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Should *ITSN1* be considered as a Mendelian Parkinson's disease gene? Description of three novel families

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Rare loss-of-function variants in *ITSN1* were recently reported to confer a high risk for Parkinson's disease (PD). From our local large exome sequencing dataset of PD cases, we identified five carriers from three families. Clinical features of *ITSN1*-PD are typical and responsive to standard treatments. Additionally, we discuss whether *ITSN1* loss-of-function variants should only be considered as a high-risk factor or a Mendelian PD gene.

Main

ITSN1 is a multidomain scaffold protein that plays an important role in synaptic vesicle endocytosis, actin cell signaling, cytoskeleton rearrangements, and the regulation of RNA-binding proteins^{1,2}. Heterozygous loss-of-function (LOF) variants in *ITSN1* were first reported to cause a childhood-onset disease with global developmental delay, autism spectrum disorder, and intellectual disability³. Recently, two different articles using overlapping large Parkinson's disease (PD) datasets have reported a strong association between *ITSN1* LOF variants and Parkinson's disease (PD), with odds ratios ranging from 7.3 (95% confidence interval [3.5–15.2])⁴ to 10.5 (95% confidence interval [5.2–21.34])⁵. Clinical information was limited, and whether *ITSN1*-PD is associated with a specific phenotype responsive to treatments remains elusive.

Here, in a cohort of 2076 PD patients who underwent whole-exome sequencing (WES), we report phenotypic and genetic data of five affected carriers from three novel families, indicating that *ITSN1* may be considered a Mendelian PD gene with reduced penetrance.

In pedigree A, a proband (III-2) and her mother (II-3) developed PD at 40 years (Fig. 1). The grandmother died at the age of 94 years, and the grandfather at 60 years after an accident without any PD symptoms. Clinical information is limited for II-3. Motor and cognitive features slowly worsened, and she died at the age of 62 years in a bedridden state. For III-2, the disease started with a rapidly progressing tremor of the left hand with a weak response to L-dopa. Cerebral magnetic resonance imaging (MRI) was normal. Deep brain stimulation (DBS) initiated at 49 years of age had a positive effect on the tremor. Clinical examination at 65 years showed

dysphonia and walking difficulties. At that time, she had a mild distal tremor, no hypertonia, no urinary impairment, and neither pyramidal nor cerebellar signs. At her last examination at the age of 66 years, she had orthostatic hypotension with frequent falls. DBS remained efficient on motor symptoms. She was treated with 575 mg of L-dopa equivalent daily dose (LEDD), and the Unified Parkinson's Disease Rating Scale (UPDRS) III motor score was 40/108 (no information whether on or off). WES identified a frameshift duplication of a single nucleotide in *ITSN1* (NM_003024.3:c.472dup; p.Leu158ProfsTer3) in individual III-2 located in exon 6/40 (Supplementary Fig. 1). This variant has three occurrences in gnomAD v4.1 (allele frequency: 2.052×10^{-6}) and none in a cohort of 4854 healthy French individuals^{6,7} and is absent from the ClinVar database and literature. WES did not find any pathogenic or likely pathogenic variants in any known PD gene. DNA was not available from any other family member.

In pedigree B, six members were affected with PD. DNA was available for two of them. III-6 is a female who presented at 62 years with a right-hand resting tremor. Cerebral computed tomography scan was normal. The initial response to L-dopa was positive (assessed at 65%), and the disease evolved slowly. At the last examination at the age of 72 years, in addition to tremor, she had an akinetorigid syndrome without any atypical neurological signs. UPDRS III was 13/108 on and 20/108 off, and the Hoehn and Yahr stage was 2/5. She had urinary incontinence and urgenturia. LEDD was 300 mg without limb-induced dyskinesia or motor fluctuations. Her son (IV-6) started at 30 years with an asymmetrical resting tremor of the left upper limb and slowly evolved. At the age of 40 years, he had no cognitive

