Novel *DYT11* gene mutation in patients without dopaminergic deficit (SWEDD) screened for dystonia

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ABSTRACT

Objective: To test the hypothesis that adult-onset primary dystonia may be the underlying etiology of tremulous patients with clinical diagnosis of Parkinson disease (PD) but without evidence of dopaminergic deficit at nigrostriatal SPECT imaging.

Methods: We retrospectively reviewed clinical and imaging data of patients with clinical diagnosis of PD assessed at our tertiary movement disorder clinic, who underwent dopamine transporter SPECT imaging consecutively between 2002 and 2011. Molecular screening for *DYT1*, *DYT5*, *DYT6*, *DYT11*, and *DYT16* dystonia genes was performed in all cases who met the following criteria at the time of SPECT scan: (1) clinical diagnosis of PD; (2) normal dopamine transporter SPECT; (3) asymmetric rest tremor, with or without postural/kinetic component; (4) ≥12-month follow-up; and (5) normal brain MRI. We excluded subjects with (6) overt dystonic features, and (7) head or voice tremor.

Results: Twenty-three subjects were eligible for molecular analysis. Positive family history for tremor or PD was present in 45% of probands. We found one patient with a novel heterozygous frameshift mutation in the *DYT11* gene (c.1058-1062 delCACCA/p.Gln352fsX376). Electrophysiologic study of tremor revealed that the main contributor was 5- to 6-Hz pseudo-rhythmic myoclonus, primarily involving extensor muscles. In 2 brothers, we found a missense variant in the *DYT5* gene (c.334A>G; p.Thr112Ala) of uncertain pathogenicity in humans.

Conclusion: Our findings provide further support to the hypothesis that adult-onset monogenic dystonia may underlie a "PD look-alike" clinical phenotype. In addition to dystonic tremor, pseudo-rhythmic myoclonus may be mischaracterized as "rest tremor." **Neurology® 2014;83:1155–1162**

GLOSSARY

DAT = dopamine transporter; ***DSM-IV-TR*** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision*; **FP-CIT** = [^{123}I]-2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)-nortropane; **M-D** = myoclonus-dystonia; **PD** = Parkinson disease; **SWEDD** = scans without evidence of dopaminergic deficit; **UPDRS-III** = Unified Parkinson's Disease Rating Scale, Part III.

Clinicopathologic studies in patients with a clinical diagnosis of idiopathic Parkinson disease (PD) suggest a diagnostic error rate reaching 50% in community settings.[1–3] In vivo imaging techniques investigating presynaptic nigrostriatal function using dopamine transporter (DAT) SPECT are currently used to improve diagnostic accuracy of PD in challenging cases.[4,5] However, 11% to 15% of patients with a clinical diagnosis of PD recruited in large drug trials unexpectedly revealed normal DAT imaging.[6–8] These cases have been defined as SWEDD (acronym for "scans without evidence of dopaminergic deficit")[4,9] and it has been suggested that these patients may have primary dystonia.[10,11] To date, the majority of SWEDD patients investigated presented with overt clinical signs of dystonia.[10–12] Dystonic movements may be tremulous[13] and patients with monogenic dystonia may present with rest tremor or parkinsonism, even before the appearance of dystonic features.[14–17] Here, we tested the hypothesis that tremulous patients with SWEDD may have monogenic dystonia.

Supplemental data at Neurology.org

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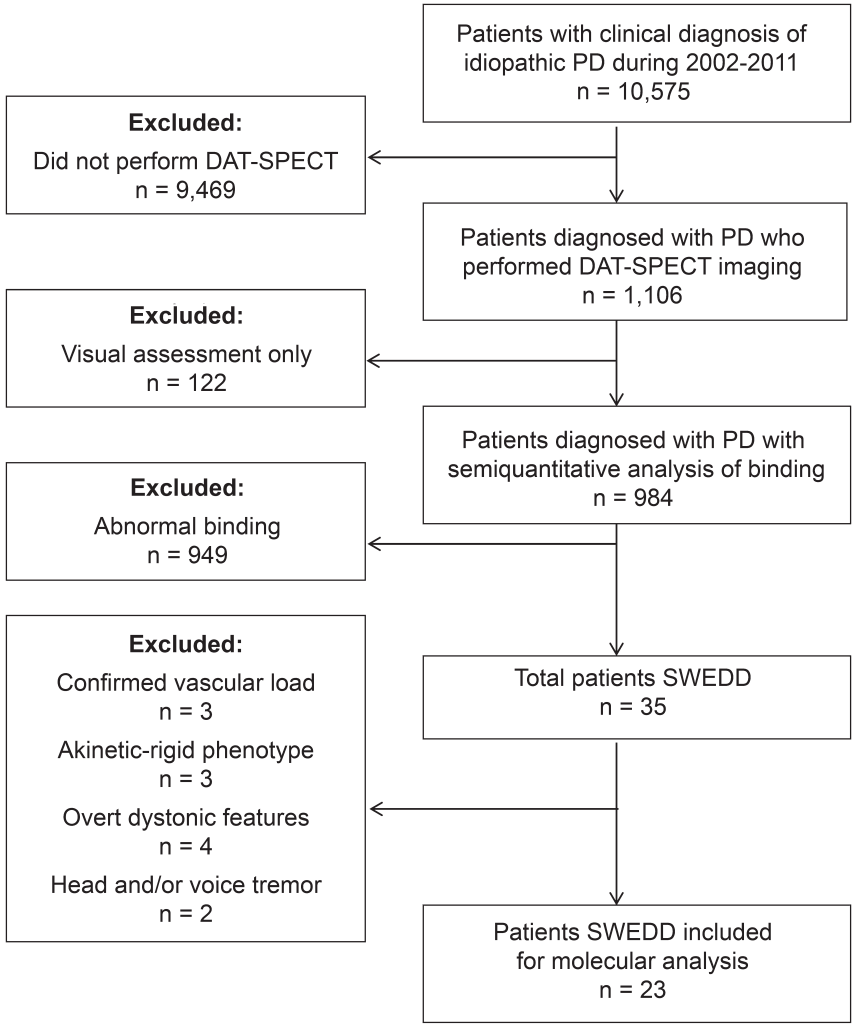
Figure 1 Flowchart of the study



