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Identification of a large homozygous *VPS13C* deletion in a patient with early-onset parkinsonism

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Letter to the Editor

We report the clinical symptoms and the causal genetic defect of an isolated patient with parkinsonism and sensorimotor polyneuropathy that was born to healthy parents

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Author's roles

Research Project (1): A. Conception (CP-R, HD), B. Organization (CP-R), C. Execution (HD, PB, AT, LJA, SR-B, AHJ, CP-R). Clinical Assessments (2): A. Design (HD, AT, SR-B, AHJ) Execution (SR-B, AHJ), C. Review and Critique (HD, AT, SR-B, AHJ). WGS and Subsequent Molecular analyses (3). A. Design (CP-R), B. Execution (CP-R, PB, LJA). Manuscript preparation (4). Writing of the first draft (CP-R), B. Review and Critique (HD, PB, AT, LJA, SR-B, AHJ).

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The authors declare they have no conflict of interest.

(Supplementary material, Fig. 1A). Whole genome sequencing (WGS), performed and processed as described in the Supplementary Material, led us to the identification of novel and rare genetic variations, including 606 non-synonymous, 69 splice-site, 24 stop-gained, stop- and start-lost, and 111 frame-shift mutations, as well as 63 different genomic deletions/duplications. Because recessive alleles may be present in normal population, all homozygous and compound-heterozygous variants were explored and included in the analysis, but only 11 homozygous missense mutations were found to be present in our patient (Supplementary Table 2). Among the identified deletions/duplications, a large homozygous genomic deletion, comprising 50 coding exons (from exon 17 to exon 66) of the Vacuolar Sorting Associated Protein 13 (*VPS13C*) gene, which was previously identified mutated in families with asymmetric akinetic rigidity and cognitive impairment (Supplementary Table 3),^{1,2} was found in the patient's genome. This large deletion consisted of c.1353+3558_9106–7010del and resulted in p.Val452_Lys3035del, (NM_020821/NM_001018088). The deletion breakpoints (chr15: 62,189,609–62,289,207) and its segregation with disease status were later confirmed through *Sanger* sequencing (Figs. 1A, 1B), which also revealed a 7-bp insertion (GCACTTC) (Fig. 1A). Three *VPS13C* exons (exons 19, 35, 61) expanding the deletion breakpoints were also subject to copy number variation (CNV) quantification by performing droplet digital PCR (ddPCR; QX100 system, Bio-rad, USA) as previously described.³ Only the affected member showed no copies of the implicated exons, further confirming this large *VPS13C* deletion as the causal genetic defect in our reported patient (Fig. 1C).

Subsequently, the proximal and distal sequences (~2kb) to the breakpoints were examined to determine their homology (<https://www.ebi.ac.uk/Tools/msa/clustalo/>) and the presence of repeated sequences (<http://www.roadmapepigenomics.org/>), as these might help to elucidate its generating mechanisms.⁴ Short homologies and two long interspersed elements (LINE) of 6kb (L1PA3: chr15: 62,188,436–62,194,473) and 1.3kb (L2a: chr15: 62,289,333–62,290,611), respectively, were found to be located nearby the breakpoints, suggesting that this deletion was originated through transposable element insertions (TEI).⁵ Both proximal and distal regions showed weak transcription and were found to be enriched for the following chromatin marks: H3K4me3, H3K4me1, HeK9me3, H3K27me3.

Because the performed electrophysiological studies revealed a demyelinating sensory-motor polyneuropathy in favor of Charcot-Marie-Tooth (CMT) disease, we examined all genetic variation identified in the known CMT genes but only found previously reported benign variants (Supplementary Material and Table 4), suggesting that the identified *VPS13C* deletion might contribute to the CMT phenotype seen in our patient, which might help with the diagnosis of prospective *VPS13C* patients.

In summary, we report the identification and characterization of a large L1 retrotransposition-mediated *VPS13C* deletion in a patient with parkinsonism, further confirming the role of the *VPS13C* in the pathogenesis of PD. Besides the strong effect of the identified mutation on the protein, our patient showed normal cognitive status and a milder clinical picture than that observed in previously reported patients. Lastly, the hypothesis that the identified *VPS13C* deletion might be responsible for the CMT phenotype

