





DNAJC12 and Dopa-Responsive Nonprogressive Parkinsonism

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Biallelic *DNAJC12* mutations were described in children with hyperphenylalaninemia, neurodevelopmental delay, and dystonia. We identified *DNAJC12* homozygous null variants (c.187A>T;p.K63* and c.79-2A>G;p.V27Wfs*14) in two kindreds with early-onset parkinsonism. Both probands had mild intellectual disability, mild nonprogressive, motor symptoms, sustained benefit from small dose of levodopa, and substantial worsening of symptoms after levodopa discontinuation. Neuropathology (Proband-A) revealed no alpha-synuclein pathology, and substantia nigra depigmentation with moderate cell loss. *DNAJC12* transcripts were reduced in both patients. Our results suggest that *DNAJC12* mutations (absent in 500 early-onset patients with Parkinson's disease) rarely cause dopa-responsive nonprogressive parkinsonism in adulthood, but broaden the clinical spectrum of *DNAJC12* deficiency.

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Biallelic mutations in *DNAJC12* were recently described in four families with hyperphenylalaninemia, dystonia, and intellectual disability.¹ While *DNAJC12* function is still unclear it is suggested to interact with aromatic amino-acid hydroxylases, including phenylalanine hydroxylase (PAH), tyrosine hydroxylase (TH), and tryptophan

hydroxylase-1 and -2 (TPH1, TPH2).¹ These enzymes are central to the synthesis of dopamine and serotonin² and share the obligatory cofactor, tetrahydrobiopterin (BH₄; Fig 1).³

Mutations in enzymes involved in the biosynthesis of monoamine neurotransmitters, including those responsible for synthesis and salvage of BH₄, present with a wide spectrum of clinical manifestations such as motor and autonomic dysfunction, cognitive impairment and sleep disturbances (Fig 1).^{4,5} Symptoms usually start during infancy although later onset may occur.⁴ Motor symptoms, largely attributed to dopamine deficiency, comprise motor delay, dystonia, parkinsonism and hypotonia.⁴

Here we identified two novel homozygous *DNAJC12* null mutations in two families with early-onset dopa-responsive nonprogressive parkinsonism not associated with overt dystonic features.

Patients and Methods

The study was performed according to the Helsinki Declaration and approved by site-specific ethics committees. Written informed

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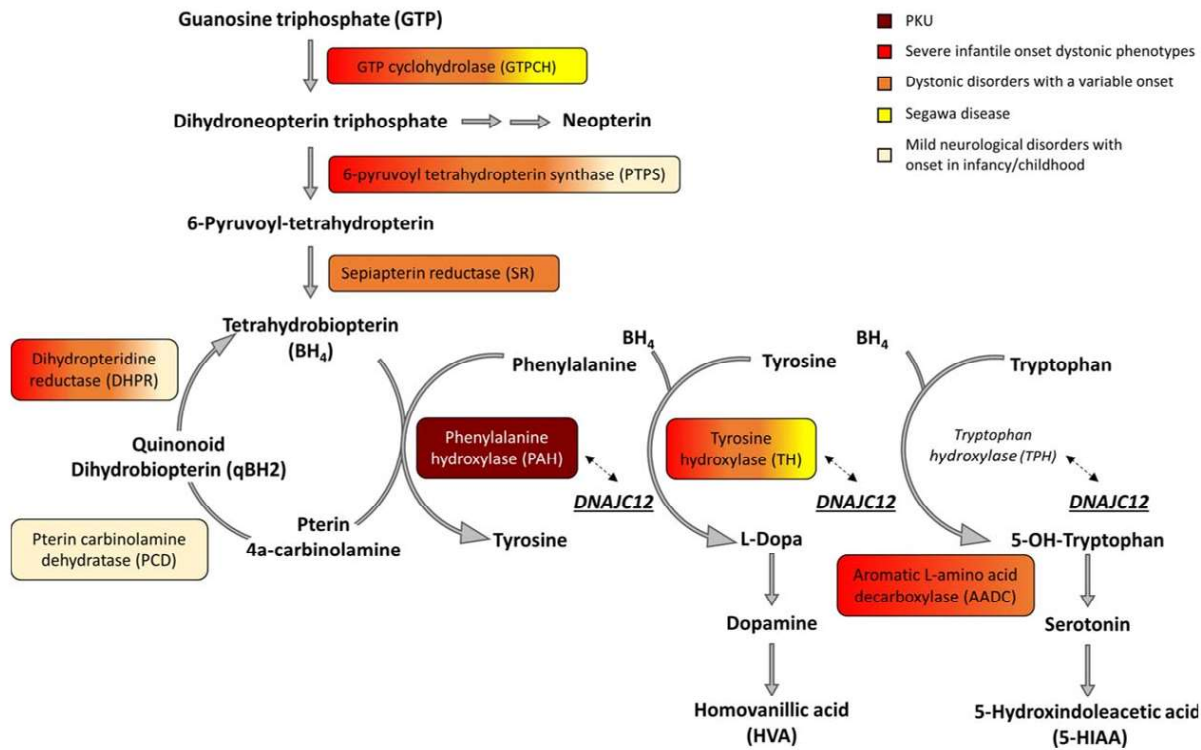


