span.

Specialized multidisciplinary clinics for individuals with 22q11.2DS, and other GNDs, have become increasingly available. In the Netherlands two specialized clinics for adults with 22q11.2DS exist, the expert center for adults with 22q11.2DS at Maastricht University Medical Center+ (MUMC) and the expert center for genetic syndromes at 's Heeren Loo. Studies of adults with 22q11.2DS described in this thesis were conducted at these clinics, often combined with other national or international clinics for 22q11.2DS.

Parkinsonism/ Parkinson's disease

Parkinson's disease is the second most common neurodegenerative disorder in the general population, after Alzheimer's disease, with an increasing prevalence worldwide.[39] It affects 0.5-2% of individuals in the general population aged 65 years and older, but is rare under the age of 50 years.[13, 40] Besides higher age, the prevalence rate of Parkinson's disease seems to be slightly higher in males relative to females in the general population.[13,41] Parkinson's disease has a large impact on an person's quality of life. It is a progressive disorder that starts with a prodromal period that may include symptoms of depression, anxiety and loss of smell, before the onset of parkinsonian motor symptoms, followed by late-stage symptoms such as cognitive impairment, pain, fatigue and falls.[42] Parkinson's disease is hard to recognize in the prodromal period and is clinically diagnosed after motor symptoms emerge.[43] The cardinal motor symptoms, referred to as parkinsonism, include bradykinesia (slowness of movement and decrement

in amplitude or speed) with either rigidity (resistance to passive movement, also called "muscle stiffness"), rest tremor in a limb, or both.[44] These motor symptoms are caused by loss of dopaminergic neurons in the substantia nigra pars compacta, resulting in dopamine depletion in the striatum.[42] Therefore, treatment of Parkinson's disease includes substitution of dopamine by a dopamine precursor, such as levodopa. The pathophysiology of Parkinson's disease is not completely understood, but seems to result from an interplay of different factors including aberrant a-synuclein (protein) aggregation, mitochondrial dysfunction, lysosomal-autophagic dysfunction and disturbed endosomal trafficking.[42, 43] Genetic, epigenetic as well as environmental factors may contribute to the vulnerability of dopaminergic neurons to develop Parkinson's disease.[43] Several monogenetic variants have been associated with Parkinson's disease, such as *SNCA*,[45] as well as the 22q11.2 deletion.[46]

In addition to Parkinson's disease, causes of parkinsonism include vascular pathology, trauma, and medication that negatively affects dopaminergic neurotransmission (in particular anti-psychotics). It is important to differentiate these forms of parkinsonism from neurodegenerative parkinsonism for patient follow-up and treatment. This differentiation may be challenging in individuals with a GND, because of higher prevalence rates of co-morbidities, including additional movement or neuropsychiatric disorders, and polypharmacy.[37, 47, 48]

A previous study in a large population-based sample of adults with an intellectual disability indicated a prevalence of Parkinson's disease and parkinsonism of 0.4%, two times higher compared to their control group without intellectual disabilities.[49] For adults with 22q11.2DS, there has been one mono-center study that indicated a 20-70 fold increased risk of Parkinson's disease compared to the general population, although in relatively small sample of adults.[46]

The sensory system

The sensory system includes visual, auditory, gustatory, olfactory, tactile, vestibular, proprioceptive and interoceptive systems. Stimuli such as light or noise are transformed into patterns of neural activity that are centrally

integrated with input from other sensory systems to guide behavior and movement.[50] Sensory systems play an important role in communication, building and maintaining social interactions, and signaling of danger. Deficits may result in accidents, including falling, and may cause or aggravate symptoms of anxiety and depression.[51, 52]

Individuals with an intellectual disability, as a group, were reported to have an increased risk of hearing and/or vision loss at an earlier age compared to individuals from the general population.[53] Knowledge of sensory (dys) function in GNDs, except for Down syndrome,[11, 54-56] is however limited. The following paragraphs give a general introduction to the auditory and ophthalmic system and to what is known so far in individuals with 22q11.2DS.

Hearing and otologic findings

Hearing can be tested with audiometry, which makes it possible to differentiate between types of hearing loss and to describe the configuration of hearing thresholds in terms of severity and frequencies (tones) that are affected.[57] Hearing loss can be conductive, resulting from problems in the middle and/or external ear, sensorineural, resulting from cochlear damage, or mixed.[58] Conductive hearing loss may be caused by, for example, ear wax or fluid in the middle ear, and sensorineural hearing loss may be caused by noise damage, medication or aging.[58] Depending on the severity and type of hearing loss, hearing aids can be prescribed.[58]

In a large sample of adults with an intellectual disability hearing loss was found in about 35%, which is higher compared to the general population.[59] The global estimate of hearing loss is 20% in the general population and increases with age, most notably after the age of 50 years.[60] Age-related hearing loss in the general population affects 40% of individuals aged 65 years and older.[61] It starts with a high-tone loss, which has an adverse effect on hearing sensitivity and speech understanding with background noise, and in a more advanced state, on localization of sounds.[61, 62]

In 22q11.2DS, there have been several studies examining hearing and otologic problems in children, with only a few that included adults.[35, 63-66]

A review on hearing loss in 22q11.2DS of all ages reported hearing loss in 6-60% of individuals with 22q11.2DS.[67] Conductive hearing loss was found to be most prevalent (6-53%), especially in children, probably related to a high prevalence of chronic otitis media and cleft palate.[67] Sensorineural hearing loss was reported in 0-19% and mixed hearing loss in 0-28% of individuals.[67] Studies that only included adults reported hearing loss in 28 - 41% of inidividuals.[35,63] Balance problems have been reported as well, mostly (42%) related to vestibular dysfunction, but some (16%) were suggestive of visual problems.[68]

Vision and ocular findings

The eye consists of several structures including the cornea, lens and retina.[50] The lens, which can accommodate, together with the cornea cause refraction of light, focusing the light onto the retina to form an image. In case of refractive errors (such as nearsightedness, farsightedness and astigmatism), the light is not projected accurately on the retina which results in blurred vision. The retina consists of several cellular layers, including ganglion cells, that process the light and generate action potentials to the optical nerve that are transmitted to the central nervous system for interpretation.[50]

Visual acuity is the ability of the eye to distinguish two points near each other.[50] Vision can be influenced by refractive errors as described before, but may also result from, for example, cataract (clouded lens) or glaucoma (damaged optic nerve, may result from increased eye pressure). In addition, amblyopia (lazy eye) or strabismus (crossed eye) may cause poor vision. Most of these ocular problems can be treated, but need intervention as early as possible. In a study of more than 500 adults with an intellectual disability in the Netherlands, it was found that visual acuity was related to the severity of the intellectual disability, but refractive errors were not.[69] Astigmatism was the most common refractive error in adults with an intellectual disability, followed by hyperopia (farsightedness) and myopia (nearsightedness),[69] similar to what has been reported for adults in the general population.[70]

There have been a few studies that reported on visual acuity and ocular findings in individuals with 22q11.2DS, mainly children, showing high prevalence rates of hyperopia, strabismus and amblyopia. [71-74] Visual acuity was (near) normal in most individuals, although in rare cases visual acuity was affected by a Peters anomaly,[74] or cataract.[75] Other common findings were retinal vascular tortuosity and posterior embryotoxon, that do not affect visual acuity or require any treatment.[71, 73, 74]

The eye as a window to the brain

Studying brain development and brain disorders, especially in individuals with a GND, is challenging but very important for understanding the pathophysiology of brain disorders and may help identifying individuals that are at increased risk at an early stage. Non-invasive and fast methods would facilitate the study of brain disorders in individuals with a GND.

Because retinal and cerebral tissue share embryological, physiological, and anatomical characteristics, retinal blood vessel morphology (referred to as retinovascular parameters) and retinal layer thickness (retinoneural parameters) have been proposed as non-invasive biomarkers for psychiatric and neurodegenerative disorders.[76-81] Since the retina is the only part of the central nervous system that can be examined from the exterior, the eye may serve as a window to the brain. Retinovascular and retinoneural parameters can be studied using non-invasive and fast methods such as fundoscopy and optical coherence tomography (OCT). Fundoscopy can be used to study retinovascular parameters such as branching pattern and vessel density, and OCT can be used to study retinoneural parameters such as thickness of the retinal nerve fiber layer and macular layer, covering different regions of the retina.[82]

Differences in these retinovascular and retinoneural parameters between adults with 22q11.2DS and controls have not been studied yet, but may help to the identify predictive biomarkers for psychiatric disorders such as schizophrenia and neurodegenerative disorders such as Parkinson's disease.

Post-traumatic stress

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that may develop after experiencing or witnessing a traumatic event, such as actual or threatened death, serious injury or sexual violence.[83] PTSD is characterized by intrusion symptoms, such as nightmares or flashbacks, avoidance of stimuli associated with the traumatic event, negative alterations in cognition and mood and alterations in arousal and reactivity, such as angry outbursts or difficulties with concentration.[83] If these symptoms are present for more than one month, cause a significant impairment in functioning, and are not attributable to substance abuse or other medical conditions, someone fulfills the criteria of PTSD according to the Diagnostic and Statistical Manual of Mental Disorders-5.[83] PTSD has a large impact on the quality of life, and makes it difficult for people to continue with their daily life activities. However, treatment has shown to be effective in both the general population and people with an intellectual disability, and may consist of eye movement desensitization and reprocessing therapy or cognitive behavior therapy.[84, 85]

The reported lifetime prevalence of PTSD in the general population is about 4%, and 6% for those who have been exposed to traumatic events.[86] Individuals with an intellectual disability or other developmental delay may have an increased exposure to traumatic events and higher risks of developing PTSD.[87-89] There has been only one study in individuals with 22q11.2DS, that reported a lifetime prevalence of PTSD of 0.9%,[32] which is lower compared to the general population.[86] However, only a minority of the participants in this study had reached adulthood.

Scope of this thesis

The previous paragraphs provide a rationale for the study of several conditions in adults with 22q11.2DS including Parkinson's disease, otolaryngologic and ophthalmologic conditions and post-traumatic stress, in addition to the study of retinovascular and retinoneural parameters. The studies described in this thesis are limited to the aforementioned topics that were selected because of their clinical relevance, few published studies on these topics so far and the clinical expertise of the specialized 22q11.2 clinics for adults at MUMC and 's Heeren Loo.

Outline of this thesis

Chapter 2 describes results and implications of a systematic literature review on parkinsonism in GNDs. More specific, this chapters provides an overview of GNDs that have been described with parkinsonism, summarizes evidence of neurodegenerative parkinsonism (Parkinson's disease), possible underlying mechanisms contributing to the neurodevelopmental disorder as well as neurodegenerative parkinsonism, and provides implications for clinical practice and research.

In **chapter 3** an estimated prevalence of Parkinson's disease in 22q11.2DS is presented, as well as possible predictors to Parkinson's disease in this population including age and sex.
The sensory system in individuals with 22q11.2DS is discussed in chapters 4 and 5, focusing on hearing and vision. The history of otolaryngologic manifestations and the prevalence and characteristics of hearing loss in adults with 22q11.2DS are examined in **chapter 4.** Ocular findings and visual acuity in children and adults with 22q11.2DS are presented in **chapter 5,** together with results from a systematic literature review on this topic. Furthermore, chapters 4 and 5 provide recommendations for screening of otolaryngologic and ophthalmologic conditions in adults with 22q11.2DS. In addition to the ocular findings, optometry results in adults with 22q11.2DS are described in **chapter 6.** This chapter examines differences in retinal vessels and retinal nerve tissue between adults with 22q11.2DS and controls and in relation to age.
Chapter 7 provides an estimated prevalence of, and possible contributors to, PTSD in adults with 22q11.2DS.

Finally, **chapter 8** includes a general discussion of the studies included in this thesis and **chapter 9** discusses the impact of study results on society and science.

References

1. Janicki MP, Henderson CM, Rubin IL. Neurodevelopmental conditions and aging: Report on the Atlanta Study Group Charrette on Neurodevelopmental Conditions and Aging*. *Disability and Health Journal*. 2008/04/01/ 2008;1(2):116-124. doi:https://doi.org/10.1016/j.dhjo.2008.02.004
2. de Graaf G, Buckley F, Skotko BG. Estimates of the live births, natural losses, and elective terminations with Down syndrome in the United States. *Am J Med Genet A*. Apr 2015;167a(4):756-67. doi:10.1002/ajmg.a.37001
3. Moliner AM, Waligora J. The European Union Policy in the Field of Rare Diseases. *Adv Exp Med Biol*. 2017;1031:561-587. doi:10.1007/978-3-319-67144-4_30
4. Blagojevic C, Heung T, Theriault M, et al. Estimate of the contemporary live-birth prevalence of recurrent 22q11.2 deletions: a cross-sectional analysis from population-based newborn screening. *CMAJ Open*. Jul-Sep 2021;9(3):E802-e809. doi:10.9778/cmajo.20200294
5. Petriti U, Dudman DC, Scosyrev E, Lopez-Leon S. Global prevalence of Rett syndrome: systematic review and meta-analysis. *Syst Rev*. Jan 16 2023;12(1):5. doi:10.1186/s13643-023-02169-6
6. van Eeghen AM, Bruining H, Wolf NI, et al. Personalized medicine for rare neurogenetic disorders: can we make it happen? *Cold Spring Harb Mol Case Stud*. Feb 2022;8(2)doi:10.1101/mcs.a006200
7. Morris-Rosendahl DJ, Crocq MA. Neurodevelopmental disorders-the history and future of a diagnostic concept . *Dialogues Clin Neurosci*. Mar 2020;22(1):65-72. doi:10.31887/DCNS.2020.22.1/macrocq
8. Schalock RL, Luckasson R, Tassé MJ. An Overview of Intellectual Disability: Definition, Diagnosis, Classification, and Systems of Supports (12th ed.). *Am J Intellect Dev Disabil*. Nov 1 2021;126(6):439-442. doi:10.1352/1944-7558-126.6.439
9. Hickman RA, O'Shea SA, Mehler MF, Chung WK. Neurogenetic disorders across the lifespan: from aberrant development to degeneration. *Nat Rev Neurol*. Feb 2022;18(2):117-124. doi:10.1038/s41582-021-00595-5
10. Fortea J, Zaman SH, Hartley S, Rafii MS, Head E, Carmona-Iragui M. Alzheimer's disease associated with Down syndrome: a genetic form of dementia. *Lancet Neurol*. Nov 2021;20(11):930-942. doi:10.1016/s1474-4422(21)00245-3
11. Picciotti PM, Carfì A, Anzivino R, et al. Audiologic Assessment in Adults With Down Syndrome. *Am J Intellect Dev Disabil*. Jul 2017;122(4):333-341. doi:10.1352/1944-7558-122.4.333
12. Bonnard Å, Hederstierna C, Bark R, Hultcrantz M. Audiometric features in young adults with Turner syndrome. *Int J Audiol*. Sep 2017;56(9):650-656. doi:10.1080/14992027.2017.1314559
13. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Mov Disord*. Nov 2014;29(13):1583-90. doi:10.1002/mds.25945
14. Boot E, Butcher NJ, Udow S, et al. Typical features of Parkinson disease and diagnostic challenges with microdeletion 22q11.2. *Neurology*. Jun 5 2018;90(23):e2059-e2067. doi:10.1212/wnl.0000000000005660
15. McDonald-McGinn DM, Sullivan KE, Marino B, et al. 22q11.2 deletion syndrome. *Nat Rev Dis Primers*. Nov 19 2015;1:15071. doi:10.1038/nrdp.2015.71
16. McDonald-McGinn DM, Tonnesen MK, Laufer-Cahana A, et al. Phenotype of the 22q11.2 deletion in individuals identified through an affected relative: cast a wide FISHing net! *Genet Med*. Jan-Feb 2001;3(1):23-9. doi:10.1097/00125817-200101000-00006
17. Babcock M, Pavlicek A, Spiteri E, et al. Shuffling of genes within low-copy repeats on 22q11 (LCR22) by Alu-mediated recombination events during evolution. *Genome Res*. Dec 2003;13(12):2519-32. doi:10.1101/gr.1549503
18. Du Q, de la Morena MT, van Oers NSC. The Genetics and Epigenetics of 22q11.2 Deletion Syndrome. *Front Genet*. 2019;10:1365. doi:10.3389/fgene.2019.01365

19. Motahari Z, Moody SA, Maynard TM, LaMantia AS. In the line-up: deleted genes associated with DiGeorge/22q11.2 deletion syndrome: are they all suspects? *J Neurodev Disord*. Jun 7 2019;11(1):7. doi:10.1186/s11689-019-9267-z
20. Baldini A, Fulcoli FG, Illingworth E. Tbx1: Transcriptional and Developmental Functions. *Curr Top Dev Biol*. 2017;122:223-243. doi:10.1016/bs.ctdb.2016.08.002
21. Morrow BE, McDonald-McGinn DM, Emanuel BS, Vermeesch JR, Scambler PJ. Molecular genetics of 22q11.2 deletion syndrome. *Am J Med Genet A*. Oct 2018;176(10):2070-2081. doi:10.1002/ajmg.a.40504
22. Zarchi O, Carmel M, Avni C, et al. Schizophrenia-like neurophysiological abnormalities in 22q11.2 deletion syndrome and their association to COMT and PRODH genotypes. *J Psychiatr Res*. Nov 2013;47(11):1623-9. doi:10.1016/j.jpsychires.2013.07.004
23. Zinkstok JR, Boot E, Bassett AS, et al. Neurobiological perspective of 22q11.2 deletion syndrome. *Lancet Psychiatry*. Nov 2019;6(11):951-960. doi:10.1016/s2215-0366(19)30076-8
24. Radoeva PD, Coman IL, Salazar CA, et al. Association between autism spectrum disorder in individuals with velocardiofacial (22q11.2 deletion) syndrome and PRODH and COMT genotypes. *Psychiatr Genet*. Dec 2014;24(6):269-72. doi:10.1097/ypg.0000000000000062
25. Devaraju P, Zakharenko SS. Mitochondria in complex psychiatric disorders: Lessons from mouse models of 22q11.2 deletion syndrome: Hemizygous deletion of several mitochondrial genes in the 22q11.2 genomic region can lead to symptoms associated with neuropsychiatric disease. *Bioessays*. Feb 2017;39(2)doi:10.1002/bies.201600177
26. Fernandez A, Meechan DW, Karpinski BA, et al. Mitochondrial Dysfunction Leads to Cortical Under-Connectivity and Cognitive Impairment. *Neuron*. Jun 19 2019;102(6):1127-1142.e3. doi:10.1016/j.neuron.2019.04.013
27. Kolar D, Krajcovic B, Kleteckova L, Kuncicka D, Vales K, Brozka H. Review: Genes Involved in Mitochondrial Physiology Within 22q11.2 Deleted Region and Their Relevance to Schizophrenia. *Schizophr Bull*. Jun 28 2023;doi:10.1093/schbul/sbad066
28. Guo WT, Wang Y. Dgcr8 knockout approaches to understand microRNA functions in vitro and in vivo. *Cell Mol Life Sci*. May 2019;76(9):1697-1711. doi:10.1007/s00018-019-03020-9
29. Gregory RI, Yan KP, Amuthan G, et al. The Microprocessor complex mediates the genesis of microRNAs. *Nature*. Nov 11 2004;432(7014):235-40. doi:10.1038/nature03120
30. Stark KL, Xu B, Bagchi A, et al. Altered brain microRNA biogenesis contributes to phenotypic deficits in a 22q11-deletion mouse model. *Nat Genet*. Jun 2008;40(6):751-60. doi:10.1038/ng.138
31. Guna A, Butcher NJ, Bassett AS. Comparative mapping of the 22q11.2 deletion region and the potential of simple model organisms. *J Neurodev Disord*. 2015;7(1):18. doi:10.1186/s11689-015-9113-x
32. Schneider M, Debbané M, Bassett AS, et al. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *Am J Psychiatry*. Jun 2014;171(6):627-39. doi:10.1176/appi.ajp.2013.13070864
33. Wallin L, Gillberg C, Fernell E, Gillberg C, Billstedt E. Neurodevelopmental and other psychiatric disorders in 22q11.2 deletion syndrome from childhood to adult age: Prospective longitudinal study of 100 individuals. *Am J Med Genet C Semin Med Genet*. May 29 2023;doi:10.1002/ajmg.c.32052
34. Óskarsdóttir S, Boot E, Crowley TB, et al. Updated clinical practice recommendations for managing children with 22q11.2 deletion syndrome. *Genet Med*. Mar 2023;25(3):100338. doi:10.1016/j.gim.2022.11.006
35. Bassett AS, Chow EW, Husted J, et al. Clinical features of 78 adults with 22q11 Deletion Syndrome. *Am J Med Genet A*. Nov 1 2005;138(4):307-13. doi:10.1002/ajmg.a.30984
36. Boot E, Óskarsdóttir S, Loo JCY, et al. Updated clinical practice recommendations for managing adults with 22q11.2 deletion syndrome. *Genet Med*. Mar 2023;25(3):100344. doi:10.1016/j.gim.2022.11.012
37. Malecki SL, Van Mil S, Graffi J, et al. A genetic model for multimorbidity in young adults. *Genet Med*. Jan 2020;22(1):132-141. doi:10.1038/s41436-019-0603-1

38. Van L, Heung T, Graffi J, et al. All-cause mortality and survival in adults with 22q11.2 deletion syndrome. *Genet Med*. Oct 2019;21(10):2328-2335. doi:10.1038/s41436-019-0509-y
39. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. May 2019;18(5):459-480. doi:10.1016/s1474-4422(18)30499-x
40. Brakedal B, Toker L, Haugarvoll K, Tzoulis C. A nationwide study of the incidence, prevalence and mortality of Parkinson's disease in the Norwegian population. *NPJ Parkinsons Dis*. Mar 2 2022;8(1):19. doi:10.1038/s41531-022-00280-4
41. Zirra A, Rao SC, Bestwick J, et al. Gender Differences in the Prevalence of Parkinson's Disease. *Mov Disord Clin Pract*. Jan 2023;10(1):86-93. doi:10.1002/mdc3.13584
42. Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. *Nat Rev Dis Primers*. Mar 23 2017;3:17013. doi:10.1038/nrdp.2017.13
43. Bloem BR, Okun MS, Klein C. Parkinson's disease. *Lancet*. Jun 12 2021;397(10291):2284-2303. doi:10.1016/s0140-6736(21)00218-x
44. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. Oct 2015;30(12):1591-601. doi:10.1002/mds.26424
45. Puschmann A. Monogenic Parkinson's disease and parkinsonism: clinical phenotypes and frequencies of known mutations. *Parkinsonism Relat Disord*. Apr 2013;19(4):407-15. doi:10.1016/j.parkreldis.2013.01.020
46. Butcher NJ, Kiehl TR, Hazrati LN, et al. Association between early-onset Parkinson disease and 22q11.2 deletion syndrome: identification of a novel genetic form of Parkinson disease and its clinical implications. *JAMA Neurol*. Nov 2013;70(11):1359-66. doi:10.1001/jamaneurol.2013.3646
47. Carfì A, Romano A, Zaccaria G, et al. The burden of chronic disease, multimorbidity, and polypharmacy in adults with Down syndrome. *Am J Med Genet A*. Jul 2020;182(7):1735-1743. doi:10.1002/ajmg.a.61636
48. McMahon M, Hatton C, Bowring DL. Polypharmacy and psychotropic polypharmacy in adults with intellectual disability: a cross-sectional total population study. *J Intellect Disabil Res*. Sep 9 2020;doi:10.1111/jir.12775
49. Cooper S-A, McLean G, Guthrie B, et al. Multiple physical and mental health comorbidity in adults with intellectual disabilities: population-based cross-sectional analysis. *BMC Family Practice*. 2015/08/27 2015;16(1):110. doi:10.1186/s12875-015-0329-3
50. Bear M, Connors B, Paradiso MA. *Neuroscience: Exploring the Brain, Enhanced Edition : Exploring the Brain, Enhanced Edition*. Jones & Bartlett Learning, LLC; 2020.
51. Parravano M, Petri D, Maurutto E, et al. Association Between Visual Impairment and Depression in Patients Attending Eye Clinics: A Meta-analysis. *JAMA Ophthalmol*. Jul 1 2021;139(7):753-761. doi:10.1001/jamaophthalmol.2021.1557
52. Blazer DG. Hearing Loss: The Silent Risk for Psychiatric Disorders in Late Life. *Clin Geriatr Med*. May 2020;36(2):201-209. doi:10.1016/j.cger.2019.11.002
53. Carvill S. Sensory impairments, intellectual disability and psychiatry. *J Intellect Disabil Res*. Dec 2001;45(Pt 6):467-83. doi:10.1046/j.1365-2788.2001.00366.x
54. Nightengale E, Yoon P, Wolter-Warmerdam K, Daniels D, Hickey F. Understanding Hearing and Hearing Loss in Children With Down Syndrome. *Am J Audiol*. Sep 18 2017;26(3):301-308. doi:10.1044/2017_aja-17-0010
55. Zalzal HG, Lawlor CM. Down Syndrome for the Otolaryngologist: A Review. *JAMA Otolaryngol Head Neck Surg*. Apr 1 2023;149(4):360-367. doi:10.1001/jamaoto.2023.0001
56. Satgunam P, Datta S, Sumalini R. Near vision in individuals with Down syndrome: a vision screening study. *Eye (Lond)*. Aug 2019;33(8):1254-1260. doi:10.1038/s41433-019-0402-6
57. Valente M. *Pure-tone audiometry and masking*. Plural Pub.; 2009.
58. Pensak ML, Choo DI. *Clinical otology*. Fourth edition. ed. Thieme; 2015.
59. Meuwese-Jongejeugd A, Vink M, van Zanten B, et al. Prevalence of hearing loss in 1598 adults with an intellectual disability: cross-sectional population based study. *Int J Audiol*. Nov 2006;45(11):660-9. doi:10.1080/14992020600920812

60. Hearing loss prevalence and years lived with disability, 1990-2019: findings from the Global Burden of Disease Study 2019. *Lancet*. Mar 13 2021;397(10278):996-1009. doi:10.1016/s0140-6736(21)00516-x
61. Gates GA, Mills JH. Presbycusis. *The Lancet*. 2005/09/24/ 2005;366(9491):1111-1120. doi:https://doi.org/10.1016/S0140-6736(05)67423-5
62. Huang Q, Tang J. Age-related hearing loss or presbycusis. *Eur Arch Otorhinolaryngol*. Aug 2010;267(8):1179-91. doi:10.1007/s00405-010-1270-7
63. Persson C, Friman V, Óskarsdóttir S, Jönsson R. Speech and hearing in adults with 22q11.2 deletion syndrome. *Am J Med Genet A*. Dec 2012;158a(12):3071-9. doi:10.1002/ajmg.a.35589
64. Verheij E, Kist AL, Mink van der Molen AB, et al. Otologic and audiologic findings in 22q11.2 deletion syndrome. *Eur Arch Otorhinolaryngol*. Feb 2017;274(2):765-771. doi:10.1007/s00405-016-4365-y
65. Zarchi O, Attias J, Raveh E, Basel-Vanagaite L, Saporta L, Gothelf D. A comparative study of hearing loss in two microdeletion syndromes: velocardiofacial (22q11.2 deletion) and Williams (7q11.23 deletion) syndromes. *J Pediatr*. Feb 2011;158(2):301-6. doi:10.1016/j.jpeds.2010.07.056
66. Van Eynde C, Swillen A, Lambeens E, et al. Prevalence and Nature of Hearing Loss in 22q11.2 Deletion Syndrome. *J Speech Lang Hear Res*. Jun 1 2016;59(3):583-9. doi:10.1044/2015_jslhr-h-15-0098
67. Verheij E, Derks LSM, Stegeman I, Thomeer H. Prevalence of hearing loss and clinical otologic manifestations in patients with 22q11.2 deletion syndrome: A literature review. *Clin Otolaryngol*. Dec 2017;42(6):1319-1328. doi:10.1111/coa.12874
68. Willaert A, Van Eynde C, Verhaert N, et al. Vestibular dysfunction is a manifestation of 22q11.2 deletion syndrome. *Am J Med Genet A*. Mar 2019;179(3):448-454. doi:10.1002/ajmg.a.7
69. van Splunder J, Stilma JS, Bernsen RM, Arentz TG, Evenhuis HM. Refractive errors and visual impairment in 900 adults with intellectual disabilities in the Netherlands. *Acta Ophthalmol Scand*. Apr 2003;81(2):123-9. doi:10.1034/j.1600-0420.2003.00035.x
70. Hashemi H, Fotouhi A, Yekta A, Pakzad R, Ostadimoghaddam H, Khabazkhoob M. Global and regional estimates of prevalence of refractive errors: Systematic review and meta-analysis. *J Curr Ophthalmol*. Mar 2018;30(1):3-22. doi:10.1016/j.joco.2017.08.009
71. Forbes BJ, Binenbaum G, Edmond JC, DeLarato N, McDonald-McGinn DM, Zackai EH. Ocular findings in the chromosome 22q11.2 deletion syndrome. *J aapos*. Apr 2007;11(2):179-82. doi:10.1016/j.jaapos.2006.08.006
72. Binenbaum G, McDonald-McGinn DM, Zackai EH, et al. Sclerocornea associated with the chromosome 22q11.2 deletion syndrome. *American journal of medical genetics Part A*. 2008;146A(7):904-909. doi:10.1002/ajmg.a.32156
73. Gokturk B, Topcu-Yilmaz P, Bozkurt B, et al. Ocular Findings in Children With 22q11.2 Deletion Syndrome. *J Pediatr Ophthalmol Strabismus*. Jul 1 2016;53(4):218-22. doi:10.3928/01913913-20160427-01
74. Casteels I, Casaer P, Gewillig M, Swillen A, Devriendt K. Ocular findings in children with a microdeletion in chromosome 22q11.2. *Eur J Pediatr*. Jul 2008;167(7):751-5. doi:10.1007/s00431-007-0582-0
75. Okazaki T, Hifumi T, Ibata T, et al. Recurrent convulsions, hypocalcemia, and hypoparathyroidism related to delayed diagnosis of 22q11.2 deletion syndrome in a middle-aged man. *Acute Med Surg*. Oct 2016;3(4):397-399. doi:10.1002/ams2.216
76. Moss HE. Retinal Vascular Changes are a Marker for Cerebral Vascular Diseases. *Curr Neurol Neurosci Rep*. Jul 2015;15(7):40. doi:10.1007/s11910-015-0561-1
77. Patton N, Aslam T, Macgillivray T, Pattie A, Deary IJ, Dhillon B. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. *J Anat*. Apr 2005;206(4):319-48. doi:10.1111/j.1469-7580.2005.00395.x
78. Appaji A, Nagendra B, Chako DM, et al. Retinal vascular abnormalities in schizophrenia and bipolar disorder: A window to the brain. *Bipolar Disord*. Nov 2019;21(7):634-641. doi:10.1111/bdi.12779

79. Wu H, Wang C, Chen C, et al. Association between Retinal Vascular Geometric Changes and Cognitive Impairment: A Systematic Review and Meta-Analysis. *J Clin Neurol*. Jan 2020;16(1):19-28. doi:10.3988/jcn.2020.16.1.19
80. Coppola G, Di Renzo A, Ziccardi L, et al. Optical Coherence Tomography in Alzheimer's Disease: A Meta-Analysis. *PLoS One*. 2015;10(8):e0134750. doi:10.1371/journal.pone.0134750
81. Ascaso FJ, Laura C, Quintanilla MÁ, et al. Retinal nerve fiber layer thickness measured by optical coherence tomography in patients with schizophrenia: A short report. *The European Journal of Psychiatry*. 2010;24:227-235.
82. Xie JS, Donaldson L, Margolin E. The use of optical coherence tomography in neurology: a review. *Brain*. Dec 19 2022;145(12):4160-4177. doi:10.1093/brain/awac317
83. Diagnostic and Statistical Manual of Mental Disorders. 5th edition: American Psychiatric Association; 2013.
84. Chen L, Zhang G, Hu M, Liang X. Eye movement desensitization and reprocessing versus cognitive-behavioral therapy for adult posttraumatic stress disorder: systematic review and meta-analysis. *J Nerv Ment Dis*. Jun 2015;203(6):443-51. doi:10.1097/nmd.0000000000000306
85. Mevissen L, de Jongh A. PTSD and its treatment in people with intellectual disabilities: a review of the literature. *Clin Psychol Rev*. Apr 2010;30(3):308-16. doi:10.1016/j.cpr.2009.12.005
86. Koenen KC, Ratanatharathorn A, Ng L, et al. Posttraumatic stress disorder in the World Mental Health Surveys. *Psychol Med*. Oct 2017;47(13):2260-2274. doi:10.1017/s0033291717000708
87. Martorell A, Tsakanikos E. Traumatic experiences and life events in people with intellectual disability. *Curr Opin Psychiatry*. Sep 2008;21(5):445-8. doi:10.1097/YCO.0b013e328305e60e
88. Nieuwenhuis JG, Smits HJH, Noorthoorn EO, Mulder CL, Penterman EJM, Nijman HLI. Not recognized enough: The effects and associations of trauma and intellectual disability in severely mentally ill outpatients. *European Psychiatry*. 2019;58:63-69. doi:10.1016/j.eurpsy.2019.02.002
89. Jones L, Bellis MA, Wood S, et al. Prevalence and risk of violence against children with disabilities: a systematic review and meta-analysis of observational studies. *Lancet*. Sep 8 2012;380(9845):899-907. doi:10.1016/s0140-6736(12)60692-8

Chapter 2

Parkinsonism in genetic neurodevelopmental disorders

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Abstract

With advances in clinical genetic testing, associations between genetic neurodevelopmental disorders and parkinsonism are increasingly recognized. In this review, we aimed to provide a comprehensive overview of reports on parkinsonism in genetic neurodevelopmental disorders and summarize findings related to genetic diagnosis, clinical features and proposed disease mechanisms. A systematic literature review was conducted in PubMed and Embase on June 15, 2021. Search terms for parkinsonism and genetic neurodevelopmental disorders, using generic terms and the Human Phenotype Ontology, were combined. Study characteristics and descriptive data were extracted from the articles using a modified version of the Cochrane Consumers and Communication Review Group's Data Extraction Template. The protocol was registered in PROSPERO (CRD42020191035). The literature search yielded 208 reports for data-extraction, describing 69 genetic disorders in 422 patients. The five most reported from most to least frequent were: 22q11.2 deletion syndrome, beta-propeller protein-associated neurodegeneration, Down syndrome, cerebrotendinous xanthomatosis, and Rett syndrome. Notable findings were an almost equal male to female ratio, an early median age of motor onset (26 years) and rigidity being more common than rest tremor. Results of dopaminergic imaging and response to antiparkinsonian medication often supported the neurodegenerative nature of parkinsonism. Moreover, neuropathology results showed neuronal loss in the majority of cases. Proposed disease mechanisms included aberrant mitochondrial function and disruptions in neurotransmitter metabolism, endosomal trafficking and the autophagic-lysosomal and ubiquitin-proteasome system. We also discuss the implications for clinical practice and highlight the potential of research in genetic neurodevelopmental disorders that may help unravel the complex processes underlying parkinsonism.

Introduction

While genetic brain disorders are traditionally dichotomized into neurodevelopmental and neurodegenerative disorders, it is becoming clear that some conditions are associated with both neurodevelopmental problems and neurodegeneration,[1] and there are indications for a shared underlying genetic susceptibility.[2, 3] Indeed, with advances in clinical genetic testing for neurological disease and an increase in life expectancy due to improved medical care, a growing number of genetic neurodevelopmental disorders (GNDs) has been associated with the development of Parkinson's disease and other forms of parkinsonism.[4-6]

Although individually rare, research in GNDs may help to better understand different pathophysiological mechanisms that are believed to play a role in the development of parkinsonism. An analogy may be found in Down syndrome that is associated with early-onset Alzheimer's dementia. Research in Down syndrome has provided important insights into dementia etiology,[7] and has facilitated research into disease-modifying treatments.[8, 9] Genetic variants associated with GNDs are often identified in childhood, before neurologic symptoms emerge, and long-term follow up of children and adolescents with GNDs may increase knowledge on disease trajectories. In addition to the potential to identify disease and/or mechanism-specific treatment through animal models that are available for many genetic conditions, recognition of GNDs associated with parkinsonism may improve anticipatory care for patients with these GNDs. Thus, knowledge about GNDs that may present with parkinsonism is important to optimize clinical practice and further research.

In this systematic literature review, a comprehensive overview is provided of studies that reported on parkinsonism in GNDs. We summarize findings related to patient characteristics, parkinsonian features and proposed disease mechanisms, and outline implications for clinical practice and future research.

Methods

The study protocol was published in the PROSPERO International Register for Systematic Reviews (CRD42020191035). We made a few minor amendments to the initial protocol, including the addition of two co-authors, a repeated search, and inclusion of non-rare GNDs (e.g., Down syndrome). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA).[10]

Search strategy and selection

We performed a comprehensive literature search in PubMed and Embase on June 15, 2021 (see the Supporting Information Supplementary Methods and Supplementary Figure S1). We used the Human Phenotype Ontology (HPO; https://hpo.jax.org/) term "neurodevelopmental abnormality" (HP:0012759) for GNDs, in combination with database-specific subheadings and text words for "Parkinson's disease/parkinsonism".[11] Two reviewers independently screened titles and abstracts for eligibility. Relevant records were screened against selection criteria for inclusion based on full-text. In case of uncertainty, two other reviewers were consulted. Discrepancies were discussed until consensus was reached.

We included all reports on patients who met the inclusion criteria for a neurodevelopmental disorder (i.e., listed in the HPO as "neurodevelopmental" and/or representing patients showing a deviation from normal of the neurological development in childhood, including any or all aspects of the development of personal, social, motor, and cognitive abilities, in the presence of a disease-causing genetic variant) and parkinsonism (bradykinesia in combination with either rigidity, rest tremor or both),[12] or who were likely to have Parkinson's disease, operationalized as a clear beneficial response to levodopa, reduced dopamine transporter binding with dopaminergic imaging and/or neuropathological hallmarks of Parkinson's disease. We considered hypokinesia, akinesia, and hypomimia equal to bradykinesia if parkinsonism was diagnosed, in case bradykinesia was not explicitly noted. We excluded: 1) reports on patients with uncertain genetic etiology; i.e., not molecularly confirmed or according to standard clinical diagnostic criteria, 2) ultra-rare genetic conditions with less than

three reported cases, because of difficulties determining whether these were associated with brain development and because significance of the variant was often uncertain, and 3) neurogenetic disorders with solely motor aspects of development in childhood, such as most spinocerebellar ataxias. Results were limited to studies written in English and reports that provided original data. We performed a thorough cross-reference check.

Quality assessment

We critically appraised full-text articles using the National Heart, Lung and Blood Institute (NIH-NHLBI) study quality assessment tools for case-control and cohort studies.[13]

Data extraction

We extracted study characteristics and descriptive data from the included studies using a modified version of the Cochrane Consumers and Communication Review Group's Data Extraction Template (https://cccrg.cochrane.org). Data extracted comprised: *general information* (e.g., first author, year of publication, study design, and number of patients reported to have parkinsonism), *patient characteristics* (e.g., age, sex, presence/absence and severity of intellectual disability, full scale intelligence quotient), *other cognitive disorders or problems on other cognitive domains*, *genetics* (e.g., specific diagnosis and results of genetic testing including those related to Parkinson's disease disease-causing and risk genes), and *parkinsonian features* (e.g., age at motor onset, presence/absence of cardinal motor features and [proposed] pathophysiology).

Data presentation

We use descriptive summaries to present our findings. Patient characteristics and parkinsonian features per genetic disorder are presented in a heatmap, illustrating which features were most reported per genetic disorder in addition to the proposed underlying mechanisms (Figure 1 and Supplementary Figure S2).

Data availability

The data that supports the findings of this study are available in the supplementary material of this article. The template that was used for data-extraction is available upon request.

Results

Of a total of 5269 identified records, 208 reports met the inclusion criteria: 186 case studies and 22 observational case-control or cohort studies (see Flow-chart, Supplementary Figure S1). The 208 reports contained individual data of 422 patients with 69 different GNDs. Sex was reported in 395 patients, and 212 (53.7%) were male. The median age at last examination in 362/422 of the patients was 35 (range 0-77) years (for a list of included studies see Supplementary Tables S1 and S2, and for excluded studies Supplementary Table S3).

Quality assessments

The assessment of study quality for cohort and case-control studies is detailed in Supplementary Tables S4 and S5. Of the twenty-two cohort and case-control studies, fifteen were rated good, six were rated fair and one case-control study was considered to be of poor quality because of a very limited description of aims and methods.

Different GNDs that presented with parkinsonism

Most patients in the cohort had a monogenic disorder, with more than ten patients, from most to least frequent, reported for each of the following: beta-propeller protein-associated neurodegeneration (BPAN), cerebrotendinous xanthomatosis, Rett syndrome, *POLG*, *SYNJ1*, *DNAJC6*, tyrosine hydroxylase deficiency, Dravet syndrome *(SCN1A)*, neurofibromatosis type I, phosphoglycerate kinase deficiency and spastic paraplegia type 11. Between five and ten patients had juvenile neuronal ceroid lipofuscinosis (JNCL), *PTRHD1*, *RAB39B*, X-linked parkinsonism with spasticity, Alexander disease, dopa-responsive dystonia-parkinsonism (*NR4A2*), Fragile-X syndrome or spastic paraplegia type 15 (SPG15). The only copy number variation (CNV) and aneuploid conditions with more than

ten reported patients were 22q11.2 deletion syndrome and Down syndrome, respectively. Between five and ten patients were reported for Klinefelter syndrome. Forty-nine patients without genetic confirmation but with a biochemical or clinical diagnosis were included, with five or more patients reported for: Rett syndrome, neurofibromatosis type I, Down syndrome, and glutaric aciduria type 1. Less than five cases were reported for another 47 GNDs (see Supplementary Figure S2).

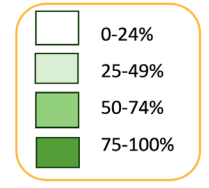
Thirteen of 422 patients (3.1%) were reported to have an additional genetic variant of potential clinical relevance for the development of parkinsonism, annotated in Figure 1 and Supplementary Figure S2.

Parkinsonian features

The median age at onset of motor symptoms, available for 349 of 422 patients, was 26 (range 0-66) years. For those with motor symptoms reported, rigidity was the most prevalent parkinsonian feature after bradykinesia, being present in 330 of 346 patients (95.4%). Rest tremor was seen in 218 of 355 (61.4%), postural instability in 138 of 179 (77.1%), asymmetry in 176 of 212 (83.0%), and progression of motor symptoms in 239 of 267 (89.5%) patients with data. Reduced DAT-binding was seen in the majority of the 39 GNDs with available dopaminergic imaging results, but not in Rett syndrome, Dravet syndrome (*SCN1A*), dihydropteridine reductase deficiency and *CLTC*. A clear and beneficial response to antiparkinsonian medication was reported in 187 of 262 patients (71.4%). GNDs with questionable or no response to antiparkinsonian medication in most cases were Rett syndrome, Dravet syndrome (*SCN1A)*, phosphoglycerate kinase deficiency, dystonia 16, Leigh syndrome, and Menkes disease. Levodopa-induced dyskinesia was described in 74 of 157 patients (47.1%).

Neurological and psychiatric comorbidity

Intellectual functioning was reported for 320 of 422 patients (75.8%), with intellectual disability present in 193 patients (60.3%). Cognitive decline or dementia was reported in 70 patients (16.6%). In 103 patients (24.4%) psychiatric comorbidity was present, such as depression, anxiety or psychosis. An additional neurologic disorder, not including dementia, was reported in 256 (60.7%) of 422 patients: dystonia in 128 (30.3%), epilepsy/seizures in 112 (26.5%) and ataxia in 38 patients (9.0%).



Genetic condition	Number of cases	Male *	Intellectual disability *	Mean age at motor onset	Bradykinesia, hypokinesia or akinesia *	Rigidity *	Rest tremor *	Postural instability *	Asymmetric motor symptoms *	Progression of motor signs *	Reduced DAT binding with dopaminergic imaging	Good response anti-parkinsonian medication *	Levodopa-induced dyskinesia *	Cognitive decline/dementia	Psychiatric symptoms	Proposed main cause of parkinsonism:	Parkinson's disease	Genetic	Drug-induced	Co-existing neurologic disorder:	Epilepsy/seizures	Dystonia	Ataxia	Other
Monogenic																								
Beta-propeller protein-associated neurodegeneration (*WDR45*)	43	6/43	41/41	25	40/41	43/43	8/34	12/17	6/6	33/33	4/4	25/32	7/13	6	2	36/42	0	35	1	40/43	21	34	1	3
Cerebrotendinous xanthomatosis (*CYP27A*)	22	8/22	14/16	34	20/20	18/20	12/18	10/11	12/13	11/12	8/10	11/16	2/4	5	5	13/22	0	13	0	14/22	1	1	10	6
Rett syndrome (*MECP2*)	21	6/21	6/8	12	21/21	16/16	6/21	1/2	1/3	4/4	0/1	0/3	0/3	3	2	1/21	0	1	0	8/21	0	8	0	0
POLG	20	10/20	1/20	51	19/19	13/15	13/15	2/2	11/13	6/6	8/8	4/5	-	1	3	14/20	0	14	0	9/20	0	1	8	0
SYNJ1	20	10/20	0/18	26	20/20	17/19	16/20	13/13	19/19	20/20	3/3	9/17	9/16	8	0	20/20	6	14	0	15/20	7	11	0	3
DNAJC6 [a]	19	8/16	8/19	16	19/19	19/19	15/19	19/19	9/1	19/19	5/5	11/17	6/8	2	5	19/19	5	14	0	11/19	7	2	0	3
Tyrosine hydroxylase deficiency (*TH*)	16	5/10	5/9	4	11/11	12/13	10/14	1/1	0/1	11/13	-	16/16	6/14	0	1	12/16	0	12	0	13/16	0	10	3	1
Dravet syndrome (*SCN1A*)	13	5/12	13/13	27	13/13	12/12	2/13	6/13	9/11	2/2	0/2	2/13	0/2	1	0	-	-	-	-	13/13	13	8	0	0
Neurofibromatosis type I, Von Recklinghausen (*NF1*) [b]	11	5/11	1/2	56	2/2	2/2	2/3	1/2	2/2	2/2	1/1	1/2	2/2	0	9	9/11	9	0	0	1/11	1	0	0	-
Phosphoglycerate kinase deficiency (*PGK1*)	10	10/10	8/10	22	10/10	9/10	9/10	6/7	8/8	10/10	5/5	3/10	3/5	0	3	4/10	0	4	0	7/10	4	3	0	6
SPG11	10	1/4	5/10	15	4/4	3/4	4/4	3/3	2/4	5/5	3/3	5/8	1/4	1	0	7/10	0	7	0	2/10	0	1	0	1
Copy number variant																								
22q11.2 deletion syndrome [c]	56	35/49	30/38	39	46/47	46/46	44/47	21/38	32/40	20/40	19/20	32/34	18/40	9	4/1	56/56	48	8	0	>17/56	16	16	0	1
Aneuploid																								
Down syndrome	23	14/18	6/6	32	20/22	21/23	10/23	1/2	5/5	6/6	-	9/13	0/5	18	2	18/23	13	5	0	17/23	14	0	0	5

Figure 1. Patient characteristics and parkinsonian features in the most reported genetic disorders

* The numerator represents how many patients were reported to present with a specific feature, and the denominator represents the number of patients with data available.
Additional genetic mutations with potential relevance to parkinsonism were reported: [a] *LRRK2*, [b] *PRKN*, [c] *PRKN*

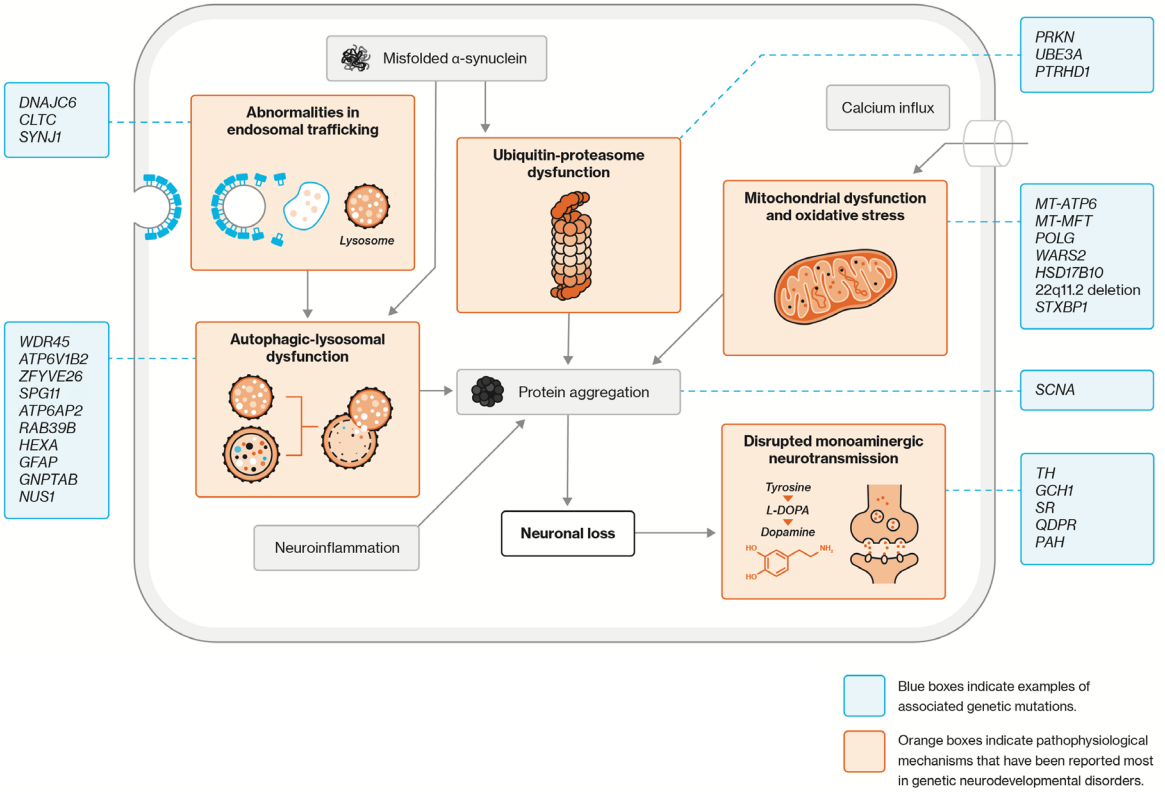


Figure 2. Mechanisms that may underly parkinsonism in genetic neurodevelopmental disorders

Schematic diagram depicting mechanisms that may underly parkinsonism in genetic neurodevelopmental disorders in orange boxes, with examples of associated genetic variants indicated in blue boxes.

Pathophysiology

The main causes of parkinsonism, as proposed in the articles, were the underlying genetic disorder, Parkinson's disease and drug-induced parkinsonism, with the latter reported in only two patients. The proposed pathophysiological mechanisms (summarized in Table 1 per genetic disorder and depicted in Figure 2), from most to least frequent, included: abnormalities in mitochondrial function and oxidative stress, lysosomal-autophagic function, endosomal trafficking and ubiquitin-proteasome system. Disruptions of monoaminergic neurotransmitter metabolism were also implicated in several GNDs that presented with parkinsonism.

Table 1. Pathophysiologic mechanisms that may underlie parkinsonism in genetic neurodevelopmental disorders

Genetic condition	Mechanisms/pathophysiology that may be considered
	Mitochondrial dysfunction
HSD10 (*HSD17B10*)	*HSD17B10* encodes an enzyme that is essential for mitochondrial maintenance.[14] Pathogenic variants may affect enzyme function and result in mitochondrial dysfunction.
Leigh syndrome (*MT-ATP6* and *MT-MFT*)	Leigh syndrome is caused by over 50 different mitochondrial and nuclear encoded genes, most often affecting the respiratory chain and oxidative phosphorylation.[15] Mitochondrial dysfunction may result in brain stem and basal ganglia lesions.
Leigh-like syndrome (*MT-TI*)	*MT-TI* is a mitochondrial gene of which pathogenic variants may result in mitochondrial dysfunction and basal ganglia lesions, similar to what has been proposed for Leigh syndrome.
MT-CYB	*MT-CYB* is a mitochondrial gene that encodes for a component of the respiratory chain. Pathogenic variants may result in mitochondrial dysfunction and progressive basal ganglia lesions, as has been proposed for Leigh syndrome.
POLG	*POLG* encodes a DNA polymerase that is essential for replication of mitochondrial DNA. Mice that were homozygous for variants that may disrupt the function of POLG protein exhibited premature ageing.[16, 17]
WARS2	Pathogenic variants in *WARS2*, that encodes for the WARS2 protein located in the mitochondrion, may result in respiratory chain defects and nigrostriatal degeneration.[18]
	Mitochondrial dysfunction combined with other mechanisms
22q11.2 deletion syndrome	The 22q11.2 deletion region encompasses several genes including *COMT*, essential for catecholamine degradation, and six mitochondrial genes.[19-21] Haploinsufficiency of these genes may result in dopamine autotoxicity and mitochondrial dysfunction.[22]
Down syndrome	Mitochondrial dysfunction, neuroinflammation, oxidative stress and lysosomal dysfunction have all been reported in Down syndrome.[23-25]

Early infantile epileptic encephalopathy 4 (*STXBP1*)	Pathogenic variants in *STXBP1* may cause significant impairment of complex I of the mitochondrial respiratory chain and may disrupt the self-replicating aggregation of α-synuclein.[26]
Glutaric aciduria type I (*GCDH*)	*GCDH* plays a key role in the catabolism of lysine, hydroxylysine, and tryptophane. Deficiency of *GCDH* leads to accumulation of glutaric acid and 3-hydroxyglutaric acid that can induce neuronal death through excitotoxicity as well as mitochondrial dysfunction and altered neurotransmission.[27]
Mevalonic aciduria (*MVK*)	Pathogenic variants in *MVK* may result in mitochondrial dysfunction, impaired cholesterol biosynthesis, toxic basal ganglia mevalonate accumulation and intracerebral inflammation.[28,29]
NR4A2	Pathogenic variants in *NR4A2* are implicated in development and survival of dopaminergic neurons in the substantia nigra, and may lower expression of genes associated with mitochondrial function and oxidative phosphorylation.[30]
Pyruvate carboxylase deficiency (*PC*)	*PC* encodes for pyruvate carboxylase, a mitochondrial enzyme that catalyzes pyruvate to oxaloacetate, intermediates in the Krebbs cycle and is important for neurotransmitter synthesis.[31]
SPG10 (*KIF5A*)	Axonal transport defect of mitochondria has been shown in a *KIF5A* knockout mouse model.[32]
	Autophagic-lysosomal system
Alexander disease (*GFAP*)	*GFAP* encodes for glial fibrillary acidic protein (GFAP), an intermediate filament protein in astrocytes. GFAP accumulation has been associated with autophagy in astrocytic cells.[33]
BPAN (*WDR45*)	Pathogenic variants of *WDR45*, encoding for WIPI4 protein, may cause iron accumulation in the basal ganglia by impeding autophagy,[34] that may result in neuroinflammation and swelling of the substantia nigra.
Christianson syndrome (*SLC9A6*)	*SLC9A6* encodes the endosomal Na+/H+ exchanger 6 and is involved in endosomal luminal pH and trafficking, synapse development and plasticity.[35] Findings in Slc9a6 knock-out mice were consistent with endosomal-lysosomal dysfunction.[36]
DOORS syndrome (*ATP6V1B2*)	*ATP6V1B2* encodes a subunit of the lysosomal transmembrane proton pump. Altered lysosomal pH is associated with chronic changes in autophagy.[37]
JNCL (*CLN3*)	*CLN3* is involved in autophagic-lysosomal function. *CLN3* is required for fusion of autophagosomes to lysosomes.[38]
Mucolipidosis type II (*GNPTAB*)	Pathogenic variants in *GNPTAB*, that encodes for GlcNAc-1-phosphotransferase, may cause lysosomal accumulation of nondegraded material, leading to neuronal dysfunction.[39]
NUS1	Deficiency of *NUS1*, encoding the Nogo B receptor, may result in lysosomal defects, most likely caused by lysosomal cholesterol accumulation.[40]
RAB39B	Ras-related proteins play an essential role in neuronal maintenance, survival and synapse formation. It has been suggested that *RAB39B* plays a role in autophagy of dopaminergic neurons. Loss of function may impair the clearance of α-synuclein.[41, 42]
SPG15 (*ZFYVE26*)	Pathogenic variants of *ZFYVE26* encoding spastizin, a protein mediating autophagic lysosome reformation, are believed to cause abnormal lysosomal storage.[43]

SPG11 (*SPG11*)	Pathogenic variants of *SPG11* encoding spatacsin, a protein mediating autophagic lysosome reformation may cause abnormal lysosomal storage.[44]
Tay-Sachs disease (*HEXA*)	*HEXA* encodes for β-hexosaminidase A, a lysosomal enzyme that degrades GM2 ganglioside. Deficiency of this enzyme A has been associated with GM2 ganglioside accumulation nerve cells.[45]
X-linked parkinsonism with spasticity (*ATP6AP2*)	*ATP6AP2* encodes an accessory unit of an essential lysosomal enzyme. Haploinsufficiency of *ATP6AP2* may lead to autophagy defects, disrupted presynaptic transmission and neurodegeneration.[46]
	Neurotransmitter metabolism
6p25 deletion, involving *FOXC1*	Pathogenic variants in *FOXC1* may affect genes involved in dopamine synthesis and dopaminergic neuronal development.[47, 48]
Dihydropteridine reductase deficiency (*QDPR*)	Deficiency of dihydropteridine reductase, that is required for resynthesis of tetrahydrobiopterin, an essential cofactor for the activity of phenylalanine-, tryptophane- and tyrosine hydroxylases, may impair neurotransmitter synthesis.[49]
DNAJC12	*DNAJC12* has a critical role in chaperoning amino-acid hydrolase interactions required for catecholamine synthesis.[50]
Dopamine transporter deficiency syndrome (*SLC6A3*)	*SLC6A3* encodes for the dopamine transporter (DAT). DAT deficiency syndrome may lead to impaired DAT activity, apoptotic neurodegeneration and dopamine toxicity.[51]
Dravet syndrome (*SCN1A*)	*SCN1A*, that encodes a voltage-gated sodium channel, may lead to impaired neurotransmitter release.[52]
GTP cyclohydrolase 1 deficiency, dopa-responsive dystonia (*GCH1*)	GTP cyclohydrolase 1 is important for the biosynthesis of tetrahydrobiopterin, an essential cofactor for the activity of phenylalanine-, tryptophane and tyrosine hydroxylases. Deficiency of this enzyme may disrupt neurotransmitter synthesis.[53]
Neurofibromatosis type I (*NF1*)	*NF1,* a tumor suppressor gene, encodes for neurofibromin. Among other genes, it is involved in the activation of GTPase, mTOR signaling, learning (via impaired long-term potentiation) and regulation of dopamine homeostasis.[54]
Phenylketonuria (*PAH*)	*PAH* encodes for phenylalanine hydroxylase. Deficiency results in a decreased conversion of phenylalanine to tyrosine. Phenylalanine inhibits dopamine and serotonin synthesis in the brain by inhibition of tyrosine and tryptophan transport, and inhibition of tyrosine and tryptophan hydroxylases.[55, 56]
PPP2R5D	*PPP2R5D* encodes a regulatory subunit of protein phosphatase-2A (PP2A), an intracellular serine/threonine phosphatase. PP2A regulates phosphorylation of one site (S129) of α-synuclein. Increased activity of PP2A influences tyrosine hydroxylase and subsequently may affect dopamine synthesis.[57, 58]
Sepiapterin reductase deficiency (*SR*)	Deficiency of sepiapterin reductase, essential for tetrahydrobiopterin biosynthesis, may result in disturbed dopaminergic and serotonergic neurotransmission.[59]
Tyrosine hydroxylase deficiency, dopa-responsive dystonia (*TH*)	Deficiency of tyrosine hydroxylase, the rate-limiting step in dopamine biosynthesis, may lead to a shortage of dopamine.[60]
	Endosomal trafficking
CLTC	A defective clathrin heavy chain polypeptide protein, caused by pathogenic variants of *CLTC*, may result in depletion of biogenic amines by altering their synaptic turnover.[61]

DNAJC6	*DNAJC6* encodes for auxilin, a neuronally expressed J-chaperone protein involved in the uncoating of clathrin-coated vesicles, that is necessary for the regeneration of synaptic vesicles. Impaired uncoating is thought to lead to neurotransmission deficits.[62]
SYNJ1	*SYNJ1* encodes a phosphoinositide phosphatase called synaptojanin1 and plays an important role in early endosomal compartments and clathrin-mediated endocytosis.[63]
	Ubiquitin-proteasome system
Angelman syndrome, involving *UBE3A*	*UBE3A* encodes the Ubiquitin-Protein Ligase E3A, part of the ubiquitin-proteolytic pathway,[64] that has been suggested to be involved in the clearance of alpha-synuclein.[65]
Partial 6q trisomy, involving *PRKN*	Pathogenic variants of *PRKN* are associated with early-onset autosomal recessive Parkinson's disease.[66] *PRKN* encodes the E3 Ubiquitin-Protein Ligase Parkin, involved in mitophagy, and possibly in the formation of Lewy bodies.[67]
PTRHD1	*PTRHD1* encodes for peptidyl-tRNA hydrolase that belongs to the PTH2 family. The deduced ubiquitin-like domain-binding protein is thought to suppress ubiquitin-mediated protein degradation.[68] Alfa-synuclein homeostasis is maintained by proper function of the ubiquitin-proteasome system.
	Other
Cerebrotendinous xanthomatosis (*CYP27A*)	Accumulation of cholesterol and cholestanol cause neurotoxicity and axonopathy.[69]
Incontinentia pigmenti (*IKBKG*)	It has been suggested that pathogenic variants in *IKBKG,* involved in neuronal anti-apoptotic signaling, may cause neurodegeneration.[70]
Klinefelter syndrome	Melatonin may have a neuroprotective role in Parkinson's disease. It has been suggested that reduced melatonin levels in Klinefelter syndrome may play a role in the development of parkinsonism.[71, 72]
L2-hydroxyglutaric aciduria (*L2HGDH*)	*L2HGDH* encodes for l-2-hydroxyglutarate (L2HG) dehydrogenase that oxidizes L-2-hydroxyglutarate to alpha-ketoglutarate. L2HG deficiency may result in impaired hippocampal neurogenesis and neurodegeneration in adult mouse brains.[73]
Menkes disease (*ATP7A*)	Haploinsufficiency of *ATP7A,* encoding a transmembrane copper-transporting ATPase, may result in dysregulation of copper metabolism in the basal ganglia.[74, 75]
Molybdenum cofactor deficiency type B (*MOCS2*)	*MOCS2* encodes for molybdenum cofactor. Deficiency leads to loss of sulfite oxidase activity, resulting in cumulative metabolic effects on the basal ganglia.[76] Elevated concentrations of S-sulfocysteine and toxic sulfite may trigger neuronal apoptosis.[77]
Partial 4q trisomy, involving *SNCA*	*SNCA* encodes α-synuclein, the primary component of Lewy bodies. The patient with partial 4q trisomy had a *de novo SNCA* duplication. Other genes in the duplicated region may have contributed to the phenotype.[78]
Phosphoglycerate kinase deficiency I (*PGK1*)	Phosphoglycerate kinase is an important enzyme in the glycolytic pathway. It has been suggested that neuronal damage occurs as a consequence of energy failure.[79]
SCA27 (*FGF14*)	*FGF14,* expressed in axons of the striatopallidal and striatonigral pathways, encodes a regulatory protein of voltage-gated sodium channels (Nav1.6). Haploinsufficiency of *FGF14* may alter expression of sodium channels with impaired firing of Purkinje neurons.[80]
Smith-Magenis syndrome (*RAI1*)	Pathogenic variants of *RAI1* may result in an inversion of circadian melatonin secretion with a lack of nocturnal melatonin, that may play a role in the development of parkinsonism.[71, 72, 81]

Neuropathology

Neuropathological findings were reported for 16 patients (11 male; 73.3%) at median age 57 (range 2-74) years: 22q11.2 deletion syndrome (*n*=3), Down syndrome (*n*=2), *POLG* (*n*=2), BPAN (*n*=1), CTX (*n*=1), Cornelia de Lange syndrome (*n*=1), *DNAJC12* (*n*=1), DOORS syndrome (*n=1*), 5,10-methylenetetrahydrofolate reductase deficiency (*n*=1), *NR4A2* (*n*=1), *PPP2R5D* (n=1) and *RAB39B* (*n*=1) (Table 2). In 14 patients, the presence of Lewy bodies was examined, with positive findings in six cases (42.9%): 22q11.2 deletion syndrome (*n*=2/3), Down syndrome (*n*=2/2), *NR4A2* (*n*=1/1) and *RAB39B* (*n*=1/1). Neurites were examined in nine patients and present in seven: 22q11.2 deletion syndrome (*n*=2/3), Cornelia de Lange syndrome (*n*=1/1), *DNAJC12* (*n*=1/1), Down syndrome (*n*=1/1), *NR4A2* (*n*=1/1) and *RAB39B* (*n*=1/1). Neuronal loss was reported in all but one patient (92.9%), the latter who had DOORS syndrome.

