

22q11.2 Deletion Syndrome–Associated Parkinson’s Disease

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Abstract: Background: 22q11.2 deletion syndrome (22q11.2DS) is a multisystem condition associated with an increased risk of early-onset Parkinson’s disease (PD).
 Methods: We review the clinical, neuroimaging, and neuropathological observations, as well as diagnostic challenges, of PD in 22q11.2DS. We conducted a search of PubMed up until June 1, 2018 and personal files to identify relevant publications.
 Results: 22q11.2DS-associated PD is responsible for approximately 0.5% of early-onset PD. The hallmark motor symptoms and neuropathology of PD, and typical findings of reduced striatal dopamine transporter binding with molecular imaging, are present in 22q11.2DS-associated PD. Mean age at PD onset in 22q11.2DS is relatively young (~40 years). Patients with 22q11.2DS-associated PD show a good response to levodopa.
 Conclusions: Further recognition of 22q11.2DS and study of PD in people with 22q11.2DS could provide insights into the mechanisms that cause PD in the general population. 22q11.2DS may serve as an identifiable PD model to study prodromal PD and disease-modifying treatments.

Parkinson’s disease (PD) is a heterogeneous condition involving genetic variability, environmental factors, and multiple pathophysiological pathways and mechanisms.¹ It is estimated that the recurrent and identifiable hemizygous 22q11.2 deletion, a copy number variation associated with 22q11.2 deletion syndrome (22q11.2DS, OMIM #192430, #188400) and affecting approximately 1 in 3,000 live births,² is responsible for approximately 0.5% of early-onset PD (EOPD).³ Conversely, within 22q11.2DS, there is an estimated 20- to 70-fold increased risk to develop PD compared to the general population.^{3,4} Whereas average age of motor onset is earlier in 22q11.2DS (~40 years), major clinical characteristics and response to standard treatments appear comparable in 22q11.2DS-associated PD to those in idiopathic PD. Nevertheless, because of the unfamiliarity of clinicians with 22q11.2DS and the clinical complexity in many cases,^{5,6} there is under-recognition of both 22q11.2DS in PD and of PD in 22q11.2DS.^{3,7} In recent years, an increasing number of studies have been directed at enhancing understanding of 22q11.2DS-

associated PD. This is not only relevant for better patient care, but studies in this relatively genetically homogeneous group of individuals may also improve our understanding of the complex pathogenesis of PD. This review provides an overview of clinical, neuroimaging, and neuropathological observations as well as diagnostic challenges, of PD in 22q11.2DS, and outlines some of the implications for clinical practice and research.

Methods

We conducted a search of PubMed up until June 1, 2018 and personal files using the terms “(22q11.2 OR velocardiofacial OR DiGeorge) AND (Parkinson’s disease OR parkinsonism OR bradykinesia OR tremor OR rigidity)” to identify publications that provided information on 22q11.2DS-associated PD.

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22q11.2 Deletion Syndrome

22q11.2DS is the most common human microdeletion syndrome.² It is a multisystem condition (Table 1) known to have significant variability in the spectrum of its features and the severity of their expression between individuals, even between affected family members.² Cardinal features often change with age. Prominent features in childhood include hypotonia, hypocalcemia (often hypocalcemic) seizures, congenital anomalies of the heart, palate and kidney, recurrent infections, autoimmune diseases, and psychiatric disorders, such as attention deficit disorder. In adolescence and adulthood, there is a high risk of psychiatric disorders, most notably anxiety disorders, schizophrenia, and other psychotic disorders.⁸ In addition to PD, parkinsonism not meeting criteria for PD,^{9,10} other movement disorders (e.g., a number of patients with non-epileptic multifocal and generalized myoclonic jerking have been reported),^{9,11–13} and cognitive deterioration,¹⁴ appear to be more common in 22q11.2DS than in the general population. Premature death has been reported in 22q11.2DS, with multiple causes (often sudden and unexpected and not necessarily related to congenital heart defects or psychiatric disorders); median age at death is in the forties.¹⁵