DAT = dopamine transporter; PD = Parkinson disease; SWEDD = scans without evidence of dopaminergic deficit.

METHODS **Standard protocol approvals, registrations, and patient consents.** The local ethical committee approved the study and written informed consent was obtained from all patients who participated in the Parkinson Institute Biobank. An additional consent form was requested for videotaping.

Participants. We retrospectively collected data related to consecutive outpatients attending the Parkinson Institute (Milan) from April 2002 to April 2011, as part of their routine clinical care. Patients had to fulfill the following criteria at the time of SPECT: (1) clinical diagnosis of possible or probable idiopathic PD according to the UK Brain Bank criteria[1]; (2) asymmetric symptoms; (3) dominant rest tremor, with or without a postural and/or action component; (4) normal DAT SPECT imaging according to a standardized semiquantitative analysis of binding values[18] (details available in supplemental data on the *Neurology*® Web site at Neurology.org); (5) ≥12-month follow-up; (6) absence of major vascular abnormalities at brain MRI. We excluded patients who presented with overt dystonic signs (including dystonic postures and task-specific dystonia)[13] and head or voice tremor. The following data were collected at the time of SPECT: (1) family history of tremor or PD in first-degree relatives and confirmed by clinical assessment (relatives not available for neurologic examination were assumed to be affected on the basis of previous diagnosis); (2) Unified PD Rating Scale, Part III (UPDRS-III) motor score; (3) response to levodopa (defined as UPDRS-III score improvement >25% from the baseline visit); (4) history of sleep disturbances and hyposmia; and (5) dementia according to *DSM-IV-TR* criteria.

Molecular analysis. Patients were screened for mutations in the *DYT1*, *DYT5*, *DYT6*, *DYT11*, and *DYT16* genes. We selected these genes because their mutation rate in the Italian population is relatively high and/or they have proven to be associated with clinical parkinsonism.[17] In addition, we performed gene dosage analysis for those genes in which whole-exon deletions (such as *DYT5* and *DYT11*) are relatively common. Details are available online.

Movement analysis. An optoelectronic motion capture system (BTS, Milano, Italy) of the 3-dimensional trajectories of the tip of the second finger was used. Reflector markers were positioned on anatomical landmarks on the head, cervical spine, and upper limbs. Free-EMG surface was used to record couples of antagonist muscles in the upper and lower limbs. Analysis was performed 7 days after medication washout. Details are available online.

RESULTS We found a normal [^{123}I]-2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)-nortropane (FP-CIT) SPECT in 35 patients of a total of N = 1,106

Table 1 Demographic data and general clinical features of the 23 patients with SWEDD

Features	
Male/female	9/14
Age at onset, mean (SD) [range], y	56.8 (13.2) [30–70]
No. (%) with positive family history[a,b]	10 (45.4)
For PD	6 (27.3)
For tremor	4 (18.2)
Disease duration at SPECT imaging, mean (SD) [range], y	5 (2.1) [3–7]
UPDRS-III, mean (SD) [range]	16.7 (8.9) [6–37]
No. (%) with clinical progression of symptoms	6 (25.8)
Nonmotor symptoms, n (%)	
Premotor depression	3 (12.9)
Sleep disturbance	4 (17.4)
Smell reduction	2 (8.6)
Cognitive impairment	1 (4.3)
Therapy,[c] n (%)	
Levodopa therapy	19 (82.6)
Positive response[d]	8 (42)
Dopamine agonist therapy	14 (60.8)
Anticholinergics	5 (21.7)
Benzodiazepines	8 (34.8)

Abbreviations: PD = Parkinson disease; SWEDD = scans without evidence of dopaminergic deficit; UPDRS-III = Unified Parkinson's Disease Rating Scale, Part III.
[a] Family history was considered positive only when confirmed by clinical examination of one or more first-degree relatives.
[b] Frequency calculated out of the number of unrelated probands (n = 22), as the 2 brothers counted as one proband.
[c] Positive response to levodopa was defined as reduction in UPDRS-III score >25% from baseline; clinical response to other drugs is based on what was reported by the neurologist in medical charts.
[d] Frequency calculated taking into consideration the patients who were taking levodopa (n = 19). In 6 of these 8 cases (75%), tremor itself was responsive to levodopa.

who had a diagnosis of possible or probable idiopathic PD and underwent FP-CIT SPECT imaging. According to our a priori criteria, 23 subjects (21 unrelated probands and 2 sibling pairs) were eligible for subsequent molecular analysis (figure 1).