seen in our patient needs to be further explored as it also might be caused by mutations in an unknown CMT gene.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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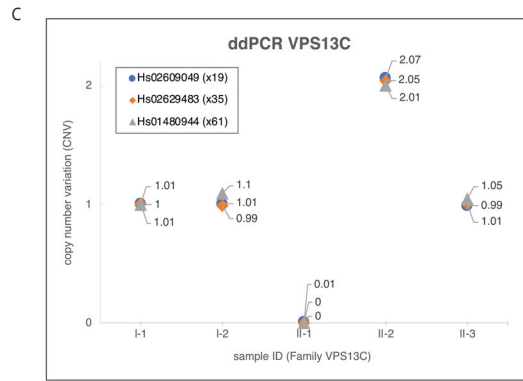
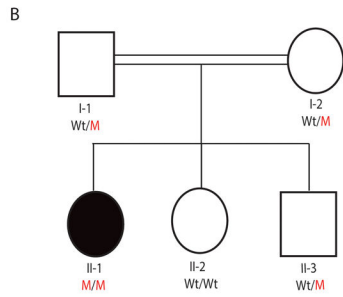
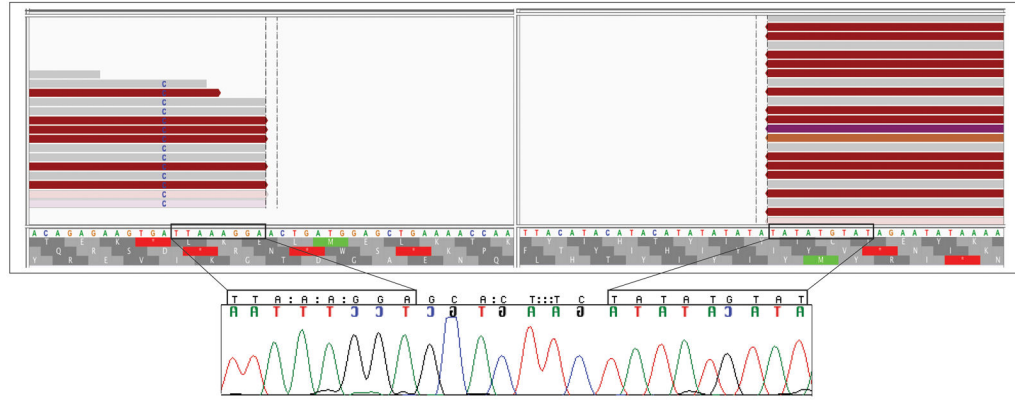
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A NG_027782.1(VPS13C_v001): c.1353+3558_9106-7010+7del



D **VPS13C isoform 2A (NP_065872.1): 3,753aa (85 exons)**
 insertion splice site missense deletion nonsense

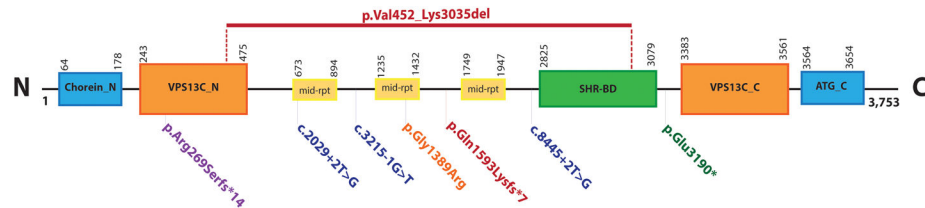


Fig 1. (A) WGS reads (Top) and *Sanger* chromatograms (Bottom) illustrating the large homozygous *VPS13C* deletion (Blank area, no reads) identified in an isolated patient with parkinsonism (<https://databases.lovd.nl/shared/variants/0000368891>). The WGS reads were visualized using the IGV tool. The *Sanger* chromatograms show the evidence of a 7-bp insertion between the deletion breakpoints (nucleotides between rectangles). The breakpoints of the deletion are highlighted with rectangles. (B) Pedigree of the family with parkinsonism and sensorimotor polyneuropathy. Wt/M indicates heterozygous carrier for the *VPS13C* large deletion; M/M indicates homozygous carrier; and Wt/Wt indicates non-carrier. Affected patient is represented with a black circle. (C) CNV plots of *VPS13C* exons 19, 35, and 61 obtained through ddPCR (QX100 system, Bio-rad) and corresponding taqman assays (Applied Biosystems) are shown. Homozygous Wt alleles are represented with a CNV score of 2 or close to 2, meaning both alleles carry a copy of the exon under

investigation; heterozygous mutant alleles are represented with a CNV score of 1 or close to 1, meaning only one allele carry a copy of the exon while the exon is absent in the other allele; homozygous mutant alleles are represented with a CNV score of 0, meaning the exon under investigation is absent in both alleles. Only subject II-1 is homozygous carrier for the identified *VPS13C* deletion. **(D)**: *VPS13C* protein (NP_065872.1) structure located at chromosome 15q22.2 and predicted by SMART (<http://smart.embl-heidelberg.de>). Functional domains along with reported *VPS13C* mutations are shown. The *VPS13C* mutation identified in this study is shown at the top of the protein. Chorein_N: N terminal region of Chorein, VPS13C_N: N terminal domain, mid-rpt: VPS13_mid_repeats, SHR-BD: SHR binding domain, VPS13C_C: C terminal domain, ATG_C: Autophagy related protein C terminal domain.