Original Investigation

DCTN1 Mutation Analysis in Families With Progressive Supranuclear Palsy–Like Phenotypes

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IMPORTANCE Progressive supranuclear palsy (PSP) is usually sporadic, but few pedigrees with familial clustering of PSP-like phenotypes have been described. Occasionally, *MAPT, C9ORF72*, and *TARDBP* mutations have been identified.

OBJECTIVE To analyze the *DCTN1* gene in 19 families with a clinical phenotype of PSP (PSP-like phenotype).

DESIGN, SETTING, AND PARTICIPANTS Sequencing of the *DCTN1* gene in familial forms of PSP at a referral center among 21 patients with familial PSP-like phenotypes. In addition, 8 patients and relatives from a family carrying a *DCTN1* mutation were evaluated.

MAIN OUTCOMES AND MEASURES Identification of the *DCTN1* mutation and clinical description of *DCTN1* mutation carriers.

RESULTS We identified a *DCTN1* mutation in a large family characterized by high intrafamilial clinical phenotype variability. Two patients had PSP-like phenotypes with dystonia, vertical gaze slowness, dysexecutive syndrome, predominant axial rigidity, and midbrain atrophy on brain magnetic resonance imaging. The other patients manifested Perry syndrome, isolated parkinsonism, or a predominant behavioral variant of frontotemporal dementia.

CONCLUSIONS AND RELEVANCE Mutations of the *DCTN1* gene have been previously associated with amyotrophic lateral sclerosis and with Perry syndrome, a rare autosomal dominant disorder characterized by weight loss, parkinsonism, central hypoventilation, and psychiatric disturbances. Our study demonstrates that *DCTN1* mutations should be searched for in patients with clinical PSP-like phenotypes and a behavioral variant of frontotemporal dementia, especially when a familial history of dementia, psychiatric disturbances, associated parkinsonism, or an autosomal dominant disorder is present.

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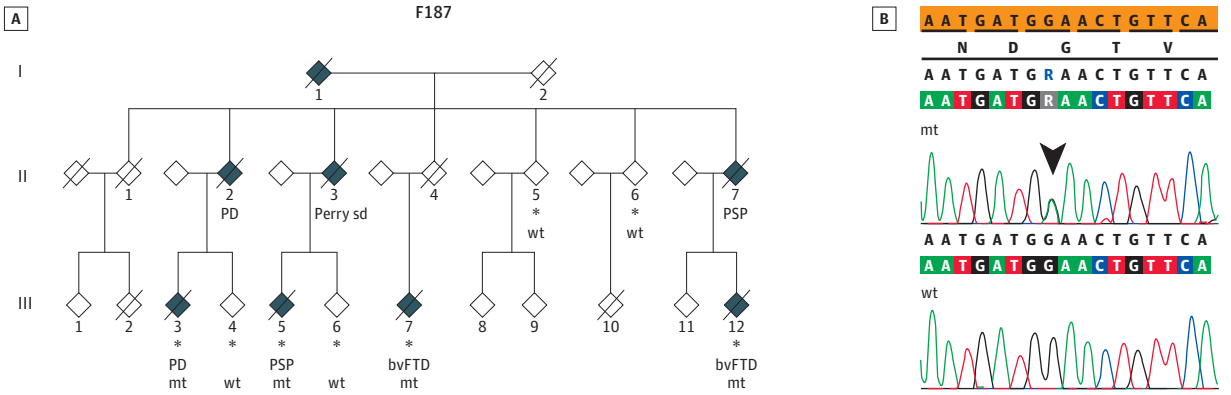
Progressive supranuclear palsy (PSP) is a neurodegenerative disorder clinically characterized by the presence of an akinetic-rigid parkinsonian syndrome associated with postural instability, frontal lobe dysfunction, and vertical supranuclear gaze palsy.[1] The National Institute of Neurological Disorders-Society for Progressive Supranuclear Palsy clinical diagnostic criteria rely on (1) age at onset older than 40 years and (2) the presence of a gradually progressive disorder, combined with (3) slow vertical saccades or supranuclear gaze palsy and (4) early postural instability and falls during the first year of the disease.[1] Modified clinical diagnostic criteria have been recently proposed (Neuroprotection and Natural History in Parkinson Plus Syndromes criteria) that allow an age at onset older than 30 years, postural instability or falls within 3 years from disease onset, and a disease duration ranging from 1 to 8 years.[2] Five distinct clinical phenotypes have been described according to the predominant symptoms.[3] Pathological diagnosis is based on the presence of neuropil threads, neurofibrillary tangles, and tau-positive astrocytes.[4] Progressive supranuclear palsy is usually sporadic; a familial aggregation of Parkinson disease and other neurodegenerative disorders, such as tremor, dementia, and parkinsonism remain controversial, having been observed in only one recent PSP case-control study.[5] Few pedigrees with familial clustering of PSP-like phenotypes have been described.[5-7] The genetic cause is unknown in most familial cases. Mutations in