Many patients suffer from a delayed 22q11.2DS diagnosis,⁷ although an increased index of suspicion together with clinical clues may help prompt genetic testing in this identifiable

condition.² Notably, family history is not a good predictor; approximately 90% of the newly identified patients have a spontaneous (*de novo*) 22q11.2 deletion, meaning that neither parent has the deletion.² Approximately 85% of 22q11.2DS patients have a typical 3-Mb deletion encompassing ~90 genes.² Another 5% to 10% of patients have a smaller, 1.5-Mb, deletion. At present, diagnosis is usually confirmed by detection of the hemizygous 22q11.2 deletion using chromosomal microarray or fluorescence in situ hybridization.² The deletions are too small to be seen using conventional karyotyping methods and are not detectable using currently available PD genetic diagnostic panels.²⁴

Microdeletion 22q11.2: A Genetic Risk Factor for PD

There is incomplete penetrance for PD in 22q11.2DS, as in other populations at genetic risk for PD. The sole prevalence estimate available reported 5.9% with PD in a cohort of 159 adults with 22q11.2DS aged 35 to 64 years.¹⁰ Additional genetic and environmental factors that contribute to the increased PD risk in this group of patients are yet to be determined. A whole-genome sequencing pilot study in patients with 22q11.2DS showed nominal enrichment in the PD cases of

TABLE 1 Multisystem involvement in 22q11.2 deletion syndrome

System	Examples of Features That May Increase the Index of Suspicion for 22q11.2DS	Estimated Prevalence in 22q11.2DS*
Nervous system	Neurological	
	Recurrent seizures, epilepsy ¹⁶	16%, 4%
	Early-onset PD ⁴	>5%
	Parkinsonism not meeting criteria for PD ^{9,10}	To be determined
	Other movement disorders (e.g., myoclonic disorders) ^{9,11–13}	To be determined
	Functional neurological disorder ⁵	To be determined
	Psychiatric	
	Attention deficit and hyperactivity disorder (pediatric history) ⁸	>30%
	Anxiety disorders ^{8,17}	~30%
	Schizophrenia ^{8,17}	20% to 25%
Cognitive ^a	Learning disabilities ⁵	>90%
	Intellectual disabilities ⁵	~35%
	Cognitive deterioration ¹⁴	To be determined
Sensory system	Hearing loss (any type, especially conductive secondary to otitis media) ¹⁸	6% to 60%
	Hyposmia ^{9,10,19}	>40%
Endocrine system	Hypocalcemia ²⁰	80%
	Obesity ²¹	>40%
	Hypothyroidism ⁵	20%
Circulatory system	Congenital heart defects requiring surgery ⁵	30% to 40%
	Thrombocytopenia (usually mild) ⁵	30%
Respiratory system and related	Hypnasal speech or other minor speech impediment ⁵	>90%
	Velopharyngeal dysfunction ²	15–30%
	Obstructive sleep apnea ²²	>10%
Skeletal system	Scoliosis (usually mild) ⁵	45%
Immune system	Recurrent infections (pediatric history) ⁵	35% to 40%
Renal system	Structural urinary tract anomaly ⁵	30%
Gastrointestinal system	Constipation (common, varying degrees) ⁵	To be determined
	Dysmotility/dysphagia (common, varying degrees) ⁵	35%

* Estimates of lifetime prevalences, all significantly higher than general population estimates, that may vary depending on the age of the patient and ascertainment sources.

^a Note also high variability from person to person. 22q11.2DS, 22q11.2 deletion syndrome.

additional rare putatively damaging missense variants involving genome-wide candidate genes with functional relevance to PD.²⁵ Larger longitudinal studies are needed to improve prevalence estimates, and to evaluate how the interaction of lifestyle and additional environmental and genetic factors may contribute to lifetime risk of developing PD in 22q11.2DS.¹