Demographic and clinical details of these cases are summarized in table 1. Of note, positive family history for tremor or PD was recorded in 45% of cases and positive response to levodopa in 42%. The majority of SPECT scans (n = 18/23, 78%) were performed in a single center (Nuclear Medicine Department of the IRCCS-Ospedale Maggiore, Milan).

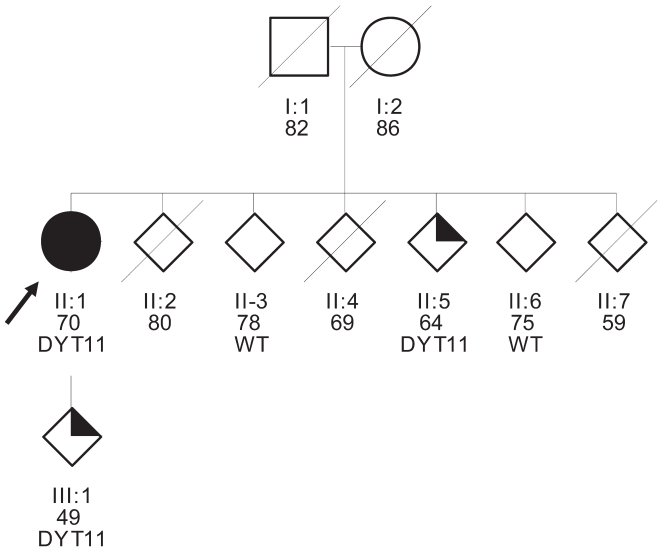
Seven patients (30.4%) were either dead (n = 2) or lost to follow-up (n = 5) when the molecular analysis was performed. Molecular screening showed 3 positive patients (including 2 siblings) for dystonia genes, as described below.

Mutation in the *DYT11* gene. A novel heterozygous frameshift mutation in the *DYT11* gene that led to a premature stop codon (c.1058-1062 delCACCA/p.Gln352fsX376) was identified in a 74-year-old woman (figure e-1). The same mutation was also found in a 64-year-old sibling and the 50-year-old patient's offspring (whose history and neurologic examination were unremarkable), confirming the reduced penetrance of the mutation (figure 2).

This woman presented at our clinic in 2009, at the age of 70 years, complaining of the recent onset of "tremor" of her right hand. She had a 4-year history of migraine and depression. Family history was unremarkable. Neurologic examination revealed rest and postural "tremor-like" movements of the right hand, with mild reduction in finger movement amplitude and reduced right arm swings. Levodopa therapy was started at 300 mg daily with good response (her UPDRS-III scores improved by 38%, diminishing from 37 to 23/108). After 2 months, she was admitted for a full workup including clinical examination, neuropsychological tests, and imaging investigations. Global cognitive functions were normal (Mini-Mental State Examination score 25.05/30; Clock Drawing Test 7/10), with mild executive dysfunction (Frontal Assessment Battery 14/18; phonologic and semantic verbal fluencies 10 and 19, respectively) and marked depression (Beck Depression Inventory 22/63, 99th percentile). Brain MRI and fluorodeoxyglucose PET were normal. Because the potential past use of antidopaminergic medications to treat depression could not be ruled out at the first visit, FP-CIT SPECT was requested and was normal (thorough investigation of medical charts confirmed she was never exposed to any dopamine blocking agent). Subsequent withdrawal of levodopa therapy was not tolerated and it was restored. At that time, she did not present any sign of myoclonus or dystonia. In 2012, she complained about gait impairment due to a "pulling sensation" affecting her right leg. At neurologic examination, she had tremor-like movements of her upper limbs (R > L), which were prominent at rest and less evident upon posture, and reemergent after a few seconds; inconstant chin movements; and mildly reduced finger movement amplitude of the right hand and lower limbs. She had a dystonic posture with dorsal extension of the fingers of the left hand and the right toe, leading to difficulty in rising from a chair and impairment of gait and balance (video segment A). A second attempt to reduce daily levodopa dosage resulted in clinical worsening. Limb dystonia and gait partially improved on anticholinergics (biperiden, 4 mg/d). Benzodiazepines caused sedation. A second FP-CIT SPECT in 2012 confirmed normal binding (figure 3).