Figure 1. Family Pedigree and *DCTN1* Mutation



A, Solid symbols indicate affected members; open symbols, unaffected individuals. Individuals are represented by diamonds for confidentiality. An asterisk indicates DNA availability; bvFTD, behavioral variant of frontotemporal dementia; mt, mutation; PD, Parkinson disease; Perry sd, Perry syndrome; PSP, progressive supranuclear palsy; slash, deceased; and wt, wild type. B, Chromatograms of coding exon 2 of the *DCTN1* gene. The c.212G>A (p.Gly71Glu) mutation is shown by the arrowhead, and the corresponding normal sequence is shown below.

the *MAPT* (Online Mendelian Inheritance in Man [OMIM] 157140)[5,8,9] gene have been identified in a few families, and *TARDBP* (OMIM 605078)[10] and *C9ORF72* (OMIM 614260)[11,12] mutations are extremely rare in patients with PSP. A locus has been mapped on chromosome 1, but the disease-causing gene has not been identified.[13] In this study, we analyzed the *DCTN1* (OMIM 601143) gene in 19 families with a clinical phenotype of PSP (PSP-like phenotype).

Methods

Patients and Families

This study was approved by the ethics committee of Assistance Publique-Hôpitaux de Paris, Paris, France. All participants signed an informed consent form for genetic studies. During the past several years, we evaluated 21 families with PSP-like phenotypes. A PSP phenotype was clinically diagnosed using National Institute of Neurological Disorders-Society for Progressive Supranuclear Palsy international diagnostic criteria.[1] The diagnosis of PSP was confirmed by pathological examination in 2 families. A positive family history was defined by at least 1 first- or second-degree relative manifesting a clinical phenotype of PSP. We recorded familial histories of related disorders, including Parkinson disease, frontotemporal dementia (FTD), and corticobasal degeneration syndrome, diagnosed according to international criteria. Clinical data and biological samples were collected for all the patients. The genealogy of the families was reconstructed, and clinical data and biological samples of relatives were collected whenever possible.

Molecular Analysis

Blood genomic DNA was extracted from peripheral white blood cells using standard methods. Point mutations, as well as gene deletions and duplications, were previously searched for in the main genes responsible for FTD (*C9ORF72*, *PGRN*, *MAPT*, *VCP*, and *TARDBP*) and for Parkinson disease (*SNCA*, *LRRK2*, *parkin*, *ATP13A2*, and *FBXO7*) by direct sequencing or repeat-primed polymerase chain reaction (for *C9ORF72*). *MAPT* and *C9ORF72* mutations were identified in one family each (7%, respectively).[8,11]

No mutations were found in the 19 remaining families. The 32 exons and exon-intron junctions of the *DCTN1* gene were then amplified by polymerase chain reaction, as previously described.[14] The purified amplified fragments were sequenced on an automated system with a cycle kit (ABI 3730, Big Dye 3.1; Applied Biosystems). The sequencing data were analyzed using available software (SeqScape 2.5; Applied Biosystems).

Results

We identified a point mutation in exon 2 of the *DCTN1* gene in a large French family. Our findings enlarge the genetic causes of familial PSP and the phenotypic spectrum associated with *DCTN1* mutations.

Molecular Analysis

In the patient (III-5) of one family (F187), we identified a heterozygous missense mutation, c.212G>A, p.Gly71Glu (NM_004082.4), in exon 2 of the *DCTN1* gene. These results are shown in **Figure 1**.

Two patients (III-5 and II-7) of family F187 manifested a PSP-like phenotype at disease onset. Other patients had clinical diagnoses of Perry syndrome (II-3), Parkinson disease (III-3 and II-2), and behavioral variant of FTD (bvFTD) (III-7 and III-12). Two patients (III-5 and III-12) were independently referred to us by their neurologist, and genealogical extension of the family allowed us to link the 2 patients to the same pedigree.

The mutation segregated with the disease: patients III-3, III-7, and III-12 carried the mutation, whereas 4 asymptomatic relatives older than 60 years (II-5, II-6, III-4, and III-6) did

