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Progressive nonparoxysmal chorea and dystonia due to myofibrillogenesis regulator-1 gene mutation

Mutations in the myofibrillogenesis regulator gene (MR-1) causes paroxysmal non -kinesigenic dyskinesia (PNKD) characterized by episodic (paroxysmal) attacks of any combination of chorea, dystonia and athetosis (*MR-1/PNKD*) [1]. This gene is transcribed into three alternatively spliced isoforms: long (MR-1L), medium (MR-1M) and small (MR-1S) [2,3]. Three mutations namely, A7V, A9V and A33P have been described in the N-terminal region common to MR-1L and MR-1S, but not MR-1M and are reported to segregate with the disease in unrelated *PNKD* families [3,4]. PNKD mutations may also be a cause for familial Tourette syndrome [5].

Here, we describe a new phenotypic presentation of *PNKD* gene mutation, A33P, causing progressive non-paroxysmal chorea and foot dystonia.

A nine-year-old girl, with normal developmental milestones developed abnormal brief, repetitive, irregular, flowing movements in both hands which started at the age of five years. At seven years of age, she developed insidious onset and gradually progressive abnormal sustained posturing and inversion of left foot causing difficulty in walking with no diurnal variation. She did not report any worsening in symptoms with caffeine, fatigue, emotional stress, hunger or heat. On clinical examination she had choreiform movements in bilateral upper limbs and tongue. During the pronator drift test myoclonus was also present in the upper extremities. She had mild to moderate dystonic posturing of left foot causing significant difficulty in walking (video). There was no Kayser–Fleischer rings on slit lamp examination and her other neurological and systemic examination was normal. She was treated with tablets of carbamazepine, levodopa/carbidopa, clonazepam, levetiracetam, gabapentin and injection OnabotulinumtoxinA, but her foot dystonia has gradually progressed. Her parents and younger brother (Two years old) are asymptomatic. One of her sister died with viral hepatitis at the age of 6 years. Her blood, cerebrospinal fluid, urine investigations including workup for Wilson's disease and brain magnetic resonance images were normal.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.08.019.

The whole-exome sequencing was performed to identify any genetic mutation explaining the clinical condition of the patient. DNA extracted from the blood samples of the affected child (index) was used to perform targeted gene capture using a custom capture kit. The libraries were sequenced to mean $>$ 80–100$\times$ coverage on Illumina sequencing platform. The sequences obtained were aligned to human reference genome (GRCh37/hg19) and analyzed to identify variants relevant to the clinical indication. Further, DNA was also extracted from the blood samples of the parents and brother. Exon 2 of *PNKD* gene was PCR-amplified using primers specific for the region carrying the variation and the product was sequenced using Sanger sequencing. The sequence was aligned to available reference sequence NG_017060.1 (REGION: 5001.81402) in NCBI GenBank database to detect variation using variant analysis software programs. The A33P variant of *PNKD* gene was detected in heterozygous condition in index patient, who presented with clinical features of progressive non-paroxysmal chorea and dystonia. This substitution variation was detected by next generation sequencing and further validated by Sanger sequencing (Fig. 1A–D). I*n silico* analysis using protein prediction tools like SIFT, PolyPhen, Mutation taster, FATHMM, ConDEL and MetaSVM revealed a damaging effect for the A33P variation. The same heterozygous variation was also detected in the father and brother of index patient, however they did not have any symptoms. Her mother, who is also asymptomatic, was not found to harbor this variation.

Mutations in the *PNKD* gene have been described in families from different ethnic origins [2–4]. Two mutations, A7V and A9V, were previously discovered in the N-terminal region common to MR-1L and MR-1S [4]. Ghezzi and colleagues reported a third mutation, A33P, in a new PNKD patient in the same region [6]. *In silico* studies conducted by them also revealed that, while the A7V and A9V variations affect one of the 2 α-helices in the mitochondrial targeting sequence (MTS), the A33P variation could alter the C-terminal orientation of the MTS. The same authors reported using functional studies that mitochondrial import and protein maturation was not affected in MR-1 protein variants carrying any of the 3 PNKD mutations. They suggest that disease may be caused by a novel mechanism, involving a mutant MTS peptide that is cleaved off during translocation into the inner mitochondrial membrane and can be directly deleterious or toxic to the host cells. This suggests that the A33P variation may have a similar functional effect as the other 2 PNKD variations. Moreover, the N- terminus of MR-1L and MR-1S, including positions A7, A9 and A33 is highly conserved in mammals.