The electrophysiologic study of the patient with *DYT11* mutation revealed pseudo-rhythmic jerks with mean frequency of 5 to 6 Hz present at rest, with arms outstretched and maintaining the finger-to-finger

Figure 2 **Pedigree of *DYT11* family**



Individual II:1 is the proband (arrow). Individuals II:5 and III:1 are asymptomatic carriers of the *DYT11* mutation. Age at last examination/death or age at onset (proband) is reported. WT = wild type.

position, but not during the finger-to-nose maneuver (figure 4, video segment B). This activity consisted of bursts of 100 milliseconds recorded mainly in the wrist and finger extensor muscles, with asynchronous reduced activity in wrist and finger flexor muscles. No motor overflow in proximal muscles in the ipsilateral upper limb was observed. In the right lower limb, we recorded longer bouffées of dystonic activity (200–300 milliseconds) in the extensor digitorum longus during rest and walking. The cocontraction index was very low in all tasks recorded in all the couples of antagonist muscles in the right forearm and lower limb (all <2.5%, data not shown). Electrophysiologic assessment of asymptomatic *DYT11* mutation carriers was normal.

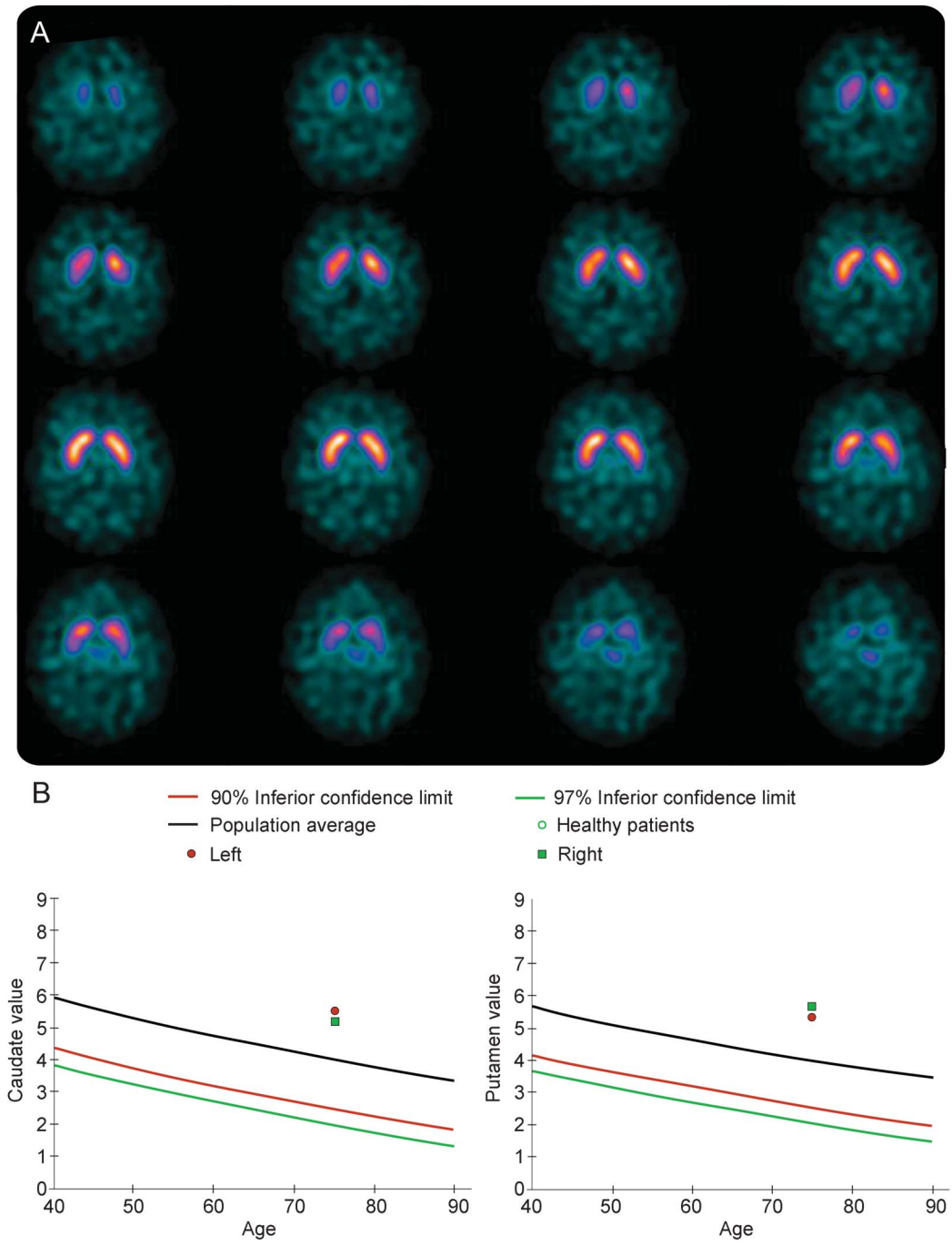
Mutation in the *DYT5* gene. In 2 brothers, we found a missense variant in the *DYT5* gene (c.334A>G; p.Thr112Ala) (figure e-2). This variant was never found in 570 alleles of dystonic patients screened for *DYT5* in the Neurogenetics Unit of the Besta Institute and in 360 alleles of normal control subjects (data not shown) and is present in the most common genetic single nucleotide polymorphism databases (http://www.1000genomes.org) with a score of 0.001. Because the analyses in silico for the prediction of the pathogenesis of the Thr112Ala mutation were controversial (details about in silico prediction are available online), we performed functional studies on *Saccharomyces cerevisiae*. Indeed, budding yeast is a valid model to test the physiologic effects of *DYT5* loss of function mutations.[19] Our findings in this experimental model did not support a clear pathogenic role of this variant (supplementary material, figure e-3). Taken as a whole, data obtained from screening patients with dystonia, prediction programs, and in vivo functional assays suggested that the Thr112Ala is a rare nonpathogenic variant.