Table 2. Neuropathological findings in patients with genetic neurodevelopmental disorders and parkinsonism

Genetic neurodevelopmental disorder	Age, y	Sex	LB	LN	Neuronal loss
22q11.2 deletion syndrome [82]	56	F	+	+	+
	58	M	+	+	+
	61	M	-	-	+
BPAN [83]	27	F	-	NR	+
CTX [69]	56	M	NR	NR	+
Cornelia de Lange syndrome [84]	38	M	-	+ *	+
DNAJC12 [85]	74	M	-	+ *	+
DOORS syndrome [37]	72	M	-	NR	-
Down syndrome [86, 87]	54	M	+	+ *	+
	49	M	+	NR	+
MTHFR deficiency [88]	2	F	NR	NR	+
NR4A2 [89]	74	NR	+	+	+
POLG [90]	61	F	-	-	+
	60	M	-	-	+
PPP2R5D [91]	61	M	-	-	+
RAB39B [92]	48	M	+	+	+

Abbreviations: y = years, LB = Lewy bodies, LN = Lewy neurites, F = female, M = male, + = present, - = absent,

BPAN = Beta-propeller protein associated neurodegeneration, NR = not reported, + * = neurites (unspecified), CTX = cerebrotendinous xanthomatosis, MTHFR = 5,10-methylenetetrahydrofolate reductase.

Discussion

In this first systematic literature review on parkinsonism in patients with GNDs, we provide a comprehensive overview of phenotypic characteristics and proposed pathophysiology in 69 different GNDs, based on a total of 422 patients. The main messages and implications of this review can be found in Figure 3.

Parkinsonism has been reported in a growing number of GNDs. This number may be expected to further increase given advances in clinical genetic testing and an increase in life expectancy due to improved medical care for patients with GNDs. Parkinsonism in these populations however appears to be underrecognized in clinical practice and to be an understudied research topic.[93-95] An explanation may be that, on the one hand, patients with GNDs may not always be aware of motor symptoms and may not be capable to express their symptoms adequately. Professionals on the other hand may attribute motor symptoms to manifestations of the GND, antipsychotic medication-induced parkinsonism or co-existing neurologic disorders, while in fact they may miss a treatable condition of parkinsonism.[82]

Phenotypic characteristics

Many patients showed the typical phenotypic characteristics found for patients with Parkinson's disease: presence of cardinal motor signs, a good response to antiparkinsonian medication and reduced DAT binding with dopaminergic imaging. However, there were some notable findings. For example, almost half of the patients included in our review were female, atypical for idiopathic Parkinson's disease sex distribution,[96] and the median age at motor onset was 26 years, much younger compared to age-related parkinsonism in the general population.[97, 98] Also, many patients had co-existing neurologic disorders, of which dystonia, seizures, and ataxia were most common.[99, 100] While previous research has suggested that patients with neurodevelopmental disorders may be susceptible to drug-induced parkinsonism,[93, 101] drug-induced parkinsonism as the main cause was reported in only two patients.

Pathophysiologic mechanisms

The group of GNDs in this review was diverse, consistent with the multiple pathways and mechanisms involved in the pathogenesis of both neurodevelopmental and neurodegenerative disorders, including autophagic, lysosomal and mitochondrial function, endosomal trafficking and the ubiquitin-proteasome system.[102-104] Dysregulation of these cellular processes, that are especially important in long-lived cells such as neurons, may affect neurogenesis,[104, 105] synaptic function,[106, 107] neuroplasticity,[108] and neuronal survival increasing the vulnerability for neurological and psychiatric disorders across a patient's lifespan.[3, 109] Also, these mechanisms may interact and when disrupted, contribute to a vicious cycle including the formation of protein aggregates, as has been implicated in Parkinson's disease.[110, 111] Studying parkinsonism in patients with GNDs, and related animal models, may be useful to unravel the complex processes underlying parkinsonism.

Interestingly, in almost all GNDs with available data on neuropathology, neuronal loss was found, consistent with growing recognition that neurodevelopmental and neurodegenerative disorders overlap, rather than should be seen as opposite conditions.[2, 3]

Clinical implications

The large number of GNDs that may present with parkinsonism prompts questions about prevention, diagnosis, and management. Given the young onset and the co-occurrence of other movement disorders seen in GNDs, early motor signs should be carefully monitored in patients with these conditions. Periodic standardized motor evaluations (e.g., MDS-UPDRS and video-recordings), and involvement of a movement disorder specialist, may be considered. When parkinsonism presents and progresses, dopaminergic imaging may assist distinguishing medication-induced parkinsonism from degenerative parkinsonism, that may be particularly difficult in patients with GNDs and complex neuropsychiatric expression.[112]

Clinicians treating patients with early-onset parkinsonism and intellectual disabilities or other neurodevelopmental problems, should consider ordering a genetic test. Identification of an underlying diagnosis can be important for long-term clinical management. It allows the opportunity for preventive

and treatment strategies, may reduce the burden on patients and their families searching for answers (sometimes referred to as the "Diagnostic Odyssey"), inform disease risks for family members, and help patients and their families connecting with patient organizations for peer support.[113] It is important to realize that patients with GNDs may develop multiple early- and late-onset comorbidities that require proactive attention depending on the condition, that are typically not restricted to neurological problems, but may involve all body systems.[114, 115] Increasingly, expert clinics specializing in specific GNDs are available, typically providing multidisciplinary care to improve patient outcomes and quality of life.

Next generation sequencing techniques, such as whole exome sequencing (WES), that may reveal a monogenic disorder,[113] or chromosomal microarray analysis, that identifies genome wide CNVs,[116] may be used as first line diagnostic tests. Certain features, including congenital anomalies and 'dysmorphic facial features', may point to the presence of a specific syndrome, but are absent in many patients. Here, it should also be noted that conventional karyotyping will not detect CNVs or monogenic disorders and that most currently available Parkinson's disease genetic diagnostic panels do typically not include GNDs. Therefore, an additional panel for intellectual disability may need to be ordered. It should also be realized that family history is often not a good predictor; many patients with a GND have a *de novo* mutation. Selecting the most appropriate genetic test can however be difficult; choosing the right test can require consultation with a clinical geneticist. Limitations of most genetic tests include the high costs; these tests are not readily available for many people, or inaccessible.

With recent advances in diagnosis and treatment of GNDs, targeted disease-modifying therapies have become available for an increasing number of patients diagnosed with a GND, i.e., for those with an inborn error of metabolism or tuberous sclerosis complex.[117-119] Early detection of such disorders allows for timely interventions to prevent further brain damage and/or disease progression. Prominent examples of treatable inborn errors of metabolism in this review include phenylketonuria and other conditions that lead to disruptions in monoaminergic neurotransmitter metabolism (e.g., *TH*, and *DNAJC12*).[117] These patients may have great benefit from

specific nutritional and/or pharmacological interventions with improvement in parkinsonism.[120] Other examples include disorders of lipid metabolism (like cerebrotendinous xanthomatosis and X-linked adrenoleukodystrophy) and 5,10-methylenetetrahydrofolate reductase deficiency.[117] Discoveries continue to be made regarding the development of treatment in inborn errors of metabolism that may have been associated with parkinsonism, making it an important and evolving group of disorders.

Management of parkinsonism requires a coordinated multidisciplinary approach in view of the comorbidity in many GNDs, that may involve clinical experts from many subspecialties in addition to the family doctor and movement disorder specialist.

- Parkinsonism has been reported in 69 different genetic neurodevelopmental disorders (GNDs).
- GNDs are genetically and clinically heterogeneous.
- Patients with both a GND and parkinsonism is a growing population due to improved detection and clinical care.
- Identification of a genetic disorder is important for several reasons, e.g.: end the 'Diagnostic Odyssey', counseling of patients and their families, connect patients to patient organizations for peer support, and to provide long-term clinical/preventative care.
- Many GNDs are multisystem diseases with neurological and non-neurological manifestations.
- Many GNDs that present with parkinsonism require coordinated multidisciplinary care involving health care professionals from several medical and non-medical disciplines.
- Treatable inborn errors that present with neurodevelopmental problems and parkinsonism are an evolving group of disorders.
- Research in GNDs may help unravel the complex processes underlying parkinsonism.
- International research collaborations with detailed phenotype analysis ('deep phenotyping') are needed to further our knowledge, and to overcome the issue of the limited number of patients with individually rare conditions.

Figure 3. Main messages

Research implications

Phenotypic heterogeneity may be significant in GNDs given incomplete penetrance of genetic variants, variable expression, and pleiotropy,[121] and may be particularly relevant in those GNDs involving multiple genes, such as is the case in 22q11.2 deletion syndrome. Detailed phenotype analysis ('deep-phenotyping') is crucial to further our knowledge on the complex relationships between genetics, pathophysiological mechanisms, environmental factors and the phenotypic characteristics of parkinsonism in GNDs. International collaborative research is needed, to overcome the issue of the limited number of patients with individually rare conditions. In addition to routine assessments including careful history taking that focusses on parkinsonian/neurological features and comorbid conditions of the genetic variant, and structured physical examinations (e.g. MDS-UPDRS), this should include careful family history taking. Periodic video assessments may also be considered. Despite the challenges, GNDs are often diagnosed at an early age, long before the onset of motor and non-motor Parkinson's disease related symptoms, facilitating early-stage research of parkinsonism. In addition to human studies, recognizing GNDs makes it possible to use cell and animal models, available for many GNDs, to expand the possibilities of studying the pathophysiologic mechanisms, identify potential biomarkers and design rational interventions.[30, 90] Disease-specific intervention strategies have been suggested in several human and animal models of GNDs and clearly demonstrate the benefits of these kind of studies.[85, 122]

With an increased life expectancy for many GNDs, future research should also focus on overlap between GNDs and other neurodegenerative disorders, e.g., major neurocognitive disorder, in order to understand shared underlying mechanisms and improve clinical care.

Strengths and Limitations

The strengths of this systematic review include the pre-registration of the protocol, the comprehensive search strategy, and the extensive data extraction on key characteristics of parkinsonism and its proposed pathophysiologic mechanisms. Several limitations should also be mentioned. The data need to be considered in view of the retrospective

nature of most studies. Notably, given the large number and wide spectrum of genetically and clinically heterogenous disorders, the absence of a perfect classification system that would prevent any inconsistency in inclusion/exclusion of reports, and differences in availability of information among genetic neurodevelopmental disorders, we cannot rule out the possibility of some inconsistencies in inclusion/exclusion of reports. Also, on the one hand, because non-English reports, studies lacking detailed information on the genetic disorder and/or criteria for parkinsonism, and studies reporting on genetic conditions with less than three reported cases, were excluded, this review may not have captured all relevant publications. On the other hand, as we included all conditions listed in HPO as "neurodevelopmental abnormality", we may have included conditions that should not be considered to affect brain development. Heterogeneity in reporting made summarization of results difficult, hampering comparability between GND phenotypic characteristics. For example, the percentages depicted in the heat map color scheme were based on the availability of data, that greatly varied from one report to the other (Figure 1 and Supplementary Figure S2). Publication bias will have influenced the findings. Variable strength of the evidence linking genes to phenotypes and the preliminary nature of some findings should be taken into account.

Conclusion

Parkinsonism has been reported in many GNDs. Findings from this study may provide clues for further research and improve management of patients with GNDs and/or parkinsonism.

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Competing interests

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that the approval of an institutional review board was not required for this work. The authors confirm that patient consent was not required for this work.

Supplementary material

Additional data is available in the Supplementary Material (online).

References

1. Hickman RA, O'Shea SA, Mehler MF, Chung WK. Neurogenetic disorders across the lifespan: from aberrant development to degeneration. *Nat Rev Neurol*. Feb 2022;18(2):117-124. doi:10.1038/s41582-021-00595-5
2. Saudubray JM, Garcia-Cazorla A. An overview of inborn errors of metabolism affecting the brain: from neurodevelopment to neurodegenerative disorders. *Dialogues Clin Neurosci*. Dec 2018;20(4):301-325. doi:10.31887/DCNS.2018.20.4/jmsaudubray
3. Morato Torres CA, Wassouf Z, Zafar F, Sastre D, Outeiro TF, Schüle B. The Role of Alpha-Synuclein and Other Parkinson's Genes in Neurodevelopmental and Neurodegenerative Disorders. *International journal of molecular sciences*. 2020;21(16):5724. doi:10.3390/ijms21165724
4. Puschmann A. New Genes Causing Hereditary Parkinson's Disease or Parkinsonism. *Curr Neurol Neurosci Rep*. Sep 2017;17(9):66. doi:10.1007/s11910-017-0780-8
5. Morales-Briceno H, Mohammad SS, Post B, et al. Clinical and neuroimaging phenotypes of genetic parkinsonism from infancy to adolescence. *Brain*. Dec 4 2019;doi:10.1093/brain/awz345
6. Niemann N, Jankovic J. Juvenile parkinsonism: Differential diagnosis, genetics, and treatment. *Parkinsonism Relat Disord*. Oct 2019;67:74-89. doi:10.1016/j.parkreldis.2019.06.025
7. Wiseman FK, Al-Janabi T, Hardy J, et al. A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome. *Nat Rev Neurosci*. Sep 2015;16(9):564-74. doi:10.1038/nrn3983
8. Finucane BM, Myers SM, Martin CL, Ledbetter DH. Long overdue: including adults with brain disorders in precision health initiatives. *Curr Opin Genet Dev*. Dec 2020;65:47-52. doi:10.1016/j.gde.2020.05.001
9. Fortea J, Vilaplana E, Carmona-Iragui M, et al. Clinical and biomarker changes of Alzheimer's disease in adults with Down syndrome: a cross-sectional study. *Lancet*. Jun 27 2020;395(10242):1988-1997. doi:10.1016/s0140-6736(20)30689-9
10. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. Jan 1 2015;4:1. doi:10.1186/2046-4053-4-1
11. Köhler S, Carmody L, Vasilevsky N, et al. Expansion of the Human Phenotype Ontology (HPO) knowledge base and resources. *Nucleic Acids Res*. Jan 8 2019;47(D1):D1018-d1027. doi:10.1093/nar/gky1105
12. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. Oct 2015;30(12):1591-601. doi:10.1002/mds.26424
13. Study Quality Assessment Tools. National Institutes of Health. Accessed April, 2020. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
14. Zschocke J. HSD10 disease: clinical consequences of mutations in the HSD17B10 gene. *J Inherit Metab Dis*. Jan 2012;35(1):81-9. doi:10.1007/s10545-011-9415-4
15. Lake NJ, Bird MJ, Isohanni P, Paetau A. Leigh syndrome: neuropathology and pathogenesis. *J Neuropathol Exp Neurol*. Jun 2015;74(6):482-92. doi:10.1097/nen.0000000000000195
16. Trifunovic A, Wredenberg A, Falkenberg M, et al. Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature*. May 27 2004;429(6990):417-23. doi:10.1038/nature02517
17. Rahman S, Copeland WC. POLG-related disorders and their neurological manifestations. *Nat Rev Neurol*. Jan 2019;15(1):40-52. doi:10.1038/s41582-018-0101-0
18. Burke EA, Frucht SJ, Thompson K, et al. Biallelic mutations in mitochondrial tryptophanyl-tRNA synthetase cause Levodopa-responsive infantile-onset Parkinsonism. *Clin Genet*. Mar 2018;93(3):712-718. doi:10.1111/cge.13172
19. Maynard TM, Meechan DW, Dudevoir ML, et al. Mitochondrial localization and function of a subset of 22q11 deletion syndrome candidate genes. *Mol Cell Neurosci*. Nov 2008;39(3):439-51. doi:10.1016/j.mcn.2008.07.027

20. Boot E, Booij J, Zinkstok J, et al. Disrupted dopaminergic neurotransmission in 22q11 deletion syndrome. *Neuropsychopharmacology*. May 2008;33(6):1252-8. doi:10.1038/sj.npp.1301508
21. Devaraju P, Zakharenko SS. Mitochondria in complex psychiatric disorders: Lessons from mouse models of 22q11.2 deletion syndrome: Hemizygous deletion of several mitochondrial genes in the 22q11.2 genomic region can lead to symptoms associated with neuropsychiatric disease. *Bioessays*. Feb 2017;39(2)doi:10.1002/bies.201600177
22. Boot E, Bassett AS, Marras C. 22q11.2 Deletion Syndrome-Associated Parkinson's Disease. *Mov Disord Clin Pract*. Jan 2019;6(1):11-16. doi:10.1002/mdc3.12687
23. Vacca RA, Bawari S, Valenti D, et al. Down syndrome: Neurobiological alterations and therapeutic targets. *Neurosci Biobehav Rev*. Mar 2019;98:234-255. doi:10.1016/j.neubiorev.2019.01.001
24. Jiang Y, Sato Y, Im E, et al. Lysosomal Dysfunction in Down Syndrome Is APP-Dependent and Mediated by APP-βCTF (C99). *J Neurosci*. Jul 3 2019;39(27):5255-5268. doi:10.1523/jneurosci.0578-19.2019
25. Valenti D, Tullo A, Caratozzolo MF, et al. Impairment of F1F0-ATPase, adenine nucleotide translocator and adenylate kinase causes mitochondrial energy deficit in human skin fibroblasts with chromosome 21 trisomy. *Biochem J*. Oct 15 2010;431(2):299-310. doi:10.1042/bj20100581
26. Lanoue V, Chai YJ, Brouillet JZ, et al. STXBP1 encephalopathy: Connecting neurodevelopmental disorders with alpha-synucleinopathies? *Neurology*. Jul 16 2019;93(3):114-123. doi:10.1212/wnl.0000000000007786
27. Jafari P, Braissant O, Bonafé L, Ballhausen D. The unsolved puzzle of neuropathogenesis in glutaric aciduria type I. *Mol Genet Metab*. Dec 2011;104(4):425-37. doi:10.1016/j.ymgme.2011.08.027
28. van der Burgh R, Ter Haar NM, Boes ML, Frenkel J. Mevalonate kinase deficiency, a metabolic autoinflammatory disease. *Clin Immunol*. Jun 2013;147(3):197-206. doi:10.1016/j.clim.2012.09.011
29. Zyss J, Vlaicu M, Gerber S, Rodallec M, Gauthier C, Zuber M. Movement disorders in mevalonic aciduria. *Movement Disorders*. 2011;26(SUPPL. 2):S256. 15th International Congress of Parkinson's Disease and Movement Disorders. Toronto, ON Canada.

(var.pagings). doi:http://dx.doi.org/10.1002/mds.23764
30. Decressac M, Volakakis N, Björklund A, Perlmann T. NURR1 in Parkinson disease--from pathogenesis to therapeutic potential. *Nat Rev Neurol*. Nov 2013;9(11):629-36. doi:10.1038/nrneurol.2013.209
31. Marin-Valencia I, Roe CR, Pascual JM. Pyruvate carboxylase deficiency: mechanisms, mimics and anaplerosis. *Mol Genet Metab*. Sep 2010;101(1):9-17. doi:10.1016/j.ymgme.2010.05.004
32. Kawaguchi K. Role of kinesin-1 in the pathogenesis of SPG10, a rare form of hereditary spastic paraplegia. *Neuroscientist*. Aug 2013;19(4):336-44. doi:10.1177/1073858412451655
33. Tang G, Yue Z, Talloczy Z, et al. Autophagy induced by Alexander disease-mutant GFAP accumulation is regulated by p38/MAPK and mTOR signaling pathways. *Hum Mol Genet*. Jun 1 2008;17(11):1540-55. doi:10.1093/hmg/ddn042
34. Hor CHH, Tang BL. Beta-propeller protein-associated neurodegeneration (BPAN) as a genetically simple model of multifaceted neuropathology resulting from defects in autophagy. *Rev Neurosci*. Apr 24 2019;30(3):261-277. doi:10.1515/revneuro-2018-0045
35. Xu M, Ouyang Q, Gong J, et al. Mixed Neurodevelopmental and Neurodegenerative Pathology in Nhe6-Null Mouse Model of Christianson Syndrome. *eNeuro*. Nov-Dec 2017;4(6)doi:10.1523/eneuro.0388-17.2017
36. Strømme P, Dobrenis K, Sillitoe RV, et al. X-linked Angelman-like syndrome caused by Slc9a6 knockout in mice exhibits evidence of endosomal-lysosomal dysfunction. *Brain : a journal of neurology*. 2011;134(Pt 11):3369-3383. doi:10.1093/brain/awr250
37. Zadori D, Szalardy L, Maszlag-Torok R, et al. Clinicopathological Relationships in an Aged Case of DOORS Syndrome With a p.Arg506X Mutation in the ATP6V1B2 Gene. *Frontiers in Neurology*. 2020;11:767. doi:http://dx.doi.org/10.3389/fneur.2020.00767

38. Yasa S, Modica G, Sauvageau E, Kaleem A, Hermey G, Lefrancois S. CLN3 regulates endosomal function by modulating Rab7A-effector interactions. *J Cell Sci*. Mar 16 2020;133(6) doi:10.1242/jcs.234047
39. Schweizer M, Markmann S, Braulke T, Kollmann K. Ultrastructural analysis of neuronal and non-neuronal lysosomal storage in mucolipidosis type II knock-in mice. *Ultrastruct Pathol*. Oct 2013;37(5):366-72. doi:10.3109/01913123.2013.810687
40. Yu SH, Wang T, Wiggins K, et al. Lysosomal cholesterol accumulation contributes to the movement phenotypes associated with NUS1 haploinsufficiency. *Genet Med*. Mar 17 2021;doi:10.1038/s41436-021-01137-6
41. Tang BL. Rabs, Membrane Dynamics, and Parkinson's Disease. *J Cell Physiol*. Jul 2017;232(7):1626-1633. doi:10.1002/jcp.25713
42. Koss DJ, Campesan S, Giorgini F, Outeiro TF. Dysfunction of RAB39B-Mediated Vesicular Trafficking in Lewy Body Diseases. *Mov Disord*. May 3 2021;doi:10.1002/mds.28605
43. Renvoisé B, Chang J, Singh R, et al. Lysosomal abnormalities in hereditary spastic paraplegia types SPG15 and SPG11. *Ann Clin Transl Neurol*. Jun 1 2014;1(6):379-389. doi:10.1002/acn3.64
44. Pozner T, Regensburger M, Engelhorn T, Winkler J, Winner B. Janus-faced spatacsin (SPG11): involvement in neurodevelopment and multisystem neurodegeneration. *Brain*. Aug 1 2020;143(8):2369-2379. doi:10.1093/brain/awaa099
45. Fernandes Filho JA, Shapiro BE. Tay-Sachs disease. *Arch Neurol*. Sep 2004;61(9):1466-8. doi:10.1001/archneur.61.9.1466
46. Dubos A, Castells-Nobau A, Meziane H, et al. Conditional depletion of intellectual disability and Parkinsonism candidate gene ATP6AP2 in fly and mouse induces cognitive impairment and neurodegeneration. *Hum Mol Genet*. Dec 1 2015;24(23):6736-55. doi:10.1093/hmg/ddv380
47. Desplats P, Patel P, Kosberg K, et al. Combined exposure to Maneb and Paraquat alters transcriptional regulation of neurogenesis-related genes in mice models of Parkinson's disease. *Mol Neurodegener*. Sep 28 2012;7:49. doi:10.1186/1750-1326-7-49
48. Fan SP, Lee NC, Lin CH. Novel Phenotype of 6p25 Deletion Syndrome Presenting Juvenile Parkinsonism and Brain Calcification. *Mov Disord*. May 5 2020;doi:10.1002/mds.28079
49. Porta F, Mussa A, Concolino D, Spada M, Ponzone A. Dopamine agonists in dihydropteridine reductase deficiency. *Mol Genet Metab*. Apr 2012;105(4):582-4. doi:10.1016/j.ymgme.2012.01.013
50. Bouchereau J, Huttlin EL, Guarani V, Pichard S, Anikster Y, Schiff M. DNAJC12: A molecular chaperone involved in proteostasis, PKU, biogenic amines metabolism and beyond? *Mol Genet Metab*. Mar 2018;123(3):285-286. doi:10.1016/j.ymgme.2018.01.006
51. Ng J, Barral S, De La Fuente Barrigon C, et al. Gene therapy restores dopamine transporter expression and ameliorates pathology in iPSC and mouse models of infantile parkinsonism. *Sci Transl Med*. May 19 2021;13(594)doi:10.1126/scitranslmed.aaw1564
52. Catterall WA. Dravet Syndrome: A Sodium Channel Interneuronopathy. *Curr Opin Physiol*. Apr 2018;2:42-50. doi:10.1016/j.cophys.2017.12.007
53. Tassin J, Durr A, Bonnet AM, et al. Levodopa-responsive dystonia. GTP cyclohydrolase I or parkin mutations? *Brain*. Jun 2000;123 (Pt 6):1112-21. doi:10.1093/brain/123.6.1112
54. Bergoug M, Doudeau M, Godin F, Mosrin C, Vallée B, Bénédetti H. Neurofibromin Structure, Functions and Regulation. *Cells*. Oct 27 2020;9(11)doi:10.3390/cells9112365
55. Curtius HC, Niederwieser A, Viscontini M, et al. Serotonin and dopamine synthesis in phenylketonuria. *Adv Exp Med Biol*. 1981;133:277-91. doi:10.1007/978-1-4684-3860-4_16
56. Boot E, Hollak CEM, Huijbregts SCJ, et al. Cerebral dopamine deficiency, plasma monoamine alterations and neurocognitive deficits in adults with phenylketonuria. *Psychol Med*. Dec 2017;47(16):2854-2865. doi:10.1017/s0033291717001398
57. Hetzelt K, Kerling F, Kraus C, et al. Early-onset parkinsonism in PPP2R5D-related neurodevelopmental disorder. *Eur J Med Genet*. Jan 2021;64(1):104123. doi:10.1016/j.ejmg.2020.104123
58. Peng XM, Tehranian R, Dietrich P, Stefanis L, Perez RG. α-Synuclein activation of protein phosphatase 2A reduces tyrosine hydroxylase phosphorylation in dopaminergic cells. *Journal of Cell Science*. 2005;118(15):3523-3530. doi:10.1242/jcs.02481

59. Zielonka M, Makhseed N, Blau N, Bettendorf M, Hoffmann GF, Opladen T. Dopamine-Responsive Growth-Hormone Deficiency and Central Hypothyroidism in Sepiapterin Reductase Deficiency. *JIMD Rep*. 2015;24:109-13. doi:10.1007/8904_2015_450

60. de Rijk-Van Andel JF, Gabreels FJ, Geurtz B, et al. L-dopa-responsive infantile hypokinetic rigid parkinsonism due to tyrosine hydroxylase deficiency. *Neurology*. Dec 26 2000;55(12):1926-8. doi:10.1212/wnl.55.12.1926

61. Manti F, Barresi S, Venditti M, et al. Neurotransmitter trafficking defect in a patient with the clathrin (CLTC) alteration presenting with hyperphenylalaninemia and Parkinsonism. *Journal of Inherited Metabolic Disease*. 2018;41(Supplement 1):S42-S43. 56th Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, SSIEM 2018. Greece. doi:http://dx.doi.org/10.1007/s10545-018-0233-9

62. Gorenberg EL, Chandra SS. The Role of Co-chaperones in Synaptic Proteostasis and Neurodegenerative Disease. *Front Neurosci*. 2017;11:248. doi:10.3389/fnins.2017.00248

63. Fasano D, Parisi S, Pierantoni GM, et al. Alteration of endosomal trafficking is associated with early-onset parkinsonism caused by SYNJ1 mutations. *Cell Death Dis*. Mar 7 2018;9(3):385. doi:10.1038/s41419-018-0410-7

64. Matsuura T, Sutcliffe JS, Fang P, et al. De novo truncating mutations in E6-AP ubiquitin-protein ligase gene (UBE3A) in Angelman syndrome. *Nat Genet*. Jan 1997;15(1):74-7. doi:10.1038/ng0197-74

65. Mulherkar SA, Sharma J, Jana NR. The ubiquitin ligase E6-AP promotes degradation of alpha-synuclein. *J Neurochem*. Sep 2009;110(6):1955-64. doi:10.1111/j.1471-4159.2009.06293.x

66. Namihira T, Hattori N, Shiroma S, Miyazato Y. Autosomal recessive juvenile Parkinson's disease with partial trisomy of chromosome 6q syndrome: a case report. *Psychiatry Clin Neurosci*. Dec 2004;58(6):672-3. doi:10.1111/j.1440-1819.2004.01321.x

67. Fishman PS, Oyler GA. Significance of the parkin gene and protein in understanding Parkinson's disease. *Curr Neurol Neurosci Rep*. Jul 2002;2(4):296-302. doi:10.1007/s11910-002-0004-7

68. Ishii T, Funakoshi M, Kobayashi H. Yeast Pth2 is a UBL domain-binding protein that participates in the ubiquitin-proteasome pathway. *Embo j*. Nov 29 2006;25(23):5492-503. doi:10.1038/sj.emboj.7601418

69. Pilo de la Fuente B, Ruiz I, Lopez de Munain A, Jimenez-Escrig A. Cerebrotendinous xanthomatosis: neuropathological findings. *J Neurol*. Jun 2008;255(6):839-42. doi:10.1007/s00415-008-0729-6

70. Chen JY, Oza VS, Gopi R, Christine CW. Rapidly progressive Parkinsonism in a patient with incontinentia pigmenti. *Movement Disorders*. 2015;30(SUPPL. 1):S476-S477. 19th International Congress of Parkinson's Disease and Movement Disorders. San Diego, CA United States.

(var.pagings). doi:http://dx.doi.org/10.1002/mds.26295

71. Tamtaji OR, Reiter RJ, Alipoor R, Dadgostar E, Kouchaki E, Asemi Z. Melatonin and Parkinson Disease: Current Status and Future Perspectives for Molecular Mechanisms. *Cell Mol Neurobiol*. Jan 2020;40(1):15-23. doi:10.1007/s10571-019-00720-5

72. Lee KS, Lee JE, Cho AH, Kim JS, Oh YS. A case of Parkinson's disease in a patient with Klinefelter's syndrome. *Acta Neurologica Belgica*. 2019;doi:http://dx.doi.org/10.1007/s13760-019-01232-1

73. Ma S, Sun R, Jiang B, et al. L2hgdh Deficiency Accumulates l-2-Hydroxyglutarate with Progressive Leukoencephalopathy and Neurodegeneration. *Mol Cell Biol*. Apr 15 2017;37(8) doi:10.1128/mcb.00492-16

74. Buongarzone G, Minafra B, Errichiello E, et al. 13.3.1. Movement disorders in a family carrying ATP7A variant. *Movement Disorders*. 2020;35(SUPPL 1):S89. MDS International Congress. Virtual. doi:http://dx.doi.org/10.1002/mds.28268

75. Vulpe C, Levinson B, Whitney S, Packman S, Gitschier J. Isolation of a candidate gene for Menkes disease and evidence that it encodes a copper-transporting ATPase. *Nat Genet*. Jan 1993;3(1):7-13. doi:10.1038/ng0193-7

76. Alkufri F, Harrower T, Rahman Y, et al. Molybdenum cofactor deficiency presenting with a parkinsonism-dystonia syndrome. *Mov Disord*. Mar 2013;28(3):399-401. doi:10.1002/mds.25276

77. Jakubiczka-Smorag J, Santamaria-Araujo JA, Metz I, et al. Mouse model for molybdenum cofactor deficiency type B recapitulates the phenotype observed in molybdenum cofactor deficient patients. *Hum Genet*. Jul 2016;135(7):813-26. doi:10.1007/s00439-016-1676-4
78. Garraux G, Caberg JH, Vanbellinghen JF, et al. Partial trisomy 4q associated with young-onset dopa-responsive parkinsonism. *Arch Neurol*. Mar 2012;69(3):398-400. doi:10.1001/archneurol.2011.802
79. Morales-Briceno H, Ha AD, London K, Farlow D, Chang FCF, Fung VSC. Parkinsonism in PGK1 deficiency implicates the glycolytic pathway in nigrostriatal dysfunction. *Parkinsonism Relat Disord*. Jul 2019;64:319-323. doi:10.1016/j.parkreldis.2019.04.004
80. Shakkottai VG, Xiao M, Xu L, et al. FGF14 regulates the intrinsic excitability of cerebellar Purkinje neurons. *Neurobiol Dis*. Jan 2009;33(1):81-8. doi:10.1016/j.nbd.2008.09.019
81. Poisson A, Nicolas A, Bousquet I, Raverot V, Gronfier C, Demily C. Smith-Magenis Syndrome: Molecular Basis of a Genetic-Driven Melatonin Circadian Secretion Disorder. *Int J Mol Sci*. Jul 19 2019;20(14)doi:10.3390/ijms20143533
82. Butcher NJ, Kiehl TR, Hazrati LN, et al. Association between early-onset Parkinson disease and 22q11.2 deletion syndrome: identification of a novel genetic form of Parkinson disease and its clinical implications. *JAMA Neurol*. Nov 2013;70(11):1359-66. doi:10.1001/jamaneurol.2013.3646
83. Hayflick SJ, Kruer MC, Gregory A, et al. beta-Propeller protein-associated neurodegeneration: a new X-linked dominant disorder with brain iron accumulation. *Brain*. Jun 2013;136(Pt 6):1708-17. doi:10.1093/brain/awt095
84. Fernandez HH, Friedman JH, Famiglietti EV. Probable Cornelia de Lange syndrome with progressive parkinsonism and dystonia. *Mov Disord*. Jul 2000;15(4):749-51. doi:10.1002/1531-8257(200007)15:4<749::aid-mds1028>3.0.co;2-p
85. Straniero L, Guella I, Cilia R, et al. DNAJC12 and dopa-responsive nonprogressive parkinsonism. *Ann Neurol*. Oct 2017;82(4):640-646. doi:10.1002/ana.25048
86. Bodhireddy S, Dickson DW, Mattiace L, Weidenheim KM. A case of Down's syndrome with diffuse Lewy body disease and Alzheimer's disease. *Neurology*. Jan 1994;44(1):159-61. doi:10.1212/wnl.44.1.159
87. Marui W, Iseki E, Kosaka K, Kato M, Adachi Y, Ueda K. An autopsied case of Down syndrome with Alzheimer pathology and alpha-synuclein immunoreactivity. *Neuropathology*. 1999;19(4):410-416. doi:http://dx.doi.org/10.1046/j.1440-1789.1999.00265.x
88. Clayton PT, Smith I, Harding B. Subacute combined degeneration of the cord, dementia and Parkinsonism due to an inborn error of folate metabolism. *Journal of Neurology Neurosurgery and Psychiatry*. 1986;49(8):920-927.
89. Sleiman PM, Healy DG, Muqit MM, et al. Characterisation of a novel NR4A2 mutation in Parkinson's disease brain. *Neurosci Lett*. Jun 26 2009;457(2):75-9. doi:10.1016/j.neulet.2009.03.021
90. Luoma P, Melberg A, Rinne JO, et al. Parkinsonism, premature menopause, and mitochondrial DNA polymerase gamma mutations: clinical and molecular genetic study. *Lancet*. Sep 4-10 2004;364(9437):875-82. doi:10.1016/s0140-6736(04)16983-3
91. Kim CY, Wirth T, Hubsch C, et al. Early-Onset Parkinsonism Is a Manifestation of the PPP2R5D p.E200K Mutation. *Ann Neurol*. Nov 2020;88(5):1028-1033. doi:10.1002/ana.25863
92. Wilson GR, Sim JC, McLean C, et al. Mutations in RAB39B cause X-linked intellectual disability and early-onset Parkinson disease with alpha-synuclein pathology. *Am J Hum Genet*. Dec 4 2014;95(6):729-35. doi:10.1016/j.ajhg.2014.10.015
93. Scheifes A, Walraven S, Stolker JJ, et al. Movement Disorders in Adults With Intellectual Disability and Behavioral Problems Associated With Use of Antipsychotics. *J Clin Psychopharmacol*. Aug 2016;36(4):308-13. doi:10.1097/jcp.0000000000000528
94. Boot E, Butcher NJ, Udow S, et al. Typical features of Parkinson disease and diagnostic challenges with microdeletion 22q11.2. *Neurology*. Jun 5 2018;90(23):e2059-e2067. doi:10.1212/wnl.0000000000005660
95. Carvalho V, Ferreira JJ, Correia Guedes L. Tremor and Parkinsonism in Chromosomopathies - A Systematic Review. *Mov Disord*. Sep 2021;36(9):2017-2025. doi:10.1002/mds.28663

96. Gillies GE, Pienaar IS, Vohra S, Qamhawi Z. Sex differences in Parkinson's disease. *Front Neuroendocrinol*. Aug 2014;35(3):370-84. doi:10.1016/j.yfrne.2014.02.002
97. Noyce AJ, Schrag A, Masters JM, Bestwick JP, Giovannoni G, Lees AJ. Subtle motor disturbances in PREDICT-PD participants. *J Neurol Neurosurg Psychiatry*. Mar 2017;88(3):212-217. doi:10.1136/jnnp-2016-314524
98. Rees RN, Noyce AJ, Schrag A. The prodromes of Parkinson's disease. *Eur J Neurosci*. Feb 2019;49(3):320-327. doi:10.1111/ejn.14269
99. Tolosa E, Compta Y. Dystonia in Parkinson's disease. *J Neurol*. Dec 2006;253 Suppl 7:Vii7-13. doi:10.1007/s00415-006-7003-6
100. Son AY, Biagioni MC, Kaminski D, Gurevich A, Stone B, Di Rocco A. Parkinson's Disease and Cryptogenic Epilepsy. *Case Rep Neurol Med*. 2016;doi:10.1155/2016/3745631
101. Butcher NJ, Boot E, Lang AE, et al. Neuropsychiatric expression and catatonia in 22q11.2 deletion syndrome: An overview and case series. *Am J Med Genet A*. Oct 2018;176(10):2146-2159. doi:10.1002/ajmg.a.38708
102. Stavoe AKH, Holzbaur ELF. Autophagy in Neurons. *Annu Rev Cell Dev Biol*. Oct 6 2019;35:477-500. doi:10.1146/annurev-cellbio-100818-125242
103. Luza S, Opazo CM, Bousman CA, Pantelis C, Bush AI, Everall IP. The ubiquitin proteasome system and schizophrenia. *Lancet Psychiatry*. Jun 2020;7(6):528-537. doi:10.1016/s2215-0366(19)30520-6
104. Khacho M, Harris R, Slack RS. Mitochondria as central regulators of neural stem cell fate and cognitive function. *Nat Rev Neurosci*. Jan 2019;20(1):34-48. doi:10.1038/s41583-018-0091-3
105. Tuoc TC, Stoykova A. Roles of the ubiquitin-proteosome system in neurogenesis. *Cell Cycle*. Aug 15 2010;9(16):3174-80. doi:10.4161/cc.9.16.12551
106. Ghavami S, Shojaei S, Yeganeh B, et al. Autophagy and apoptosis dysfunction in neurodegenerative disorders. *Prog Neurobiol*. Jan 2014;112:24-49. doi:10.1016/j.pneurobio.2013.10.004
107. Andres-Alonso M, Kreutz MR, Karpova A. Autophagy and the endolysosomal system in presynaptic function. *Cell Mol Life Sci*. Mar 2021;78(6):2621-2639. doi:10.1007/s00018-020-03722-5
108. Mattson MP, Gleichmann M, Cheng A. Mitochondria in neuroplasticity and neurological disorders. *Neuron*. Dec 10 2008;60(5):748-66. doi:10.1016/j.neuron.2008.10.010
109. Zoghbi HY. Postnatal neurodevelopmental disorders: meeting at the synapse? *Science*. Oct 31 2003;302(5646):826-30. doi:10.1126/science.1089071
110. Kurtishi A, Rosen B, Patil KS, Alves GW, Møller SG. Cellular Proteostasis in Neurodegeneration. *Mol Neurobiol*. May 2019;56(5):3676-3689. doi:10.1007/s12035-018-1334-z
111. Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. *Nat Rev Dis Primers*. Mar 23 2017;3:17013. doi:10.1038/nrdp.2017.13
112. Catafau AM, Tolosa E. Impact of dopamine transporter SPECT using 123I-Ioflupane on diagnosis and management of patients with clinically uncertain Parkinsonian syndromes. *Mov Disord*. Oct 2004;19(10):1175-82. doi:10.1002/mds.20112
113. Manickam K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). *Genetics in Medicine*. 2021/11/01 2021;23(11):2029-2037. doi:10.1038/s41436-021-01242-6
114. Crawford K, Bracher-Smith M, Owen D, et al. Medical consequences of pathogenic CNVs in adults: analysis of the UK Biobank. *J Med Genet*. Mar 2019;56(3):131-138. doi:10.1136/jmedgenet-2018-105477
115. van Eeghen AM, Bruining H, Wolf NI, et al. Personalized medicine for rare neurogenetic disorders: can we make it happen? *Cold Spring Harb Mol Case Stud*. Feb 2022;8(2)doi:10.1101/mcs.a006200
116. Durmaz AA, Karaca E, Demkow U, Toruner G, Schoumans J, Cogulu O. Evolution of genetic techniques: past, present, and beyond. *Biomed Res Int*. 2015;2015:461524. doi:10.1155/2015/461524

117. Hoytema van Konijnenburg EMM, Wortmann SB, Koelewijn MJ, et al. Treatable inherited metabolic disorders causing intellectual disability: 2021 review and digital app. *Orphanet J Rare Dis*. Apr 12 2021;16(1):170. doi:10.1186/s13023-021-01727-2

118. Ebrahimi-Fakhari D, Van Karnebeek C, Münchau A. Movement Disorders in Treatable Inborn Errors of Metabolism. *Mov Disord*. May 2019;34(5):598-613. doi:10.1002/mds.27568

119. Overwater IE, Rietman AB, van Eeghen AM, de Wit MCY. Everolimus for the treatment of refractory seizures associated with tuberous sclerosis complex (TSC): current perspectives. *Ther Clin Risk Manag*. 2019;15:951-955. doi:10.2147/tcrm.S145630

120. Tufekcioglu Z, Cakar A, Bilgic B, Hanagasi H, Gurvit H, Emre M. Adult-onset phenylketonuria with rapidly progressive dementia and parkinsonism. *Neurocase*. Jun 2016;22(3):273-5. doi:10 .1080/13554794.2016.1142567

121. Magrinelli F, Balint B, Bhatia KP. Challenges in Clinicogenetic Correlations: One Gene - Many Phenotypes. *Mov Disord Clin Pract*. Apr 2021;8(3):299-310. doi:10.1002/mdc3.13165

122. Manti F, Nardecchia F, Barresi S, et al. Neurotransmitter trafficking defect in a patient with clathrin (CLTC) variation presenting with intellectual disability and early-onset parkinsonism. *Parkinsonism Relat Disord*. Apr 2019;61:207-210. doi:10.1016/j.parkreldis.2018.10.012

Supplementary legend

Supplementary Text S1. Additional details for the methods of this review.
Supplementary Figure S1. Flow diagram depicting the different phases of the review.
Supplementary Figure S2. Complete heat map with patient characteristics and parkinsonian features per genetic disorder
Supplementary Tables S1 and 2. List of included reports.
Supplementary Table S3. Studies excluded from data-extraction.
Supplementary Tables S4 and 5. Quality assessments of included studies.

sMethods 1. Search strategy

Description

General search terms related to "genetic disease", "neurodevelopmental disorder" and "Parkinson's disease/parkinsonism" were included in the search. Mesh terms in the first subheading of "genetic disease, inborn" were included if they have been associated with a neurodevelopmental disorder. General search terms were combined with a list of genetic disorders associated with a neurodevelopmental abnormality. This list of search terms was composed using the human phenotype ontology (HPO) database on http://www.orphadata.org/cgi-bin/index.php. All terms describing a rare genetic disease assigned to the subontology neurodevelopmental abnormality, defined by HPO as '*A deviation from normal of the neurological development of a child, which may include any or all of the aspects of the development of personal, social, gross or fine motor, and cognitive abilities*' were included; collectively, the 'HPO/ND-list'.

PubMed

General search terms

Parkinson/parkinsonism

"Parkinsonian Disorders"[Mesh] OR Parkinson*[tiab] OR "lewy body dementia"[tiab] OR lewy body disease*[tiab]

AND

Genetic disease/neurodevelopemental disorder

"Genetic Diseases, Inborn"[Mesh:NoExp] OR genetic disease*[tiab] OR genetic disorder*[tiab] OR hereditary disease*[tiab] OR hereditary disorder*[tiab] OR single-gene defect*[tiab] OR "Chromosome Disorders"[Mesh] OR chromosome disorder*[tiab] OR chromosomal disorder*[tiab] OR "Metabolism, Inborn Errors"[Mesh] OR inborn error metabolism*[tiab] OR inborn metabolism error*[tiab] OR "Intellectual Disability"[Mesh] OR intellectual disabilit*[tiab] OR mental retardation*[tiab] OR Intellectual Development Disorder*[tiab] OR Intellectual Developmental Disorder*[tiab] OR mental deficienc*[tiab] OR neurodevelopmental delay[tiab] OR neurodevelopment delay[tiab] OR "Alagille Syndrome"[Mesh] OR syndrome

Alagille*[tiab] OR Alagille syndrome*[tiab] OR Arteriohepatic Dysplasia*[tiab] OR Cardiovertebral Syndrome*[tiab] OR Arteriohepatic Dysplasia*[tiab] OR Watson miller syndrome*[tiab] OR Hepatic Ductular Hypoplasia*[tiab] OR alagille-watson*[tiab] OR "CHARGE Syndrome"[Mesh] OR CHARGE syndrome*[tiab] OR hall hittner syndrome*[tiab] OR Charge association*[tiab] OR "Costello Syndrome"[Mesh] OR Costello syndrome*[tiab] OR FCS syndrome*[tiab] OR Faciocutaneoskeletal Syndrome*[tiab] OR "Genetic Diseases, X-Linked"[Mesh] OR X-linked genetic disease*[tiab] OR "Lennox Gastaut Syndrome"[Mesh] OR lennox gastaut syndrome*[tiab] OR "Oculocerebrorenal Syndrome"[Mesh] OR lowe syndrome*[tiab] OR oculocerebrorenal syndrome*[tiab] OR Lowe Bickel Syndrome*[tiab] OR lowe diseas*[tiab] OR "Orofaciodigital Syndromes"[Mesh] OR orofaciodigital syndrome*[tiab] OR Dysplasia Linguofacialis[tiab] OR Gorlin Psaume Syndrome*[tiab] OR Mohr Syndrome*[tiab] OR "Ataxia Telangiectasia"[Mesh] OR ataxia telangiectas*[tiab] OR Louis Bar Syndrome*[tiab] OR "Pain Insensitivity, Congenital"[Mesh] OR Congenital Analgesia*[tiab] OR "Congenital Insensitivity To Pain"[tiab] OR Congenital Pain Indifference*[tiab] OR Congenital Pain Insensitivit*[tiab] OR "Congenital Indifference to Pain"[tiab] **OR #(list ND/HPO for PubMed)**

NOT

"Wolff-Parkinson-White Syndrome"[Mesh] OR "wolff-parkinson-white" OR WPW syndrome* OR "Fragile X Tremor Ataxia Syndrome"[Supplementary Concept] OR "Fragile X Tremor Ataxia" OR "FXTAS" OR "premutation" OR "Gaucher" OR "Gaucher Disease"[Mesh] OR Glucocerebrosidase deficienc* OR GBA deficienc* OR Wilson's dis* OR Wilson dis* OR "Hepatolenticular Degeneration"[Mesh] OR "hepatolenticular Degeneration"

Embase

General search terms

Parkinson/parkinsonism

*Parkinson disease/ or *parkinsonism/ or Parkinson*.ti,ab,kw.

AND

Genetic disease/neurodevelopmental disorder

genetic disorder/de or exp chromosome disorder/ or exp sequence of congenital defects/ or multiple malformation syndrome/ or intellectual impairment/de or exp mental deficiency/ or "inborn error of metabolism"/ or exp X chromosome linked disorder/ or ("genetic disease*" or "genetic disorder*" or "hereditary disease*" or "hereditary disorder*" or "single-gene defect*" or "chromosome disorder*" or "chromosomal disorder*" or "inborn error metabolism*" or "inborn metabolism error*" or "intellectual disabilit*" or "mental retardation*" or "Intellectual Development Disorder*" or "Intellectual Developmental Disorder*" or "mental deficienc*" or "neurodevelopmental delay*" or "neurodevelopment delay*" or "X-linked genetic disease*"). ti,ab,kw. **OR #(list ND/HPO for Embase)**

NOT

exp Wolff Parkinson White syndrome/ or exp Wilson disease/ or exp Gaucher disease/ or ("wolff-parkinson-white" or WPW syndrome* or "Fragile X Tremor Ataxia" or "FXTAS" or "premutation" or Wilson dis* or Wilson`s dis* or "hepatolenticular degeneration" or "Gaucher" OR GBA deficienc* or glucocerebrosidase deficienc*).ti,ab,kw.

List of genetic disorders associated with neurodevelopmental abnormality (ND/HPO-list)

Adjustments to the original HPO/ND-list in order to increase the number of relevant results

1. Removal of every "-", e.g. "cerebro-oculo-nasal syndrome" → "cerebro oculo nasal syndrome"
2. Removal of "microdeletion/duplication" and "syndrome" from all notations concerning copy number variations (CNVs), e.g. "22q11.2 ~~microduplication~~ ~~syndrome~~"
3. Removal of "syndrome" from all notations concerning sex chromosomal abnormalities, e.g. "49,XXXYY ~~syndrome~~"
4. Removal of "syndrome" and "disease" at the end of diseases named after persons, e.g. "Prader Willi ~~syndrome~~", in exception of e.g. "Down syndrome", "Weaver syndrome" and "Cohen

syndrome" to avoid hits with the word "down", "weaver" (index/technique) and "Cohen" (-kappa) in another meaning.

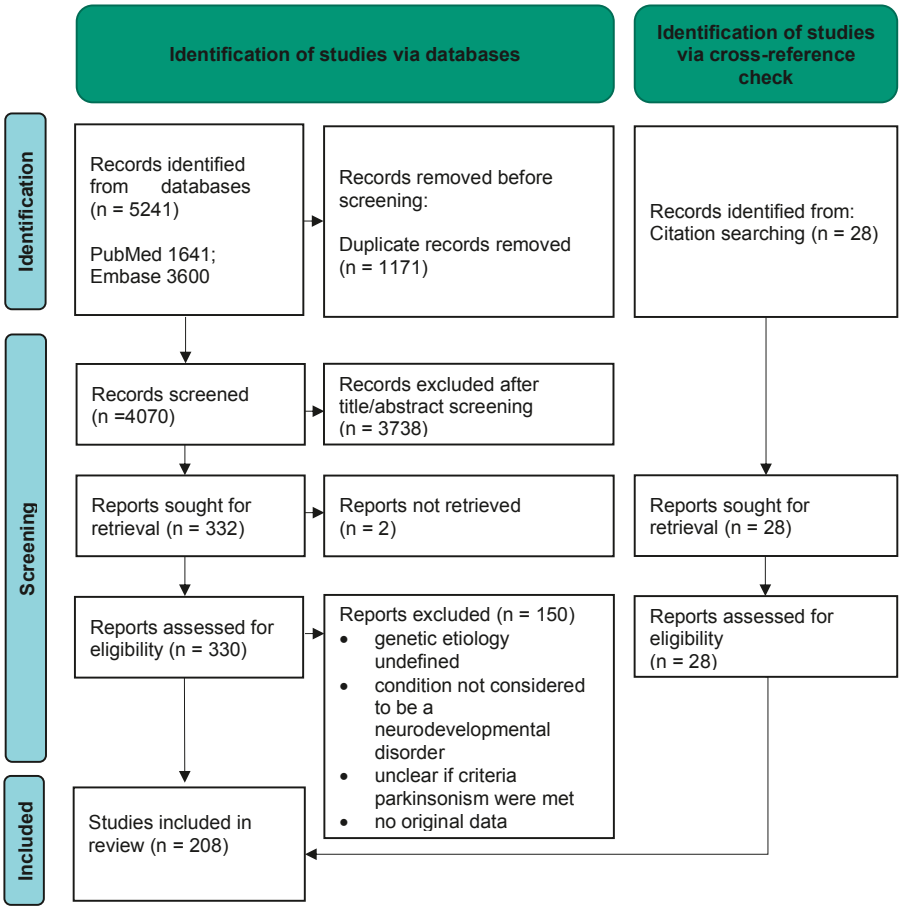
5. Removal of "syndrome" after the term "intellectual disability", e.g. "Spastic paraplegia glaucoma intellectual disability ~~syndrome~~"
6. Simplification of descriptive search terms:
   "Partial deletion of the short arm of chromosome 7" → "7p deletion"
   "Partial trisomy/tetrasomy of the short arm of chromosome 9" →"trisomy 9p" OR "tetrasomy 9p"

Terms not found in the search database and replaced** by synonym (n=4) derived from Orphanet:

"Thyrocerebrorenal syndrome" → "Cutler Bass Romshe"
"Amelocerebrohypohidrotic syndrome"→ "Kohlschütter Tönz"
"Autosomal recessive cerebelloparenchymal disorder type 3" → "Autosomal recessive spinocerebellar ataxia type 2"
"Osteoglophonic dysplasia" →"Osteoglophonic dwarfism"

***An exception for these disorders was made because of an error that resulted in the search of only the word "syndrome" or "disorder" or "dysplasia"*

Figure S1. Flow diagram depicting the different phases of the systematic review



Adapted from the PRISMA 2020 flow diagram.[1]

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Figure S2. Patient characteristics and parkinsonian features per genetic disorder

Genetic condition	Number of cases	Male *	Intellectual disability *	Mean age at motor onset	Bradykinesia, hypokinesia or akinesia *	Rigidity *	Rest tremor *	Postural instability *	Asymmetric motor symptoms *
Monogenic									
Beta-propeller protein-associated neurodegeneration (*WDR45*)	43	6/43	41/41	25	40/41	43/43	8/34	12/17	6/6
Cerebrotendinous xanthomatosis (*CYP27A*)	22	8/22	14/16	34	20/20	18/20	12/18	10/11	12/13
Rett syndrome (*MECP2*)	21	6/21	6/8	12	21/21	16/16	6/21	1/2	1/3
POLG	20	10/20	1/20	51	19/19	13/15	13/15	2/2	11/13
SYNJ1	20	10/20	0/18	26	20/20	17/19	16/20	13/13	19/19
DNAJC6 [a]	19	8/16	8/19	16	19/19	19/19	15/19	19/19	9/11
Tyrosine hydroxylase deficiency (*TH*)	16	5/10	5/9	4	11/11	12/13	10/14	1/1	/1
Dravet syndrome (*SCN1A*)	13	5/12	13/13	27	13/13	12/12	2/13	6/13	9/11
Neurofibromatosis type I, Von Recklinghausen (*NF1*) [b]	11	5/11	1/2	56	2/2	2/2	2/3	1/2	2/2
Phosphoglycerate kinase deficiency (*PGK1*)	10	10/10	8/10	22	10/10	9/10	9/10	6/7	8/8
SPG11	10	1/4	5/10	15	4/4	3/4	4/4	3/3	2/4
Neuronal ceroid lipofuscinosis, juvenile (*CLN3*)	8	8/8	0/8	< 19	8/8	8/8	0/8	8/8	0/8
PTRHD1 [c]	7	4/7	6/7	24	6/6	3/7	4/6	6/6	5/5
RAB39B	7	7/7	7/7	38	7/7	5/5	6/6	1/1	3/3
X-linked parkinsonism with spasticity (*ATP6AP2*)	7	7/7	2/7	18	7/7	1/2	4/7	2/2	1/1
Alexander disease (*GFAP*)	5	2/5	1/5	55	5/5	5/5	1/2	0/1	2/2
Dopa-responsive dystonia-Parkinsonism (*NR4A2*)	5	3/4	3/5	41	5/5	5/5	4/5	2/2	5/5
Fragile X syndrome (*FMR1*) [d]	5	5/5	1/1	58	5/5	1/1	0/1	1/1	-
SPG15 (*ZFYVE26*)	5	4/5	3/4	11	5/5	4/5	2/5	-	5/5
Christianson syndrome – NHE6 (*SLC9A6*) [e]	4	2/4	0/3	44	4/4	3/3	1/2	3/4	3/3
Dihydropteridine reductase deficiency (*QDPR*)	4	3/3	2/2	13	2/2	3/3	3/4	-	-
DNAJC12	4	2/4	4/4	27	2/2	1/1	1/4	-	-

Progression of motor signs *	Reduced DAT binding with dopaminergic	Good response anti-parkinsonian medication	Levodopa-induced dyskinesia *	Cognitive decline/	Psychiatric symptoms	Proposed main cause of parkinsonism:	Parkinson's disease	Genetic	Drug-induced	Co-existing neurologic disorder:	Epilepsy/seizures	Dystonia	Ataxia	Other
33/33	4/4	25/32	7/13	6	2	36/42	0	35	1	40/43	21	34	1	3
11/12	8/10	11/16	2/4	5	5	13/22	0	13	0	14/22	1	1	10	6
4/4	0/1	0/3	0/3	3	2	1/21	0	1	0	8/21	0	8	0	0
6/6	8/8	4/5		1	3	14/20	0	14	0	9/20	0	1	8	0
20/20	3/3	9/17	9/16	8	0	20/20	6	14	0	15/20	7	11	0	3
19/19	5/5	11/17	6/8	2	5	19/19	5	14	0	11/19	7	2	0	3
11/13	-	16/16	6/14	0	1	12/16	0	12	0	13/16	0	10	3	1
2/2	0/2	2/13	0/2	1	0	-	-	-	-	13/13	13	8	0	0
2/2	1/1	1/2	2/2	0	9	9/11	9	0	0	1/11	1	0	0	-
10/10	5/5	3/10	3/5	0	3	4/10	0	4	0	7/10	4	3	0	6
5/5	3/3	5/8	1/4	1	0	7/10	0	7	0	2/10	0	1	0	1
8/8	8/8	-	-	0	0	-	-	-	-	8/8	8	0	0	0
7/7	1/1	6/6	2/6	1	3	7/7	0	7	0	5/7	1	1	0	3
6/6	3/7	6/7	3/6	1	4	7/7	1	6	0	5/7	0	1	0	4
-	-	-	-	0	0	7/7	0	7	0	5/7	2	0	0	4
1/1	1/2	1/1		2	0	3/5	0	2	1	4/5	0	0	3	1
5/5	3/3	4/4	1/2	1	1	5/5	2	3	0	3/5	1	3	0	0
1/1	-	-	-	5	5	5/5	4	1	0	1/5	0	1	0	-
5/5	4/4	3/4	1/2	2	0	3/5	0	3	0	2/5	0	0	0	2
2/2	1/1	1/1	-	2	0	4/4	0	4	0	2/4	0	1	0	1
4/4	0/2	3/3	2/4	0	3	2/2	0	2	0	1/4	1	0	0	1
1/4	1/3	4/4	3/3	0	2	4/4	0	4	0	1/4	0	1	0	0

Figure S2. continued

Genetic condition	Number of cases	Male *	Intellectual disability *	Mean age at motor onset	Bradykinesia, hypokinesia or akinesia *	Rigidity *	Rest tremor *	Postural instability *	Asymmetric motor symptoms *
Dopa-responsive dystonia (*GCH1*)	4	2/4	0/4	40	3/3	2/2	2/2	1/1	1/2
Dystonia 16 (*PRKRA*)	4	3/4	0/4	11	3/3	1/1	1/1	-	3/3
Glutaric aciduria type 1	4	3/4	-	< 21	4/4	4/4	-	-	-
Phenylketonuria (*PAH*)	4	1/4	3/4	34	4/4	3/4	3/3	1/1	1/1
PPP2R5D	4	2/4	4/4	27	3/3	3/3	3/4	2/2	3/3
Leigh syndrome (*MT-ATP6* and *MT-MFT*)	3	1/3	1/3	31	2/2	2/2	2/3	0/1	0/1
Menkes disease (*ATP7A*)	3	0/3	1/1	50	-	-	1/1	-	3/3
Dopa-responsive dystonia, Sepiapterin reductase deficiency (*SR*)	2	2/2	1/2	15	1/1	1/1	1/2	-	1/1
Early infantile epileptic encephalopathy 4 (*STXBP1*)	2	0/2	2/2	9	2/2	2/2	2/2	1/1	2/2
L2-hydroxyglutaric aciduria (*L2HGDH*)	2	1/2	0/1	38	2/2	2/2	1/2	2/2	1/2
SPG10 (*KIF5A*)	2	0/2	0/2	55	2/2	1/1	1/2	-	2/2
WARS2 [f]	2	2/2	0/1	1	1/1	0/1	2/2	1/1	1/1
X-linked adrenoleukodystrophy (*ABCD1*)	2	2/2	0/2	58	1/1	1/1	0/1	-	1/1
5,10-methylenetetrahydrofolate reductase deficiency	1	0/1	-	2	1/1	1/1	1/1	-	-
Argininosuccinate Lyase Deficiency [g]	1	0/1	1/1	61	1/1	1/1	1/1	1/1	0/1
CLTC [h]	1	0/1	1/1	4	1/1	1/1	0/1	-	-
Cornelia de Lange syndrome	1	1/1	1/1	30	1/1	1/1	0/1	1/1	0/1
Cowden syndrome (*PTEN*)	1	0/1	0/1	66	-	-	-	-	-
MT-CYB	1	1/1	0/1	15	1/1	1/1	1/1	1/1	1/1
DOORS syndrome (*ATP6V1B2*)	1	1/1	1/1	63	-	1/1	1/1	-	1/1
Dopamine transporter deficiency syndrome (*SLC6A3*)	1	-	-	0.5	1/1	1/1	0/1	0/1	-
Early-onset Lafora disease (*EPM2A*)	1	0/1	0/1	14	1/1	1/1	1/1	-	-
HSD10 (*HSD17B10*)	1	0/1	1/1	17	1/1	1/1	0/1	-	1/1
Incontinentia Pigmenti (*IKBKG*)	1	0/1	0/1	48	1/1	-	-	-	1/1
Leigh-like syndrome (*MT-TI*)	1	1/1	-	16	1/1	1/1	0/1	-	-

0-24%
24-49%
50-74%
75-100%

Progression of motor signs *	Reduced DAT binding with dopaminergic imaging	Good response anti-parkinsonian medication *	Levodopa-induced dyskinesia *	Cognitive decline/	Psychiatric symptoms	Proposed main cause of parkinsonism:	Parkinson's disease	Genetic	Drug-induced	Co-existing neurologic disorder:	Epilepsy/seizures	Dystonia	Ataxia	Other
2/2	1/1	3/3	2/3	1	0	-	-	-	-	2/4	0	2	0	0
3/3	-	0/3	-	0	0	-	-	-	-	4/4	0	4	0	0
-	-	-	-	0	0	-	-	-	-	4/4	0	4	0	1
1/2	1/2	3/3	0/2	0	0	2/4	1	1	0	1/4	1	0	0	0
4/4	2/2	4/4	1/4	1	2	4/4	0	4	0	4/4	1	2	0	2
3/3	1/1	0/2	-	0	1	2/3	1	1	0	3/3	2	1	1	1
-	1/1	0/2	-	0	0	3/3	0	3	0	1/3	1	0	0	0
2/2	-	2/2	2/2	0	0	1/1	0	1	0	2/2	1	2	0	1
2/2	-	-	-	0	0	2/2	0	2	0	2/2	2	1	1	2
2/2	1/1	1/2	0/1	1	0	2/2	1	1	0	2/2	0	1	1	1
1/1	-	1/1	-	0	0	-	-	-	-	1/2	0	0	0	1
2/2	1/1	2/2	1/1	0	0	1/1	0	1	0	2/2	0	2	0	1
1/1	1/1	1/1	-	0	0	1/1	1	0	0	1/2	0	0	0	1
1/1	1/1	-	0/1	0	0	-	-	-	-	1/1	0	0	1	0
-	-	-	-	0	0	-	-	-	-	1/1	0	0	1	1
1/1	0/1	0/1	-	0	1	1/1	0	1	0	1/1	0	0	1	1
1/1	-	1/1	0/1	0	0	-	-	-	-	1/1	1	1	0	1
-	-	-	-	0	1	1/1	1	0	0		0	0	0	0
1/1	-	-	-	0	0	-	-	-	-	1/1	1	0	0	1
1/1	-	0/1	-	0	1	0/1				1/1	1	0	0	1
1/1	-	-	-	0	0	1/1	0	1	0	1/1	0	1	0	1
1/1	-	-	-	1	0	-	-	-	-	1/1	1	0	0	1
1/1	1/1	-	-	1	1	-	-	-	-	0/1	0	0	0	0
1/1	1/1	1/1	-	1	0	1/1	0	1	0	0/1	0	0	0	0
1/1	-	1/1	-	1	1	-	-	-	-	0/1	0	0	0	0

Figure S2. continued

Genetic condition	Number of cases	Male *	Intellectual disability *	Mean age at motor onset	Bradykinesia, hypokinesia or akinesia *	Rigidity *	Rest tremor *	Postural instability *	Asymmetric motor symptoms *
Mevalonic aciduria	1	1/1	0/1	32	1/1	1/1	0/1	-	1/1
Molybdenum cofactor deficiency type B (*MOCS2*)	1	0/1	0/1	23	1/1	1/1	0/1	-	1/1
Mucolipidosis type II (*GNPTAB*)	1	1/1	1/1	16	1/1	1/1	1/1	-	1/1
Myotonic dystrophy type 1 (*DMPK*)	1	0/1	0/1	53	1/1	1/1	0/1	1/1	0/1
NUS1	1	1/1	-	-	1/1	0/1	1/1	1/1	-
PNPLA6	1	1/1	0/1	45	1/1	-	1/1	-	-
Rapid onset dystonia-parkinsonism (ATP1A3)	1	0/1	1/1	10	1/1	1/1	0/1	-	1/1
SCA27 (*FGF14*)	1	1/1	0/1	20	1/1	1/1	1/1	1/1	1/1
Seipinopathy (BSCL2)	1	1/1	0/1	-	1/1	1/1	1/1	0/1	1/1
Smith-Magenis Syndrome (*RAI1*) [e]	(1)	1/1	-	33	1/1	1/1	0/1	-	-
Tay Sachs disease (*HEXA*)	1	1/1	0/1	2	1/1	0/1	1/1	1/1	-
Copy number variant									
22q11.2 deletion syndrome [j]	56	35/49	30/38	39	46/47	46/46	44/47	21/38	32/40
Angelman syndrome/ 15q11-13 deletion or uniparental disomy	2	1/2	2/2	19	2/2	2/2	2/2	-	-
16p11.2 deletion syndrome	1	1/1	1/1	17	1/1	1/1	0/1	1/1	1/1
16p11.2 duplication syndrome	1	1/1	1/1	35	1/1	1/1	1/1	-	0/1
6p25 deletion	1	0/1	1/1	20	1/1	1/1	0/1	1/1	1/1
Partial 4q trisomy	1	0/1	1/1	30	1/1	1/1	1/1	-	1/1
Partial 6q trisomy [j]	1	1/1	1/1	35	1/1	1/1	1/1	1/1	1/1
Aneuploid									
Down syndrome	23	14/18	6/6	32	20/22	21/23	10/23	1/2	5/5
Klinefelter syndrome [k]	7	7/7	0/2	23	6/6	7/7	6/7	1/2	3/4
Turner syndrome [l]	2	0/2	0/1	50	1/1	1/1	0/1	-	-

0-24% | 24-49% | 50-74% | 75-100%

* The numerator represents how many patients were reported to present with a specific feature, and the denominator represents the number of patients with data available.

