Movement Disorders
CLINICAL PRACTICE
LETTERS: GENOTYPE AND PHENOTYPE

Novel *RAB39B* Mutation Causes Parkinsonism in Males with Developmental Disorder

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Associations between non-progressive intellectual disability in the context of neurodevelopmental disorders that are recognized early in life and neurodegenerative disorders that are diagnosed decades later, are intriguing. *RAB39B*-associated parkinsonism, a rare form of early-onset parkinsonism in patients with X-linked intellectual disability[1] and with Lewy pathology,[2] may serve as a model for such association. By studying a novel mutation in *RAB39B* we show here that in addition to clinical similarity, the electrophysiological features and the response to subthalamic deep brain stimulation (STN-DBS) are similar to those observed in Parkinson's disease (PD).

Phenotype

The studied family is of 13 siblings (Fig. 1A) born to non-consanguineous parents of a Jewish-Persian origin. Family history includes three deceased maternal uncles with reported PD (II-2, II-3, and II-4). Four siblings with mild and non-progressive intellectual disability developed parkinsonism. The first parkinsonian symptom in three of the affected siblings (III-7, III-10, and III-12, onset age 46, 47, and 40 years, respectively) was unilateral, upper limb, and resting tremor. Their examination also revealed asymmetrical rigidity and bradykinesia. The presenting symptom in III-4 (onset age early 50s) was impaired gait and truncal dystonia. His examination also revealed unilateral upper limb bradykinesia and rigidity. The affected siblings did not report hyposmia, constipation, or rapid eye movement (REM)-sleep behavioral disorders. Parkinsonian features significantly improved in two of the siblings that received levodopa (III-7 and III-10). Two siblings (III-4 and III-12) did not receive symptomatic treatment. The examination of all other siblings was normal.

In addition to the parkinsonian findings, two affected siblings had mild upper motor neurons signs; individual III-7 had lower limbs non-progressive spasticity, and III-12 had increased deep tendon reflex ipsilateral to the parkinsonian signs. Reduced deep tendon reflexes were observed in III-4. Brain computed tomography and magnetic resonance imaging, performed on III-7 and III-10, demonstrated small basal ganglia calcification in III-10 (Fig. 1B).

Patient III-7 had bilateral STN-DBS stimulation 6 years after disease onset because of early wearing-off of levodopa and peak-dose dyskinesia of the trunk. At baseline, neuropsychological examination revealed mildly impaired executive, visuospatial, and memory functions with preserved language (Addenbrooke's Cognitive Examination, 80/100 and Frontal Assessment Battery, 13/18). The procedure led to a significant improvement in his parkinsonian signs, mostly the tremor, but, as expected, did not improve his spastic gait. A follow-up of 18 months after the procedure revealed that *off* medications his motor Unified Parkinson's Disease Rating Scale improved by 45% (preoperative, 55/108; postoperative STN-DBS ON; 30/108), the patient's levodopa equivalent daily dose was reduced by 64% (from 1800 mg–650 mg), and no additional cognitive impairments were reported.

Extracellular electrophysiological activity was recorded in III-7 during STN-DBS surgery (Fig. 1C). β oscillatory activity (13–30 Hz) was demonstrated bilaterally (peak at 13–14 Hz). Additionally, there were peaks in the power spectrums in the θ frequency range, 6 Hz in the left hemisphere and 7 Hz in the right.

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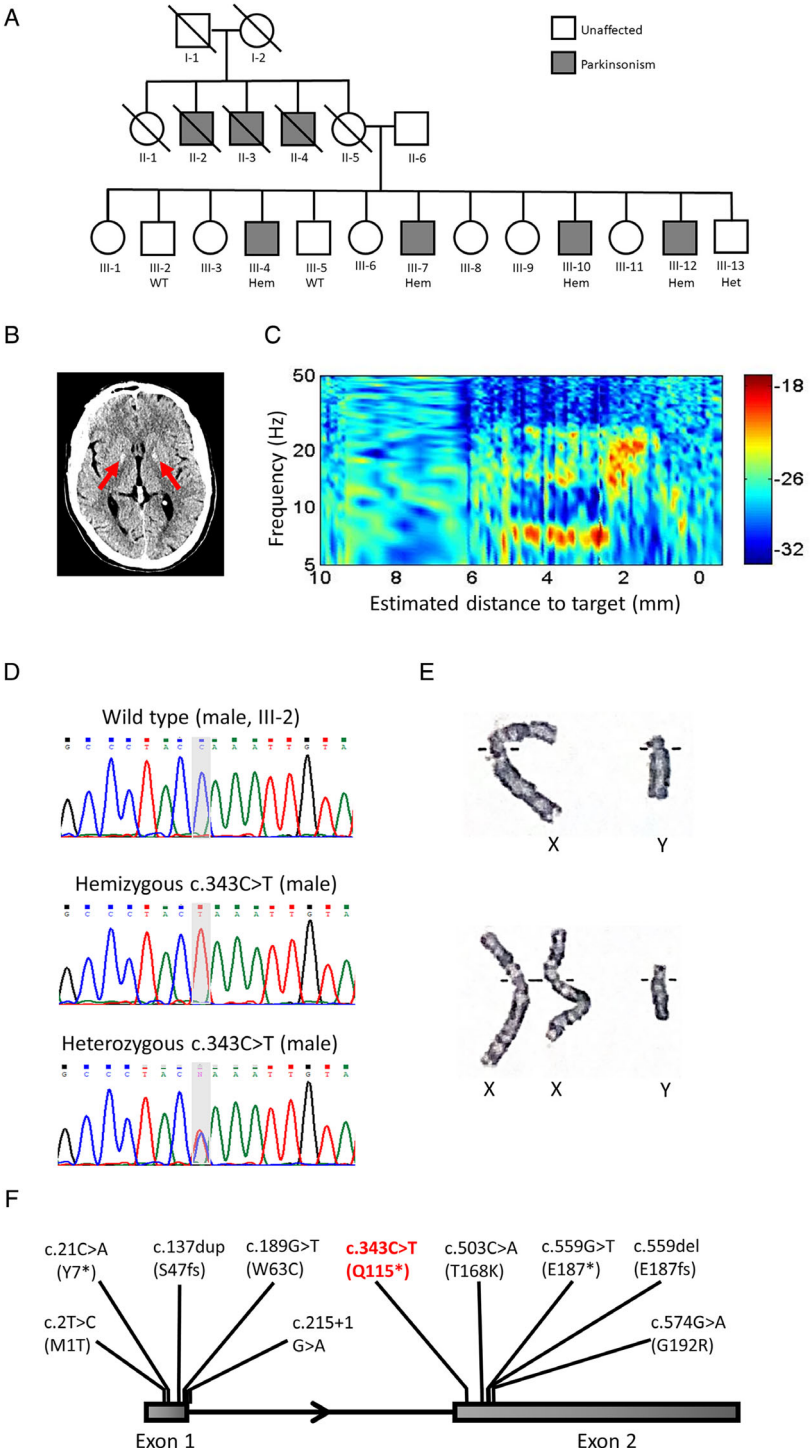

