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Short communication

Parkinsonism, cognitive deﬁcit and behavioural disturbance caused by a novel mutation in the polymerase gamma gene



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# a b s t r a c t

Polymerase γ (POLG) is the enzyme responsible for the replication and maintenance of mitochondrial DNA (mtDNA). Mutations in the *POLG1* gene can lead to mitochondrial dysfunction, producing a wide range of neuro- logical and non-neurological phenotypes. Neurological manifestations include ataxia, muscular weakness, epi- lepsy, progressive external ophthalmoplegia (PEO), ptosis, neuropathy, psychiatric disorders and, more rarely, parkinsonism. We present the case of an 80-year old female patient with a history of PEO, ptosis, childish behav- iour, obsessive disorder, cognitive decline, and parkinsonism. A comprehensive study showed striatal dopamine deﬁciency on DaT Scan and ragged red ﬁbres as evidenced by Gomori staining in a biopsy of the biceps brachii. Multiple deletions of mtDNA were detected, and sequencing of the *POLG1* gene identiﬁed a novel substitution,

2834ANT, in exon 18, changing the p.His945Leu amino acid. *In silico* analysis using PolyPhen-2 ([http://](http://genetics.bwh.hardvard.edu/pph2/) [genetics.bwh.hardvard.edu/pph2/](http://genetics.bwh.hardvard.edu/pph2/)) predicted that this change is probably damaging, with a score of 1.0 (0–1).

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1. Introduction

Mitochondrial respiratory chain dysfunction can cause a variety of diseases known as mitochondrial disorders. Polymerase γ (POLG) is the enzyme responsible for the replication and repair of mitochondrial DNA (mtDNA). Pol γA, the catalytic core of the enzyme, is encoded by the nuclear *POLG1* gene. Mutations of this gene are associated with mul- tiple deletions and/or depletion of mtDNA, which may lead to impaired energy production in the mitochondria and the so-called POLG syndromes [[1]](#_bookmark8). Since the discovery of the gene in 1996, more than 100 pathogenic mutations have been linked to a wide range of non- neurological and neurological disorders. Among the neurological mani- festations, there is an overlapping phenotypic spectrum that may include myopathy, neuropathy, ptosis, epilepsy, muscle pain, ataxia and progressive external ophthalmoplegia (PEO). Although rare, cases of parkinsonism have also been described in association with *POLG1* mutations. We report on a patient with parkinsonism, PEO, ptosis, and

*Abbreviations:* POLG, polymerase γ; mtDNA, mitochondrial DNA; PEO, progressive external ophthalmoplegia; PD, Parkinson's disease

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behavioural and cognitive abnormalities associated with a novel muta- tion in the *POLG1* gene.

1. Case report

The patient is an 80-year-old female, and the third of ﬁve siblings. She was born at term after an uneventful pregnancy and labour. Her family history was positive for external ophthalmoplegia with bilateral ptosis and behavioural disturbances in only one of her brothers. Her mother suffered repetitive abortions, but other disorders were not known in either of her parents, who were not consanguineous, as reported by the patient. She ﬁrst presented with progressive bilateral ptosis in her forties and received corrective left eyelid surgery with suboptimal outcome, refusing further interventions. She underwent bilateral cataract extraction at the age of 67. She demonstrated childish behaviour and learning difﬁculties throughout her adult life, as well as compulsive habits such as gathering items over the last twenty years. She also suffered progressive cognitive decline, with difﬁculties in performing her habitual tasks and a degree of social impairment (lack of interaction, indifference, etc.) during the past three years. In the last year, right hand rest tremor and clumsiness were observed. In addition, a loss of facial expression had become evident in the last few years.