FIGURE 1: Monoamine neurotransmitter metabolism and related clinical phenotypes. Enzymes whose deficiencies can affect the pathway are boxed and shaded according to the associated spectrum of clinical manifestations. The possible interaction of *DNAJC12* with different hydroxylases, as proposed by Anikster et al,³ is indicated by two-headed arrows. [Color figure can be viewed at www.annalsofneurology.org]

consent was obtained from all subjects. Parkinson's disease (PD) was diagnosed by movement disorders expert neurologists, and the Hoehn and Yahr stage (H&Y) was used to assess PD symptoms/progression.

Whole-Exome Sequencing

WES was performed using the Ion AmpliSeq Exome Kit and the Ion Proton System (Thermo Fisher Scientific, Waltham, MA). Reads were aligned against the human reference genome, hg19. Variant annotation was performed with ANNOVAR (<http://annovar.openbioinformatics.org/en/latest/>). Variant confirmation, segregation analysis, and *DNAJC12* screening were performed by Sanger sequencing.

RNA Analysis

RNA from frozen brain tissue was isolated using the RNeasy Mini kit (Qiagen, Hilden, Germany) and reverse-transcribed with the Superscript VILO cDNA synthesis kit (Thermo Fisher Scientific). Whole-blood RNA was extracted using the PAXgene Blood miRNA Kit (Qiagen) and reverse-transcribed with the ImProm-II Reverse Transcription System (Promega, Madison, WI). For splicing assays, *DNAJC12* exons 1 to 3 were reverse-transcribed and polymerase chain reaction (RT-PCR) amplified to obtain products for Sanger sequencing. *DNAJC12* transcripts were assessed by real-time RT-PCR using: (1) a TaqMan assay on a 7900HT instrument (Thermo Fisher Scientific) (Proband-A) and (2) the SYBR Premix ExTaqII (TAKARA, Mountain

View, CA) on a LightCycler480 (Roche, Basel, Switzerland) (Proband-B).

Neuropathology

Autopsy was performed 60 hours after death. Brain specimens were paraffin-embedded, cut into 5- μ m-thick sections, deparaffinized and rehydrated. Following epitope unmasking monoclonal antibodies to α -synuclein and p62 (BD Transduction Laboratories, Oxford, UK); β -amyloid (Signet; BioLegend, San Diego, CA); phospho-tau (Innogenetics, Ghent, Belgium); and phospho-TDP-43 (Cosmo Bio, Tokyo, Japan) were applied, incubated overnight (4°C) and detected using the Dako REAL EnVision System (Agilent Technologies, Santa Clara, CA). Alzheimer's disease neuropathological diagnosis was based on β -amyloid plaques distribution (according to Thal's phase), neurofibrillary tangle pathology distribution (according to Braak's staging) and neocortical neuritic plaque density (according to Consortium to Establish a Registry for Alzheimer's disease [CERAD]).⁶