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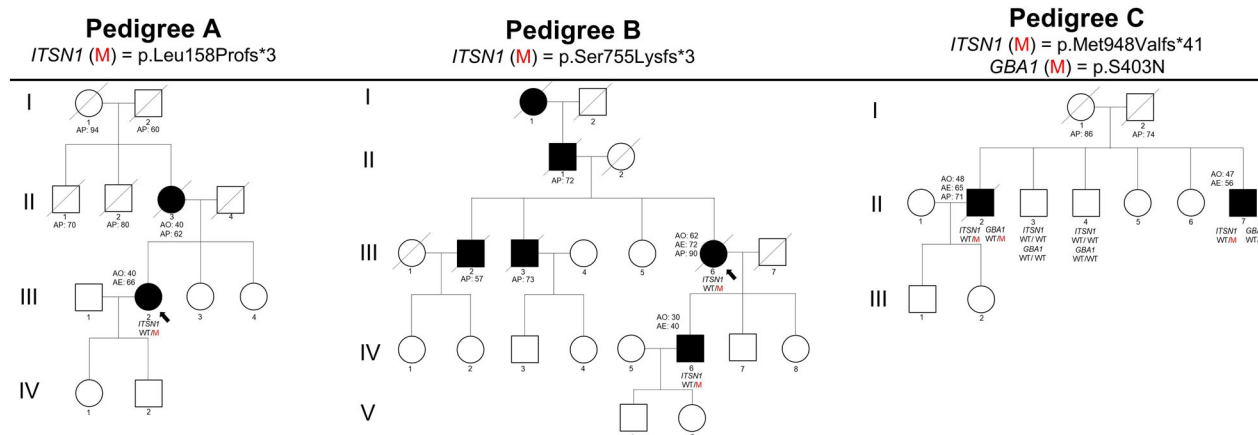


Fig. 1 | Family pedigree of *ITSN1* loss-of-function variant carriers. The first two pedigrees suggested an autosomal dominant inheritance, while the third suggested an autosomal recessive inheritance. Of note, the two siblings in pedigree C were

carriers of the *GBA1* p.S403N variant classified as “mild risk” in Gaucher disease. The unaffected individuals II-3 and II-4 carried neither the *ITSN1* nor the *GBA1* variant. AO age at onset, AP age at passing, AE age at last examination.

impairment (mini mental status examination score 30/30), no urinary impairment, and no atypical signs. UPDRS III was 24/108 on, and the Hoehn and Yahr stage was 2/5. WES revealed that they both carry a frameshift duplication of one nucleotide in *ITSN1* (NM_003024.3:c.2263dup; p.Ser755LysfsTer3) located in exon 19/40 (Supplementary Fig. 1). This variant is absent from gnomAD v4.1 and from a cohort of 4854 healthy French individuals^{6,7}, ClinVar database, and literature. WES did not find any pathogenic or likely pathogenic variants in any known PD gene.

In pedigree C, two males (II-2 and II-7) from a three-generation pedigree were affected. Their parents died at the ages of 86 and 74 years without any PD symptoms and were not related. The disease started in their sons at the ages of 48 years (II-2) and 47 years (II-7). For the proband (II-7), the disease started with a left upper and lower limb akinesia. Cerebral MRI was normal. Rapidly, tremor and rigidity were present. He was on 150 mg LEDD of dopaminergic agonists. Hoehn and Yahr stage was 1/5. Nine years after disease onset at 56 years, he suffered from an akinetorigid syndrome. No atypical sign was noted. UPDRS III was 8/108 off. At that time, he had 400 mg LEDD. For II-2, the disease started with an asymmetrical akinesia and then slowly worsened. DBS was initiated 13 years after disease onset at 61 years. Four years later, at 65 years, he had an additional tremor and rigidity. No atypical sign had developed; however, he had cognitive impairment (no score from any scale available) and urinary incontinence. LEDD was 200 mg with dyskinesia and motor fluctuations. At that time, UPDRS III score was assessed at 10/108 on, and the Hoehn and Yahr stage was still at 1/5. WES in both individuals identified a frameshift heterozygous deletion NM_003024.3:c.2842_2843del p.Met948ValfsTer41 located in exon 23/40 (Supplementary Fig. 1). Allele count in gnomAD v4.1 was eight (allele frequency: 5.472×10^{-6}) and none in a cohort of 4854 healthy French individuals^{6,7}, and this variant was absent from the ClinVar database. This variant was already reported as being de novo in an individual with autism spectrum disorder⁸. Both affected individuals from pedigree C also carried a missense mutation in *GBA1* (NM_000157.4:c.1208G>A; p.S403N). Although this mutation was already reported in six publications in the MDSgene database (website visited on 02/10/25), five of them report the affected siblings described in this study; therefore, only one other individual has been reported in the literature^{9,10}. This mutation is considered “mild” in the *GBA1* classification¹¹. Subsequent segregation analysis revealed that the unaffected individuals II-3 and II-4, who are now in their 70s, carried neither the *ITSN1* nor the *GBA1* variants (Supplementary Fig. 1). DNA was not available from any other family member.