Physical examination showed bilateral ptosis with right predomi- nance, PEO, dysphonia, right hand rest tremor, bilateral mild rigidity

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and bradykinesia in the upper extremities. No cerebellar or pyramidal signs were found. The patient's Mini Mental State Examination score was 22/30. Neuropsychological tests revealed cognitive impairment with executive dysfunction, language domain impairment and mild apraxia. Serum analyses showed a total CK activity of 92 U/l (normal ≤ 169). Other serum parameters, including the levels of pyruvate, copper, ceruloplasmin, folic acid, vitamin B12 and thyroid hormones, were normal. A brain MRI scan revealed moderate enlarge- ment of the ventricles and diffuse brain atrophy. Bilateral striatal dopa- mine deﬁciency, which was most marked in the left putamen, was evidenced by N-ﬂuoropropyl-2β-carbomethoxy-3β-4-[123I]iodophenyl- tropane SPECT. The patient was initiated on levodopa/carbidopa (300/75 mg per day), to which she exhibited a partial response (mild reduction in bradykinesia and rigidity). Electromyography and nerve con- duction studies showed no abnormalities, and echocardiography revealed no signiﬁcant disturbances. A mitochondrial disorder was suspected, and a muscle biopsy of the biceps brachii demonstrated ragged red ﬁbres based on Gomori staining ([Fig. 1](#_bookmark6)). Southern blot hybridization analysis identiﬁed multiple mtDNA deletions that were conﬁrmed using the long-PCR technique. Given this ﬁnding, the *POLG1* gene was sequenced by the standard Sanger method. Total DNA was extracted from blood following written informed consent, and using standard methods. Direct sequencing of PCR amplicons of coding exons of *POLG1* was performed as described previously [[2]](#_bookmark8). A novel heterozygous nucleotidic variant, c.2834AN T, was identiﬁed in exon 18 of the *POLG1* gene, producing the p.His945Leu amino acid change. *In silico* analysis using PolyPhen-2 (<http://genetics.bwh.hardvard.edu/pph2/>) predicted that this change was probably damaging, with a score of 1.000 (sensitivity: 0.00; speci- ﬁcity: 1.000). In addition, an analysis conducted in control subjects in-

cluded in the 1000 Genomes free database using the tool “Variant

Effect Predictor” ([http://browser.1000genomes.org/Homo\_sapiens/](http://browser.1000genomes.org/Homo_sapiens/UserData/UploadVariations) [UserData/UploadVariations](http://browser.1000genomes.org/Homo_sapiens/UserData/UploadVariations)) determined that the nucleotide variant we have found in this patient was not present in any subject. A targeted mutational analysis for speciﬁc point mutations in mtDNA did not ﬁnd any of the following mutations: m.3243ANG in gene *MTTL1*; m.3460GNA in gene *MTND1*; m.8344ANG in gene *MTTK*; m.8993TNG,

m.8993TNC, m.9176TNC and m.9176TNG in gene *MTATP6*; m.10158TNC and m.10191TNC in gene *MTND3*; m.11777CNA,

m.11778GNA and m.11832GNA in gene *MTND4*; m.13513GNA and m.13514ANG in gene *MTND5*; and m.14459GNA, m.14482CNA, m.14482CNG, m.14484TNC, and m.14487TNC in gene *MTND6*.

1. Discussion

We report on a case of parkinsonism, PEO, ptosis, and behavioural and cognitive abnormalities associated with a novel mutation in the *POLG1* gene. In contrast to other manifestations, parkinsonism is less frequently observed in mutations of this gene. It was ﬁrst described in ﬁve families, with some members presenting levodopa-responsive parkinsonism (n = 15), cataracts, ataxia and hypoacusis in different combinations. Two previously known mutations in the *POLG1* gene, as well as one novel mutation, were described in these patients. Two sib- lings with parkinsonism underwent [18F]β-CFT PET that revealed re- duced uptake in the putamen and caudate, in contrast to their healthy siblings who had normal uptake [[3]](#_bookmark8). Since this initial report, 19 more

cases of parkinsonism in *POLG1* gene mutation carriers have been re- ported. Their main clinical features are summarized in [Table 1](#_bookmark7) [[1,4–20]](#_bookmark8). Previous literature shows that all except seven cases presented with PEO and/or ptosis, signs that were also present in our patient. Muscle weakness, neuropathy and ataxia were also common features, not pres- ent in the case we report. Similar to our patient, the average age of onset

