Typical features of Parkinson disease and diagnostic challenges with microdeletion 22q11.2

Erik Boot, MD, PhD, Nancy J. Butcher, PhD, Sean Udow, MD, FRCP(C), Connie Marras, MD, PhD, Kin Y. Mok, FRCP, Satoshi Kaneko, MD, PhD, Matthew J. Barrett, MD, MSc, Paolo Prontera, MD, PhD, Brian D. Berman, MD, MS, Mario Maselli, MD, PhD, Boris Dufournet, MD, Karine Nguyen, MD, Perrrine Charles, MD, Eugénie Mutez, MD, PhD, Teodor Danaila, MD, PhD, Aurélia Jacquette, MD, Olivier Colin, MD, Sophie Drapier, MD, Michel Borg, MD, Ania M. Fiksinski, MSc, Elfri Vergeaelen, MD, Ann Swillen, PhD, Annick Vogels, MD, PhD, Annika Plate, MD, Claudia Perandones, MD, PhD, Thomas Gasser, MD,Kristien Clerinx, MD, Frédéric Bourdain, MD, Kelly Mills, MD, MHS, Nigel M. Williams, PhD, Nicholas W. Wood, PhD, FRCP, FMedSci, Jan Booj, MD, PhD, Anthony E. Lang, MD, MRCP, and Anne S. Bassett, MD, FRCP, On behalf of the International Research Group on 22q11.2DS-associated Parkinson's Disease

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Abstract

Objective
To delineate the natural history, diagnosis, and treatment response of Parkinson disease (PD) in individuals with 22q11.2 deletion syndrome (22q11.2DS), and to determine if these patients differ from those with idiopathic PD.

Methods
In this international observational study, we characterized the clinical and neuroimaging features of 45 individuals with 22q11.2DS and PD (mean follow-up 7.5 ± 4.1 years).

Results
22q11.2DS PD had a typical male excess (32 male, 71.1%), presentation and progression of hallmark motor symptoms, reduced striatal dopamine transporter binding with molecular imaging, and initial positive response to levodopa (93.3%). Mean age at motor symptom onset was relatively young (39.5 ± 8.5 years); 71.4% of cases had early-onset PD (<45 years). Despite having a similar age at onset, the diagnosis of PD was delayed in patients with a history of antipsychotic treatment compared with antipsychotic-naive patients (median 5 vs 1 year, p = 0.001). Preexisting psychotic disorders (24.5%) and mood or anxiety disorders (31.1%) were common, as were early dystonia (19.4%) and a history of seizures (33.3%).

Conclusions
Major clinical characteristics and response to standard treatments appear comparable in 22q11.2DS-associated PD to those in idiopathic PD, although the average age at onset is earlier. Importantly, treatment of preexisting psychotic illness may delay diagnosis of PD in 22q11.1DS patients. An index of suspicion and vigilance for complex comorbidity may assist in identifying patients to prioritize for genetic testing.