Additional genetic mutations with potential relevance to parkinsonism were reported: [a] *LRRK2*, [b] *PRKN*, [c] *ADORA* (2 patients), [d] *FMR1* premutation, [e] One case was known to have a pathogenic variant in both *SLC9A6* and *RAI1*, [f] *CHRNA6*, [g] atypical 22q11.2 deletion of 108kb involving *PRODH*

Progression of motor signs *	Reduced DAT binding with dopaminergic imaging	Good response anti-parkinsonian medication *	Levodopa-induced dyskinesia *	Cognitive decline/	Psychiatric symptoms	Proposed main cause of parkinsonism:	Parkinson's disease	Genetic	Drug-induced	Co-existing neurologic disorder:	Epilepsy/seizures	Dystonia	Ataxia	Other
1/1	-	-	-	-	0	-	-	-	-	1/1	0	1	0	0
1/1	-	0/1	-	0	0	-	-	-	-	1/1	0	0	0	1
1/1	-	-	-	0	0	-	-	-	-	1/1	0	0	0	1
1/1	1/1	0/1	-	0	0	-	-	-	-	0/1	0	0	0	0
1/1	-	0/1	-	0	0	1/1	0	1	0	1/1	0	0	1	1
1/1	1/1	1/1	-	0	0	1/1	0	1	0	1/1	0	1	1	1
1/1	-	-	-	1	0	1/1	0	1	0	1/1	0	1	0	0
1/1	-	1/1	-	0	1	1/1	0	1	0	1/1	0	0	1	0
-	-	1/1	-	0	0	1/1	1	0	0	1/1	0	0	0	1
-	-	-	-	0	0	1/1	0	1	0	0/1	0	0	0	0
0/1	-	-	-	0	0	-	-	-	-	1/1	1	0	1	1
20/40	19/20	32/34	18/40	9	41	56/56	48	8	0	>17/56	16	16	0	1
-	-	2/2	-	0	0	2/2	0	2	0	2/2	2	0	1	2
-	-	1/1	-	0	0	-	-	-	-	1/1	0	0	1	1
1/1	1/1	0/1	0/1	0	0	1/1	0	1	0	1/1	0	0	0	1
1/1	1/1	1/1	-	0	0	1/1	0	1	0	1/1	0	0	0	1
1/1	1/1	1/1	1/1	0	0	-	-	-	-	1/1	0	0	1	1
1/1	-	1/1	0/1	1	0	1/1	1	0	0	0/1	0	0	0	0
6/6	-	9/13	0/5	18	2	18/23	13	5	0	17/23	14	0	0	5
2/2	3/3	2/2	0/1	0	3	7/7	4	3	0	1/7	0	1	0	0
2/2	1/1	-	1/1	0	0	-	-	-	-	1/2	0	0	0	1

and *DGCR2*, [h] mild phenylalanine hydroxylase deficit with compound heterozygosity for two missense variants, [i] *HTRA2* (2 patients), 45,X[3]/46,XX] mosaic Turner syndrome, [j] *PRKN*, [k] *PRKN*, [l] *TAF1* (mosaicism): "XDP-disease-specific change 3". - = unknown.

sTable 1. List of included reports describing data on an individual level

	Study specifications				
Search date study number	First author	Publication year	Journal	Publication type	Countries of study
May 31, 2020					
1	Lipton[2]	2009	Neurology	Letter	U.S.A.
2	Roeben[3]	2019	Journal of Neurology	Letter	Germany
3	Baudoin[4]	2010	Movement disord	Abstract	France
4	Booij[5]	2010	Am J Med Genet Part A	Article	The Netherlands
5	Boot[6]	2015	Am J Med Genet Part A	Article	Canada, The Netherlands
5					
6	Gambardella[7]	2018	Parkinsons Dis	Article	Italy
7	Hu[8]	2019	Clin Parkinsonism Relat Disord	Article	China
8	Krahn[9]	1998	Mayo Clin Proc	Article	U.S.A.
9	Mills[10]	2016	Ann Neurol	Abstract	U.S.A.
10	Moreira[11]	2018	Movement disord	Abstract	Portugal
11	Oki[12]	2016	Intern Med	Article	Japan
12	Pollard[13]	2016	Parkinsonism Relat D	Article	U.S.A.
13	Rehman[14]	2015	Movement disord	Article	U.S.A.
14	Verhoeven[15]	2017	Eur Arch Psychiatry Clin Neurosci	Article	The Netherlands
14					
15	Zaleski[16]	2009	Am J Med Genet Part A	Article	U.S.A., Canada
15					
16	Foo[17]	2016	Movement disord	Article	Singapore
17	Clayton[18]	1986	J neurol neurosur psy	Article	U.K.
18	Fan[19]	2020	Movement disord	Article	Taiwan
19	Park[20]	2020	BMC Neurology	Article	Korea
20	Sechi[21]	2008	Prog Neuro-Psychoph	Letter	Italy
21	Vázquez-Justes[22]	2020	Clin neurol neurosur	Article	Spain
22	Yoshida[23]	2011	Acta Neurol Scand	Article	Japan
22					
23	Harbord[24]	2001	J clin neurosci	Article	Australia
23					
24	Woodward[25]	2017	Movement disord	Abstract	U.S.A.
25	Akçakaya[26]	2019	Neuromol Med	Article	Turkey
26	Hornemann[27]	2020	Neuropediatrics	Article	Germany
27	Kumada[28]	2015	movement disord	Abstract	Japan

		Patient characteristics		
Study design	Number of subjects with parkinsonism	Age (y)	Sex	Specific genetic diagnosis
case report	1	17	male	16p11.2 deletion
case report	1	69	male	16p11.2 duplication
case report	1	45	male	22q11.2 deletion
case report	1	52	male	22q11.2 deletion
case series	2	54	male	22q11.2 deletion
		38	male	22q11.2 deletion
case report	1	35	female	22q11.2 deletion
case report	1	49	male	22q11.2 deletion
case report	1	30	male	22q11.2 deletion
case report	1	39	male	22q11.2 deletion
case report	1	36	male	22q11.2 deletion
case report	1	43	male	22q11.2 deletion
case report	1	34	female	22q11.2 deletion
case report	1	37	male	22q11.2 deletion
hidden case	2	45	male	22q11.2 deletion
		48	female	22q11.2 deletion
case series	2	46	male	22q11.2 deletion
		56	male	22q11.2 deletion
case report	1	55	female	22q11.2 deletion
case report	1	2	female	5,10-methylenetetrahydrofolate reductase deficiency
case series	1	24	female	6p25 deletion
case report	1	58	female	Alexander disease
case report	1	39	female	Alexander disease
case report	1	55	male	Alexander disease
case series	2	73	female	Alexander disease
		67	male	Alexander disease
case series	2	23	male	Angelman syndrome
		43	female	Angelman syndrome
case report	1	61	female	Argininosuccinate Lyase Deficiency
case report	1	34	male	Beta-propeller protein-associated neurodegeneration
case report	1	11	female	Beta-propeller protein-associated neurodegeneration
case report	1	35	female	Beta-propeller protein-associated neurodegeneration

sTable 1. continued

	Study specifications				
Search date study number	First author	Publication year	Journal	Publication type	Countries of study
28	Machado[29]	2017	Neurology	Abstract	unknown
29	Ohi[30]	2017	J of Neur Sci	Abstract	Japan
30	Fonderico[31]	2017	Front Neurol	Article	Italy
31	Ichinose[32]	2014	Neurol Clin Pract	Article	Japan
32	Verhoeven[33]	2014	Parkinsonism Related D	Article	The Netherlands
32					
33	Zhang[34]	2019	Neurology	Abstract	U.S.A.
34	Zitser[35]	2018	Movement disorders	Article	Israel
35	Endo[36]	2017	Neurol Clin Neurosci	Article	Japan
36	Dotti[37]	2000	Movement disord	Article	Italy
37	Fujiyama[38]	1991	Jpn J Med	Article	Japan
38	Grandas[39]	2002	Movement disord	Letter	Spain
39	Kuwabara[40]	1996	j neurol sci	Article	Japan
40	Li[41]	2020	Movement disord	Letter	China
41	Mignarri[42]	2012	Parkinsonism Relat D	Letter	Italy
42	Pilo de la Fuente[43]	2008	J Neurol	Article	Spain
43	Schotsmans[44]	2012	Acta Neurol Belg	Article	Belgian
44	Su[45]	2010	Movement disord	Article	Taiwan
44					
45	Wakamatsu[46]	1999	J Neurol Neurosurg Ps	Article	Japan
45					
45					
46	Yunisova[47]	2020	Neurodegener Dis	Article	Turkey
47	Zadori[48]	2017	Neurol Sci	Article	Hungary
47					
48	Rubio Agusti[49]	2012	Movement disorders	Abstract	U.K.
48					
49	Manti[50]	2019	Parkinsonism relat d	Article	Italy
50	Fernandez[51]	2000	Movement disord	Other	U.S.A.
51	Rana[52]	2018	J am geriatr soc	Abstract	U.S.A.

		Patient characteristics		
Study design	Number of subjects with parkinsonism	Age (y)	Sex	Specific genetic diagnosis
case report	1	27	female	Beta-propeller protein-associated neurodegeneration
case report	1	38	female	Beta-propeller protein-associated neurodegeneration
case report	1	36	female	Beta-propeller protein-associated neurodegeneration
case report	1	31	female	Beta-propeller protein-associated neurodegeneration
case series	2	52	female	Beta-propeller protein-associated neurodegeneration
		42	female	Beta-propeller protein-associated neurodegeneration
case report	1	34	male	Beta-propeller protein-associated neurodegeneration
case report	1	34	female	Beta-propeller protein-associated neurodegeneration
case report	1	40	female	Beta-propeller protein-associated neurodegeneration
case report	1	52	male	Cerebrotendinous Xanthomatosis
case report	1	44	male	Cerebrotendinous Xanthomatosis
case report	1	51	female	Cerebrotendinous Xanthomatosis
case report	1	34	female	Cerebrotendinous Xanthomatosis
case report	1	40	male	Cerebrotendinous Xanthomatosis
case report	1	67	female	Cerebrotendinous Xanthomatosis
case report	1	52	male	Cerebrotendinous Xanthomatosis
case report	1	44	male	Cerebrotendinous Xanthomatosis
case report	2	54	female	Cerebrotendinous Xanthomatosis
		49	male	Cerebrotendinous Xanthomatosis
case series	3	46	female	Cerebrotendinous Xanthomatosis
		43	female	Cerebrotendinous Xanthomatosis
		33	female	Cerebrotendinous Xanthomatosis
case series	1	58	female	Cerebrotendinous Xanthomatosis
case series	2	40	female	Cerebrotendinous Xanthomatosis
		40	female	Cerebrotendinous Xanthomatosis
case report	2	49	male	Cerebrotendinous Xanthomatosis
		63	male	Cerebrotendinous Xanthomatosis
case report	1	30	female	*CLTC*
case report	1	30	male	Cornelia de Lange syndrome
case report	1	71	female	Cowden syndrome

sTable 1. continued

	Study specifications				
Search date study number	First author	Publication year	Journal	Publication type	Countries of study
52	De Coo[53]	1999	Ann neurol	Article	The Netherlands
53	Sedel[54]	2006	Neurology	Article	France
54	Takahashi[55]	2017	Case rep neurol	Article	Japan
55	Porta[56]	2012	Mol genet metab	Article	Italy
55					
56	Straniero[57]	2017	Ann neurol	Article	Canada
56					
56					
57	Anikster[58]	2017	Am J Hum Genet	Article	Israel
58	Koroglu[59]	2013	Parkinsonism relat d	Article	Turkey
58					
58					
58					
59	Ng[60]	2020	Movement disord	Article	Pakistan
59					
59					
59					
59					
59					
60	Termsarasab [61]	2015	Movement disord	Abstract	U.S.A.
61	Edvardson[62]	2012	Plos one	Article	Israel
61					
62	Elsayed[63]	2016	Ann neurol	Letter	France
63	Tassin[64]	2000	Brain	Article	France
63					
63					
64	Kikuchi[65]	2004	Movement disord	Article	Japan
65	Wirth[66]	2020	Movement disord	Article	France
65					
66	Zielonka[67]	2015	J inherit metab dis	Article	Kuwait
67	Bodhireddy[68]	1994	Neurology	Letter	U.S.A.
68	Brandel[69]	1994	Neurology	Letter	France
69	Agarwal[70]	2010	Movement disord	Abstract	U.S.A.

		Patient characteristics		
Study design	Number of subjects with parkinsonism	Age (y)	Sex	Specific genetic diagnosis
case series	1	20	male	*CYTB*
case report	1	29	male	Dihydropteridine reductase deficiency
case report	1	16	male	Dihydropteridine reductase deficiency
case series	2	7	male	Dihydropteridine reductase deficiency
		22	unknown	Dihydropteridine reductase deficiency
case series	3	73	male	*DNAJC12*
		59	female	*DNAJC12*
		58	male	*DNAJC12*
hidden case	1	13	female	*DNAJC12*
case series	4	24	female	*DNAJC6*
		44	female	*DNAJC6*
		31	female	*DNAJC6*
		17	male	*DNAJC6*
case series	6	20	female	*DNAJC6*
		12	male	*DNAJC6*
		10	male	*DNAJC6*
		28	female	*DNAJC6*
		19	female	*DNAJC6*
		18	female	*DNAJC6*
case report	1	14	female	*DNAJC6*
case series	2	13	male	*DNAJC6*
		18	male	*DNAJC6*
case report	1	12	female	*DNAJC6*
case series	3	76	female	Dopa-responsive dystonia
		66	male	Dopa-responsive dystonia
		54	female	Dopa-responsive dystonia
case report	1	54	male	Dopa-responsive dystonia autosomal dominant/ Segawa
case series	2	29	male	Dopa-responsive Dystonia-Parkinsonism
		57	female	Dopa-responsive Dystonia-Parkinsonism
case report	1	7	male	Dopa-responsive dystonia, Sepiapterin reductase deficiency
case report	1	54	male	Down syndrome
case report	1	45	male	Down syndrome
case report	1	21	female	Down syndrome

sTable 1. continued

	Study specifications				
Search date study number	First author	Publication year	Journal	Publication type	Countries of study
70	Marui[71]	1999	Neuropathology	Article	Japan
71	Palat[72]	2018	Case Rep Neurol Med	Article	U.S.A.
72	Singer[73]	1990	Eur j neurol	Article	U.S.A.
73	Storm[74]	1990	Res dev disabil	Article	Germany
74	Sturman[75]	1989	Lancet	Letter	U.K.
75	Camargos[76]	2008	Lancet neurol	Article	Brazil
75					
75					
75					
76	Keogh[77]	2014	Neurogenetics	Letter	U.K.
77	Rezazadeh[78]	2019	Epilepsy behav	Article	Canada
78	Yildiz[79]	2017	Seizure	Article	Turkey
79	Hall[80]	2010	Movement disord	Article	U.S.A.
80	Rosario[81]	2018	Movement disord	Abstract	Portugal
81	Chen[82]	2015	Movement disord	Abstract	U.S.A.
82	Bach[83]	2008	Movement Disord	Letter	Germany
83	Lee[84]	2019	Acta Neurol Belgica	Letter	Korea
84	Yu[85]	2019	Movement disord	Abstract	China
85	Fabbri[86]	2018	Neurol sci	Letter	Portugal
86	Owens[87]	2004	J neurol neurosur ps	Letter	U.S.A.
87	Martikainen[88]	2016	JAMA neurol	Article	U.K.
88	Baumgartner[89]	2013	J neurol sci	Abstract	Austria
89	Hemelsoet[90]	2018	Neurol genet	Article	Belgium
90	Martikainen[91]	2013	Mitochondrion	Article	Finland
91	Zyss[92]	2011	Movement disord	Abstract	France
92	Alkufri[93]	2013	Movement disord	Article	United Kingdom
93	Hara[94]	2013	Brain dev-jpn	Article	Japan
94	Choi[95]	2018	Mov disord	Article	Korea
95	Pradotto[96]	2014	Clin neuropathol	Abstract	Italy
96	Wattanapanom[97]	2011	J am geriatr soc	Abstract	U.S.A.
97	D'Ambrosio[98]	1984	Acta neurol Napoli	Article	Israel
98	Hattori[99]	1998	Pathol res prac	Article	Japan
99	Chandra[100]	2018	Movement Disord	Abstract	U.S.A.
100	Pescosolido[101]	2019	Mol Neuropsychiatry	Article	U.S.A.
100					

		Patient characteristics		
Study design	Number of subjects with parkinsonism	Age (y)	Sex	Specific genetic diagnosis
case report	1	49	male	Down syndrome
case report	1	20	female	Down syndrome
case report	1	45	male	Down syndrome
case report	1	21	male	Down syndrome
case report	1	23	male	Down syndrome
case series	4	35	male	Dystonia 16
		34	male	Dystonia 16
		48	female	Dystonia 16
		64	male	Dystonia 16
case report	1	12	female	Early infantile epileptic encephalopathy 4/ *STXBP1*
hidden case	1	46	female	Early infantile epileptic encephalopathy 4/*STXBP1*
case report	1	13	female	Early-onset Lafora disease
case report	1	61	male	Fragile X syndrome
case report	1	22	female	Hydroxysteroid dehydrogenase type 10 deficiency (HSD10)
case report	1	48	female	Incontinentia Pigmenti
case report	1	27	male	Klinefelter syndrome
case report	1	60	male	Klinefelter syndrome
case report	1		male	Klinefelter syndrome
case report	1	37	male	Klinefelter syndrome
case report	1	54	male	L2-hydroxyglutaric aciduria
hidden case	1	40	female	Leigh syndrome/ *mt-ATP6*
case report	1	44	male	Leigh syndrome/ *mt-ATP6*
case report	1	44	female	Leigh syndrome/*mt-FMT*
case report	1	16	male	Leigh-like syndrome
case report	1	44	male	Mevalonic aciduria
case report	1	6	female	Molybdenum cofactor deficiency type B
case report	1	36	male	Mucolipidosis type II
case report	1	54	female	Myotonic dystrophy type 1
case report	1	65	female	Neurofibromatosis type 1
hidden case	1	70	male	Neurofibromatosis type 1
case report	1	54	female	Neurofibromatosis type 1
case report	1	58	female	Neurofibromatosis type 1
case report	1	33	male	NHE6 - Christianson syndrome in males/ *SLC9A6*
other	2	65	female	NHE6 - Christianson syndrome in males/ *SLC9A6*
		55	female	NHE6 - Christianson syndrome in males/ *SLC9A6*

sTable 1. continued

	Study specifications				
Search date study number	First author	Publication year	Journal	Publication type	Countries of study
101	Araki[102]	2020	Epilepsy res	Article	Japan
102	Namihira[103]	2004	Psychiat Clin Neuros	Letter	Japan
103	Garraux[104]	2012	Arch neurol	Article	Belgium
104	Daelman[105]	2014	Rev Neurol	Article	France
105	Evans[106]	2004	Movement disord	Article	U.K.
106	Velema[107]	2015	JIMD Reports	Article	The Netherlands
107	Leuzzi[108]	1995	J Inher Metab Dis	Article	Italy
108	Konrad[109]	1973	J of Pediatr	Article	U.S.A.
109	Sakaue[110]	2016	NPJ Parkinson's dis	Article	Japan
110	Virmani[111]	2014	Movement disord	Article	U.S.A.
110					
111	Morales-Briceno[112]	2019	Parkinsonism relat d	Article	Australia
111					
111					
112	Rotstein[113]	2012	Movement disord	Abstract	Israel
113	Sotiriou[114]	2010	Muscle nerve	Article	U.S.A.
114	Echaniz-Laguna[115]	2019	J inherit metab dis	Article	France
87	Martikainen[88]	2016	JAMA neurol	Article	U.K.
87					
87					
87					
87					
115	Bandettini di Poggio[116]	2013	BMC med genet	Article	Italy
116	De Pue[117]	2016	Eur j neurol	Abstract	Belgium
117	Khodadadi[118]	2017	Movement disord	Article	Iran
117					
118	Jaberi[119]	2016	Movement disord	Article	Iran
118					
119	Kuipers[120]	2018	Movement disord	Article	Netherlands
119					
119					
120	Ortez[121]	2013	Gene	Article	Spain
121	Ciammola[122]	2017	Parkinsonism relat d	Article	
121					

		Patient characteristics		
Study design	Number of subjects with parkinsonism	Age (y)	Sex	Specific genetic diagnosis
case series	1	77	male	*NUS1*
case report	1	40	male	partial 6q trisomy
case report	1	31	female	partial 4q trisomy
case series	1	47	female	phenylketonuria
case report	1	37	female	phenylketonuria
case report	1	56	female	phenylketonuria
hidden case	1	16	male	phenylketonuria
case series	1	19	male	Phosphoglycerate kinase deficiency
case series	1	16	male	Phosphoglycerate kinase deficiency
case series	2	30	male	Phosphoglycerate kinase deficiency
		24	male	Phosphoglycerate kinase deficiency
case series	3	34	male	Phosphoglycerate kinase deficiency
		32	male	Phosphoglycerate kinase deficiency
		42	male	Phosphoglycerate kinase deficiency
case report	1	21	male	Phosphoglycerate kinase deficiency
case report	1	25	male	Phosphoglycerate kinase deficiency
case report	1	48	male	Phosphoglycerate kinase deficiency
cohort	5	48	male	*POLG*
		81	male	*POLG*
		59	male	*POLG*
		63	male	*POLG*
		69	female	*POLG*
case report	1	48	female	*POLG*
case report	1	80	female	*POLG*
case series	2	39	male	*PTRHD1*
		37	male	*PTRHD1*
case series	2	34	male	*PTRHD1*
		30	male	*PTRHD1*
case series	3	26	female	*PTRHD1*
		29	female	*PTRHD1*
		44	female	*PTRHD1*
case report	1	0 (5d)	female	Pyruvate carboxylase deficiency
case series	3	67	male	*RAB39B*
		94	male	*RAB39B*

sTable 1. continued

	Study specifications				
Search date study number	First author	Publication year	Journal	Publication type	Countries of study
121					
122	Guldner[123]	2016	Parkinsonism relat d	Letter	Germany
123	Lesage[124]	2015	Neurol genet	Article	France
124	Wilson[125]	2014	Am j human genet	Article	Australia
124					
125	Roze[126]	2007	Movement disord	Other	France
126	Chahil[127]	2018	Cureus	Article	U.S.A.
127	Venkateswaran[128]	2014	Dev med child neurol	Article	Canada
128	Pollini[129]	2020	Movement disord	Letter	Italy
129	Ollivier[130]	2015	Neuromuscular Disord	Article	France
130	Goizet[131]	2009	Hum mutat	Other	France
130					
131	Anheim[132]	2009	J neurol	Article	France
131					
132	Guidubaldi[133]	2011	Movement disord	Article	Italy
133	Kang[134]	2004	Parkinsonism relat d	Article	South Korea
134	Damasio[135]	2014	Movement disord	Abstract	Portugal
135	Mallaret[136]	2014	j neurol	Letter	France
136	Schicks[137]	2011	Movement disord	Letter	Germany
136					
137	Groth[138]	2018	Tremor Other Hyperkinet Mov	Article	U.S.A.
138	Ebrahimi-Fakhari[139]	2018	Movement disord	Article	U.S.A.
139	Nitschke[140]	2011	Schweitz arch neurol	Abstract	Switzerland
140	Westenberger[141]	2013	Movement disord	Article	Germany
141	De Rijk-van Andel[142]	2000	Neurology	Article	The Netherlands
141					
141					
141					
142	Pons[143]	2010	Movement disord	Other	Greece
142					
142					
143	Grattan-Smith[144]	2002	Movement disord	Article	Australia
144	Haugarvoll[145]	2011	J parkinson dis	Article	Norway
145	Ludecke[146]	1996	Hum mol genet	Article	Norway

		Patient characteristics		
Study design	Number of subjects with parkinsonism	Age (y)	Sex	Specific genetic diagnosis
		49	male	*RAB39B*
case series	1	48	male	*RAB39B*
case report	1	39	male	*RAB39B*
case series	2	44	male	*RAB39B*
		45	male	*RAB39B*
case report	1	49	female	Rett syndrome
case report	1	16	male	Rett syndrome/ *MECP2*
case report	1	15	female	Rett syndrome/ *MECP2*
case report	1	17	male	Rett syndrome/ *MECP2*
case series	1	46	male	Seipinopathy
case series	2	70	female	Spastic paraplegia type 10
		41	female	Spastic paraplegia type 10
case series	2	28	female	Spastic paraplegia type 11
		15	male	Spastic paraplegia type 11
case report	1	32	female	Spastic paraplegia type 11
case series	1	16	female	Spastic paraplegia type 11
case report	1	39	male	Spastic paraplegia type 15
case report	1	17	female	Spastic paraplegia type 15
case series	2	31	male	Spastic paraplegia type 15
		20	male	Spastic paraplegia type 15
case report	1	70	male	Spinocerebellar ataxia 27
hidden case	1	4	male	Tay Sachs disease
case report	1	45	female	Turner syndrome
case report	1	57	female	Turner syndrome, atypical
case series	4	0 (4m)	male	Tyrosine hydroxylase deficiency
		0 (5m)	unknown	Tyrosine hydroxylase deficiency
		0 (3m)	unknown	Tyrosine hydroxylase deficiency
		0 (3m)	unknown	Tyrosine hydroxylase deficiency
case series	3	2	unknown	Tyrosine hydroxylase deficiency
		0 (5m)	unknown	Tyrosine hydroxylase deficiency
		0 (5m)	unknown	Tyrosine hydroxylase deficiency
case report	1	2	female	Tyrosine hydroxylase deficiency
case report	1	27	male	Tyrosine hydroxylase deficiency
case report	1	3	female	Tyrosine hydroxylase deficiency

sTable 1. continued

	Study specifications				
Search date study number	First author	Publication year	Journal	Publication type	Countries of study
146	Swaans[147]	2000	Ann hum genet	Article	The Netherlands, France
146					
146					
147	Burke[148]	2018	Clin genet	Article	U.S.A.
148	Galosi[149]	2019	Movement disord	Abstract	Italy
149	Horn[150]	2016	Clin case rep	Article	Norway
150	Serra Soler[151]	2017	Endocrinol diabetes nutr	Letter	Spain
151	Gupta[152]	2015	Parkinsonism Relat D	Letter	U.S.A.
151					
June 15, 2021					
152	Meytin[153]	2020	Movement disord	Abstract	U.S.A.
153	Buongarzone[154]	2020	Movement disord	Abstract	Italy
153					
153					
154	Maric[155]	2020	Eur j med genet	Abstract	Spain
155	Umehara[156]	2020	Neurol clin neuroschi	Article	Japan
156	Samanta[157]	2020	J pedriatr neurosci	Article	U.S.A.
157	Yunisova[47]	2020	Neurodegener dis	Article	Turkey
158	Munoz-delgado[158]	2020	Movement disord	Abstract	Spain
159	Zadori[159]	2020	Front neurol	Article	Hungary
160	Jesus[160]	2021	Neurol genet	Article	Spain
161	Sleiman[161]	2009	Neurosci lett	Article	U.K.
162	Grimes[162]	2006	Movement dis	Article	Canada
163	Kanatani[163]	2021	Brain dev-jpn	Article	Japan
163					
164	Malaquias[164]	2021	Parkinsonism Relat D	Article	Portugal
165	Witt[165]	2020	Movement disord	Abstract	Sweden
166	Kim[166]	2020	Ann neurol	Article	U.S.A.
166					

		Patient characteristics		
Study design	Number of subjects with parkinsonism	Age (y)	Sex	Specific genetic diagnosis
case series	3	5	male	Tyrosine hydroxylase deficiency
		9	male	Tyrosine hydroxylase deficiency
		34	male	Tyrosine hydroxylase deficiency
case report	1	9	male	*WARS2*
case report	1	11	male	*WARS2*
case report	1	61	male	X-linked adrenoleukodystrophy
case report	1	61	male	X-linked adrenoleukodystrophy
case series	2	20	male	X-linked parkinsonism with spasticity */ATP6AP2*
		31	male	X-linked parkinsonism with spasticity/ *ATP6AP2*
case report	1	50	male	22q11.2 deletion
case series	3	49	female	*ATP7A*
		54	female	*ATP7A*
		50	female	*ATP7A*
case report	1	10	female	Beta-propeller protein-associated neurodegeneration
case report	1	46	female	Beta-propeller protein-associated neurodegeneration
case report	1	13	female	Beta-propeller protein-associated neurodegeneration
case series	1	58	female	Cerebrotendinous xanthomatosis
case report	1	40	male	Christianson syndrome
case report	1	72	male	DOORS syndrome
case report	1	30	male	Dopa-responsive dystonia parkinsonism
case report	1	74	unknown	Dopa-responsive dystonia parkinsonism
case report	1	77	male	Dopa-responsive dystonia parkinsonism
case series	2	20	male	Dravet syndrome
		42	female	Dravet syndrome
case report	1	49	female	L2-hydroxyglutaric aciduria
case report	1	45	male	*PNPLA6*
case series	3	61	male	*PPP2R5D*
		34	male	*PPP2R5D*

sTable 1. continued

	Study specifications				
Search date study number	First author	Publication year	Journal	Publication type	Countries of study
166					
167	Hetzelt[167]	2021	Eur j med genet	Article	Germany
168	Nomura[168]	2021	Brain dev-jpn	Article	Japan
169	Araujo[169]	2020	Movement disord	Article	Brazil
170	Lesage[170]	2021	Front neurol	Article	France
170					
170					
170					
171	Krebs[171]	2013	Hum mutat	Article	U.S.A.
171					
172	Quadri[172]	2013	Hum mutat	Article	Italy
172					
173	Olgiati[173]	2014	Neurogenetics	Article	Italy
173					
174	Kirola[174]	2016	Parkinsonism relat d	Article	India
174					
175	Taghavi[175]	2018	Mol neurobiol	Article	Iran
175					
176	Ben Romdhan[176]	2018	J mol neurosci	Article	Tunisia
176					
177	Hong[177]	2019	Parkinsonism relat d	Article	China
177					
178	Xie[178]	2019	Parkinsonism relat d	Article	China
178					

Light blue: identified through cross-reference check. Orange: overlap in study population with other studies but additional information provided (patients were only included once in the review). Abbreviations: U.S.A.=United States of America, U.K.=United Kingdom, y=years, m=months, d=days.

		Patient characteristics		
Study design	Number of subjects with parkinsonism	Age (y)	Sex	Specific genetic diagnosis
		44	female	*PPP2R5D*
case report	1	29	female	*PPP2R5D*
case report	1	14	female	Rapid-onset dystonia-parkinsonism
case report	1	17	male	Spastic paraplegia type 15
case series	4	25	male	*SYNJ1*
		31	female	*SYNJ1*
		35	male	*SYNJ1*
		61	female	*SYNJ1*
case series	2	29	male	*SYNJ1*
		39	female	*SYNJ1*
case series	2	47	male	*SYNJ1*
		31	female	*SYNJ1*
case series	2	31	male	*SYNJ1*
		27	female	*SYNJ1*
case series	2	32	male	*SYNJ1*
		22	female	*SYNJ1*
case series	2	30	male	*SYNJ1*
		47	female	*SYNJ1*
case series	2	23	male	*SYNJ1*
		24	female	*SYNJ1*
case series	2	35	female	*SYNJ1*
		30	male	*SYNJ1*
case series	2	52	female	*SYNJ1*
		54	male	*SYNJ1*

sTable 2. List of included reports describing data at group level

	Study specifications				
Search date and study number	First Author	Year of publication	Journal	Publication type	Countries of study
May 31, 2020					
1	Boot[179]	2018	Neurology	Article	Canada, The Netherlands, U.K., Japan, Italy, Belgium, France, U.S.A., Germany, Chile
2	Boot[180]	2020	Movement disord	Article	Canada
3	Butcher[181]	2018	Am J Med Genet Part A	Article	Canada
4	Butcher[182]	2013	JAMA Neurol	Article	Canada
5	Butcher[183]	2017	Brain	Article	Canada
6	Dufournet[184]	2017	Rev Neurol	Article	France
7	Mok[185]	2016	Lancet Neurol	Article	U.K., The Netherlands, France, Germany
8	Nishioka[186]	2015	Neurobiol Aging	Article	Japan
9	Morales-Briceño[187]	2018	Movement disord	Letter	Australia, Mexico, U.K.
10	Hayflick[188]	2013	Brain	Article	U.S.A., Germany, U.K., France, Italy, Canada, The Netherlands
11	Ohno[189]	2001	J Neurol Sci	Article	Japan
12	Olgiati[190]	2016	Ann neurol	Article	Italy, The Netherlands, Brazil, Portugal, Spain, and Turkey

			Patient characteristics			
Study design	Study design	Number of subjects with parkinsonism	Available for subgroup with parkinsonism	Age (y)	Sex (ratio male: total)	Specific genetic diagnosis
other	retrospective	45:45	yes	unknown	32:45	22q11.2 deletion
Case-control/ cohort	prospective	7:82	partially	x=44.0	unknown	22q11.2 deletion
case series	retrospective	1	yes	50	1:1	22q11.2 deletion
cohort	retrospective	4:68	yes	unknown	3:4	22q11.2 deletion
case-control	cross-sectional	9:14	yes	x=43.4 ±6.5	5:9	22q11.2 deletion
case series	retrospective	9:9	yes	unknown	8:9	22q11.2 deletion
case-control	other	8:8	partially	unknown	6:8	22q11.2 deletion
cohort	Cross-sectional	7:7	yes	M=35 (33-41), x=35±3.5	0:7	Beta-propeller protein-associated neurodegeneration/ *WDR45*
case series	retrospective	3:3	yes	M=34 (32-41), x=36.1 ± 3.8	1:3	Beta-propeller protein-associated neurodegeneration/ *WDR45*
cohort	retrospective	19:23	yes	M=37, x=36±8.1	3:19	Beta-propeller protein-associated neurodegeneration/ *WDR45*
case series	retrospective	3:3	no	M=31 (31-34), x=32±1.7	0:3	Cerebrotendinous xanthomatosis
cohort	cross-sectional	5:274	yes	x=51.4	3:5	*DNAJC6*

sTable 2. continued

	Study specifications				
Search date and study number	First Author	Year of publication	Journal	Publication type	Countries of study
13	Clot[191]	2009	Brain	Article	France, Ireland, Switzerland
14	Ng[192]	2012	J inherit metab dis	Abstract	U.K.
15	Lai[193]	1989	Arch neurol	Article	U.S.A.
16	Vieregge[194]	1991	J neurol neurosur ps	Article	Germany
17	Fasano[195]	2014	Neurology	Letter	Canada
18	Utari[196]	2010	J neurodevelop disord	Article	U.S.A.
19	Gitiaux[197]	2008	Movement disord	Article	France
20	Ruottinen[198]	1997	J neurol neurosur ps	Article	Finland
21	Aberg[199]	2000	Neurology	Article	Finland
22	Aberg[200]	2001	Neurology	Article	Finland
23	Hunter[201]	1969	Brit j psychiat	Article	U.K.
24	Madubata[202]	2015	Genet med	Article	U.S.A.
25	Luoma[203]	2004	Lancet	Article	Finland
26	Orrico[204]	2000	FEBS lett	Letter	Italy
27	FitzGerald[205]	1990	Movement disord	Article	U.S.A.
28	Kara[206]	2016	Brain	Article	United Kingdom
29	Zouari[207]	2009	J neurol sci	Abstract	Tunisia
30	Korvatska[208]	2013	Hum Mol Genet	Article	U.S.A.

[a] No additional studies meeting inclusion criteria were found with the search on June 15th, 2021.

Green: identified through cross-reference check. Brown: overlap in study population with other studies but additional information provided (patients were only included once in the review). Abbreviations: U.S.A.=United States of America, U.K.=United Kingdom, y=years, m=months, M=median, r=range, x=mean with standard deviation.

			Patient characteristics			
Study design	Study design	Number of subjects with parkinsonism	Available for subgroup with parkinsonism	Age (y)	Sex (ratio male: total)	Specific genetic diagnosis
cohort	prospective	4:5	yes	x=14.3	1:4	Dopa-responsive dystonia (*TH* (n=3); *SPR* (n=1))
case series	retrospective	1:5	no	r: 2-9m	unknown	Dopamine transporter deficiency syndrome/ *SLC6A3*
cohort	prospective	10:49	yes	x=54	8:10	Down syndrome
cohort	cross-sectional	5:14	no	x=59.8 ±6.7	34:54	Down syndrome
cohort	prospective	11:12	yes	x=28.1 (r: 20-43)	4:12	Dravet syndrome
cohort	retrospective	4:62	no	x=49.7 ± 8.0	4:4	Fragile X syndrome
cohort	prospective	4:16	yes	21	3:4	Glutaric aciduria type 1
case-control	cross-sectional	8:9	no	19.1	8:9	juvenile neuronal ceroid lipofuscinosis
case-control	cross-sectional	?:17	no	unknown	unknown	juvenile neuronal ceroid lipofuscinosis
case-control	experimental	?:21	no	x=15 at start treatment	9:21	juvenile neuronal ceroid lipofuscinosis
case-control	cross-sectional	3:16	no	x=37.6±13.7 (r: 17-60)	16:16	Klinefelter syndrome
case-control	retrospective	7:8579	yes	x=56±5.2	4:7	Neurofibromatosis type I
case series	retrospective	13:23	yes	x= 58.9 (r:40-75)	6:13	*POLG*
case series	retrospective	4:12	yes	r:27-40	4:4	Rett syndrome/ *MECP2*
cohort	prospective	±13:32	no	r:30m-28y	0:13	Rett syndrome/ *MECP2*
cohort	cross-sectional	5:30	no	x=14.3 (r 4-27)	unknown	Spastic paraplegia type 11
case series	retrospective	1:5	no	27.5	unknown	Spastic paraplegia type 11
case series	retrospective	5:5	no	r:14-58	5:5	X-linked parkinsonism with spasticity / *AT-P6AP2*

sTable 3. Studies excluded from data-extraction

Search date and study number	First author	Year of publication	Journal	Reason for exclusion
May 31, 2020				
1	Aggarwal	2010	Movement disord	parkinsonism unclear
2	Air	2011	J neurosurg pediat	No clear genetic diagnosis
3	Al-Thihli	2010	j inherit metab dis	parkinsonism unclear
4	Aljaafari	2017	Neurology	parkinsonism unclear
5	Alvarez	2018	European J of Epilepsy	parkinsonism unclear
6	Baide-Mairena	2018	Movement disord	No clear genetic diagnosis
7	Banka S. et al	2011	am j hum genet	parkinsonism unclear
8	Banuelos	2017	F1000res	parkinsonism unclear
9	Barnes	2011	ann neurol	parkinsonism unclear
10	Barnes	2011	ann neurol	parkinsonism unclear
11	Behnecke	2018	med genet	parkinsonism unclear
12	Belezhanska	2017	Arch Balkan Med Union	parkinsonism unclear
13	Bijarnia-Mahay	2018	j inherit metab dis	parkinsonism unclear
14	Blau	2015	mol genet metab	no new data
15	Bodzioch	2011	Movement disord	parkinsonism unclear
16	Bouchereau	2018	mol genet metab	no new data
17	Brahem	2017	Movement disord	Other: not clear which patient had parkinsonism (with or without GND)
18	Brahm	2007	Clinical Schizophrenia and Related Psychoses	No clear genetic diagnosis
19	Brajkovic	2010	Eur J Nucl Med Mol I	No clear genetic diagnosis
20	Brajkovic	2012	Hell J nucl med	No clear genetic diagnosis
21	Brautigam	1999	cin chem	parkinsonism unclear
22	Buckley	2017	NeuroReport	parkinsonism unclear
23	Burt	1980	Eur Neurol	Other: unclear of the patient with Down syndrome had parkinsonism, also for other GNDs outcome measures are on group level
24	Butcher	2016	Biol Psychiat	no new data
25	Butcher	2014	Mov Disord	no new data
26	Butcher	2015	Mov Disord	no new data
27	Butcher	2017	PLOS ONE	no new data
28	Byrne	2015	neuromuscular disord	parkinsonism unclear

sTable 3. continued

Search date and study number	First author	Year of publication	Journal	Reason for exclusion
29	Carecchio	2017	Eur J Neurol	Other: Information on the whole group is provided, including genetic disorders not meeting our definition.
30	Carecchio	2011	movement disord	No clear genetic diagnosis
31	Castello	2012	clin neuropathol	parkinsonism unclear
32	Chitty	2016	aust nz j psychiat	No clear genetic diagnosis
33	Cubells	2010	Neuropsychopharmacol	not relevant
34	Cukiert	2009	epilepsia	No clear genetic diagnosis
35	de Kuijper	2013	res dev disabil	No clear genetic diagnosis
36	De Lonlay	2000	j inherit metab dis	parkinsonism unclear
37	Demirbas	2018	mol genet metab	parkinsonism unclear
38	Deuel	2019	Neurology	parkinsonism unclear
39	Dhivya	2016	Int J Hum Genet	Other: Aim, methods, and results all unclear
40	Dobyns	1993	Neurology	No clear genetic diagnosis
41	Dufournet	2015	Eur J Neurol	no new data
42	Dulovic	2016	movement disord	parkinsonism unclear
43	Ekinci	2004	movement disord	No clear genetic diagnosis
44	Elahi	2017	movement disord	no new data
45	Fan	2020	movement disord	parkinsonism unclear
46	Fanella	2019	J Med Genet	parkinsonism unclear
47	Finsterer	2011	acta neurol belg	Other: heterozygous for autosomal recessive disorder; usually asymptomatic
48	Fitzgerald	1990	neurology	no new data
49	Fraser	2019	Ann Neurol	No clear genetic diagnosis
50	Galati	2015	j neuropsych clin n	No clear genetic diagnosis
51	Gao	2020	movement disord	no new data
52	Gascon	1994	brain & development	parkinsonism unclear
53	Grant	1992	eur j pediatr	No clear genetic diagnosis
54	Gunzler	2007	movement disord	No clear genetic diagnosis

sTable 3. continued

Search date and study number	First author	Year of publication	Journal	Reason for exclusion
55	Haack	2012	Am J Hum Genet	Other: No patient data (apart from genetic data) is available.
56	Habermeyer	2009	j neuropsych clin n	No clear genetic diagnosis
57	Hama	2017	j neurol sci	No clear genetic diagnosis
58	Hermann	2017	Tremor Other Hyperkinet Mov	parkinsonism unclear
59	Hernandez Navarro	2017	eur j neurol	parkinsonism unclear
60	Hestnes	1997	j neurol neurosur psy	parkinsonism unclear
61	Hjalgrim	2011	epilepsia	parkinsonism unclear
62	Humphreys	2016	can j neurol sci	parkinsonism unclear
63	Humphreys	2010	can j neurol sci	no new data
64	Illsinger	2011	eur j paediatr neuro	parkinsonism unclear
65	Jacobsen	1998	j med genet	parkinsonism unclear
66	Kaleka	2019	Cureus	parkinsonism unclear
67	Kalsner	2013	ann neurol	No clear genetic diagnosis
68	Kara	2013	Movement disord	parkinsonism unclear
69	Kim	2018	Int J Neurosci	No clear genetic diagnosis
70	Klysz	2014	neurol neurochir pol	parkinsonism unclear
71	Konrad	1973	J of Pediatr	parkinsonism unclear
72	Kruer	2009	dev med child neurol	No clear genetic diagnosis
73	Kuiper	2014	movement disord	parkinsonism unclear
74	Kuipers	2019	parkinsonism relat d	No/unclear Neurodevelopmental disorder
75	Larnaout	2008	j inherit metab dis	parkinsonism unclear
76	Laxova	1985	am j med genet	No clear genetic diagnosis
77	Lee	2012	movement disord	No/unclear Neurodevelopmental disorder
78	Leuzzi	2010	Clin Genet	parkinsonism unclear
79	Lindsay	1996	Am J Hum Genet	No clear genetic diagnosis
80	Lohmann	2019	eur j hum genet	Other: unclear which participants with genetic variants had parkinsonism
81	Lorea	2015	j inherit metab dis	parkinsonism unclear

sTable 3. continued

Search date and study number	First author	Year of publication	Journal	Reason for exclusion
82	Masingue	2017	eur j neurol	parkinsonism unclear
83	Matsuura	2019	Movement disord	Other: no GND (specifically mentioned) with parkinsonism. There may be patients in the group "other".
84	Melberg	1996	muscle nerve	No clear genetic diagnosis
85	Mellick	2004	movement disord	No clear genetic diagnosis
86	Morales	2017	Movement disord	No new data
87	Morton	1997	dev med child neurol	parkinsonism unclear
88	Neri	2012	neuromuscular disord	No clear genetic diagnosis
89	Nissenkorn	2012	J Child Neurol	parkinsonism unclear
90	Olszewska	2018	movement disord	no new data
91	Ortez	2015	mol genet metab	parkinsonism unclear
92	Palumbo	2016	Mol Syndromol	parkinsonism unclear
93	Panteghini	2016	Movement disord	parkinsonism unclear
94	Papendreou	2017	dev med child neurol	Other: unclear which participant/ genetic disorder had parkinsonism
95	Park	2014	Movement disord	parkinsonism unclear
96	Peer Zada	2015	movement disord	No new data
97	Pilotto	2017	Eur J Neurol	parkinsonism unclear
98	Pilotto	2017	J Inborn Errors Metab Screen	parkinsonism unclear
99	Pilotto	2019	Eur J Neurol	parkinsonism unclear
100	Porta	2010	mol genet metab	no new data
101	Porta	2009	Neurology	parkinsonism unclear
102	Raghavan	1993	can j neurol sci	parkinsonism unclear
103	Ramerman	2018	rev des disabil	No clear genetic diagnosis
104	Riahi	2016	Eur J Neurol	No clear genetic diagnosis
105	Rodan	2018	mol genet metab	parkinsonism unclear
106	Rosini	2014	J Neurol	parkinsonism unclear
107	Rubio-Agusti	2011	movement disord	parkinsonism unclear
108	Russo	2019	Movement disord	parkinsonism unclear
109	Sarpong	2009	clin genet	parkinsonism unclear
110	Scheifes	2016	j clin pharmacol	No clear genetic diagnosis
111	Schicks	2011	movement disord	parkinsonism unclear

sTable 3. continued

Search date and study number	First author	Year of publication	Journal	Reason for exclusion
112	Schicks	2010	movement disord	no new data
113	Sheehan	2017	bmj brit med j	No clear genetic diagnosis
114	shi	2016	movement disorders	parkinsonism unclear
115	Singh	1986	brit j psychiat	parkinsonism unclear
116	Soto	2017	J Inborn Errors Metab Screen	parkinsonism unclear
117	Stagnaro	2018	eur j paediatr neuro	parkinsonism unclear
118	Stelten	2018	Neurology	parkinsonism unclear
119	Straniero	2019	eur j hum genet	no new data
120	Surtees	1998	movement disord	no new data
121	Tan	2016	Lancet Neurol	Not relevant
122	Tanaka	1989	Eur J Pediatr	parkinsonism unclear
123	Temudo	2008	movement disord	parkinsonism unclear
124	Troncoso	2015	j neurol sci	No clear genetic diagnosis
125	Tufekcioglu	2016	Neurocase	parkinsonism unclear
126	Valadares	2011	arq neuro-psiquiat	parkinsonism unclear
127	Vellingiri	2018	Parkinsonism Relat Disord	Other: Aim, methods, and results all unclear
128	Verhoeven	2015	Eur Arch Psychiatry Clin Neurosci	no new data
129	Wang	2017	Stem cel res	not relevant
130	Waschbisch	2010	j neurol sci	parkinsonism unclear
131	Weinshenker	2008	nature	not relevant
132	Wille	2018	neuropediatrics	parkinsonism unclear
133	Wise	2012	dev med child neurol	no new data
134	Yemni	2019	nature	No/unclear Neurodevelopmental disorder
135	Yoon	2008	J Neurol Neurosurg Ps	parkinsonism unclear
136	Zouari	2018	movement disord	Other: unclear which participants had a GND with parkinsonism
137	Zweije-Hofman	1982	clin neurol neurosur	parkinsonism unclear
June 15, 2021				
138	Agabna	2021	dev med child neurol	parkinsonism unclear
139	De Jesus	2020	movement disord	parkinsonism unclear
140	Di lazarro	2020	parkinsonism relat d	Parkinsonism unclear
141	Eis	2020	front neurol	No/unclear Neurodevelopmental disorder
142	Jan	2021	nature	Parkinsonism unclear

sTable 3. continued

Search date and study number	First author	Year of publication	Journal	Reason for exclusion
143	Kisa	2021	metab brain dis	Parkinsonism unclear
144	Krbanjevic	2021	am j dermatopathol	parkinsonism unclear
145	Manti	2020	movement disord	parkinsonism unclear
146	Munoz	2020	movement disord	Other: unclear which symptoms were present in which patients
147	Nardecchia	2020	movement disord	Parkinsonism unclear
148	Shabeer	2021	J Neurosci Rural Pract	Parkinsonism unclear
149	Skrahina	2020	movement disord	Other: no specific GND was mentioned
150	Yuan	2002	neurodegener dis	parkinsonism unclear

Abbreviations: GND= genetic neurodevelopmental disorder.

sTable 4. Quality assessment of observational cohort and cross-sectional studies

First author	Year of publication	Journal	Clear research question	Clear subject population	At least 50% participation rate	Subjects recruited from the same population. Prespecified in/ exclusion criteria	Sample size justification, power description, variance/effect estimate	Exposure(s) of interest measured prior to the outcome(s) being measured
Boot	2018	Neurology	+	+	na	+	na	na
Butcher	2013	JAMA Neurol	+	+	+	+	+	na
Clot	2009	Brain	+	+	cd	+	na	na
Fasano	2014	Neurology	+	cd	cd	+	na	na
Fitzgerald	1990	Movement disord	+	+	+	+	na	na
Gitiaux	2008	Movement disord	+	+	cd	+	na	na
Hayflick	2013	Brain	+	+	na	+	na	na
Kara	2016	Brain	+	+	cd	+	na	na
Lai	1989	Arch neurol	+	+	+	+	na	na
Martikainen	2016	JAMA neurol	+	+	+	+	na	na
Nishioka	2015	Neurobiol Aging	+	+	na	+	na	na
Olgiati	2016	Ann neurol	+	+	cd	+	na	na
Utari	2010	J neurodevelop disord	+	+	cd	+	na	na
Vieregge	1991	J neurol neurosur ps	+	+	cd	cd	na	na

Abbreviations: yes (+) / no (-) / cannot determine (cd) /not applicable (na) / not reported (nr).
G=Good, F=Fair.
Source assessment form: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

Sufficient timeframe between exposure and outcome	Different levels of the exposure examined as related to the outcome	Exposure measures clearly defined, valid, reliable, and implemented consistently	Exposure assessed more than once over time	Outcome measures clearly defined, valid, reliable, and implemented consistently	Outcome assessors blinded to the exposure status	Loss to follow-up 20% or less	Potential confounding variables measured and adjusted statistically	Rating
na	na	na	na	+	na	na	na	G
na	na	na	na	+	na	na	na	G
na	na	na	na	+	na	cd	na	G
na	na	na	na	+	na	nr	na	F
na	na	na	na	+	na	nr	na	G
na	na	na	na	-	na	nr	na	F
na	na	na	na	+	na	na	na	G
na	na	na	na	+	na	na	na	F
na	na	na	na	+	na	nr	na	G
na	na	na	na	+	na	na	na	G
na	na	na	na	+	na	na	na	G
na	na	na	na	+	na	na	na	G
na	na	na	na	+	na	na	na	G
na	na	na	na	+	na	na	na	F

sTable 5. Quality assessment of case-control studies

First author	Year of publication	Journal	Clear research question	Clear study population	Sample size justification included	Subjects recruited from same population	Definitions, in/exclusion criteria were valid, reliable, and implemented consistently	Clearly defined cases and controls
Aberg	2000	Neurology	+	+	-	-	+	+
Aberg	2001	Neurology	+	+	-	+	+	+
Boot	2020	Movement Disord	+	+	-	+	+	+
Butcher	2017	Brain	+	+	-	+	+	+
Hunter	1969	Brit j psychiat	-	+	-	+	-	+
Madubata	2014	Genet med	+	+	-	+	+	+
Mok	2016	Lancet Neurol	+	+	-	+	+	+
Ruottinen	1997	J neurol neurosur ps	+	+	-	-	+	+

[a] Considered poor because of a very limited description of aims and methods. However, data regarding parkinsonism in Klinefelter syndrome were clear enough to be used for data-extraction. Abbreviations: yes (+) / no (-) / cannot determine (cd) /not applicable (na) / not reported (nr). G=Good, F=Fair, P=Poor.