of the neurological signs was between the 3rd and 4th decades, and par- kinsonism usually appeared after several years, tended to improve with dopaminergic treatment, and was associated with a striatal dopaminer- gic deﬁcit as observed in DaT Scan studies in a few cases. Other features, such as cognitive dysfunction or psychiatric symptoms including depression, anxiety, and obsessive disorders, were much less prevalent. In our patient, behavioural (childish performance) and cognitive abnor- malities (learning difﬁculties) were probably the initial manifestations of the disease, emerging in early adulthood, although these symptoms had not previously been investigated. The clinical picture subsequently evolved, with two well recognized phases: an initial stage in which PEO

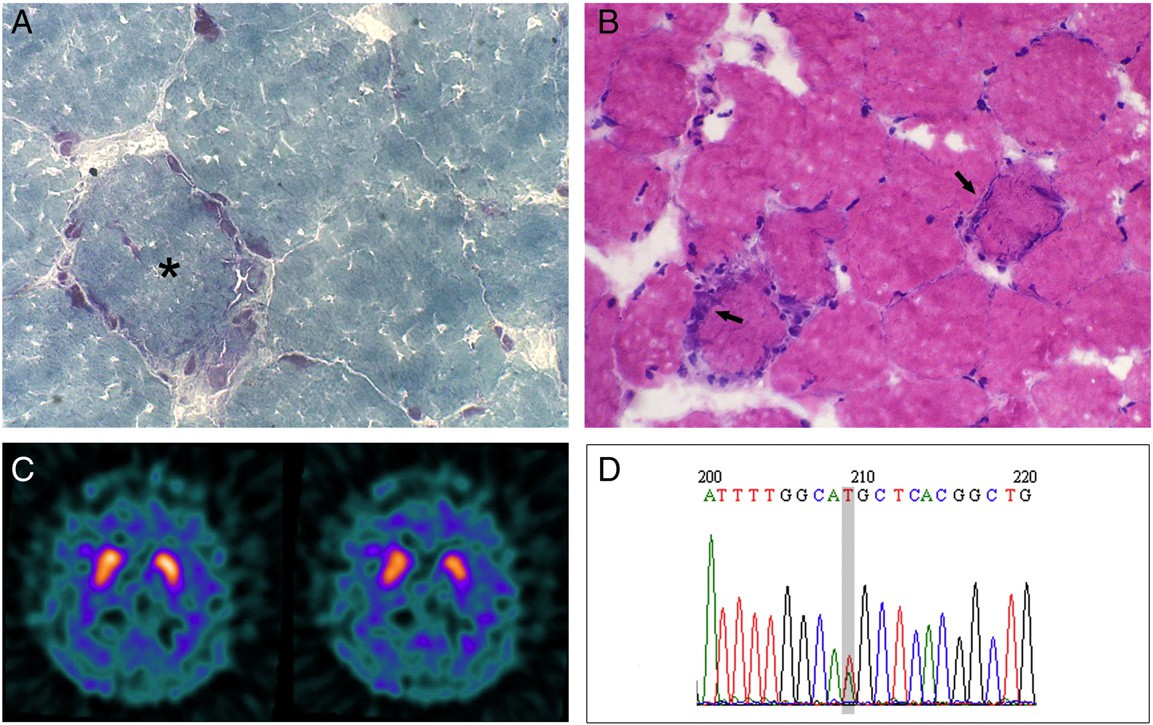


Fig. 1. Biceps brachii muscle biopsy specimen showing ragged red ﬁbre (Gomori trichrome stain; original magniﬁcation ×200) (A, \*) and muscle ﬁbres with a peripheral rim due to mitochondrial proliferation (haematoxylin and eosin stain; original magniﬁcation ×100) (B, arrows). N-ﬂuoropropyl-2β-carbomethoxy-3β-4-[123I]iodophenyl-tropane SPECT showing reduced uptake in the left putamen (C). Electropherogram of the reverse strand sequence of exon 18 of the *POLG1* gene, demonstrating a c.2834ANT heterozygous substitution (D).

