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PTRHD1 (C2orf79) mutations lead to autosomal recessive intellectual disability and parkinsonism

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Abstract

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Background—We aimed to identify the disease-causing mutations in a consanguineous family featuring intellectual disability and parkinsonism.

Methods—Full phenotypic characterization, followed by genome-wide SNP genotyping and whole genome sequencing, was carried out in all available family members.

Results—The chromosome 2p23.3 was identified as the disease-associated locus, and a homozygous *PTRHD1* mutation (c.157C>T) was then established as the disease-causing mutation. The pathogenicity of this *PTRHD1* mutation was supported by its segregation with the disease status, its location in a functional domain of the encoding protein, as well as its absence in public databases and ethnicity-matched control chromosomes.

Conclusions—Given the role of 2p23 locus in patients with intellectual disability and the previously reported *PTRHD1* mutation (c.155G>A) in patients with parkinsonism and cognitive dysfunction, we concluded that the *PTRHD1* mutation identified in this study is likely to be responsible for the phenotypic features of the family under consideration.

Keywords

Intellectual disability; parkinsonism; 2p23.3; *PTRHD1* mutation

Introduction

Early-onset parkinsonism (EOP) is a neurodegenerative disease characterized by the young-onset presentations of tremor, muscular rigidity, postural instability, and slowing of movements.[1] The most common cause of parkinsonism is Parkinson's disease (PD), accounting for approximately 80% of the cases with parkinsonism. Atypical juvenile parkinsonism (AJP) usually refers to a complex form of EOP that is inherited in a recessive manner and manifests with diverse neurological and psychiatric manifestations, including pyramidal signs, abnormalities of eye movements, depression, anxiety, psychosis, impulse control disorders, and intellectual disability (ID), among others.[2] To date, pathogenic mutations in at least eight different genes have been reported in AJP. These include *ATP13A2* [1p36; MIM# 606693], *DNAJC6* [1p31.3; MIM# 608375], *FBXO7* [22q12.3; MIM# 260300], *PLA2G6* [22q12.3; MIM# 612953], *SPG11* [15q13-q15; MIM# 610844], *SPG15* [14q24.1; MIM# 270700], *SYNJ1* [21q22.2; MIM #615530], and *VPS13C* [15q22.2; MIM# 616840] genes.[2–7]

ID is characterized by below-average intelligence or mental ability to perform activities of daily living. It is well known that some patients with parkinsonism may manifest ID or some kind of cognitive dysfunction. For instance, patients with null *DNAJC6* mutations or large *DNAJC6* deletions may develop ID with or without parkinsonism.[8, 9] More recently, two other genes have been identified as causatives for ID and PD or motor impairment. These are *RAB39B* [Xq28; MIM# 300271], mutations of which are reported in ID[10] and in patients with ID and parkinsonism,[11, 12] and *RARB* [3p24.2; MIM# 615524], mutations of which have been found in patients with microphthalmia, ID, and progressive motor impairment.[13]

The goal of this study was to identify the disease-causing mutations in a consanguineous family with two affected siblings featuring ID and parkinsonism without mutations in known genes.

Methods

Subjects

An Iranian consanguineous family featuring early-onset autosomal recessive parkinsonism and ID was clinically examined. The family consisted of healthy parents, two affected sons, and unaffected daughter (Fig. 1A). DNA samples from probands of 15 unrelated families with ID and a movement disorder phenotype and from 504 ethnicity-matched control individuals were as well available. The local ethics committee at Shahid Beheshti University of Medical Sciences approved this study, and informed consent according to the Declaration of Helsinki was obtained from all participants. DNA samples from all participants were isolated from whole blood using standard procedures.

Clinical evaluation

All participants underwent a series of structured questionnaires and a comprehensive neurological and neuropsychological assessment undertaken at the Movement Disorders Unit by three experienced movement disorder specialists. The performed neuropsychological examinations are fully described in the Supplementary Material.

Homozygosity mapping

High-throughput SNP genotyping was carried out in all available family members (Fig. 1A) by using the HumanOmniExpress Exome arrays v1.3 and HiScanSQ system (Illumina Inc., San Diego, CA, USA). Genotyping data was used to perform homozygosity mapping (HM) as previously described (Fig. 1B).[3]

Whole genome sequencing

WGS was carried out at the New York Genome Center (NYGC) in the two affected family members (II-I, II-II) as described in the Supplementary Material.