Source assessment form: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

Cases and/or controls randomly selected from those eligible	Use of concurrent controls	exposure/risk occurred prior to the development of the condition that defined a participant as a case	Measures of exposure clearly defined, valid, reliable, and implemented consistently	Assessors of exposure were blinded to the case or control status	Confounding variables measured and adjusted statistically or account for matching during analysis	Rating
na	na	na	na	na	-	F
na	+	na	na	na	-	G
na	na	na	na	na	+	G
na	na	na	na	na	+	G
na	cd	na	na	na	-	P[a]
na	+	na	na	na	+	G
na	na	na	na	na	+	G
na	na	na	na	na	-	F

sReferences

1. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
2. Lipton J, Rivkin MJ. 16p11.2-related paroxysmal kinesigenic dyskinesia and dopa-responsive parkinsonism in a child. *Neurology*. 2009;73(6):479-480. doi:http://dx.doi.org/10.1212/WNL.0b013e3181b16393
3. Roeben B, Blum D, Gabriel H, Synofzik M. Atypical parkinsonism with severely reduced striatal dopamine uptake associated with a 16p11.2 duplication syndrome. *J Neurol*. Mar 2019;266(3):775-776. doi:10.1007/s00415-019-09182-7
4. Baudoin H, Jacquette A, Grabli D, Whalen S, Lenglet T. The co-occurence of early onset Parkinson's disease (PD) and 22q11.2 deletion syndrome (22qDS): More than a coincidence. *Movement Disorders*. 2010;25(SUPPL. 2):S468-S469. 14th International Congress of Parkinson's Disease and Movement Disorders. Buenos Aires Argentina.(var.pagings). doi:http://dx.doi.org/10.1002/mds.23162
5. Booij J, van Amelsvoort T, Boot E. Co-occurrence of early-onset Parkinson disease and 22q11.2 deletion syndrome: Potential role for dopamine transporter imaging. *Am J Med Genet A*. Nov 2010;152a(11):2937-8. doi:10.1002/ajmg.a.33665
6. Boot E, Butcher NJ, van Amelsvoort TA, et al. Movement disorders and other motor abnormalities in adults with 22q11.2 deletion syndrome. *Am J Med Genet A*. Mar 2015;167a(3):639-45. doi:10.1002/ajmg.a.36928
7. Gambardella S, Ferese R, Scala S, et al. Mitochondrial Serine Protease HTRA2 p.G399S in a Female with Di George Syndrome and Parkinson's Disease. *Parkinsons Dis*. 2018;2018:5651435. doi:10.1155/2018/5651435
8. Hu ZX, Lu XD, Lou DN, et al. A case report of a Chinese patient with 22q11.2 deletion accompanied with EOPD, severe dystonia and hypocalcemia. *Clinical Parkinsonism and Related Disorders*. 2019;1:72-73. doi:http://dx.doi.org/10.1016/j.prdoa.2019.07.002
9. Krahn LE, Maraganore DM, Michels VV. Childhood-onset schizophrenia associated with parkinsonism in a patient with a microdeletion of chromosome 22. *Mayo Clinic Proceedings*. 1998;73(10):956-959. doi:http://dx.doi.org/10.4065/73.10.956
10. Mills KA, Reich SG. Early onset parkinson's disease and chromosome 22q11 deletion: Case report. *Annals of Neurology*. 2016;80(Supplement 20):S94. 141st Annual Meeting of the American Neurological Association, ANA 2016. United States. doi:http://dx.doi.org/10.1002/ana.24759
11. Moreira F, Bras A, Lopes JR, Januario C. Parkinson's disease with hypocalcaemia: adult presentation of 22q11.2 deletion syndrome. *BMJ Case Rep*. Mar 22 2018;2018doi:10.1136/bcr-2017-223751
12. Oki M, Hori S, Asayama S, Wate R, Kaneko S, Kusaka H. Early-onset Parkinson's Disease Associated with Chromosome 22q11.2 Deletion Syndrome. *Intern Med*. 2016;55(3):303-5. doi:10.2169/internalmedicine.55.5485
13. Pollard R, Hannan M, Tanabe J, Berman BD. Early-onset Parkinson disease leading to diagnosis of 22q11.2 deletion syndrome. *Parkinsonism Relat Disord*. Apr 2016;25:110-1. doi:10.1016/j.parkreldis.2016.01.027
14. Rehman AF, Dhamija R, Williams ES, Barrett MJ. 22q11.2 deletion syndrome presenting with early-onset Parkinson's disease. *Mov Disord*. Aug 2015;30(9):1289-90. doi:10.1002/mds.26305
15. Verhoeven WMA, Egger JIM, De Leeuw N. Psychopathology and differentiated psychopharmacological treatment strategy in subtypes of 22q11.2 deletion syndrome. *European Archives of Psychiatry and Clinical Neuroscience*. 2017;267(1 Supplement 1):S64-S65. 6th European Conference on Schizophrenia Research: Advancing Research - Promoting Recovery. Germany. doi:http://dx.doi.org/10.1007/s00406-017-0824-8
16. Zaleski C, Bassett AS, Tam K, Shugar AL, Chow EW, McPherson E. The co-occurrence of early onset Parkinson disease and 22q11.2 deletion syndrome. *Am J Med Genet A*. Mar 2009;149a(3):525-8. doi:10.1002/ajmg.a.32650

17. Foo JN, Lee J, Tan LC, Liu J, Tan EK. Large 3-Mb deletions at 22q11.2 locus in Parkinson's disease and schizophrenia. *Mov Disord*. Dec 2016;31(12):1924-1925. doi:10.1002/mds.26822
18. Clayton PT, Smith I, Harding B. Subacute combined degeneration of the cord, dementia and Parkinsonism due to an inborn error of folate metabolism. *Journal of Neurology Neurosurgery and Psychiatry*. 1986;49(8):920-927.
19. Fan SP, Lee NC, Lin CH. Novel Phenotype of 6p25 Deletion Syndrome Presenting Juvenile Parkinsonism and Brain Calcification. *Mov Disord*. May 5 2020;doi:10.1002/mds.28079
20. Park J, Park ST, Kim J, Kwon KY. A case report of adult-onset Alexander disease clinically presenting as Parkinson's disease: is the comorbidity associated with genetic susceptibility? *BMC Neurol*. Jan 17 2020;20(1):27. doi:10.1186/s12883-020-1616-8
21. Sechi GP, Conti M, Sau GF, Cocco GA. Valproate-induced parkinsonism, glial cells and Alexander's disease. *Prog Neuropsychopharmacol Biol Psychiatry*. Jul 1 2008;32(5):1351-2. doi:10.1016/j.pnpbp.2008.03.022
22. Vazquez-Justes D, Penalva-Garcia J, Lopez R, Mitjana R, Begue R, Gonzalez-Mingot C. Parkinsonism phenotype in a family with adult onset Alexander disease and a novel mutation of GFAP. *Clin Neurol Neurosurg*. May 6 2020;195:105893. doi:10.1016/j.clineuro.2020.105893
23. Yoshida T, Sasayama H, Mizuta I, et al. Glial fibrillary acidic protein mutations in adult-onset Alexander disease: clinical features observed in 12 Japanese patients. *Acta Neurol Scand*. Aug 2011;124(2):104-8. doi:10.1111/j.1600-0404.2010.01427.x
24. Harbord M. Levodopa responsive Parkinsonism in adults with Angelman Syndrome. *J Clin Neurosci*. Sep 2001;8(5):421-2. doi:10.1054/jocn.2000.0753
25. Woodward K, Bhatti D, Rush E. First reported case of parkinsonism in a patient with argininosuccinate lyase deficiency. *Movement Disorders*. 2017;32(Supplement 2):703-704. 21st International Congress of Parkinson's Disease and Movement Disorders. Canada. doi:http://dx.doi.org/10.1002/mds.27087
26. Akcakaya NH, Salman B, Gormez Z, et al. A Novel and Mosaic WDR45 Nonsense Variant Causes Beta-Propeller Protein-Associated Neurodegeneration Identified Through Whole Exome Sequencing and X chromosome Heterozygosity Analysis. *Neuromolecular Med*. Mar 2019;21(1):54-59. doi:10.1007/s12017-018-08522-6
27. Hornemann F, Le Duc D, Roth C, Pfaffle R, Huhle D, Merkenschlager A. Childhood Dystonia-Parkinsonism Following Infantile Spasms-Clinical Clue to Diagnosis in Early Beta-Propeller Protein-Associated Neurodegeneration. *Neuropediatrics*. Feb 2020;51(1):22-29. doi:10.1055/s-0039-1696688
28. Kumada S, Hayakawa I, Nakata Y, et al. A functional neuroradiological study in an adult case of betapropeller protein-associated neurodegeneration. *Movement Disorders*. 2015;30(SUPPL. 1):S384-S385. 19th International Congress of Parkinson's Disease and Movement Disorders. San Diego, CA United States.(var.pagings). doi:http://dx.doi.org/10.1002/mds.26295
29. Machado D. Genetic testing for beta-propeller protein-associated neurodegeneration (BPAN). *Neurology*. 2017;88(16 Supplement 1)69th American Academy of Neurology Annual Meeting, AAN 2017. United States.
30. Ohi K, Kageyama Y, Ichikawa K, Nishioka K. Clinical investigation of beta-propeller protein associated neurogeneration (BPAN). *Journal of the Neurological Sciences*. 2017;381(Supplement 1):701-702. 23rd World Congress of Neurology, WCN 2017. Japan. doi:http://dx.doi.org/10.1016/j.jns.2017.08.1975
31. Fonderico M, Laudisi M, Andreasi NG, et al. Patient Affected by Beta-Propeller Protein-Associated Neurodegeneration: A Therapeutic Attempt with Iron Chelation Therapy. *Front Neurol*. 2017;8:385. doi:10.3389/fneur.2017.00385
32. Ichinose Y, Miwa M, Onohara A, et al. Characteristic MRI findings in beta-propeller protein-associated neurodegeneration (BPAN). *Neurol Clin Pract*. Apr 2014;4(2):175-177. doi:10.1212/01.CPJ.0000437694.17888.9b
33. Verhoeven WM, Egger JI, Koolen DA, et al. Beta-propeller protein-associated neurodegeneration (BPAN), a rare form of NBIA: novel mutations and neuropsychiatric phenotype in three adult patients. *Parkinsonism Relat Disord*. Mar 2014;20(3):332-6. doi:10.1016/j.parkreldis.2013.11.019
34. Zhang L, Malhado-Chang N, Shankar S, Hagerman R. Autistic parkinsonism: NBIA with mosaic WDR45 mutation and datscan positive dopa-responsiveness. *Neurology*. 2019;92(15

Supplement 1)71st Annual Meeting of the American Academy of Neurology, AAN 2019. United States.

35. Zitser J, Giladi N, Gurevich T. A Case with Beta-Propeller Protein Associated Neurodegeneration with Smooth Response to Levodopa Treatment. *Movement Disorders Clinical Practice*. 2018;5(3):327-329. doi:http://dx.doi.org/10.1002/mdc3.12604
36. Endo H, Uenaka T, Satake W, et al. Japanese WDR45 de novo mutation diagnosed by exome analysis: A case report. *Neurol Clin Neurosci*. Jul 2017;5(4):131-133. doi:10.1111/ncn3.12132
37. Dotti MT, Federico A, Garuti R, Calandra S. Cerebrotendinous xanthomatosis with predominant parkinsonian syndrome: further confirmation of the clinical heterogeneity. *Mov Disord*. Sep 2000;15(5):1017-9. doi:10.1002/1531-8257(200009)15:5<1017::aid-mds1043>3.0.co;2-f
38. Fujiyama J, Kuriyama M, Yoshidome H, et al. Parkinsonism in cerebrotendinous xanthomatosis. *Jpn J Med*. Mar-Apr 1991;30(2):189-92. doi:10.2169/internalmedicine1962.30.189
39. Grandas F, Martin-Moro M, Garcia-Munozguren S, Anaya F. Early-onset parkinsonism in cerebrotendinous xanthomatosis. *Mov Disord*. Nov 2002;17(6):1396-7. doi:10.1002/mds.10287
40. Kuwabara K, Hitoshi S, Nukina N, et al. PET analysis of a case of cerebrotendinous xanthomatosis presenting hemiparkinsonism. *J Neurol Sci*. Jun 1996;138(1-2):145-9. doi:10.1016/0022-510x(96)00011-1
41. Li J, Xu EH, Mao W, et al. Parkinsonism with Normal Dopaminergic Presynaptic Terminals in Cerebrotendinous Xanthomatosis. *Mov Disord Clin Pract*. Jan 2020;7(1):115-116. doi:10.1002/mdc3.12846
42. Mignarri A, Falcini M, Vella A, et al. Parkinsonism as neurological presentation of late-onset cerebrotendinous xanthomatosis. *Parkinsonism Relat Disord*. Jan 2012;18(1):99-101. doi:10.1016/j.parkreldis.2011.06.004
43. Pilo de la Fuente B, Ruiz I, Lopez de Munain A, Jimenez-Escrig A. Cerebrotendinous xanthomatosis: neuropathological findings. *J Neurol*. Jun 2008;255(6):839-42. doi:10.1007/s00415-008-0729-6
44. Schotsmans K, De Cauwer H, Baets J, et al. Cerebrotendinous xanthomatosis presenting with asymmetric parkinsonism: a case with I-123-FP-CIT SPECT imaging. *Acta Neurol Belg*. Sep 2012;112(3):287-9. doi:10.1007/s13760-012-0064-7
45. Su CS, Chang WN, Huang SH, et al. Cerebrotendinous xanthomatosis patients with and without parkinsonism: clinical characteristics and neuroimaging findings. *Mov Disord*. Mar 15 2010;25(4):452-8. doi:10.1002/mds.22979
46. Wakamatsu N, Hayashi M, Kawai H, et al. Mutations producing premature termination of translation and an amino acid substitution in the sterol 27-hydroxylase gene cause cerebrotendinous xanthomatosis associated with parkinsonism. *J Neurol Neurosurg Psychiatry*. Aug 1999;67(2):195-8. doi:10.1136/jnnp.67.2.195
47. Yunisova G, Tufekcioglu Z, Dogu O, et al. Patients with Lately Diagnosed Cerebrotendinous Xanthomatosis. *Neurodegener Dis*. Apr 29 2020:1-7. doi:10.1159/000506770
48. Zadori D, Szpisjak L, Madar L, et al. Different phenotypes in identical twins with cerebrotendinous xanthomatosis: case series. *Neurol Sci*. Mar 2017;38(3):481-483. doi:10.1007/s10072-016-2776-6
49. Rubio-Agusti I, Kojovic M, Edwards MJ, et al. Atypical parkinsonism and cerebrotendinous xanthomatosis: report of a family with corticobasal syndrome and a literature review. *Mov Disord*. Dec 2012;27(14):1769-74. doi:10.1002/mds.25229
50. Manti F, Nardecchia F, Barresi S, et al. Neurotransmitter trafficking defect in a patient with clathrin (CLTC) variation presenting with intellectual disability and early-onset parkinsonism. *Parkinsonism Relat Disord*. Apr 2019;61:207-210. doi:10.1016/j.parkreldis.2018.10.012
51. Fernandez HH, Friedman JH, Famiglietti EV. Probable Cornelia de Lange syndrome with progressive parkinsonism and dystonia. *Mov Disord*. Jul 2000;15(4):749-51. doi:10.1002/1531-8257(200007)15:4<749::aid-mds1028>3.0.co;2-p
52. Rana S. Multidisciplinary care of a patient with cowden syndrome at a geriatric center. *Journal of the American Geriatrics Society*. 2018;66(Supplement 2):S187. 2018 Annual Scientific Meeting of the American Geriatrics Society, AGS 2018. United States. doi:http://dx.doi.org/10.1111/jgs.15376

53. De Coo IF, Renier WO, Ruitenbeek W, et al. A 4-base pair deletion in the mitochondrial cytochrome b gene associated with parkinsonism/MELAS overlap syndrome. *Ann Neurol*. Jan 1999;45(1):130-3. doi:10.1002/1531-8249(199901)45:1<130::aid-art21>3.3.co;2-q
54. Sedel F, Ribeiro MJ, Remy P, Blau N, Saudubray JM, Agid Y. Dihydropteridine reductase deficiency: levodopa's long-term effectiveness without dyskinesia. *Neurology*. Dec 26 2006;67(12):2243-5. doi:10.1212/01.wnl.0000249335.35585.3e
55. Takahashi Y, Manabe Y, Nakano Y, et al. Parkinsonism in Association with Dihydropteridine Reductase Deficiency. *Case Rep Neurol*. Jan-Apr 2017;9(1):17-21. doi:10.1159/000456610
56. Porta F, Mussa A, Concolino D, Spada M, Ponzone A. Dopamine agonists in dihydropteridine reductase deficiency. *Mol Genet Metab*. Apr 2012;105(4):582-4. doi:10.1016/j.ymgme.2012.01.013
57. Straniero L, Guella I, Cilia R, et al. DNAJC12 and dopa-responsive nonprogressive parkinsonism. *Ann Neurol*. Oct 2017;82(4):640-646. doi:10.1002/ana.25048
58. Anikster Y, Haack TB, Vilboux T, et al. Biallelic Mutations in DNAJC12 Cause Hyperphenylalaninemia, Dystonia, and Intellectual Disability. *Am J Hum Genet*. Feb 2 2017;100(2):257-266. doi:10.1016/j.ajhg.2017.01.002
59. Koroglu C, Baysal L, Cetinkaya M, Karasoy H, Tolun A. DNAJC6 is responsible for juvenile parkinsonism with phenotypic variability. *Parkinsonism Relat Disord*. Mar 2013;19(3):320-4. doi:10.1016/j.parkreldis.2012.11.006
60. Ng J, Cortes-Saladelafont E, Abela L, et al. DNAJC6 Mutations Disrupt Dopamine Homeostasis in Juvenile Parkinsonism-Dystonia. *Mov Disord*. May 30 2020;doi:10.1002/mds.28063
61. Termsarasab P, Pearson TS. Juvenile Parkinsonism and epilepsy due to homozygous mutations in DNAJC6. *Movement Disorders*. 2015;30(SUPPL. 1):S459-S460. 19th International Congress of Parkinson's Disease and Movement Disorders. San Diego, CA United States. (var.pagings). doi:http://dx.doi.org/10.1002/mds.26295
62. Edvardson S, Cinnamon Y, Ta-Shma A, et al. A deleterious mutation in DNAJC6 encoding the neuronal-specific clathrin-uncoating co-chaperone auxilin, is associated with juvenile parkinsonism. *PLoS One*. 2012;7(5):e36458. doi:10.1371/journal.pone.0036458
63. Elsayed LE, Drouet V, Usenko T, et al. A Novel Nonsense Mutation in DNAJC6 Expands the Phenotype of Autosomal-Recessive Juvenile-Onset Parkinson's Disease. *Ann Neurol*. Feb 2016;79(2):335-7. doi:10.1002/ana.24591
64. Tassin J, Durr A, Bonnet AM, et al. Levodopa-responsive dystonia. GTP cyclohydrolase I or parkin mutations? *Brain*. Jun 2000;123 (Pt 6):1112-21. doi:10.1093/brain/123.6.1112
65. Kikuchi A, Takeda A, Fujihara K, et al. Arg(184)His mutant GTP cyclohydrolase I, causing recessive hyperphenylalaninemia, is responsible for dopa-responsive dystonia with parkinsonism: a case report. *Mov Disord*. May 2004;19(5):590-3. doi:10.1002/mds.10712
66. Wirth T, Mariani LL, Bergant G, et al. Loss-of-Function Mutations in NR4A2 Cause Dopa-Responsive Dystonia Parkinsonism. *Mov Disord*. May 2020;35(5):880-885. doi:10.1002/mds.27982
67. Zielonka M, Makhseed N, Blau N, Bettendorf M, Hoffmann GF, Opladen T. Dopamine-Responsive Growth-Hormone Deficiency and Central Hypothyroidism in Sepiapterin Reductase Deficiency. *JIMD Rep*. 2015;24:109-13. doi:10.1007/8904_2015_450
68. Bodhireddy S, Dickson DW, Mattiace L, Weidenheim KM. A case of Down's syndrome with diffuse Lewy body disease and Alzheimer's disease. *Neurology*. Jan 1994;44(1):159-61. doi:10.1212/wnl.44.1.159
69. Brandel JP, Marconi R, Serdaru M, Vidailhet M, Agid Y. Down's syndrome and Parkinson's disease. *Neurology*. Dec 1994;44(12):2419-20. doi:10.1212/wnl.44.12.2419-c
70. Agarwal P, Griffith AF, Borromeo-Wesner M. Case report and literature review of levodopa-reponsive young onset Parkinson's disease in a patient with Down's syndrome. *Movement Disorders*. 2010;25(SUPPL. 2):S499-S500. 14th International Congress of Parkinson's Disease and Movement Disorders. Buenos Aires Argentina. (var.pagings). doi:http://dx.doi.org/10.1002/mds.23162
71. Marui W, Iseki E, Kosaka K, Kato M, Adachi Y, Ueda K. An autopsied case of Down syndrome with Alzheimer pathology and alpha-synuclein immunoreactivity. *Neuropathology*. 1999;19(4):410-416. doi:http://dx.doi.org/10.1046/j.1440-1789.1999.00265.x

72. Palat P, Hickey F, Patel L, Sannar E. Levodopa-Responsive Early-Onset Parkinsonism in Down Syndrome. *Case Rep Neurol Med*. 2018;2018:2314791. doi:10.1155/2018/2314791
73. Singer C, Sanchez-Ramos J, Weiner WJ. Levodopa-responsive parkinsonism in a patient with Down's syndrome. *Eur Neurol*. 1990;30(5):247-8. doi:10.1159/000117355
74. Storm W. Differential diagnosis and treatment of depressive features in Down's syndrome: a case illustration. *Res Dev Disabil*. 1990;11(2):131-7. doi:10.1016/0891-4222(90)90031-3
75. Sturman SG, Williams AC. Parkinsonism and Down syndrome. *Lancet*. Oct 14 1989;2(8668):920-1. doi:10.1016/s0140-6736(89)91581-x
76. Camargos S, Scholz S, Simon-Sanchez J, et al. DYT16, a novel young-onset dystonia-parkinsonism disorder: identification of a segregating mutation in the stress-response protein PRKRA. *Lancet Neurol*. Mar 2008;7(3):207-15. doi:10.1016/s1474-4422(08)70022-x
77. Keogh MJ, Daud D, Pyle A, et al. A novel de novo STXBP1 mutation is associated with mitochondrial complex I deficiency and late-onset juvenile-onset parkinsonism. *Neurogenetics*. 2014;16(1):65-67. doi:http://dx.doi.org/10.1007/s10048-014-0431-z
78. Rezazadeh A, Lira V, Silberberg A, et al. Stxbp1 is associated with bruxism in awake patients. *Neurology*. 2019;92(15 Supplement 1)71st Annual Meeting of the American Academy of Neurology, AAN 2019. United States.
79. Yildiz EP, Yesil G, Ozkan MU, Bektas G, Caliskan M, Ozmen M. A novel EPM2A mutation in a patient with Lafora disease presenting with early parkinsonism symptoms in childhood. *Seizure*. Oct 2017;51:77-79. doi:10.1016/j.seizure.2017.07.011
80. Hall D, Pickler L, Riley K, Tassone F, Hagerman R. Parkinsonism and cognitive decline in a fragile X mosaic male. *Mov Disord*. Jul 30 2010;25(10):1523-4. doi:10.1002/mds.23150
81. Rosario M, Moldovan O, Reimao S, et al. Juvenile parkinsonism associated with a novel HSD17B10 mutation in a patient with HSD10 disease. *Movement Disorders*. 2018;33(Supplement 2):S218. 22nd International Congress of Parkinson's Disease and Movement Disorders, MDS 2018. Hong Kong.
82. Chen JY, Oza VS, Gopi R, Christine CW. Rapidly progressive Parkinsonism in a patient with incontinentia pigmenti. *Movement Disorders*. 2015;30(SUPPL. 1):S476-S477. 19th International Congress of Parkinson's Disease and Movement Disorders. San Diego, CA United States. (var. pagings). doi:http://dx.doi.org/10.1002/mds.26295
83. Bach JP, Sommer N, Moller JC, Oertel WH, Dodel R, Gasser T. Parkinson's syndrome in a young patient with Klinefelter's syndrome--a case report. *Mov Disord*. Apr 15 2008;23(5):771-2. doi:10.1002/mds.21948
84. Lee KS, Lee JE, Cho AH, Kim JS, Oh YS. A case of Parkinson's disease in a patient with Klinefelter's syndrome. *Acta Neurologica Belgica*. 2019;doi:http://dx.doi.org/10.1007/s13760-019-01232-1
85. Yu W, He Y, Liu Y. Combined Klinefelter syndrome and hereditary early-onset Parkinson's disease: A case report. *Movement Disorders Clinical Practice*. 2019;6(Supplement 1):S82. 6th Asian and Oceanian Parkinson's Disease and Movement Disorders Congress. China. doi:http://dx.doi.org/10.1002/mdc3.12744
86. Fabbri M, Zibetti M, Martone T, Lopiano L. Expanding the spectrum of movement disorders in Klinefelter syndrome. *Neurol Sci*. Jul 2018;39(7):1303-1304. doi:10.1007/s10072-018-3296-3
87. Owens WE, Okun MS. Dystonia, tremor, and parkinsonism in a 54 year old man with 2-hydroxyglutaric aciduria. *J Neurol Neurosurg Psychiatry*. Sep 2004;75(9):1362-3. doi:10.1136/jnnp.2003.033571
88. Martikainen MH, Ng YS, Gorman GS, et al. Clinical, genetic, and radiological features of extrapyramidal movement disorders in mitochondrial disease. *JAMA Neurology*. 2016;73(6):668-674. doi:http://dx.doi.org/10.1001/jamaneurol.2016.0355
89. Baumgartner A, Nia S, Erdler M, et al. A novel heteroplasmic mutation in the mitochondrial ATP6 gene associated with Parkinson's syndrome and epilepsy. *Journal of the Neurological Sciences*. 2013;333(SUPPL. 1):e706. 21st World Congress of Neurology. Vienna Austria.

(var.pagings). doi:http://dx.doi.org/10.1016/j.jns.2013.07.2437

90. Hemelsoet DM, Vanlander AV, Smet J, et al. Leigh syndrome followed by parkinsonism in an adult with homozygous c.626C>T mutation in MTFMT. *Neurology: Genetics*. 2018;4(6):e298. doi:http://dx.doi.org/10.1212/NXG.0000000000000298
91. Martikainen MH, Kytovuori L, Majamaa K. Juvenile parkinsonism, hypogonadism and Leigh-like MRI changes in a patient with m.4296G>A mutation in mitochondrial DNA. *Mitochondrion*. Mar 2013;13(2):83-6. doi:10.1016/j.mito.2013.01.012
92. Zyss J, Vlaicu M, Gerber S, Rodallec M, Gauthier C, Zuber M. Movement disorders in mevalonic aciduria. *Movement Disorders*. 2011;26(SUPPL. 2):S256. 15th International Congress of Parkinson's Disease and Movement Disorders. Toronto, ON Canada. (var.pagings). doi:http://dx.doi.org/10.1002/mds.23764
93. Alkufri F, Harrower T, Rahman Y, et al. Molybdenum cofactor deficiency presenting with a parkinsonism-dystonia syndrome. *Mov Disord*. Mar 2013;28(3):399-401. doi:10.1002/mds.25276
94. Hara M, Inokuchi T, Taniwaki T, et al. An adult patient with mucolipidosis III alpha/beta presenting with parkinsonism. *Brain Dev*. May 2013;35(5):462-5. doi:10.1016/j.braindev.2012.07.009
95. Choi J, Lee J, Kim H, Jeon B. A patient with myotonic dystrophy type 1 and parkinsonism. *Movement Disorders*. 2018;33(Supplement 2):S803-S804. 22nd International Congress of Parkinson's Disease and Movement Disorders, MDS 2018. Hong Kong.
96. Pradotto L, Mencarelli M, Di Blasio AM, Mauro A. Co-occurrence of Parkinson's disease and neurofibromatosis: A casual association or an underlying unique genetic cause? *Clinical Neuropathology*. 2014;33(3):232. Joint Meeting 50th Congress of the Italian Association of Neuropathology and Clinical Neurobiology, AINPeNC - 40th Congress of the Italian Association for Research on Brain Aging, AIRIC. Verbania Italy. (var.pagings).
97. Wattanapanom P, May C, Jain R. Weight loss as an atypical presentation of pheochromocytoma in an older man. *Journal of the American Geriatrics Society*. 2011;59(SUPPL. 1):S117. 2011 Annual Scientific Meeting of the American Geriatrics Society. National Harbor, MD United States. (var.pagings). doi:http://dx.doi.org/10.1111/j.1532-5415.2011.03416.x
98. D'Ambrosio G, Vizioli R. Recklinghausen disease and Parkinson disease: an unusual association. *Acta Neurol (Napoli)*. Aug 1984;6(4):274-9.
99. Hattori S, Kiguchi H, Ishii T, Nakajima T, Yatsuzuka H. Moyamoya disease with concurrent von Recklinghausen's disease and cerebral arteriovenous malformation. *Pathol Res Pract*. 1998;194(5):363-9. doi:10.1016/s0344-0338(98)80061-7
100. Chandra S, Rao K, Ghosh A, Ray J, Northrup H, Stimming E. Parkinsonism in Christianson syndrome: A unique presentation of a unique syndrome. *Movement Disorders*. 2018;33(Supplement 2):S219. 22nd International Congress of Parkinson's Disease and Movement Disorders, MDS 2018. Hong Kong.
101. Pescosolido MF, Kavanaugh BC, Pochet N, et al. Complex Neurological Phenotype in Female Carriers of NHE6 Mutations. *Mol Neuropsychiatry*. Apr 2019;5(2):98-108. doi:10.1159/000496341
102. Araki K, Nakamura R, Ito D, et al. NUS1 mutation in a family with epilepsy, cerebellar ataxia, and tremor. *Epilepsy Res*. May 22 2020;164:106371. doi:10.1016/j.eplepsyres.2020.106371
103. Namihira T, Hattori N, Shiroma S, Miyazato Y. Autosomal recessive juvenile Parkinson's disease with partial trisomy of chromosome 6q syndrome: a case report. *Psychiatry Clin Neurosci*. Dec 2004;58(6):672-3. doi:10.1111/j.1440-1819.2004.01321.x
104. Garraux G, Caberg JH, Vanbellinghen JF, et al. Partial trisomy 4q associated with young-onset dopa-responsive parkinsonism. *Arch Neurol*. Mar 2012;69(3):398-400. doi:10.1001/archneurol.2011.802
105. Daelman L, Sedel F, Tourbah A. Progressive neuropsychiatric manifestations of phenylketonuria in adulthood. *Rev Neurol (Paris)*. Apr 2014;170(4):280-7. doi:10.1016/j.neurol.2013.09.012
106. Evans AH, Costa DC, Gacinovic S, et al. L-Dopa-responsive Parkinson's syndrome in association with phenylketonuria: In vivo dopamine transporter and D2 receptor findings. *Mov Disord*. Oct 2004;19(10):1232-6. doi:10.1002/mds.20146
107. Velema M, Boot E, Engelen M, Hollak C. Parkinsonism in phenylketonuria: a consequence of dopamine depletion? *JIMD Rep*. 2015;20:35-8. doi:10.1007/8904_2014_386

108. Leuzzi V, Trasimeni G, Gualdi GF, Antonozzi I. Biochemical, clinical and neuroradiological (MRI) correlations in late-detected PKU patients. *J Inherit Metab Dis*. 1995;18(5):624-34. doi:10.1007/bf02436009

109. Konrad PN, McCarthy DJ, Mauer AM, Valentine WN, Paglia DE. Erythrocyte and leukocyte phosphoglycerate kinase deficiency with neurologic disease. *J Pediatr*. Mar 1973;82(3):456-60. doi:10.1016/s0022-3476(73)80120-9

110. Sakaue S, Kasai T, Mizuta I, et al. Early-onset parkinsonism in a pedigree with phosphoglycerate kinase deficiency and a heterozygous carrier: do PGK-1 mutations contribute to vulnerability to parkinsonism? *NPJ Parkinsons Dis*. 2017;3:13. doi:10.1038/s41531-017-0014-4

111. Virmani T, Rotstein M, Spiegel R, Akman HO, DiMauro S, Greene PE. Levodopa Responsive Parkinsonism in Two Patients With Phosphoglycerate Kinase Deficiency. *Mov Disord Clin Pract*. Sep 2014;1(3):240-242. doi:10.1002/mdc3.12055

112. Morales-Briceno H, Ha AD, London K, Farlow D, Chang FCF, Fung VSC. Parkinsonism in PGK1 deficiency implicates the glycolytic pathway in nigrostriatal dysfunction. *Parkinsonism Relat Disord*. Jul 2019;64:319-323. doi:10.1016/j.parkreldis.2019.04.004

113. Rotstein M, Spiegel R, DiMauro S. Juvenile parkinsonism and myopathy caused by a T378P mutation of the phosphoglycerate kinase gene PGK1. *Movement Disorders*. 2012;27(SUPPL. 1):S69. 16th International Congress of Parkinson's Disease and Movement Disorders. Dublin Ireland. (var.pagings). doi:http://dx.doi.org/10.1002/mds.25051

114. Sotiriou E, Greene P, Krishna S, Hirano M, DiMauro S. Myopathy and parkinsonism in phosphoglycerate kinase deficiency. *Muscle Nerve*. May 2010;41(5):707-10. doi:10.1002/mus.21612

115. Echaniz-Laguna A, Nadjar Y, Behin A, et al. Phosphoglycerate kinase deficiency: A nationwide multicenter retrospective study. *J Inherit Metab Dis*. Sep 2019;42(5):803-808. doi:10.1002/jimd.12087

116. Bandettini di Poggio M, Nesti C, Bruno C, Meschini MC, Schenone A, Santorelli FM. Dopamine-agonist responsive Parkinsonism in a patient with the SANDO syndrome caused by POLG mutation. *BMC Med Genet*. Oct 7 2013;14:105. doi:10.1186/1471-2350-14-105

117. De Pue A, Santens P. Late onset ophthalmoplegia and parkinsonism due to a novel POLG mutation. *European Journal of Neurology*. 2016;23(SUPPL. 2):297. 2nd Congress of the European Academy of Neurology. Copenhagen Denmark. (var.pagings). doi:http://dx.doi.org/10.1111/ene.13092

118. Khodadadi H, Azcona LJ, Aghamollaii V, et al. PTRHD1 (C2orf79) mutations lead to autosomal-recessive intellectual disability and parkinsonism. *Mov Disord*. Feb 2017;32(2):287-291. doi:10.1002/mds.26824

119. Jaberi E, Rohani M, Shahidi GA, et al. Mutation in ADORA1 identified as likely cause of early-onset parkinsonism and cognitive dysfunction. *Mov Disord*. Jul 2016;31(7):1004-11. doi:10.1002/mds.26627

120. Kuipers DJS, Carr J, Bardien S, et al. PTRHD1 Loss-of-function mutation in an african family with juvenile-onset Parkinsonism and intellectual disability. *Mov Disord*. Nov 2018;33(11):1814-1819. doi:10.1002/mds.27501

121. Ortez C, Jou C, Cortes-Saladelafont E, et al. Infantile parkinsonism and GABAergic hypotransmission in a patient with pyruvate carboxylase deficiency. *Gene*. Dec 15 2013;532(2):302-6. doi:10.1016/j.gene.2013.08.036

122. Ciammola A, Carrera P, Di Fonzo A, et al. X-linked Parkinsonism with Intellectual Disability caused by novel mutations and somatic mosaicism in RAB39B gene. *Parkinsonism and Related Disorders*. 2017;44:142-146. doi:http://dx.doi.org/10.1016/j.parkreldis.2017.08.021

123. Guldner M, Schulte C, Hauser AK, Gasser T, Brockmann K. Broad clinical phenotype in Parkinsonism associated with a base pair deletion in RAB39B and additional POLG variant. *Parkinsonism Relat Disord*. Oct 2016;31:148-150. doi:10.1016/j.parkreldis.2016.07.005

124. Lesage S, Bras J, Cormier-Dequaire F, et al. Loss-of-function mutations in RAB39B are associated with typical early-onset Parkinson disease. *Neurol Genet*. Jun 2015;1(1):e9. doi:10.1212/nxg.0000000000000009

125. Wilson GR, Sim JC, McLean C, et al. Mutations in RAB39B cause X-linked intellectual disability and early-onset Parkinson disease with alpha-synuclein pathology. *Am J Hum Genet*. Dec 4 2014;95(6):729-35. doi:10.1016/j.ajhg.2014.10.015
126. Roze E, Cochen V, Sangla S, et al. Rett syndrome: an overlooked diagnosis in women with stereotypic hand movements, psychomotor retardation, Parkinsonism, and dystonia? *Mov Disord*. Feb 15 2007;22(3):387-9. doi:10.1002/mds.21276
127. Chahil G, Yelam A, Bollu PC. Rett Syndrome in Males: A Case Report and Review of Literature. *Cureus*. Oct 4 2018;10(10):e3414. doi:10.7759/cureus.3414
128. Venkateswaran S, McMillan HJ, Doja A, Humphreys P. Adolescent onset cognitive regression and neuropsychiatric symptoms associated with the A140V MECP2 mutation. *Dev Med Child Neurol*. Jan 2014;56(1):91-4. doi:10.1111/dmcn.12334
129. Pollini L, Galosi S, Nardecchia F, et al. Parkinsonism, Intellectual Disability, and Catatonia in a Young Male With MECP2 Variant. *Mov Disord Clin Pract*. Jan 2020;7(1):118-119. doi:10.1002/mdc3.12865
130. Ollivier Y, Magot A, Latour P, et al. Clinical and electrophysiological features in a French family presenting with seipinopathy. *Neuromuscul Disord*. Feb 2015;25(2):161-4. doi:10.1016/j.nmd.2014.10.006
131. Goizet C, Boukhris A, Mundwiller E, et al. Complicated forms of autosomal dominant hereditary spastic paraplegia are frequent in SPG10. *Human mutation*. 2009;30(2):E376-E385. doi:http://dx.doi.org/10.1002/humu.20920
132. Anheim M, Lagier-Tourenne C, Stevanin G, et al. SPG11 spastic paraplegia. A new cause of juvenile parkinsonism. *J Neurol*. Jan 2009;256(1):104-8. doi:10.1007/s00415-009-0083-3
133. Guidubaldi A, Piano C, Santorelli FM, et al. Novel mutations in SPG11 cause hereditary spastic paraplegia associated with early-onset levodopa-responsive Parkinsonism. *Movement Disorders*. 2011;26(3):553-556. doi:http://dx.doi.org/10.1002/mds.23552
134. Kang SY, Lee MH, Lee SK, Sohn YH. Levodopa-responsive parkinsonism in hereditary spastic paraplegia with thin corpus callosum. *Parkinsonism and Related Disorders*. 2004;10(7):425-427. doi:http://dx.doi.org/10.1016/j.parkreldis.2004.05.003
135. Damasio J, Correia AP, Silva J, Alonso I, Bastos Lima A, Magalhaes M. Childhood-onset levodopa-responsive Parkinsonism in hereditary spastic paraplegia 15. *Movement Disorders*. 2014;29(SUPPL. 1):S397. 18th International Congress of Parkinson's Disease and Movement Disorders. Stockholm Sweden. (var.pagings). doi:http://dx.doi.org/10.1002/mds.25914
136. Mallaret M, Lagha-Boukbiza O, Biskup S, et al. SPG15: A cause of juvenile atypical levodopa responsive Parkinsonism. *Movement Disorders*. 2014;29(SUPPL. 1):S55-S56. 18th International Congress of Parkinson's Disease and Movement Disorders. Stockholm Sweden. (var.pagings). doi:http://dx.doi.org/10.1002/mds.25914
137. Schicks J, Synofzik M, Petursson H, et al. Atypical juvenile parkinsonism in a consanguineous SPG15 family. *Mov Disord*. Feb 15 2011;26(3):564-6. doi:10.1002/mds.23472
138. Groth CL, Berman BD. Spinocerebellar ataxia 27: A review and characterization of an evolving phenotype. *Tremor and Other Hyperkinetic Movements*. 2018;8doi:http://dx.doi.org/10.7916/D80S0ZJQ
139. Ebrahimi-Fakhari D, Hildebrandt C, Davis PE, Rodan LH, Anselm I, Bodamer O. The Spectrum of Movement Disorders in Childhood-Onset Lysosomal Storage Diseases. *Mov Disord Clin Pract*. Mar-Apr 2018;5(2):149-155. doi:10.1002/mdc3.12573
140. Nitschke S, Hagele-Link S, Bauer R, Mock B, Tettenborn B. Deep brain stimulation of the STN in a patient suffering from Parkinson's disease and Turner syndrome. *Schweizer Archiv fur Neurologie und Psychiatrie*. 2011;162(SUPPL. 4):9S. Gemeinsame Jahrestagung Schweizerische Neurologische Gesellschaft Schweizerische Gesellschaft fur Schlafforschung, Schlafmedizin und Chronobiologie 2011. St. Gallen Switzerland. (var.pagings).
141. Westenberger A, Rosales RL, Heinitz S, et al. X-linked Dystonia-Parkinsonism manifesting in a female patient due to atypical turner syndrome. *Mov Disord*. May 2013;28(5):675-8. doi:10.1002/mds.25369
142. de Rijk-Van Andel JF, Gabreels FJ, Geurtz B, et al. L-dopa-responsive infantile hypokinetic rigid parkinsonism due to tyrosine hydroxylase deficiency. *Neurology*. Dec 26 2000;55(12):1926-8. doi:10.1212/wnl.55.12.1926

143. Pons R, Serrano M, Ormazabal A, et al. Tyrosine hydroxylase deficiency in three Greek patients with a common ancestral mutation. *Movement Disorders*. 2010;25(8):1086-1090. doi:http://dx.doi.org/10.1002/mds.23002

144. Grattan-Smith PJ, Wevers RA, Steenbergen-Spanjers GC, Fung VS, Earl J, Wilcken B. Tyrosine hydroxylase deficiency: clinical manifestations of catecholamine insufficiency in infancy. *Mov Disord*. Mar 2002;17(2):354-9. doi:10.1002/mds.10095

145. Haugarvoll K, Bindoff LA. A novel compound heterozygous tyrosine hydroxylase mutation (p.R441P) with complex phenotype. *J Parkinsons Dis*. 2011;1(1):119-22. doi:10.3233/jpd-2011-11006

146. Lüdecke B, Knappskog PM, Clayton PT, et al. Recessively inherited L-DOPA-responsive parkinsonism in infancy caused by a point mutation (L205P) in the tyrosine hydroxylase gene. *Hum Mol Genet*. Jul 1996;5(7):1023-8. doi:10.1093/hmg/5.7.1023

147. Swaans RJ, Rondot P, Renier WO, Van Den Heuvel LP, Steenbergen-Spanjers GC, Wevers RA. Four novel mutations in the tyrosine hydroxylase gene in patients with infantile parkinsonism. *Ann Hum Genet*. Jan 2000;64(Pt 1):25-31. doi:10.1017/s0003480000007922

148. Burke EA, Frucht SJ, Thompson K, et al. Biallelic mutations in mitochondrial tryptophanyl-tRNA synthetase cause Levodopa-responsive infantile-onset Parkinsonism. *Clin Genet*. Mar 2018;93(3):712-718. doi:10.1111/cge.13172

149. Galosi S, Martinelli S, Cordeddu V, et al. Digenic inheritance of WARS2 and CHRNA6 mutations in infantile Parkinsonism. *Movement Disorder*. 2019;34(Supplement 2):S209. 2019 International Parkinson and Movement Disorder Society, MDS 2019. France.

150. Horn MA, Mikaelsen KB, Ferdinandusse S, et al. Mild phenotype in an adult male with X-linked adrenoleukodystrophy - case report. *Clin Case Rep*. Feb 2016;4(2):177-81. doi:10.1002/ccr3.434

151. Serra Soler G, Gogorza Perez MS, Jimenez Portilla A, Pereg Macazaga V. Primary adrenal insufficiency due to X-linked adrenoleukodystrophy diagnosed in adulthood. *Endocrinol Diabetes Nutr*. Oct 2017;64(8):458-459. Insuficiencia suprarrenal debida a adrenoleucodistrofia ligada al cromosoma X diagnosticada en la edad adulta. doi:10.1016/j.endinu.2017.07.001

152. Gupta HV, Vengoechea J, Sahaya K, Virmani T. A splice site mutation in ATP6AP2 causes X-linked intellectual disability, epilepsy, and parkinsonism. *Parkinsonism Relat Disord*. Dec 2015;21(12):1473-5. doi:10.1016/j.parkreldis.2015.10.001

153. Meytin L. S-PR, Swan M. . Myoclonus and parkinsonism in 22q11.2 syndrome-expanding the phenotype. *Mov Disord Clin Pract*. 2020;(7(Supplement 1)):S83. doi:doi:10.1002/mdc3.12905

154. Buongarzone G, Minafra B, Errichiello E, et al. 13.3.1. Movement disorders in a family carrying ATP7A variant. *Movement Disorders*. 2020;35(SUPPL 1):S89. MDS International Congress. Virtual. doi:http://dx.doi.org/10.1002/mds.28268

155. Maric N, Luna J, Codina M, Armengol L. Severe scoliosis in the patient with a novel variant p. Pro237ArgfsTer7 in the WDR45 gene. *Eur J Hum Genet*. 2020;(28(SUPPL 1)):453-454. doi:doi:10.1038/s41431-020-00739-z

156. Umehara F, Iwama K, Mizuguchi T, Matsumoto N. Basal ganglia calcification in a patient with static encephalopathy of childhood with neurodegeneration in adulthood/β-propeller protein-associated neurodegeneration. *Neurology and Clinical Neuroscience*. 2020;8(5):332-334. doi:https://doi.org/10.1111/ncn3.12427

157. Samanta D, Ramakrishnaiah R. Early-Onset Parkinsonism and Halo Sign: Beta-propeller Proteinassociated Neurodegeneration. *J Pediatr Neurosci*. Jul-Sep 2020;15(3):325-327. doi:10.4103/jpn.JPN_62_20

158. Munoz-Delgado L, Jesus S, Macias-Garcia D, et al. Atypical parkinsonism due to a mutation in the SLC9A6 gene. . *Mov Disord*. 2020;(35(SUPPL 1)):S516-S517. doi:doi:10.1002/mds.28268

159. Zadori D, Szalardy L, Maszlag-Torok R, et al. Clinicopathological Relationships in an Aged Case of DOORS Syndrome With a p.Arg506X Mutation in the ATP6V1B2 Gene. *Frontiers in Neurology*. 2020;11:767. doi:http://dx.doi.org/10.3389/fneur.2020.00767

160. Jesús S, Hinarejos I, Carrillo F, et al. NR4A2 Mutations Can Cause Intellectual Disability and Language Impairment With Persistent Dystonia-Parkinsonism. *Neurol Genet*. Feb 2021;7(1):e543. doi:10.1212/nxg.0000000000000543

161. Sleiman PM, Healy DG, Muqit MM, et al. Characterisation of a novel NR4A2 mutation in Parkinson's disease brain. *Neurosci Lett*. Jun 26 2009;457(2):75-9. doi:10.1016/j.neulet.2009.03.021

162. Grimes DA, Han F, Panisset M, et al. Translated mutation in the Nurr1 gene as a cause for Parkinson's disease. *Mov Disord*. Jul 2006;21(7):906-9. doi:10.1002/mds.20820

163. Kanatani M, Adachi T, Sakata R, et al. Dravet syndrome with parkinsonian symptoms and intact dopaminergic neurons: A case report. *Brain Dev*. Mar 2021;43(3):486-489. doi:10.1016/j.braindev.2020.10.015

164. Malaquias MJ, Costa D, Pinto E, et al. Parkinsonism and iron deposition in two adult patients with L-2-hydroxiglutaric aciduria. *Parkinsonism Relat Disord*. May 2021;86:45-47. doi:10.1016/j.parkreldis.2021.03.025

165. Witt J, Davis M. PNPLA6-related disorder with expanded phenotype including parkinsonism, dystonia, and abnormal dopamine transporter imaging. *Mov Disord*. 2020;(35(SUPPL 1)):S575. doi:doi:10.1002/mds.28268

166. Kim CY, Wirth T, Hubsch C, et al. Early-Onset Parkinsonism Is a Manifestation of the PPP2R5D p.E200K Mutation. *Ann Neurol*. Nov 2020;88(5):1028-1033. doi:10.1002/ana.25863

167. Hetzelt K, Kerling F, Kraus C, et al. Early-onset parkinsonism in PPP2R5D-related neurodevelopmental disorder. *Eur J Med Genet*. Jan 2021;64(1):104123. doi:10.1016/j.ejmg.2020.104123

168. Nomura S, Kashiwagi M, Tanabe T, et al. Rapid-onset dystonia-parkinsonism with ATP1A3 mutation and left lower limb paroxysmal dystonia. *Brain Dev*. Apr 2021;43(4):566-570. doi:10.1016/j.braindev.2020.12.009

169. Araujo FMM, Junior WM, Tomaselli PJ, Pimentel Â V, Macruz Brito MC, Tumas V. SPG15: A Rare Correlation with Atypical Juvenile Parkinsonism Responsive to Levodopa. *Mov Disord Clin Pract*. Oct 2020;7(7):842-844. doi:10.1002/mdc3.13027

170. Lesage S, Mangone G, Tesson C, et al. Clinical Variability of SYNJ1-Associated Early-Onset Parkinsonism. Brief Research Report. *Frontiers in Neurology*. 2021-March-25 2021;12(366) doi:10.3389/fneur.2021.648457

171. Krebs CE, Karkheiran S, Powell JC, et al. The Sac1 domain of SYNJ1 identified mutated in a family with early-onset progressive Parkinsonism with generalized seizures. *Hum Mutat*. Sep 2013;34(9):1200-7. doi:10.1002/humu.22372

172. Quadri M, Fang M, Picillo M, et al. Mutation in the SYNJ1 gene associated with autosomal recessive, early-onset Parkinsonism. *Hum Mutat*. Sep 2013;34(9):1208-15. doi:10.1002/humu.22373

173. Olgiati S, De Rosa A, Quadri M, et al. PARK20 caused by SYNJ1 homozygous Arg258Gln mutation in a new Italian family. *Neurogenetics*. Aug 2014;15(3):183-8. doi:10.1007/s10048-014-0406-0

174. Kirola L, Behari M, Shishir C, Thelma BK. Identification of a novel homozygous mutation Arg459Pro in SYNJ1 gene of an Indian family with autosomal recessive juvenile Parkinsonism. *Parkinsonism Relat Disord*. Oct 2016;31:124-128. doi:10.1016/j.parkreldis.2016.07.014

175. Taghavi S, Chaouni R, Tafakhori A, et al. A Clinical and Molecular Genetic Study of 50 Families with Autosomal Recessive Parkinsonism Revealed Known and Novel Gene Mutations. *Mol Neurobiol*. Apr 2018;55(4):3477-3489. doi:10.1007/s12035-017-0535-1

176. Ben Romdhan S, Sakka S, Farhat N, Triki S, Dammak M, Mhiri C. A Novel SYNJ1 Mutation in a Tunisian Family with Juvenile Parkinson's Disease Associated with Epilepsy. *J Mol Neurosci*. Oct 2018;66(2):273-278. doi:10.1007/s12031-018-1167-2

177. Hong D, Cong L, Zhong S, et al. Clonazepam improves the symptoms of two siblings with novel variants in the SYNJ1 gene. *Parkinsonism Relat Disord*. May 2019;62:221-225. doi:10.1016/j.parkreldis.2018.11.020

178. Xie F, Chen S, Cen ZD, et al. A novel homozygous SYNJ1 mutation in two siblings with typical Parkinson's disease. *Parkinsonism Relat Disord*. Dec 2019;69:134-137. doi:10.1016/j.parkreldis.2019.11.001

179. Boot E, Butcher NJ, Udow S, et al. Typical features of Parkinson disease and diagnostic challenges with microdeletion 22q11.2. *Neurology*. Jun 5 2018;90(23):e2059-e2067. doi:10.1212/wnl.0000000000005660

180. Boot E, Mentzel TQ, Palmer LD, et al. Age-Related Parkinsonian Signs in Microdeletion 22q11.2. *Mov Disord*. May 9 2020;doi:10.1002/mds.28080

181. Butcher NJ, Boot E, Lang AE, et al. Neuropsychiatric expression and catatonia in 22q11.2 deletion syndrome: An overview and case series. *Am J Med Genet A*. Oct 2018;176(10):2146-2159. doi:10.1002/ajmg.a.38708

182. Butcher NJ, Kiehl TR, Hazrati LN, et al. Association between early-onset Parkinson disease and 22q11.2 deletion syndrome: identification of a novel genetic form of Parkinson disease and its clinical implications. *JAMA Neurol*. Nov 2013;70(11):1359-66. doi:10.1001/jamaneurol.2013.3646

183. Butcher NJ, Marras C, Pondal M, et al. Neuroimaging and clinical features in adults with a 22q11.2 deletion at risk of Parkinson's disease. *Brain*. May 1 2017;140(5):1371-1383. doi:10.1093/brain/awx053

184. Dufournet B, Nguyen K, Charles P, et al. Parkinson's disease associated with 22q11.2 deletion: Clinical characteristics and response to treatment. *Rev Neurol (Paris)*. Jun 2017;173(6):406-410. doi:10.1016/j.neurol.2017.03.021

185. Mok KY, Sheerin U, Simon-Sanchez J, et al. Deletions at 22q11.2 in idiopathic Parkinson's disease: a combined analysis of genome-wide association data. *Lancet Neurol*. May 2016;15(6):585-96. doi:10.1016/s1474-4422(16)00071-5

186. Nishioka K, Oyama G, Yoshino H, et al. High frequency of beta-propeller protein-associated neurodegeneration (BPAN) among patients with intellectual disability and young-onset parkinsonism. *Neurobiol Aging*. May 2015;36(5):2004.e9-2004.e15. doi:10.1016/j.neurobiolaging.2015.01.020

187. Morales-Briceno H, Sanchez-Hernandez BE, Meyer E, et al. Beta-propeller-associated neurodegeneration can present with dominant or isolated parkinsonism. *Mov Disord*. Apr 2018;33(4):654-656. doi:10.1002/mds.27294

188. Hayflick SJ, Kruer MC, Gregory A, et al. beta-Propeller protein-associated neurodegeneration: a new X-linked dominant disorder with brain iron accumulation. *Brain*. Jun 2013;136(Pt 6):1708-17. doi:10.1093/brain/awt095

189. Ohno T, Kobayashi S, Hayashi M, Sakurai M, Kanazawa I. Diphenylpyraline-responsive parkinsonism in cerebrotendinous xanthomatosis: long-term follow up of three patients. *J Neurol Sci*. Jan 1 2001;182(2):95-7. doi:10.1016/s0022-510x(00)00441-x

190. Olgiati S, Quadri M, Fang M, et al. DNAJC6 Mutations Associated With Early-Onset Parkinson's Disease. *Ann Neurol*. Feb 2016;79(2):244-56. doi:10.1002/ana.24553

191. Clot F, Grabli D, Cazeneuve C, et al. Exhaustive analysis of BH4 and dopamine biosynthesis genes in patients with Dopa-responsive dystonia. *Brain*. Jul 2009;132(Pt 7):1753-63. doi:10.1093/brain/awp084

192. Ng J, Meyer E, Li Y, et al. Expansion of the genotypic and phenotypic spectrum of hereditary dopamine transporter deficiency syndrome. *Journal of Inherited Metabolic Disease*. 2012;35(1 SUPPL. 1):S19. Annual Symposium of the Society for the Study of Inborn Errors of Metabolism, SSIEM 2012. Birmingham United Kingdom. (var.pagings). doi:http://dx.doi.org/10.1007/s10545-012-9512-z

193. Lai F, Williams RS. A prospective study of Alzheimer disease in Down syndrome. *Arch Neurol*. Aug 1989;46(8):849-53. doi:10.1001/archneur.1989.00520440031017

194. Vieregge P, Ziemens G, Freudenberg M, Piosinski A, Muysers A, Schulze B. Extrapyramidal features in advanced Down's syndrome: clinical evaluation and family history. *J Neurol Neurosurg Psychiatry*. Jan 1991;54(1):34-8. doi:10.1136/jnnp.54.1.34

195. Fasano A, Borlot F, Lang AE, Andrade DM. Antecollis and levodopa-responsive parkinsonism are late features of dravet syndrome. *Neurology*. 2014;82(24):2250-2251. doi:http://dx.doi.org/10.1212/WNL.0000000000000521

196. Utari A, Adams E, Berry-Kravis E, et al. Aging in fragile X syndrome. *J Neurodev Disord*. Jun 2010;2(2):70-76. doi:10.1007/s11689-010-9047-2

197. Gitiaux C, Roze E, Kinugawa K, et al. Spectrum of movement disorders associated with glutaric aciduria type 1: a study of 16 patients. *Mov Disord*. Dec 15 2008;23(16):2392-7. doi:10.1002/mds.22313

198. Ruottinen HM, Rinne JO, Haaparanta M, et al. [18F]fluorodopa PET shows striatal dopaminergic dysfunction in juvenile neuronal ceroid lipofuscinosis. *J Neurol Neurosurg Psychiatry*. Jun 1997;62(6):622-5. doi:10.1136/jnnp.62.6.622
199. Aberg L, Liewendahl K, Nikkinen P, Autti T, Rinne JO, Santavuori P. Decreased striatal dopamine transporter density in JNCL patients with parkinsonian symptoms. *Neurology*. Mar 14 2000;54(5):1069-74. doi:10.1212/wnl.54.5.1069
200. Aberg LE, Rinne JO, Rajantie I, Santavuori P. A favorable response to antiparkinsonian treatment in juvenile neuronal ceroid lipofuscinosis. *Neurology*. May 8 2001;56(9):1236-9. doi:10.1212/wnl.56.9.1236
201. Hunter H. A controlled study of the psychopathology and physical measurements of Klinefelter's syndrome. *Br J Psychiatry*. Apr 1969;115(521):443-8. doi:10.1192/bjp.115.521.443
202. Madubata CC, Olsen MA, Stwalley DL, Gutmann DH, Johnson KJ. Neurofibromatosis type 1 and chronic neurological conditions in the United States: an administrative claims analysis. *Genet Med*. Jan 2015;17(1):36-42. doi:10.1038/gim.2014.70
203. Luoma P, Melberg A, Rinne JO, et al. Parkinsonism, premature menopause, and mitochondrial DNA polymerase gamma mutations: clinical and molecular genetic study. *Lancet*. Sep 4-10 2004;364(9437):875-82. doi:10.1016/s0140-6736(04)16983-3
204. Orrico A, Lam C, Galli L, et al. MECP2 mutation in male patients with non-specific X-linked mental retardation. *FEBS Lett*. Sep 22 2000;481(3):285-8. doi:10.1016/s0014-5793(00)01994-3
205. FitzGerald PM, Jankovic J, Percy AK. Rett syndrome and associated movement disorders. *Mov Disord*. 1990;5(3):195-202. doi:10.1002/mds.870050303
206. Kara E, Tucci A, Manzoni C, et al. Genetic and phenotypic characterization of complex hereditary spastic paraplegia. *Brain*. Jul 2016;139(Pt 7):1904-18. doi:10.1093/brain/aww111
207. Zouari M, Nehdi H, Ben Hamed M, Hentati F, Amouri R. Hereditary spastic paraplegia with thin corpus callosum: Clinical, radiological and genetic study. *Journal of the Neurological Sciences*. 2009;285(SUPPL. 1):S106. 19th World Congress of Neurology. Bangkok Thailand. (var.pagings).
208. Korvatska O, Strand NS, Berndt JD, et al. Altered splicing of ATP6AP2 causes X-linked parkinsonism with spasticity (XPDS). *Hum Mol Genet*. Aug 15 2013;22(16):3259-68. doi:10.1093/hmg/ddt180

Chapter 3

The estimated prevalence of Parkinson's disease in 22q11.2 deletion syndrome

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Article in preparation

Abstract

Previous research has suggested that the prevalence of Parkinson's disease (PD) in adults with 22q11.2 deletion syndrome (22q11.2DS) is ~6%. However, this estimate was based on a relatively small sample of adults with 22q11.2DS, aged 35-64 years. Therefore, we conducted an international multicenter study including 856 adults (47% male, mean age 46.5 ± 15.4 years) with 22q11.2DS, and examined the prevalence of, and potential contributors to, established PD (defined as a clinical diagnosis by a neurologist, including bradykinesia and at least one of either rest tremor or rigidity). Established PD was found in 1.8% (95% CI: 0.9–2.6) of the study sample, and 3.4% (95% CI: 2.2–4.6%) when suspected of PD was also included. A sharp increase in the prevalence of PD was seen in adults aged 50 years and older; 11.7% had PD. In contrast to sporadic PD, male sex was not associated with an increased PD risk. In conclusion, results of this study showed a prevalence of PD of 1.8% in 22q11.2DS, that increased to >10% in those aged 50 years and older. Periodic neurological evaluation, preferably by a movement disorder specialist, is warranted in all adults with 22q11.2DS aged 40 years and older, in order to enable early diagnosis and treatment.

Introduction

The 22q11.2 deletion syndrome (22q11.2DS), a genetic neurodevelopmental disorder with a birth prevalence of ~1:2000,[1] has been identified as a risk factor for early-onset Parkinson's disease (PD).[2, 3] Previous research has suggested that the prevalence of PD in adults with 22q11.2DS aged 35-64 years is ~6%, indicating a 20-70 fold increased risk of Parkinson's disease (PD) in 22q11.2DS compared to the general population.[2, 3] Importantly, PD in 22q11.2DS is comparable to PD in the general population in terms of its major clinical characteristics, including good response to standard treatment.[4] Also, the importance of early diagnosis and early treatment of PD are well-recognized in 22q11.2DS.[5]

However, there are still uncertainties regarding the actual PD risk in 22q11.2DS, hindering the provision of adequate information to affected individuals and their families and the introduction of screening and monitoring strategies in at risk groups. We therefore aimed to characterize the prevalence of, and contributors to PD in a large sample of adults with 22q11.2DS. We hypothesized that the prevalence of PD would be higher in 22q11.2DS than in the general population, and that age and male sex would be contributors to PD risk. In particular, we expected a sharp increase in the prevalence at a younger age than in PD in the general population, where PD is rare under the age of 50 years.[6]

Materials and methods

We conducted a cross-sectional multicenter study in 4 countries: 1 North American (Canada), 1 South American (Chile) and 2 European (Belgium and the Netherlands). Participants were recruited across five 22q11.2DS specialty clinics. The Institutional Review Board of each participating site approved this study or provided a waiver for formal ethical approval. All data were collected and analyzed according to national and international regulations. Written informed consent was obtained from all patients and/or legal representatives, unless a waiver for written consent was given by the Institutional Review Board for the use of pseudonymized clinical data.

Sample

In total, 856 individuals (454 females, 53.0%) aged 16 years and older with a molecularly confirmed typical 22q11.2 deletion (i.e., including the LCR22A-LCR22B region)[7] entered the study. The median age of the study sample was 29 (range 16 – 76) years. Additional information regarding demographic and patient characteristics of the study sample is presented in Supplementary Table 1.

Identification and characterization of adults with Parkinson's disease

We systematically extracted data on demographic variables (sex and age at last clinical assessment, death, or at the time of chart review (Toronto)), results of genetic analysis, history of medication use, medical history, and available information on PD expression (including dopaminergic imaging) and treatment. We defined PD as a clinical diagnosis by a neurologist, including bradykinesia and at least one of either rest tremor or rigidity,[8] and suspected PD as a clinical diagnosis or suspicion of PD but failure to meet all above criteria for PD. This separate category of adults with suspected PD was included to account for the fact that there were several adults with a clinical suspicion of PD, who did not meet all criteria for PD. Reasons for not meeting the formal criteria included lack of information in the medical file regarding parkinsonian motor features in the presence of a clinical PD diagnosis (n=3), or a clinical suspicion of PD based on supportive criteria, such as positive treatment response, without a formal PD diagnosis (n=11). Seven cases with PD and no cases with suspected PD were reported previously.[2, 4]

Data presentation and analysis

We calculated prevalence rates of PD and their 95% confidence intervals (95% CIs), using the formula CI= $p \pm 1.96^* \sqrt{(p(1-p)/n)}$, per sex and age group.[8] Pearson's chi-square tests were used to compare PD prevalence rates between groups (i.e., sex and age). The observed number of PD cases in adults with 22q11.2DS was compared with the expected number of PD cases based on data from the general population within the age group of 40-69 years, using an age adjusted standardized morbidity ratio (SMR).[8] This age group was based on the availability of population based data from the age of 40 years,[8] and the limited number of adults with 22q11.2DS

aged ≥70 years (n=5). A binary logistic regression analysis was used to identify possible predictors of the presence of established PD. For this we considered age and sex based on previous studies.[8] In order to limit the risk of underestimating PD prevalence, we repeated the analyses including individuals with suspected PD. All analyses used two-tailed, with statistical significance defined as $P<0.05$ using IBM SPSS software (Statistics 28; Inc., Chicago, IL, USA).

Data availability statement

The data are not publicly available due to privacy and ethical restrictions. Any data requests can be directed to the corresponding author.

Results

PD was reported in 1.8% (95% CI: 0.9–2.6, n=15) of the adults with 22q11.2DS, and in 11.7% (95% CI: 5.7–17.7, n=13/111) of those aged 50 years and older (Table 1). Clinical features can be found in Table 2. In the majority of cases (86.7%, n=13), the neurologist who confirmed the diagnosis was known to be a movement disorder specialist. The SMR for PD in 22q11.2DS was 27.9 (95% CI: 14.9–46.8). Mean age at motor onset and diagnosis of PD were not significantly different between males and females (p=0.3 and p=0.4, respectively). Only four adults were known to be tested for variants in PD genes (*LRRK2*, *PARK2*, *PINK1*, *SNCA* or *DJ-1*), all with negative results.

Table 1. Prevalence of Parkinson's disease in 22q11.2 deletion syndrome by sex and age

	Total study sample				Male					Female				
Established PD	**n**	**PD n**	**PD %**	**PD 95% CI**	**n**	**%**	**PD N**	**PD %**	**PD 95% CI**	**n**	**%**	**PD n**	**PD %**	**PD 95% CI**
Age group, y														
<20	97	0	0.0	0.0 – 0.0	50	51.5	0	0.0	0.0 – 0.0	47	48.5	0	0.0	0.0 – 0.0
20 – 29	332	1	0.3	0.0 – 0.9	171	51.5	0	0.0	0.0 – 0.0	161	48.5	1	0.6	0.0 – 1.8
30 – 39	195	1	0.5	0.0 – 1.5	80	41.0	1	1.3	0.0 – 3.7	115	59.0	0	0.0	0.0 – 0.0
40 – 49	121	0	0.0	0.0 – 0.0	57	47.1	0	0.0	0.0 – 0.0	64	52.9	0	0.0	0.0 – 0.0
50 – 59	75	9	12.0	4.7 – 19.4	32	42.7	4	12.5	1.0 – 24.0	43	57.3	5	11.6	2.1 – 21.2
60 – 69	31	3	9.7	0.0 – 20.1	10	32.2	2	20.0	0.0 – 44.8	21	67.7	1	4.8	0.0 – 13.9
70+	5	1	20.0	0.0 – 55.1	2	40.0	1	50.0	0.0 – 100	3	60.0	0	0.0	0.0 – 0.0
Overall, y	856	15	1.8	0.9 – 2.6	402	47.0	8	2.0	0.6 – 3.4	454	53.0	7	1.5	0.4 – 2.7
50+, y	111	13	11.7	5.7 – 17.7	44	39.6	7	15.9	5.1 – 26.7	67	60.3	6	9.0	2.1 – 15.8
Including suspected PD	**n**	**PD n**	**PD %**	**PD 95% CI**	**n**	**%**	**PD N**	**PD %**	**PD 95% CI**	**n**	**%**	**PD n**	**PD %**	**PD 95% CI**
Age group, y														
<20	97	0	0.0	0.0 – 0.0	50	51.5	0	0.0	0.0 – 0.0	47	48.5	0	0.0	0.0 – 0.0
20 – 29	332	2	0.6	0.0 – 1.4	171	51.5	1	0.6	0.0 – 1.7	161	48.5	1	2.1	0.0 – 1.8
30 – 39	195	1	0.5	0.0 – 1.5	80	41.0	1	1.3	0.0 – 3.7	115	59.0	0	0.0	0.0 – 0.0
40 – 49	121	4	3.3	0.1 – 6.5	57	47.1	2	3.5	0.0 – 8.3	64	52.9	2	3.1	0.0 – 7.4
50 – 59	75	14	18.7	9.9 – 27.5	32	42.7	5	15.6	3.0 – 28.2	43	57.3	9	20.9	8.9 – 33.1
60 – 69	31	7	22.6	7.9 – 37.3	10	32.2	3	30.0	1.6 – 58.4	21	67.7	4	19.0	2.3 – 35.8
70+	5	1	20.0	0.0 – 55.1	2	40.0	1	50.0	0.0 – 100	3	60.0	0	0.0	0.0 – 0.0
Overall, y	856	29	3.4	2.2 – 4.6	402	47.0	13	3.2	1.5 – 5.0	454	53.0	16	3.5	1.8 – 5.2
50+	111	22	19.8	12.4 – 27.2	44	39.6	9	20.5	8.5 – 32.4	67	60.3	13	19.4	9.9 – 28.9

y = years, n = number, PD = Parkinson's disease, 95% CI = 95% confidence interval.