Initially, Skuladottir et al. identified 18 PD carriers of *ITSN1* LOF variants⁴. Subsequently, Spargo et al. replicated this finding in overlapping cohorts, providing additional evidence of an association between *ITSN1* LOF variants and PD in *Drosophila* and in vitro assays⁵. This study reports

the first *ITSN1* multiplex pedigrees, provides details on the phenotype, and further discusses whether *ITSN1* is a risk factor or a Mendelian gene for PD.

On the clinical level, no atypical symptoms for PD were identified. Instead, *ITSN1*-PD motor phenotype appears to be typical, with a good response to dopaminergic treatments. DBS in two cases was efficient on motor symptoms, suggesting DBS might be a good therapeutic option for *ITSN1*-PD. Non-motor symptoms are not at the forefront of *ITSN1*-PD phenotype. Disease course is slow, since after about 10 years, the available UPDRS motor score ranged from 8 to 25 (pedigrees B and C). Interestingly, this pattern is similar to the one reported in three *ITSN1*-PD cases by Spargo et al.⁵. The mean ages at onset of PD in carriers reported by Skuladottir et al. and Spargo et al. were 62 and 64 years, respectively, earlier than non-carriers (70 years, $p = 0.022$ and $p = 0.05$, respectively)^{4,5}. Here, median age at onset is 47 years, with great variability (range 30–62). Interestingly, pedigrees A and C show a high concordance in age at onset (and disease course as well). In contrast, the gap in pedigree B is 32 years between the two affected carriers. Therefore, *ITSN1*-PD shows intrafamilial and interfamilial variability. Other factors, genetics or environmental, likely play a role.

The cumulative *ITSN1* LOF variant frequency in the various PD cohorts ranges between 0.11%⁴ and 0.24%⁵, about 6–13 times greater than the ~0.018% in control populations⁴. In our cohort, we find a similar frequency of proband carriers of *ITSN1* LOF variants (3/2076, 0.14%). When we only consider pedigrees compatible with autosomal dominant inheritance ($n = 454$), the frequency reaches 0.7%. Several elements show that *ITSN1* LOF variants may be considered as a Mendelian PD gene rather than a high-risk factor. First, the odds ratio for *ITSN1* LOF variants may be underestimated due to the potential future PD conversion of some unaffected carriers in both studies^{4,5}. Second, in the latest reports of genetic mutations in large PD cohorts^{12–14}, *GBA1* risk and mild variants as well as *LRRK2* G2019S were considered to contribute to monogenic PD, even though the odds ratios for these variants are estimated to be lower than or equivalent to *ITSN1* LOF variants, ranging from 1.4 to 7.8 for the former, and about 10 for the latter^{11,15}. Third, although segregation analysis was not performed, six *ITSN1*-PD cases from the study of Spargo et al. reported a first-degree family history of PD and/or Alzheimer’s disease, among which four specifically reported PD⁵. The discovery of three novel families provides new evidence for the monogenic hypothesis because all genotyped affected individuals are carriers of *ITSN1* LOF variants. However, this hypothesis should be taken with caution for several reasons. First, the existence of several unaffected parents that are likely to be carriers in pedigrees A and C, with ages ranging from 60 to 80 years, points toward a censor effect or an age-dependent and reduced penetrance. Second, the lack of DNA from the affected mother (II-3) in pedigree A did not allow for the determination of her genotype. Third, the age at onset difference between III-6 and IV-6 in