Table 1. Demographic and Clinical Variables of Affected Participants

Variable	I-1	II-2	II-3	II-7	III-3	III-5	III-7	III-12
Age at onset, y	50	NA	NA	49	46	59	40	39
Duration of disease, y	4	4	NA	3	5	5	14	4
Age at death, y	54	50	47	52	51	64	54	43
Clinical diagnosis	PD	PD	PD or Perry syndrome	PSP	PD	PSP	bvFTD	bvFTD
Symptoms at onset	Parkinsonism	Parkinsonism	Parkinsonism	Depression, anxiety	Parkinsonism	Apathy	Gait imbalance, falls	Depression, apathy, eating conduct disorders
Parkinsonism	+	+	+	+	+	+	+	+
Rigidity	NA	+	+	+	+	+	NA	+
Akinesia	NA	+	+	+	+	+	NA	+
Tremor	NA	NA	+	–	–	–	–	+
Levodopa or dopamine agonist response, adverse effects	NA	NA	NA	NA	+	NA	NA	Levodopa-induced dyskinesia, hallucinations
Dystonia	–	–	–	+	–	+	–	–
Oculomotor disorders	NA	NA	NA	+ PSP-like	NA	+ PSP-like	NA	–
Frontal signs	NA	NA	NA	+	+	+	+	+
Disinhibition				+	–	–	+	–
Apathy or inertia				+	+	+	–	+
Hyperorality				–	–	–	+	+
Archaic reflexes				+	NA	+	NA	+
Dysexecutive syndrome				NA	NA	+	NA	+
Psychiatric symptoms	NA	NA	+	+ Anxiety, obsessions	–	–	+ Depression, suicidal ideation	+ Depression, anxiety
Weight loss	NA	NA	NA	NA	–	–	–	+
Hypoventilation	NA	NA	+	+	–	NA	+	–
Cause of death	NA	NA	Respiratory arrest	Respiratory arrest	Unknown	Unknown	Respiratory arrest	Acute alcoholism
Brain magnetic resonance imaging/ single-photon emission computed tomography	NA	NA	NA	Normal	NA	Frontotemporal and midbrain atrophy /prefrontal superior hypoperfusion	Normal	Moderate frontal atrophy/bilateral frontal hypoperfusion

Abbreviations: bvFTD, behavioral variant of frontotemporal dementia; NA, not available; PD, Parkinson disease; PSP, progressive supranuclear palsy; +, present; –, absent.

not carry the mutation. The DNA of patients II-2, II-3, and II-7, who were obligate carriers, was unavailable.

The c.212G>A, p.Gly71Glu mutation has been previously identified in an apparently unrelated French family with a phenotype of Perry syndrome.[14,15] The glycine at codon 212 is conserved among multiple species. This mutation is located in the cytoskeleton-associated protein, glycine-rich domain, which contains the most conserved GKNDG motif (Gly-Lys-Asn-Asp-Gly). In silico analysis of missense substitutions pathogenicity revealed that p.Gly71Glu was classified as pathogenic using the following 4 algorithms: (1) PolyPhen-2 (Polymorphism Phenotyping version 2) software (http://genetics.bwh.harvard.edu/pph2), (2) Align GVGD (http://agvgd.iarc.fr/), (3) SIFT (Sorting Intolerant From Tolerant) (http://sift.jcvi.org), and (4) Mutation Taster (http://www.mutationtaster.org). It was not detected in 949 control subjects from another study[14] and was not present in 6503 individuals from an available database (Exome Variant Server [http://evs.gs.washington.edu/EVS/]), supporting its pathogenicity.

Clinical Features

Detailed clinical features were available for 8 patients of the family (**Table 1**). Four patients (III-3, III-5, III-7, and III-12) were examined and followed up by one of us (C.B.B., M.S., T.L., A.-M.B., R.L., or M.V.). Clinical data of deceased patients (I-1, II-2, II-3, and II-7) were collected from their medical records and by interview with their relatives.

In 6 patients, the mean (SD) age at onset was 47 (7) years (age range, 39-59 years). The first symptom was parkinsonism in 4 of 8 patients. Parkinsonism was predominantly of rigid-akinetic type; asymmetric tremor was present in one patient. Beneficial effect of levodopa was variable and often mild. It was often not well tolerated, rapidly causing levodopa-induced delirium, dyskinesias, and hallucinations. Initial depression and behavioral disorders (each in 2 of 8 patients) were less frequent. None of the patients developed clinical symptoms of amyotrophic lateral sclerosis (ALS). Among 8 patients, the mean (SD) age at death was 52 (6) years (age range, 43-64 years). Among 7 patients, the mean