From The Dalglish Family 22q Clinic for Adults and Department of Psychiatry (E.B., AM.E., AS.B.), Toronto General Research Institute (AS.B.), and Division of Cardiology, Department of Medicine (AS.B.), University Health Network, Toronto, Canada; De Hartekamp Groep (E.B.), Centre for People with Intellectual Disability, Haarlem; Department of Nuclear Medicine (E.B., J.B.), Academic Medical Center, Amsterdam, the Netherlands; Clinical Genetics Research Program and Campbell Family Mental Health Research Institute (N.J.B., A.M.E.), Centre for Addiction and Mental Health, Toronto; Institute of Medical Science (N.J.B., M.M., A.E.L., AS.B.), Division of Neurology, Department of Medicine (C.M., M.M., A.E.L), and Department of Psychiatry (AS.B.), University of Toronto; Deer Lodge Movement Disorders Centre (S.U.), Section of Neurology (S.U.), Division of Internal Medicine, Ready Faculty of Health Sciences, University of Manitoba, Winnipeg; Morton and Gloria Sluivan Movement Disorders Centre and the Edmond J. Safra Program in Parkinson’s Disease Research (C.M., A.E.L.), Toronto Western Hospital and University of Toronto, Canada; Department of Molecular Neuroscience (K.T.M., N.H.W.), UCL Institute of Neurology, London, UK; Department of Neurology (E.S.K.), Kansai Medical University, Osaka, Japan; Department of Neurology (M.J.B.), University of Virginia School of Medicine, Charlottesville; Medical Genetics Unit (P.P.), Perugia University Hospital, Italy; Department of Neurology (B.D.B.), University of Colorado Anschutz Medical Campus, Aurora; Neurology Section (B.D.B.), VA Eastern Colorado Health Care System, Denver; Cognitive & Movement Disorders Clinic and Hurvitz Brain Sciences Research Program (M.M.), Sunnybrook Health Sciences Centre, Toronto, Canada; Departments of Clinical Neurosciences (Movement Disorders) (B.D.B.) and Genetics (Neurogenetics) (K.N.), Timone University Hospital (AP-HM), Provence-Alpes-Côte d’Azur; Aix-Marseille University (B.D., K.N.), Marseille; Department of Genetics (Neurogenetics) (P.C., A.J.), Pitie-Salpétrière University Hospital; Sorbonne University (P.C., A.J.), Paris; Department of Neurosciences (Movement Disorders) (E.M.L.), Lille University Hospital; Lille University (E.M.L.); Department of Neurology (Movement Disorders) (T.G.), Pierre Wertheimer University Hospital; Lyons; Marc Jeannerod Center for Cognitive Neurosciences (T.G.), Lyon 1 University; Department of Neurology (Movement Disorders) and Clinical Investigation Center (Clinical and Experimental Neurosciences) (O.C.), Pitié-Salpétrière University Hospital; Department of Neurology (Movement Disorders) (S.D.), Rennes University Hospital; Rennes-1 University (S.D.); Department of Clinical Neurosciences (Movement Disorders) (M.B.), Nice University Hospital, France; Department of Psychiatry (A.M.F.), Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, the Netherlands; Center for Human Genetics (A.S.), KU Leuven, Belgium; Department of Neurology (A.P.), University of Munich, Germany; Scientific and Technological Coordination Unit of the ANLIS Directorate (C.P.), National Administration of Laboratories and Institutes of Health, Argentina; Department of Neurodevelopmental Diseases (T.G.), Center of Neurology and Hertie-Institute for Clinical Brain Research, University of Tübingen; German Center for Neurodevelopmental Diseases (DZNE) (T.G.); Department of Neurology (K.C.), AZ Turnhout, Antwerp, Belgium; Neurology Unit and Stroke Center (P.B.), Hospital Foch, Suresnes, France; Movement Disorder Division (K.M.), Johns Hopkins University, Baltimore, MD; and Psychological Medicine and Clinical Neurosciences (N.M.W.), MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Cardiff, UK.

Coinvestigators are listed at http://links.lww.com/WNL/A512.

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PD, the recurrent hemizygous 22q11.2 deletion associated with 22q11.2 deletion syndrome (22q11.2DS). ^3^4 Previously known as DiGeorge or velocardiofacial syndrome, 22q11.2DS is an underdiagnosed multisystem genetic condition that can include birth defects, intellectual and developmental disabilities, seizures, psychotic disorders, and endocrine abnormalities. The associated 22q11.2 deletion, detectable on clinical genetic testing, is estimated to be present in 1 in 3,000 live births. ^5^

Although multiple case reports and 2 case series have been important in discovering the connection between PD and 22q11.2 deletions, and neuropathologic examination has shown classic loss of midbrain dopaminergic neurons with variable Lewy body pathology, ^3^ it is essential to compile a larger sample with more comprehensive data to understand how this genetic subtype may be similar to—or different from—typical idiopathic PD and other genetic forms of PD. We therefore obtained clinical and neuroimaging data from physicians for all identified 22q11.2DS PD cases around the world, in order to delineate the natural history, diagnosis, and treatment response of this genetic subtype of PD. The results indicate that, while many features are similar to those of typical PD, an increased index of suspicion together with clinical clues from the patient’s history may help prompt genetic testing for 22q11.2 deletion and prevent delayed diagnosis of PD.