pedigree B (30 years) could be the consequence of a different cause, such as biallelic pathogenic variants in a recessive gene for IV-6. However, WES did not identify any additional variants in known AR-EOPD genes. Fourth, a *GBA1* variant was identified in the two affected individuals of pedigree C. Although this variant was found only once in an individual affected with PD¹⁰, it is known to contribute to Gaucher disease type I (non-neurological) when associated with another pathogenic variant and was demonstrated to result in a marked reduction in enzymatic activity^{16,17}. Therefore, it is possible that this variant plays a role in PD in general and that it may influence the phenotype and penetrance of the *ITSN1* LOF variant in this pedigree. Finally, apart from *GBA1*, we were not able to experimentally demonstrate the postulated haploinsufficiency of *ITSN1* LOF variants, either in terms of mRNA expression levels or nonsense-mediated decay involvement, due to a lack of available material.

Nevertheless, this study demonstrates that *ITSN1* LOF variants may be responsible for autosomal dominant familial PD with reduced penetrance, which will help genetic counseling of *ITSN1*-PD cases. The description of additional families with positive segregation is required to further investigate the Mendelian inheritance hypothesis for *ITSN1* LOF variants.

Methods

Study participants

Participants were selected based on their early age at onset and their family medical history from a large cohort of 2076 PD probands who underwent WES and were enrolled through the French Parkinson Disease genetics Study Group and international collaborations between 1990 and 2024^{18,19}. PD was diagnosed among the cohort by clinical assessment based on the diagnosis criteria of the UK Parkinson's Disease Society Brain Bank.

Written informed consent was obtained from participants, and the local ethics committee CCPPRB (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) of the Groupe Hospitalier Pitié-Salpêtrière, Paris, France approved genetic analyses.

WES and Sanger sequencing

WES was performed on individuals III-2 (pedigree A), III-6 and IV-6 (pedigree B), II-2 and II-7 (pedigree C) as previously described (Fig. 1)^{20,21}. In brief, DNA was extracted from blood. Exons were captured using the Roche Seqcap Ez MedExome (Roche Diagnostics Corporation, Indianapolis, IN) kits, followed by 150-bp paired-end sequencing performed on an Illumina NovaSeq 6000 instrument (Illumina Inc., San Diego, CA). FastQC was used to check the quality of the reads, and low-quality reads were removed using Trimmomatic. The DRAGENTM DNA pipeline v3.8.4 (Illumina) was used to align the reads to the human hg19 reference genome, mark the PCR duplicates, and perform the calling of the copy number variants (CNVs) using the panel of normals approach. Within the data set, each sample's depth of coverage is first corrected for the GC bias and then normalized against the depth of all the unrelated samples in the same sequencing batch. Only the events passing the default filters were considered for analysis and annotated with AnnotSV v3.1.1. Single-nucleotide variants were analyzed according to ACMG guidelines and CNVs to ACMG/AMP guidelines^{22,23}. *ITSN1* LOF variants identified, as well as the *GBA1* variant in pedigree C, were confirmed by Sanger sequencing according to the manufacturer's guidelines (Supplementary Fig. 1).

Data availability

Data from this manuscript are available upon request.

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Author contributions

G.C., C.T., F.C., E.L., S.L., A.B.: designed, reviewed, and critiqued the study. G.C., C.T., L.W., F.C.: performed the analysis of the genomic sequencing data. A.D., M.P., B.D., G.M., F.C.-D.: clinically followed the participants of this study. A.L.: reviewed and critiqued the analysis.

Competing interests

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Additional information

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