When including individuals with a clinical suspicion of PD, 3.4% (95% CI: 2.2–4.6, n=29) was found to have PD and 19.8% (95% CI: 12.4-27.2, n=22) of those aged 50 years and older (Table 1). The SMR increased to 57.3 (95% CI: 37.9–83.4). Clinical characteristics of the 14 adults with suspected PD are presented in Table 3. For the two adults who died, no postmortem results were available.

Table 2. Patient characteristics and parkinsonian features in 15 adults with 22q11.2 deletion syndrome and Parkinson's disease

Patient characteristics	N	%
History of anti-psychotic medication	10/15	66.7
Intellectual functioning		
Normal	2	13.3
Borderline	3	20.0
Mild intellectual disability	4	26.7
Moderate intellectual disability	3	20.0
Severe intellectual disability	3	20.0
Parkinsonian features	**N**	**Mean ± SD**
Age at PD diagnosis, y	15	49.0 ± 10.7
Male	8	51.4 ± 10.9
Female	7	46.2 ± 10.5
Age at motor onset, y	15	43.5 ± 12.2
Male	8	46.8 ± 11.8
Female	7	39.9 ± 12.5
	N	%
Bradykinesia	15/15	100.0
Rigidity	15/15	100.0
Rest tremor	11/14	78.6
Postural instability	8/11	72.7
Progression motor symptoms	13/13	100.0
Symmetrical motor symptoms	1/8	12.5
Asymmetrical motor symptoms	7/8	87.5
Anti-parkinsonian medication	15/15	100.0
Good response	11/14	78.6
Questionable response	3/14	21.4
Typical findings dopaminergic imaging [a]	5/7	71.4

[a] One adult without typical findings had dopaminergic imaging several years prior to PD diagnosis, the second adult without typical findings presented with asymmetrical parkinsonism with symptoms that were stable on risperidone and neuropathology results that included extensive nigral degeneration and loss of TH immunoreactivity in the striatum, extensive degeneration of TH-positive cells in the substantia nigra pars compacta without Lewy bodies or Lewy neurite pathology.[2]

PD= Parkinson's disease, n=number, SD= standard deviation, y= year.

Table 3. Clinical features of 14 adults with 22q11.2 deletion syndrome and suspected Parkinson's disease

Case	Sex	Age, y	PD diagnosis	Bradykinesia	Rigidity	Rest tremor	Progression	Antiparkinson use	Antipsychotic use	Comorbid conditions, remarks
1	F	48	√ [a]	NR	NR	NR	NR	-	-	Korsakoff syndrome
2	F	57	√ [a]	√	NR	NR	NR	√	√	CD, wheelchair user
3	F	63	√ [a]	√	-	-	√	√ [b]	√	
4 [c]	M	20	-	√	-	√	NR	-	-	
5	F	46	-	-	√	√	√	-	√	
6	M	46	-	√	√	-	√	-	√	
7	M	48	-	√	NR	√	NR	-	√	CD, oral tardive dyskinesia
8	F	50	-	√	-	-	√	√	√	
9	M	55	-	√	√	√	√	√ [b]	√	CD
10	F	55 [d]	-	√	√	√	√	√	√	CD, Wheelchair user
11	F	56	-	√	√	-	√	-	√	
12	M	66	-	√	√	-	√	√ [b]	√	CD, myoclonus, antecollis
13	F	62 [d]	-	NR	NR	NR	NR	NR	-	
14	F	69	-	√	-	√	√	-	-	CD, wheelchair user

[a] All 3 had a clinical PD diagnosis: case 2 by a neurologist, and case 3 by a movement disorder specialist.
[b] Three patients were known to have a good response on antiparkinsonian medication.
[c] The only patient with dopaminergic imaging results available showed typical reduced presynaptic dopaminergic signaling.
[d] Age at death.
√ = yes, - = no, y = year, NR = not reported/unknown, PD = Parkinson's disease, CD = cognitive decline.

Predictors to Parkinson's disease

Binary logistic regression analysis showed that age, but not sex, was significantly related to PD in adults with 22q11.2DS (Table 4).

Table 4. Possible predictors of Parkinson's disease in 856 adults with 22q11.2 deletion syndrome

	Wald	P	OR	95% CI
Parkinson's disease [a]				
Age (y)	27.57	<0.001	1.11	1.07 – 1.16
Male sex	0.99	0.32	1.73	0.59 – 5.06
Parkinson's disease, including suspected cases [b]				
Age (y)	49.67	<0.001	1.12	1.08 – 1.15
Male sex	0.18	0.672	1.19	0.53 – 2.67

Table 2. Binary logistic regression analysis of possible predictors of Parkinson's disease in adults with 22q11.2DS. Both models were significant: [a]p<0.001, Nagelkerke=0.237, [b]p<0.001, Nagelkerke=0.279. Y=years, OR= odds ratio, CI= confidence interval.

Discussion

The results of this study confirm that the prevalence of PD is higher in 22q11.2DS compared to the general population,[8] 1.8% vs 0.3%, and indicate that PD is related to age, but not sex, with a sharp increase in prevalence to more than 10% in those aged 50 years and older.

Parkinson's disease in adults with 22q11.2DS

The increase in PD prevalence is comparable to the sharp increase reported in the general population,[8] although with an earlier onset in 22q11.2DS. This study was an extension of a previous single-center study that reported a prevalence of PD of 5.9% in 68 adults aged 35 to 64 years, based on a PD diagnosis according to the UK Parkinson's Disease Society Brain Bank criteria.[2] In that study, adults aged 18-34 years were not included in the reported PD prevalence, however if they were, PD prevalence of the total study sample (n=158)[2] would be 2.5% (95% CI: 0.01-4.98), comparable to the findings of the current study.

In contrast to studies in the general population,[8, 9] and previous findings in 22q11.2DS,[4] there were no differences in the prevalence of PD or age at motor onset, between males and females. In the general population there

is a male predominance of PD, and motor symptoms usually start at an earlier age compared to females.[8] One possible explanation may be that other factors than sex, such as genetic susceptibility, are more dominant in 22q11.2DS.[10] Speculatively, another explanation may be related to hemizygosity of *COMT*, a gene located within the typically deleted 22q11.2 region and encoding for the enzyme (catechol-*O*-methyltransferase) important for degradation of catecholamines, that may result in dopamine autotoxicity.[11] *COMT* expression is inhibited by estrogen, resulting in lower COMT activity in females than in males, which may lead to increased dopamine levels,[12] and autotoxicity, resulting in a higher vulnerability to develop PD. Our results showing an increase in PD prevalence in males aged 50 years and older but a decrease in females, may also be explained by changes in estrogen levels in females before and after menopause.

A separate category of adults with suspected PD was included to account for the fact that there were several adults with a clinical suspicion of PD, although not meeting all criteria for PD. Limiting results to adults with a formal diagnosis of PD would most likely result in an underestimation of PD prevalence in 22q11.2DS. In case adults with a suspicion of PD were included in our analysis, it was found that PD estimates almost doubled (3.4%). Although hallmark features of PD in the general population were found in adults with 22q11.2DS,[2, 4] there may be several reasons for clinicians to be hesitant to diagnose PD in adults with 22q11.2DS. Adults with 22q11.2DS often have a complex neuropsychiatric presentation, with additional movement disorders such as dystonia and catatonia, [13, 14] and/or psychiatric disorders such as psychosis and (a history of) medication-induced parkinsonism,[15] that may overshadow and/or complicate recognition of parkinsonian features. The atypical early age of motor onset may further increase the likelihood of parkinsonian symptoms to be attributed to other conditions associated with 22q11.2DS. In addition, clinicians may be hesitant with referring to a neurologist because of the added burden of hospital visits, follow-up examinations or doubt about potential benefits.

Clinical implications

In individuals with 22q11.2DS under the age of 40 years, clinicians should be aware of the possibility of PD. Motor examination, preferably by a movement

disorder specialist, may be considered in case of parkinsonian motor signs including bradykinesia, rigidity and rest tremor. After the age of 40 years standard neurological examinations seem justified, since treatment options exist and ideally start as soon as possible for optimal effect.[16] Individuals with 22q11.2DS at any age (with suspicion of) medication-induced parkinsonism may benefit from careful monitoring and referral for neurological examination in case of doubt. Similarly to individuals from the general population, dopaminergic imaging may aid in differentiating between neurodegenerative and medication-induced parkinsonism,[4, 17] and standard treatments for PD, such as levodopa, are recommended.[11] Based on studies in the general population, exercise interventions may have protective effects on the quality of life and functional mobility of individuals with PD,[18] and information regarding possible beneficial effects of exercise and healthy diet, such as avoiding obesity and consuming uric acid and poly-unsaturated fatty acid rich diets,[19] may be included in clinical counseling of adults with (suspicion of) PD.[20] However, there are still many controversies regarding the relationship between diet and other factors and PD.[16, 19] Prior to screening of motor symptoms, the possible benefits and harms of identification of PD should be discussed since for some individuals the psychological harm of being diagnosed with a progressive disorder that cannot be cured may outweigh benefits of (potentially) slowing down disease progression.[21] Future research may study how and when counseling and screening of PD in individuals who receive a 22q11.2DS diagnosis should take place. Previous studies in adults with Down syndrome, who have an increased risk of early-onset Alzheimer's disease, and relatives of patients with PD and genetic variants in *GBA* or *LRRK2*, showed that they valued counseling about their increased risk and screening possibilities of the neurodegenerative disorder. [21 22]

Features related to prodromal PD in the general population, such as constipation, loss of smell, depression and anxiety are more frequent in adults with 22q11.2DS in general.[15, 23-25] It is still unclear if features such as hyposmia or rapid eye movement sleep behavior disorder (RMD) are predictive of PD in 22q11.2DS,[11] although RMD has been reported in combination with parkinsonism,[26] and no objective evidence of RMD in 26 non-PD adults (18-51 years) with 22q11.2DS was found using polysomnography.[27]

Research implications

Although genetic variants have been found to explain only a small portion of PD,[28, 29] identification of these genes has contributed to the understanding of PD pathophysiology. For example, studies of duplications and triplications of *SNCA*, encoding for alpha-synuclein, provided evidence for the relation between gene dosage and severity of parkinsonian features.[30] Although 22q11.2DS has been reported most related to PD, other genetic neurodevelopmental disorders have been associated with neurodegenerative parkinsonism as well, and several shared underlying mechanisms related to the neurodevelopmental disorder and PD have been proposed.[31] Research of the influence of genetic variants on PD risk and disease trajectory are crucial for the identification of novel treatment strategies that may prevent or slow down disease progression. Since 22q11.2DS and other genetic neurodevelopmental disorders are often identified at an early age, long-term follow up of asymptomatic/pre-symptomatic individuals may generate knowledge of contributors to the development of PD and the ability of (environmental) factors to delay or slow down PD. Studies may include evaluation of parkinsonian symptoms using the Unified Parkinson's Disease Rating Scale, prodromal features such as RMD using polysomnography, and questionnaires for the study of environmental factors such as diet and exercise. Results may help to improve counseling of individuals at risk of developing PD. Furthermore, identification of genetic variants such as 22q11.2DS, that are associated with an increased risk of PD, facilitates the use of cell and animal models, [32, 33] that may help to identify disease-modifying agents for adults with 22q11.2DS and PD which may also be of relevance to the general population.

Strengths and limitations

Strengths include the large study sample of adults with a, relatively rare, diagnosis of 22q11.2DS and recruitment from different sites, covering different regions and organizations. An important limitation includes the retrospective study design. Under-recognition of PD prevalence may be related to clinical notes that may have lacked relevant information regarding a PD diagnosis and the fact that most adults were not screened for PD. In addition, adults may have had difficulties with signalizing symptoms of PD and/or seeking help.[5] Since genetic testing in adults with an intellectual

disability (ID) is less common compared to children, it is likely that 22q11.2DS is underdiagnosed in individuals (with an ID) over 50 years, who were found to have the highest PD prevalence rates.
It is also possible that PD prevalence rates were influenced in the opposite direction, since all included sites were 22q11.2 outpatient specialty clinics adults with a less severe phenotype may not have visited these clinics resulting in selection bias.
Age groups of individuals aged 50 years and older were rather small, making it difficult to provide reliable prevalence rates for the highest age groups. Other studies in the general population often did not report prevalence rates for PD under the age of 30,[9] or even 40 years,[8, 34] making it difficult to compare results of the youngest age groups to the general population. Only four adults were tested for variants in PD genes (*LRRK2*, *PARK2*, *PINK1*, *SNCA* or *DJ-1*), all with negative results. Therefore, presence of additional disease-causing variants in the remaining 11 adults with PD cannot be ruled out.

Conclusion

This study provides more insight into the course of neurologic manifestations of 22q11.2DS, showing an increased risk of developing PD compared to individuals from the general population, without a difference in PD prevalence between males and females. Periodic neurological evaluation, preferably by a movement disorder specialist, is warranted in all adults with 22q11.2DS aged 40 years and older, in order to enable early diagnosis and treatment.

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Competing interests
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References

1. Blagojevic C, Heung T, Theriault M, et al. Estimate of the contemporary live-birth prevalence of recurrent 22q11.2 deletions: a cross-sectional analysis from population-based newborn screening. *CMAJ Open*. Jul-Sep 2021;9(3):E802-e809. doi:10.9778/cmajo.20200294
2. Butcher NJ, Kiehl TR, Hazrati LN, et al. Association between early-onset Parkinson disease and 22q11.2 deletion syndrome: identification of a novel genetic form of Parkinson disease and its clinical implications. *JAMA Neurol*. Nov 2013;70(11):1359-66. doi:10.1001/jamaneurol.2013.3646
3. Mok KY, Sheerin U, Simón-Sánchez J, et al. Deletions at 22q11.2 in idiopathic Parkinson's disease: a combined analysis of genome-wide association data. *Lancet Neurol*. May 2016;15(6):585-96. doi:10.1016/s1474-4422(16)00071-5
4. Boot E, Butcher NJ, Udow S, et al. Typical features of Parkinson disease and diagnostic challenges with microdeletion 22q11.2. *Neurology*. Jun 5 2018;90(23):e2059-e2067. doi:10.1212/wnl.0000000000005660
5. Boot E, Óskarsdóttir S, Loo JCY, et al. Updated clinical practice recommendations for managing adults with 22q11.2 deletion syndrome. *Genet Med*. Mar 2023;25(3):100344. doi:10.1016/j.gim.2022.11.012
6. Twelves D, Perkins KS, Counsell C. Systematic review of incidence studies of Parkinson's disease. *Mov Disord*. Jan 2003;18(1):19-31. doi:10.1002/mds.10305
7. McDonald-McGinn DM, Sullivan KE, Marino B, et al. 22q11.2 deletion syndrome. *Nat Rev Dis Primers*. Nov 19 2015;1:15071. doi:10.1038/nrdp.2015.71
8. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Mov Disord*. Nov 2014;29(13):1583-90. doi:10.1002/mds.25945
9. Brakedal B, Toker L, Haugarvoll K, Tzoulis C. A nationwide study of the incidence, prevalence and mortality of Parkinson's disease in the Norwegian population. *NPJ Parkinsons Dis*. Mar 2 2022;8(1):19. doi:10.1038/s41531-022-00280-4
10. Cerri S, Mus L, Blandini F. Parkinson's Disease in Women and Men: What's the Difference? *J Parkinsons Dis*. 2019;9(3):501-515. doi:10.3233/jpd-191683
11. Boot E, Bassett AS, Marras C. 22q11.2 Deletion Syndrome-Associated Parkinson's Disease. *Mov Disord Clin Pract*. Jan 2019;6(1):11-16. doi:10.1002/mdc3.12687
12. Harrison PJ, Tunbridge EM. Catechol-O-methyltransferase (COMT): a gene contributing to sex differences in brain function, and to sexual dimorphism in the predisposition to psychiatric disorders. *Neuropsychopharmacology*. Dec 2008;33(13):3037-45. doi:10.1038/sj.npp.1301543
13. Butcher NJ, Boot E, Lang AE, et al. Neuropsychiatric expression and catatonia in 22q11.2 deletion syndrome: An overview and case series. *Am J Med Genet A*. Oct 2018;176(10):2146-2159. doi:10.1002/ajmg.a.38708
14. Boot E, Marras C, Bassett AS. Spectrum of movement disorders and motor abnormalities in adults with a 22q11.2 microdeletion: Comment on the literature and retrospective study of 92 adults. *Eur J Hum Genet*. Dec 2022;30(12):1314-1317. doi:10.1038/s41431-022-01152-4
15. Schneider M, Debbané M, Bassett AS, et al. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *Am J Psychiatry*. Jun 2014;171(6):627-39. doi:10.1176/appi.ajp.2013.13070864
16. Bloem BR, Okun MS, Klein C. Parkinson's disease. *Lancet*. Jun 12 2021;397(10291):2284-2303. doi:10.1016/s0140-6736(21)00218-x
17. Booij J, van Amelsvoort T, Boot E. Co-occurrence of early-onset Parkinson disease and 22q11.2 deletion syndrome: Potential role for dopamine transporter imaging. *Am J Med Genet A*. Nov 2010;152a(11):2937-8. doi:10.1002/ajmg.a.33665
18. Rafferty MR, Schmidt PN, Luo ST, et al. Regular Exercise, Quality of Life, and Mobility in Parkinson's Disease: A Longitudinal Analysis of National Parkinson Foundation Quality Improvement Initiative Data. *J Parkinsons Dis*. 2017;7(1):193-202. doi:10.3233/jpd-160912

19. Boulos C, Yaghi N, El Hayeck R, Heraoui GN, Fakhoury-Sayegh N. Nutritional Risk Factors, Microbiota and Parkinson's Disease: What Is the Current Evidence? *Nutrients*. Aug 14 2019;11(8)doi:10.3390/nu11081896
20. Giladi N, Mirelman A, Thaler A, Bar-Shira A, Gurevich T, Orr-Urtreger A. Fighting the risk of developing Parkinson's disease; clinical counseling for first degree relatives of patients with Parkinson's disease. *J Neurol Sci*. Nov 15 2011;310(1-2):17-20. doi:10.1016/j.jns.2011.06.005
21. Mulhern M, Bier L, Alcalay RN, Balwani M. Patients' Opinions on Genetic Counseling on the Increased Risk of Parkinson Disease among Gaucher Disease Carriers. *J Genet Couns*. Jun 2018;27(3):675-680. doi:10.1007/s10897-017-0161-0
22. Tsou AY, Bulova P, Capone G, et al. Medical Care of Adults With Down Syndrome: A Clinical Guideline. *JAMA*. 2020;324(15):1543-1556. doi:10.1001/jama.2020.17024
23. Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. *Nat Rev Dis Primers*. Mar 23 2017;3:17013. doi:10.1038/nrdp.2017.13
24. Moberg PJ, Turetsky BI, Moberg EA, et al. Meta-analysis of olfactory dysfunction in 22q11.2 deletion syndrome. *Psychiatry Res*. Jan 16 2020;285:112783. doi:10.1016/j.psychres.2020.112783
25. Bassett AS, Chow EW, Husted J, et al. Clinical features of 78 adults with 22q11 Deletion Syndrome. *Am J Med Genet A*. Nov 1 2005;138(4):307-13. doi:10.1002/ajmg.a.30984
26. Buckley E, Siddique A, McNeill A. Hyposmia, symptoms of rapid eye movement sleep behavior disorder, and parkinsonian motor signs suggest prodromal neurodegeneration in 22q11 deletion syndrome. *Neuroreport*. Aug 2 2017;28(11):677-681. doi:10.1097/wnr.0000000000000815
27. Mauro J, Diaz M, Córdova T, et al. Analysis of REM sleep without atonia in 22q11.2 deletion syndrome determined by domiciliary polysomnography: a cross sectional study. *Sleep*. 2022;45(2):zsab300. doi:10.1093/sleep/zsab300
28. Nalls MA, Blauwendraat C, Vallerga CL, et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. *The Lancet Neurology*. 2019/12/01/ 2019;18(12):1091-1102. doi:https://doi.org/10.1016/S1474-4422(19)30320-5
29. Blauwendraat C, Nalls MA, Singleton AB. The genetic architecture of Parkinson's disease. *Lancet Neurol*. Feb 2020;19(2):170-178. doi:10.1016/s1474-4422(19)30287-x
30. Ross OA, Braithwaite AT, Skipper LM, et al. Genomic investigation of alpha-synuclein multiplication and parkinsonism. *Ann Neurol*. Jun 2008;63(6):743-50. doi:10.1002/ana.21380
31. von Scheibler E, van Eeghen AM, de Koning TJ, et al. Parkinsonism in Genetic Neurodevelopmental Disorders: A Systematic Review. *Mov Disord Clin Pract*. Jan 2023;10(1):17-31. doi:10.1002/mdc3.13577
32. Chia SJ, Tan EK, Chao YX. Historical Perspective: Models of Parkinson's Disease. *Int J Mol Sci*. Apr 2 2020;21(7)doi:10.3390/ijms21072464
33. Sumitomo A, Horike K, Hirai K, et al. A mouse model of 22q11.2 deletions: Molecular and behavioral signatures of Parkinson's disease and schizophrenia. *Sci Adv*. Aug 2018;4(8):eaar6637. doi:10.1126/sciadv.aar6637
34. Hirsch L, Jette N, Frolkis A, Steeves T, Pringsheim T. The Incidence of Parkinson's Disease: A Systematic Review and Meta-Analysis. *Neuroepidemiology*. 2016;46(4):292-300. doi:10.1159/000445751

Supplementary

Supplementary Table 1. Demographic data and patient characteristics of adults with 22q11.2DS

	N/856	Years
Median age at death, y	75	47.0 (18-76)
	N/856	%
Site of inclusion		
Dalglish Family 22q clinic, Toronto, Canada	413	48.2
University Hospital Leuven, Belgium	244	28.5
's Heeren Loo, Amersfoort, The Netherlands	82	9.6
Maastricht University Medical Centre+, The Netherlands	80	9.3
University of Santiago, Chile	37	4.3
	N/420	%
Intellectual functioning		
Normal	48	11.4
Borderline	115	27.4
Mild intellectual disability	162	38.6
Moderate intellectual disability	83	19.8
Severe intellectual disability	12	2.9
	N/442	%
History of anti-psychotic medication	97	21.9

22q11.2DS= 22q11.2 deletion syndrome, n=number.

Chapter 4

Hearing loss and history of otolaryngologic conditions in adults with microdeletion 22q11.2

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Submitted

Abstract

Previous studies have shown that the 22q11.2 microdeletion, associated with 22q11.2 deletion syndrome (22q11.2DS), conveys an increased risk of chronic otitis media and hearing loss at young age. This study reports on hearing loss and history of otolaryngologic conditions in adults with 22q11.2DS. Therefore, we conducted a retrospective study of 60 adults with 22q11.2DS (41.7% male) at median age 25 (range 16-74) years who had visited an otolaryngologist and audiologist for routine assessment at an 22q11.2 expert center. Demographic, genetic, audiometric, and otolaryngologic data were systematically extracted from the medical files. Regression analysis was used to evaluate the effect of age, sex, full-scale intelligence quotient and history of chronic otitis media on the severity of hearing loss. Hearing loss, mostly high-frequency sensorineural, was found in 78.3% of adults. Higher age and history of chronic otitis media were associated with more severe hearing loss. Otolaryngologic conditions with possible treatment implications included chronic otitis media (56.7%), globus pharyngeus (18.3%), balance problems (16.7%) and obstructive sleep apnea (8.3%). In conclusion, in 22q11.2DS, high-frequency hearing loss appears to be common from a young adult age, and often unrecognized. Therefore, we recommend periodic audiometric screening in all adults, including high-frequency ranges.

Introduction

The 22q11.2 deletion syndrome (22q11.2DS) is a multisystem disorder with an estimated prevalence of 1 in 2148 live births, and is caused by recurrent heterozygous microdeletions on chromosome 22q11.2.[1, 2] The majority (~85%) of individuals with 22q11.2DS have a *de novo* deletion[1]. Individuals with 22q11.2DS show a marked variability in clinical manifestations, that may include palatal abnormalities, congenital heart defects, intellectual disability, and an increased risk of developing psychiatric disorders (e.g., schizophrenia) and neurodegenerative disorders that may present at young age (e.g., early-onset Parkinson's disease).[3-6] Previous studies in 22q11.2DS, mainly performed in children, have indicated an increased prevalence of hearing loss (6-60%), with a predominance of the conductive type (6-53%), most likely related to otitis media and Eustachian tube dysfunction.[7] However, little is known about hearing loss in adults with 22q11.2DS.[3, 8]

Therefore, we aimed to study the prevalence and predictors of hearing loss in adults with 22q11.2DS. We hypothesized that the severity of hearing loss would be greater in those with higher age, with history of chronic otitis media, and with lower full-scale IQ (FSIQ), based on previous research.[9-11] Secondary aims were to investigate lifetime history of other otolaryngological conditions in 22q11.2DS.

Methods

Editorial Policies and Ethical Considerations

The study was approved by the Medical Ethics Review Board of MUMC+ (#2019-1440, METC 19-044/NL70681.068.19) that waived the need for written consent to use pseudonymized clinical data.

Study design and setting

This was a retrospective study of otolaryngological conditions in patients who visited the Dutch expert clinic for adults with 22q11.2DS at Maastricht University Medical Center+ (MUMC+), The Netherlands, between January 2016 and April 2023.

Participants and data sources

We included 60 adults (25 male) aged 16 years and older with a molecularly confirmed 22q11.2 deletion that included the LCR22A-LCR22B region, using standard methods.[1] Participants were ascertained through referrals from general practice (n=21), pediatrics (n=15), intellectual disability medicine (n=11), clinical genetics (n=5), psychiatry (n=5), neurology (n=1), internal medicine (n=1), and otolaryngology (n=1). In one patient, reasons for referral included otolaryngological problems, i.e., globus pharyngeus. We excluded subjects with no audiometry data (n=3), including one 39-year-old female with history of hearing loss and hearing aids.

We used available medical information to record data on demographics, molecular diagnosis, lifetime history of otolaryngological conditions, and most recent FSIQ score. All adults were routinely evaluated by an otolaryngologist and audiologist. Standard examinations included a semi-structured interview, a complete ear-nose and throat examination, and audiometric testing. Two had their most recent audiogram at MUMC+ before 2016.

Audiological assessments

Data for audiological assessments included pure-tone air and bone-conduction audiometry. Unaided ear-specific hearing thresholds were measured from 0.25 to 8 kHz with pure-tone audiometry. Presence/absence and severity of hearing loss were classified with the Muenster classification because this classification includes criteria for high-frequency hearing loss (Table 1),[12] that was often found in adults with 22q11.2DS. Thus, hearing loss was defined as having loss with a severity of grade two or higher.[12] Type and laterality of hearing loss, frequency ranges and audiometric configuration were classified using the European Working Group on the Genetics of Hearing Impairment definitions.[13] Because most audiometric abnormalities in the 22q11.2DS sample concerned the high-frequencies, adaptations were made to these definitions, i.e.: 1) we averaged the pure-tone hearing thresholds over 0.5, 1, 2 and 4 kHz instead of 0.5, 1 and 2 kHz, to define type and laterality of hearing loss, 2) we introduced u-shaped configurations in order to classify individuals that performed best at the mid-frequencies, and 3) in addition to the standard criteria for gently and

steeply sloping, we considered audiometric configurations showing a decrease of ≥15-29 dB HL or ≥30 dB HL between 4 and 8 kHz gently- and steeply-sloping as well (Table 1).

Tympanometry

If deemed to be indicated (n=24; 40%), tympanometry was used to measure the tympanic membrane's response to changes in pressure in order to detect effusion or depression in the middle ear. Abnormal responses were classified using the Jerger classification that was adapted for adults.[14]

Statistical analyses

For hearing loss and history of otolaryngological conditions, we calculated prevalence rates and related 95% confidence intervals (CI) using the formula CI= p ± 1.96* √(p(1-p)/n). We calculated the prevalence of hearing loss of at least one ear, in addition to the better-hearing ear. We used ordinal regression analysis to evaluate the effect of age, sex, FSIQ and history of chronic otitis media on the severity of hearing loss of the better-hearing ear according to the Muenster classification. Mathematica (Wolfgang mathematica 13.2, Oxfordshire, United Kingdom) was used to plot the sensory thresholds (dB HL) in adults with 22q11.2DS at 0.25, 0.5, 1, 2, 4 and 8 kHz, relative to 50th and 90th percentiles in the general population.[15] Two-tailed p-values <0.05 were considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics 25 (SPSS Inc., Chicago, Illinois, USA).

Table 1. Definitions

Hearing loss, grading of severity [a]	
Normal or borderline hearing (0-1)	≤20 dB HL over all frequencies
Loss, limited to high-frequencies (2)	≥4 kHz >20 dB HL
Mild (2a)	>20 ≤40 dB HL
Moderate (2b)	>40 ≤60 dB HL
Severe (2c)	>60 dB HL
Loss, corrigible with hearing aids (3)	<4 kHz >20 dB HL
Mild (3a)	>20 ≤ 40 dB HL
Moderate (3b)	>40 ≤ 60 dB HL
Severe (3c)	>60 dB HL

Table 1. continued

Hearing loss, grading of severity [a]	
Type of hearing loss [b]	
Conductive	Normal BC thresholds (<20 dB HL) and ABG >15 dB averaged over 0.5, 1, 2 and 4 kHz
Sensorineural	BC thresholds >20 dB HL and ABG <15 dB HL averaged over 0.5, 1, 2 and 4 kHz
Mixed	BC thresholds >20 dB HL and ABG >15 dB averaged over 0.5, 1, 2 and 4 kHz
Audiometric configuration [b]	
Low-frequency ascending	>15 dB HL difference between the worst low frequency thresholds and the better high frequency thresholds
Mid-frequency n-shaped	>15 dB HL difference between the worst mid frequency thresholds and the better low and high frequency thresholds
High-frequency	
Gently sloping	15-29 dB HL difference between the mean of 0.5 and 1 kHz and the mean of 4 and 8 kHz, or 15 -29 dB HL between 4 and 8 kHz
Steeply sloping	≥30 dB HL difference between the above frequencies or ≥30 dB HL between 4 kHz and 8 kHz
Flat	<15 dB HL difference between the mean of 0.25 and 1 kHz, the mean of 1 and 2 kHz, and the mean of 4 and 8 kHz
Frequency ranges	
Low frequencies	≤0.5 kHz
Mid frequencies	>0.5 kHz and ≤2 kHz
High frequencies	>2 kHz and ≤8 kHz
Symmetry of hearing impairment	
Unilateral	>10 dB HL difference between the ears in at least two frequencies <20 dB HL average over 0.5, 1, 2 and 4 kHz of the better ear
Bilateral symmetrical	<10 dB HL difference between the ears in at least two frequencies. Average over 0.5, 1, 2 and 4 kHz of both ears >20 dB
Bilateral asymmetrical	>10 dB HL difference between the ears in at least two frequencies >20 dB HL average over 0.5, 1 ,2 and 4 kHz of the better ear

[a]=increasing severity of hearing loss according to the Muenster classification,[12] [b]=of the better-hearing ear. Adapted from the definitions by the European Working Group on the Genetics of Hearing Impairment (See methods section for details),[13] HL=hearing level, kHz=kilo Hertz, ABG=air-bone gap, BC=bone-conduction.

Results

Demographics

Sixty adults (25 male, 41.7%) with 22q11.2DS were included. The median age at audiometry was 24.5 (range 16-62) years and the median age at otolaryngologic examination was 25.0 (range 16-74) years. Mean FSIQ scores, available for 57 adults, were 65.3±11.1 at median age 23.0 (range 13-57) years.

Table 2. Hearing loss in 60 adults with 22q11.2 deletion syndrome

Prevalence of hearing loss	number	%	95% CI
Hearing loss, ≥ 1 ear [a]	47	78.3	67.9 – 88.8
Hearing loss, better-hearing ear [a]	39	65.0	52.9 – 77.1
limited to high-frequencies (2)	25	41.7	29.2 – 54.1
Mild (2a)	16	26.7	15.5 – 37.9
Moderate (2b)	7	11.7	3.5 – 19.8
Severe (2c)	2	4.3	0.0 – 7.9
Corrigible with hearing aids (3)	14	23.3	12.6 – 34.0
Mild (3a)	12	20.0	9.9 – 30.1
Moderate (3b)	1	1.7	0.0 – 4.9
Severe (3c)	1	1.7	0.0 – 4.9
Laterality of hearing loss			
Bilateral, symmetrical	24	40.0	27.6 – 52.4
Bilateral, asymmetrical	15	25.0	14.0 – 36.0
Unilateral	8	13.3	4.7 – 21.9
Type of hearing loss [b]			
Sensorineural	14	35.9	20.8 – 51.0
Conductive	5	12.8	2.3 – 23.3
Mixed	2	5.1	0.0 – 12.1
Undefined [c]	18	46.2	30.5 – 61.8
Audiometric configuration			
Flat	27	45.0	32.4 – 57.6
High-frequency steeply sloping	14	23.3	12.6 – 34.0
High-frequency gently sloping	11	18.3	8.5 – 28.1
Mid-frequency n-shaped	7	11.7	3.5 – 19.8
Low-frequency ascending	1	1.7	0.0 – 4.9

[a] severity according to the Muenster classification.[12]
[b] Proportions of a total of 39 adults with hearing loss of the better-hearing ear.
[c] Hearing loss limited to the high-frequencies could often not be classified due to missing bone conduction thresholds at 6 and 8 kHz.
CI=confidence interval.

Audiometry

Table 2 shows data on audiological assessments. Hearing loss in at least one ear was found in 47 adults (78.3%) of whom 8 had unilateral hearing loss. Of the better-hearing ear, 39 adults (65.0%) showed hearing loss that was mostly limited to the high-frequencies (n=25, 41.7%). In 14 adults (23.3%) more severe hearing loss was found that also included loss at the

mid-frequencies. Of those with hearing loss, sensorineural loss was most common (n=14, 35.9%). Because of missing bone conduction thresholds, that were not measured at 6 and 8 kHz, the type of hearing loss could not be established in 18 adults (46.2%). The audiometric configuration that was observed most, was flat (n=27, 45.0%, Figure 1).

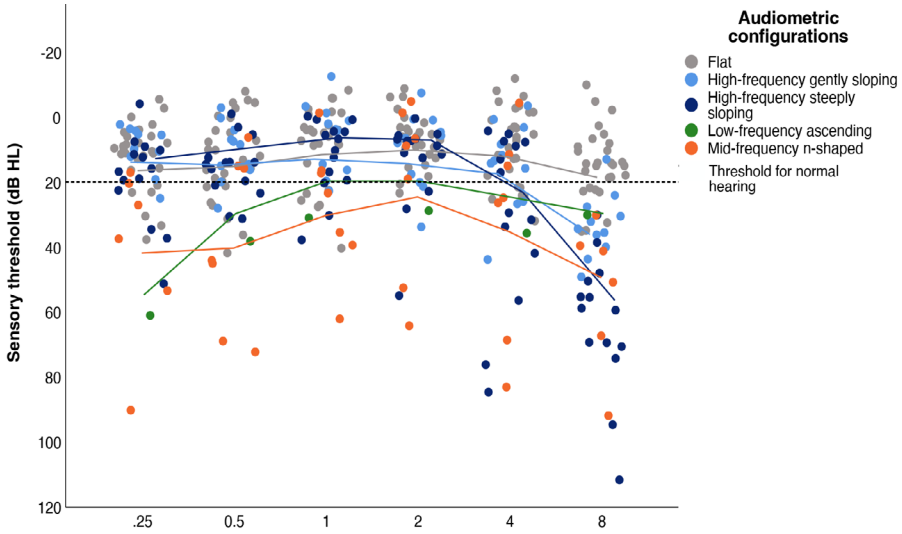

Figure 1. Audiometric configurations of 60 adults with 22q11.2 deletion syndrome.

Audiometric configurations were mostly flat (45%), or high-frequency steeply (23.3%) or gently (18.3%) sloping. Dotted horizontal line represents the threshold for normal hearing at 20 dB HL. dB HL=decibel hearing level, kHz=kilo Hertz.

Plots of individual sensory thresholds against the 90th and 50th percentile of normative data showed that the majority of adults with 22q11.2DS performed worse than the 90th percentile (Figure 2). For the mid-frequency of 1 kHz, 52 adults (86.7%) scored worse than the 50th and 25 (41.7%) scored worse than the 90th percentile of normative data. At 8 kHz, 56 adults (93.3%) scored worse than the 50th percentile and 55 (91.7%) had sensory thresholds above the 90th percentile.

Tympanometry

Tympanometry was performed in 24 adults (40.0%) for the better-hearing ear. Most (n=13, 54.2%) had a normal tympanogram (type A) as per the Jerger classification for adults,[14] 5 (20.8%) had normal admittance with the

peak occurring at a negative middle ear pressure (type C), 3 (12.5%) had abnormally high admittance with normal tympanometric pressure (type Ad), 2 (8.3%) had abnormally low admittance with no discernable peak (type B), and 1 (4.2%) had abnormally low admittance with normal tympanometric pressure (type As).

Otolaryngological conditions and treatments

The majority of the study sample had history of one or more otolaryngological conditions (Table 3). Chronic/recurrent otitis media was reported most often (n=34, 56.7%), followed by hearing loss (n=19, 31.7%), globus pharyngeus (n=11, 18.3%), balance problems (n=10, 16.7%), swallowing difficulties (n=6, 10.0), obstructive sleep apnea (OSA, n=5, 8.3%), and nasal regurgitation (n=5, 8.3%).

Table 3. Lifetime history of otolaryngological conditions and treatments in 60 adults with 22q11.2 deletion syndrome

Conditions	Number	%	95% CI
Chronic/recurrent otitis media	34	56.7	44.1 – 69.2
Hearing loss	19	31.7	19.9 – 43.4
Globus pharyngeus	11	18.3	8.5 – 28.1
Balance problems	10	16.7	7.2 – 26.1
Swallowing difficulties	6	10.0	2.4 – 17.6
Obstructive sleep apnea	5	8.3	1.3 – 15.3
Nasal regurgitation	5	8.3	1.3 – 15.3
Treatments	**Number**	**%**	**95% CI**
Speech-language therapy [a]	47	78.3	67.9 – 88.8
Speech	40	66.7	54.7 – 78.6
Feeding/swallowing	7	11.7	3.5 – 19.8
Indication not specified	7	11.7	3.5 – 19.8
ENT-surgery	43	71.7	60.3 – 83.1
Ear tube placement	23	38.3	26.0 – 50.6
Pharyngoplasty	17	28.3	16.9 – 39.7
Tonsillectomy	9	15.0	6.0 – 24.0
Tympanoplasty/myringoplasty	9	15.0	6.0 – 24.0
Palatoplasty	7	11.7	3.5 – 19.8
Adenotomy	6	10.0	2.4 – 17.6
Nose/septum surgery	2	3.3	0.0 – 7.9
Ear reconstruction surgery	2	3.3	0.0 – 7.9
Laryngeal web resection	1	1.7	0.0 – 4.9
Tracheotomy and vocal cord surgery	1	1.7	0.0 – 4.9
Mastoidectomy	1	1.7	0.0 – 4.9
Hearing aid	5	8.3	1.3 – 15.3
Bilateral	4	6.7	0.3 – 13.0
Unilateral	1	1.7	0.0 – 4.9

[a] Seven adults with 22q11.2DS received speech-language therapy for both speech and feeding/swallowing issues. ENT=ear-nose-throat, CI=confidence interval.

Most adults had received speech therapy (n=47, 78.3%). Ear tube placement was the most reported surgical intervention (n=23, 38.3%). Five adults (8.3%) had hearing aids prescribed prior to their visit (at age 57, 55, 32, 21 and 19 years), of whom 4 (6.7%) bilateral (Table 3). The 21-year-old female, and the excluded 39-year-old female, reported not to use the hearing aids. Another five adults (8.3%) were advised to consider hearing aids after audiologic examination. Treatments that were recommended after routine examination included muscle relaxation therapy for globus (n=4, 6.7%) and dysphagia (n=1, 1.7%), and balance exercises for benign paroxysmal positional vertigo (n=1, 1.7%). Additional examinations were recommended for sleep disorders (n=2, 3.3%; i.e., polysomnography) and vestibular dysfunction (n=1, 1.7%). Five adults were advised to start medication for otitis externa (n=2, 3.3%), rhinitis (n=2, 3.3%), and otitis media (n=1, 1.7%), respectively. Eight adults were advised to start (n=6, 10%) or continue (n=2, 3.3%) aural toileting for ear wax. Two adults (3.3%) qualified for surgical correction of nasal septum deviation.

Factors related to severity of hearing loss

The regression model predicting severity of hearing loss in 22q11.2DS was significant (p=0.002, Nagelkerke=0.29). Higher age (OR=1.08, 95% CI=1.03-1.12, Wald=11.30, p=0.001) and a history of chronic otitis media (OR=2.87, 95% CI=1.07-7.67, Wald=4.43, p=0.04), but not male sex (OR=0.65, 95% CI=0.24-1.73, Wald=0.74, p=0.39) or FSIQ (OR=0.99, 95% CI=0.95-1.03, Wald=0.26, p=0.61), were related to the severity of hearing loss.

Discussion

The results of this study involving a relatively young adult sample of 22q11.2DS indicate that a large proportion of adults with 22q11.2DS have hearing loss, mostly limited to the higher frequencies, and often unrecognized. Age and a history of chronic otitis media, but not sex or FSIQ, were positively related to the severity of hearing loss. Lifetime history of otolaryngologic conditions that were frequently reported included chronic otitis media, globus pharyngeus, swallowing difficulties, balance problems and OSA.

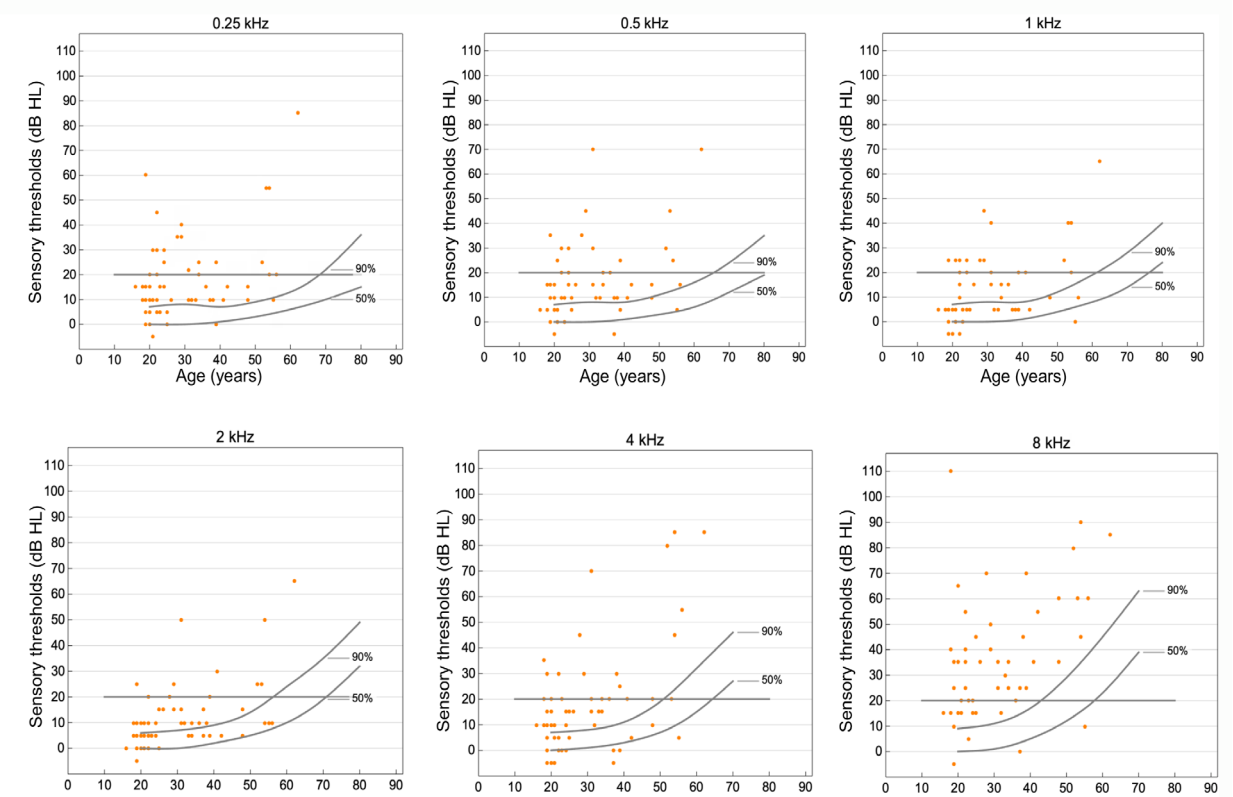

Figure 2. Individual sensory thresholds of the better-hearing ear in 60 adults with 22q11.2 deletion syndrome.

Individual sensory thresholds of the better-hearing ear plotted against 90th and 50th percentiles obtained from normative data for 0.25, 0.5, 1, 2, 4, and 8 kHz [15] Black horizontal lines indicate the threshold for normal hearing at 20 dB HL. dB HL=decibel hearing level, kHz=kilo Hertz.

Hearing loss

The proportion of adults with hearing loss (78.3%) was much higher in comparison to two previous studies in adults with 22q11.2DS that reported hearing loss in 28.5% and 40.9%, respectively.[3, 8] However, when interpreting the findings, it is important to take into account the study designs, definitions for hearing loss, and age and size of the samples in the different studies. The first study was a retrospective chart review in 78 adults at a mean age of 31.5±10.5 years, and included those with hearing loss reported in the medical records.[3] No audiological assessments were performed. The proportion of adults with a documented history of hearing loss was similar to this study (28.5% versus 31.7%). In the second study, 22 of 24 adults underwent an audiological assessment at a mean age of 25 (range 19-38) years.[8] The same definition for hearing loss was used as in this study. However, in the current study hearing was measured up to 8, instead of 6 kHz. Also, sensorineural hearing loss was found in 33.3% (n=3) of those with hearing loss, comparable to findings in the current study (35.9%). Unilateral conductive hearing loss was found in a much higher proportion of the participants (44.4% versus 12.8%) compared to this study. However, absolute numbers were low affecting reliability of those findings, and results were possibly influenced by a few younger participants.[8]

Another study, reporting on hearing in 40 children and adults at a mean age of 15 years (range 6 -36 years), who received audiological testing as part of the research study, found 60% of participants to have hearing loss in at least one ear, defined as >20 dB HL from 0.5-1-2 kHz.[16] Conductive hearing loss was the most common type (54%), sensorineural (4%) or mixed (2%) were found less often.[16] In line with results from our study, they did find high-frequency hearing loss in the majority of individuals, which was assumed to be of sensorineural origin.

Potential contributors to hearing loss in 22q11.2DS

There are several potential contributors to hearing loss in adults with 22q11DS.[7, 17] First, chronic otitis media, with or without congenital inner ear abnormalities,[18] may result in the cochlea being more vulnerable in individuals with 22q11.2DS compared to the general population.[7, 16] Second, early physiological degeneration and other medical conditions and their treatment, may lead to hearing loss.[19] Age-related disorders such as Parkinson's disease

and type 2 diabetes mellitus,[20, 21] and multimorbidity and polypharmacy are often seen in 22q11.2DS at a relatively young age.[22] Third, genetic susceptibility should be considered.[19] For example, young-onset and age-related hearing loss has been reported in other genetic neurodevelopmental disorders, such as in Down syndrome,[23] and Turner syndrome.[24] Importantly, findings may be specific per genetic variant. When comparing the sensory thresholds found in Turner syndrome to those reported in 22q11.2DS it is striking that adults with Turner syndrome scored worst at the mid-frequency (2 kHz),[25] whereas adults with 22q11.2DS performed best at the mid-frequencies and worst at the highest and lowest frequencies.

Genes that may possibly play a role in 22q11.2DS include *TBX1* and genes involved in mitochondrial function.[17, 26] *TBX1* is involved in the development of the vascular system including the stria vascularis (an important cochlear structure that is rich in vascular tissue), the central nervous system, and the semicircular canal.[17, 27] In mice with a homozygous missense mutation in *Tbx1* inner ear malformations, an undeveloped stria vascularis, and deafness have been found.[17] Other candidate genes include those involved in mitochondrial function; at least six lie within the 22q11.2 region.[28] Mitochondrial dysfunction and oxidative stress have been proposed as possible contributors to degenerative changes in the cochlear duct (i.e., in the stria vascularis, hair cells and neurons) which may result in age-related hearing loss.[26]

Clinical implications of the hearing findings

High-frequency hearing loss makes it more difficult to understand speech with background noise, for example during group conversations, and to localize sounds.[19] It often precedes, and is a predictor of, hearing loss at the lower frequencies.[29] Similarly, loss at the mid-frequencies may negatively affect daily life functioning by reduced understanding of speech or hearing in traffic. If diagnosed late, hearing loss may contribute to the development of depressive symptoms, stress, anxiety, social isolation and reduced quality of life.[30, 31] Early identification of hearing loss enables interventions through adjustments to someone's work or living environment, and/or the prescription of hearing aids, if indicated. Therefore, given the high proportion of adults with 22q11.2DS with high-frequency hearing loss, we recommend periodic audiological screening (e.g., every five years), including high-frequency ranges (8 kHz), in all adults with 22q11.2DS.

History of otolaryngologic conditions

Chronic otitis media was reported most (56.7%), with an occurrence comparable to what was previously reported in 22q11.2DS.[7, 32] Globus pharyngeus was reported in 18.3%, and related to feelings of stress in some. Adults with globus may benefit from muscle relaxation therapy by a speech-language therapist.[33] Swallowing difficulties (10.0%) were often accompanied by globus and were mostly related to eating solid food such as dry meat. In a tertiary reference center for immunodeficiencies, a prospective cohort study of 25 children and adolescents with 22q11.2DS, that were all examined using videofluoroscopy, found swallowing anomalies in 16%, including hypopharyngeal residues after swallowing and nasal regurgitation.[32] Sixteen percent of the participants in that study had history of laryngeal aspiration.[32] In a study in infants with 22q11.2DS who were referred for swallow studies, 80% was found to have silent tracheal aspirations.[34] Another study in children reported a history of feeding difficulties in 35.5%. Using barium swallow studies, it became clear that dysmotility probably played an important role in these children.[35] In a mouse model of 22q11.2DS, feeding and swallowing difficulties at young age were found to persist in adult mice.[36] Balance problems, reported in 16.7%, may relate to abnormalities of the vestibulum, cerebellum, and/or proprioceptive system, lower muscle strength, and/or visual problems.[18, 37-39] Movement disorders, such as Parkinson's disease, may also be considered in older adults with 22q11.2DS.[37, 40] The occurrence of OSA was comparable to that previously reported in children and adults with 22q11.2DS.[41, 42] OSA can have a negative effect on quality of life, and may increase the risk of cardiometabolic diseases.[43] Given that OSA is a treatable condition, polysomnography should be considered with a low threshold.[44]

We recommend otolaryngologic examination at least once for adults with 22q11.2DS. Special attention should be paid to conditions that may present at adult age and may have treatment implications such as OSA, globus pharyngeus, dysphagia and vestibular dysfunction.

Strengths and limitations

To our knowledge, this is the largest sample of adults with 22q11.2DS who received audiometric testing and standardized otolaryngologic examinations. Limitations of the study mainly relate to the retrospective

design. On the one hand, data concerning the medical history may not be complete resulting in an underestimation of some otolaryngologic conditions. On the other hand, referral bias may have resulted in higher prevalence rates because individuals with 22q11.2DS with a more severe clinical presentation may be more likely to be referred to a 22q11 specialty clinic. In addition, some adults did not have audiometric results because of difficulties with performing the test or noncooperation, which may have influenced results. Last, due to missing bone conduction thresholds at higher frequencies, the type of hearing impairment could not be established for some adults with 22q11.2DS, mainly those with loss limited to the higher frequencies, probably resulting in an underestimation of sensorineural hearing loss.

Conclusions

Hearing loss at a relatively young age, especially at the higher frequencies, appears to be common in adults with 22q11.2DS. Higher age and history of chronic otitis media are associated with more severe hearing loss. Therefore, we recommend periodic audiometric screening, including high-frequency testing (8 kHz), from early adulthood in all adults with 22q11.2DS.

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Disclosures

The authors declare no conflicts of interest.

Data availability statement

The data are not publicly available due to privacy and ethical restrictions. Any data requests can be directed to the corresponding author.

References

1. McDonald-McGinn DM, Sullivan KE, Marino B, et al. 22q11.2 deletion syndrome. *Nat Rev Dis Primers*. Nov 19 2015;1:15071. doi:10.1038/nrdp.2015.71
2. Blagojevic C, Heung T, Theriault M, et al. Estimate of the contemporary live-birth prevalence of recurrent 22q11.2 deletions: a cross-sectional analysis from population-based newborn screening. *CMAJ Open*. Jul-Sep 2021;9(3):E802-e809. doi:10.9778/cmajo.20200294
3. Bassett AS, Chow EW, Husted J, et al. Clinical features of 78 adults with 22q11 Deletion Syndrome. *Am J Med Genet A*. Nov 1 2005;138(4):307-13. doi:10.1002/ajmg.a.30984
4. Campbell IM, Sheppard SE, Crowley TB, et al. What is new with 22q? An update from the 22q and You Center at the Children's Hospital of Philadelphia. *Am J Med Genet A*. Oct 2018;176(10):2058-2069. doi:10.1002/ajmg.a.40637
5. Schneider M, Debbané M, Bassett AS, et al. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *Am J Psychiatry*. Jun 2014;171(6):627-39. doi:10.1176/appi.ajp.2013.13070864
6. Boot E, Bassett AS, Marras C. 22q11.2 Deletion Syndrome-Associated Parkinson's Disease. *Mov Disord Clin Pract*. Jan 2019;6(1):11-16. doi:10.1002/mdc3.12687
7. Verheij E, Derks LSM, Stegeman I, Thomeer H. Prevalence of hearing loss and clinical otologic manifestations in patients with 22q11.2 deletion syndrome: A literature review. *Clin Otolaryngol*. Dec 2017;42(6):1319-1328. doi:10.1111/coa.12874
8. Persson C, Friman V, Óskarsdóttir S, Jönsson R. Speech and hearing in adults with 22q11.2 deletion syndrome. *Am J Med Genet A*. Dec 2012;158a(12):3071-9. doi:10.1002/ajmg.a.35589
9. Golub JS, Brickman AM, Ciarleglio AJ, Schupf N, Luchsinger JA. Association of Subclinical Hearing Loss With Cognitive Performance. *JAMA Otolaryngol Head Neck Surg*. Jan 1 2020;146(1):57-67. doi:10.1001/jamaoto.2019.3375
10. Golub JS, Brickman AM, Ciarleglio AJ, Schupf N, Luchsinger JA. Audiometric Age-Related Hearing Loss and Cognition in the Hispanic Community Health Study. *J Gerontol A Biol Sci Med Sci*. Feb 14 2020;75(3):552-560. doi:10.1093/gerona/glz119
11. Zarchi O, Attias J, Raveh E, Basel-Vanagaite L, Saporta L, Gothelf D. A comparative study of hearing loss in two microdeletion syndromes: velocardiofacial (22q11.2 deletion) and Williams (7q11.23 deletion) syndromes. *J Pediatr*. Feb 2011;158(2):301-6. doi:10.1016/j.jpeds.2010.07.056
12. Schmidt CM, Bartholomäus E, Deuster D, Heinecke A, Dinnesen AG. [The "Muenster classification" of high frequency hearing loss following cisplatin chemotherapy]. *Hno*. Apr 2007;55(4):299-306. Die "Münsteraner Klassifikation": Eine neue Einteilung der Hochtonschwerhörigkeit nach Cisplatingabe. doi:10.1007/s00106-005-1368-1
13. Mazzoli M, Camp GUY, Newton V, Declau F, Parving A. Recommendations for the Description of Genetic and Audiological Data for Families with Nonsyndromic Hereditary Hearing Impairment. *Audiological Medicine*. 07/11 2009;1:148-150. doi:10.1080/16513860301713
14. Margolis RH, Heller JW. Screening tympanometry: criteria for medical referral. *Audiology*. 1987;26(4):197-208. doi:10.3109/00206098709081549
15. ISO. *Acoustics — Statistical distribution of hearing thresholds related to age and gender*. 2017. *7029:2017* https://www.iso.org/standard/42916.html
16. Van Eynde C, Swillen A, Lambeens E, et al. Prevalence and Nature of Hearing Loss in 22q11.2 Deletion Syndrome. *J Speech Lang Hear Res*. Jun 1 2016;59(3):583-9. doi:10.1044/2015_jslhr-h-15-0098
17. Tian C, Johnson KR. TBX1 is required for normal stria vascularis and semicircular canal development. *Dev Biol*. Jan 1 2020;457(1):91-103. doi:10.1016/j.ydbio.2019.09.013
18. Loos E, Verhaert N, Willaert A, et al. Malformations of the middle and inner ear on CT imaging in 22q11 deletion syndrome. *Am J Med Genet A*. Nov 2016;170(11):2975-2983. doi:10.1002/ajmg.a.37872
19. Huang Q, Tang J. Age-related hearing loss or presbycusis. *Eur Arch Otorhinolaryngol*. Aug 2010;267(8):1179-91. doi:10.1007/s00405-010-1270-7
20. Boot E, Butcher NJ, Udow S, et al. Typical features of Parkinson disease and diagnostic challenges with microdeletion 22q11.2. *Neurology*. Jun 5 2018;90(23):e2059-e2067. doi:10.1212/wnl.0000000000005660
21. Van L, Heung T, Malecki SL, et al. 22q11.2 microdeletion and increased risk for type 2 diabetes. *EClinicalMedicine*. Sep 2020;26:100528. doi:10.1016/j.eclinm.2020.100528

22. Malecki SL, Van Mil S, Graffi J, et al. A genetic model for multimorbidity in young adults. *Genet Med*. Jan 2020;22(1):132-141. doi:10.1038/s41436-019-0603-1
23. Picciotti PM, Carfì A, Anzivino R, et al. Audiologic Assessment in Adults With Down Syndrome. *Am J Intellect Dev Disabil*. Jul 2017;122(4):333-341. doi:10.1352/1944-7558-122.4.333
24. Bonnard Å, Hederstierna C, Bark R, Hultcrantz M. Audiometric features in young adults with Turner syndrome. *Int J Audiol*. Sep 2017;56(9):650-656. doi:10.1080/14992027.2017.1314559
25. King KA, Makishima T, Zalewski CK, et al. Analysis of auditory phenotype and karyotype in 200 females with Turner syndrome. *Ear Hear*. Dec 2007;28(6):831-41. doi:10.1097/AUD.0b013e318157677f
26. Keithley EM. Pathology and mechanisms of cochlear aging. *J Neurosci Res*. Sep 2020;98(9):1674-1684. doi:10.1002/jnr.24439
27. Baldini A, Fulcoli FG, Illingworth E. Tbx1: Transcriptional and Developmental Functions. *Curr Top Dev Biol*. 2017;122:223-243. doi:10.1016/bs.ctdb.2016.08.002
28. Motahari Z, Moody SA, Maynard TM, LaMantia AS. In the line-up: deleted genes associated with DiGeorge/22q11.2 deletion syndrome: are they all suspects? *J Neurodev Disord*. Jun 7 2019;11(1):7. doi:10.1186/s11689-019-9267-z
29. Dubno JR, Eckert MA, Lee FS, Matthews LJ, Schmiedt RA. Classifying human audiometric phenotypes of age-related hearing loss from animal models. *J Assoc Res Otolaryngol*. Oct 2013;14(5):687-701. doi:10.1007/s10162-013-0396-x
30. Chia EM, Wang JJ, Rochtchina E, Cumming RR, Newall P, Mitchell P. Hearing impairment and health-related quality of life: the Blue Mountains Hearing Study. *Ear Hear*. Apr 2007;28(2):187-95. doi:10.1097/AUD.0b013e31803126b6
31. Jayakody DMP, Almeida OP, Speelman CP, et al. Association between speech and high-frequency hearing loss and depression, anxiety and stress in older adults. *Maturitas*. Apr 2018;110:86-91. doi:10.1016/j.maturitas.2018.02.002
32. Grasso F, Cirillo E, Quaremba G, et al. Otolaryngological features in a cohort of patients affected with 22q11.2 deletion syndrome: A monocentric survey. *Am J Med Genet A*. Oct 2018;176(10):2128-2134. doi:10.1002/ajmg.a.40518
33. Khalil HS, Bridger MW, Hilton-Pierce M, Vincent J. The use of speech therapy in the treatment of globus pharyngeus patients. A randomised controlled trial. *Rev Laryngol Otol Rhinol (Bord)*. 2003;124(3):187-90.
34. Wong NS, Feng Z, Rappazzo C, Turk C, Randall C, Ongkasuwan J. Patterns of Dysphagia and Airway Protection in Infants with 22q11.2-Deletion Syndrome. *Laryngoscope*. Nov 2020;130(11):2532-2536. doi:10.1002/lary.28317
35. Eicher PS, McDonald-Mcginn DM, Fox CA, Driscoll DA, Emanuel BS, Zackai EH. Dysphagia in children with a 22q11.2 deletion: unusual pattern found on modified barium swallow. *J Pediatr*. Aug 2000;137(2):158-64. doi:10.1067/mpd.2000.105356
36. Welby L, Caudill H, Yitsege G, et al. Persistent Feeding and Swallowing Deficits in a Mouse Model of 22q11.2 Deletion Syndrome. *Front Neurol*. 2020;11:4. doi:10.3389/fneur.2020.00004
37. Willaert A, Van Eynde C, Verhaert N, et al. Vestibular dysfunction is a manifestation of 22q11.2 deletion syndrome. *Am J Med Genet A*. Mar 2019;179(3):448-454. doi:10.1002/ajmg.a.7
38. Rogdaki M, Gudbrandsen M, McCutcheon RA, et al. Magnitude and heterogeneity of brain structural abnormalities in 22q11.2 deletion syndrome: a meta-analysis. *Mol Psychiatry*. Aug 2020;25(8):1704-1717. doi:10.1038/s41380-019-0638-3
39. Enkelaar L, Smulders E, van Schrojenstein Lantman-de Valk H, Geurts AC, Weerdesteyn V. A review of balance and gait capacities in relation to falls in persons with intellectual disability. *Res Dev Disabil*. Jan-Feb 2012;33(1):291-306. doi:10.1016/j.ridd.2011.08.028
40. Boot E, Marras C, Bassett AS. Spectrum of movement disorders and motor abnormalities in adults with a 22q11.2 microdeletion: Comment on the literature and retrospective study of 92 adults. *Eur J Hum Genet*. Dec 2022;30(12):1314-1317. doi:10.1038/s41431-022-01152-4
41. Cancelliere S, Heung T, Fischbach S, Klaiman P, Bassett AS. Adult-onset obstructive sleep apnea and pediatric pharyngoplasty in 22q11.2 deletion syndrome. *Sleep Med*. Apr 2023;104:49-55. doi:10.1016/j.sleep.2023.02.010
42. Kennedy WP, Mudd PA, Maguire MA, et al. 22q11.2 Deletion syndrome and obstructive sleep apnea. *International Journal of Pediatric Otorhinolaryngology*. 2014/08/01/ 2014;78(8):1360-1364. doi:https://doi.org/10.1016/j.ijporl.2014.05.031
43. Gottlieb DJ, Punjabi NM. Diagnosis and Management of Obstructive Sleep Apnea: A Review. *JAMA*. 2020;323(14):1389-1400. doi:10.1001/jama.2020.3514
44. Boot E, Óskarsdóttir S, Loo JCY, et al. Updated clinical practice recommendations for managing adults with 22q11.2 deletion syndrome. *Genet Med*. Mar 2023;25(3):100344. doi:10.1016/j.gim.2022.11.012

Chapter 5

Ocular findings in 22q11.2 deletion syndrome: A systematic literature review and results of a Dutch multicenter study

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Abstract

The 22q11.2 deletion syndrome (22q11.2DS) is a multi-system disorder with an estimated prevalence of 1:3000 live births. Manifestations show a marked variability in expression and include speech- and language delay, intellectual disability and neuropsychiatric disorders. We aim to provide an overview of ocular findings in 22q11.2DS in order to optimize recommendations for ophthalmic screening. Therefore, we combined results from a systematic literature review with results from a multicenter cross-sectional study of patients with 22q11.2DS who were assessed by an ophthalmologist. Our systematic literature search yielded four articles, describing 270 patients. We included 132 patients in our cross-sectional study (median age 8.9 (range 0-56) years). Most reported ocular findings were retinal vascular tortuosity (32-78%), posterior embryotoxon (22-50%), eye lid hooding (20-67%), strabismus (12-36%), amblyopia (2-11%), ptosis (4-6%) and refractive errors, of which hyperopia (6-48%) and astigmatism (3-23%) were most common. Visual acuity was (near) normal in most patients (91-94%). In conclusion, refractive errors, strabismus and amblyopia are treatable conditions that are frequently present in patients with 22q11.2DS and should be corrected at an early stage. Therefore, in 22q11.2DS, we recommend ophthalmic and orthoptic screening at the age of three years or at diagnosis, and a low-threshold referral in adults.