Natural History of PD in 22q11.2 Deletion Syndrome

PD in 22q11.2DS appears largely indistinguishable from idiopathic PD with respect to major clinical PD features.²³ In 22q11.2DS-associated PD, the male-to-female ratio (~2.5:1) shows a male predominance, motor onset is asymmetric in most cases, and cardinal motor features (i.e., bradykinesia, rigidity, and tremors) predominate in the early stages. Over time, there is progression of the cardinal motor features and the emergence of other motor features (e.g., postural instability, gait disorders, and dyskinesia) and neuropsychiatric symptoms (i.e., psychosis, anxiety, and/or depression) in patients with no history of these.²³

However, there are also some differences from idiopathic PD. For example, age at PD onset in 22q11.2DS is often earlier with mean age 39.5 ± 8.5 years (range, 18–58), and >70% having onset < 45 years of age.²³ Features that appear to be more common in 22q11.2DS than in idiopathic PD include early dystonia, history of seizures, and neuropsychiatric symptoms (e.g., psychosis and anxiety) preceding PD onset.²³ Importantly, though, some nonmotor features that are observed in prodromal and manifest idiopathic PD are known to be common in patients with 22q11.2DS, with or without PD. These include sleep disorders (it is unknown whether this includes REM sleep behavior disorder),²⁶ olfactory deficits,^{9,10,19} and constipation.²⁷ It is also unknown whether any of these features are predictive of future development of PD in 22q11.2DS. Other nonmotor and motor features (e.g., freezing of gait) and levodopa-induced motor complications (e.g., end of dose wearing off) have yet to be studied systematically in 22q11.2DS.

Diagnostic Challenges

The hallmark symptoms of PD are present in 22q11.2DS-associated PD.²³ However, PD in 22q11.2DS may be difficult to diagnose as a result of the clinically complex multisystem nature of the condition with lack of familiarity with the syndrome, even compared to rarer conditions.⁶ For example, Wilson's disease was considered, but not confirmed, in at least 4 reported patients with 22q11.2DS and abnormal movements.^{28–31} Use of antipsychotic medications may delay the diagnosis of PD significantly, given that parkinsonism may be assumed to be drug induced.²³ Other medications that may be associated with parkinsonism, including selective serotonin reuptake inhibitors,³² are also frequently taken by individuals with 22q11.2DS. Nonmotor features that can help distinguish between medication-induced parkinsonism and PD,³³ for example, sleep disorders and

olfactory deficits, are common in individuals with 22q11.2DS without PD,^{9,10,19,26} as is fatigue.³⁴

In addition to PD, parkinsonism not meeting criteria for PD may be more common in individuals with 22q11.2DS than in the general population.^{9,10} Molecular imaging, particularly dopamine transporter (DAT) imaging, may be helpful to distinguish PD from nondegenerative parkinsonism.³⁵ Typical findings of reduced striatal DAT binding has been reported in several individuals with 22q11.2DS-associated parkinsonism.²³ However, it is uncertain whether DAT binding levels in individuals with 22q11.2DS at a young age may be increased compared to the general population,¹⁰ possibly complicating the interpretation for some 22q11.2DS individuals with parkinsonism and normal imaging results. Large-scale longitudinal studies are needed to evaluate how parkinsonian features and DAT binding levels change over time in 22q11.2DS, to assess whether the finding of greater SN echogenicity using transcranial sonography in adults with 22q11.2DS in comparison to healthy controls can be replicated,¹⁰ and to evaluate the suitability of this and other PD biomarkers in 22q11.2DS.

Management

Standard treatments for PD are recommended for 22q11.2DS-associated PD. The largest study to date on 22q11.2DS-associated PD showed a positive response to pharmacological replacement of dopamine with L-dopa in the majority of the patients (>90%).²³ The response to other medications in this study was reported for such a small number of patients that no conclusions could be drawn. One could speculate that catechol-O-methyltransferase (COMT) enzyme inhibitors and monoamine oxidase B enzyme inhibitors, which are both required for degradation of dopamine, may not be as effective in 22q11.2DS as in idiopathic PD, because individuals with 22q11.2DS are already believed to have impaired dopamine metabolism.³⁶ There is, however, as yet no evidence for this. A positive response to DBS was found in 4 of 5 reported cases and further specified in 3 cases as 30% to 70% improvement in UPDRS-III motor scores.^{23,37} In the fifth case, no electrodes were implanted because no discharge pattern of the microelectrode recordings typical for the STN was observed, nor could a reduction of rigidity be achieved with intraoperative test stimulation.²³