Validation and disease-segregating analyses

Primer sequences for the entire coding region of the *PTRHD1* gene, which stands for peptidyl-tRNA hydrolase domain containing 1, were designed by using a public primer design website (http://ihg.gsf.de/ihg/ExonPrimer.html). Direct *Sanger* sequencing using primers flanking the exon 1 of the *PTRHD1* (*C2orf79*) gene was used to validate the c. 157C>T mutation (Fig. 1C). Once validated, the mutation was examined in available family members for disease segregation analyses. The entire *PTRHD1* gene was examined in 15 familial cases with ID and a movement disorder phenotype, including parkinsonism and/or tremor. The *PTRHD1* exon 1 was additionally examined in 104 Iranian control individuals through *Sanger* sequencing and in 400 Iranian control individuals through allele-specific amplification. For *Sanger* assays, all purified PCR products were sequenced, resolved, and analyzed as previously described.[3] Allele-specific detection was performed using designed

primers for the identified mutation and PCR products were analyzed by agarose gel electrophoresis.

Results

Patients' clinical details

The proband (II-I) presented with ID, muscle stiffness, rest and postural tremor, postural instability, gait disturbances, speech difficulties, as well as psychiatric symptoms such as anxiety, hypersomnia, and hypersexuality. His brother showed similar symptoms but milder, and no additional family members were affected. Full patient's clinical details are described in the Supplementary Material.

Molecular Analyses

The performed HM identified a total of six potential disease-associated loci shared only by the two affected individuals (Supplementary Table 1). WGS was then performed on the two affected individuals (II-I and II-II). After filtering for common genetic variation, 194 genomic variations, including missense (n = 133), frameshift, splice-site, stop-gained, and start-lost (n = 61) mutations, were found to be present in both patients. Among these, only a homozygous missense mutation was located in one out of the six previously identified disease-associated loci (Fig. 1B). No other homozygous or compound heterozygous mutations were identified outside the disease-associated loci. We then investigated whether genomic deletions to be shared exclusively by affected individuals might as well be causative; however, no genomic deletions were found in the identified disease-associated homozygous segments, and no common genomic deletions were identified within the exome. Due to the presence of parkinsonism in both the affected individuals, PD- and parkinsonism-associated loci were as well examined, but no shared region of homozygosity was observed within the known parkinsonism loci, and no pathogenic mutation was identified within the known PD and parkinsonism genes.

The only homozygous mutation identified in a previously identified disease-associated locus was located in the *PTRHD1* gene (C2orf79) at chromosome 2p23.3. It consisted in a C to T transition at nucleotide 157 (c.157C>T), leading to the p.His53Tyr change on the protein level. It did segregate with disease status and was highly conserved among other orthologous (Fig. 1A–C). It was predicted to be pathogenic by various computational methods, was not previously reported, and was not found in any public SNV database, including the NHLBI GO Exome Sequencing Project and the Exome Aggregation Consortium (ExAC; exac.broadinstitute.org) (Table 1). The *PTRHD1* c.157C>T mutation was then examined in 504 ethnicity-matched neurologically normal individuals and found to be absent in 1,008 control chromosomes, further supporting its pathogenicity. Fifteen additional families with ID and a movement disorder were selected and screened for *PTRHD*1 mutations; however, no pathogenic *PTRHD1* mutation was identified in these newly recruited cases.

Discussion

Here, we describe the identification of a novel causative gene for a complex form of autosomal recessive ID with parkinsonism. The combination of HM and WGS led us to

assign the chromosome 2p23.3 locus as the disease-associated locus, and to identify a homozygous variation in the *PTRHD1* gene as the disease-causing mutation (Fig. 1; Table 1). The disease-segregating *PTRHD1* mutation, predicted to be pathogenic by various computational methods, was shown to be absent in over 1,000 ethnicity-matched control chromosomes and SNV public databases, likely supporting its pathogenicity.