Introduction

The 22q11.2 deletion syndrome (22q11.2DS) is a multisystem disorder with an estimated prevalence of 1 in 3000 live births.[1] Patients show a marked variability in the clinical expression. Well-known manifestations include speech-language and developmental delay, intellectual disability and an increased risk of developing psychiatric disorders such as schizophrenia and anxiety disorders.[2-4] Sensory dysfunction has been described as well. For example, hearing loss is frequently reported in 22q11.2DS and large deficits in olfactory function have been described in several studies.[5, 6] A number of studies have reported on ocular findings in 22q11.2DS, mainly focusing on children.[7-9]

The aim of this study is to provide a systematic review of the literature on ocular findings in patients with 22q11.2DS and to present the results of a Dutch multicenter cross-sectional study of children and adults with 22q11.2DS in order to provide recommendations for ophthalmic screening in 22q11.2DS.

Patients and Methods

Systematic review of the literature

Search strategy and study selection

On January 14th 2021, we performed a systematic literature search in PubMed, Embase and Cochrane medical databases (See Supplementary 1 for details). After removing duplicates, titles and abstracts were independently screened by two reviewers (EV, MN and/or EVS). Subsequently, full-text articles were assessed for eligibility by the three reviewers. All studies that reported on ocular findings, that were assessed by a physician specialized in ophthalmology, in patients with 22q11.2DS were included. We excluded research reporting on patients with a clinical diagnosis of 22q11.2DS, velocardiofacial syndrome, or DiGeorge syndrome, that lacked molecular confirmation. We excluded studies that did not provide prevalence rates for specific ocular findings. Reviews, case studies, conference abstracts and non-human studies were excluded. Discrepancies between authors were

resolved by discussion. Reference lists of the included studies were hand-searched for additional relevant articles.

Quality assessment

To assess the relevance and validity of the included articles, we performed a critical appraisal using the Risk of bias assessment tool for prevalence studies,[10] which was adapted and specified to our research question (See Supplementary 2). The quality of the studies was assessed independently by two reviewers (EV, MN and/or EVS) and discrepancies were resolved by discussion. In the absence of reference scores, we decided to exclude studies with a very high risk of bias (≥7/10 points) for data extraction. Risk of bias assessment included selection bias, standardization, measurement bias and non-response bias. In case of overlap of populations of the same research group, the study with the lowest risk of bias was included.

Data extraction

Data on visual acuity (VA), refractive errors, eye position and motility, eye lid abnormalities, biomicroscopic and fundoscopic results were extracted by one reviewer and verified by a second reviewer. VA measurements were transformed to logarithm of the minimum angle of resolution (LogMAR) for uniformity. We categorized VA as (near) normal (≤0.30 LogMAR), mild (>0.30 – <0.50 LogMAR), moderate (≥0.50 – <1.0 LogMAR) or severely impaired (≥1.0 LogMAR) according to criteria of the World Health organization.[11]

Dutch multicenter cross-sectional study

Study design and setting

The study was approved by the institutional ethical committees of the University Medical Center Utrecht (UMCU, #18-510/C), Máxima Medical Center Veldhoven (MMCV, #L20.044), and Maastricht University Medical Center+ (MUMC+, #2019-1321). Through a review of medical records, we systematically compiled data of 22q11.2DS patients that visited the ophthalmological outpatient clinic of UMCU, MMCV, and/or MUMC+ between January 1992 and January 2021. All centers are multidisciplinary outpatient clinics for 22q11.2DS. Ophthalmic screening was carried out as regular screening after diagnosis or referral in all clinics and only in a minority of cases upon clinical indication.

Study subjects

We included patients with a genetically confirmed 22q11.2 deletion. Atypical 22q11.2 deletions were excluded, i.e. not involving the A-B region.[1]

Data collection

Data on demographic and clinical characteristics included molecular test results, sex, age at most recent ophthalmic screening, reason for referral, congenital heart defects, ophthalmological abnormalities, presence of a headache, prescription of glasses and treatment and/or ocular surgery in the past and results of most recent ophthalmic screening. Prevalence rates of vascular tortuosity, posterior embryotoxon and optic disk abnormalities are based on the total number of patients who were examined using fundoscopy and slit lamp.

Best corrected visual acuity measurements were transformed to LogMAR and categorized as described above.[11] Spherical refractive errors were divided into six groups comparable to previous studies on ocular findings in 22q11.2DS.[8, 9] Refractive errors, myopia and hyperopia, were considered mild in case of more than 0.5 diopters (D) to 2.0D, moderately severe in case of >2.0D and <4.0D and severe in case of ≥4.0D. Finally, astigmatism with cylindrical errors of ≤ -2.0D were extracted and considered high. Astigmatism was classified as with-the-rule, against-the-rule and oblique as described before.[12]

Statistical analysis

Categorical data are presented as frequencies with percentage (%) and continuous data are presented as median with ranges. For prevalence rates in our cross-sectional study, 95% confidence intervals were calculated. We used Spearman's Rank-Order correlation for studying the degree of association between age and refractive errors, given the asymmetric data distribution. We used Chi-square tests to compare ophthalmic findings, such as retinal vascular tortuosity, between men and women and between those with and without congenital heart defects. All analyses were two-tailed, with statistical significance defined as $P < 0.05$, using IBM SPSS software (Statistics 25; SPSS, Inc., Chicago, IL).

Retinal vascular tortuosity	Abnormal curvature of the retinal blood vessels
Posterior embryotoxon	Corneal abnormality with a thickened and anteriorly displaces Schwalbe's line
Distichiasis	Eyelashes that arise from an abnormal part of the eye lid
Against-the-rule astigmatism	Occurs when the horizontal meridian of the cornea is steeper than the vertical meridian
With-the-rule astigmatism	Occurs when the vertical meridian of the cornea is steeper than the horizontal meridian
Dacryostenosis	Tear duct obstruction
Dacryocystorhinostomy	Surgical intervention to restore tear flow
Keratoconus	Cone shaped cornea caused by thinning of the cornea
Peters' anomaly	Corneal opacity due to anterior segment dysgenesis

Box 1. Ocular concepts and definitions.

Results

Systematic review of the literature

Study selection

The flow diagram in Figure 1 shows the study selection process. We identified 1213 records through a literature search in PubMed, Embase and the Cochrane Library. After deduplicating we screened 871 titles and abstracts for relevance, resulting in 180 articles of which full-text was screened for eligibility. One article was added after manual search of the reference sections.[13] Four studies, including a total of 270 patients, were included for data-extraction in this systematic review. Four studies were excluded because of a high risk of bias (Supplementary 3).[13-16]

Study characteristics

Table 1 shows the study characteristics of the included studies, all published between 2007 and 2016. Three were prospective cohort studies,[7-9] and one was a retrospective cohort study.[17] Median number of included patients was 63 (range 16-128).

In three studies ophthalmic assessment was done by an ophthalmologist,[7-9] and in one study by a subspecialized pediatrician.[17] In this study, additional data were collected through a medical and developmental checklist that was completed by the patient's parents.[17] Two studies reported only on children,[7,

[9] and two other included mainly children.[8, 17] All studies included patients with a 22q11.2 deletion confirmed by fluorescence in situ hybridization test and/or multiplex ligation-dependent probe amplification technique.[7-9, 17]

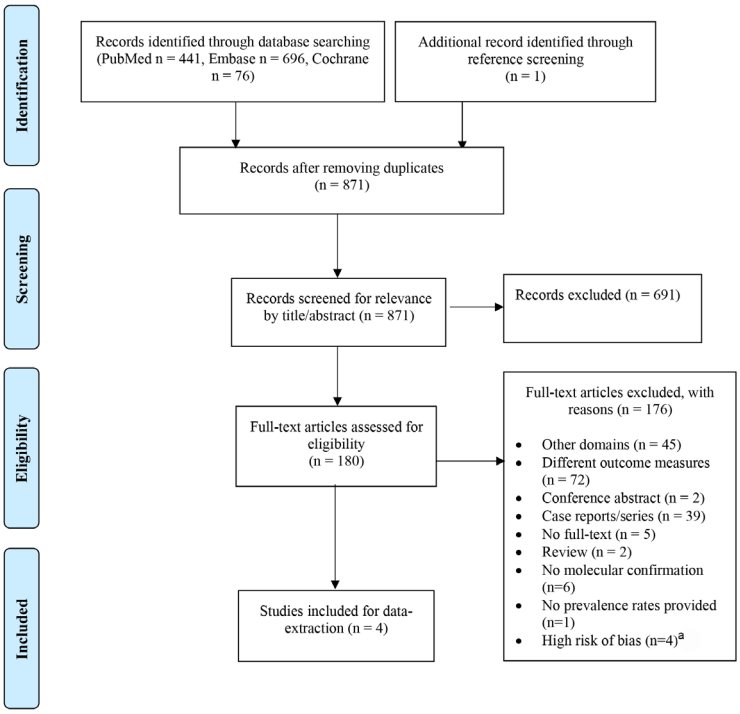

Figure 1. Flow diagram depicting the different phases of the systematic review on ocular findings in patients with 22q11.2DS (adapted from the PRISMA 2009 flow diagram; http://prisma-statement.org/)

[a] For the complete list of risk of bias of studies, see Supplementary material 3.

Quality assessment

Substantial heterogeneity was present among studies concerning demographics, methods, definitions and outcome measures. The methodology of the studies was poorly described or missing in most studies, complicating comparative evaluation.

Ocular findings

VA was (near) normal in most patients (91-94%). In one patient one eye was severely impaired because of a Peters' anomaly.[7] One study described that VA was "lower than normal" in two eyes with high hyperopia and one eye with exotropia and high myopia.[9]

Refractive errors were frequently reported in all included studies (Table 1). Hyperopia was the most common refractive error, with a prevalence ranging from 6% to 48% for moderate to severe hyperopia. Moderate to severe myopia (3-10%) and high astigmatism (3-12%) were less frequent. One study showed an increase in high astigmatism with age.[8]

Ocular findings that were most frequently reported were retinal vascular tortuosity (4-78%), posterior embryotoxon (41-50%), strabismus (12-36%), amblyopia (2-6%) and optic disc abnormalities (0-6%) (Table 1). Optic disk abnormalities consisted of hypoplastic or small optic discs (6%), and tilted optic discs (1%). Other ophthalmic findings that were reported were ptosis (4-6%), distichiasis (2-6%),[8, 9] lens opacities (3-6%),[7, 9] glaucoma (6%),[9] cataract (3%),[7] iriscoloboma (3%),[7] Peters' anomaly (3%)[7] and keratoconus (1%).[17]

Dutch multicenter study

Results

In our cross-sectional study, 132 patients (60 males, [45%]) were included. Median age at last ophthalmic screening was 8.9 (range 0-56) years, with 23% aged 18 years or older. Twenty-two patients (17%) were referred to the ophthalmologist for: suspected visual impairment (n=9), suspected reduced color vision (n=1), persistent conjunctivitis (n=1), recurrent eye lid infection (n=2), entropion (n=1), vitreous floaters (n=1), suspected papilledema (n=1), suspected eye movement disorder (n=1), suspected amblyopia (n=1), strabismus (n=2) and two patients for a second opinion because of esotropia (n=1) and amblyopia (n=1). Five patients received ophthalmic screening because of another underlying condition (juvenile idiopathic arthritis (n=4), diabetes mellitus (n=1)). VA was available for 109 patients (83%) and was normal in the majority (*N*=101, [93%]). Of the 23 patients who had no quantitative VA measurement, nine patients (39%) showed good fixation during ophthalmic screening. Reasons for a mild visual impairment (*N*=5, [5%]) were bilateral or unilateral amblyopia, mild cataract and high myopia. Three of these five patients (60%) were adults. Moderate visual impairment was found in two children (2%) with only dacryostenosis in one and mild hypoplastic optic disks in the other patient. Both patients were reported to have difficulties with performing the test.

Table 1. Literature review of ocular findings in patients with 22q11.2DS.

Author and year	Study design	Country	Patient number	Age (y)[a]	Age range (y)	Retinal tortuosity (%)	Posterior embryotoxon (%)	Optic disk abnormalities (%)	Strabismus (%)	Amblyopia (%)	Ptosis (%)	Eye lid hooding (%)	Hyperopia (%)	Myopia (<2D, %)	Astigmatism (≥2.0D, %)
Midbari Kufert et al., 2016	Retrospective cohort	Israel	128	12.9 (11)	1-55	4	NR	NR	12	2	NR	NR	2[b]	18[b]	2[b]
Forbes et al., 2007	Prospective cohort	U.S.A.	90	9	3wk-37	34	49	1	18	4	4	20	(>2D) 28	4	12
Casteels et al., 2008	Prospective cohort	Belgium	36	7	3-14	78	41	0	36	6	NR	67	(≥2D) 48	10	6
Gokturk et al., 2016	Prospective cohort	Turkey	16	M:7	4m-37	56	50	6	25	NR	6	50	(>2D) 6	3	3

Prevalence rates were based on the total number of patients except for the prevalence of refractive errors which was based on the number of eyes examined. Abbreviations: y=year, m=months, wk= weeks, M=median, D=diopters, NR=not reported, CD=cannot determine because cylinder error was reported for 2 cases only (both >1D and less than 2D), U.S.A.= United states of America. [a] Ages are reported as mean (SD), unless indicated otherwise. [b] Cut-off values for refractive errors were not defined.

One child, with consanguine parents, had a VA of 2.5 logMAR probably caused by keratoconus, subcapsular cataract and tapetoretinal degeneration. One of the siblings of this patient also had tapetoretinal degeneration. This was the only patient referred to the ophthalmologist for suspected visual impairment in whom visual impairment was found.

Refractive measurements were available for 212 eyes of 106 patients (80%) (Table 2). Moderate to severe hyperopia was seen in 87 eyes (41%) and was persistently high in children from the age of 6 years up to adulthood. Moderate to severe myopia was present in only a small number of eyes (*N*=12 eyes, [6%]). High astigmatism was reported in 49 eyes (23%). A moderate statistically significant negative correlation was found between age and cylinder power (Spearman's Rho OD: -0.538, p=0.000, OS: -0.510, p=0.000). Most common was against-the-rule astigmatism (*N*=57/128 eyes, [45%]). With-the-rule astigmatism (*N*=37/128 eyes, [29%]) and oblique astigmatism (*N*=34/128 eyes, [27%]) were seen almost equally often. Glasses were prescribed for 35 children (35%) and 23 adults (74%), prior or during last ophthalmic screening. A headache was reported for 32 patients (24%) recently before or during last ophthalmic screening.

Table 2. Refractive errors found in 212 eyes of 106 patients with 22q11.2DS.

	<6y	6-11.9y	12-17.9y	≥18y	total
Number of eyes examined	56	68	32	56	212
Spherical equivalent	%	%	%	%	%
≤-4.0D (severe)	4	0	0	7	3
-4.0D- -2.01D (moderate)	0	1	6	5	3
-2.0- -0.51D (mild)	2	9	3	18	8
-0.5- 0.5D	11	7	16	16	12
0.51- 2.0D (mild)	46	31	22	32	34
2.01- 4.0D (moderate)	25	29	31	16	25
≥4.0D (severe)	13	25	22	5	16
Cylindrical error					
≤-2D (high)	5	24	25	39	23

Abbreviations: D=diopters, y=years.

Most reported ocular findings are shown in Table 3 and include retinal vascular tortuosity (*N*=38, [32%]), posterior embryotoxon (*N*=23, [22%]),

strabismus (*N*=16, [12%]), amblyopia (*N*=15, [11%]) of which 20% were refractive amblyopia, and optic disk abnormalities (*N*=15, [13%]) such as hyperpigmentation, hypoplastic, small or tilted optic disks and excavations. Nine patients (7%) had a history of eye surgery, which included strabismus correction (*N*=3, [2%]), dacryocystorhinostomy (*N*=3, [2%]), eye lid correction (*N*=2, [2%]) and entropion correction (*N*=1, [1%]). All surgeries, except for one eye lid correction, have taken place in childhood. Prevalence rates of ocular findings in patients younger than 18 years at time of examination were in general slightly lower compared to prevalence rates in all patients. However, it should be noted that some of the ocular findings in adults, especially those that typically manifest in childhood such as amblyopia or embryotoxon posterior, are likely to have been present at an earlier age. Less frequent ocular findings were nystagmus (*N* =2, [2%]), uveitis (*N*=1, [1%]), cataract (*N*=1, [1%]), iris remnants (*N*=1, [1%]), bilateral corneal ectasia (*N*=1, [1%]) and one patient with keratoconus, subcapsular cataract and tapetoretinal degeneration. There was no association between retinal vascular tortuosity and the presence of a congenital heart defect (Chi^2=2.19, p=0.33). There were no differences in ocular abnormalities between males and females, except for posterior embryotoxon which was significantly more prevalent in women (18/60, [30%]) compared to men (5/46, [11%]) (Chi^2 = 5.61, p=0.02).

Table 3. Ocular findings in 132 patients with 22q11.2DS.

Ocular findings	Number of patients	% of patients <18y [95% CI] [a]	% of total [95% CI] [b]
Retinal vascular tortuosity [c]	38/120	24 [19-39]	32 [23-40]
Posterior embryotoxon [c]	23/106	15 [11-30]	22 [14-30]
Strabismus	16/132	10 [5-18]	12 [6-18]
Eye surgery	9/132	6 [2-13]	7 [2-11]
Optic disk abnormalities [c]	15/120	9 [5-18]	13 [7-19]
Amblyopia	15/132	6 [2-13]	11 [6-17]
Epicanthus	11/132	4 [1-10]	8 [4-13]
Ptosis	6/132	3 [1-8]	5 [1-8]
Motility disorder	3/132	0 [0-4]	2 [0-5]
Dacryostenosis	3/132	3 [1-8]	2 [0-5]
Glasses prescribed	58/132	35 [26-45]	44 [35-53]

[a] Proportion of patients <18 years at time of examination (n=101).
[b] Proportion of the total sample (n=132).
[c] For 12 patients no fundoscopy and for 26 patients no slit lamp examination data was available.
Abbreviation: CI= confidence interval, y=years.

Discussion

The results of our study indicate that ocular findings are frequently present in patients with 22q11.2DS. We report on ocular findings in the largest cohort of 22q11.2DS patients to date.

Importantly, VA was (near) normal in almost all patients. Severe visual impairment was reported for two children, one with Peters' anomaly and one with keratoconus, posterior subcapsular cataract and tapetoretinal degeneration with a suspected second genetic hit. It is important to detect visual impairment because of its impact on language and communication development and for its negative effect on psychiatric illness such as depression or anxiety.[18, 19] Patients with intellectual disabilities and visual impairment may have an atypical presentation, such as self-injurious behavior or functional deterioration.[20] Also, fatigue and headaches are common in 22q11.2DS,[21] and may be caused by visual impairment in some cases. When measuring VA of patients with 22q11.2DS, cognitive abilities should be taken into account.

We found a high prevalence of moderate to severe hyperopia, especially in children with 22q11.2DS aged six years and older, compared to children and adults in the general population and also children with intellectual disabilities.[22-24] Studies in the general population have shown that emmetropisation takes place during early development resulting in a reduction and stabilization of refractive errors in early teenage years,[25, 26] which was not the case in our cohort. A possible reason for the high prevalence of hyperopia may be that the axial length of the eye is too short relative to the refractive power of the lens or cornea because of a delay in growth. Also, lag in accommodation has been found in children with severe hyperopia in the general population and may have contributed to the high prevalence of moderate to severe hyperopia in our study.[27] In addition, the prevalence of astigmatism in children and adults with 22q11.2DS was much higher compared to the general population and compared to adults with intellectual disabilities.[23, 28] Also, in our cross-sectional study, high astigmatism was more frequently present compared to previous studies in 22q11.2DS. This may be explained by a higher inclusion rate of adults in our study, in whom astigmatism was found more often. Against-the-rule

astigmatism was most common in all age groups in our cohort and can be influenced by a reduction in lid pressure,[25] which may have contributed to the disturbed emmetropisation in our cohort. Eye lid hooding and ptosis were reported in a substantial number of patients with 22q11.2DS (20-67% and 4-6% respectively). Myopia was less frequently reported in children with 22q11.2DS compared to the general population, but a similar prevalence was found for adults.[22] Correction of refractive errors in patients with 22q11.2DS at an early stage is important because it can improve reading abilities.[29] Also, high refractive errors and anisometropia have been associated with amblyopia.[30, 31] Strabismus and amblyopia were frequently reported in 22q11.2DS and may have direct clinical consequences. The prevalence of strabismus and amblyopia is higher compared to the general population (12-36% versus 1-3% and 2-11% versus 1-4% respectively),[32-34] but comparable to what has been reported in children with intellectual disabilities (14% for strabismus).[23] This may suggest that these results are not specific for a 22q11.2 deletion. Clinicians treating patients with 22q11.2DS should be aware of the increased prevalence of refractive errors, strabismus and amblyopia and their influence on VA and language and communication development if not treated correctly.[35-37] Management of amblyopia includes correction of refractive errors or occlusion therapy and intervention preferably takes place as young as possible because of reduced plasticity of the visual cortex after the age of seven years.[38] The management of strabismus also depends upon the etiology and includes surgical and non-surgical strategies.

The most common ocular finding, though without clinical consequences, in both the systematic review studies and our cross-sectional study, was retinal vascular tortuosity (32-78%). There was one study that reported a prevalence of 4% but did not provide additional information regarding measurement method or an explanation for this very low prevalence compared to other 22q11.2DS studies.[17] Retinal vascular tortuosity has a prevalence of 6% in the general population and therefore may be considered as a typical finding in patients with 22q11.2DS.[39] Importantly, retinal vascular tortuosity has been associated with other disorders including obstructive sleep apnea,[40] diabetes mellitus[41] and schizophrenia[42] in non-22q11.2DS populations. These disorders are also frequently reported in patients with 22q11.2DS.[4, 43-45] In accordance with previous studies in 22q11.2DS, we did not find a correlation between retinal vascular tortuosity and cardiac anomalies.[7, 9]

Another common finding in 22q11.2DS was posterior embryotoxon (22-50%), that also has a higher prevalence compared to the general population (7%).[46] As proposed by others, posterior embryotoxon and other anterior segment abnormalities may be a result of defects in migration, proliferation and differentiation of neural crest cells in an early embryologic stage in 22q11.2DS.[7, 9, 47] Anterior segment dysgenesis may increase the risk of glaucoma, which was reported only once in the included review studies[9] and in not a single patient in our cohort. Other findings supporting a role of a 22q11.2 deletion in anterior segment dysgenesis were scarce, including Peter's anomaly, iris remnants and lens opacities.[7, 9]

With advances in clinical genetic testing, ophthalmic screening is no longer important for diagnosing 22q11.2DS. Another reason for screening after birth could be an increased prevalence of congenital cataract because of its impact on the development of the visual system. However, based on our results, we cannot conclude that congenital cataract has a higher prevalence in 22q11.2DS compared to the general population.

Table 4. Recommendations for ophthalmic and orthoptic screening in 22q11.2DS.

Assessment	At diagnosis	At three years old	At adulthood
Strabismus	√	√	
Amblyopia	√	√	
Refractive errors	√	√	Low-threshold
Visual acuity	√	√	Low-threshold

Each √ refers to a single assessment with follow-up as needed. Ophthalmic screening should be done at least once by an ophthalmologist.

We would recommend that children with 22q11.2DS receive screening by an ophthalmologist and orthoptist at the age of three years in order to detect and treat strabismus, amblyopia and refractive errors, which have high prevalence rates in 22q11.2DS. From the age of three years a reliable monocular VA measurement should be possible. Also, detection of amblyopia is important at an early age because of reduced plasticity of the visual cortex after the age of 7 years. Patients diagnosed with 22q11.2DS after the age of three years should receive ophthalmic and orthoptic screening at diagnosis with follow-up as needed.

For young adults with 22q11.2DS we recommend low-threshold referral for ophthalmic and orthoptic screening because of a high prevalence of hyperopia and astigmatism. Clues for visual impairment may be headaches, fatigue, behavioral problems or functional deterioration. We have no reasons to believe that clinically relevant ocular findings in adults with 22q11.2DS and an intellectual disability are much different from what has been reported for adults with intellectual disabilities in general. Consequently, we have no reasons to deviate from the general guidelines for ophthalmic screening in patients with intellectual disabilities recommending regular screening in late-adulthood.[48, 49] Recommendations for monitoring are provided in Table 4.

Finally, we would recommend ophthalmological consultation and subsequent testing for a suspected second genetic hit in case of a second, possibly genetic, diagnosis such as tapetoretinal degeneration or congenital cataract.

Large prospective studies with standardized ophthalmological examination and long-term follow-up in children and adults are necessary to evaluate the frequency of ocular findings and to study associations between ocular findings and age in 22q11.2DS. Future studies may consider measuring the axial length of the eyeball, corneal shape and accommodation in order to better understand the high prevalence of hyperopia and delay in emmetropization in children with 22q11.2DS. Also, more research is needed on sensory disorders in general because of their importance for speech-language and communication development and in the context of psychiatric co-morbidities in 22q11.2DS. These studies will be of value for informing guidelines, especially for adults with 22q11.2DS, which will be updated next year.

Strengths of our cross-sectional study include the relatively large 22q11.2DS sample and systematic examination by a small number of ophthalmologists. There are also some limitations. First, it is important to note that findings may be difficult to compare between studies due to different definitions, measurement techniques, age and ethnic and racial groups. Prevalence rates of some variables such as posterior embryotoxon and vascular tortuosity may differ to a certain extent because of subjective assessment. Nevertheless, our results and previous findings all indicate that these ocular findings are more prevalent in 22q11.2DS compared to the

general population. Second, the cross-sectional study with a retrospective study design made it possible that clinicians have not specifically assessed or reported on all variables for patients who visited the outpatient clinic. Also, age of onset of ocular findings was often lacking from medical files or unknown, making it difficult to report prevalence rates of adult-onset ocular findings. Taking into account that some patients had difficulties with performing the full examination due to non- cooperativity or not understanding instructions, prevalence rates may have been underestimated.

Third, there is a risk of selection bias since most participants in our cross-sectional study and studies included in this review were assessed in tertiary 22q11.2 centers. However, most participants are referred to these tertiary centers for congenital heart defects, speech and language disorders (including velopharyngeal insufficiency), and / or developmental, psychological or psychiatric problems. Therefore, we do not expect overestimated ophthalmologic prevalence rates.

Conclusion

Refractive errors, strabismus and amblyopia are common, clinically relevant and treatable ocular findings in patients with 22q11.2DS. Clinicians should be aware of these manifestations and the beneficial result of detection and correction at an early age. Therefore, we would recommend standardized ophthalmic and orthoptic screening in children with 22q11.2DS at the age of three years or at diagnosis, and a low-threshold for referral in adults.

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Conflict of interests
The authors declare no conflict of interest.

Data availability statement
The data that support our findings are available from the corresponding author on reasonable request.

References

1. McDonald-McGinn DM, Sullivan KE, Marino B, et al. 22q11.2 deletion syndrome. *Nat Rev Dis Primers*. Nov 19 2015;1:15071. doi:10.1038/nrdp.2015.71
2. Bassett AS, Chow EW, Husted J, et al. Clinical features of 78 adults with 22q11 Deletion Syndrome. *Am J Med Genet A*. Nov 1 2005;138(4):307-13. doi:10.1002/ajmg.a.30984
3. Campbell IM, Sheppard SE, Crowley TB, et al. What is new with 22q? An update from the 22q and You Center at the Children's Hospital of Philadelphia. *Am J Med Genet A*. Oct 2018;176(10):2058-2069. doi:10.1002/ajmg.a.40637
4. Schneider M, Debbané M, Bassett AS, et al. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *Am J Psychiatry*. Jun 2014;171(6):627-39. doi:10.1176/appi.ajp.2013.13070864
5. Moberg PJ, Turetsky BI, Moberg EA, et al. Meta-analysis of olfactory dysfunction in 22q11.2 deletion syndrome. *Psychiatry Res*. Jan 16 2020;285:112783. doi:10.1016/j.psychres.2020.112783
6. Verheij E, Derks LSM, Stegeman I, Thomeer H. Prevalence of hearing loss and clinical otologic manifestations in patients with 22q11.2 deletion syndrome: A literature review. *Clin Otolaryngol*. Dec 2017;42(6):1319-1328. doi:10.1111/coa.12874
7. Casteels I, Casaer P, Gewillig M, Swillen A, Devriendt K. Ocular findings in children with a microdeletion in chromosome 22q11.2. *Eur J Pediatr*. Jul 2008;167(7):751-5. doi:10.1007/s00431-007-0582-0
8. Forbes BJ, Binenbaum G, Edmond JC, DeLarato N, McDonald-McGinn DM, Zackai EH. Ocular findings in the chromosome 22q11.2 deletion syndrome. *J aapos*. Apr 2007;11(2):179-82. doi:10.1016/j.jaapos.2006.08.006
9. Gokturk B, Topcu-Yilmaz P, Bozkurt B, et al. Ocular Findings in Children With 22q11.2 Deletion Syndrome. *J Pediatr Ophthalmol Strabismus*. Jul 1 2016;53(4):218-22. doi:10.3928/01913913-20160427-01
10. Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol*. Sep 2012;65(9):934-9. doi:10.1016/j.jclinepi.2011.11.014
11. International classification of diseases for mortality and morbidity statistics (11th Revision) (World Health Organization) (2018).
12. Núñez MX, Henriquez MA, Escaf LJ, et al. Consensus on the management of astigmatism in cataract surgery. *Clin Ophthalmol*. 2019;13:311-324. doi:10.2147/opth.S178277
13. Ryan AK, Goodship JA, Wilson DI, et al. Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. *J Med Genet*. Oct 1997;34(10):798-804. doi:10.1136/jmg.34.10.798
14. Cirillo E, Giardino G, Gallo V, et al. Intergenerational and intrafamilial phenotypic variability in 22q11.2 deletion syndrome subjects. *BMC Med Genet*. Jan 2 2014;15:1. doi:10.1186/1471-2350-15-1
15. Vieira TP, Monteiro FP, Sgardioli IC, et al. Clinical Features in Patients With 22q11.2 Deletion Syndrome Ascertained by Palatal Abnormalities. *Cleft Palate Craniofac J*. Jul 2015;52(4):411-6. doi:10.1597/13-233
16. Veerapandiyan A, Abdul-Rahman OA, Adam MP, et al. Chromosome 22q11.2 deletion syndrome in African-American patients: a diagnostic challenge. *Am J Med Genet A*. Sep 2011;155a(9):2186-95. doi:10.1002/ajmg.a.34226
17. Midbari Kufert Y, Nachmani A, Nativ E, Weizman A, Gothelf D. Association between prematurity and the evolution of psychotic disorders in 22q11.2 deletion syndrome. *J Neural Transm (Vienna)*. Dec 2016;123(12):1491-1497. doi:10.1007/s00702-016-1607-5
18. Mosca R, Kritzinger A, van der Linde J. Language and communication development in preschool children with visual impairment: A systematic review. *S Afr J Commun Disord*. 2015;62(1):e1-e10. doi:10.4102/sajcd.v62i1.119

19. Demmin DL, Silverstein SM. Visual Impairment and Mental Health: Unmet Needs and Treatment Options. *Clin Ophthalmol*. 2020;14:4229-4251. doi:10.2147/opth.S258783
20. de Winter CF, Jansen AA, Evenhuis HM. Physical conditions and challenging behaviour in people with intellectual disability: a systematic review. *J Intellect Disabil Res*. Jul 2011;55(7):675-98. doi:10.1111/j.1365-2788.2011.01390.x
21. Vergaelen E, Claes S, Kempke S, Swillen A. High prevalence of fatigue in adults with a 22q11.2 deletion syndrome. *Am J Med Genet A*. Apr 2017;173(4):858-867. doi:10.1002/ajmg.a.38094
22. Hashemi H, Fotouhi A, Yekta A, Pakzad R, Ostadimoghaddam H, Khabazkhoob M. Global and regional estimates of prevalence of refractive errors: Systematic review and meta-analysis. *J Curr Ophthalmol*. Mar 2018;30(1):3-22. doi:10.1016/j.joco.2017.08.009
23. Akinci A, Oner O, Bozkurt OH, Guven A, Degerliyurt A, Munir K. Refractive errors and ocular findings in children with intellectual disability: a controlled study. *J AAPOS*. 2008;12(5):477-481. doi:10.1016/j.jaapos.2008.04.009
24. Williams KM, Verhoeven VJ, Cumberland P, et al. Prevalence of refractive error in Europe: the European Eye Epidemiology (E(3)) Consortium. *Eur J Epidemiol*. Apr 2015;30(4):305-15. doi:10.1007/s10654-015-0010-0
25. Read SA, Collins MJ, Carney LG. A review of astigmatism and its possible genesis. *Clin Exp Optom*. Jan 2007;90(1):5-19. doi:10.1111/j.1444-0938.2007.00112.x
26. Harb EN, Wildsoet CF. Origins of Refractive Errors: Environmental and Genetic Factors. *Annu Rev Vis Sci*. Sep 15 2019;5:47-72. doi:10.1146/annurev-vision-091718-015027
27. Tarczy-Hornoch K. Accommodative lag and refractive error in infants and toddlers. *J AAPOS*. Apr 2012;16(2):112-7. doi:10.1016/j.jaapos.2011.10.015
28. van Splunder J, Stilma JS, Bernsen RM, Arentz TG, Evenhuis HM. Refractive errors and visual impairment in 900 adults with intellectual disabilities in the Netherlands. *Acta Ophthalmol Scand*. Apr 2003;81(2):123-9. doi:10.1034/j.1600-0420.2003.00035.x
29. Crewther SG, Kiely PM, Kok LL, Crewther DP. Anomalies of genetic development as predictors of oculo-visual abnormalities in velo-cardio-facial syndrome. *Optom Vis Sci*. Oct 1998;75(10):748-57. doi:10.1097/00006324-199810000-00020
30. Brown SA, Weih LM, Fu CL, Dimitrov P, Taylor HR, McCarty CA. Prevalence of amblyopia and associated refractive errors in an adult population in Victoria, Australia. *Ophthalmic Epidemiol*. Dec 2000;7(4):249-58.
31. Mocanu V, Horhat R. Prevalence and Risk Factors of Amblyopia among Refractive Errors in an Eastern European Population. *Medicina (Kaunas)*. Mar 20 2018;54(1)doi:10.3390/medicina54010006
32. Hashemi H, Pakzad R, Heydarian S, et al. Global and regional prevalence of strabismus: a comprehensive systematic review and meta-analysis. *Strabismus*. Jun 2019;27(2):54-65. doi:10.1080/09273972.2019.1604773
33. Yekta A, Hashemi H, Norouzirad R, et al. The Prevalence of Amblyopia, Strabismus, and Ptosis in Schoolchildren of Dezful. *Eur J Ophthalmol*. Jan/Feb 2017;27(1):109-112. doi:10.5301/ejo.5000795
34. Webber AL, Wood J. Amblyopia: prevalence, natural history, functional effects and treatment. *Clin Exp Optom*. Nov 2005;88(6):365-75. doi:10.1111/j.1444-0938.2005.tb05102.x
35. Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. *British Journal of Ophthalmology*. 2012;96(5):614. doi:10.1136/bjophthalmol-2011-300539
36. Blair K, Cibis G, Gulani AC. Amblyopia. *StatPearls*. StatPearls Publishing

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37. Catalano JD. Strabismus. *Pediatr Ann*. May 1990;19(5):289, 292-7. doi:10.3928/0090-4481-19900501-05
38. Sengpiel F. Plasticity of the visual cortex and treatment of amblyopia. *Curr Biol*. Sep 22 2014;24(18):R936-r940. doi:10.1016/j.cub.2014.05.063
39. Henkind P, Walsh JB. Retinal vascular anomalies. Pathogenesis, appearance, and history. *Trans Ophthalmol Soc U K*. Sep 1980;100(3):425-33.

40. Mohsenin A, Mohsenin V, Adelman RA. Retinal vascular tortuosity in obstructive sleep apnea. *Clin Ophthalmol*. 2013;7:787-92. doi:10.2147/opth.S41795
41. Sasongko MB, Wong TY, Nguyen TT, Cheung CY, Shaw JE, Wang JJ. Retinal vascular tortuosity in persons with diabetes and diabetic retinopathy. *Diabetologia*. Sep 2011;54(9):2409-16. doi:10.1007/s00125-011-2200-y
42. Appaji A, Nagendra B, Chako DM, et al. Retinal vascular tortuosity in schizophrenia and bipolar disorder. *Schizophr Res*. Oct 2019;212:26-32. doi:10.1016/j.schres.2019.08.020
43. Van L, Heung T, Malecki SL, et al. 22q11.2 microdeletion and increased risk for type 2 diabetes. *EClinicalMedicine*. Sep 2020;26:100528. doi:10.1016/j.eclinm.2020.100528
44. Zinkstok JR, Boot E, Bassett AS, et al. Neurobiological perspective of 22q11.2 deletion syndrome. *Lancet Psychiatry*. Nov 2019;6(11):951-960. doi:10.1016/s2215-0366(19)30076-8
45. Kennedy WP, Mudd PA, Maguire MA, et al. 22q11.2 Deletion syndrome and obstructive sleep apnea. *Int J Pediatr Otorhinolaryngol*. Aug 2014;78(8):1360-4. doi:10.1016/j.ijporl.2014.05.031
46. Rennie CA, Chowdhury S, Khan J, et al. The prevalence and associated features of posterior embryotoxon in the general ophthalmic clinic. *Eye (Lond)*. Apr 2005;19(4):396-9. doi:10.1038/sj.eye.6701508
47. Mansour AM, Goldberg RB, Wang FM, Shprintzen RJ. Ocular findings in the velo-cardio-facial syndrome. *J Pediatr Ophthalmol Strabismus*. Sep-Oct 1987;24(5):263-6.
48. Evenhuis HM. *Early Identification of Hearing and Visual Impairment in Children and Adults with an Intellectual Disability*. IASSID International Consensus Statement, IASSID, SIRG Health Issues; 1998.
49. van Splunder J, Stilma JS, Bernsen RM, Evenhuis HM. Prevalence of visual impairment in adults with intellectual disabilities in the Netherlands: cross-sectional study. *Eye (Lond)*. Sep 2006;20(9):1004-10. doi:10.1038/sj.eye.6702059

Supplementary legend

Supplementary 1. Search terms for Pubmed, Embase and Cochrane.
Supplementary 2. Critical appraisal form.
Supplementary 3. Summary of risk of bias of studies on ocular findings in 22q11.2DS that underwent a critical appraisal.

Supplementary

1. Search terms for PubMed, Embase and Cochrane

1.1 PubMed search terms

	Search terms used in Pubmed
Domain	((("22q11 Deletion Syndrome" [MeSH] OR 22q11* [tiab] OR del22q* [tiab] OR DiGeorge [tiab] OR di-george [tiab] OR Velocardiofacial [tiab] OR velo-cardio-facial[tiab] OR VCF-syndrome[tiab] OR (Conotruncal[tiab] AND anomal* [tiab] AND face [tiab]) OR CTAF [tiab] OR "Autosomal dominant Opitz" [tiab] OR "opitz G" [tiab] OR G/BBB [tiab] OR GBBB [tiab] OR "G BBB" [tiab] OR sedlackova [tiab] OR Cayler [tiab] OR catch22 [tiab] OR "catch 22" [tiab] OR shprintzen [tiab] OR "thymic aplasia" [tiab] OR 22q11.2 Deletion Syndrome [tiab]))))
Outcome	(((((("Eye Diseases"[Mesh] OR "Eye"[Mesh] OR "Ocular Physiological Phenomena"[Mesh] OR refraction [tiab] OR vision [tiab] OR visual [tiab] OR ophthalm* [tiab] OR eye* [tiab] OR conjunctiv* [tiab] OR cornea* [tiab] OR ocular [tiab] OR optic* [tiab] OR orbit* [tiab] OR retina* [tiab] OR sclera* [tiab] OR uvea* [tiab] OR optic-nerve [tiab] OR eyelid* [tiab] OR lacrima* [tiab] OR lens* [tiab] OR pupil* [tiab] OR iris [tiab] OR intra-ocular [tiab] OR intraocular[tiab] OR cataract [tiab] OR blindness [tiab] OR embryotoxon [tiab] OR tortuous-retinal-veins [tiab] OR retinal-vascular-tortuosity [tiab] OR tortuous-retinal-vessels [tiab] OR refract* [tiab] OR strabismus [tiab] OR exotropia [tiab] OR esotropia [tiab] OR amblyopia [tiab] OR ptosis [tiab] OR distichiasis [tiab] or astigmati* [tiab]))))
Excluding	Animals [Mesh:NoExp] OR "mice"[ti] OR "mouse"[ti] OR rat*[ti] OR "nonhuman"[ti] OR veterin*[ti] OR monkey*[ti]

1.2 Embase search terms

	Search terms Embase
Domain	exp chromosome deletion 22q11/ or exp DiGeorge syndrome/ or exp velocardiofacial syndrome/ or exp opitz syndrome/ or (22q11*).ti,ab. **OR** (del22q*OR digeorge OR 'di george' OR velocardiofacial OR 'velo cardio facial' OR 'vcf syndrom*').ti,ab. **OR** ('conotruncal' AND anomal* AND 'face').ti,ab,kw. OR ('ctaf' OR 'autosomal dominant opitz' OR 'opitz g' OR 'gbbb' OR 'g bbb' OR 'sedlackova' OR 'cayler' OR 'catch22' OR 'catch 22' OR 'shprintzen' OR 'thymic aplasia').ti,ab.
Outcome	(exp eye disease/ OR exp eye/ OR exp 'visual system parameters'/ OR exp 'visual system function'/) **OR** (refraction OR vision OR visual OR ophthalm* OR eye* OR conjunctiv* OR cornea* OR ocular OR optic* OR orbit* OR retina* OR sclera* OR uvea* OR 'optic nerve' OR eyelid* OR lacrima* OR lens* OR pupil* OR iris OR 'intra ocular' OR intraocular OR cataract OR blindness OR embryotoxon OR 'tortuous retinal veins' OR 'retinal vascular tortuosity' OR 'tortuous retinal vessels' OR refract* OR strabismus OR exotropia OR esotropia OR amblyopia OR ptosis OR distichiasis OR astigmati*).ti,ab.
Excluding	(animal/ or animal experiment/ or animal model/ or nonhuman/) not human/ (mice or mouse or rat? or nonhuman or veterin* or monkey?).ti.
Limitations	conference abstract or chapter or conference paper or "conference review" or editorial or erratum or letter or note or "review"

1.3 Cochrane search terms

	Search terms used in Cochrane
Domain	((refraction OR vision OR visual OR ophthalm* OR eye OR eyes OR conjunctiv* OR cornea* OR ocular OR optic* OR orbit* OR retina* OR sclera* OR uvea* OR optic-nerve OR eyelid* OR lacrima* OR lens* OR pupil* OR iris OR intra-ocular OR intraocular OR cataract OR blindness OR embryotoxon OR tortuous-retinal-veins OR retinal-vascular-tortuosity OR tortuous-retinal-vessels OR refract* OR strabismus OR exotropia OR esotropia OR amblyopia OR ptosis OR distichiasis or astigmati*):ti,ab,kw
Outcome	(22q11* OR del22q* OR DiGeorge OR di-george OR Velocardiofacial OR velo-cardio-facial OR VCF-syndrome OR Conotruncal anomal* face OR CTAF OR Autosomal dominant Opitz OR opitz G OR GBBB OR G BBB OR sedlackova OR Cayler OR catch22 OR catch 22 OR shprintzen OR thymic aplasia OR 22q11.2 Deletion Syndrome):ti,ab,kw)

2. Critical appraisal form

Risk of bias item	Scoring	
External validity		
1. Was the study's target population a close representation of the standard 22q11.2DS population?	1 = yes	0 = no or unclear description
2. Was the diagnosis genetically confirmed in all patients?	1 = yes	0 = no or unclear description
3. Was some form of random selection used to select the sample, or was a census undertaken?	1 = yes	0 = no or unclear description
4. Was the response rate for the study ≥ 75% or was an analysis performed that showed no significant difference in relevant demographic characteristics between responders and non-responders?	1 = yes	0 = no or unclear description
Internal validity		
5. Were data collected directly from the subjects (as opposed to proxy)?	1 = yes	0 = no or unclear description
6. Was an acceptable definition of ocular features measured in the study used?	1 = yes	0 = no or unclear description
7. Was methods of eye examination described?	1 = yes	0 = no or unclear description
8. Was the same mode of data collection used for all subjects?	1 = yes	0 = no or unclear description
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	1 = yes	0 = no or unclear description
10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	1 = yes	0 = no or unclear description

Source: *Risk of bias assessment tool for prevalence studies*, Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65(9):934-9.

3. Summary of risk of bias of studies on ocular findings in 22q11.2DS that underwent a critical appraisal

Study / Risk of bias item	Gokturk et al., 2016	Cirillo et al., 2014	Casteels et al., 2008	Forbes et al., 2007	Vieira et al., 2015	Veerapandiyan et al., 2011	Ryan et al., 1997	Midbari Kufert et al., 2016
1. Target population a close representation of the national 22q11.2DS population?								
2. Was 22q11.2DS genetically proven in all patients?								
3. Some form of random selection used to select the sample?								
4. Likelihood of non-response bias minimal?								
5. Data collected directly from the subjects?								
6. Acceptable case definition of ocular manifestations used in the study?								
7. Methods of ocular examination described?								
8. Same mode of data collection used for all subjects?								
9. Length of the shortest prevalence period for ocular manifestations appropriate?								
10. Were the numerator and denominator for ocular manifestations appropriate?								
Overall risk of bias (out of 10 points) *	3	7	1	4	7	7	7	5

Light blue= yes (low risk), light orange=no/unclear (high risk). *≥7/10 points = very high risk of bias, excluded from data extraction.

Chapter 6

Optometry in adults with microdeletion 22q11.2: The eye as a window to the brain

Emma von Scheibler, Abhishek Appaji, Tos Berendschot, Noël Bauer, Naren Rao, Agnies van Eeghen, Thérèse van Amelsvoort, Erik Boot

Submitted

Abstract

The 22q11.2 deletion syndrome (22q11.2DS) has an estimated prevalence of 1:2148 live births and is associated with an increased risk of schizophrenia, cognitive decline and early-onset Parkinson's disease. Because retinal and cerebral tissue share embryological, physiological and anatomical characteristics, retinal blood vessel morphology and retinal nerve fiber layer (RNFL) thickness have been proposed as non-invasive biomarkers for psychiatric and neurodegenerative disorders. In this exploratory study, we examined these potential biomarkers in adults with 22q11.2DS relative to controls and in relation to age. Therefore, the central retinal artery and vein equivalent, fractal dimension, and vascular tortuosity, obtained through fundoscopy, and peripapillary RNFL and macular thickness, obtained through optical coherence tomography, were compared between adults with 22q11.2DS and sex- and age-matched controls. Mean retinal vascular fractal dimension and tortuosity values were significantly higher in the group of adults with 22q11.2DS than in controls ($p<0.001$; $p<0.001$). RNFL was thicker in the nasal segment ($p=0.002$) in 22q11.2DS, and a trend for thinner RNFL in the nasal inferior segment ($p=0.05$) was found. There were significant negative correlations with age for fractal dimension ($p<0.001$) and RNFL thickness in the global ($p=0.007$), temporal inferior ($p=0.005$) and temporal superior ($p=0.04$) segments in adults with 22q11.2DS, but not in controls. In conclusion, our results indicate higher retinal vascular fractal dimension and tortuosity, and a decrease in fractal dimension and RNFL thickness in relation to age in adults with 22q11.2DS. Our findings support future studies that focus on retinal fractal dimension and RNFL thickness as potential biomarkers for age-related manifestations in 22q11.2 including psychotic and (early) neurodegenerative disorders.

Introduction

The recurrent heterozygous 22q11.2 deletion is associated with 22q11.2 deletion syndrome (22q11.2DS), a multisystem disorder with an estimated prevalence of 1 in 2148 live births.[1, 2] Manifestations of 22q11.2DS include congenital heart defects, intellectual disability and an increased risk of developing schizophrenia and early-onset Parkinson's disease.[3-6] A notable proportion of individuals with 22q11.2DS display a substantial cognitive decline,[7, 8] partially related to psychotic disorders.[8, 9]

Because retinal and cerebral tissue share embryological, physiological, and anatomical characteristics, retinal blood vessel morphology and retinal layer thickness have been proposed as non-invasive biomarkers for, and increasingly studied in, neuropsychiatric and neurodegenerative disorders.[10-15] For example, wider venules and increased tortuosity of retinal blood vessels have been reported in patients with schizophrenia relative to healthy controls.[12, 16, 17] Also, thinning in retinal nerve fiber layer (RNFL) has been found in patients with cognitive impairment in comparison to healthy controls.[18, 19] Given that retinal vessel morphology and retinal layer thickness may reflect cerebral vessel and nerve tissue changes in different conditions, and can be assessed using non-invasive, fast and cost-effective methods, study of these parameters as possible biomarkers for neuropsychiatric disorders seems promising.

In this exploratory study, we examined retinal vascular parameters and retinal layer thickness in adults with 22q11.2DS relative to sex- and age-matched controls and in relation to age.

Methods

Study design and setting

This was a cross-sectional study conducted at the 22q11 outpatient clinic of Maastricht University Medical Center+ (MUMC+), The Netherlands. The Institutional Review Board at MUMC+ (2019-1321-A-10) approved the study and waived the need for written consent to use pseudonymized clinical data of adults with 22q11.2DS. All controls provided written informed consent.

Study participants

Adults with a molecularly confirmed 22q11.2 deletion (i.e., including the LCR22A-LCR22B region) and with clinically acquired retinal images available were included in the study. Controls were recruited through flyers posted at the MUMC+. Exclusion criteria for controls were: a history of retinal disease, hypertension, diabetes mellitus, a psychotic disorder, and/or cognitive decline. Two different control groups were recruited: one for blood vessel morphology and one for retinal layer thickness measurements, because initially we only aimed to investigate blood vessel morphology. For both groups, controls were selected so that on group level they did not differ in sex and age with the 22q11.2DS group.

Clinical characterization

All adults with 22q11.2DS were examined by an ophthalmologist, psychiatrist and neurologist as part of standard of care at the 22q11 clinic at MUMC+. None of the adults with 22q11.2DS were referred to this clinic for ophthalmic problems. Clinical data regarding the presence or absence of psychiatric disorders were extracted from the medical files. Smoking status was assessed for the study of retinal blood vessel morphology: seven adults with 22q11.2DS and three controls smoked. Optometric assessments were performed between January 2016 and April 2022. Eight adults with 22q11.2DS had no OCT data available because fundoscopy was implemented earlier as standard clinical care, resulting in more fundoscopic data compared to OCT. From 2017, measurements of macular thickness were added to the assessments, but subsequently had to be discontinued in 2021 due to the COVID pandemic, resulting in more peripapillary RNFL data than macular data. All retinal images were taken in a dark room to enable auto-dilation of the pupil, using non-mydriatic cameras.

Fundoscopy

Fundoscopic images were obtained with a TopCon TRC-TRC-50EX camera (Topcon Europe Medical BV, The Netherlands) between 2016 and 2020, and with a Clarus 700™ camera (Carl Zeiss Meditec Inc., California, USA) between 2020 and 2022. All fundoscopic images were assessed by an ophthalmologist (N.B.) to rule out retinal and optic nerve abnormalities, and to assess the image quality. All images were coded for the researcher who

performed the retinal blood vessel assessments (A.A.). Images of the right eye were used for analyses. In case the quality was poor, the left eye image was used.

Four vascular parameters were calculated, as described previously:[12, 16, 20, 21] central retinal artery and central retinal vein equivalent (CRAE and CRVE; both measures of vessel diameter), fractal dimension (FD; measure of the branching pattern and vessel density) and vascular tortuosity (measure of the vessel trajectory). Vessel length was determined with customized semi-automated MATLAB 2022a software (MathWorks, Inc., Natick, Massachusetts, United States). [20]

CRAE and *CRVE* were calculated with the revised Knudtson-Parr-Hubbard formula and averaged over the six largest arterioles and venules in the zone between 0.5- and 2-disc diameters from the optic disc.[22] In order to adjust for magnification differences of the two cameras, image resolution and refractive errors, a calibration factor was multiplied by individual CRAE and CRVE to convert values in pixels to micrometers (μm).[12] *FD* was calculated with automated MATLAB 2018a software, using the box-counting method, in which images are divided into multiple equally sized square boxes. [23] The number of boxes containing the skeletonized line tracing was counted and the process was repeated for different sized squares. FD was calculated as the gradient of logarithms of the number of boxes and the size of the boxes.[16] *Vascular tortuosity* was calculated as the ratio of the arc length (i.e., actual length of the vessel) divided by the chord length (i.e., length of a straight line drawn from the start to end point of the vessel, Figure 1) averaged over all vessels. [24, 25]

Optical coherence tomography

An HRA+OCT Spectralis Tracking Laser Tomography camera (Heidelberg Engineering, United States of America) was used to obtain peripapillary RNFL thickness and macular thickness. Thickness of peripapillary *RNFL* was evaluated as a 3.4 mm diameter circle surrounding the optic disk which was segmented into four sectors: superior, inferior, temporal, and nasal (Figure 2). The superior and inferior sectors were further divided into temporal-superior, nasal-superior, temporal-inferior and nasal-inferior

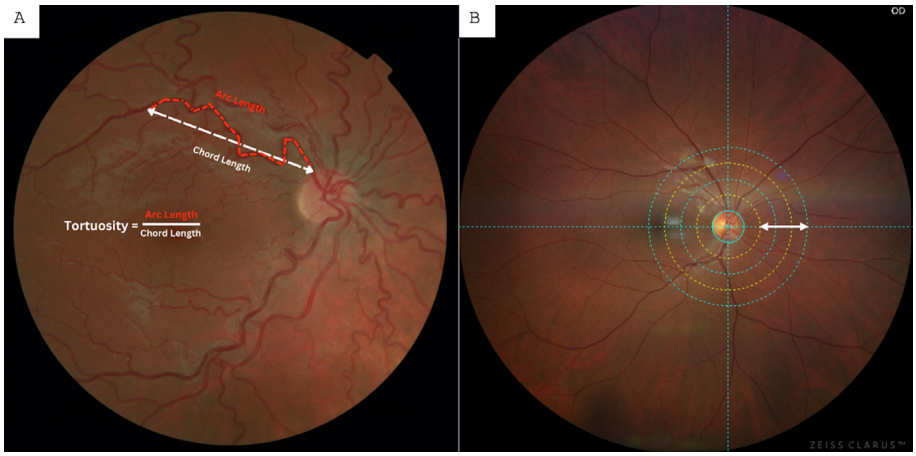

Figure 1. Fundoscopic retinal images of the right eye.

A) Fundus photograph illustrating a high degree of tortuosity; calculated as arc length divided by chord length, averaged over all vessels. B) The white arrow depicts the region for measurements of the central retinal artery and central retinal vein equivalents calculated with the revised Knudtson-Parr-Hubbard formula,[22] using the region between 0.5 (inner orange circle; dashed line) and 2.0 (outer blue circle; dashed line) disc diameters from the disc margin (inner blue circle; solid line).

subsections. The global RNFL thickness represents the average thickness of the six subsections. For measurements of the *macula*, the early treatment diabetic retinopathy study grid was used, which consists of 3 concentric circles with diameters of 1, 3 and 6 mm.[26] The inner and outer rings (parafoveal and perifoveal, respectively) were each divided into four quadrants: superior, inferior, temporal, and nasal. For OCT analyses, the left eye was used because right eye measurements failed in two adults with 22q11.2DS.

Statistical analysis

Independent samples T-tests were used to compare continuous variables and Fisher's exact tests to compare categorical variables between groups. Pearson correlations were used to test for any effects of age on retinal vascular parameters and retinal layer thickness. Two-tailed p-values <0.05 were considered statistically significant. All analyses were performed using the Statistical Package for Social Sciences (SPSS), version 25 (Inc., Chicago, IL).

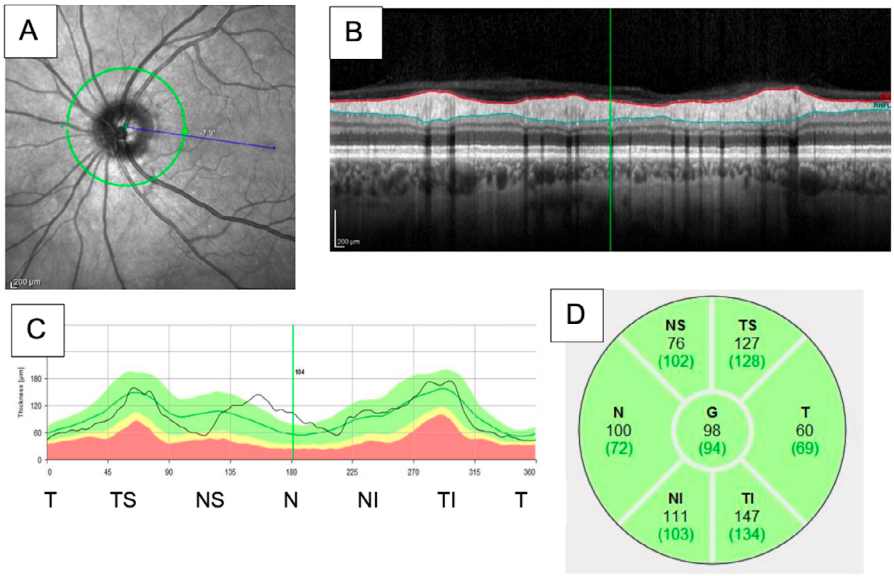

Figure 2. Optical coherence tomography for assessments of the thickness of retinal nerve fiber layers.

A) Image of the optic disc (left eye). The green circle indicates the peripapillary region used for RNFL thickness measurements and the blue line shows the orientation of the papil relative to the macula. B) Cross section of the peripapillary retina obtained by OCT. The RNFL is the tissue between the red and turquoise line. C) Representation of RNFL thickness (black line) of the different parts of the peripapillary region as assessed with OCT. The green line indicates the reference line, the green area the reference range, the yellow area the borderline range, and the red area the abnormal range. D) Example of an RNFL thickness map.

OCT=optical coherence tomography, RNFL=retinal nerve fiber layer, G=global, NS=nasal superior, N=nasal, NI=nasal inferior, TI=temporal inferior, T=temporal, TS=temporal superior.

Table 1. Demographic characteristics.

	22q11.2DS	Controls	Statistics P [a]
Fundoscopy			
Vessel morphology	N=49	N=57	
Mean age, years	29.9 ± 10.9	26.9 ± 8.3	0.11
Male sex	24 (49.0%)	22 (38.6%)	0.33
Optical coherence tomography			
RNFL	N=41	N=40	
Mean age, years	29.7 ± 10.2	33.0 ± 12.7	0.20
Male sex	17 (41.5%)	17 (42.5%)	1.00
Macula	N=16	N=40	
Mean age, years	30.8 ± 9.7	32.8 ± 12.9	0.57
Male sex	7 (43.8%)	16 (40.0%)	0.80

[a] Independent samples T-tests were used to compare ages and Fisher's exact tests to compare sex differences between-groups.

22q11.2DS=22q11.2 deletion syndrome, RNFL=retinal nerve layer thickness.

Results

Demographics

Demographic characteristics are presented in Table 1. For the study of retinal vessel morphology, 49 adults with 22q11.2DS were included. Of 60 potential controls, 2 were excluded from participation due to a retinal disease, and 1 was excluded from analyses due to technical problems. OCT data were available for 41 adults with 22q11.2DS, 16 with data on macular thickness, and 40 controls. By design, no statistically significant differences were found in mean age or sex distribution between adults with 22q11.2DS and controls.

Retinal vessel morphology

Table 2 shows the results for vascular parameter measurements. No differences were found in CRAE or CRVE between adults with 22q11.2DS and controls. However, adults with 22q11.2DS had significantly higher FD and vascular tortuosity compared to controls, with large effect sizes.

Retinal layer thickness

Results for peripapillary RNFL and macular thickness are shown in Table 2. Significant between-group differences were found with increased nasal RNFL thickness in the group of adults with 22q11.2DS as compared to controls. A trend for thinner RNFL of the nasal inferior segment was observed in adults with 22q11.2DS. No differences in macular thickness were found between adults with 22q11.2DS and controls.

Optometric variables in relation to age

Correlations of age with retinal vessel morphology and retinal layer thickness are shown in Table 3. There were no significant correlations of age with CRAE or CRVE in either adults with 22q11.2DS or controls. A moderate negative correlation was found of age with FD in adults with 22q11.2DS but not in controls. No significant correlations were found of age with tortuosity in adults with 22q11.2DS or controls.