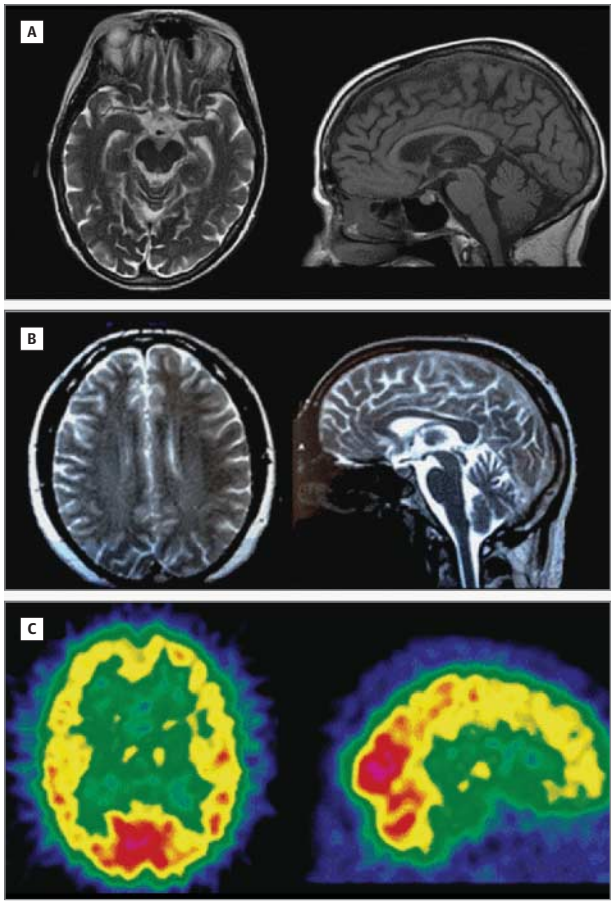
(SD) duration of disease was 6 (4) years (range, 3-14 years). The disease duration was long (14 years) in one patient (Table 1).

Four patients (III-5, II-7, III-12, and III-7) had uncommon presentations. Patient III-5 manifested apathy at age 59 years. At age 61 years, he developed bilateral blepharospasm, environmental adherence, and predominant axial akinetic-rigid parkinsonism. Brain magnetic resonance imaging revealed mild midbrain atrophy (**Figure 2**A), and brain ethyl cysteinate dimer-single-photon emission computed tomography showed prefrontal superior hypoperfusion. At age 62 years, the patient manifested anxiety, collectionism, and loss of interest, in the absence of depression. Examination showed marked axial rigid-akinetic parkinsonism with perseverations, buccolingual apraxia, bilateral grasping reflex, and severe postural instability. Examination of gaze showed slowing of voluntary vertical saccades. An electroneuromyogram was normal. Eye movement recording showed severe hypometry (gain = 0.75) but normal latency and velocity of horizontal visually guided saccades (225 milliseconds for right latency, 221 milliseconds for left latency; normal value 130-220). Saccade velocity was slightly reduced in downward vertical movements. Antisaccades were mildly abnormal (errors of 47% on the right side and 20% on the left side). A dysexecutive syndrome with perseverations, poor lexical phonological evocation, and attention and working memory deficits was present (**Table 2**). A diagnosis of PSP was made based on the clinical phenotype. The disease rapidly worsened, and death occurred at age 64 years.

From age 49 years, patient II-7 demonstrated obsessional personality traits; severe panic attacks characterized his disease, which led to a diagnosis of hypochondria. At age 51 years, the patient developed severe axial parkinsonian rigidity with postural instability associated with right upper limb dystonia. Parkinsonism only partially responded to levodopa treatment. An examination revealed a massive frontal syndrome with grasping reflex. Eye movement recording showed saccade hypometry. A diagnosis of PSP was made based on the clinical presentation. The disease rapidly worsened. Death occurred from pulmonary infection and acute respiratory failure at age 52 years.

Patient III-12 had depression and anxiety associated with behavioral changes at age 39 years. He progressively developed apathy, hyperorality, personal neglect, loss of initiative, indifference to others, and eating conduct changes. An examination at age 41 years revealed severe psychomotor slowness and reduction of speech output. Perseverative errors were present on the Wisconsin Card Sorting Test[19] (Table 2). Mild frontal atrophy was seen on brain magnetic resonance imaging, and brain single-photon emission computed tomography showed bilateral frontal hypoperfusion (Figure 2B and C). A diagnosis of bvFTD was made. An electroneuromyogram was normal. A polysomnographic recording revealed a sleep apnea syndrome. At age 42 years, he developed predominant axial rigidity associated with moderate right upper and lower limb tremor and rigidity. Levodopa treatment was complicated by drug-induced dyskinesia and hallucinations. The patient manifested severe depression with suicidal ideation (score of 20 on the Montgomery-Åsberg Depression Rating Scale[22]) that was resistant to antidepressant treatment. He later developed alcohol abuse, motor stereotypies, and progressive weight loss. Death occurred at age 43 years during an episode of acute alcoholism.

Figure 2. Brain Magnetic Resonance Imaging in Patients III-5 and III-12 and Single-Photon Emission Computed Tomography in Patient III-12



A, Brain magnetic resonance imaging in patient III-5 showing mild midbrain and frontal atrophy. B, Brain magnetic resonance imaging in patient III-12 showing mild frontal atrophy. C, Ethyl cysteinate dimer–single-photon emission computed tomography in patient III-12 showing marked frontotemporal hypoperfusion. According to radiological convention, right is left.