Biochemical Analyses

Phenylalanine, biogenic amine metabolites (5-hydroxyindoleacetic acid [5-HIAA]; homovanillic acid [HVA]), pterins, dihydropteridine reductase (DHPR) activity and amino acids were measured either in blood, dried blood, cerebrospinal fluid (CSF) or urine as described.¹

Results

We analyzed two kindreds, from Saskatchewan (Canada; family A) and from Italy (family B) with recessive early-onset parkinsonism (Fig 2). Both probands had mild, nonprogressive motor symptoms and derived marked and sustained benefit from a small dose of levodopa. These clinical features challenged the diagnosis of idiopathic PD, so that attempts were made to discontinue levodopa, invariably leading to worsening of symptoms in both probands.

Proband-A⁷ had juvenile parkinsonism (age at onset [AAO] = 13 years) that marginally progressed to H&Y 3 by age 31, and remained stable over the subsequent 43 years (Video 1). Psychometric testing at 32 years revealed mild intellectual disability (IQ = 68) that did not worsen (Table). ¹⁸Fluoro(F)-Dopa positron emission tomography (PET) imaging at 56 and 73 years revealed a mild reduction in uptake that was nonprogressive over time, and some degree of asymmetry (Fig 2). The patient died at 74 years.

Proband-B was diagnosed with early-onset tremulous parkinsonism (AAO = 32 years). She had marginal progression of motor and nonmotor symptoms over 30 years (H&Y 1; Video 2). She developed mild peak-dose levodopa-induced dyskinesias that disappeared by fractioning levodopa dose. Her scholastic performance was below average. Neuropsychological assessment (55 years) revealed mild cognitive impairment and borderline intellectual ability (IQ = 71; Table). Dopamine transporter single-photon emission computed tomography (DaT-SPECT) imaging at 52 years was at the lower limit of normality in the right putamen. A second DaTSCAN at 57 years was normal (Fig 2).

Proband-B's younger brother had mild nonprogressive tremulous parkinsonism (AAO = 51 years). Early and prominent psychotic symptoms were noted, without overt cognitive dysfunction. Presynaptic nigrostriatal function appeared normal at DaTSCAN (54 years; data not shown).

WES identified *DNAJC12* homozygous null variants in both subjects: a nonsense substitution (NM_021800.2:c.187A>T;p.K63*) in Proband-A and a splicing mutation (NM_021800.2:c.79-2A>G;p.V27Wfs*14) in Proband-B. Both variants are absent from public databases (GnomAD). No other mutations were detected in genes previously linked/associated with PD. Variants were confirmed by Sanger sequencing; segregation analysis within families was consistent with autosomal-recessive inheritance (Fig 2). No other causal mutations were identified in 127 early-onset (<45 years) PD with exome data, nor in

87 Asian and 283 Caucasian early-onset patients screened by Sanger sequencing.

RT-PCR and sequence analysis on Proband-B's RNA revealed that the c.79-2A>G mutation causes exon-2 skipping, resulting in a frameshift and a premature stop (p.V27Wfs*14). *DNAJC12* transcript levels were significantly decreased in Proband-A's cerebellum and Proband-B's whole blood (Fig 2).