Table 2. Blood vessel morphology and retinal layer thickness.

	22q11.2DS N=49		Controls N=57		Effect size [a]	Statistics [b]
Blood vessel morphology	Mean	SD	Mean	SD	Cohen's *d*	*P*
CRAE, µm	143.45	31.65	140.34	30.43	0.10	0.61
CRVE, µm	251.93	36.63	250.10	35.03	0.05	0.79
FD	1.38	0.10	1.26	0.14	0.99	**<0.001**
Tortuosity	1.47	0.17	1.36	0.07	0.85	**<0.001**
	22q11.2DS N=41		Controls N=40		Effect size [a]	Statistics [b]
Peripapillary RNFL, µm	Mean	SD	Mean	SD	Cohen's *d*	*P*
Global [c]	99.59	12.57	99.75	8.85	- 0.01	0.95
Nasal superior	107.66	25.98	100.90	17.80	0.30	0.18
Nasal	84.95	18.36	73.10	14.17	0.72	**0.002**
Nasal inferior	96.93	30.60	109.45	25.77	- 0.44	0.05
Temporal inferior	136.95	28.18	147.15	18.49	- 0.43	0.06
Temporal	74.24	14.51	76.73	12.59	- 0.18	0.41
Temporal superior	136.66	20.43	140.18	20.74	- 0.17	0.44
	22q11.2DS N=16		Controls N=40		Effect size [a]	Statistics [b]
Macula, µm	Mean	SD	Mean	SD	Cohen's *d*	*P*
Fovea	279.75	26.0	282.2	22.08	- 0.10	0.72
Parafovea						
Temporal	330.31	18.86	335.40	13.76	- 0.31	0.27
Superior	344.44	11.69	345.40	15.76	- 0.07	0.83
Nasal	344.81	12.55	348.63	13.12	- 0.30	0.33
Inferior	338.31	12.58	343.40	12.08	- 0.41	0.17
Perifovea						
Temporal	290.19	10.06	290.05	13.36	0.01	0.97
Superior	306.13	16.52	301.00	13.18	0.34	0.23
Nasal	311.88	20.89	317.74	14.29	- 0.33	0.23
Inferior	287.81	10.70	293.64	15.04	- 0.45	0.17

[a] Cohen's *d* effect sizes were determined by the mean difference between the groups, divided by the pooled SD.

[b] Independent samples T-tests were used to compare continuous variables between groups.

[c] The global RNFL thickness represents the average thickness of the six subsections.

Bold font indicates statistical significance.

22q11.2DS=22q11.2 deletion syndrome, SD=standard deviation, CRAE=central retinal artery equivalent, CRVE=central retinal vein equivalent, FD=fractal dimension, RNFL=retinal nerve fiber layer.

Regarding the peripapillary RNFL, moderate significant negative correlations were found of age with retinal thickness of the global, temporal inferior and temporal superior segments in adults with 22q11.2DS, but not in controls. For macular thickness, there was a significant moderate negative correlation of age with the perifoveal superior segment in both adults with 22q11.2DS and controls.

Table 3. Blood vessel morphology and retinal layer thickness in relation to age.

	22q11.2DS N=49		Controls N=57	
Blood vessel morphology	r [a]	*P*	r [a]	*P*
CRAE, µm	0.03	0.85	0.14	0.32
CRVE, µm	0.01	0.96	- 0.04	0.76
FD	- 0.57	**<0.001**	- 0.07	0.60
Tortuosity	0.04	0.78	- 0.08	0.56
	22q11.2DS N=41		Controls N=40	
Peripapillary RNFL, µm	r [a]	*P*	r [a]	*P*
Global [b]	- 0.42	**0.007**	- 0.07	0.68
Nasal superior	- 0.22	0.17	- 0.13	0.41
Nasal	- 0.25	0.11	0.02	0.89
Nasal inferior	- 0.10	0.53	- 0.01	0.94
Temporal inferior	- 0.43	**0.005**	- 0.01	0.95
Temporal	- 0.19	0.22	0.03	0.87
Temporal superior	- 0.32	**0.04**	- 0.16	0.31
	22q11.2DS N=16		Controls N=40	
Macula, µm	r [a]	*P*	r [a]	*P*
Fovea	- 0.19	0.48	0.21	0.20
Parafovea				
Temporal	0.02	0.96	- 0.06	0.72
Superior	- 0.07	0.79	- 0.28	0.08
Nasal	0.13	0.63	- 0.10	0.54
Inferior	- 0.18	0.52	- 0.07	0.68
Perifovea				
Temporal	- 0.41	0.12	- 0.25	0.13
Superior	- 0.50	**<0.05**	- 0.38	**0.02**
Nasal	- 0.06	0.82	- 0.25	0.13
Inferior	- 0.45	0.08	- 0.07	0.68

[a] Pearson correlation coefficient.

[b] The global RNFL thickness represents the average thickness of the six subsections.

Bold font indicates statistical significance.

22q11.2DS=22q11.2 deletion syndrome, CRAE=central retinal artery equivalent, CRVE=central retinal vein equivalent, FD=fractal dimension, RNFL=retinal nerve fiber layer.

Discussion

To the best of our knowledge, this is the first study that systematically assessed retinal blood vessel morphology and retinal layer thickness quantitatively in individuals with 22q11.2DS. Confirming the previously reported increased prevalence of vascular tortuosity,[27] we also found that adults with 22q11.2DS had increased retinal vascular FD and RNFL thickness of the nasal segment, and a trend for thinner RNFL in the nasal

inferior segment, as compared to controls. In addition, we found negative correlations of age with FD and RNFL thickness in the global, temporal inferior and temporal superior segments in adults with 22q11.2DS, that were not found in controls.

Retinal vascular morphometric abnormalities

Increased retinal vascular FD and tortuosity in the peripapillary region have been also reported in patients with community-based schizophrenia, [16, 20] a psychiatric disorder that affects about 1 in 4 patients with 22q11.2DS.[5] However, findings in this new research area are inconsistent. For example, lower macular FD has also been found in an independent sample of patients with schizophrenia.[17] Similarly, both smaller and wider arterioles, and wider venules, have been reported in patients with schizophrenia.[12, 16, 17] Wagner et al. recently discussed possible explanations for the inconsistent findings between studies, like the complex relationship between disease duration, retinovascular parameters, age, and comorbidities such as diabetes and hypertension.[17] Another contributing factor in this regard might be the retinal region studied, i.e., macular or peripapillary region, in the concerning studies.

The finding of a negative correlation of FD with age in adults with 22q11.2DS is consistent with studies in much older adults in the general population with (mild) cognitive impairment and Alzheimer's disease.[13, 28] This raises the question to what extent this finding indicates premature neurodegenerative processes, that may underly cognitive decline and early-onset Parkinson's disease in 22q11.2DS.[6, 8] Interesting in this context is that studies in a mouse model of aging have shown a negative relationship in retinal branching with age.[29, 30]

Retinal nerve fiber layer thickness

Thicker RNFL of the nasal, and a trend for thinner RNFL in the nasal inferior, segments in 22q11.2DS were found compared to controls. Findings from studies examining RNFL in idiopathic schizophrenia spectrum disorders have been inconsistent. Some studies found the RNFL to be significantly reduced, specifically in the nasal and superior segments,[15, 31] but not all.[17, 32, 33]

In 22q11.2DS, thinning of RNFL segments with increasing age are consistent with findings of a study in adults in the general population.[34] In that study, retinal layer thinning increasing with age was mainly found in the macular RNFL and the retinal ganglion cell layer. In Parkinson's disease, loss of retinal ganglion cells and axons has been found, with thinning of the peripapillary RNFL in the inferotemporal segments,[35] which is in line with our findings in adults with 22q11.2DS.

Implications

Together, findings of this study, and considering the consistency with previous studies in community-based schizophrenia spectrum and neurodegenerative disorders,[16, 20, 34, 35] suggest that retinal FD and tortuosity may be useful biomarkers for psychotic disorders, and FD and RNFL thickness for (early) neurodegenerative processes in 22q11.2DS. Similarly, it may aid in our understanding of disease trajectories in other genetic neurodevelopmental disorders.[36] An example may be found in a study in adults with Down syndrome that observed thinning of macular RNFL to be related to early Alzheimer's disease pathology.[37] To account for the earlier discussed factors that may contribute to retinal vessel morphology, and the medical complexity, adequately powered longitudinal studies are needed to better understand the changes that may occur within patients with 22q11.2DS.

Mechanisms underlying retinovascular and retinoneural abnormalities in 22q11.2DS

Potential biological mechanisms that may play a role in retinovascular and retinoneural abnormalities in 22q11.2DS include genetic variants, excessive mitophagy, cardiovascular abnormalities, and tissue oxygenation changes.[29, 38, 39] One candidate gene for retinal vascular abnormalities that lies within the LCR22A-LCR22B region is *TBX1*, encoding a T-box transcription factor. *TBX1* is important for cardiovascular development and regulates the vascular endothelial growth factor receptor 3-gene *VEGFR3* in brain endothelial cells.[40-42] Studies in mice have indicated an important role for *VEGFR3* in regulating angiogenesis and controlling branching of blood vessels in the retina and hindbrain.[43] Inactivation of *tbx1* in mice has shown to result in vascular abnormalities, impaired vascular functioning, and insufficient oxygenation in affected brain regions.[40] Another gene that has been postulated to be involved in retinal abnormalities in 22q11.2DS,

and that lies within the distal region of the typical 22q11.2 deletion, i.e., within LCR22C-LCR22D, is *SNAP29* (synaptosome associated protein 29).[44] This gene encodes a protein involved in several membrane trafficking steps, and is present in protein complexes that play a role in the subretinal neovascularization of age-related macular degeneration.[45, 46] Mice with a loss of function mutation of *Snap29* have shown significant thinning of the inner and outer nuclear layers of the retina.[47] In addition, excessive mitophagy, responsible for removal of damaged mitochondria, has been suggested to play a role in retinal ganglion cell neurodegeneration.[48] This is of interest, since it has also been hypothesized that mitochondrial dysfunction plays an important role in neurodegenerative processes in individuals with 22q11.2DS.[49, 50] Thus, the apparent decrease in RNFL (that is formed by axons of ganglion cells) with age in 22q11.2DS, and not in controls, may be indicative of increased mitochondrial dysfunction and axonal damage and may therefore be a potential biomarker for early neurodegeneration in 22q11.2DS. Vascularization of the central nervous system may play a role, but has been scarcely studied in 22q11.2DS. Findings of the few studies include hypoplastic and smaller cerebral arteries,[51] thicker cortical veins in patients with migrational disorders (e.g., polymicrogyria), and smaller veins of abnormal number or disorganized appearance.[52] Research has also shown elevated cerebral blood flow in the left and right putamen, the right fusiform gyrus, and the left middle temporal gyrus in 22q11.2DS, overlapping with regions of elevated blood flow in patients with idiopathic schizophrenia.[53] Increased cerebral blood flow has been found to be positively associated with retinal vascular FD in a cohort of healthy adults aged 65 years and over.[54] Another factor that may relate to retinovascular and retinoneural abnormalities is cyanotic congenital heart disease, through a complex interplay of factors including hypoxemia.[55]

Strengths and limitations

The study provides the first systematic quantitative assessment of retinal morphological features in 22q11.2DS, in a relatively large study sample for a rare disorder. Retinal vascular parameters and retinal layer thickness were assessed using (semi-)automated software, minimizing interrater differences. Limitations of the study include the cross-sectional design and young average age of the study sample. Future longitudinal studies are needed to study changes in retinal vascular parameters and RNFL thickness

over time, and to investigate the effects of comorbid conditions such as refractive errors, diabetes mellitus and blood pressure,[17, 27, 56-58] and effects of medications. It will also have to become clear to what extent abnormal retinal morphological findings are biomarkers of 22q11.2DS associated disease processes, or are merely manifestations of 22q11.2DS in themselves.

Conclusion

In conclusion, this exploratory study identified several retinovascular and retinoneural abnormalities in adults with 22q11.2DS compared to controls. The results of this study support future research that focus on retinal FD, tortuosity and RNFL thickness as potential biomarkers for psychotic and (early) neurodegenerative disorders in 22q11.2DS.

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Disclosures

The authors report there are no competing interests to declare.

Data availability

The data that support the findings of this study are available on request from the corresponding author, E.B. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

References

1. Blagojevic C, Heung T, Theriault M, et al. Estimate of the contemporary live-birth prevalence of recurrent 22q11.2 deletions: a cross-sectional analysis from population-based newborn screening. *CMAJ Open*. Jul-Sep 2021;9(3):E802-e809. doi:10.9778/cmajo.20200294
2. McDonald-McGinn DM, Sullivan KE, Marino B, et al. 22q11.2 deletion syndrome. *Nat Rev Dis Primers*. Nov 19 2015;1:15071. doi:10.1038/nrdp.2015.71
3. Bassett AS, Chow EW, Husted J, et al. Clinical features of 78 adults with 22q11 Deletion Syndrome. *Am J Med Genet A*. Nov 1 2005;138(4):307-13. doi:10.1002/ajmg.a.30984
4. Campbell IM, Sheppard SE, Crowley TB, et al. What is new with 22q? An update from the 22q and You Center at the Children's Hospital of Philadelphia. *Am J Med Genet A*. Oct 2018;176(10):2058-2069. doi:10.1002/ajmg.a.40637
5. Schneider M, Debbané M, Bassett AS, et al. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *Am J Psychiatry*. Jun 2014;171(6):627-39. doi:10.1176/appi.ajp.2013.13070864
6. Butcher NJ, Kiehl TR, Hazrati LN, et al. Association between early-onset Parkinson disease and 22q11.2 deletion syndrome: identification of a novel genetic form of Parkinson disease and its clinical implications. *JAMA Neurol*. Nov 2013;70(11):1359-66. doi:10.1001/jamaneurol.2013.3646
7. Evers LJ, van Amelsvoort TA, Candel MJ, Boer H, Engelen JJ, Curfs LM. Psychopathology in adults with 22q11 deletion syndrome and moderate and severe intellectual disability. *J Intellect Disabil Res*. Oct 2014;58(10):915-25. doi:10.1111/jir.12117
8. Vorstman JA, Breetvelt EJ, Duijff SN, et al. Cognitive decline preceding the onset of psychosis in patients with 22q11.2 deletion syndrome. *JAMA Psychiatry*. Apr 2015;72(4):377-85. doi:10.1001/jamapsychiatry.2014.2671
9. Morrison S, Chawner S, van Amelsvoort T, et al. Cognitive deficits in childhood, adolescence and adulthood in 22q11.2 deletion syndrome and association with psychopathology. *Transl Psychiatry*. Feb 3 2020;10(1):53. doi:10.1038/s41398-020-0736-7
10. Moss HE. Retinal Vascular Changes are a Marker for Cerebral Vascular Diseases. *Curr Neurol Neurosci Rep*. Jul 2015;15(7):40. doi:10.1007/s11910-015-0561-1
11. Patton N, Aslam T, Macgillivray T, Pattie A, Deary IJ, Dhillon B. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. *J Anat*. Apr 2005;206(4):319-48. doi:10.1111/j.1469-7580.2005.00395.x
12. Appaji A, Nagendra B, Chako DM, et al. Retinal vascular abnormalities in schizophrenia and bipolar disorder: A window to the brain. *Bipolar Disord*. Nov 2019;21(7):634-641. doi:10.1111/bdi.12779
13. Wu H, Wang C, Chen C, et al. Association between Retinal Vascular Geometric Changes and Cognitive Impairment: A Systematic Review and Meta-Analysis. *J Clin Neurol*. Jan 2020;16(1):19-28. doi:10.3988/jcn.2020.16.1.19
14. Coppola G, Di Renzo A, Ziccardi L, et al. Optical Coherence Tomography in Alzheimer's Disease: A Meta-Analysis. *PLoS One*. 2015;10(8):e0134750. doi:10.1371/journal.pone.0134750
15. Ascaso FJ, Laura C, Quintanilla MÁ, et al. Retinal nerve fiber layer thickness measured by optical coherence tomography in patients with schizophrenia: A short report. *The European Journal of Psychiatry*. 2010;24:227-235.
16. Appaji A, Nagendra B, Chako DM, et al. Retinal vascular fractal dimension in bipolar disorder and schizophrenia. *J Affect Disord*. Dec 1 2019;259:98-103. doi:10.1016/j.jad.2019.08.061
17. Wagner SK, Cortina-Borja M, Silverstein SM, et al. Association Between Retinal Features From Multimodal Imaging and Schizophrenia. *JAMA Psychiatry*. Mar 22 2023;doi:10.1001/jamapsychiatry.2023.0171
18. Ascaso FJ, Cruz N, Modrego PJ, et al. Retinal alterations in mild cognitive impairment and Alzheimer's disease: an optical coherence tomography study. *J Neurol*. Aug 2014;261(8):1522-30. doi:10.1007/s00415-014-7374-z

19. Demirkaya N, van Dijk HW, van Schuppen SM, et al. Effect of age on individual retinal layer thickness in normal eyes as measured with spectral-domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. Jul 22 2013;54(7):4934-40. doi:10.1167/iovs.13-11913
20. Appaji A, Nagendra B, Chako DM, et al. Retinal vascular tortuosity in schizophrenia and bipolar disorder. *Schizophr Res*. Oct 2019;212:26-32. doi:10.1016/j.schres.2019.08.020
21. Downie E, Tokarev J, Divani A, Koozekanani DD. Comparison of two free retinal vascular measurement software packages: IVAN and VAMPIRE. *Investigative Ophthalmology & Visual Science*. 2015;56(7):3320-3320.
22. Knudtson MD, Lee KE, Hubbard LD, Wong TY, Klein R, Klein BE. Revised formulas for summarizing retinal vessel diameters. *Curr Eye Res*. Sep 2003;27(3):143-9. doi:10.1076/ceyr.27.3.143.16049
23. Vico PG, Cartilier LH. A New Approach to the Study of Skin Vascularization. *Plastic and Reconstructive Surgery*. 1993;92(3)
24. Benitez-Aguirre P, Craig ME, Sasongko MB, et al. Retinal Vascular Geometry Predicts Incident Retinopathy in Young People With Type 1 Diabetes. *Diabetes Care*. 2011;34(7):1622. doi:10.2337/dc10-2419
25. Benitez-Aguirre PZ, Sasongko MB, Craig ME, et al. Retinal Vascular Geometry Predicts Incident Renal Dysfunction in Young People With Type 1 Diabetes. *Diabetes Care*. 2012;35(3):599. doi:10.2337/dc11-1177
26. Röhlig M, Prakasam RK, Stüwe J, Schmidt C, Stachs O, Schumann H. Enhanced Grid-Based Visual Analysis of Retinal Layer Thickness with Optical Coherence Tomography. *Information*. 2019;10(9):266.
27. von Scheibler E, van der Valk Bouman ES, Nuijts MA, et al. Ocular findings in 22q11.2 deletion syndrome: A systematic literature review and results of a Dutch multicenter study. *Am J Med Genet A*. Feb 2022;188(2):569-578. doi:10.1002/ajmg.a.62556
28. Lemmens S, Devulder A, Van Keer K, Bierkens J, De Boever P, Stalmans I. Systematic Review on Fractal Dimension of the Retinal Vasculature in Neurodegeneration and Stroke: Assessment of a Potential Biomarker. *Front Neurosci*. 2020;14:16. doi:10.3389/fnins.2020.00016
29. Lowerison MR, Sekaran NVC, Zhang W, et al. Aging-related cerebral microvascular changes visualized using ultrasound localization microscopy in the living mouse. *Sci Rep*. Jan 12 2022;12(1):619. doi:10.1038/s41598-021-04712-8
30. Murugesan N, Demarest TG, Madri JA, Pachter JS. Brain regional angiogenic potential at the neurovascular unit during normal aging. *Neurobiol Aging*. May 2012;33(5):1004.e1-16. doi:10.1016/j.neurobiolaging.2011.09.022
31. Ascaso FJ, Rodriguez-Jimenez R, Cabezón L, et al. Retinal nerve fiber layer and macular thickness in patients with schizophrenia: Influence of recent illness episodes. *Psychiatry Res*. Sep 30 2015;229(1-2):230-6. doi:10.1016/j.psychres.2015.07.028
32. Lee WW, Tajunisah I, Sharmilla K, Peyman M, Subrayan V. Retinal Nerve Fiber Layer Structure Abnormalities in Schizophrenia and Its Relationship to Disease State: Evidence From Optical Coherence Tomography. *Investigative Ophthalmology & Visual Science*. 2013;54(12):7785-7792. doi:10.1167/iovs.13-12534
33. Lai A, Crosta C, Loftin M, Silverstein SM. Retinal structural alterations in chronic versus first episode schizophrenia spectrum disorders. *Biomarkers in Neuropsychiatry*. 2020/06/01/2020;2:100013. doi:https://doi.org/10.1016/j.bionps.2020.100013
34. Wei Y, Jiang H, Shi Y, et al. Age-Related Alterations in the Retinal Microvasculature, Microcirculation, and Microstructure. *Invest Ophthalmol Vis Sci*. Jul 1 2017;58(9):3804-3817. doi:10.1167/iovs.17-21460
35. Huang L, Wang C, Wang W, Wang Y, Zhang R. The specific pattern of retinal nerve fiber layer thinning in Parkinson's disease: a systematic review and meta-analysis. *J Neurol*. Nov 2021;268(11):4023-4032. doi:10.1007/s00415-020-10094-0
36. Hickman RA, O'Shea SA, Mehler MF, Chung WK. Neurogenetic disorders across the lifespan: from aberrant development to degeneration. *Nat Rev Neurol*. Feb 2022;18(2):117-124. doi:10.1038/s41582-021-00595-5
37. Walpert MJ, Normando EM, Annus T, et al. Age-related retinal thickness in Down's syndrome: A high-risk population for dementia. *Alzheimers Dement (Amst)*. Dec 2019;11:744-751. doi:10.1016/j.dadm.2019.08.007

38. Mansour AM, Bitar FF, Traboulsi EI, et al. Ocular pathology in congenital heart disease. *Eye*. 2005/01/01 2005;19(1):29-34. doi:10.1038/sj.eye.6701408
39. Khansari MM, Garvey SL, Farzad S, Shi Y, Shahidi M. Relationship between retinal vessel tortuosity and oxygenation in sickle cell retinopathy. *Int J Retina Vitreous*. 2019;5:47. doi:10.1186/s40942-019-0198-3
40. Cioffi S, Martucciello S, Fulcoli FG, et al. Tbx1 regulates brain vascularization. *Hum Mol Genet*. Jan 1 2014;23(1):78-89. doi:10.1093/hmg/ddt400
41. Baldini A, Fulcoli FG, Illingworth E. Tbx1: Transcriptional and Developmental Functions. *Curr Top Dev Biol*. 2017;122:223-243. doi:10.1016/bs.ctdb.2016.08.002
42. Cioffi S, Flore G, Martucciello S, Bilio M, Turturo MG, Illingworth E. VEGFR3 modulates brain microvessel branching in a mouse model of 22q11.2 deletion syndrome. *Life Sci Alliance*. Dec 2022;5(12)doi:10.26508/lsa.202101308
43. Tammela T, Zarkada G, Nurmi H, et al. VEGFR-3 controls tip to stalk conversion at vessel fusion sites by reinforcing Notch signalling. *Nat Cell Biol*. Sep 11 2011;13(10):1202-13. doi:10.1038/ncb2331
44. Cordovez JA, Capasso J, Lingao MD, et al. Ocular manifestations of 22q11.2 microduplication. *Ophthalmology*. Jan 2014;121(1):392-398. doi:10.1016/j.ophtha.2013.06.040
45. Rotem-Yehudar R, Galperin E, Horowitz M. Association of insulin-like growth factor 1 receptor with EHD1 and SNAP29. *J Biol Chem*. Aug 31 2001;276(35):33054-60. doi:10.1074/jbc.M009913200
46. Rosenthal R, Wohlleben H, Malek G, et al. Insulin-like growth factor-1 contributes to neovascularization in age-related macular degeneration. *Biochem Biophys Res Commun*. Oct 29 2004;323(4):1203-8. doi:10.1016/j.bbrc.2004.08.219
47. Keser V, Lachance JB, Alam SS, et al. Snap29 mutant mice recapitulate neurological and ophthalmological abnormalities associated with 22q11 and CEDNIK syndrome. *Commun Biol*. 2019;2:375. doi:10.1038/s42003-019-0601-5
48. Carelli V, La Morgia C, Ross-Cisneros FN, Sadun AA. Optic neuropathies: the tip of the neurodegeneration iceberg. *Hum Mol Genet*. Oct 1 2017;26(R2):R139-r150. doi:10.1093/hmg/ddx273
49. Fernandez A, Meechan DW, Karpinski BA, et al. Mitochondrial Dysfunction Leads to Cortical Under-Connectivity and Cognitive Impairment. *Neuron*. Jun 19 2019;102(6):1127-1142.e3. doi:10.1016/j.neuron.2019.04.013
50. Bose A, Beal MF. Mitochondrial dysfunction in Parkinson's disease. *J Neurochem*. Oct 2016;139 Suppl 1:216-231. doi:10.1111/jnc.13731
51. Chow EW, Mikulis DJ, Zipursky RB, Scutt LE, Weksberg R, Bassett AS. Qualitative MRI findings in adults with 22q11 deletion syndrome and schizophrenia. *Biol Psychiatry*. Nov 15 1999;46(10):1436-42. doi:10.1016/s0006-3223(99)00150-x
52. Bohm LA, Zhou TC, Mingo TJ, et al. Neuroradiographic findings in 22q11.2 deletion syndrome. *Am J Med Genet A*. Aug 2017;173(8):2158-2165. doi:10.1002/ajmg.a.38304
53. Pasternak M, Shirzadi Z, Mutsaerts H, et al. Elevated regional cerebral blood flow in adults with 22q11.2 deletion syndrome. *World J Biol Psychiatry*. Jul 15 2022:1-6. doi:10.1080/15622975.2022.2093969
54. Nadal J, Deverdun J, de Champfleur NM, et al. Retinal vascular fractal dimension and cerebral blood flow, a pilot study. *Acta Ophthalmol*. Feb 2020;98(1):e63-e71. doi:10.1111/aos.14232
55. Cordina R, Leaney J, Golzan M, Grieve S, Celermajer DS, Graham SL. Ophthalmological consequences of cyanotic congenital heart disease: vascular parameters and nerve fibre layer. *Clin Exp Ophthalmol*. Mar 2015;43(2):115-23. doi:10.1111/ceo.12401
56. Cheung CY, Thomas GN, Tay W, et al. Retinal vascular fractal dimension and its relationship with cardiovascular and ocular risk factors. *Am J Ophthalmol*. Oct 2012;154(4):663-674.e1. doi:10.1016/j.ajo.2012.04.016
57. Myers CE, Klein R, Knudtson MD, et al. Determinants of retinal venular diameter: the Beaver Dam Eye Study. *Ophthalmology*. Dec 2012;119(12):2563-71. doi:10.1016/j.ophtha.2012.06.038
58. Califf RM. Biomarker definitions and their applications. *Exp Biol Med (Maywood)*. Feb 2018;243(3):213-221. doi:10.1177/1535370217750088

Chapter 7

Post-traumatic stress in adults with 22q11.2 deletion syndrome

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Abstract

22q11.2 deletion syndrome (22q11.2DS) is associated with an elevated genetic risk of several psychiatric disorders. The prevalence of post-traumatic stress disorder (PTSD) has however been reported to be only 0.9%; lower compared to the general population. We explored occurrence of PTSD and traumatic events in a Dutch cohort of 112 adults with 22q11.2DS. PTSD was reported in 8.0%, traumatic events in 20.5%, and trauma-focused treatment in 17.9% of patients. Our novel findings suggest PTSD may be underdiagnosed in 22q11.2DS. Clinicians and other caregivers should be alert to trauma in this population in order to enable treatment and minimize psychiatric burden.

Introduction

22q11.2 deletion syndrome (22q11.2DS) is a genetic multisystem disorder with an estimated prevalence of 1 in 2148 live births.[1] Patients with 22q11.2DS have the highest known genetic risk for schizophrenia, and other psychiatric disorders are collectively even more common.[2] Counterintuitively, the reported prevalence of post-traumatic stress disorder (PTSD), a psychiatric disorder related to the experience or witnessing of a traumatic event, is much lower compared to the reported prevalence in the general population; 0.9% in 22q11.2DS *vs* 3.9%.[2, 3] Despite advances in treatment of PTSD,[4] multiple factors including under-recognition of PTSD and experiences of traumatic events could limit implementation of these best practices, contributing to psychiatric burden in 22q11.2DS.[5]

We hypothesized a higher prevalence of PTSD in adults with 22q11.2DS compared to the general population.[3] Therefore, we aimed to explore: 1) the prevalence of, and potential predictors to, PTSD and 2) the prevalence of potentially traumatic events in 112 adult patients who visited one of the two Dutch specialty clinics.

Methods

As part of ongoing studies on 22q11.2DS, we retrospectively reviewed documentation of direct assessments and available medical records from patients who were 16 years or older at the 22q11.2 outpatient clinic at Maastricht University Medical Centre+ (MUMC) and/or 's Heeren Loo.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects at MUMC were approved by the medical ethics committee of MUMC (#14-2044, #19-044). A waiver for formal approval of the study at 's Heeren Loo was obtained from the medical ethics committee of Amsterdam UMC, the Netherlands (#W20_098). Written informed consent was obtained from all patients and/or legal representatives.

Sample

We studied data of 112 patients (mean age 32.5±12.4 years, 45% male) with a molecularly confirmed 22q11.2 deletion. Patients were ascertained through referrals from five main sources, from most to least frequent: family medicine, intellectual disability medicine, paediatrics, psychiatry, and medical genetics.

Outcome measures

We recorded information on demographic variables, cognitive functioning (full-scale intelligence quotient; FSIQ), and psychiatric history. A clinical diagnosis of PTSD was the primary outcome measure. We also recorded traumatic events, defined as in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) subsection A of PTSD (i.e., exposure to actual or threatened death, serious injury or sexual violence according), additional potentially traumatic events affecting daily functioning, and any treatment for traumatic events.

Statistical analysis

We assessed prevalence rates of PTSD and frequencies of patients with a history of traumatic events and/or treatment for trauma in our sample, and calculated 95% confidence intervals (95% CI) using the formula CI= $p \pm 1.96^* \sqrt{(p(1-p)/n)}$. A logistic regression analysis was used to identify potential predictors to the presence of a clinical diagnosis of PTSD. For this, we considered sex and FSIQ based on previous studies.[6] All analyses were two-tailed p-values with statistical significance defined as <0.05 using IBM SPSS software (Statistics 25; Inc., Chicago, IL).

Results

Nine patients (8.0%, 95% CI: 3.0%-13.0%) had a clinical diagnosis of PTSD, of whom two were referred to specialized 22q11 clinics for trauma-related problems and treatment (Table 1). Twenty-three (20.5%) of all patients experienced one or more traumatic events according to DSM-5 criteria, with 12 (10.7%) reporting sexual violence, 11 (9.8%) serious injury (including physical abuse), and 4 (3.6%) actual or threatened death. Neglect was

reported in only one patient. An additional 17 patients (15.2%) experienced other potential traumatic events including bullying (n=13, 11.6%), multiple hospitalizations/surgeries (n=4, 3.6%) and out-of-home placement (n=4, 3.6%). Neither sex nor FSIQ were predictors of a PTSD diagnosis (p=0.58 and p=0.53 respectively).

Table 1. Trauma in 112 adults with 22q11.2 deletion syndrome

History of trauma	N	%	95% CI, %
Clinical PTSD diagnosis	9	8.0	3.0-13.0
Traumatic events [a,b]	23	20.5	13.0-28.0
Sexual violence	12	10.7	5.0-16.4
Serious injury	11	9.8	4.3-15.3
Actual or threatened death	4	3.6	0.2-7.1
Other potential traumatic events [c]	17	15.2	8.6-21.8
Multiple (≥ 2) traumatic events [d]	14	12.5	6.4-18.6
Treatment for trauma-related conditions	**N**	**%**	**95% CI, %**
Treatment for any traumatic event	20	17.9	10.8-25.0
Eye Movement Desensitization Reprocessing	19	17.0	10.0-24.0
Cognitive behavioural therapy	2	1.8	0-4.3
Other	2	1.8	0-4.3

[a] In one patient with PTSD, traumatic events were not specified.

[b] Meeting DSM-5 criteria for a traumatic event.

[c] Events not meeting DSM-5 criteria for a traumatic event.

[d] Irrespective whether DSM-5 criteria were met.

N=number, 95% CI=95% confidence interval, PTSD=post-traumatic stress disorder.

Treatment for trauma was reported in 20 patients (17.9%) and included eye movement desensitization reprocessing (EMDR; n=19, 17.0%) therapy and cognitive behavioural therapy (CBT; n=2, 1.8%); one patient received both therapies. Of the 9 patients with PTSD, 8 were treated with EMDR therapy, including one 1 with additional CBT. In those with PTSD, the treatment response was noted to be effective in four, and minimal to absent in another three patients. For one patient with PTSD the response to treatment was not reported. Another patient with PTSD did not receive therapy; this was considered not feasible due to significant neurocognitive decline.

Discussion

The results of this first explorative study focusing on trauma in adults with 22q11.2DS support our hypothesis of an elevated risk of developing PTSD (8.0%) as compared with the general population (3.9%).[2, 3]

There is growing evidence that intellectual disability and borderline intellectual functioning, both often seen in 22q11.2DS, increase the risk of exposure to traumatic events and the development of PTSD symptoms,[5-7] with direct negative effects on emotional, behavioural and adaptive functioning.[8] Also, life events are more likely to be experienced as traumatic in people with intellectual disabilities, even though DSM-5 criteria are not always met.[5] PTSD and traumatic experiences are however often not recognized in these populations.[5,6] One reason may be that symptoms may be overshadowed by, or attributed to, other psychiatric disorders such as psychotic illness.[6] Another reason may be that patients and/or their relatives themselves do not recognize trauma-related symptoms,[6] or find it hard to ask for help for trauma-related symptoms. Also, professionals may hesitate to pay attention to past traumatic experiences, out of fear of aggravating symptoms and causing a crisis.[6] Therefore, we presume under-recognition and/or under-reporting of PTSD and traumatic experiences in 22q11.2DS. Here, it should also be noted that adults and patients with intellectual disability were underrepresented in previous 22q11.2DS research.[2]

Recognition of trauma and PTSD is important since it allows for treatment which may also have the potential of reducing psychosis risk in high-risk populations,[9] such as 22q11.2DS. While we are not aware of any study reporting on the effectiveness of interventions for trauma in 22q11.2DS, an increasing number of studies have shown positive effects of EMDR and CBT in individuals with intellectual disability.[10]

Strengths and limitations

The strengths of this study include the relatively large adult 22q11.2DS sample and the fact that the focus on trauma was not limited to strict DSM-5 criteria for PTSD. There were also several limitations, mostly related to the retrospective nature of the study. For example, data were limited to the

available clinical reports. As a consequence, PTSD prevalence may still have been underestimated.[6] On the other hand, bias towards patients with 22q11.2DS with more severe mental health problems is possible, given that all patients were referred to a 22q11.2DS specialty clinic. Prospective studies are needed to replicate our findings, to further explore the risk of trauma, and to assess the effectiveness of trauma-focused treatments and resilience in 22q11.2DS.

Conclusions

In conclusion, PTSD and traumatic events appear to be more prevalent than previously assumed in adults with 22q11.2DS. Clinicians and other caregivers should thus be alert to PTSD in 22q11.2DS in order to minimize psychiatric burden with reduced quality of life. Systematic studies in individuals with 22q11.2DS are needed to improve diagnosis, using strategies adjusted to their strengths and weaknesses and including attention to seemingly unimportant life events that may be traumatic, and evaluate the efficacy of treatments in this population.

Declaration of interest

Declaration of Interest: None.

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Data-availability

The data that support the findings of this study are available from the corresponding author, EB, upon reasonable request.

References

1. Blagojevic C, Heung T, Theriault M, et al. Estimate of the contemporary live-birth prevalence of recurrent 22q11.2 deletions: a cross-sectional analysis from population-based newborn screening. *CMAJ Open*. Jul-Sep 2021;9(3):E802-e809. doi:10.9778/cmajo.20200294
2. Schneider M, Debbané M, Bassett AS, et al. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *Am J Psychiatry*. Jun 2014;171(6):627-39. doi:10.1176/appi.ajp.2013.13070864
3. Koenen KC, Ratanatharathorn A, Ng L, et al. Posttraumatic stress disorder in the World Mental Health Surveys. *Psychol Med*. Oct 2017;47(13):2260-2274. doi:10.1017/s0033291717000708
4. Aliev G, Beeraka NM, Nikolenko VN, et al. Neurophysiology and Psychopathology Underlying PTSD and Recent Insights into the PTSD Therapies-A Comprehensive Review. *J Clin Med*. Sep 12 2020;9(9)doi:10.3390/jcm9092951
5. Martorell A, Tsakanikos E. Traumatic experiences and life events in people with intellectual disability. *Curr Opin Psychiatry*. Sep 2008;21(5):445-8. doi:10.1097/YCO.0b013e328305e60e
6. Nieuwenhuis JG, Smits HJH, Noorthoorn EO, Mulder CL, Penterman EJM, Nijman HLI. Not recognized enough: The effects and associations of trauma and intellectual disability in severely mentally ill outpatients. *European Psychiatry*. 2019;58:63-69. doi:10.1016/j.eurpsy.2019.02.002
7. Jones L, Bellis MA, Wood S, et al. Prevalence and risk of violence against children with disabilities: a systematic review and meta-analysis of observational studies. *Lancet*. Sep 8 2012;380(9845):899-907. doi:10.1016/s0140-6736(12)60692-8
8. Wigham S, Taylor JL, Hatton C. A prospective study of the relationship between adverse life events and trauma in adults with mild to moderate intellectual disabilities. *Journal of Intellectual Disability Research*. 2014;58(12):1131-1140.
9. Brand RM, McEnery C, Rossell S, Bendall S, Thomas N. Do trauma-focussed psychological interventions have an effect on psychotic symptoms? A systematic review and meta-analysis. *Schizophr Res*. May 2018;195:13-22. doi:10.1016/j.schres.2017.08.037
10. Mevissen L, de Jongh A. PTSD and its treatment in people with intellectual disabilities: a review of the literature. *Clin Psychol Rev*. Apr 2010;30(3):308-16. doi:10.1016/j.cpr.2009.12.005

Chapter 8

General discussion and future perspectives

General discussion and future perspectives

The natural life course of most genetic neurodevelopmental disorders (GNDs) has been understudied, resulting in a knowledge gap and health disparities, particularly for manifestations at adult age.[1] The studies included in this thesis have contributed to our knowledge of prevalence rates and characteristics of conditions including parkinsonism, otolaryngologic and ophthalmic conditions and post-traumatic stress in adults with 22q11.2 deletion syndrome (22q11.2DS) and other GNDs. Most results were obtained by routine examinations at specialized 22q11.2 clinics including the expert center for adults at Maastricht University Medical Center and 's Heeren Loo. In this chapter the clinical findings in adults with 22q11.2DS and other GNDs are discussed, in addition to predictive markers and pathophysiology of conditions at adult age, methodological considerations and recommendations for clinical practice and future research.

Expanding the phenotype of adults with 22q11.2 deletion syndrome

Presented in **chapters 3-5 and 7**, adults with 22q11.2DS were found to have an increased risk of early-onset Parkinson's disease, hearing loss, refractive errors and PTSD compared to the general population.[2-5] There are two important notes. First, results often showed a high variability among adults with 22q11.2DS, for example in severity of hearing loss, refractive errors and retinovascular parameters (**chapter 6**). This inter-individual variability has also been reported in other conditions in 22q11.2DS and, although contributors are not yet fully understood, may be related to the many genes involved in the 22q11.2 deletion, additional genetic variants, stochastic events during embryogenesis and environmental effects.[6, 7] Second, an increased prevalence of these conditions in adults with 22q11.2DS compared to the general population does not implicate that they are specific expressions of a 22q11.2 microdeletion. For example, a comparable prevalence and type of hearing loss has also been found in adults with Down syndrome,[8] and children with an intellectual disability are reported to have prevalence rates of strabismus and amblyopia comparable to those found in children with 22q11.2DS.[9] Also, the increased risk to post-traumatic stress may not be specific for individuals with 22q11.2DS, with prevalence rates in line with results reported for individuals with an

intellectual disability.[10] Prevalence rates that seem to be higher compared to the general population and to adults with an intellectual disability, included for example Parkinson's disease, astigmatism, posterior embryotoxon and retinal vascular tortuosity,[2, 3, 11-13] although not all of these conditions have been studied well in other GNDs. In the following paragraphs, the most important results and recommendations for clinical practice and future studies in adults with 22q11.2DS are discussed per study topic.

Parkinson's disease

In **chapter 3**, it was found that adults with 22q11.2DS have an increased risk of Parkinson's disease; much higher compared to what has been reported in the general population.[2] This suggests that hemizygosity of one or more genes within the typically deleted 22q11.2 region convey an increased risk of Parkinson's disease. Future study of these genes and underlying mechanisms may provide insights into the pathophysiology of Parkinson's disease in 22q11.2DS, that may possibly also be of importance for the study of idiopathic Parkinson's disease. Other main findings included a sharp increase in Parkinson's disease after the age of 50 years, with motor onset about one decade earlier, and the equal prevalence of Parkinson's disease between males and females with 22q11.2DS, different from what has been reported in the general population and previous studies of adults with 22q11.2DS.[2, 14] These insights do not only provide directions for future research but are also of clinical relevance. Based on these findings and the impact of Parkinson's disease on a person's life, standard neurological assessments seem warranted after the age of 40 years to screen for parkinsonian (motor) features. Early detection of Parkinson's disease can be beneficial,[15] since it allows for early treatment with anti-parkinsonian medication which was found to be able to reduce motor symptoms in the majority of individuals with 22q11.2DS.[14]

Hearing loss and otolaryngological findings

In **chapter 4**, it was found that the majority of adults with 22q11.2DS had hearing loss, mostly of the higher frequencies, while only ~30% of adults were known to have hearing loss prior to the routine audiometric screening. Hearing loss started at a much younger age compared to the general population, though with a pattern suggestive of age-related hearing loss

as seen in the general population, and comparable to what has been found in adults with Down syndrome as mentioned before.[8, 16] Otolaryngologic findings that were reported in previous studies in individuals with 22q11.2DS, such as obstructive sleep apnea and balance problems, were found in this study as well,[17, 18] in addition to globus pharyngeus which has not been reported before in studies of adults with 22q11.2DS. In some adults globus pharyngeus was accompanied by, and potentially related to, feelings of stress. It may therefore be interesting to study stress in relation to other prevalent, not yet fully understood, symptoms in individuals with 22q11.2DS, such as fatigue and gastro-intestinal manifestations, [19, 20] because of possible altered stress reactivity and cortisol levels in 22q11.2DS,[21] and links between stress and several physical and mental conditions in the general population.[22, 23] Results of the study discussed in **chapter 4** may help to close the knowledge gap concerning conditions that are present at adult age and may improve clinical practice. Based on results of this study, periodic audiometric screening is recommended, including high-frequency testing at 8 kHz, and otolaryngologic examination at least once in adulthood. Depending on the severity of hearing loss, hearing aids may be prescribed to amplify sounds to improve hearing, which may even prevent or diminish depressive symptoms, stress, anxiety and improve quality of life.[24, 25]

Vision and ocular findings

Because only a minority of adults had ocular findings of clinical relevance, low-threshold referral to an ophthalmologist upon indication is recommended in **chapter 5**. Because ophthalmic findings in adults seemed to be comparable to those in adults with an intellectual disability in general, adults with 22q11.2DS may adhere to regular screening guidelines for individuals with an intellectual disability.[26] In addition, as a result of some clinically relevant but rare findings, testing for a second genetic hit is recommended in case of a second, possibly genetic, diagnosis such as tapetoretinal degeneration or congenital cataract. Dual diagnoses have been reported in previous studies in individuals with 22q11.2DS, sometimes resulting from genetic variants on the non-affected allele, and may have implications for clinical care and genetic counseling.[27]

Post-traumatic stress

In **chapter 7**, it was found that adults with 22q11.2DS have a higher prevalence of PTSD compared to the general population. Based on these findings clinicians and caregivers are advised to be alert to trauma and PTSD in 22q11.2DS, and to consider treatment interventions such as eye movement desensitization reprocessing therapy. Good clinical care early in life may prevent the onset, or delay progression, of conditions at adult age. This may also be the case for trauma and PTSD.[28, 29] Some traumatic events reported by adults with 22q11.2DS occurred earlier in life, including bullying, hospital admissions and surgeries. The study of trauma and PTSD in adults with 22q11.2DS raises awareness for these potential traumatic events and PTSD in both adults and children. Discussion within the family or with care givers about possible traumatic events is important at any age and may facilitate early intervention. In addition, education about (sexual) boundaries, relationships or interventions aimed to reinforce resilience may be helpful in childhood or adolescent age in dealing with, or preventing, potentially traumatic events and PTSD later in life.[28, 29]

Predictive markers for late-onset disorders in adults with 22q11.2 deletion syndrome

When considering the adult phenotype of 22q11.2DS, it is important to realize that its associated conditions may have their roots earlier in life. Therefore, it is crucial to study conditions over the life course to get a good understanding of factors contributing to late-onset conditions and in order to recognize, prevent or treat these conditions timely. It is still unclear which individuals with 22q11.2DS will develop disorders associated with the adult phenotype such as Parkinson's disease. There have been attempts to identify early predictors, mainly for psychosis, in individuals with 22q11.2DS.[30-32] For example, cognitive decline was found to precede the development of psychosis,[30] and olfactory deficit and brain connectivity patterns have been proposed as potential biomarkers.[31, 32] Possible contributors to several late-onset disorders were studied in adults with 22q11.2DS described in this thesis.

In **chapter 3**, age, but not sex, was found to be related to the development of Parkinson's disease. In the study on hearing described in **chapter 4**, age and

a history of chronic otitis media were related to more severe hearing loss. For PTSD, described in **chapter 7**, no relationship was found with either sex or full-scale intelligence quotient. These results may provide clues to which individuals may be at increased risk of conditions that develop over the life course. However, it is important to take into account the retrospective study design, that makes it impossible to draw conclusions about causality.

With respect to prediction, ideally, a risk biomarker (*a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention*, according to the FDA-NIH working group)[33] could be used to identify individuals with 22q11.2DS with an increased risk of developing, for example, Parkinson's disease or schizophrenia. This would facilitate screening and early interventions in individuals that are of increased risk, and may potentially limit hospital visits and examinations for those who are not. In **chapter 6**, retinovascular and retinoneural parameters were explored in adults with 22q11.2DS, and outcomes were compared with those in controls. The rationale for this lies in the fact that these parameters may possibly be used as biomarkers for psychiatric and neurodegenerative disorders in 22q11.2DS, given similarities with cerebral tissue; changes may reflect cerebral vascular and neural changes.[34-39] Fundoscopy and optical coherence tomography (OCT) are non-invasive imaging techniques that were used to visualize and quantify these retinal parameters. OCT and fundoscopy have benefits over brain imaging, because they are faster, less-expensive, easier to operate and can therefore be used in smaller hospitals or other care facilities.[37, 40] Results showed differences in retinovascular parameters between adults with 22q11.2DS and controls. In addition, some retinovascular and retinoneural parameters decreased with age in adults with 22q11.2DS but not in controls. Unfortunately, due the retrospective study design and lack of standardized assessments of cognitive function and psychosis in this study, it was not possible to compare these parameters between adults with 22q11.2DS with and without psychosis or cognitive decline. However, findings in adults with 22q11.2DS compared to controls and in relation to age were in the same direction as results reported in previous studies in community-based schizophrenia and neurodegenerative disorders,[41-44] and support future studies that focus on these parameters as potential

biomarkers for psychiatric and (early) neurodegenerative disorders in individuals with 22q11.2DS. The ability to identify individuals with an increased risk may be further increased by combining multiple biomarkers, such as neurofilament light chain for neurodegenerative disorders.[45] In addition, studying retinovascular and retinoneural parameters in other GNDs may aid in our understanding of disease trajectories,[46] and may identify individuals at risk of other late-onset disorders such as Alzheimer's disease in adults with Down syndrome.[47]

Late-onset disorders in 22q11.2DS and other GNDs; potential (shared) underlying mechanisms

In the study described in **chapter 3,** it was found that adults with 22q11.2DS have a high prevalence of Parkinson's disease,[48] and in **chapter 2** many other GNDs were found to be associated with neurodegenerative parkinsonism as well. Although no conclusions can be drawn regarding the prevalence of (neurodegenerative) parkinsonism in these GNDs, and under-recognition and under-study of parkinsonism in GNDs probably resulted in an incomplete list, the literature study in **chapter 2** provides clues as to which GNDs may be more susceptible to (neurodegenerative) parkinsonism and raises awareness for parkinsonism in the group of GNDs as a whole. Findings of early-onset and progressive motor symptoms combined with neuronal loss in the majority of individuals with neuropathological results, were supportive of neurodegeneration in a substantial proportion of the included individuals. In addition, for several GNDs cellular mechanisms could be identified, including mitochondrial dysfunction, that may be involved in the pathophysiology of both developmental as well as neurodegenerative disorders (Figure 1). A genetic susceptibility to neurodegeneration may also include dysfunction of micro RNAs, that may alter the expression of multiple genes and provide the basis for neuronal cell deteriotion.[49] Micro RNAs are important for cell regulation, development, differentiation, stress response and apoptosis, and age-related changes in expression have been found.[49, 50] Several micro RNAs lie within the 22q11.2 deletion region, and were suggested to be important for the maturation of the adolescent and early adult brain.[51]

Dysregulation of cellular processes in 22q11.2DS and other GNDs may result in an increased susceptibility of long-lived neurons to develop neurologic and psychiatric disorders over the life span, morbidities that were frequently reported in GNDs described in **chapter 2**.

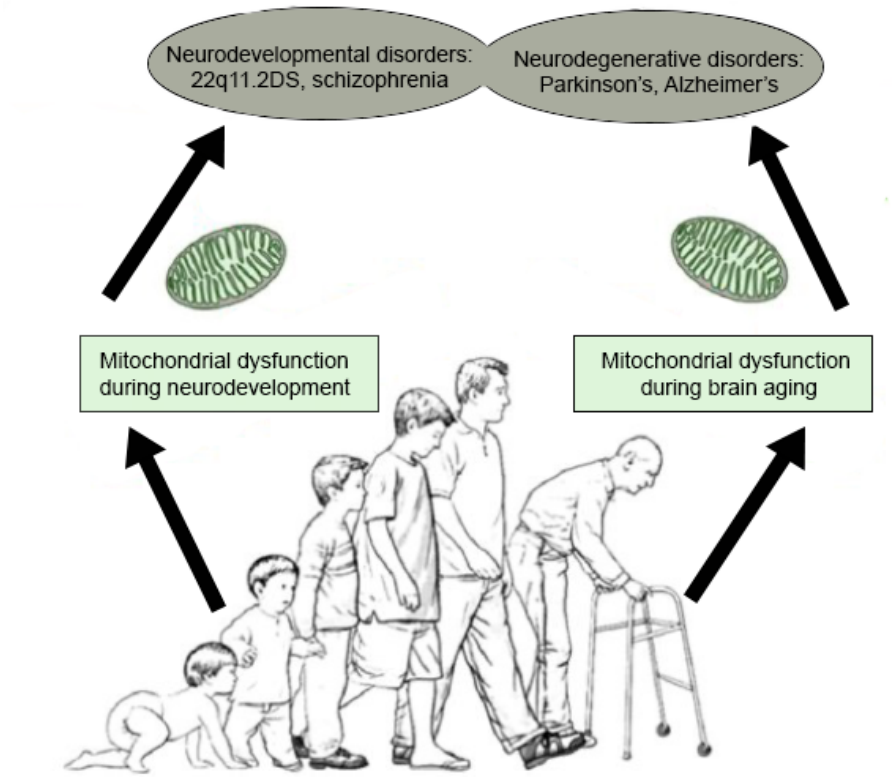

Figure 1. Mitochondrial dysfunction may contribute to both neurodevelopmental and neurodegenerative disorders (adapted from Granat at el.[52])

These findings may support the hypothesis of a neurodevelopmental neurodegenerative continuum.[46, 53] Other findings in adults with 22q11.2DS, described in **chapters 4 and 6**, may be indicative of this overlap as well. Hearing loss was found to be positively related to age, comparable to what has been reported in the general population,[4] but presented at a much younger age in adults with 22q11.2DS. In addition, the decrease of retinal fractal dimension with age in adults with 22q11.2DS, described in

chapter 6, has also been reported in individuals from the general population but only after the age of 65 years.[43] These examples may suggest that some of the mechanisms contributing to age-related disorders are similar between adults with 22q11.2DS and the general population, but have their onset earlier in life. These findings may also suggest the presence of other neurodegenerative conditions in GNDs at an earlier age than would be expected based on results from the general population. In future research it would be interesting to study other neurodegenerative conditions in GNDs, such as cognitive decline/dementia.

With respect to 22q11.2DS, hemizygosity of protein-coding genes within the 22q11.2 deletion region that were suggested to contribute to conditions at adult age included *TBX1* and genes involved in mitochondrial function.[54] *TBX1* is important for the 22q11.2DS somatic phenotype, and is involved in the development of the cardiac and vascular system, including the stria vascularis, central nervous system and inner ear, including the semicircular canal. [55, 56] Described in **chapter 4**, hemizygosity of *TBX1* may result in vulnerability of the cochlea and contribute to age-related hearing loss. In addition, *TBX1* may be responsible for retinovascular abnormalities found in individuals with 22q11.2DS because of its involvement in angiogenesis and vessel branching described in **chapter 6**.[57] Other candidate genes include those involved in mitochondrial function; at least six are located in the 22q11.2 region.[54] Mitochondrial dysfunction and oxidative stress have been proposed, in **chapters 3, 4 and 6**, as possible contributors to degenerative changes which may contribute to the development of age-related hearing loss, retinal abnormalities, Parkinson's disease as well as other conditions outside the scope of this thesis but important for the adult phenotype, such as schizophrenia. [58-61]

Methodological considerations

Results described in this thesis should be considered in the context of several strengths and limitations. Some related to more than one study and will be discussed in the following paragraphs because they may be of relevance to future studies. Strengths included the relatively large samples of adults with 22q11.2DS. In addition, adults were often examined as part of routine 22q11.2DS-related care.[62] For example, ophthalmic, neurologic

and otolaryngologic examinations are part of standard routine care at the 22q11.2 expert clinic at Maastricht University Medical Center. Only a minority of adults were examined upon indication for (suspicion of) ophthalmic, otolaryngologic or movement disorders. Limitations mainly related to the retrospective or cross-sectional design of most studies. Data concerning the medical history may not be complete resulting in an underestimation of the studied conditions. In some cases, patients that were examined were noncooperative or had difficulties with performing tasks, which most likely concerned individuals with a more severe phenotype, that may have resulted in a slight underestimation of the prevalence rates of studied conditions. However, referral bias may have resulted in higher prevalence rates because individuals with 22q11.2DS with a more severe phenotype may have higher probabilities of being referred to a 22q11 specialty clinic. Age of onset of conditions such as hearing loss, refractive errors or sleep apnea was often not reported in the medical files, and was therefore not subject of study. This hampers the ability to differentiate between manifestations with early- or adult-onset, which is important information for the improvement of screening recommendations. In addition, the average age of the study participants in most studies was still quite young. Because most conditions may increase with age, this will have resulted in an underestimation of prevalence rates of late-onset conditions.

Comparisons of studied conditions with previous studies was often complicated due to the use of different definitions, cut-off values and measurement techniques or because other studies did not distinguish findings in children from findings in adults.[63-65]

The systematic literature review, described in **chapter 2,** had some specific limitations of which the most important one relates to the definition that was used for a GND. Inclusion of all conditions listed in HPO as "neurodevelopmental abnormality", in addition to the large number and wide spectrum of genetically and clinically heterogeneous disorders and the absence of a perfect classification system, may have resulted in the inclusion of conditions that should not be considered to affect brain development.

Future perspectives

If neurodevelopment and neurodegeneration are a continuum rather than distinct entities this implicates that research aimed at identifying novel treatment targets should focus on shared underlying mechanisms rather than specific conditions or symptoms. However, characterization of manifestations that develop over the life course may aid in our understanding of possible underlying mechanisms and will help to improve recommendations for clinical care and genetic counseling. Changes in phenotype may occur in mid or late adulthood and be informative of gene expression or gene-environment interactions.[66] In addition, recognition of GNDs that are at increased risk of, for example Parkinson's disease, may facilitate the use of animal and cell models that will further our understanding of underlying mechanisms and move drug discovery. With advances in diagnosis and treatment of GNDs, targeted disease-modifying therapies have become available for an increasing number of individuals diagnosed with a GND.[67-69] Examples in relation to parkinsonism were discussed in **chapter 2,** and included individuals with phenylketonuria and other inherited disorders of (neurotransmitter) metabolism, who may benefit from nutritional or pharmacological treatments.[67, 70]

Studies described in this thesis provided clinical recommendations for management of individuals with a GND, including 22q11.2DS, and recommendations for future research. In the following paragraphs recommendations for future research are further discussed and some new research ideas are introduced.

First, future studies may focus on treatment strategies for conditions that were found (relatively) frequent in adults with 22q11.2DS. For example, in **chapter 7** it was reported that almost one out of five adults with 22q11.2DS received treatment for trauma. Although treatment interventions for trauma showed positive effects in people with an intellectual disability,[10] the effect of treatment in adults with 22q11.2DS is still unclear. Treatment for trauma was often offered by regional care providers and treatment effects were not always discussed during the visits to specialized 22q11.2DS clinics, but for those with available data in the medical files, some reported no or minor effects of treatment interventions. Larger samples of individuals with

22q11.2DS would be needed to study the efficacy of treatment interventions for trauma and to identify if and how these interventions need to be adapted to the strengths and weaknesses of individuals with 22q11.2DS. Another example can be found in our study of hearing in **chapter 4**. About one out of three adults with 22q11.2DS were prescribed hearing aids but reported not to use them.[71, 72] Given the high prevalence of hearing loss and the impact it may have on daily life functioning, strategies to increase the use of hearing aids may be examined.

Second, longitudinal studies starting in childhood up to late adulthood in individuals with different GNDs are needed to further close the knowledge gap regarding conditions that develop over the life course.[46, 62] Since genetic variants associated with GNDs are often identified at an early age, long-term follow up of individuals with these GNDs provides the opportunity to generate knowledge of disease trajectories.[73, 74] The need for longitudinal studies starting early in life is further emphasized by the fact that symptoms of late-onset disorders such as motor symptoms of Parkinson's disease often present after cells, such as dopaminergic neurons, have already died. Ideally, future studies include comprehensive (epi)genetic testing,[75] detailed phenotyping and assessment of environmental factors (such as diet, physical exercise, stress and trauma)[76] in minor to severely affected individuals. In order to obtain adequate sample sizes of individuals with GNDs multi-center and/or consortia studies are required.[66] Longitudinal studies are crucial for the identification of early predictors and biomarkers for late-onset disorders, such as proposed in **chapter 6**, for optimizing screening and monitoring of at-risk groups, and for identifying windows of opportunity for treatment interventions. Qualification of retinovascular and retinoneural parameters as susceptibility biomarkers for psychosis or neurodegenerative disorders in 22q11.2DS depends on whether the change in these parameters explain the change in clinical state (e.g., from normal cognitive functioning to cognitive decline). Therefore, longitudinal studies would be needed to evaluate such parameters as susceptibility biomarkers in 22q11.2DS.

Third, cross-GND studies may help to understand differences and overlap between GNDs and identify, potentially shared, underlying mechanisms

and contributors.[77-79] Brain imaging studies, such as done by the ENIGMA working groups for copy number variants,[80] mouse models and (stem) cell studies may be used to better understand the pathophysiology of conditions associated with GNDs over the life span or to identify new treatment targets.[79, 81-83] An example can be found in a study that made use of mouse models of Fragile X syndrome, Rett syndrome and Down syndrome in addition to cell cultures to demonstrate that astrocytes contribute to the abnormal neural development found in these GNDs,[78] thereby providing insights into shared underlying mechanisms. Although individually rare, GNDs are collectively common affecting about 3% of the population,[84] and inclusion or identification of individuals with GNDs in population-based prospective cohort studies, such as Lifelines DEEP or the Maastricht study,[85, 86] may facilitate the study of the pathophysiology and biomarkers for disease by, for example, studies of the metabolome or microbiome,[87, 88] and comparison between GNDs and with the general population. These large population-based studies often use standardized measurements and extensive phenotyping, in addition to assessment of genetic and environmental factors of all participants, which is not always feasible in smaller studies of individual GNDs.

Last, improvement and study of the use of wearables and applications, such as used for experience sampling, may help to understand the effects of stress, nutrition or physical exercise on physical and mental health in GNDs, and can be used to study effects of interventions aimed at improving healthy living and aging. Experience sampling has already been applied in individuals with 22q11.2DS in the study of cortisol reactivity to subjective stress, demonstrating altered cortisol response to daily stress in individuals with 22q11.2DS compared to controls.[21] This may aid in our understanding of conditions such as post-traumatic stress in adults with 22q11.2DS (**chapter 7**), and other physical symptoms that may be related to stress. Actigraphy may be used to study the effect of sleep interventions, which has been done in children with Down syndrome,[89] and may be used to study sleep disorders and interventions in other GNDs as well, including obstructive sleep apnea in adults with 22q11.2DS (**chapter 4**).

Individuals with a GND often benefit from a coordinated multidisciplinary approach that can be provided by expert clinics. With advances in molecular testing and clinical care, the group of older individuals with GNDs is expected to increase. Restrictions in availability or accessibility of care providers may be overcome with the use of telehealth and telemonitoring.[90, 91] Future studies may focus on adjusting applications and techniques for telehealth and monitoring to the abilities and needs of individuals with a GND.

Together, findings of studies included in this thesis help to close the knowledge gap related to conditions associated with 22q11.2DS and other GNDs at adult age, and improve recommendations for clinical care. In addition, results may indicate precocious aging in adults with 22q11.2DS and stress the need for natural history studies of individuals with 22q11.2DS and other GNDs. These and future studies may pave the way for a personalized approach in patient care and may help to improve lives of individuals with a GND.