DISCUSSION We performed molecular screening for a large set of dystonia genes in a relatively large and well-characterized cohort of subjects with SWEDD and found a heterozygous frameshift mutation in the *DYT11* gene that has never been described before. This finding supports the hypothesis that adult-onset monogenic dystonia may underlie a "PD look-alike" clinical phenotype even when there are no obvious signs of clinical dystonia. Our data confirm that clinical distinction between PD and SWEDDs may be challenging even at specialized movement disorders centers.[4,16] Although rest tremor that does not reemerge upon posture and the lack of decremental bradykinesia suggest dystonia rather than PD,[10,11] this distinction may be very difficult to make even by movement disorders specialists.[4,10,12,20,21] However, asymmetry of symptoms, hypomimia, reduced arm swing, and reemergent tremor have also been reported in patients with dystonia.[10,20,21] In our cohort, the chances of misdiagnosis were increased by a number of confounders, including not only reduced arm swings and reemergent tremor, but also nonmotor symptoms, progressive clinical course, and even positive family history for PD and response to levodopa.

We describe a patient with a novel mutation in the epsilon-sarcoglycan gene who was clinically misdiagnosed with PD that expands the clinical phenotype of *DYT11* myoclonus-dystonia (M-D) syndrome.[22] Here, the onset of motor symptoms was characterized by myoclonic jerks selectively involving the right upper limb, while clinical signs of overt dystonia appeared later during the course of disease, when she developed abnormal posture of the right lower limb and the left hand. This is in line with previous observations that adult-onset dystonia may be misdiagnosed as tremulous PD because of delayed appearance of dystonic features.[14,16] *DYT11* is inherited as an autosomal dominant trait with incomplete penetrance. This is consistent with the lack of clinical features in the patient's 64-year-old sibling and 50-year-old offspring, the latter finding being consistent also with the suggested maternal imprinting in its transmission.[23]

According to our a priori hypothesis, we expected that a patient with SWEDD who screened positive for a monogenic dystonia would have dystonic tremor. However, clinical and electrophysiologic characteristics were suggestive of subcortical myoclonus[24,25] rather than "jerky" dystonic movements.[13,24] From a clinical standpoint, this patient presented with unilateral rest tremor with a frequency comparable to typical PD rest

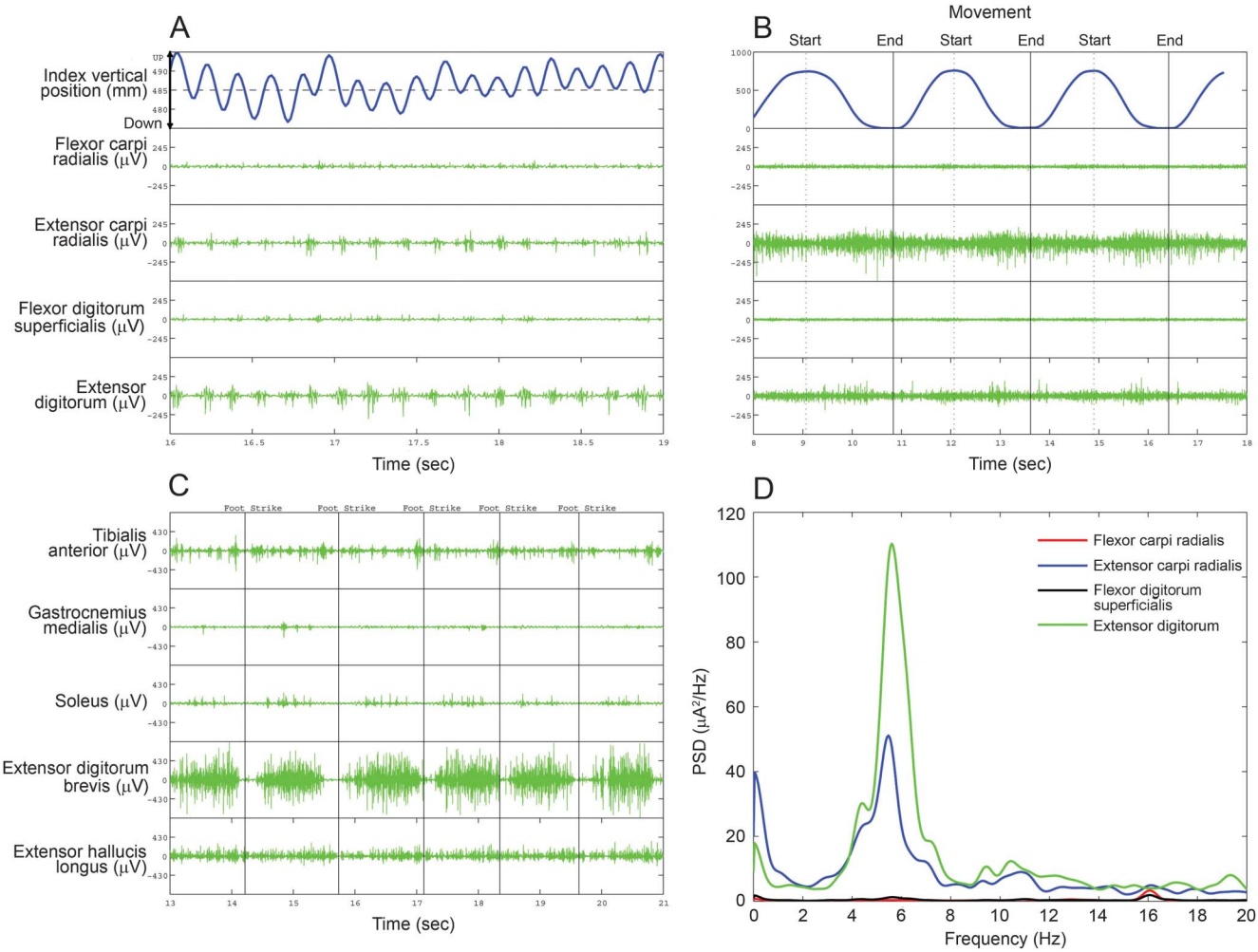
Figure 3 FP-CIT SPECT scans of the patient with mutation in the *DYT11* gene