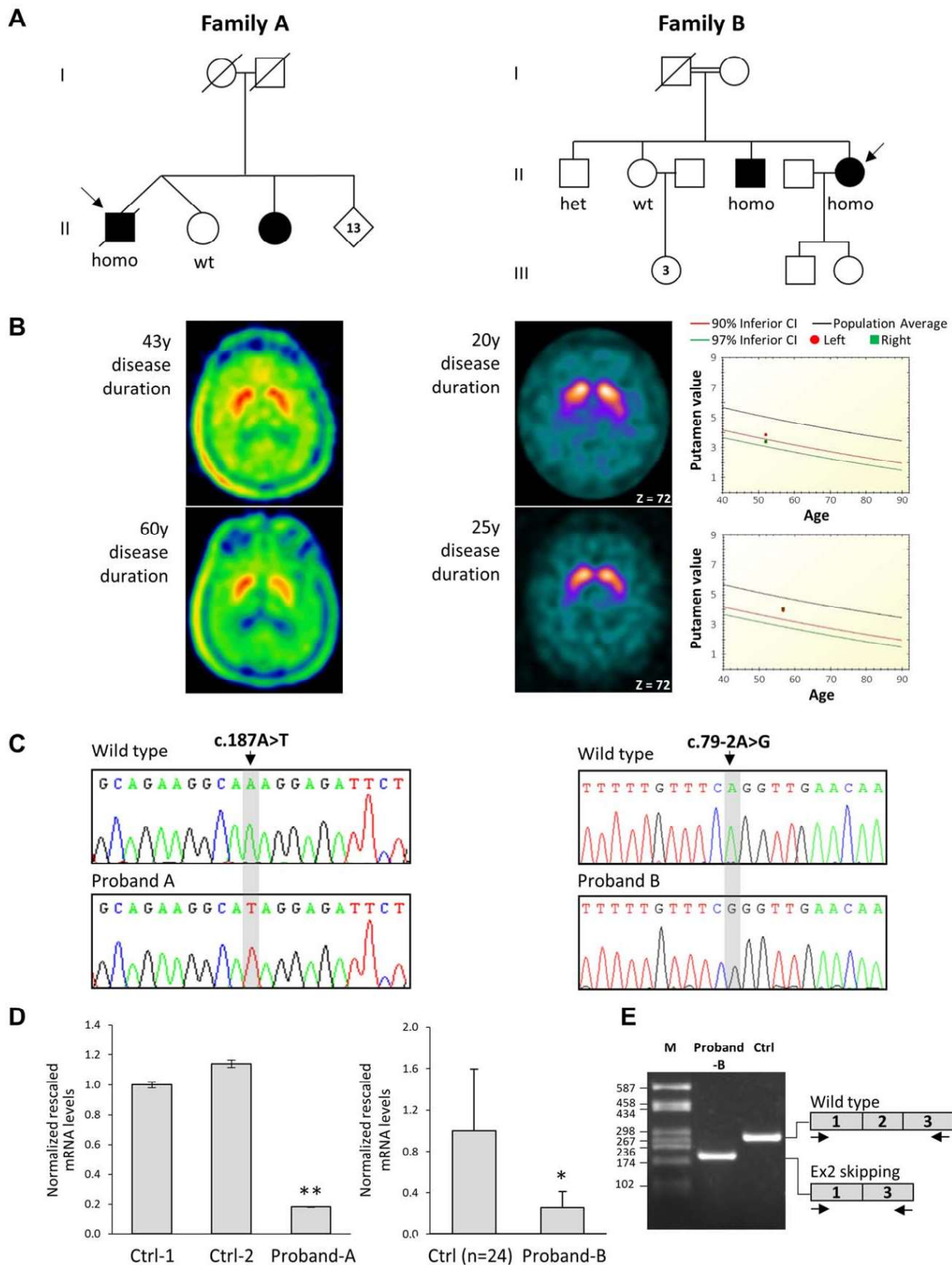
Gross examination of Proband-A's brain was unremarkable except the substantia nigra (SN) appeared hypopigmented. There was no evidence of α -synuclein pathology in brainstem nuclei. The pigmented neurons in the locus coeruleus (LC) appeared well preserved, whereas in the SN there was a moderate loss with marked depigmentation. Some tau-positive neurofibrillary tangles (NFTs) and neurites were noted in the LC, reticular formation, basis pontis, and hippocampus and moderate NFTs/neurites in the entorhinal cortex fulfilling Braak's neurofibrillary tangle stage 2. Moderate diffuse amyloid plaques were observed in frontal/parietal cortices together with sparse neuritic plaques (CERAD A). Some β -amyloid deposits were found in the central gray of the midbrain and red nucleus, reaching Thal amyloid phase 4. Thus, the case would be assigned A3-B1-C1.⁶ No changes were observed with phospho-TDP-43, whereas p62 showed diffuse staining in spinal cord motor neurons and glial aggregation that was positive for β -amyloid.