### Methods

#### Identification and characterization of cases

We obtained clinical and neuroimaging data for 45 individuals with 22q11.2DS who met the inclusion criteria for this study: a molecularly confirmed 22q11.2 deletion involving the typically deleted region and PD defined as a clinical diagnosis by a neurologist, ^2^ ^5^ including bradykinesia and at least one of either rest tremor or rigidity. We excluded individuals deemed to have drug-induced parkinsonism or parkinsonism of unknown etiology. ^2^ We used the standard EOPD definition of age at onset <45 years. ^2^ We used comprehensive data forms to systematically collect anonymized clinical data on each patient with PD and 22q11.2DS (see appendix e-1, links.lww.com/WNL/A515); these were completed by the participating physicians using medical records or direct assessment for 26 (74.3%) of 35 previously reported cases identified through an extensive literature review and 10 unpublished cases identified through the International Consortium on Brain and Behavior in 22q11.2DS, a Canadian adult cohort, and personal communications (figure 1 [study flow chart]; table e-1, links.lww.com/WNL/A513 [published cases with PD and 22q11.2DS]; and appendix e-2 [results of literature search]).

### Results

#### Diagnosis of 22q11.2DS, family history of PD, and other genetic factors

Patients tended to have a late diagnosis of the 22q11.2 deletion (mean age 40.2 ± 13.0 years, n = 38), with the genetic diagnosis in more cases occurring after (n = 24 [63.1%]) than before (n = 12 [31.6%]) PD motor symptom onset (n = 2 age at onset unknown). With respect to associated developmental features, there were just 11 (24.4%) patients with a congenital heart defect reported but 28 (62.2%) with intellectual disability, most in the mild range (table e-2, links.lww.com/WNL/A513).

As expected, ^5^ most cases with information on inheritance status had a de novo 22q11.2 deletion (n = 16 of 19 [84.2%]).
Three had maternally inherited deletions, including one rare mosaic deletion. Two female patients had an additional genetic finding of possible clinical relevance: 45,X[3]/46,XX[7] mosaic Turner syndrome, and a maternally inherited 3q29 duplication with unknown pathogenicity, respectively. Wilson disease was considered, but ruled out, in 2 male patients (at ages 30 and 46 years, respectively).

There were 4 cases (8.9%) reported to have a parent with PD: 1 where the parent had EOPD (31 years); 1 other also had 3 paternal second-degree relatives with a history of PD (1 with onset <50 years). A fifth patient had a brother with amyotrophic lateral sclerosis. The inheritance status of the 22q11.2 deletion was unknown in all of these 5 cases.

Genetic testing was performed for known PD genes using various strategies for 17 patients, including 2 of the 5 with family history of neurodegenerative disease. The only finding was a missense mutation (HTRA2 p.G399S) of uncertain relevance to PD, inherited from an unaffected mother.

**Sex distribution, age at motor symptom onset, and PD diagnosis**

Of 45 individuals with 22q11.2DS-associated PD, 32 (71.1%) were male, indicating a typical PD sex distribution. Onset was early in 22q11.2DS-associated PD, as expected. For the 35 (81.4%) cases with data available, mean age at onset of motor symptoms was 39.5 ± 8.5 years, and 25 (71.4%) met EOPD criteria. Motor symptom onset on average was 2 years later in women, a nonsignificant sex difference (women [40.9 ± 8.2 years, n = 11], men [38.8 ± 8.7 years, n = 24]; p = 0.51). The mean age at PD diagnosis was 42.1 ± 9.0 years (n = 38 [88.4%]) with no significant sex difference (p = 0.30).
Despite having similar ages at median motor symptom onset, individuals with a history of antipsychotic use had a longer median time to PD diagnosis (5, range 0–14 years) than antipsychotic-naive patients (1, range 0–7 years; \( p = 0.001 \), figure 2). Although clozapine is not expected to cause parkinsonism, there were 2 patients with a time to PD diagnosis of 9 years, on clozapine monotherapy for most of that time period.

**Motor symptoms, response to treatment, and mortality**

Table 1 shows data available on motor symptoms in the onset year and at last assessment. For those with distribution of motor symptom onset documented (\( n = 30 \)), the majority had asymmetric onset, including 20 of 22 (90.9%) antipsychotic-naive cases and 7 of 8 (87.5%) antipsychotic-exposed cases. A less typical finding at presentation was dystonia (table 1). Neither sex nor history of antipsychotic medication use appeared to affect the presence of motor symptoms.