(A) FP-CIT SPECT scans of the patient with mutation in the *DYT11* gene. (B) Binding values as calculated using the Basal Ganglia Matching Tool; caudate nucleus binding values are displayed on the left, putamen values on the right. The black line represents the population average values adjusted for age; the red line and the green line represent the 90% and the 97% lower confidence limit, respectively. FP-CIT = [^{123}I]-2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)-nortropane.

tremor[11,16,26] and, remarkably, it was more evident at rest than during target-directed movements, in contrast to typical presentation of dystonic tremor[10,11,26] and rhythmic myoclonus.[26] Depressive symptoms before the onset of motor symptoms and subtle executive dysfunction were additional confounders, because they overlap between PD and *DYT11* M-D.[27,28] Patients with SWEDD usually do not benefit from anti-PD medications,[10,11] but sustained response to dopaminergic medications may occur.[29,30] In the present cohort, we found a surprisingly high response rate to levodopa therapy among PD look-alikes, including rest tremor itself. Response to levodopa in patients with M-D phenotype has been reported in association with genes that are involved in the dopaminergic pathway.[31,32] In particular, a marked improvement in myoclonus at

Figure 4 **Electrophysiologic study of the patient with the *DYT11* mutation**



(A) EMG recordings in right upper limb with patient at rest: pseudo-rhythmic bursts of 100 milliseconds in extensor muscles of wrist and fingers at frequency of 5 to 6 Hz. Irregular movement of the marker on the vertical plane. (B) EMG recordings in right upper limb during finger-to-nose movements: tonic activity of extensor muscles of wrist and fingers, without any irregular burst. Regular repetitive movement of the marker on the vertical plane. (C) EMG recordings in right lower limb during gait: dystonic activity of extensor digitorum brevis muscle in stance phase of gait and tonic activity of extensor hallucis longus during all gait cycles, along with hypoactivation of plantar flexor muscles. (D) Spectrum of EMG activity of the right forearm muscles at rest (linear scale on vertical axis): peak of frequency at 5 to 6 Hz of extensor muscles. PSD = power spectral density.

300 mg/d levodopa has been described in patients with epsilon-sarcoglycan deletions.[33] Taken as a whole, these findings challenge the importance of robust and sustained response to levodopa as a reliable feature of PD (and dopa-responsive dystonia). Although we cannot fully explain the underlying mechanisms, we could argue that the levodopa response might involve postsynaptic dopaminergic transmission,[15] as described in experimental models of *DYT11* M-D.[34]

While the frameshift mutation in the *DYT11* gene was definitely pathogenic, the mutation found in the *DYT5* gene in 2 brothers is likely to be a rare nonpathogenic variant. Indeed, this mutation is present as a very rare variant (0.001) in the most common genetic single nucleotide polymorphism databases and it was not found in any of the 570 patients' alleles and in the 360 alleles of normal controls screened for the *DYT5* gene in our laboratory. Because data from in silico models and databases currently available online were controversial, we tested its possible pathogenic effects in a yeast experimental model, which yielded negative results. Nevertheless, we cannot definitively exclude a possible pathogenic role in humans, and further studies are needed to elucidate the role of this *DYT5* variant in SWEDDs.