Proband-B had elevated blood phenylalanine (449 μ M; Table) comparable to previously described patients.¹ CSF analysis showed very low concentrations of 5-HIAA and HVA, increased HVA/HIAA ratio, increased phenylalanine concentration (74 μ M), along with an elevation of several amino acids (Table). Defects in BH₄ metabolism were excluded based on normal levels of urinary pterins and DHPR activity in the dried-blood spot (Table).

Discussion

Homozygous null mutations in *DNAJC12* were identified in two kindreds with early-onset parkinsonism, broadening the clinical spectrum of *DNAJC12* deficiency, which was reported¹ to clinically mimic deficits in BH₄ metabolism, leading to a progressive movement disorder with prominent dystonia and intellectual disability.¹ However, our data suggest that *DNAJC12* mutations may also present with disease onset in adolescence/adulthood, with parkinsonism as the main symptom, mild intellectual disability and no overt dystonic features.

Such variability parallels that observed in patients with *GCHI* mutations.⁸ Whereas the classical phenotype is childhood-onset dopa-responsive dystonia, *GCHI*



carriers may present in adulthood with slowly progressing parkinsonism, similar to idiopathic PD.⁹ Levodopa-responsive parkinsonism has been occasionally reported in patients with hyperphenylalaninemia attributed to PAH mutations or to defects in BH₄ metabolism.^{10–13} However, even if some of these patients^{13–15} can fulfil clinical criteria for idiopathic PD, little or no evidence of dopaminergic deficit is apparent by presynaptic nigrostriatal imaging. Hence these patients might represent cases of “scans without evidence of dopaminergic deficit.”¹⁶

In Proband-A, the biochemical neurotransmitter imbalance was not associated with a degenerative process. The SN hypopigmentation is likely a consequence of a chronic deficiency in dopamine, the main precursor of neuromelanin in dopaminergic neurons.¹⁷ The lack of histologically evident neurodegeneration is consistent with neuropathological and neuroimaging data reported in patients with biogenic amine disorders,¹³ and with the nonprogressive course of the disease.

Hitherto, all neuronally expressed DNAJ class-III (DNAJC) members (*DNAJC6*/auxilin, *DNAJC26*/GAK, *DNAJC5*/CSP α , *DNAJC13*/Rme-8, and *DNAJC12*/HSP40) have been implicated in parkinsonism.¹⁸ *DNAJC12* has a critical role in chaperoning amino-acid hydrolase interactions required for catecholamine synthesis.¹ In line with this, TH was shown to interact with

VMAT2 transporter, which is required to package dopamine at the synapse.¹⁹ Thus, the coupling between synthesis and packaging of dopamine may be tightly regulated by the chaperone properties of *DNAJC12*. *DNAJC* proteins appear to contribute to the maintenance of an equilibrium within the presynaptic compartment that ensures viability of the synapse, repopulation of synaptic vesicle machinery, and folding of intrinsically disordered proteins, such as α -synuclein.¹⁸

In summary, we report a different phenotype associated with mutations in *DNAJC12*. This finding adds to the recent article by van Spronsen et al²⁰ describing a more mild and heterogeneous clinical spectrum of *DNAJC12*-deficient hyperphenylalaninemia. Pleiotropy is emerging as an important contributor to genetic disorders. The utilization of the same protein in multiple biological processes well suits the multiple functions and interactors hypothesized for *DNAJC12*. From a clinical perspective, our results suggest that patients with mild nonprogressive parkinsonian symptoms, response to low-dose levodopa, and possibly intellectual disability should be screened for hyperphenylalaninemia. If positive, they should be tested for *DNAJC12* variants. Such patients may have great benefit from combined administration of BH₄, dopamine, and serotonin precursors, as previously suggested.¹