References

1. Janicki MP, Henderson CM, Rubin IL. Neurodevelopmental conditions and aging: Report on the Atlanta Study Group Charrette on Neurodevelopmental Conditions and Aging*. *Disability and Health Journal*. 2008/04/01/ 2008;1(2):116-124. doi:https://doi.org/10.1016/j.dhjo.2008.02.004
2. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Mov Disord*. Nov 2014;29(13):1583-90. doi:10.1002/mds.25945
3. Hashemi H, Fotouhi A, Yekta A, Pakzad R, Ostadimoghaddam H, Khabazkhoob M. Global and regional estimates of prevalence of refractive errors: Systematic review and meta-analysis. *J Curr Ophthalmol*. Mar 2018;30(1):3-22. doi:10.1016/j.joco.2017.08.009
4. Hearing loss prevalence and years lived with disability, 1990-2019: findings from the Global Burden of Disease Study 2019. *Lancet*. Mar 13 2021;397(10278):996-1009. doi:10.1016/s0140-6736(21)00516-x
5. Koenen KC, Ratanatharathorn A, Ng L, et al. Posttraumatic stress disorder in the World Mental Health Surveys. *Psychol Med*. Oct 2017;47(13):2260-2274. doi:10.1017/s0033291717000708
6. Bassett AS, Chow EW, Husted J, et al. Clinical features of 78 adults with 22q11 Deletion Syndrome. *Am J Med Genet A*. Nov 1 2005;138(4):307-13. doi:10.1002/ajmg.a.30984
7. Morrow BE, McDonald-McGinn DM, Emanuel BS, Vermeesch JR, Scambler PJ. Molecular genetics of 22q11.2 deletion syndrome. *Am J Med Genet A*. Oct 2018;176(10):2070-2081. doi:10.1002/ajmg.a.40504
8. Picciotti PM, Carfì A, Anzivino R, et al. Audiologic Assessment in Adults With Down Syndrome. *Am J Intellect Dev Disabil*. Jul 2017;122(4):333-341. doi:10.1352/1944-7558-122.4.333
9. Akinci A, Oner O, Bozkurt OH, Guven A, Degerliyurt A, Munir K. Refractive errors and ocular findings in children with intellectual disability: a controlled study. *J aapos*. Oct 2008;12(5):477-81. doi:10.1016/j.jaapos.2008.04.009
10. Mevissen L, de Jongh A. PTSD and its treatment in people with intellectual disabilities: a review of the literature. *Clin Psychol Rev*. Apr 2010;30(3):308-16. doi:10.1016/j.cpr.2009.12.005
11. van Splunder J, Stilma JS, Bernsen RM, Arentz TG, Evenhuis HM. Refractive errors and visual impairment in 900 adults with intellectual disabilities in the Netherlands. *Acta Ophthalmol Scand*. Apr 2003;81(2):123-9. doi:10.1034/j.1600-0420.2003.00035.x
12. Liao P, Vajdic C, Trollor J, Reppermund S. Prevalence and incidence of physical health conditions in people with intellectual disability - a systematic review. *PLoS One*. 2021;16(8):e0256294. doi:10.1371/journal.pone.0256294
13. Cooper S-A, McLean G, Guthrie B, et al. Multiple physical and mental health comorbidity in adults with intellectual disabilities: population-based cross-sectional analysis. *BMC Family Practice*. 2015/08/27 2015;16(1):110. doi:10.1186/s12875-015-0329-3
14. Boot E, Butcher NJ, Udow S, et al. Typical features of Parkinson disease and diagnostic challenges with microdeletion 22q11.2. *Neurology*. Jun 5 2018;90(23):e2059-e2067. doi:10.1212/wnl.0000000000005660
15. Bloem BR, Okun MS, Klein C. Parkinson's disease. *Lancet*. Jun 12 2021;397(10291):2284-2303. doi:10.1016/s0140-6736(21)00218-x
16. Huang Q, Tang J. Age-related hearing loss or presbycusis. *Eur Arch Otorhinolaryngol*. Aug 2010;267(8):1179-91. doi:10.1007/s00405-010-1270-7
17. Cancelliere S, Heung T, Fischbach S, Klaiman P, Bassett AS. Adult-onset obstructive sleep apnea and pediatric pharyngoplasty in 22q11.2 deletion syndrome. *Sleep Med*. Apr 2023;104:49-55. doi:10.1016/j.sleep.2023.02.010
18. Willaert A, Van Eynde C, Verhaert N, et al. Vestibular dysfunction is a manifestation of 22q11.2 deletion syndrome. *Am J Med Genet A*. Mar 2019;179(3):448-454. doi:10.1002/ajmg.a.7
19. Vergaelen E, Claes S, Kempke S, Swillen A. High prevalence of fatigue in adults with a 22q11.2 deletion syndrome. *Am J Med Genet A*. Apr 2017;173(4):858-867. doi:10.1002/ajmg.a.38094

20. Giardino G, Cirillo E, Maio F, et al. Gastrointestinal involvement in patients affected with 22q11.2 deletion syndrome. *Scandinavian Journal of Gastroenterology*. 2014/03/01 2014;49(3):274-279. doi:10.3109/00365521.2013.855814
21. van Duin EDA, Vaessen T, Kasanova Z, et al. Lower cortisol levels and attenuated cortisol reactivity to daily-life stressors in adults with 22q11.2 deletion syndrome. *Psychoneuroendocrinology*. Aug 2019;106:85-94. doi:10.1016/j.psyneuen.2019.03.023
22. Cohen S, Janicki-Deverts D, Miller GE. Psychological Stress and Disease. *JAMA*. 2007;298(14):1685-1687. doi:10.1001/jama.298.14.1685
23. Foster JA, Rinaman L, Cryan JF. Stress & the gut-brain axis: Regulation by the microbiome. *Neurobiol Stress*. Dec 2017;7:124-136. doi:10.1016/j.ynstr.2017.03.001
24. Jayakody DMP, Almeida OP, Speelman CP, et al. Association between speech and high-frequency hearing loss and depression, anxiety and stress in older adults. *Maturitas*. Apr 2018;110:86-91. doi:10.1016/j.maturitas.2018.02.002
25. Chia EM, Wang JJ, Rochtchina E, Cumming RR, Newall P, Mitchell P. Hearing impairment and health-related quality of life: the Blue Mountains Hearing Study. *Ear Hear*. Apr 2007;28(2):187-95. doi:10.1097/AUD.0b013e31803126b6
26. van Splunder J, Stilma JS, Bernsen RM, Evenhuis HM. Prevalence of visual impairment in adults with intellectual disabilities in the Netherlands: cross-sectional study. *Eye (Lond)*. Sep 2006;20(9):1004-10. doi:10.1038/sj.eye.6702059
27. Cohen JL, Crowley TB, McGinn DE, et al. 22q and two: 22q11.2 deletion syndrome and coexisting conditions. *Am J Med Genet A*. Oct 2018;176(10):2203-2214. doi:10.1002/ajmg.a.40494
28. Svae GB, Blixt L, Søndenaa E. Personal and sexual boundaries: the experiences of people with intellectual disabilities. *BMC Public Health*. Sep 19 2022;22(1):1773. doi:10.1186/s12889-022-14181-x
29. Moonen X, Festen D, Bakker-van Gijsel E, Vervoort-Schel J. A Dutch Perspective on Two Health Related Issues Regarding Children and Adolescents with Intellectual Disabilities. *Int J Environ Res Public Health*. Sep 16 2022;19(18)doi:10.3390/ijerph191811698
30. Vorstman JA, Breetvelt EJ, Duijff SN, et al. Cognitive decline preceding the onset of psychosis in patients with 22q11.2 deletion syndrome. *JAMA Psychiatry*. Apr 2015;72(4):377-85. doi:10.1001/jamapsychiatry.2014.2671
31. Scariati E, Schaer M, Richiardi J, et al. Identifying 22q11.2 deletion syndrome and psychosis using resting-state connectivity patterns. *Brain Topogr*. Nov 2014;27(6):808-21. doi:10.1007/s10548-014-0356-8
32. Tang SX, Moberg PJ, Yi JJ, et al. Olfactory deficits and psychosis-spectrum symptoms in 22q11.2 deletion syndrome. *Schizophr Res*. Dec 2018;202:113-119. doi:10.1016/j.schres.2018.07.012
33. FDA-NIH Biomarker Working Group. *BEST (Biomarkers, EndpointS, and other Tools) Resource*. Food and Drug Administration (US)

National Institutes of Health (US); 2016.

34. Moss HE. Retinal Vascular Changes are a Marker for Cerebral Vascular Diseases. *Curr Neurol Neurosci Rep*. Jul 2015;15(7):40. doi:10.1007/s11910-015-0561-1
35. Patton N, Aslam T, Macgillivray T, Pattie A, Deary IJ, Dhillon B. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. *J Anat*. Apr 2005;206(4):319-48. doi:10.1111/j.1469-7580.2005.00395.x
36. Appaji A, Nagendra B, Chako DM, et al. Retinal vascular abnormalities in schizophrenia and bipolar disorder: A window to the brain. *Bipolar Disord*. Nov 2019;21(7):634-641. doi:10.1111/bdi.12779
37. Wu H, Wang C, Chen C, et al. Association between Retinal Vascular Geometric Changes and Cognitive Impairment: A Systematic Review and Meta-Analysis. *J Clin Neurol*. Jan 2020;16(1):19-28. doi:10.3988/jcn.2020.16.1.19
38. Coppola G, Di Renzo A, Ziccardi L, et al. Optical Coherence Tomography in Alzheimer's Disease: A Meta-Analysis. *PLoS One*. 2015;10(8):e0134750. doi:10.1371/journal.pone.0134750

39. Ascaso FJ, Laura C, Quintanilla MÁ, et al. Retinal nerve fiber layer thickness measured by optical coherence tomography in patients with schizophrenia: A short report. *The European Journal of Psychiatry*. 2010;24:227-235.
40. Xie JS, Donaldson L, Margolin E. The use of optical coherence tomography in neurology: a review. *Brain*. Dec 19 2022;145(12):4160-4177. doi:10.1093/brain/awac317
41. Appaji A, Nagendra B, Chako DM, et al. Retinal vascular fractal dimension in bipolar disorder and schizophrenia. *J Affect Disord*. Dec 1 2019;259:98-103. doi:10.1016/j.jad.2019.08.061
42. Appaji A, Nagendra B, Chako DM, et al. Retinal vascular tortuosity in schizophrenia and bipolar disorder. *Schizophr Res*. Oct 2019;212:26-32. doi:10.1016/j.schres.2019.08.020
43. Wei Y, Jiang H, Shi Y, et al. Age-Related Alterations in the Retinal Microvasculature, Microcirculation, and Microstructure. *Invest Ophthalmol Vis Sci*. Jul 1 2017;58(9):3804-3817. doi:10.1167/iovs.17-21460
44. Huang L, Wang C, Wang W, Wang Y, Zhang R. The specific pattern of retinal nerve fiber layer thinning in Parkinson's disease: a systematic review and meta-analysis. *J Neurol*. Nov 2021;268(11):4023-4032. doi:10.1007/s00415-020-10094-0
45. Gaetani L, Blennow K, Calabresi P, Di Filippo M, Parnetti L, Zetterberg H. Neurofilament light chain as a biomarker in neurological disorders. *J Neurol Neurosurg Psychiatry*. Aug 2019;90(8):870-881. doi:10.1136/jnnp-2018-320106
46. Hickman RA, O'Shea SA, Mehler MF, Chung WK. Neurogenetic disorders across the lifespan: from aberrant development to degeneration. *Nat Rev Neurol*. Feb 2022;18(2):117-124. doi:10.1038/s41582-021-00595-5
47. Walpert MJ, Normando EM, Annus T, et al. Age-related retinal thickness in Down's syndrome: A high-risk population for dementia. *Alzheimers Dement (Amst)*. Dec 2019;11:744-751. doi:10.1016/j.dadm.2019.08.007
48. Butcher NJ, Kiehl TR, Hazrati LN, et al. Association between early-onset Parkinson disease and 22q11.2 deletion syndrome: identification of a novel genetic form of Parkinson disease and its clinical implications. *JAMA Neurol*. Nov 2013;70(11):1359-66. doi:10.1001/jamaneurol.2013.3646
49. Persengiev S, Kondova I, Bontrop R. Insights on the functional interactions between miRNAs and copy number variations in the aging brain. *Front Mol Neurosci*. Oct 2 2013;6:32. doi:10.3389/fnmol.2013.00032
50. Hébert SS, De Strooper B. Alterations of the microRNA network cause neurodegenerative disease. *Trends Neurosci*. Apr 2009;32(4):199-206. doi:10.1016/j.tins.2008.12.003
51. Thomas KT, Zakharenko SS. MicroRNAs in the Onset of Schizophrenia. *Cells*. Oct 6 2021;10(10) doi:10.3390/cells10102679
52. Granat L, Hunt RJ, Bateman JM. Mitochondrial retrograde signalling in neurological disease. *Philos Trans R Soc Lond B Biol Sci*. Jun 22 2020;375(1801):20190415. doi:10.1098/rstb.2019.0415
53. Schor NF, Bianchi DW. Neurodevelopmental Clues to Neurodegeneration. *Pediatr Neurol*. Oct 2021;123:67-76. doi:10.1016/j.pediatrneurol.2021.07.012
54. Motahari Z, Moody SA, Maynard TM, LaMantia AS. In the line-up: deleted genes associated with DiGeorge/22q11.2 deletion syndrome: are they all suspects? *J Neurodev Disord*. Jun 7 2019;11(1):7. doi:10.1186/s11689-019-9267-z
55. Baldini A, Fulcoli FG, Illingworth E. Tbx1: Transcriptional and Developmental Functions. *Curr Top Dev Biol*. 2017;122:223-243. doi:10.1016/bs.ctdb.2016.08.002
56. Tian C, Johnson KR. TBX1 is required for normal stria vascularis and semicircular canal development. *Dev Biol*. Jan 1 2020;457(1):91-103. doi:10.1016/j.ydbio.2019.09.013
57. Tammela T, Zarkada G, Nurmi H, et al. VEGFR-3 controls tip to stalk conversion at vessel fusion sites by reinforcing Notch signalling. *Nat Cell Biol*. Sep 11 2011;13(10):1202-13. doi:10.1038/ncb2331
58. Keithley EM. Pathology and mechanisms of cochlear aging. *J Neurosci Res*. Sep 2020;98(9):1674-1684. doi:10.1002/jnr.24439

59. Fernandez A, Meechan DW, Karpinski BA, et al. Mitochondrial Dysfunction Leads to Cortical Under-Connectivity and Cognitive Impairment. *Neuron*. Jun 19 2019;102(6):1127-1142.e3. doi:10.1016/j.neuron.2019.04.013
60. Bose A, Beal MF. Mitochondrial dysfunction in Parkinson's disease. *J Neurochem*. Oct 2016;139 Suppl 1:216-231. doi:10.1111/jnc.13731
61. Kolar D, Krajcovic B, Kleteckova L, Kuncicka D, Vales K, Brozka H. Review: Genes Involved in Mitochondrial Physiology Within 22q11.2 Deleted Region and Their Relevance to Schizophrenia. *Schizophr Bull*. Jun 28 2023;doi:10.1093/schbul/sbad066
62. Boot E, Óskarsdóttir S, Loo JCY, et al. Updated clinical practice recommendations for managing adults with 22q11.2 deletion syndrome. *Genet Med*. Mar 2023;25(3):100344. doi:10.1016/j.gim.2022.11.012
63. Zarchi O, Attias J, Raveh E, Basel-Vanagaite L, Saporta L, Gothelf D. A comparative study of hearing loss in two microdeletion syndromes: velocardiofacial (22q11.2 deletion) and Williams (7q11.23 deletion) syndromes. *J Pediatr*. Feb 2011;158(2):301-6. doi:10.1016/j.jpeds.2010.07.056
64. Forbes BJ, Binenbaum G, Edmond JC, DeLarato N, McDonald-McGinn DM, Zackai EH. Ocular findings in the chromosome 22q11.2 deletion syndrome. *J aapos*. Apr 2007;11(2):179-82. doi:10.1016/j.jaapos.2006.08.006
65. Van Eynde C, Swillen A, Lambeens E, et al. Prevalence and Nature of Hearing Loss in 22q11.2 Deletion Syndrome. *J Speech Lang Hear Res*. Jun 1 2016;59(3):583-9. doi:10.1044/2015_jslhr-h-15-0098
66. Dykens EM. Aging in rare intellectual disability syndromes. *Developmental Disabilities Research Reviews*. 2013/08/01 2013;18(1):75-83.
67. Hoytema van Konijnenburg EMM, Wortmann SB, Koelewijn MJ, et al. Treatable inherited metabolic disorders causing intellectual disability: 2021 review and digital app. *Orphanet J Rare Dis*. Apr 12 2021;16(1):170. doi:10.1186/s13023-021-01727-2
68. Ebrahimi-Fakhari D, Van Karnebeek C, Münchau A. Movement Disorders in Treatable Inborn Errors of Metabolism. *Mov Disord*. May 2019;34(5):598-613. doi:10.1002/mds.27568
69. Overwater IE, Rietman AB, van Eeghen AM, de Wit MCY. Everolimus for the treatment of refractory seizures associated with tuberous sclerosis complex (TSC): current perspectives. *Ther Clin Risk Manag*. 2019;15:951-955. doi:10.2147/tcrm.S145630
70. Tufekcioglu Z, Cakar A, Bilgic B, Hanagasi H, Gurvit H, Emre M. Adult-onset phenylketonuria with rapidly progressive dementia and parkinsonism. *Neurocase*. Jun 2016;22(3):273-5. doi:10.1080/13554794.2016.1142567
71. Hendrix JA, Amon A, Abbeduto L, et al. Opportunities, barriers, and recommendations in down syndrome research. *Transl Sci Rare Dis*. 2021;5(3-4):99-129. doi:10.3233/trd-200090
72. Meuwese-Jongejeugd A, Verschuure H, Evenhuis HM. Hearing aids: expectations and satisfaction of people with an intellectual disability, a descriptive pilot study. *J Intellect Disabil Res*. Nov 2007;51(Pt 11):913-22. doi:10.1111/j.1365-2788.2007.00952.x
73. Zinkstok JR, Boot E, Bassett AS, et al. Neurobiological perspective of 22q11.2 deletion syndrome. *Lancet Psychiatry*. Nov 2019;6(11):951-960. doi:10.1016/s2215-0366(19)30076-8
74. Fortea J, Zaman SH, Hartley S, Rafii MS, Head E, Carmona-Iragui M. Alzheimer's disease associated with Down syndrome: a genetic form of dementia. *Lancet Neurol*. Nov 2021;20(11):930-942. doi:10.1016/s1474-4422(21)00245-3
75. Starr JM. Ageing and epigenetics: linking neurodevelopmental and neurodegenerative disorders. *Dev Med Child Neurol*. Oct 2019;61(10):1134-1138. doi:10.1111/dmcn.14210
76. Snihirova Y, Linden DEJ, van Amelsvoort T, van der Meer D. Environmental Influences on the Relation between the 22q11.2 Deletion Syndrome and Mental Health: A Literature Review. *Genes (Basel)*. Nov 2 2022;13(11)doi:10.3390/genes13112003
77. Bach S, Shovlin S, Moriarty M, Bardoni B, Tropea D. Rett Syndrome and Fragile X Syndrome: Different Etiology With Common Molecular Dysfunctions. *Front Cell Neurosci*. 2021;15:764761. doi:10.3389/fncel.2021.764761

78. Caldwell ALM, Sancho L, Deng J, et al. Aberrant astrocyte protein secretion contributes to altered neuronal development in multiple models of neurodevelopmental disorders. *Nat Neurosci*. Sep 2022;25(9):1163-1178. doi:10.1038/s41593-022-01150-1

79. Susco SG, Ghosh S, Mazzucato P, et al. Molecular convergence between Down syndrome and fragile X syndrome identified using human pluripotent stem cell models. *Cell Rep*. Sep 6 2022;40(10):111312. doi:10.1016/j.celrep.2022.111312

80. Sønderby IE, Ching CRK, Thomopoulos SI, et al. Effects of copy number variations on brain structure and risk for psychiatric illness: Large-scale studies from the ENIGMA working groups on CNVs. *Hum Brain Mapp*. Jan 2022;43(1):300-328. doi:10.1002/hbm.25354

81. Guy J, Gan J, Selfridge J, Cobb S, Bird A. Reversal of neurological defects in a mouse model of Rett syndrome. *Science*. Feb 23 2007;315(5815):1143-7. doi:10.1126/science.1138389

82. Sabitha KR, Shetty AK, Upadhya D. Patient-derived iPSC modeling of rare neurodevelopmental disorders: Molecular pathophysiology and prospective therapies. *Neurosci Biobehav Rev*. Feb 2021;121:201-219. doi:10.1016/j.neubiorev.2020.12.025

83. Valassina N, Brusco S, Salamone A, et al. Scn1a gene reactivation after symptom onset rescues pathological phenotypes in a mouse model of Dravet syndrome. *Nat Commun*. Jan 10 2022;13(1):161. doi:10.1038/s41467-021-27837-w

84. van Eeghen AM, Bruining H, Wolf NI, et al. Personalized medicine for rare neurogenetic disorders: can we make it happen? *Cold Spring Harb Mol Case Stud*. Feb 2022;8(2)doi:10.1101/mcs.a006200

85. Tigchelaar EF, Zhernakova A, Dekens JA, et al. Cohort profile: LifeLines DEEP, a prospective, general population cohort study in the northern Netherlands: study design and baseline characteristics. *BMJ Open*. Aug 28 2015;5(8):e006772. doi:10.1136/bmjopen-2014-006772

86. Schram MT, Sep SJ, van der Kallen CJ, et al. The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. *Eur J Epidemiol*. Jun 2014;29(6):439-51. doi:10.1007/s10654-014-9889-0

87. Falony G, Joossens M, Vieira-Silva S, et al. Population-level analysis of gut microbiome variation. *Science*. Apr 29 2016;352(6285):560-4. doi:10.1126/science.aad3503

88. Chen L, Zhernakova DV, Kurilshikov A, et al. Influence of the microbiome, diet and genetics on inter-individual variation in the human plasma metabolome. *Nat Med*. Nov 2022;28(11):2333-2343. doi:10.1038/s41591-022-02014-8

89. Esbensen AJ, Hoffman EK, Beebe DW, et al. Randomized Behavioral Sleep Clinical Trial to Improve Outcomes in Children With Down Syndrome. *Am J Intellect Dev Disabil*. Mar 1 2022;127(2):149-164. doi:10.1352/1944-7558-127.2.149

90. Downs J, Blackmore AM, Wong K, et al. Can telehealth increase physical activity in individuals with Rett syndrome? A multicentre randomized controlled trial. *Dev Med Child Neurol*. Apr 2023;65(4):489-497. doi:10.1111/dmcn.15436

91. Bullard L, Harvey D, Abbeduto L. Exploring the feasibility of collecting multimodal multiperson assessment data via distance in families affected by fragile X syndrome. *J Telemed Telecare*. Apr 12 2021:1357633x211003810. doi:10.1177/1357633x211003810

Chapter 9

Impact

Impact

The overall aim of this thesis was to gain insight into conditions that develop, or are present, in adults with a genetic syndrome, with a focus on 22q11.2 deletion syndrome (22q11.2DS). Study topics included parkinsonism, otolaryngology, ophthalmology and post-traumatic stress. In this chapter the societal and research impact of the studies included in this thesis are discussed.

The main findings included an increased risk of Parkinson's disease, hearing loss, chronic middle ear infections, swallowing difficulties, balance problems, obstructive sleep apnea (a sleep disorder), refractive errors (for example farsightedness) and post-traumatic stress in adults with 22q11.2DS. Treatment options exist for most of these conditions and preferably start as soon as possible in order to minimize disease burden and improve quality of life. The studies described in this thesis include recommendations for clinical care, mostly aimed at improving screening in order to early detect conditions that may frequently be present in adults with 22q11.2DS. A summary of the most important recommendations is provided in the first section of the discussion in **chapter 8**. Some of the published findings and recommendations have already been incorporated in the recently updated international clinical practice recommendations for children and adults with 22q11.2DS,[1, 2] that provide guidance for clinicians treating individuals with 22q11.2DS and for genetic counseling. Results are relevant to clinicians and other care givers of various medical specialties. Therefore, results have been presented at local, national and international symposia and conferences for patient organizations and for clinicians that treat individuals with 22q11.2DS including clinical geneticists, physicians for people with an intellectual disability, neurologists, otolaryngologists and ophthalmologists. In addition to scientific publications in peer-reviewed journals, results related to sensory deficits and post-traumatic stress in adults with 22q11.2DS have been made available in Dutch in a magazine for clinicians who treat people with an intellectual disability.

For genetic syndromes that were associated with parkinsonism described in **chapter 2**, recommendations were provided to improve recognition

and treatment of parkinsonism, Parkinson's disease in particular, in these genetic syndromes. This study indicated that regular antiparkinsonian medication showed positive effects in most individuals with (suspicion of) Parkinson's disease, which is of direct clinical relevance. In this study it is recommended that dopaminergic imaging techniques may be considered in patients with a genetic syndrome - who often use anti-psychotic medication - to distinguish neurodegenerative parkinsonism (e.g., Parkinson's disease) from parkinsonism as side-effect of medication. In addition to a scientific publication, results have been presented at international and national conferences for movement disorders specialists and other neurologists, as well as for physicians for people with intellectual disabilities.

The goal of sharing results with different target audiences was to make clinicians aware of the conditions that were frequently present in adults with 22q11.2DS or other genetic syndromes, to improve screening and to emphasize the possibilities for treatment that may ultimately result in better care for adults with a genetic syndrome. In addition, results of the studies included in this thesis demonstrated how a genetic diagnosis may improve clinical care for individuals with an intellectual disability, since some conditions were more frequently seen in adults with 22q11.2DS compared to other genetic syndromes or adults with an intellectual disability in general. For example, knowledge of an increased risk of early-onset Parkinson's disease in 22q11.2DS compared to the general population and people with an intellectual disability, contributes to recommendations for screening specifically for adults with 22q11.2DS. Therefore, a genetic diagnosis may facilitate a more personalized approach by care providers.

Findings of these studies provide information to adults with 22q11.2DS and their relatives about what may be expected at adult age. In addition, it may raise awareness of an increased risk of conditions such as Parkinson's disease or hearing loss at relatively young-adult age and may help adults with 22q11.2DS or relatives to seek help at an early stage. To make results directly available to adults with 22q11.2DS and their relatives, a presentation was given about post-traumatic stress in 22q11.2DS at the information day of the Dutch 22q11 family organization Stichting Steun 22Q11, and results have been shared via their annual magazine, 's Heeren Loo website, and

via newsletters to adults with 22q11.2DS who participated in studies at Maastricht University Medical Center, which together with 's Heeren Loo, offers a specialized clinic for adults with 22q11.2DS.

Results of the studies included in this thesis may inform future studies aimed at finding or improving treatment for conditions that are frequently present in adults with 22q11.2DS. For example, a study of the efficacy of treatment for trauma in adults with 22q11.2DS has recently started.

In addition to the societal impact of the included studies, mostly health care related, results may also have research implications.

The studies described in this thesis that were performed in adults with 22q11.2DS may suggest that 22q11.2DS is associated with precocious aging, which has also been suggested in some other genetic syndromes such as Down syndrome. Because previous research already provided substantial knowledge of genes and affected mechanisms involved in the development of genetic syndromes such as 22q11.2DS, they may serve as a model to study mechanisms and novel treatment options of age-related conditions such as Parkinson's disease. Recognition of conditions that are common at adult age in genetic syndromes enables future studies that use mouse models or (stem)cells of genetic syndromes. Results of these studies may not only be relevant to adults with a genetic syndrome but may also improve our understanding of the etiology and treatment of these age-related conditions in the general population.

References

1. Boot E, Óskarsdóttir S, Loo JCY, et al. Updated clinical practice recommendations for managing adults with 22q11.2 deletion syndrome. *Genet Med*. Mar 2023;25(3):100344. doi:10.1016/j.gim.2022.11.012
2. Óskarsdóttir S, Boot E, Crowley TB, et al. Updated clinical practice recommendations for managing children with 22q11.2 deletion syndrome. *Genet Med*. Mar 2023;25(3):100338. doi:10.1016/j.gim.2022.11.006

Appendix I

Summary

Summary

The overall aim of this thesis was to characterize genetic neurodevelopmental disorders (GNDs) at adult age, with a focus on 22q11.2 deletion syndrome (22q11.2DS). Study topics included parkinsonism, otolaryngology, ophthalmology and trauma-related disorders. In this appendix, a summary of the individual studies is presented. **Chapter 1** provides a general introduction to 22q11.2DS and study topics included in this thesis.

In **chapter 2** results are discussed of a systematic review of the literature on parkinsonism in GNDs. It is increasingly recognized that individuals with GNDs can suffer from parkinsonism, including neurodegenerative parkinsonism. With advances in clinical genetic testing for neurologic disease, the number of GNDs associated with parkinsonism is growing fast. In this chapter an overview of the literature is provided that reports on parkinsonism in GNDs. The literature search yielded over two hundred full-text publications for data-extraction, reporting on 422 individuals with 69 different GNDs and parkinsonism. The five most reported GNDs from most to least frequent were: beta-propeller protein-associated neurodegeneration, 22q11.2DS, Down syndrome, cerebrotendinous xanthomatosis, and Rett syndrome. Notable findings were an almost equal male to female ratio, an early median age of motor onset (26 years old), and rigidity being more common than rest tremor. Results of dopaminergic imaging and response to antiparkinsonian medication often supported the neurodegenerative nature of parkinsonism. Moreover, neuropathology results showed neuronal loss in the majority of cases. Proposed disease mechanisms included aberrant mitochondrial function and disruptions in neurotransmitter metabolism, endosomal trafficking, and the autophagic-lysosomal and ubiquitin-proteasome system. Together, many GNDs have been associated with parkinsonism and results were often supportive of neurodegenerative parkinsonism, with typical findings with dopaminergic imaging and a good response to antiparkinsonian medication. Clinicians who take care of individuals with GNDs included in this study should be aware of a possible increased risk of parkinsonism, that may have an atypical presentation. Similarly, parkinsonism combined with a history of a neurodevelopmental disorder could prompt clinicians to consider

genetic testing. Further recognition of parkinsonism in these GNDs may provide insights into the mechanisms causing parkinsonism in the general population, crucial for the development of disease-modifying treatments.

In **chapter 3** the estimated prevalence of Parkinson's disease is examined in adults with 22q11.2DS. An increased risk of Parkinson's disease, of 20-to-70-fold, has previously been suggested in adults with 22q11.2DS. However, prevalence estimates were based on only 68 individuals with 22q11.2DS, at a relatively young age of 35 to 64 years. A multicenter cross-sectional study was conducted that included 856 adults (47% male, at mean age 46.5 ± 15.4 years) with 22q11.2DS who visited one of the specialized 22q11.2DS clinics in the Netherlands (Maastricht University Medical Centre and 's Heeren Loo), Belgium (University Hospital Leuven), Canada (Dalglish Family 22q Clinic, Toronto) and Chile (University of Santiago). Parkinson's disease was defined as a clinical diagnosis by a neurologist, and presence of bradykinesia and at least one of either rest tremor or rigidity. Suspected Parkinson's disease was defined as a clinical diagnosis of Parkinson's disease or a clinical suspicion of Parkinson's disease without complying to the formal criteria. The results indicate a prevalence of 1.8% for Parkinson's disease (95% CI: 0.9 – 2.6) and 3.4% (95% CI: 2.2 – 4.6%) in case adults suspected of Parkinson's disease were included. A sharp increase in the prevalence of Parkinson's disease was seen in adults with 22q11.2DS aged 50 years and older (11.7%). In contrast to Parkinson's disease in the general population, male sex was not associated with an increased risk in adults with 22q11.2DS. Based on these findings, periodic evaluation of motor symptoms by a neurologist, preferably a movement disorder specialist, seems justified in adults with 22q11.2DS aged 40 years and older. Individuals with 22q11.2DS at any age showing parkinsonian motor signs may benefit from careful monitoring and referral for neurological examination in case of doubt of the etiology.

In **chapter 4** results regarding hearing loss and otolaryngological conditions in adults with 22q11.2DS are reported. Previous studies showed an increased prevalence of hearing loss and chronic otitis media in 22q11.2DS. Since most studies focused on children, and the knowledge on adults is still scarce, the aim of this study was to report on hearing and otolaryngological findings in adults. Therefore, a cross-sectional study was

conducted including 60 adults (42% male, median age 25.0 (range 16-74) years) with 22q11.2DS who visited an otolaryngologist and audiologist at the 22q11.2 expert center in Maastricht. Results of this study indicate a high prevalence, of 78.3%, of hearing loss in adults with 22q11.2DS, which was mostly high-frequency sensorineural loss. Higher age and a history of chronic otitis media were associated with more severe hearing loss. Otolaryngologic conditions with possible treatment implications included chronic otitis media (56.7%), globus pharyngeus (18.3%), balance problems (16.7%) and obstructive sleep apnea (8.3%). Based on these findings, periodic audiometric screening is recommended in all adults, including high-frequency ranges, and otolaryngological examination at least once.

In **chapter 5** results are presented of a systematic literature review and multi-center cross-sectional study of ocular findings in children and adults with 22q11.2DS. The systematic literature search yielded four articles, describing 270 individuals and the cross-sectional study included 132 individuals (45% male, median age 8.9 (range 0-56) years). Most reported ocular findings were retinal vascular tortuosity (32-78%), posterior embryotoxon (22-50%), eye lid hooding (20-67%), strabismus (12-36%), amblyopia (2-11%), ptosis (4-6%) and refractive errors, of which hyperopia (6-48%) and astigmatism (3-23%) were most common. Visual acuity was (near) normal in most individuals (91-94%).

Results of this study indicate that clinicians should be aware of refractive errors, strabismus and amblyopia, and the beneficial result of detection and correction at an early age. Therefore, standardized ophthalmic and orthoptic screening is recommended in children with 22q11.2DS at the age of three years or at diagnosis, and a low-threshold for referral in adults.

In **chapter 6** differences are explored in retinoneural and retinovascular parameters between adults with 22q11.2DS and controls, and in relation to age. Because retinal and cerebral tissue share embryological, physiological and anatomical characteristics, retinal blood vessel morphology and retinal nerve fiber layer (RNFL) thickness have been proposed as non-invasive biomarkers for psychiatric and neurodegenerative disorders. Central retinal artery and vein equivalent, fractal dimension, and vascular tortuosity,

obtained through fundoscopy, and peripapillary RNFL and macular thickness, obtained through optical coherence tomography, were compared between adults with 22q11.2DS and sex- and age-matched controls. Results indicate that retinal vascular fractal dimension and tortuosity are significantly higher in adults with 22q11.2DS compared to controls. In addition, significant negative correlations with age were found for fractal dimension and RNFL thickness in the global, temporal inferior and temporal superior segments in adults with 22q11.2DS, but not in controls. These findings support future studies that focus on retinal fractal dimension and RNFL thickness as potential biomarkers for age-related manifestations in 22q11.2 including psychotic and (early) neurodegenerative disorders.

In **chapter 7** findings are presented related to trauma and post-traumatic stress disorder (PTSD) in adults with 22q11.2DS. Previous studies indicated a lower prevalence of PTSD in individuals with 22q11.2DS compared to the general population; 0.9% *vs* 3.6% respectively. The prevalence of PTSD was hypothesized to be higher. Therefore, PTSD prevalence, and potential predictors to PTSD, were studied in 112 adults with 22q11.2DS (45% male, mean age 32.5 ± 12.4 years). A chart review was performed of individuals with 22q11.2DS who visited the Dutch specialty clinic for adults with 22q11.2DS at Maastricht or 's Heeren Loo. Results indicate a prevalence of PTSD of 8.0% (95% CI 3.0% - 13.0%) in adults with 22q11.2DS. A traumatic event was experienced in 23 adults (20.5%): mostly sexual violence (10.7%) or serious injury (9.8%). An additional 17 adults (15.2%) experienced other potential traumatic events, including bullying (11.6%) and multiple hospitalizations/surgeries (3.6%). Treatment for trauma was reported in 20 adults (17.9%), of whom 8 with PTSD, and included Eye Movement Desensitization Reprocessing (EMDR, 17.0%) and cognitive behavioral therapy (1.8%). Neither sex nor full-scale intelligence quotient was associated with PTSD. Findings of this study indicate that PTSD and trauma appear to be prevalent in adults with 22q11.2DS, and may have been overshadowed by, or attributed to, other psychiatric disorders in previous research. Previous studies have shown that treatment strategies for trauma, including EMDR, were effective in people with an intellectual disability in general. Given the large impact PTSD can have on a person's wellbeing, clinicians should be alert to PTSD in 22q11.2DS in order to minimize

psychiatric burden. Systematic studies in individuals with 22q11.2DS are needed to improve diagnosis, using strategies adjusted to their cognitive profile and including attention for seemingly innocuous life events that may be traumatic, and to evaluate the efficacy of treatments in this population.

In **chapter 8** results of individual studies of this thesis are discussed in a broader context and in relation to previous research. Collectively, studies included in this thesis seem to point to precocious aging in adults with 22q11.2DS. In addition, this chapter provides recommendations for future research, including longitudinal studies over the life course of individuals with 22q11.2DS or other GNDs and cross-GND studies that may aid in our understanding of the (shared) underlying mechanisms and move treatment discoveries.

In **chapter 9** the impact of the included studies in this thesis is discussed on society, including health care, and science. Mostly, impact was achieved by implementation of study results and recommendations described in this thesis into the clinical recommendations for children and adults with 22q11.2DS, and by sharing results with a broad audience of physicians of various medical specialties and adults with 22q11.2DS and their families in order to improve care and quality of life of adults with 22q11.2DS.

Appendix II

Summary in Dutch (Nederlandse samenvatting)

Summary in Dutch (Nederlandse samenvatting)

Het doel van de onderzoeken beschreven in dit proefschrift was om inzicht te krijgen in aandoeningen die zich voordoen bij volwassenen met genetische neuro-ontwikkelingsaandoeningen (genetische syndromen), in het bijzonder het 22q11.2 deletiesyndroom (22q11.2DS). De onderzoeken waren gericht op parkinsonisme, aandoeningen aan de ogen, keel, neus en oren (KNO) en post-traumatische stress. In deze bijlage worden samenvattingen gegeven van de individuele studies.

In **hoofdstuk 1** wordt een algemene introductie gegeven over 22q11.2DS en de onderzoeksonderwerpen. In het kort, de definitie voor een genetisch syndroom, zoals gebruikt in dit proefschrift, is een afwijking van de normale neurologische ontwikkeling van een kind in de sociale, persoonlijke, motorische en/of cognitieve ontwikkeling, in de aanwezigheid van een ziekte veroorzakende erfelijke variant. Een bekend voorbeeld is Downsyndroom, dat voorkomt bij ongeveer 1 op de 800 geboortes. Dit proefschrift focust met name op 22q11.2DS, dat voorkomt bij ongeveer 1 op de 2000 geboortes, waardoor het nog net binnen de groep van zeldzame aandoeningen valt. Mensen met 22q11.2DS hebben een verhoogd risico op een flink aantal gezondheidsproblemen, zoals bijvoorbeeld aangeboren hartaandoeningen, verstandelijke beperking, gehemelteafwijkingen en psychoses, maar de gezondheidsproblemen verschillen sterk per persoon. Eerdere onderzoeken waren voornamelijk gericht op kinderen. Over aandoeningen die voorkomen bij volwassenen met 22q11.2DS is minder bekend. Om deze reden is er in de onderzoeken in dit proefschrift gekeken naar de ziekte van Parkinson, oogheelkundige bevindingen, KNO-problemen en post-traumatische stress bij volwassenen met 22q11.2DS.

In **hoofdstuk 2** worden de resultaten beschreven van een systematisch literatuuronderzoek naar parkinsonisme bij genetische syndromen. Het wordt steeds meer herkend dat parkinsonisme, een bewegingsstoornis die veroorzaakt kan worden door bepaalde medicatie of de ziekte van Parkinson, kan voorkomen bij mensen met een genetisch syndroom zoals 22q11.2DS. Door verbeterde technieken voor genetische testen, en doordat mensen met genetische syndromen steeds ouder worden door verbeterde

zorg, neemt het aantal genetische syndromen met parkinsonisme toe. Door middel van het literatuuronderzoek zijn er meer dan 200 studies gevonden die 422 mensen beschreven met 69 verschillende genetische syndromen en parkinsonisme. De 5 meest voorkomende genetische syndromen in deze studies waren, van meest naar minst: beta-propeller eiwit-geassocieerde neurodegeneratie, 22q11.2DS, Downsyndroom, cerebrotendineuze xanthomatose en Rett syndroom. Opmerkelijke bevindingen waren de vrijwel gelijke verdeling tussen mannen en vrouwen (in tegenstelling tot de ziekte van Parkinson in de algemene bevolking dat daar vaker voorkomt bij mannen), vroege ontstaan van bewegingsproblemen (gemiddeld op 26-jarige leeftijd), en waarbij rigiditeit (stijfheid van spieren) vaker werd gezien dan een rust tremor (ongewild trillen/schokken van een lichaamsdeel). Resultaten van hersenscans en het effect van anti-Parkinson medicatie waren vaak suggestief voor de ziekte van Parkinson als oorzaak van parkinsonisme. Daarnaast worden er onderliggende mechanismen besproken die mogelijk bijdragen aan zowel de ontwikkelingsstoornissen bij het genetisch syndroom als aan het ontwikkelen van de ziekte van Parkinson. Dit literatuuronderzoek heeft informatie opgeleverd die relevant kan zijn voor de zorg voor mensen met een genetisch syndroom en parkinsonisme en voor vervolgonderzoek. Het onderzoek laat zien dat veel verschillende genetische syndromen zijn beschreven met parkinsonisme en dat de presentatie van parkinsonisme vaak atypisch is bij mensen met een genetisch syndroom. Daarnaast zouden zorgverleners die patiënten behandelen met parkinsonisme die bekend zijn met zwakbegaafdheid of lichte verstandelijk beperking (of een vermoeden daarop) deze patiënten kunnen testen op de aanwezigheid van een genetische aandoening. Een genetische diagnose kan naast erkenning ook bijdragen aan verbetering van de zorg voor die persoon, begeleiding bij een kinderwens en geeft de mogelijkheid tot lotgenotencontact. Erkenning van genetische syndromen waarbij parkinsonisme voorkomt kan bijdragen aan vervolgonderzoek naar mogelijke onderliggende mechanismen en nieuwe behandelingen, die ook relevant kunnen zijn voor mensen met parkinsonisme zonder genetisch syndroom.

In **hoofdstuk 3** wordt onderzocht hoe vaak de ziekte van Parkinson voorkomt bij volwassenen met 22q11.2DS. Eerder onderzoek liet zien dat

de ziekte van Parkinson mogelijk 20 tot 70 keer vaker voorkomt bij mensen met 22q11.2DS vergeleken met mensen uit de algemene bevolking. Deze resultaten waren echter gebaseerd op onderzoek in een relatief kleine groep van 68 mensen met 22q11.2DS van 35 tot 64 jaar. Het onderzoek, beschreven in dit hoofdstuk, is gedaan bij 856 volwassenen met 22q11.2DS (waarvan 47% man, gemiddelde leeftijd 47 jaar) in vijf klinieken gespecialiseerd in 22q11.2DS, waarvan 2 in Nederland (Maastricht Universitair Medisch Centrum en 's Heeren Loo in Hoofddorp), 1 in België (Universiteitsziekenhuis Leuven, België), 1 in Noord-Amerika (Dalglish Family 22q Clinic, Toronto, Canada) en 1 in Zuid-Amerika (Universiteit van Santiago, Chili). De ziekte van Parkinson moest zijn vastgesteld door een neuroloog en de aanwezigheid van de hoofdkenmerken van de bewegingsstoornis (parkinsonisme) moest zijn beschreven in het medisch dossier. Daarnaast wordt er in dit onderzoek gekeken naar volwassenen met 22q11.2DS bij wie er een verdenking was op de ziekte van Parkinson maar die niet voldeden aan alle criteria voor de ziekte van Parkinson, zoals die in het onderzoek gesteld waren. De resultaten laten zien dat de ziekte van Parkinson werd vastgesteld bij 1.8% van de volwassenen (95% betrouwbaarheidsinterval: 0.9 – 2.6%) en 3.4% (95% betrouwbaarheidsinterval: 2.2 – 4.6%) als volwassenen met verdenking op de ziekte van Parkinson werden meegenomen. Bij volwassenen met 22q11.2DS ouder dan 50 jaar lag het voorkomen van de ziekte van Parkinson zelfs op 11.7%. Oudere leeftijd, maar niet het geslacht, was gerelateerd aan het voorkomen van de ziekte van Parkinson. Op basis van de resultaten wordt geadviseerd om periodiek onderzoek te laten doen door een neuroloog naar parkinsonisme bij volwassenen met 22q11.2DS vanaf de leeftijd van 40 jaar. Volwassenen van alle leeftijden met parkinsonisme als bijwerking van medicatie zouden goed gemonitord moeten worden en verwezen naar een neuroloog indien er twijfel bestaat over de oorzaak van parkinsonisme.

In **hoofdstuk 4** worden de bevindingen gepresenteerd van gehoorverlies en KNO-problemen bij volwassenen met 22q11.2DS. Eerdere onderzoeken lieten zien dat gehoorverlies en chronische middenoorinfecties vaker voorkomen bij mensen met 22q11.2DS. Omdat de meeste onderzoeken zijn gebaseerd op kinderen met 22q11.2DS, en er nog weinig bekend was over volwassenen, was het doel van dit onderzoek om het voorkomen

van gehoorverlies en KNO-problemen bij volwassenen te onderzoeken. Het onderzoek beschrijft resultaten van 60 volwassenen met 22q11.2DS (waarvan 42% man, mediane leeftijd 25 (16 tot 74) jaar) die door een KNO-arts en audioloog zijn onderzocht tijdens de 22q11 polikliniek in het Maastricht Universitair Medisch Centrum. De resultaten laten zien dat de meerderheid (78,3%) van de volwassenen gehoorverlies had, voornamelijk in de hoge tonen. Oudere leeftijd en een voorgeschiedenis van chronische middenoorontstekingen waren gerelateerd aan ernstiger gehoorverlies. KNO-problemen die vaker werden vermeld, en waarvan meestal behandeling mogelijk is, waren een gevoel van een brok in de keel (18,3%), soms met slikproblemen, evenwichtsproblemen (16,7%) en obstructief slaapapneu (een slaapstoornis, 8,3%). Gebaseerd op deze resultaten wordt geadviseerd om volwassenen met 22q11.2DS herhaaldelijk te testen op gehoorverlies, inclusief de hoge tonen, en om ten minste eenmaal een KNO-onderzoek te verrichten op jongvolwassen leeftijd.

In **hoofdstuk 5** worden de resultaten gedeeld van een literatuuronderzoek gecombineerd met een onderzoek in meerdere Nederlandse centra naar oogbevindingen bij kinderen en volwassenen met 22q11.2DS. Het literatuuronderzoek bevat 4 studies waarin 270 mensen met 22q11.2DS zijn onderzocht. In de Nederlandse centra zijn oogbevindingen van 132 mensen met 22q11.2DS (45% man, mediane leeftijd 89 jaar (0-56 jaar)) onderzocht. De oogbevindingen die het meest werden gerapporteerd waren kronkeling van de bloedvaatjes in het netvlies (32-78%), posterieur embryotoxon (afwijking bij de iris, 22-50%), overmatig huid boven het oog (20-67%), scheelzien (12-36%), lui oog (2-11%), hangend ooglid (4-6%) en brekingsafwijkingen zoals verziendheid (6-48%) en astigmatisme (3-23%). De gezichtsscherpte was normaal of vrijwel normaal bij de meeste kinderen en volwassenen met 22q11.2DS (91-94%). Op basis van de onderzoeksresultaten wordt zorgverleners geadviseerd rekening te houden met aanwezigheid van brekingsafwijkingen, scheelzien en lui oog bij 22q11.2DS, omdat deze bij voorkeur zo vroeg mogelijk behandeld worden. Het advies is om standaard een oogheelkundige screening te doen bij kinderen met 22q11.2DS op de leeftijd van 3 jaar of bij diagnose, en volwassenen met 22q11.2DS laagdrempelig te verwijzing naar een oogarts bij oogheelkundige klachten.

In **hoofdstuk 6** wordt onderzocht of er verschillen zijn in de zenuwlaagjes en bloedvaatjes van het netvlies tussen volwassenen met 22q11.2DS en controlepersonen, en of er een relatie is met de leeftijd. Het netvlies en hersenweefsel hebben overeenkomsten wat betreft de ontwikkeling, fysiologie en anatomie. Daarom zouden veranderingen van het zenuwweefsel of de bloedvaatjes in het netvlies een voorspellende waarde kunnen hebben voor veranderingen in de hersenen ten gevolge van veroudering of psychiatrische aandoeningen. Geheugenachteruitgang en psychoses komen vaker voor bij mensen met 22q11.2DS, en voorspellende waardes zouden kunnen helpen om mensen met 22q11.2DS die een verhoogd risico hebben op deze aandoeningen intensiever te monitoren en de aandoening vroeg op te sporen. Door middel van oogfoto's (fundoscopie) en scans (optical coherence tomography) van het netvlies zijn de dikte, kronkeling en vertakkingen van de bloedvaatjes en de dikte van zenuwlaagjes van het netvlies gemeten. De resultaten laten zien dat volwassenen met 22q11.2DS meer kronkelingen en vertakkingen hebben van de bloedvaatjes dan de controlepersonen. Daarnaast werd bij volwassenen met 22q11.2DS, maar niet bij controlepersonen, gezien dat de vertakkingen van de bloedvaatjes en de dikte van de zenuwvezellaag afnamen met de leeftijd. Deze resultaten steunen toekomstig onderzoek naar de veranderingen van bloedvaatjes en de zenuwlaagjes van het netvlies als mogelijke voorspellers voor leeftijd gerelateerde aandoeningen bij 22q11.2DS zoals psychoses en geheugenachteruitgang.

In **hoofdstuk 7** worden de bevindingen besproken met betrekking tot trauma en post-traumatische stress stoornis (PTSS) bij volwassenen met 22q11.2DS. De hypothese achter dit onderzoek was dat het voorkomen van PTSS hoger zou liggen bij volwassenen met 22q11.2DS dan in de algemene bevolking (3,6%). Daarnaast zijn mogelijke bijdragende factoren voor PTSS onderzocht. Het onderzoek vond plaats bij 112 volwassenen met 22q11.2DS (45% man, gemiddelde leeftijd 32,5 jaar) die een van de twee Nederlandse 22q11.2DS poliklinieken voor volwassenen hebben bezocht, namelijk Maastricht Universitair Medisch Centrum en 's Heeren Loo. De resultaten van dit onderzoek laten zien dat PTSS bij tenminste 8,0% (95% betrouwbaarheidsinterval 3,0% - 13,0%) van de volwassenen met 22q11.2DS werd vastgesteld. Een traumatische gebeurtenis werd

vermeld bij 23 volwassenen (20,5%), voornamelijk ongewenst seksueel gedrag (10,7%) en ernstige verwonding (9,8%). Daarnaast werden er andere gebeurtenissen vermeld die als traumatisch werden ervaren, maar buiten de formele criteria vielen, bij nog eens 17 volwassenen (15,2%), zoals pestgedrag (11,6%) en ziekenhuisopnames en operaties (3,6%). In totaal kregen 20 volwassenen (17.9%) behandeling voor trauma, meestal was dit Eye Movement Desensitization Reprocessing (EMDR, 17,0%) therapie en in enkele gevallen cognitieve gedragstherapie (CGT, 1,8%). Geslacht of de hoogte van het cognitief functioneren, gemeten aan de hand van het laatste IQ, hadden geen relatie tot het voorkomen van PTSS. Op basis van deze resultaten worden zorgverleners geadviseerd om alert te zijn op het voorkomen van traumatische ervaringen en PTSS bij mensen met 22q11.2DS zodat tijdig behandeling kan worden voorgesteld en de nadelige gevolgen op de kwaliteit van leven worden beperkt. Vervolgonderzoek is nodig om het stellen van de diagnose van PTSS en behandeling van trauma bij volwassenen met 22q11.2DS te verbeteren, aangepast aan de cognitieve mogelijkheden en met aandacht voor ogenschijnlijk onschuldige levensgebeurtenissen.

In **hoofdstuk 8** worden de resultaten van de verschillende onderzoeken in dit proefschrift in bredere context besproken, ook in relatie tot ander wetenschappelijk onderzoek. Een belangrijke bevinding is dat de resultaten van verschillende onderzoeken in dit proefschrift lijken te wijzen op vroegtijdige veroudering bij volwassenen met 22q11.2DS. Daarnaast worden er in dit hoofdstuk aanbevelingen gedaan voor toekomstig onderzoek, voornamelijk onderzoeken die mensen met 22q11.2DS of een ander genetisch syndroom opvolgen over de tijd en die onderzoeken bij mensen met verschillende genetische syndromen combineren. Dit kan helpen om overlap en verschillen in onderliggende mechanismen beter te begrijpen en kan bijdragen aan de ontwikkeling van nieuwe behandelingen.

In **hoofdstuk 9** wordt de impact van de verschillende onderzoeken besproken op de maatschappij waaronder de zorg, en de wetenschap. Impact heeft met name plaatsgevonden doordat resultaten zijn of zullen worden geïmplementeerd in richtlijnen voor diagnostiek en behandeling van mensen met 22q11.2DS en door het delen van de aanbevelingen met

brede doelgroepen, waaronder artsen van verschillende specialismen en volwassenen met 22q11.2DS en hun families, zodat de resultaten en adviezen kunnen bijdragen aan het verbeteren van de zorg en de kwaliteit van leven van mensen met 22q11.2DS en andere genetische syndromen.

Appendix III

List of publications, presentations and grants

Publications in international peer-reviewed journals

Emma N.M.M. von Scheibler, MD; Agnies M. van Eeghen, MD, PhD; Tom J. de Koning, MD, PhD; Mark L. Kuijf, MD, PhD; Janneke R. Zinkstok, MD, PhD; Annelieke R. Müller; Thérèse A.M.J. van Amelsvoort, MD, PhD; Erik Boot, MD, PhD. Parkinsonism in genetic neurodevelopmental disorders: A systematic review. *Mov Dis Clin Pract.* 2022. DOI: 10.1002/mdc3.13577. (*Open Access*)

Emma N.M.M. von Scheibler, MD; Thérèse A.M.J. van Amelsvoort, MD, PhD; Claudia Vingerhoets, PhD; Agnies M. van Eeghen, MD, PhD; Erik Boot, MD, PhD. Post-traumatic stress in adults with 22q11.2 deletion syndrome. *BJPsych Open, 2022.* DOI: 10.1192/bjo.2022.525. (*Open Access*)

Emma N.M.M. von Scheibler, Emy S. van der Valk Bouman, Myrthe A. Nuijts, Noël J.C. Bauer, Tos T.J.M. Berendschot, Pit Vermeltfoort, Levinus A. Bok, Agnies M. van Eeghen, Michiel L. Houben, Thérèse A.M.J. van Amelsvoort, Erik Boot, Michelle B. van Egmond-Ebbeling. Ocular findings in 22q11.2 deletion syndrome: A systematic literature review and results of a Dutch multicenter study. *Am J Med Genet A*. 2022 Feb;188(2):569-578. doi: 10.1002/ajmg.a.62556. Epub 2021 Nov 12. PMID: 34773366. (*Open Access*)

Friederike Ehrhart, Ana Silva, Therese van Amelsvoort, **Emma von Scheibler**, Chris Evelo, David E.J. Linden. Converging pathways found in copy number variation syndromes with high schizophrenia risk. bioRxiv 2022.02.07.479370; doi: https://doi.org/10.1101/2022.02.07.479370. (*Preprint*)

Submitted and in progress articles

Emma N.M.M. von Scheibler, Josine C.C. Widdershoven, Denise C.P.B.M. van Barneveld, Nina Schröder, Agnies M. van Eeghen, Thérèse A.M.J. van Amelsvoort, Erik Boot. Hearing loss and history of otolaryngologic conditions in adults with 22q11.2DS. *Submitted.*

Emma N.M.M. von Scheibler, Abhishek Appaji, Tos T.J.M. Berendschot, Noël J.C. Bauer, Naren P. Rao, Agnies M. van Eeghen, Thérèse A.M.J. van Amelsvoort, Erik Boot. Optometry in adults with microdeletion 22q11.2: the eye as a window to the brain. *Submitted.*

Emma von Scheibler, Agnies van Eeghen, Thérèse van Amelsvoort, Erik Boot et al. Prevalence of Parkinson's disease in 22q11.2 deletion syndrome: A multicenter study. *Article in progress.*

Publications in national non-peer-reviewed journals

Emma N.M.M. von Scheibler, MD; Thérèse A.M.J. van Amelsvoort, MD, PhD; Claudia Vingerhoets, PhD; Agnies M. van Eeghen, MD, PhD; Erik Boot, MD, PhD. Post-traumatische stress bij volwassenen met 22q11.2 deletiesyndroom. *TAVG*, nummer 4, 2022. (*Dutch)*

Emma von Scheibler, Agnies van Eeghen, Tos Berendschot, Denise van Barneveld, Josine Widdershoven, Therese van Amelsvoort, Erik Boot. Zintuigproblematiek bij 22q11.2 deletiesyndroom. *TAVG*, nummer 3, 2020. (*Dutch)*

Scientific communications with accepted/published abstracts

Agnies van Eeghen, Erik Boot, **Emma von Scheibler,** Annelieke Müller, Hadassa Kwetsie, Hester Jaspers Faijer – Westerink. Workshops (oral presentations) at the "Focus op Onderzoek" symposium, Amersfoort, The Netherlands, 2023.

Emma N.M.M. von Scheibler, Agnies M. van Eeghen, Tom J. de Koning, Mark L. Kuijf, Janneke R. Zinkstok, Annelieke R. Müller; Thérèse A.M.J. van Amelsvoort, Erik Boot, MD PhD. Parkinsonism in genetic neurodevelopmental disorders: A systematic review. Poster presentation at EuroNDD, Amsterdam, The Netherlands, 2023.

Emma N.M.M. von Scheibler, Thérèse A.M.J. van Amelsvoort, Claudia Vingerhoets, Agnies M. van Eeghen, Erik Boot. Post-traumatic stress in adults with 22q11.2 deletion syndrome. Poster presentation at Society of the Study of Behavioral Phenotypes conference, Oslo, Norway, 2022.

Emma N.M.M. von Scheibler, Josine C.C. Widdershoven, Denise C.P.B.M. Breukels-van Barneveld, Nina Schröder, Thérèse A.M.J. van Amelsvoort, Agnies M. van Eeghen, Erik Boot. Age-related hearing loss in adults with

microdeletion 22q11.2. Oral presentation at the Biennial international 22q11.2 deletion syndrome conference, Split, Croatia, 2022.

Emma N.M.M. von Scheibler, Emy S. van der Valk Bouman, Myrthe A. Nuijts, Noël J.C. Bauer, Tos T.J.M. Berendschot, Pit Vermeltfoort, Levinus A. Bok, Agnies M. van Eeghen, Michiel L. Houben, Thérèse A.M.J. van Amelsvoort, Erik Boot, Michelle B. van Egmond-Ebbeling. Ocular findings in 22q11.2 deletion syndrome: A systematic literature review and results of a Dutch multicenter study. Oral presentation at the Biennial international 22q11.2 deletion syndrome conference, Split, Croatia, 2022.

Emma N.M.M. von Scheibler, Thérèse A.M.J. van Amelsvoort, Claudia Vingerhoets, Agnies M. van Eeghen, Erik Boot. Post-traumatic stress in adults with 22q11.2 deletion syndrome. Oral presentation at the Biennial international 22q11.2 deletion syndrome conference, Split, Croatia, 2022.

Emma N.M.M. von Scheibler, Abhishek Appaji, Tos T.J.M. Berendschot, Noël J.C. Bauer, Naren P. Rao, Thérèse A.M.J. van Amelsvoort, Agnies M. van Eeghen, Erik Boot. Retinal vessel geometry: A biomarker for major neurocognitive decline in 22q11.2 deletion syndrome? Oral presentation at the Biennial international 22q11.2 deletion syndrome conference, Split, Croatia, 2022.

Emma N.M.M. von Scheibler, Agnies M. van Eeghen, Tom J. de Koning, Mark L. Kuijf, Janneke R. Zinkstok, Annelieke R. Müller; Thérèse A.M.J. van Amelsvoort, Erik Boot, MD PhD. Parkinsonism in genetic neurodevelopmental disorders: A systematic review. Lecture at the Dutch Parkinson Scientists Congress, Amsterdam UMC, Amsterdam, The Netherlands, 2021.

E.N.M.M. von Scheibler, M. Kuijf, T.J. de Koning, J.R. Zinkstok, A. Muller, T.A.M.J. van Amelsvoort, A.M. van Eeghen, H.J.G. Boot. Parkinsonism in individuals with rare genetic neurodevelopmental disorders: A systematic review. Oral presentation at the International Parkinson and Movement Disorder Society Congress, 2021.

E.N.M.M. von Scheibler, M. Kuijf, T.J. de Koning, J.R. Zinkstok, A. Muller, T.A.M.J. van Amelsvoort, A.M. van Eeghen, H.J.G. Boot. Parkinsonism in individuals with rare genetic neurodevelopmental disorders: A systematic review. Poster presentation at the Society of the Study of Behavioral Phenotypes conference, 2021.

Emma N.M.M. von Scheibler, Josine C.C. Widdershoven, Denise C.P.B.M. van Barneveld, Nina Schröder, Agnies M. van Eeghen, Thérèse A.M.J. van Amelsvoort, Erik Boot. Age-related high-frequency hearing loss in adults with microdeletion 22q11.2. Oral presentation; 6th IASSIDD Europe congress 2021, Amsterdam, the Netherlands.

Emma N.M.M. von Scheibler, Emy S. van der Valk Bouman, Tos T.J.M. Berendschot, Noël J.C. Bauer, Levinus A. Bok, Pit B.J. Vermeltfoort, Thérèse A.M.J. van Amelsvoort, Agnies M. van Eeghen, Michiel Houben, Erik Boot, Michelle B. van Egmond. Ocular findings in 142 individuals with 22q11.2 deletion syndrome. Oral presentation; 6th IASSIDD Europe congress 2021, Amsterdam, Netherlands.

Grants

Les and Robbie Fountain bursary award by the Society of the Study of Behavioral Phenotypes (SSBP) to attend the international SSBP conference in Oslo, 2022.

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Appendix IV

About the author

Emma Boersma- von Scheibler was born on March 7th, 1992 in Verwoerdburg, South-Africa. At the age of three she moved with her family to Weert, the Netherlands. In 2010 she graduated from secondary school (Atheneum) at Philips van Horne in Weert. After this she obtained her bachelor's degree in Biomedical Sciences at Maastricht University in 2013. She completed the first year of the Master Health Food Innovation Management before she started in 2014 with the Master Physician-Clinical Investigator to graduate as a medical doctor in 2018 at Maastricht University. During her last year she did a 9-month internship at the Department of Clinical Genetics at the Maastricht University Medical Center+ (MUMC+) to study genetic variants associated with dilated cardiomyopathy. After graduating she worked for one year as a resident at the Department of Internal Medicine at the Maxima Medical Center (MMC) in Veldhoven. In 2019 she started as a PhD candidate at Advisium, 's Heeren Loo, Amersfoort, and the Department of Psychiatry and Neuropsychology at Maastricht University.

During her PhD trajectory she was involved in several projects with national and international collaborations to increase knowledge of conditions associated with the adult phenotype of genetic neurodevelopmental disorders, with a focus on 22q11.2 deletion syndrome, aimed at improving medical care for this population. She spent one month at the Department of Human Genetics at the Catholic University of Leuven (Belgium) for research collaborations and a clinical internship. She also spoke at multiple national and international conferences and has been on the organizing committee of national symposia. In addition, she was involved in educational roles as a tutor and supervisor for bachelor and master students of Maastricht University and has been a reviewer for the American Journal of Medical Genetics Part A. During her trajectory she received a mobility grant from

the European Graduate School of Neuroscience and the Les and Robbie Fountain bursary award from the Society for the Study of Behavioural Phenotypes. Because of her interest in nutrition, she completed a course in Nutrition and Disease at Wageningen University.

She is currently working as a physician and researcher at Koraal, a Dutch organization for people with an intellectual disability, and is affiliated with the Department of Psychiatry and Neuropsychology at Maastricht University.

Appendix V

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