Patient III-7 had a long history of depression with numerous suicide attempts. He demonstrated loss of balance, a gait in small steps, and falls at age 40 years. A behavioral disorder with puerilism, coarseness, hyperorality, anosognosia, bizarre conduct, and disinhibition with seductress behavior was consistent with a diagnosis of bvFTD. The patient died at age 54 years of respiratory arrest.

Other patients (I-1, II-2, II-3, and III-3) are summarized in Table 1. Patients I-1, II-2, and III-3 had a diagnosis of early-onset parkinsonism. The phenotype of the other patient (II-3) included hypoventilation, severe depression, and associated parkinsonism with respiratory failure, which was consistent with the diagnostic criteria of Perry syndrome.

Table 2. Cognitive Profiles of Patients III-5 and III-12

Variable	III-5	III-12
Age at examination, y	62	39
Evolution time, y	3	2
Mini-Mental State Examination[16] score (range, 1-30)	24	30
Mattis Dementia Rating Scale[17]		NA
Score (range, 1-144)	137	
Attention (range, 1-37)	37	
Initiation (range, 1-37)	31	
Construction (range, 1-6)	6	
Concepts (range, 1-39)	39	
Memory (range, 1-25)	24	
Digit Span Forward	5	NA
Digit Span Backward	4	NA
Free and Cued Recall Test[18]		
Identifications (range, 1-16)	16	16
Immediate cued recall (range, 1-16)	14	15
Immediate free recall (range, 1-48)	20[a]	26[a]
Immediate total recall (range, 1-48)	48	47
Delayed free recall (range, 1-16)	11[a]	12
Delayed total recall (range, 1-16)	16	16
Recognitions (range, 1-16)	16	16
Wisconsin Card Sorting Test[19]		
Criteria (range, 1-6)	2	6
Errors, %	16[a]	5[a]
Perseverations, %	25[a]	60[a]
Verbal Fluency[20]		
Semantic (animals)	16	21
Phonological (letter M)	3[a]	16
Frontal Assessment Battery[21]		
Total score (range, 1-18)	15[a]	16[a]
Similarities (range, 1-3)	3	3
Phonological fluency (range, 1-3)	1[a]	2[a]
Grasping (range, 1-3)	3	3
Motor sequences (range, 1-3)	2[a]	3
Conflicting instructions (range, 1-3)	3	3
Go-no go (range, 1-3)	3	2[a]

Abbreviation: NA, not available.

[a] Under the cutoff.

Discussion

We have described herein a French family characterized by high intrafamilial variability with different phenotypes, including bvFTD, Perry syndrome, PSP-like phenotype, and isolated parkinsonism caused by the p.Gly71Glu mutation in exon 2 of the *DCTN1* gene. Another apparently unrelated French family carried the p.Gly71Glu mutation[14,15] (**Table 3**). Although these 2 families originated from different regions of France, we cannot firmly exclude a founder effect for this mutation.

DCTN1 mutations were first identified in patients with distal spinal and bulbar muscular atrophy[33,34] and in patients with ALS.[35,36] A cluster of mutations in exon 2 of the *DCTN1* gene was identified later in 11 families with Perry syndrome, a rare autosomal dominant form of parkinsonism associated with weight loss, severe depression, and central hypoventilation (Table 3).[14,15,23-32] Clinical diagnostic criteria of Perry syndrome, as defined by Wider and Wszolek,[37] include 5 cardinal characteristics (weight loss, parkinsonism, hypoventilation, psychiatric symptoms, and familial autosomal dominant history) and 5 supportive features (rapid progression, suicidal thoughts or attempts, no or transient response to levodopa, onset between the ages of 30 and 60 years, and dyspnea or apnea with night predominance). The phenotypes associated with *DCTN1* mutations are correlated with the genotype because all the mutations located in exon 2 except one (p.Gly59Ser) are responsible for Perry syndrome. The p.Gly59Ser mutation led to slowly progressive distal spinal and bulbar muscular atrophy with vocal cord paralysis.[33] All other mutations producing ALS are in the other exons of the gene (see eTable 1 in the Supplement).[35,36]