The patient reported by Ghezzi and colleagues, was a 57-year-old obese man, who experienced recurrent episodes of involuntary movements, lasting several minutes and consisting of a sense of muscle tightening, followed by dystonic posturing of the extremities. The patient also had paroxysmal episodes of blepharospasm, unsteady gait and slurred speech. Neurological examination between attacks was consistently normal. His father, a paternal half-brother, and his grandfather had episodes of blepharospasm and muscle cramps, but they were unavailable for further studies. However, our patient had symptom onset with choreiform movements of fingers at the age of five years and progressive non-paroxysmal dystonic posturing of left foot at the age of seven years. Since then her symptoms have slowly progressed and her left foot dystonia has worsened. This report highlights that the clinical presentation of *PNKD* mutated families may not be homogeneous and some patients may have progressive non-paroxysmal chorea and dystonia also.

The manuscript has been prepared according to the ethical norms of the institute and the journal. We have taken the informed written consent from the patient appearing in videos and video still.

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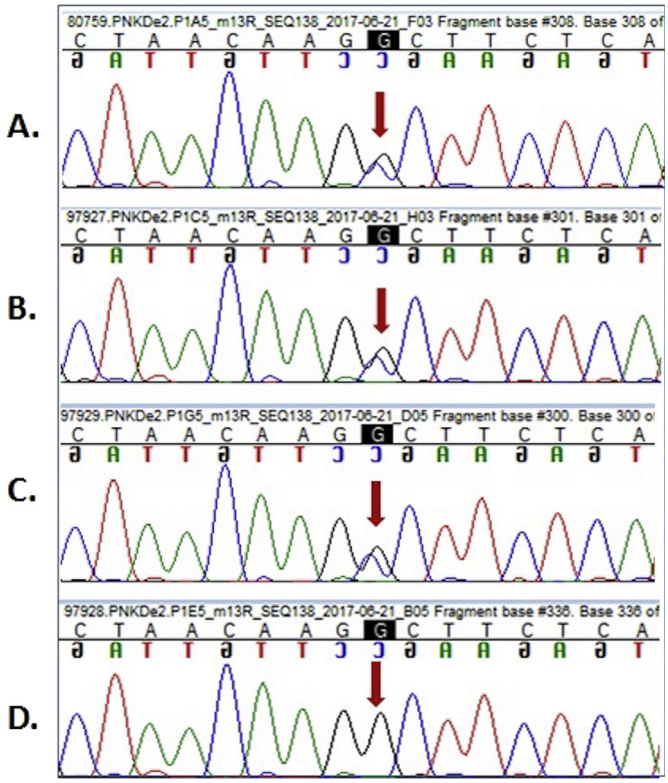

Fig. 1. Sequence chromatogram showing the variation (chr2:219136133G > G/C; c.97G > G/C; p.Ala33Pro) in exon 2 of *PNKD* gene detected in heterozygous condition in the index patient (A), her father (B) and her brother [C] The variation was not detected in her mother (D).

Authors' roles

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript: A. Writing of the first draft, B. Review and Critique.

Sanjay Pandey (SP): 1A, 1B, 2A, 2B, 3A, 3B.
Laxmikant Ramkumarsingh Tomar: 1A, 2A, 2B, 3A, 3B.
Lakshmi Mahadevan: 1A, 2B, 3A, 3B.

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Roles of the authors

Dr. Sanjay Pandey, Dr. Laxmikant Ramkumarsingh **Tomar and Dr. Lakshmi Mahadevan** contributed in manuscript preparation by writing the first draft, review and critique.

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