There was evidence of progression of motor symptoms over the course of PD with worsening for all typical features of PD except writing/loss of dexterity, where results were at the trend level (table 1). Neither presence of dystonia nor dyskinesia at last assessment was associated with sex or duration of follow-up (data not shown). Dyskinesia, however, was less likely to emerge with PD progression in women than men (odds ratio 0.10, 95% confidence interval 0.01–0.91; \( p = 0.04 \)).

Most patients received typical PD treatments (table e-3, links. lww.com/WNL/AS13) with response reported as positive (table 2).Polypharmacy and deep brain stimulation were fairly common (table 2).

Seven patients had died, 3 of whom met EOPD criteria. Median age at death was 56 years (range 42–61) after a median time from onset of motor symptoms of 9 years (5–18) for the 6 patients with data. There were only 3 patients with known cause of death: pneumonia (\( n = 2 \)) and cardiac failure (\( n = 1 \)).

**Neurological and psychiatric symptoms**

Before PD onset, there were 11 (24.4%) patients with a history of a psychotic disorder, and 14 (31.1%) with mood or anxiety disorder, in line with expectations for adults with 22q11.2DS.11,12 Fifteen (33.3%) patients had a lifetime history of seizures, a somewhat greater proportion than in a recent survey of 22q11.2DS (15.8%).13 With progression of PD, symptoms of psychosis, anxiety, or depression emerged in 7 (20.6%), 6 (17.6%), and 6 (18.2%) patients with no history of these, respectively. Emergence of cognitive decline was reported in 8 (17.8%) cases. Other emerging symptoms included impulse control disorders (\( n = 6 \)), emotional lability (\( n = 3 \)), altered sleep or eating habits (\( n = 3 \)), confusion (\( n = 1 \)), and self-injurious behavior (\( n = 1 \)).

Emergence of psychiatric symptoms with progression of PD was attributed to antiparkinsonian medication in 8 patients. There were only 10 (22.2%) cases with no known history of any lifetime neuropsychiatric disorder or symptoms at last assessment or death.

**Dopaminergic imaging**

Twenty (44.4%) patients had presynaptic dopaminergic imaging results available. Of 18 patients with dopamine transporter (DAT) SPECT imaging results, 17 showed typical findings of reduced (contralateral or bilateral) striatal binding.4,9,14,15 This included 6 (33.3%) patients taking antipsychotic medication.
One of the 18 patients showed a marked loss of striatal DATs in the ipsilateral putamen, and a slight reduction in binding in the contralateral caudate nucleus.

Two patients had data from a scientific study using PET and 11C-dihydrotetrabenazine ([11C]DTBZ), a radioligand that binds to the presynaptic vesicular monoamine transporter 2.16 One patient showed the typical pattern of severely reduced striatal [11C]DTBZ binding.16 The patient with the next lowest striatal binding levels among the patients with 22q11.2DS studied, in the lower range of that for the healthy control group, was a 55-year-old man with parkinsonism.6,16–18 He subsequently had further decline in motor and cognitive functioning, and at age 57 years, demonstrated an unequivocal improvement in motor symptoms following levodopa treatment, and was deemed to meet criteria for PD.

### Discussion

This international collaborative study is the largest to date on 22q11.2DS-associated PD, providing new data on the clinical presentation, progression, and treatment response. The results (summarized in table 3) suggest that a male excess and the main clinical features of PD, including response to levodopa with development of dyskinesia in a high proportion of patients, would be indistinguishable from idiopathic PD.8,19 The majority of the cases met EOPD criteria. We note however that given a median age at death in 22q11.2DS in the mid-40s,20 many patients may not live long enough to develop PD. Congenital or other later onset features could prompt clinicians to consider genetic testing for the 22q11.2 deletion, especially in individuals with early-onset PD, early dystonia, a history of seizures, and neurodevelopmental disorders such as schizophrenia or intellectual disability.

