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Isolated Paroxysmal Non-kinesigenic Dystonia Associated with Homozygous *PDHB* Variant in an Indian Family

Although *MR-1/PNKD* variants are the most common cause of inherited paroxysmal non-kinesigenic dyskinesia (PNKD), in a large proportion of PNKD patients, the underlying genetic basis remains unknown.[1] Pyruvate dehydrogenase (PDH) complex deficiency causes phenotypes ranging from fatal infantile lactic acidosis to mental retardation or intermittent ataxia.[2] Brain imaging may reveal cortical atrophy, ventricular dilatation, basal ganglia (BG) abnormalities, and corpus callosum agenesis.[2] PDH deficiency might result from variants in genes encoding discrete subunits of the PDH complex. The majority is caused by *PDHA1* variants, whereas a minority is caused by variants in *PDHB*, *DLAT*, *DLD*, *PDHX*, or *PDP1*. Paroxysmal dyskinesia (PxD) is an infrequent, poorly characterized feature in a few cases of PDH deficiency caused by *PDHA1* or *DLAT* variants.[3,4] Here, we report isolated PNKD in 2 siblings, associated with a novel homozygous pathogenic variant in *PDHB*, the gene coding for the E1β subunit of the PDH complex.

The siblings were born to consanguineous parents of Indian origin (Fig. 1A). The proband (II-1) experienced repeated falls due to episodes of hemi- or bilateral lower-limb predominant dystonia, with onset at age 5 years (Video S1, Segment 1). The episodes typically lasted 1 to 2 hours, were not precipitated by movement, and would occur without warning. Interictal examination was normal. Serum biochemistry, electrolytes, calcium, urine gas chromatography/tandem mass spectrometry for metabolic diseases, and tests for Wilson's disease were unrevealing. Nerve conduction studies and electroencephalograms were normal. Lactate and pyruvate levels in blood and cerebrospinal fluid were normal, as observed previously in individuals with *DLAT* variants.[3] Brain magnetic resonance imaging (MRI) revealed symmetric T2 pallidal hyperintensities on T2 and FLAIR (Fig. 1C, II-1). Levodopa, trihexyphenidyl, clonazepam, and baclofen were unhelpful. Carbamazepine (CBZ) at 300 mg/day led to a 90% to 95% reduction in frequency, severity, and duration of the episodes.

Three years later, his younger brother (II-2) manifested identical episodic hemidystonia mainly affecting one foot or leg (Video S2, Segment 2), with T2 hyperintensities in the dentate nucleus (Fig. 1C, II-2). His attacks also responded near-completely to CBZ (200 mg/day).

Pallidal lesions in patients with isolated paroxysmal dystonia have been described in patients with PDH deficiency (due to variants in *DLAT*[3], *PDHA1*,[4] and *PDHX*) and due to *ECHS1* variants.[5] However, analysis in the proband's WES (Whole Exome Seqencing) (Appendix S1) did not reveal any variants in these genes or other genes causing PxD (Table S1). Instead, we found a homozygous variant in *PDHB*, c.856A>G/p.Thr286Ala (Table S2), absent in databases and predicted damaging by most in silico tools (Table S3).

The phenotypic spectrum observed with biallelic *PDHB* variants is similar to that observed with *PDHA1*[6] but with unclear genotype–phenotype correlations. A review of 82 patients with PDH deficiency included 65 patients with *PDHA1* variants, 9 with *PDHX*, 7 with *PDHB*, and 1 with *DLD*.[7] In these patients, dystonia was reported in those with *PDHA1* and *PDHX* variants but in none with *PDHB* variants.[7] In contrast, mild dystonia without additional clinical characterization was mentioned in 1 patient with *PDHB* variants and other clinical features.[6] Furthermore, other *PDHB* patients showed abnormal BG/dentate MRI lesions.[6,7] To our knowledge, isolated paroxysmal dystonia has not been described in patients with *PDHB* variants.