Although the retrospective nature of the study design enabled the collection of a relatively large and homogeneous sample of patients with SWEDD, there are some limitations to acknowledge. First, tremor was not specifically assessed for the presence of clinical "red flags" suggesting an etiology other than PD (e.g., jerkiness, thumb hyperextension, reemergent tremor[10,11,16]), and the clinical diagnosis could not be confirmed by a blinded assessment by a second movement disorder

specialist, including video analysis. However, clinical diagnosis was performed by experienced neurologists at a highly specialized tertiary movement disorder clinic, and blinded video rating has been shown not to help even in specialized settings.[4] Second, we could not perform electrophysiologic studies in all subjects with SWEDD, because approximately one-third were dead or lost to follow-up when the molecular analysis was performed. However, this was not the aim of the present study and differential electrophysiologic parameters between PD and SWEDD have been extensively investigated in previous studies.[10,11] Finally, the etiology remained unclear for most patients of our cohort. We did not screen all currently known dystonia genes[17]; therefore, monogenic dystonia cannot be definitively excluded. In addition, other nonmonogenic forms of adult-onset dystonia may occur. However, it is likely that alternative causes other than dystonia may explain a number of cases with SWEDD.[30]

This study has several strengths to highlight. First, to minimize possible confounders, we used strict a priori inclusion/exclusion criteria to investigate a homogeneous population, fulfilling the original definition of SWEDD.[6–9] Accordingly, we excluded all cases with major cerebrovascular abnormalities.[29,35] Second, we included only scans performed with high-quality standardized semiquantitative analysis to reduce potential false-negative findings.[36] In our experience, visual analysis of FP-CIT SPECT may consider very mild DAT binding reduction to be within the normal range and thus possibly lead clinicians to misdiagnose patients with benign tremulous parkinsonism as SWEDD. Finally, our study protocol included comprehensive functional studies of novel variants of uncertain pathogenicity[19] to disclose new mutations potentially associated with SWEDDs, such as the one we found in the *DYT5* gene.

Our findings provide further support to the hypothesis that "monogenic dystonia" may underlie a "PD look-alike" phenotype. In the near future, next-generation sequencing testing several genes for dystonia and other disorders[34] at relatively low cost might be included in the routine workup of all patients presenting with rest tremor and negative DAT imaging. Further studies are mandatory to broaden the spectrum of causes of SWEDDs and, critically, reliable clinical "red flags" that can help clinicians in the differential diagnosis of tremulous patients. This would minimize inappropriate FP-CIT SPECT scans.[37]

AUTHOR CONTRIBUTIONS

All of the authors have participated sufficiently in the work to fulfill the criteria for authorship. The contributions were as follows. Study concept and design: Cilia, Goldwurm, Garavaglia. Acquisition of data: Cilia, Reale, Castagna, Barzaghi, Marzegan, Marotta, Goldwurm, Sacilotto, Garavaglia. Analysis and interpretation of data: Cilia, Reale, Castagna, Nasca, Muzi-Falconi, Barzaghi, Marzegan, Granata, Marotta, Pezzoli, Goldwurm, Garavaglia. Drafting of the manuscript: Cilia. Critical revision of the manuscript for important intellectual content: Reale, Castagna, Muzi-Falconi, Marzegan, Marotta, Vallauri, Pezzoli, Goldwurm, Garavaglia. Statistical analysis: Cilia. Obtained funding: Pezzoli, Goldwurm, Garavaglia. Administrative, technical, or material support: Vallauri. Study supervision: Pezzoli, Goldwurm, Garavaglia. Study guarantor: Dr. Cilia had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. Neurology 1992;42:1142–1146.
2. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain 2002;125:861–870.
3. Meara J, Bhowmick BK, Hobson P. Accuracy of diagnosis in patients with presumed Parkinson's disease. Age Ageing 1999;28:99–102.
4. Bajaj NPS, Gontu V, Birchall J, Patterson J, Grosset DG, Lees AJ. Accuracy of clinical diagnosis in tremulous parkinsonian patients: a blinded video study. J Neurol Neurosurg Psychiatry 2010;81:1223–1228.
5. Kupsch AR, Bajaj N, Weiland F, et al. Impact of DaTscan SPECT imaging on clinical management, diagnosis, confidence of diagnosis, quality of life, health resource use and safety in patients with clinically uncertain parkinsonian syndromes: a prospective 1-year follow-up of an open-label