Patients exposed to antipsychotic treatment were diagnosed with PD later than antipsychotic-naïve patients, despite the fact that few had symmetric parkinsonism.21 Some have proposed that nonmotor features including fatigue and hyposmia could help distinguish between medication-induced parkinsonism and PD.22 However, we did not assess these features in this study and believe them unlikely to be helpful as they are common manifestations of 22q11.2DS itself.16,23,24

The DAT imaging findings suggest that dopaminergic imaging, where available, may be helpful in the differentiation of PD from nondegenerative 22q11.2DS-related parkinsonism.25 This is particularly important when one considers that ~25% of 22q11.2DS patients will need antipsychotic treatment.26 Potentially complicating the interpretation of imaging results for individuals with 22q11.2DS, however, are observations of paradoxical elevated striatal [11C]DTBZ and [18F]-F-PRO4.MZ (a DAT ligand) binding levels in some adults.16 This emphasizes the need for longitudinal imaging studies.

### Table 1 Motor symptom features and progression of Parkinson disease (PD) in 36 patients with 22q11.2 deletion syndrome

| Symptom Description                                                                 | Initial Presentation | Last Assessment | p Value |
|------------------------------------------------------------------------------------|----------------------|----------------|---------|
| **Symptoms used for diagnosis of PD**                                              |                      |                |         |
| Bradykinesia*                                                                       | 24 (66.7%)           | 35 (97.2%)     | 0.002   |
| Muscle stiffness/rigidity/reduced arm swing                                        | 25 (63.9%)           | 36 (100.0%)    | 0.001   |
| Tremor b                                                                           | 29 (80.6%)           | 35 (97.2%)     | 0.03    |
| **Other typical features of PD**                                                   |                      |                |         |
| Dyskinesia c                                                                        | 1 (2.8%)             | 16 (44.4%)     | <0.0001 |
| Falls or assistance needed with ambulation                                         | 1 (2.8%)             | 17 (47.2%)     | <0.0001 |
| Postural instability                                                                | 4 (11.1%)            | 19 (52.8%)     | <0.0001 |
| Gait changes                                                                       | 11 (30.6%)           | 24 (66.7%)     | <0.001  |
| Swallowing disturbances worsened from baseline                                      | 3 (8.3%)             | 13 (36.1%)     | 0.002   |
| Change in writing/loss of dexterity                                                | 15 (41.7%)           | 19 (52.8%)     | 0.06    |
| **Other motor symptoms**                                                           |                      |                |         |
| Dystonia d                                                                         | 7 (19.4%)            | 15 (41.7%)     | 0.008   |

Data on motor symptoms (in year of initial presentation and with progression in PD) and on follow-up time was available for 36 cases (26 male, 72.2%).

* Bradykinesia could not be established formally in one patient (with tremor and rigidity) due to cognitive impairment.

b Rest tremor was reported in 28 of 36 (77.8%) cases at last assessment. In 4 cases (11.1%), the tremor type was not specified.

c Dyskinesia was associated with antiparkinsonian medication in the vast majority of cases; see table 2 for correlation with levodopa use.

d Five of the 7 cases with dystonia in the year of initial PD presentation were antipsychotic-naïve.
Neuropsychiatric disorders are common features in 22q11.2DS. Nevertheless, a significant proportion of the patients in this study demonstrated emergence of psychotic symptoms with progression of PD. It remains unclear to what extent symptoms such as cognitive decline, psychosis, anxiety, and depression are due to PD, and/or effects of antiparkinsonian medications. Given the complex neuropsychiatric expression, including intellectual disability, other movement disorders, and the multisystem nature of 22q11.2DS, optimal management of 22q11.2DS-associated PD would involve collaboration between a movement disorders neurologist and specialist in 22q11.2DS.

If a 22q11.2 deletion is suspected, standard clinical microarrays will detect this structural change. It is important to realize that currently available PD genetic diagnostic panels do not include the 22q11.2 deletion. However, as for other PD-related mutations, much remains to be known about interacting factors that may contribute to the risk for PD imparted by a 22q11.2 deletion. Absence of an affected relative would not affect decision-making for genetic testing; the 22q11.2 deletion occurs as a spontaneous (de novo) mutation in most individuals.