After the identification of the *PDHB* variant, the siblings were commenced on thiamine and multivitamin supplementation. The younger brother continues to respond to CBZ, without attack recurrence. In contrast, the proband remains asymptomatic at 3-year follow-up after stopping CBZ. These observations might be of therapeutic relevance, given reports of improvement and even complete reversibility[4] in some patients after thiamine. A trial of thiamine supplementation should be considered in cases of isolated PNKD or PED (Paroxysmal Exercise-induced dyskinesia) with bilateral pallidal lesions.

In conclusion, our patients with PNKD as the only and prominent clinical presentation represent a relevant expansion of the phenotype associated with *PDHB*. Our observation suggests that *PDHB* should be included among the genetic causes of isolated PNKD.

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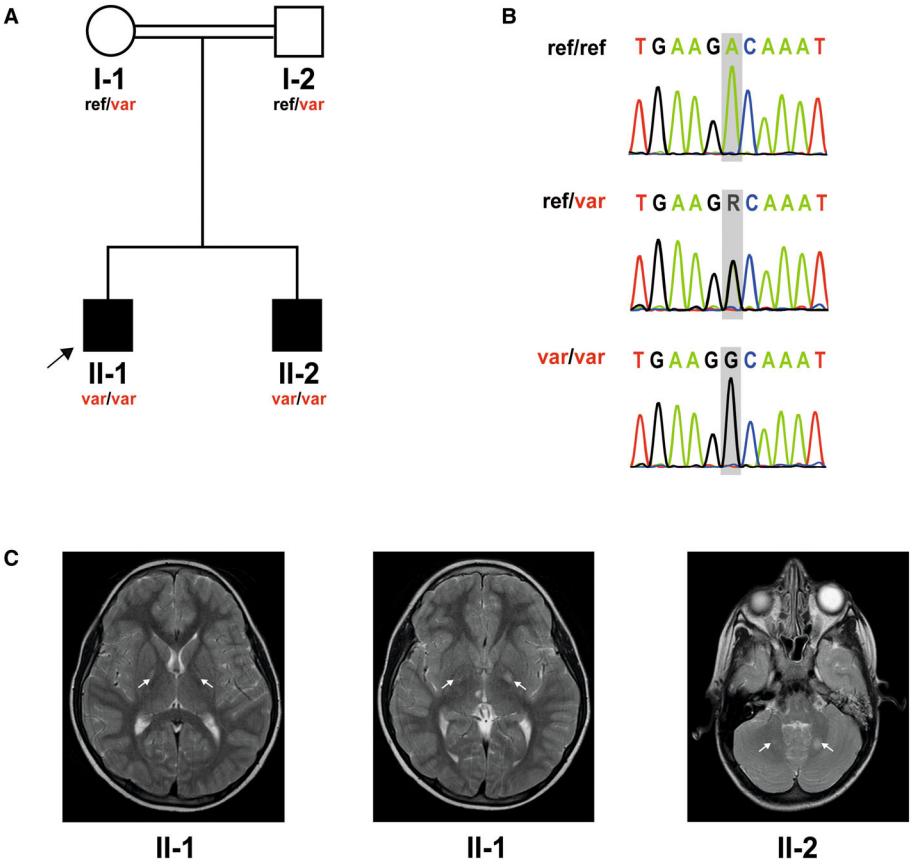

FIG.. 1. (**A**) Pedigree of the Indian family with the c.856A > G (p.Thr286Ala) *PDHB* variant. The arrow indicates the proband. var, variant allele; ref, reference allele. (**B**) Electropherograms of the *PDHB* c.856A > G (p.Thr286Ala) variant, present in homozygous state in the affected siblings and in heterozygous state in the unaffected parents; the control (wild-type) sequence is also shown as reference. (**C**) T2-weighted MRI brain images showing abnormal, bilateral symmetric hyperintensities in the globus pallidus in the proband (subject II-1) (arrows) and in dentate nucleus of the cerebellum in the younger sibling (II-2) (arrows). [Color figure can be viewed at wileyonlinelibrary.com]

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Data Availability Statement

Data available in article supplementary material.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.