The patient of family F187 (III-5) and his relative (II-7) manifested a clinical phenotype that matched the criteria for PSP, which is an uncommon presentation in families with *DCTN1*. A clinical diagnosis of Perry syndrome could not be considered in the 2 patients at early stages of disease. Indeed, the phenotype of III-5, with only 2 cardinal features (parkinsonism and autosomal dominant inheritance) without weight loss, hypoventilation, or psychiatric symptoms was inconsistent with probable or possible criteria for Perry syndrome (see eTable 2 in the Supplement). The phenotype of II-7 was ultimately consistent with a probable diagnosis of Perry syndrome but not at the early stage of disease. Initially, both patients manifested a progressive rigid-akinetic syndrome after age 40 years, combining early postural instability with falls, slow vertical saccades, or supranuclear gaze palsy and a disease duration shorter than 8 years, which fit well with criteria for PSP by the National Institute of Neurological Disorders-Society for Progressive Supranuclear Palsy,[1] as well as criteria by the Neuroprotection and Natural History in Parkinson Plus Syndromes.[2] Oculomotor recordings in both patients showed hypometric horizontal saccades and a speed reduction downward in vertical movements, which were unusual in Perry syndrome but were characteristic of PSP. In addition, both patients had frontal syndrome and dystonia (blepharospasm or upper limb dystonia), and midbrian atrophy was present in patient III-5; these symptoms are uncommon in Perry syndrome but suggest the diagnosis of PSP. One other patient carrying a p.Gly71Arg *DCTN1* mutation demonstrated slowing of vertical downward saccades and progressive midbrain atrophy on neuroimaging that were suggestive of PSP.[31] This patient and our series support that PSP-like phenotypes may be included in the clinical spectrum of disorders associated with *DCTN1* mutations. These cases also suggest that phenotypic presentations are related to an anatomical distribution of the lesions rather than to a specific histopathological condition because *DCTN1* mutations are associated with pathological transactive response DNA-binding protein 43 (TDP-43),[32] although most other PSP phenotypic presentations are tauopathies.[4]

Table 3. Clinical Features of Previously Reported Patients With Perry Syndrome and of Family 187

Variable	Perry et al,[23,24] 1975, 1990	Purdy et al,[25] 1979	Roy et al,[26] 1988	Lechevalier et al,[15] 1992	Bhatia et al,[27] 1993	Elibol et al,[28] 2002	Tsuboi et al,[29] 2002	Ohshima et al,[30] 2010	Newsway et al,[31] 2010	Wider et al,[32] 2010	Present Study
No. of families (geographical origin)	1 (Canada)	1 (Canada)	1 (United States)	1 (France)	1 (United Kingdom)	1 (Turkey)	1 (Japan)	1 (Japan)	1 (United Kingdom)	2 (Japan)	1 (France)
No. of affected participants (male-female ratio)	10 (8:2)	5 (3:2)	6 (3:3)	8 (3:5)	6 (3:3)	2 (1:1)	5 (5:0)	3 (1:2)	1 (1:0)	2 (First [0:2]), 2 (second [1:1])	8
Age at onset, mean (range), y	49 (45-52)	46 in 2 patients	51 (44-56) in 4 patients	49 (45-56) in 5 patients	43 (35-51) in 5 patients	48 (46-50)	41 (38-43)	56 (46-61)	46	47 (First), 61 (second)	47 (39-59) in 6 patients
Duration, mean (range), y	5 (4-6)	2.5 (2-3)	3 (3-5)	8 (6-10)	5 (3-10) in 5 patients	4 (3-5)	6 (6-2)	4	9	NA (first), 3 (second)	5 (3-14) in 7 patients
First symptoms	Depression, weight loss	Depression, weight loss	Parkinsonism, depression	Parkinsonism, depression	Parkinsonism	Apathy	Parkinsonism, depression	Parkinsonism, weight loss	Parkinsonism, depression	Parkinsonism (first); resting tremor, weight loss (second)	Parkinsonism in 4 patients; depression, apathy, anxiety in 3 patients
Parkinsonism	+	+	+	+	+	+	+	+	+	+	+
Akinesia	-	+	+	+	+	+	+	+	+	+	+
Rigidity	+ Axial	+	+	+	+	NA	+	+	+	+	+
Tremor	+	+	+	+	+	+	+	+	-	+ Second	+ In 2 patients
Levodopa or dopamine agonist response (adverse effects)	-	-	+	+	+	+	+ Hypomanic state in 1 patient	-	+ Levodopa-induced dyskinesia	+	+ Levodopa-induced dyskinesia, hallucinations
Other features	-	-	-	-	-	-	-	Autonomic dysfunction	Vertical gaze palsy	-	Vertical gaze palsy in 2 patients
Psychiatric disturbances	+	+	+	+	+	NA	+ In 4 patients	+ In 1 patient	-	-	+ In 4 patients
Hypoventilation	+	+	+	+	-	+	+ In 3 patients	+	+	+	+ In 3 patients
Weight loss	+	+	+	+	-	+	+ In 4 patients	+	+	-	+ In 1 patient
Cause of death	Suicide in 1 patient, respiratory arrest in 2 patients	Respiratory arrest	Respiratory arrest	Respiratory arrest	Pneumonia in 1 patient, sudden death in 1 patient	Respiratory arrest in 1 patient, pneumonia in 1 patient	Suicide in 1 patient, respiratory arrest in 1 patient	Respiratory and cardiac arrest	NA	Respiratory arrest	Respiratory arrest in 3 patients

Abbreviations: NA, not available; +, present; –, absent.