FIGURE 2: *DNAJC12* mutations in families with early-onset recessive parkinsonism. (A) Pedigree of family A (left) and consanguineous family B (right). The affected subjects are represented by black symbols; the proband, analyzed by WES, is indicated by an arrow. The *DNAJC12* mutation genotype is reported, when available, under each family member. wt = wild type (c.187A, Family A; c.79-2C, Family B); Het = heterozygote (c.79-2A/c.79-2G, Family B); Homo = homozygote (c.187T, Family A; c.79-2G, Family B). (B) Imaging results. Imaging study of the presynaptic nigrostriatal function was performed by using ¹⁸F-dopa PET for Proband-A (left), with the tissue input uptake rate constant, K_{occ} , as outcome variable and DaT-SPECT for Proband-B (right). ¹⁸Fluoro(F)-Dopa PET: index case at 43- and 60-year disease duration. First scan: Putamen R 0.0065, L 0.0086; Put/Caud R 0.71, L 0.72, normal value > 0.7; Putamen asymmetry 32% L>R, normal value < 25%. Second scan: Putamen R 0.0062, L 0.0081; Put/Caud R 0.77, L 0.74, normal value > 0.7; Putamen asymmetry 31% L>R, normal value < 25%. Images represent tracer concentration (Bq/ml) averaged from 30 to 90 minutes after tracer injection. The patient was injected with the same amount of tracer and was of the same weight. Both images are scaled to the same maximum. DaT-SPECT: index case at 20- and 25-year disease duration. Putamen R 3.40, L 3.84; Put/Caud R 0.70, L 0.78, normal value > 0.7; Putamen asymmetry 12% L>R, normal value < 25%. SPECT images were normalized and Z scores are displayed at the bottom of the scan. Below each scan, FP-CIT SPECT binding values are shown, as calculated using the Basal Ganglia Matching Tool V2 Semi-quantitative; caudate nucleus binding values are displayed on the left, putamen values on the right. The population average values adjusted for age and the 90% and 97% inferior confidence limits are indicated. (C) Sanger sequencing electropherograms showing the nucleotide sequence surrounding the *DNAJC12* mutations (c.187A>T left; c.79-2A>G, right). The mutated nucleotide is indicated by an arrow and shaded in gray. (D) Quantification of total *DNAJC12* mRNA levels by real-time RT-PCR. Left: Proband-A and 2 controls. All reactions were performed in triplicate on RNA extracted from cerebellum and data normalized using three housekeeping genes (*DNAJC12* Hs01113092_m1; *GAPDH*: Hs01105870_m1; *HPRT1*: Hs02800695_m1 and *SYP*: Hs00300531_m1; Thermo Fisher Scientific, Waltham, MA). Right: Proband-B and 24 controls. All reactions were performed in triplicate on RNA extracted from total blood. *HMB5* (hydroxymethylbilane synthase) was used as internal reference. Results were analyzed with the software GeNorm (<https://genorm.cmgg.be>) and are presented as normalized rescaled values, and analyzed by unpaired t test. * $p < 0.05$; ** $p < 0.01$. (E) Agarose-gel electrophoresis of the RT-PCR assay performed on the RNA extracted from total blood of the Proband-B and of a control individual (Ctrl). PCR products showed amplification of a lower-molecular-weight fragment (199bp) compared to the control (278bp). Sequencing of the shorter PCR product confirmed complete skipping of exon 2. On the right, schematic representation of the amplicons obtained from the RT-PCR with the position of the primers used in the assay. Exons are represented by boxes, primers by arrows. DaT-SPECT = dopamine transporter single-photon emission computed tomography; L = left; PET = positron emission tomography; Put/Caud = putamen/caudate; R = right; RT-PCR = reverse-transcription polymerase chain reaction; WES = whole-exome sequencing. [Color figure can be viewed at www.annalsofneurology.org]

TABLE 1. Demographic, clinical, and biochemical characteristics of patients carrying DNAJC12 variants.