The strengths of the study include the collaborative nature of the work and the large number of patients, given that both EOPD and 22q11.2DS are relatively uncommon conditions. There were, however, several limitations. First, we acknowledge the lack of a typical PD comparison group. Second, publication bias has to be considered. For example, it is conceivable that patients with less typical PD or uncertain PD diagnosis, yet with true PD, are underrepresented. Third, it cannot be ruled out that handling of conflicting, ambiguous, missing, or unknown data may have influenced the study results. Fourth, survey responders may have interpreted definitions of variables differently. Fifth, there was a wide range of follow-up time from 0 to 21 years. Sixth, physicians did not systematically obtain clinical information on non-neurologic comorbidities; therefore we opted not to report on other 22q11.2DS-associated comorbidities (table e-2, links.lww.com/WNL/AS13) in this study.

Further prospective clinical, neuropathologic, molecular, and animal studies promise to help clarify the pathogenesis of this molecular subtype of PD and indicate how well 22q11.2DS-PD could act as a genetic model for other forms of PD.

**Author contributions**

Erik Boot: study concept and design, designing checklists for collection of relevant clinical data, literature search, screening of locally available 22q11.2 deletion syndrome cohort for Parkinson disease diagnoses, data acquisition, analysis and interpretation of data, preparation and revision of manuscript. Nancy J. Butcher: study concept and design, designing checklists for collection of relevant clinical data, data acquisition, critical revision of manuscript. Sean Udow: data acquisition, critical revision of manuscript. Connie Marras: critical revision of checklists for collection of relevant clinical data, critical revision of manuscript. Kin Y. Mok: data acquisition, critical revision of manuscript. Satoshi Kaneko: data acquisition, critical revision of manuscript. Matthew J. Barrett: data acquisition, critical revision of manuscript. Paolo Prontera: data acquisition, critical revision of manuscript. Brian D. Berman: data acquisition, critical revision of manuscript. Boris Dufoournet: data acquisition, critical revision of manuscript. Karine Nguyen: data acquisition, critical revision of manuscript. Perrine Charles: data acquisition, critical revision of manuscript. Eugénie Mutez: data acquisition, critical revision of manuscript. Teodor Danaila: data acquisition, critical revision of manuscript. Aurélia Jacquette: data acquisition, critical revision of manuscript. Olivier Colin: data acquisition, critical revision of manuscript. Sophie Drapier: data acquisition, critical revision of manuscript. Michel Borg: data acquisition, critical revision of manuscript. Ania M. Fiksinski: data acquisition, critical revision of manuscript. Elfi Vergaelen: data acquisition, critical revision of manuscript. Ann Swillen: data acquisition, critical revision of manuscript. Annick Vogels: data acquisition, critical revision of manuscript. Annika Plate: data acquisition, critical revision of manuscript. Claudia Perandones: data acquisition, critical revision of manuscript. Thomas Gasser: data acquisition, critical revision of manuscript. Kristien Clerinx: data acquisition, critical revision of manuscript. Frédéric Bourdain: data acquisition, critical revision of manuscript. Kelly Mills: data acquisition,
Table 3  Comparison of idiopathic and 22q11.2 deletion syndrome–associated Parkinson disease

