TITLE :- GENETIC INSIGHTS INTO PROGRESSIVE MYOCLONIC EPILEPSY: A RARE AUTOSOMAL DOMINANT CASE WITH KCNC1 MUTATION

INTRODUCTION

- Progressive Myoclonic Epilepsy (PME): Rare neurogenetic disorder with clinically and genetically heterogeneous group of myoclonic epilepsy and progressive cognitive decline.
- Addition features:- other seizure type (focal/ atonic/ atypical absence / GTCS), ataxia, vision loss or weakness depending upon the types
- KCNC1 gene mutation – a recently recognized cause of Autosomal Dominant PME .
- KCNC1 encodes Kv3.1 potassium channel, essential for high-frequency neuronal firing, Mutation leads to neuronal hyperexcitability and progressive neurodegeneration.
- Early genetic identification aids in diagnosis, counseling, and prognostic evaluation.

Case history :-: 14 years old male, Aditya Rawat

Onset: At 8 years – GTCS with tonic posturing & LOC, Seizures increased → controlled on AEDs for last 2 years.

After 2–3 yrs: developed action & postural myoclonus, tremulousness during activity, Gait ataxia.

Gradual slurred speech and cognitive decline

Family history: Father with similar seizures and myoclonus and cognitive decline at 15 years of age

Examination

Cognition: Mild impairment -Mocha (19/25), fundus :- Normal, V/A:- 6 /6

Motor: Normal bulk, mild LL hypotonia, DTR :- diminished

Cerebellar signs: Impaired FNF, heel–shin, intentional tremor present, Gait ataxia

Myoclonus: Predominantly action-induced.

Investigations

EEG: Asymmetric right frontal predominant spike and wave 2 years back, currently normal .

MRI Brain + MRS: Mild cerebral & cerebellar atrophy, no lactate peak.

VEP, BERA, NCS, Serum lactate: Normal.

Genetic testing advised: Whole genome sequencing + mitochondrial panel → KCNC1 mutation.

MedGenome Labs Ltd.
Sy. Nos. 94/1C and 94/2, Tower 1, Ground Floor, Veerasandra Village, Attibele Hobli, Electronic City Phase-1, Electronics City, Bangalore, Bangalore South, Karnataka, India, 560100.
Tel : 1800 296 9696, Web: www.medgenome.com

MEDGENOME

DNA TEST REPORT - MEDGENOME LABS

Full Name / Ref No:	ADITYA	Order ID/Sample ID:	1168439/8911277
Gender:	Male	Sample Type:	Blood
Date of Birth / Age:	14 years	Date of Sample Collection:	12th January 2025
Referring Clinician:	Dr. Dinesh khandelwal, GSS Diagnostic, Jaipur	Date of Sample Receipt:	13th January 2025
		Date of Order Booking:	15th January 2025
		Date of Report:	14th February 2025
Test Requested:	ExomeMAX [Enhanced Whole Exome and Mitochondrial Genome Sequencing]		

CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

Master Aditya, presented with clinical indications of sudden loss of consciousness with tonic upper limb spasms six years ago, abnormal limb tremulousness, tongue biting, frothing of saliva, seizures, abnormal jerky limb, limiting functionality, slows speech with increased pauses and decreased pitch of the voice, clarity cognitive decline, memory loss, decreased school performance, and delayed responses. EEG (three years ago) showed an asymmetrical spike-and-wave pattern with a normal background. He had a history of GTCS, action myoclonus, cerebellar involvement (intentional tremor), and mild cognitive decline. MRI with MRS showed mid-cerebral and cerebellar atrophy but no lactate peak. His father has a history of seizures from age 15, jerky movements from age 17, low IQ, and an EEG suggestive of generalized epileptic discharges. *Master Aditya* is suspected to be affected with myoclonus epilepsy with ragged-red fibers or progressive myoclonus epilepsy or mitochondrial disease and has been evaluated for pathogenic variations.

RESULTS

PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

SNV(s)/INDELS

Gene[4] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification[5]
KCNC1 **(+)** (ENST00000265969.8)	Exon 2	c.959G>A **(p.Arg320His)**	Heterozygous	Progressive myoclonic epilepsy-7 (OMIM#616187)	Autosomal dominant	Pathogenic **(PS3, PS4)**

Parental testing is recommended, and classification of the variant(s) may change based on segregation analysis.

No significant clinically relevant variants were detected in the mitochondrial genome.

The mitochondrial genome was completely covered.

COPY NUMBER VARIANTS CNV(s)

No significant CNVs for the given clinical indications that warrants to be reported was detected.

CAP ACCREDITED

DISCUSSION

- Progressive Myoclonic Epilepsies (PMEs) are rare neurogenetic disorders presenting with action myoclonus, seizures, ataxia, and cognitive decline.
- In this patient, the combination of action myoclonus, cerebellar signs, cognitive slowing, and positive family history suggested a hereditary PME.
- Normal metabolic tests and absence of lactate peak on MRS ruled out mitochondrial causes (e.g., MERRF).
- The KCNC1 gene encodes the Kv3.1 potassium channel, essential for high-frequency neuronal firing; mutations lead to neuronal hyperexcitability and autosomal dominant PME (EPM7).
- Mild cerebellar atrophy and familial clustering support KCNC1-related PME, highlighting the importance of genetic testing and counseling for diagnosis and management.