FIG. 1. Clinical, radiological, electrophysiological, and genetic characteristics. (**A**) Family tree of the studied family. Genetic status of *RAB39B* mutation is depicted for wild-type (WT), hemizygous (Hem), and heterozygous (Het) tested individuals. (**B**) Non-contrast computed tomography of patient III-10 demonstrates small basal ganglia calcifications (red arrows). (**C**) Power spectral density plot demonstrates increased β-oscillatory activity in the lower range (~13 Hz) in the left subthalamic trajectory of patient III-7, as a function of distance along the surgical trajectory. Estimated distance to target was preoperatively defined based on magnetic resonance imaging. The color scale represents log10 of power spectral density/average power spectral density. (**D**) Sanger sequencing of WT (patient III-2, upper panel), Hem male (patient III-10, middle panel), and Het male (patient III-13, lower panel). (**E**) Karyotype of patient III-13 demonstrating mosaicism to Klinefelter syndrome (XXY). (**F**) Position of all pathogenic and likely pathogenic single nucleotide variants of *RAB39B* deposited in ClinVar. The novel NM_171998.4:c.343C>T p.Gln115Ter variant is marked with red.

Genetic Analysis

Whole exome sequencing (WES) in III-7 revealed a novel hemizygous variant NM_171998.4: c.343C>T p.Gln115Ter in *RAB39B* that leads to a premature termination codon in exon 2. This variant has not been observed in our local WES database (including Persian-Jews), nor in any of the publicly available large-scale sequencing databases, such as gnomAD and Iranome.[3] Based on American College of Medical Genetics and Genomics guidelines,[4] this variant has been classified as likely pathogenic. No additional suspicious variants were found in PD-related genes.

Segregation analysis revealed that all affected individuals were hemizygous for this *RAB39B* variant (Fig. 1D). Two healthy male individuals were not carriers of this pathogenic variant. Surprisingly, individual III-13, a 40-year-old apparently healthy man without parkinsonian symptoms or signs, was heterozygous for the familial *RAB39B* variant. Evaluation of his medical records showed that because of infertility and azoospermia, he previously underwent karyotype testing. Karyotype analyzing of 22 metaphases identified mosaicism for Klinefelter syndrome: 47, XXY(15)/46, XY (7) (Fig. 1E).

Neurodevelopmental disorders that are associated with mutations in *RAB39*B include (in addition to intellectual disability) autism, epilepsy, macrocephaly,[5] and spastic paraparesis.[6] Basal ganglia calcifications are frequently observed.[6,7] The parkinsonian syndrome that appears years later may resemble levodopa-responsive[1,8] PD superimposed on previous neurological findings.

Heterozygosity to the mutated X chromosome in individual III-13 in the described pedigree could be the result of non-disjunction either in the first maternal meiosis or in the first paternal meiosis, with mosaicism represents post-zygotic event such as the loss of the affected X chromosome in some of the cells. A few case reports describe male carriers of X-linked recessive disorders because of co-occurrence with Klinefelter syndrome.[9] Being unaffected with parkinsonism, it could be speculated that at least in the brain, many of the cells are either heterozygote to the mutated allele (in similar with healthy carrier women) or contain the normal allele. However, one cannot be certain the patient will not develop parkinsonism in the future because the normal X chromosome may be inactivated in the heterozygous neurons.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

R.D.: 1A, 1C, 3A, 3B
S.S.R.: 1A, 1C, 3A, 3B
H.B.E.: 1C, 3B
C.W.: 1C, 3B
A.S.: 1C
V.M.: 1C, 3B
D.A.: 1A, 1C, 3A, 3B.

Disclosures

Ethical Compliance Statement: The study was approved by the local institutional review board and all participants signed informed consent forms before beginning the study (0393–17-HMO). We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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