Despite *PTRHD1* mutations having never been reported in parkinsonism or ID, deletions at the 2p23 locus, encompassing the *PTRHD1* gene, are known to be associated with several ID syndromes (Supplementary Table 2).[14–20] Furthermore, Jaberi et al recently identified a missense *PTRHD1* mutation (c.155G>A; p.Cys52Tyr) in a family with early-onset parkinsonism and cognitive dysfunction.[21] Although they claimed that the strongest candidate gene for the disease was *ADORA1* due to the role of adenosine receptors in brain function and neuronal activity, there were no substantial proofs to discard *PTRHD1* as a causative gene, as was well acknowledged in their report.[21] The *PTRHD1* p.Cys52Tyr mutation was predicted to be pathogenic by various computational methods, was found with extremely low frequency in public SNV databases, and was absent in 208 ethnicity-matched control chromosomes sequenced by us (Table 1). In any case, to exclude *ADORA1* as a causative gene, we further investigated the coverage of *ADORA1* gene in our SNPs genotyping and WGS data. A total of 33 SNPs covering the *ADORA1* locus were genotyped with only 63% of the SNPs being homozygous for Patient 1 (Supplementary Table 3), further excluding *ADORA1* as the disease-associated locus. Sequencing of the *ADORA1* gene at more than 30x coverage identified no pathogenic mutations, further supporting the role of *PTRHD1* as a causative gene in both the reported families.

Although little is known about the function of PTRHD1, both *PTRHD1* mutations identified in families with ID and parkinsonism lie within the PTH2 domain (25-139 amino-acids) of the PTRHD1 protein (Table 1). The PTH2 domain is a ubiquitin-like (UBL) domain-binding protein that is known to participate in the ubiquitin-proteasome pathway and has been shown to suppress ubiquitin-mediated degradation.[22] In yeast, overexpression of PTH2 has been shown to cause accumulation of polyubiquitinated proteins and to inhibit growth. It is also known that PTH2 binds to the UBL domain of Rad23 and Dsk2 and interacts with polyubiquitinated proteins through their ubiquitin-associated domains.[22] The role of ubiquitin-mediated proteolysis in the pathogenesis of ID and neurodegenerative diseases, such as PD and Alzheimer's disease, is well known and documented.[23] Indeed, PD is characterized by the loss of dopaminergic neurons and the progressive neuronal accumulation of protein inclusions containing alpha-synuclein and ubiquitin;[24] two different protein ubiquitin ligases (Parkin and FBXO7) are well established as causative genes for early-onset forms of parkinsonism;[2, 25–27] and overexpression of mutant alpha-synuclein as well as downregulation of Parkin have been shown to increase sensitivity to proteasome inhibitors, decreasing proteasomal function.[28]

Moreover, mutations in various ubiquitin enzymes participating in the ubiquitin-proteasome system are known to be associated with the pathophysiology of ID. This is the case of *UBE3A* (MIM# 105830), mutations of which cause Angelman syndrome[29], as well as *UBE2A* (MIM# 300860), *CUL4B* (MIM# 300354), and *BRWD3* (MIM# 300659), mutations of which are known to cause X-linked ID syndromes.[30–32]

Therefore, given the role that the ubiquitin proteasome system plays in brain development, synaptic plasticity, and long-term memory formation,[33] and the previous association of the chromosome 2p23.3 locus with ID, we speculated that *PTRHD1* genetic variability might cause ID and parkinsonism through defects in the ubiquitin-proteasome system, as observed in other inherited forms of parkinsonism and ID.