Table 1

Summary of reported cases of parkinsonism due to mutations in the *POLG1* gene. Abbreviations: PEO: progressive external ophthalmoplegia; PTO: ptosis; NRP: neuropathy; EPI: epilepsy; ATX: ataxia; WKN: weakness; DYS: dysphagia; DYT: dystonia; CAT: Cataracts; and POF: premature ovarian failure.

Author/Year Genotype

Gender/age

Parkinsonism

Presenting signs Neurological clinical manifestations DAergic

DaT

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|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | (substitution) | of onset | onset |  | PEO | PTO | NRP | EPI | ATX | WKN | DYS | DYT | CAT | POF | Other | treatment  response | scan |
| Luoma et al. (2004) | N468D | Male/30 | 36 | Ptosis and PEO | + | + | + |  |  | + |  |  | + |  | Exercise intolerance | NA | NA |
|  | A1105T |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | N468D | Female/b33 | 46 | Ptosis and PEO | + | + |  |  |  | + |  |  |  | + | Depression | + | NA |
|  | A1105T |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | N468D | Male/21 | 36 | Ptosis and PEO | + | + | + |  |  |  |  |  |  |  | Exercise intolerance, pain | + | NA |
|  | A1105T |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | T955C | Female/10 | 46 | Ptosis and PEO |  |  |  |  |  |  |  |  | + |  | Depression, dementia | + | NA |
|  | T955C | Female/30 | 60s | Ptosis and PEO | + | + |  |  |  | + |  |  |  | + | Hypoacusia | + | NA |
|  | T955C | Female/22 | b59 | Ptosis and PEO | + | + | + |  | + |  |  |  | + | + | Prebyacusis | + | NA |
|  | T955C | Male/35 | 50s | Ptosis and PEO | + | + | + |  | + | + |  |  | + |  |  | + | NA |
|  | T955C | Male/25 | 58 | Ptosis and PEO | + | + | + |  | + | + |  |  | + |  |  | NA | NA |
|  | T955C | Female/23 | 59 | Ptosis and PEO | + | + | + |  | + | + |  |  | + | + | Mental retardation | + | NA |
|  | T955C | Female/20s | 62 | Ptosis and PEO | + | + |  |  | + |  |  |  | + | + |  | + | NA |
|  | T955C | Female/NA | NA | NA | NA | + | NA | NA | NA | NA | NA | NA |  |  | NA | NA | NA |
|  | T955C | Male/NA | b50 | Ptosis and PEO | + | + | + |  |  | + |  |  |  |  |  | NA | NA |
|  | T955C | Male/30 | 68 | Ptosis and PEO | + | + | + |  |  | + |  |  | + |  |  | + | NA |
|  | T955C | Male/49 | 72 | Ptosis and PEO | + | + | + |  |  | + |  |  | + |  |  | + | NA |
|  | A1105T | Female/54 | 75 | Ptosis and PEO | + | + |  |  |  | + |  |  | + |  | Goitre | NA | NA |
| Mancuso et al. (2004) | Y831C | Female/28 | 47 | Ptosis and diplopia | + | + | + |  |  | + |  |  |  |  | Exercise intolerance | NA | NA |
| Tzoulis et al. (2006) | W748S | Female/55 | NA | Epilepsy | + |  |  | + | + |  |  |  |  |  | Nystagmus | NA | NA |
| Pagnamenta et al. (2006) | Y955Z | Female/20s | NA | Ptosis and PEO | + | + |  |  | + | + |  |  |  |  |  | NA | NA |
| Davidzon et al. (2006) | G737R | Female/26 | 26 | Dystonia, parkinsonism and |  |  | + |  |  | + |  | + |  |  |  | + | NA |
|  | R853W |  |  | weakness |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | G737R | Female/20 | 26 | Dystonia, parkinsonism |  |  | + |  |  | + |  | + |  |  |  | + | NA |