controlled study. J Neurol Neurosurg Psychiatry 2012;83:620–628.
6. Parkinson Study Group. Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. JAMA 2002;287:1653–1661.
7. Whone AL, Watts RL, Stoessl AJ, et al. Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL–PET study. Ann Neurol 2003;54:93–101.
8. Fahn S; Parkinson Study Group. Does levodopa slow or hasten the rate of progression of Parkinson's disease? J Neurol 2005;252(suppl 4):IV37–IV42.
9. Marek K, Jennings D, Seibyl J. Imaging the dopamine system to assess disease modifying drugs: studies comparing dopamine agonists and levodopa. Neurology 2003;61(6 suppl 3):S43–S48.
10. Schneider SA, Edwards MJ, Mir P, et al. Patients with adult-onset dystonic tremor resembling parkinsonian tremor have scans without evidence of dopaminergic deficit (SWEDDs). Mov Disord 2007;22:2210–2215.
11. Schwingenschuh P, Ruge D, Edwards MJ, et al. Distinguishing SWEDDs patients with asymmetric resting tremor from Parkinson's disease: a clinical and electrophysiological study. Mov Disord 2010;25:560–569.
12. Bain PG. Dystonic tremor presenting as parkinsonism: long-term follow-up of SWEDDs. Neurology 2009;72:1443–1445.
13. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013;28:863–873.
14. Quinn NP, Schneider SA, Schwingenschuh P, Bhatia KP. Tremor: some controversial aspects. Mov Disord 2011;26:18–23.
15. Morgante F, Klein C. Dystonia. Continuum 2013;19(5 movement disorders):1225–1241.
16. Erro R, Rubio-Agusti I, Saifee TA, et al. Rest and other types of tremor in adult-onset primary dystonia. J Neurol Neurosurg Psychiatry Epub 2013 Nov 18.
17. Klein C. Genetics in dystonia. Parkinsonism Relat Disord 2014;20(suppl 1):S137–S142.
18. Calvini P, Rodriguez G, Inguglia F, Mignone A, Guerra UP, Nobili F. The basal ganglia matching tools package for striatal uptake semi-quantification: description and validation. Eur J Nucl Med Mol Imaging 2007;34:1240–1253.
19. Garavaglia B, Invernizzi F, Carbone ML, et al. GTP-cyclohydrolase I gene mutations in patients with autosomal dominant and recessive GTP-CH1 deficiency: identification and functional characterization of four novel mutations. J Inherit Metab Dis 2004;27:455–463.
20. Kägi G, Schwingenschuh P, Bhatia KP. Arm swing is reduced in idiopathic cervical dystonia. Mov Disord 2008;23:1784–1787.
21. de Laat KF, van de Warrenburg BP. Re-emergent tremor in a dystonic SWEDD case. Mov Disord 2012;27:462–463.
22. Foncke EM, Gerrits MC, van Ruissen F, et al. Distal myoclonus and late onset in a large Dutch family with myoclonus-dystonia. Neurology 2006;67:1677–1680.
23. Zimprich A, Grabowski M, Asmus F, et al. Mutations in the gene encoding epsilon-sarcoglycan cause myoclonus dystonia syndrome. Nat Genet 2001;29:66–69.
24. Marelli C, Canafoglia L, Zibordi F, et al. A neurophysiological study of myoclonus in patients with DYT11 myoclonus-dystonia syndrome. Mov Disord 2008;23:2041–2048.
25. Roze E, Apartis E, Clot F, et al. Myoclonus-dystonia: clinical and electrophysiologic pattern related to SGCE mutations. Neurology 2008;70:1010–1016.
26. Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. Mov Disord 1998;13:2–23.
27. van Tricht MJ, Dreissen YE, Cath D, et al. Cognition and psychopathology in myoclonus-dystonia. J Neurol Neurosurg Psychiatry 2012;83:814–820.
28. Peall KJ, Waite AJ, Blake DJ, Owen MJ, Morris HR. Psychiatric disorders, myoclonus dystonia, and the epsilon-sarcoglycan gene: a systematic review. Mov Disord 2011;26:1939–1942.
29. Marshall VL, Patterson J, Hadley DM, Grosset KA, Grosset DG. Two-year follow-up in 150 consecutive cases with normal dopamine transporter imaging. Nucl Med Commun 2006;27:933–937.
30. Hall DA, Jennings D, Seibyl J, Tassone F, Marek K. FMR1 gene expansion and scans without evidence of dopaminergic deficits in parkinsonism patients. Parkinsonism Relat Disord 2010;16:608–611.
31. Leuzzi V, Carducci C, Cardona F, Artiola C, Antonozzi I. Autosomal dominant GTP-CH deficiency presenting as a dopa-responsive myoclonus-dystonia syndrome. Neurology 2002;59:1241–1243.
32. Stamelou M, Mencacci NE, Cordivari C, et al. Myoclonus-dystonia syndrome due to tyrosine hydroxylase deficiency. Neurology 2012;79:435–441.
33. Luciano MS, Ozelius L, Sims K, Raymond D, Liu L, Saunders-Pullman R. Responsiveness to levodopa in epsilon-sarcoglycan deletions. Mov Disord 2009;24:425–428.
34. Zhang L, Yokoi F, Parsons DS, Standaert DG, Li Y. Alteration of striatal dopaminergic neurotransmission in a mouse model of DYT11 myoclonus-dystonia. PLoS One 2012;7:e33669.
35. Antonini A, Vitale C, Barone P, et al. The relationship between cerebral vascular disease and parkinsonism: the VADO study. Parkinsonism Relat Disord 2012;18:775–780.
36. Tolosa E, Borght TV, Moreno E; DaTSCAN Clinically Uncertain Parkinsonian Syndromes Study Group. Accuracy of DaTSCAN (123I-Ioflupane) SPECT in diagnosis of patients with clinically uncertain parkinsonism: 2-year follow-up of an open-label study. Mov Disord 2007;22:2346–2351.
37. Perlmutter JS, Eidelberg D. To scan or not to scan: DaT is the question. Neurology 2012;78:88–89.