22q11.2DS-specific management considerations necessitate a multidisciplinary approach.²⁶ Prevalent comorbid conditions in 22q11.2DS that may affect PD expression and/or treatment outcome include, but are not limited to, recurrent seizures,¹⁶ the possible association between 22q11.2DS and other movement disorders (e.g., myoclonic disorders),^{9,11–13} psychiatric disorders,⁸ intellectual disability,²⁶ sensory dysfunction,^{5,9,10,19} endocrinological disorders (i.e., thyroid dysfunction, hypoparathyroidism, hypocalcemia, and hypomagnesemia),^{5,20,30} and obstructive sleep apnea.²² In the case of planned treatment with clozapine,³⁸ which has proven efficacy for schizophrenia in 22q11.2DS,³⁹ prophylactic anticonvulsant treatment is recommended given the lowered seizure threshold.³⁹ Non-PD-related aspects of management are described in more detail elsewhere.^{5,26} Close collaboration between a movement disorders neurologist and a specialist in 22q11.2DS is recommended.²³

Pathophysiology/Mechanisms

Neuropathological findings have been reported in 3 patients with 22q11.2DS-associated PD.⁴ The core neuropathological features of PD, extensive loss of dopaminergic neurons in the SN and Lewy pathology, were found in 3 and 2 of these patients, respectively.⁴ Similar, but less profound, dopaminergic loss and comparable degrees of Lewy pathology were found in many other brain regions of these patients. Although several 22q11.2 deletion mouse models are available,⁴⁰ only one study in a 22q11.2 deletion mouse model focused on neuropathological findings that may be relevant to 22q11.2DS-associated PD.⁴¹ In this study in mice carrying a heterozygous deletion of mouse chromosome 16 (*Df1/+* mice) that is highly similar in gene content and size to the human 22q11.2 deletion,⁴² elevated expression of α -synuclein proteins (1.3- to 1.8-fold increase compared to wild-type control mice) was found in the anterior cingulate cortex, dorsolateral part of caudate putamen, and SNpc at 3.5 and 8 months of age (roughly equivalent to the twenties and forties in humans, respectively). Homologues of individual genes within the 22q11.2 region may also be studied in other simple model organisms using knockdown or knockout models, some of which display motor abnormalities, for example, a *Drosophila* homologue of *PRODH* knockout (*slgA*).⁴³

Several pathways and mechanisms previously implicated in idiopathic PD may also play a role in 22q11.2DS-associated PD. One of these is a proposed hyperdopaminergic mechanism with dopamine autotoxicity.^{44,45} Patients with a 22q11.2 deletion carry only one copy of the *COMT* gene that is involved in the degradation of catecholamines, including dopamine. Indeed, blood samples from individuals with 22q11.2DS have shown reduced *COMT* expression and enzyme activity levels^{46,47} and decreased levels of the dopamine metabolite, homovanillic acid.³⁶ Moreover, a study with PET and ¹¹C-dihydrotetrabenazine (¹¹C-DTBZ), a radioligand that binds to the presynaptic vesicular monoamine transporter, reported elevated binding of ¹¹C-DTBZ in the striatum in individuals with 22q11.2DS over age 30 years but without PD, compared to healthy age- and sex-matched controls, indicating a hyperdopaminergic state.¹⁰

Also, mitochondrial dysfunction is thought to play a central role in PD.¹ Interestingly, there are at least six genes—*MRPL40*, *PRODH*, *SLC25A1*, *TANGO2*, *TXNRD2*, and *ZDDHC8*—in the typical 3-Mb 22q11.2 deletion region that are involved in different aspects of mitochondrial function (data on these genes and their roles within mitochondria was reviewed by Devaraju and colleagues in 2017).⁴⁸ Decreased dosage of these genes may be involved in the pathogenesis of PD in 22q11.2DS. Additional support for the likelihood that mitochondrial dysfunction plays a role in the pathogenesis of 22q11.2DS-associated PD comes from a study in mice carrying a hemizygous 1.3-Mb chromosomal deletion of murine chromosome 16 (*Df(16)A^{+/−}*), encompassing a segment syntenic to the 1.5-Mb human 22q11.2 deletion.⁴⁹ This well-characterized mouse model of the human 22q11.2DS reported substantial alterations of mitochondrial proteins.