|  | R853W |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hudson et al. (2007) | S510K | Male/46 |  | Fatigue and ptosis | + | + |  |  | + |  |  |  |  |  | Hypoacusia | NA | NA |
|  | L463F |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Invernizzi et al. (2008) | W917R | Male/30 | 50 | Ptosis and PEO | + | + | + |  |  | + | + |  |  |  | Dysphonia | + | + |
|  | M429L |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Remes et al. (2008) | W748S | Male/46 | 60 | Gait and balance difﬁculties | + |  | + |  | + |  | + | + |  |  |  | + | + |
|  | (homozygous) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Betts-Henderson et al. | S1104C | Male/22 | 51 | Ptosis | + |  |  |  |  | + | + |  |  |  | Dysarthria, cognitive impairment | + | NA |
| (2009) | G848S |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Synofzik et al. (2010) | T955C | Female/45 | 52 | PEO, ptosis and exercise intolerance | + | + |  |  |  | + |  |  |  |  | Depression | + | + |
| Sato et al. (2011) | H277L | Male/50s | 60 | Ptosis and diplopia | + |  |  |  |  |  |  |  |  |  |  | + | NA |
|  | R943C |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Milone et al. (2011) |  | Male/40s | NA | Hypoacusia, exercise intolerance | + | + |  |  |  | + |  |  | + |  | Dysphagia, hypoacusia, exercise intolerance | + | NA |
| Gurgel-Giannetti et al. | R953C | Male/20 | 33 | PEO and gait abnormality | + |  | + |  |  |  |  |  |  |  | Cognitive impairment, depression, psychotic | + | NA |
| (2012) |  |  |  |  |  |  |  |  |  |  |  |  |  |  | symptoms |  |  |
| Lax et al. (2012) | A467T | Male/50 | NA | NA | + |  | + | + | + |  | + |  |  |  | Dementia, dysarthria | NA | NA |
|  | X1240C |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Brandon et al. (2013) | F943H | NA/63 | 67 | PEO, ptosis, cataracts, vision loss, | + | + | + |  | + |  |  |  | + |  | Vision loss, dysarthria, cardiomyopathy, | + | NA |
|  |  |  |  | dysarthria, |  |  |  |  |  |  |  |  |  |  | headache, hypoacusia |  |  |
|  |  |  |  | dysphagia, cardiomyopathy and |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  | depression |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | R303W | Male/66 | 70 | Nocturnal cramps, reduced dexterity | + |  |  |  |  | + |  |  |  |  |  | NA | NA |
| Dolhun et al. (2013) | K512M | Male/30s | NA | Ptosis and double vision | + | + |  |  |  |  |  |  |  |  | Dementia, camptocormia | + | NA |
| Bandettini di Poggio et al. | A899T | Female/26 | NA | Ptosis and PEO | + | + | + |  | + | + |  |  |  |  | Anxiety and obsessive disorder | + | + |
| (2013) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mukai et al. (2013) | Y955C | Female/30s | 50 | Ptosis and PEO | + | + | + | + | |  |  | | |  | | + | NA |
|  | Y955C | Female/50s | 65 | Ptosis and PEO | + | + | + |  | | + |  | | |  | | + | NA |
| Ylönen et al. (2013) | P587L | Male/49 | 49 | Parkinsonism |  |  |  |  | |  |  | | | Muscle cramps, hypoacusia | | + | + |
|  | W748S |  |  |  |  |  |  |  | |  |  | | |  | |  |  |
| Delgado-Alvarado et al. | H945L | Female/30s | 78 | Behaviour disturbances, PEO, ptosis | + | + |  |  | |  | + | | | Obsessive disorder | | + | + |
| (2014) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