| Similarities                                           | Idiopathic PD<sup>a</sup> | 22q11.2DS-associated PD |
|--------------------------------------------------------|---------------------------|-------------------------|
| Male to female ratio – 2:1                             | Yes<sup>b</sup>           | Yes (2.5:1)             |
| Cardinal motor symptoms                                |                           |                         |
| Bradykinesia, rigidity, and tremors in early-stage PD  | Yes                       | Yes                     |
| Asymmetric motor symptoms at onset                     | Yes                       | Yes: ~90% with or without antipsychotic medication use |
| Progression of motor symptoms over time                | Yes                       | Yes                     |
| Neuropathologic features<sup>a</sup>                   |                           |                         |
| Loss of dopaminergic neurons                           | Yes                       | Yes                     |
| Lewy pathology                                         | Yes<sup>c</sup>           | 2 of 3 reported patients<sup>d</sup> |
| Dopaminergic imaging                                   |                           |                         |
| Reduced striatal DAT/VMAT-2 binding                     | Yes<sup>e</sup>           | Yes<sup>b</sup>         |
| Good response to levodopa                              | Yes: 70%-100%<sup>f</sup> | Yes: 93.3%              |
| With development of dyskinesia                         | Yes                       | Yes                     |
| New-onset neuropsychiatric symptoms in the course of PD and its treatment | Yes<sup>g</sup> | Yes (but see below, Differences) |
| Differences (potential clinical clues)                  |                           |                         |
| Mean age at onset of motor symptoms, y                 | 60.3 ± 12.8<sup>h</sup>   | 39.2 ± 8.6              |
| Low proportion with EOPD (<45 y)                       | Yes: 5%<sup>i</sup>       | No: 71.4%               |
| Often with first-degree relative affected by PD         | Yes: 10%-20%<sup>j</sup>  | Maybe less common: 8.9% |
| Early dystonia                                         | No<sup>k</sup>            | Yes: 19.4% in the year of initial presentation of motor symptoms |
| Development of dyskinesia more common in women         | Yes                       | No: OR = 0.10           |
| Preexisting neuropsychiatric complexity<sup>l</sup>    | No                        | Yes: often              |
| Intellectual disability                                | No (population rate ~2.5%) | Yes: ~33% (usually mild)<sup>m</sup> |
| IQ distribution shifted downward                       | No                        | Yes: ~30 IQ points<sup>n</sup> |
| Schizophrenia and other psychotic illnesses            | No (population rate ~3%)  | Yes: ~25%<sup,o,p</sup> |
| Preexisting antipsychotic medication use               | No                        | Yes: ~25%               |
| Anxiety, depression                                    | Yes (population rate ~10%) | Yes: ~20%<sup,q</sup>   |
| Epilepsy, seizures                                     | No (population rate ~1, 2%-5%) | Yes: 4%, 16%<sup>r</sup> |
| Preexisting motor symptoms of PD                       | No                        | Yes, often (but not always), e.g.: |
|                                                        |                           | Dysphagia                |
|                                                        |                           | Dysphonia                |
|                                                        |                           | Postural instability     |
|                                                        |                           | Impaired manual dexterity |
| Other preexisting nonmotor symptoms of PD              | No                        | Yes, often (but not always), e.g.: |
|                                                        |                           | Hyposmia<sup>s</sup>     |
|                                                        |                           | Fatigue (~80%)<sup>t</sup>|
|                                                        |                           | Constipation<sup>u</sup> |

Continued
Table 3 Comparison of idiopathic and 22q11.2 deletion syndrome–associated Parkinson disease (continued)

| Preexisting conditions from childhood<sup>a</sup> | Idiopathic PD<sup>b</sup> | 22q11.2DS-associated PD |
|-----------------------------------------------|-------------------------|-------------------------|
| No                                            | Yes, often (but not always), e.g.: |
|                                               | Hypernasal speech/velopharyngeal insufficiency |
|                                               | Congenital heart defect (~40%)<sup>c</sup> |
| Other preexisting conditions                  | No                      | Hypocalcemia (~80%, often undetected)<sup>d</sup> |
|                                               | Hypothyroidism (~20%)<sup>d</sup> |
|                                               | Hearing loss (6%–60%, often undetected)<sup>d</sup> |
|                                               | Cholelithiasis (~20%)<sup>d</sup> |

Overall considerations

- Neurologic assessment may be hindered by the complex neuropsychiatric expression of 22q11.2DS, including intellectual disability.
- Although young patients with antipsychotic medication and parkinsonism have a low risk of PD in general, in 22q11.2DS the risk is relatively high.
- Consider presynaptic dopaminergic imaging for patients with 22q11.2DS with parkinsonism on antipsychotic medication to reduce time to diagnosis, potentially.
- Consider consulting a clinician with expertise in 22q11.2DS<sup>e</sup>.

Abbreviations: COMT = catechol-O-methyl transferase; DAT = dopamine transporter; EOPD = early-onset Parkinson disease; MAO = monoamine oxidase; OR = odds ratio; VMAT-2 = vesicular monoamine transporter 2; 22q11.2DS = 22q11.2 deletion syndrome; PD = Parkinson disease.

<sup>a</sup> Not investigated in this study.
<sup>b</sup> Baseline ligand uptake uncertain.<sup>f</sup>
<sup>c</sup> Estimated lifetime prevalence of features in 22q11.2DS will vary from patient to patient, depending on age and how cases are ascertained.

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Erik Boot, Nancy J. Butcher, Sean Udow, et al.

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