Two other patients had unusual presentations of predominant behavioral disorders consistent with the diagnostic criteria of bvFTD.[38] Only mild to moderate frontal atrophy was present at brain imaging, although single-photon emission computed tomography showed marked bilateral frontal hypoperfusion in one patient. Neither patient had clinical symptoms of ALS. Another patient having FTD with a family history of ALS carried a p.Arg1101Lys mutation in exon 27. Frontotemporal type of dementia is not included in the clinical criteria for Perry syndrome,[37] but our cases showed that it may be the predominant initial phenotype in patients with *DCNT1* mutations.

It has recently been shown that Perry syndrome is a genetically and pathologically heterogeneous syndrome; however, neuropathological investigations demonstrated severe neuronal loss in the substantia nigra without Lewy bodies but with TDP-43-positive inclusions in Perry syndrome caused by *DCTN1* mutations.[32] *MAPT* mutations have also recently been identified in 2 families with associated weight loss, parkinsonism, and central hypoventilation, a phenotype resembling Perry syndrome, and with a pathological 4-repeat tau suggestive of PSP.[39] *DCTN1* codes for the large subunit p150glued of the dynein-dynactin motor protein complex are involved in retrograde axonal transport. Tau is a microtubule-binding protein that strongly interacts with tubulin to assemble and stabilize the microtubule and is crucial for axonal transport. Mutations in *DCTN1* and *MAPT* in dementia, parkinsonism, and motor neuron disor-

der support that axonal transport injury might have a key role in the pathogenesis of these conditions.[33]

The frequency of *DCTN1* mutations was low (1 of 21 patients) in our series of familial forms of PSP-like phenotypes. However, our study demonstrates that *DCTN1* mutations should be searched for in patients with clinical PSP-phenotypes, especially when bvFTD, psychiatric disturbances, associated parkinsonism, or a familial history of an autosomal dominant disorder is present.

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REFERENCES

1. Litvan I, Hauw JJ, Bartko JJ, et al. Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supranuclear palsy and related disorders. *J Neuropathol Exp Neurol*. 1996;55(1):97-105.

2. Bensimon G, Ludolph A, Agid Y, Vidailhet M, Payan C, Leigh PN; NNIPPS Study Group. Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: the NNIPPS study. *Brain*. 2009;132(pt 1):156-171.

3. Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. *Lancet Neurol*. 2009;8(3):270-279.

4. Hauw JJ, Daniel SE, Dickson D, et al. Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). *Neurology*. 1994;44(11):2015-2019.

5. Donker Kaat L, Boon AJ, Azmani A, et al. Familial aggregation of parkinsonism in progressive supranuclear palsy. *Neurology*. 2009;73(2):98-105.

6. de Yébenes JG, Sarasa JL, Daniel SE, Lees AJ. Familial progressive supranuclear palsy: description of a pedigree and review of the literature. *Brain*. 1995;118(pt 5):1095-1103.

7. Rojo A, Pernaute RS, Fontán A, et al. Clinical genetics of familial progressive supranuclear palsy. *Brain*. 1999;122(pt 7):1233-1245.

8. Choumert A, Poisson A, Honnorat J, et al. G303V tau mutation presenting with progressive supranuclear palsy-like features. *Mov Disord*. 2012;27(4):581-583.

9. Ogaki K, Li Y, Takanashi M, et al. Analyses of the *MAPT*, *PGRN*, and *C9orf72* mutations in Japanese patients with FTLD, PSP, and CBS. *Parkinsonism Relat Disord*. 2013;19(1):15-20.

10. Cannas A, Borghero G, Floris GL, et al. The p.A382T *TARDBP* gene mutation in Sardinian patients affected by Parkinson's disease and other degenerative parkinsonisms. *Neurogenetics*. 2013;14(2):161-166.

11. Le Ber I, Camuzat A, Guillot-Noel L, et al. C9ORF72 repeat expansions in the frontotemporal dementias spectrum of diseases: a flow-chart for genetic testing. *J Alzheimers Dis*. 2013;34(2):485-499.

12. Lesage S, Le Ber I, Condroyer C, et al; French Parkinson's Disease Genetics Study Group. *C9orf72* repeat expansions are a rare genetic cause of parkinsonism. *Brain*. 2013;136(pt 2):385-391.

13. Ros R, Gómez Garre P, Hirano M, et al. Genetic linkage of autosomal dominant progressive supranuclear palsy to 1q31.1. *Ann Neurol*. 2005;57(5):634-641.