In conclusion, this study describes for the first time the association of *PTRHD1*, known to participate in the ubiquitin-proteasome pathway, with the pathogenesis of ID and parkinsonism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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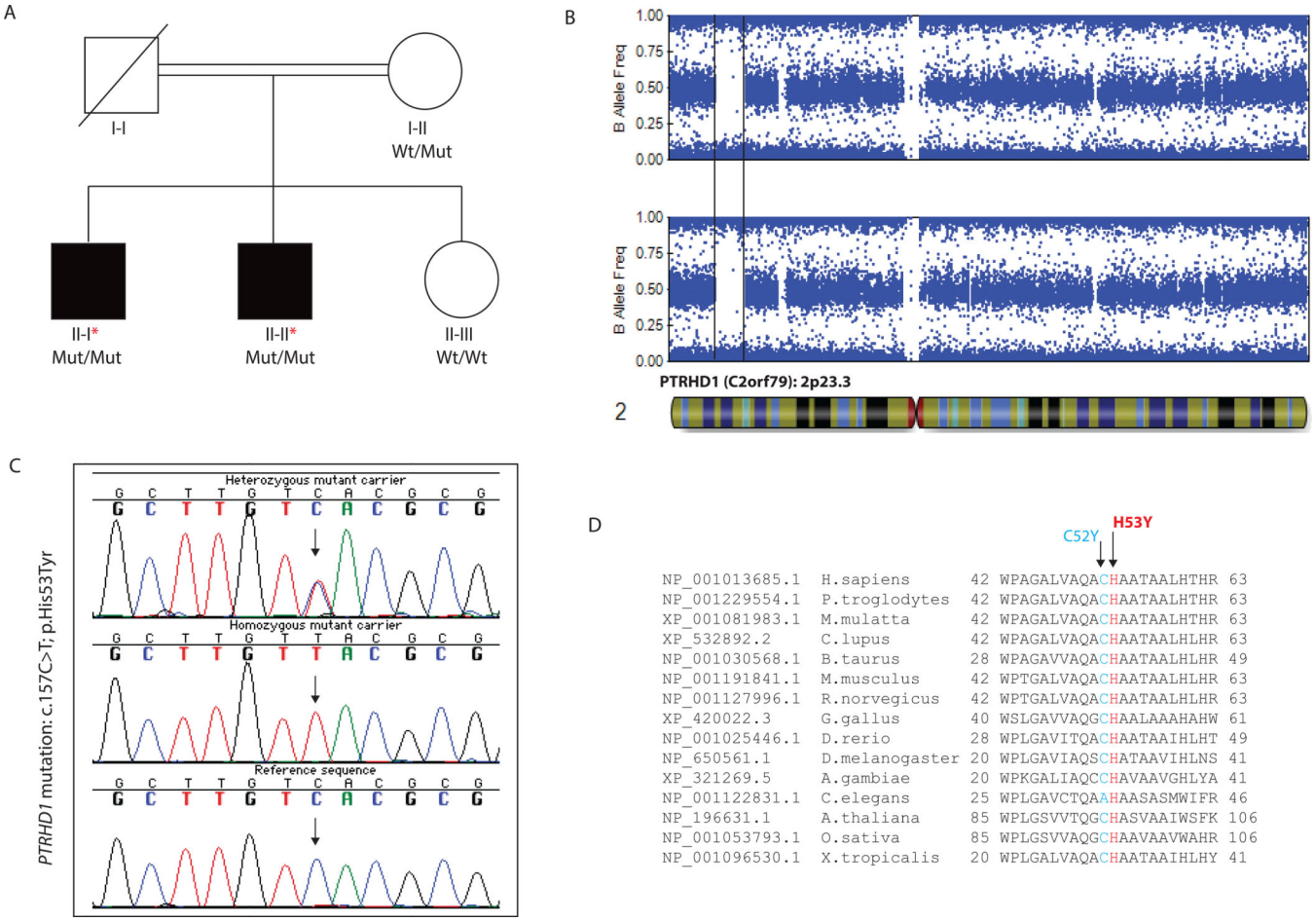

FIG. 1.

(**A**) Pedigree of the family featuring ID and parkinsonism. Wt/Mut indicates heterozygous carrier for the *PTRHD1* c.157C>T mutation; Mut/Mut indicates homozygous carrier; and Wt/Wt indicates non-carrier. Affected siblings are represented with black squares. (**B**) B allele frequency plots of patients' chromosome 2 acquired from the Illumina Genome Viewer (IGV) tool within the GS software (Illumina). The final disease-associated homozygous track of 8.2 Mb (2p23.3) is represented between black lines. (**C**) Sanger chromatogram sequences of the *PTRHD1* exon 1 containing the c.157C>T mutation (arrow). (**D**) Conservation among other orthologous of the two reported *PTRHD1* mutations. The mutation reported in this study is highlighted in red while the mutation reported by Jaberi and colleagues is highlighted in blue.

Table 1

PTRHD1 mutations in Families with ID and parkinsonism

Gene	Nucleotide Change	Amino Acid Change	Protein Domain	Pathogenicity Predictions					Iranian Control Population	ExAC Browser	References
				SIFT	Polyphen2	MutPred	SNPs&GO	CADD-phred			
PTRHD1 (C2orf29)	c.155G>A	p.Cys52Tyr	PTH2	Deleterious	Probably damaging	0.749	0.604	34	0/208 *	1 / 119394	Jaberi at al, 2016
PTRHD1 (C2orf29)	**c.157C>T**	**p.His53Tyr**	**PTH2**	**Deleterious**	**Deleterious**	**0.783**	**0.764**	**37**	**0/1008**	**Not Found**	**This study**

The mutation identified in this study is shown in bold. PTH2 stands for peptidyl-tRNA hydrolase 2.

* These controls individuals were sequenced in this study as Jaberi and colleagues did not report control data for this specific mutation.