	Demographic and clinical characteristics			Biochemical characteristics ^a	
	Proband-A	Proband-B	Proband-B's brother	Proband-B <i>Blood</i>	
Origin	Canada	Italy	Italy		
Family	A	B	B	Phenylalanine (37–115 µM)	449
Gender	M	F	M	Prolactin ^b (4.8–23.3 ng/mL)	12.3
AAO motor symptoms	13	32 (tremor)	51	Cerebrospinal fluid	
AAO non-motor symptoms	-	26 (anxiety/depression)	53	HVA (115–455 nM)	37
Age at diagnosis	31	32	51	5-HIAA (51–204 nM)	7
At last assessment	73	59	58	HVA/5-HIAA ratio (1.1–3.7)	5.3
Parkinsonism	++	++	+	7,8-dihydrobiopterin (<18 nM)	2
Dystonic features	-	-	-	Tetrahydrobiopterin (18–53 nM)	3
Levodopa response	+++	+++	++	Total neopterin (10–31 nM)	19
Levodopa induced dyskinesias	+	++	+	5-Methyl tetrahydrofolate (26–118 nM)	40
Intellectual disability	+ (IQ 68)	± (IQ 71)	+ (IQ n.a.)	3-O-Methyl-dopa (<50 nM)	35
Education	6 (scholastic performance below average)	8 (scholastic performance below average)	8	L-Dopa (<15 nM)	6
Cognitive dysfunction	- Normal (MMSE 28/30, n.v>24) one year before death	+ Mild global impairment (MMSE 22/30, n.v>24) with mild frontal-lobe (FAB 12.1/18, n.v>13.4) and visuo-spatial dysfunction	+	5-Hydroxytryptophan (<10 nM)	<2
				Phenylalanine (7–11 µM)	74
				Urine	
Psychiatric features	None	Anxiety/depression	Psychosis (hallucinations, delusions)	Neopterin (0.2–1.7 mmol/molKrea)	0.4
Sleep Disorders	None	++ ^c	++		
Fatigue	None	+++	+++	Biopterin (0.5–2.7 mmol/molKrea)	0.9
Brain MRI	Normal	Normal	Normal		
Presynaptic nigrostriatal Imaging	F-Dopa PET. Mild non-progressive reduction	DAT SPECT normal	DAT SPECT normal	%B = 100*B/(N+B) (49–85)	69
				Dried blood	
Brain metabolism PET	n.a.	Normal	n.a.	DHPR activity (>1.1 mU/mg Hb)	1.4

^a Normal ranges are reported in brackets; ^b Under chronic levodopa treatment; ^c Sleep disturbances responded to 5-Hydroxy-Tryptophan (dose of 1mg/kg/day, slowly titrated from 25 mg to 75 mg/day); Abbreviations: AAO, Age at onset; FAB, Frontal assessment Battery; MMSE, Mini Mental State Examination; n.a. data not available; n.v., normal values; PD; Parkinson's disease; PET, positron emission tomography; SPECT, single photon emission computed tomography.

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Author Contributions

L.S., I.G., and R.C. contributed to acquisition and analysis of data and to drafting the text and preparing the figures. R.A. and G.S. contributed to data analysis and drafting the text. L.P., V.R., A.Y., V.S., J.S., A.P., J.F., K.N., N.H., A.R., A.H.R., S.G., and N.B. contributed to acquisition and/or analysis of data. M.J.F. and S.D. contributed to conception and design of the study. L.S., I.G., R.C., and N.B. contributed equally to this work. A.H.R., and S.D. contributed equally to this work.

Potential Conflicts of Interest

Nothing to report.

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