Box 1. Main messages of the review

- The hallmark motor symptoms and neuropathology of PD are present in 22q11.2DS-associated PD.^{4,23}
- The mean age at PD onset is relatively young (~40 years) in patients with 22q11.2DS.²³
- In addition to PD, parkinsonism not meeting criteria for PD and other movement disorders may be more common in 22q11.2DS than in the general population.^{9,10}
- Dopaminergic imaging may be helpful in the differentiation of PD from nondegenerative 22q11.2DS-associated parkinsonism.³⁵
- Patients with 22q11.2DS-associated PD show a good response to L-dopa.²³
- Patients with 22q11.2DS are clinically identifiable and genetic testing is readily available.^{2,23}
- 22q11.2DS is a multisystem condition requiring a multidisciplinary approach.^{2,5,17}
- 22q11.2DS-associated PD is an important genetic PD subtype,²³ responsible for approximately 0.5% of early-onset PD,³ and a valuable model of neurodegenerative mechanisms involved in the pathogenesis of PD.
- 22q11.2DS provides a unique opportunity for studying prodromal PD and the effects of disease-modifying treatments.²³

Outlook

The recurrent hemizygous 22q11.2 deletion is a recently discovered risk factor for PD, with the knowledge about a 22q11.2DS-specific PD-phenotype growing rapidly. Current knowledge is, however, based on a relatively small number of patients. Large-scale, prospective, longitudinal studies in 22q11.2DS are needed to improve understanding. Challenges include the identification of prodromal symptoms, biomarkers, and/or other individual differences at a young age that may help pinpoint risk and protective factors for developing PD in 22q11.2DS and their comparability to such factors for idiopathic PD.

Despite the challenges, 22q11.2DS, a human genetic model, provides a unique opportunity to study mechanisms that cause idiopathic PD and to study the effect of disease-modifying treatments.⁵⁰ An analogy may be found in another genetic multisystem condition; Down syndrome, that has been used successfully as a genetic model for Alzheimer's disease, typically with early onset.⁵¹ Advantages of the 22q11.2DS-associated PD model include: (1) the fact that, in contrast to other genetic forms of PD, patients with 22q11.2DS are clinically identifiable (see Table 1 for comorbid features that may increase the index of suspicion for 22q11.2DS) and that genetic testing is readily available; (2) young average age at PD onset (~40 years), reducing the risk for age-related neurodegenerative processes other than PD that

may affect study findings; (3) testable hypotheses concerning major mechanisms underlying idiopathic and 22q11.2DS-associated PD, including dopamine autotoxicity related to impaired dopamine clearance (genes of potential interest in the 22q11.2 deletion region: *COMT*, *PRODH*) and mitochondrial dysfunction (genes in the 22q11.2 deletion region encoding mitochondrial proteins: *MRPL40*, *PRODH*, *SLC25A1*, *TANGO2*, *TXNRD2*, and *ZDDHC8*)⁴⁸; and (4) the fact that animal models for the 22q11.2 deletion are available.³⁹ Incomplete penetrance for PD in 22q11.2DS may be a limiting factor. However, the only prevalence estimate for PD thus far may represent underestimates given that ~25% of patients receive antipsychotic treatment and thus some patients diagnosed with putative drug-induced parkinsonism may actually have PD. Synergistic with other genetic models of PD (e.g., *LRRK2*-PD),⁵² research in 22q11.2DS-associated PD may help unravel the complex processes underlying PD, that are likely to involve multiple pathophysiological pathways and mechanisms. Moreover, 22q11.2DS provides an opportunity for studying prodromal PD and the effects of disease-modifying treatments.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

E.B.: 3A, 3B

A.S.B.: 3B

C.M.: 3B

Disclosures

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