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and ptosis appeared in her 3rd decade, and a second one in which obses- sive disorder developed some years later, followed by cognitive decline and parkinsonism, in her 6th decade. It has to be admitted that although all these clinical manifestations can be explained by the genetic variant we report, the lack of genetic study in the sibling with a similar clinical picture or in any other relative (she only has a healthy sister who has declined to be studied) impedes to assess the segregation of this clinical picture. In addition, parkinsonism could be a coexisting condition, par- ticularly if we consider the prevalence of this entity at the age of our pa- tient. Be that as it may, similarly to the patient we describe, it has to be noticed that in contrast to typical PD, parkinsonism associated with *POLG1* mutations has additional features, accounting for a more com- plex clinical phenotype and departing from a diagnosis of PD. On this re- gard, cognitive impairment is a particularly interesting feature as it is observed in other mitochondrial disorders [[21,22]](#_bookmark10), suggesting that the complexity of its pathogenesis extends beyond the dopaminergic system.

Although the exact mechanism by which mitochondrial dysfunction leads to parkinsonism is not clearly understood, accumulating evidence suggests that it plays a crucial role in the pathogenesis of Parkinson's disease (PD). 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and rote- none, inhibitors of the mitochondrial respiratory chain complex I, have been reported to cause parkinsonism in humans and other pri- mates [[23]](#_bookmark10). Furthermore, several of the genes causative of familial forms of PD are involved in mitochondrial function, including Pink1, parkin and DJ-1 [[23]](#_bookmark10). In addition, mtDNA deletions have been shown in substantia nigra (SN) neurons of PD patients, suggesting that this may be a predisposing factor to the death of these dopaminergic neu- rons, which are believed to be more vulnerable to mitochondrial dys- function than other types of neurons [[24]](#_bookmark10). The extent to which *POLG1* variants may play a role in the pathogenesis of PD is not well established, but it has been shown that among 441 cases of early onset PD, two cases carried compound heterozygous mutations and the frequency of affected siblings was higher in patients carrying het- erozygous *POLG1* mutations [[19]](#_bookmark9). In addition, rare variants of the *POLG1* CAG-repeat (non-10/11Q variants) in the exon 2 which encodes a polyglutamine tract, are more frequent in PD patients than in controls

[[25–29]](#_bookmark10).

Human Pol γ is a heterotrimer comprising a catalytic subunit, Pol γA, and a dimer of an accessory subunit, Pol γB. Pol γA is a 140-kDa poly- peptide which has three major domains: a N-terminal Exo domain (which contains the exo active site), a C-terminal Pol domain (which contains the pol active site), and a spacer domain (which separates the Exo and Pol domains in primary sequence). The clinical phenotype of *POLG1* mutations depends on the severity of the resultant Pol γ func- tional defect and the zygosity of the nucleotide variant. A ﬁve-cluster model of Pol γ based on functional aspects has recently been designed, and is capable of predicting the pathogenic potential and biochemical defects of novel mutations [[30]](#_bookmark10). According to this model, the novel mu- tation reported here (p.His945Leu change) is placed in subcluster 1E

(residues 914–966), which acts to bind the correct deoxynucleotide tri-

phosphate substrate (dNTP). Within this region there is a motif known as the Pol B motif (residues 943–958) which establishes speciﬁc con- tacts with correctly base-paired dNTP in the closed conformation. Muta- tions at this level disrupt the speciﬁc contacts with the incoming dNTP and reduce the ﬁdelity without affecting DNA binding afﬁnity. Accord- ingly, mutations at this site are capable of competing for dNTP binding

with wild-type Pol γ but are unable to polymerize nucleotides effective- ly, causing mtDNA damage [[30]](#_bookmark10).

1. Conclusion

We report on a novel mutation in the *POLG1* gene which leads to an amino acid change, p.His945Leu, associated with parkinsonism accom- panied by a nigro-striatal dopaminergic deﬁcit and response to levodo- pa, cognitive disturbances, obsessive disorder, PEO and ptosis. *POLG1*

gene mutations should therefore be considered in cases of parkinsonism that display these characteristics.

Conﬂict of interest

The authors declare that they do not have any conﬂict of interest.

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