14. Farrer MJ, Hulihan MM, Kachergus JM, et al. *DCTN1* mutations in Perry syndrome. *Nat Genet*. 2009;41(2):163-165.

15. Lechevalier B, Schupp C, Fallet-Bianco C, et al. Familial parkinsonian syndrome with athymhormia and hypoventilation [in French]. *Rev Neurol (Paris)*. 1992;148(1):39-46.

16. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading cognitive status of patients for the clinician. *J Psych Res*. 1975;12:189-198.

17. Mattis S. *Dementia Rating Scale Professional Manual*. Odessa, FL: Psychological Assessment Resources; 1973.

18. Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. *Neurology*. 1988;38(6):900-903.

19. Grant DA, Berg EA. A behavioral analysis of degree of reinforcement and ease of shifting to new

responses in a Weigl-type card-sorting problem. *J Exp Psychol*. 1948;38(4):404-411.

20. Thuillard F, Assal G. Données neuropsychologiques chez le sujet âgé normal. In: Habib M, Joanette Y, Puel M, eds. *Démences et Syndromes Démentiels: Approche Neuropsychologique*. Paris, France: Masson; 1991:125-133.

21. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology*. 2000;55(11):1621-1626.

22. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382-389.

23. Perry TL, Bratty PJ, Hansen S, Kennedy J, Urquhart N, Dolman CL. Hereditary mental depression and Parkinsonism with taurine deficiency. *Arch Neurol*. 1975;32(2):108-113.

24. Perry TL, Wright JM, Berry K, Hansen S, Perry TL Jr. Dominantly inherited apathy, central hypoventilation, and Parkinson's syndrome: clinical, biochemical, and neuropathologic studies of 2 new cases. *Neurology*. 1990;40(12):1882-1887.

25. Purdy A, Hahn A, Barnett HJ, et al. Familial fatal Parkinsonism with alveolar hypoventilation and mental depression. *Ann Neurol*. 1979;6(6):523-531.

26. Roy EP III, Riggs JE, Martin JD, Ringel RA, Gutmann L. Familial parkinsonism, apathy, weight loss, and central hypoventilation: successful long-term management. *Neurology*. 1988;38(4):637-639.

27. Bhatia KP, Daniel SE, Marsden CD. Familial parkinsonism with depression: a clinicopathological study. *Ann Neurol*. 1993;34(6):842-847.

28. Elibol B, Kobayashi T, Atac FB, et al. *Familial Parkinsonism With Apathy, Depression and Central Hypoventilation (Perry's Syndrome): Mapping the Progress of Alzheimer's and Parkinson's Disease*. New York, NY: Kluwer Academic/Plenum Publishers; 2002:285-290.

29. Tsuboi Y, Dickson DW, Nabeshima K, et al. Neurodegeneration involving putative respiratory neurons in Perry syndrome. *Acta Neuropathol*. 2008;115(2):263-268.

30. Ohshima S, Tsuboi Y, Yamamoto A, et al. Autonomic failures in Perry syndrome with *DCTN1* mutation. *Parkinsonism Relat Disord*. 2010;16(9):612-614.

31. Newsway V, Fish M, Rohrer JD, et al. Perry syndrome due to the *DCTN1* G71R mutation: a distinctive levodopa responsive disorder with behavioral syndrome, vertical gaze palsy, and respiratory failure. *Mov Disord*. 2010;25(6):767-770.

32. Wider C, Dachsel JC, Farrer MJ, Dickson DW, Tsuboi Y, Wszolek ZK. Elucidating the genetics and pathology of Perry syndrome. *J Neurol Sci*. 2010;289(1-2):149-154.

33. Puls I, Jonnakuty C, LaMonte BH, et al. Mutant dynactin in motor neuron disease. *Nat Genet*. 2003;33(4):455-456.

34. Puls I, Oh SJ, Sumner CJ, et al. Distal spinal and bulbar muscular atrophy caused by dynactin mutation. *Ann Neurol*. 2005;57(5):687-694.

35. Münch C, Sedlmeier R, Meyer T, et al. Point mutations of the p150 subunit of *dynactin* (*DCTN1*) gene in ALS. *Neurology*. 2004;63(4):724-726.

36. Münch C, Rosenbohm A, Sperfeld AD, et al. Heterozygous R1101K mutation of the *DCTN1* gene in a family with ALS and FTD. *Ann Neurol*. 2005;58(5):777-780.

37. Wider C, Wszolek ZK. Rapidly progressive familial parkinsonism with central hypoventilation, depression and weight loss (Perry syndrome): a literature review. *Parkinsonism Relat Disord*. 2008;14(1):1-7.

38. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134(pt 9):2456-2477.

39. Omoto M, Suzuki S, Ikeuchi T, et al. Autosomal dominant tauopathy with parkinsonism and central hypoventilation. *Neurology*. 2012;78(10):762-764.