Movement Disorders
CLINICAL PRACTICE
LETTERS: GENOTYPE AND PHENOTYPE

Dystonia as Presenting Feature of Compound Heterozygous PMPCA Gene Variants

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Dystonia can be the manifestation of a plethora of genetic diseases. With the advances of diagnostic techniques, an ever-expanding spectrum of genes causing various dystonia syndromes is recognized.[1] Genetic syndromes combining dystonia and ataxia constitute a non-rare occurrence. Attempts to organize this clinical area differentiated syndromes where dystonia and ataxia are concomitant from those where they are occasionally combined.[2]

Biallelic pathogenic variants in the peptidase mitochondrial processing subunit alpha (*PMPCA*) gene are known to cause autosomal recessive spinocerebellar ataxia type 2 (OMIM #213200), whose phenotype has been characterized only in recent years.[3] Dystonia was not observed in these patients, who showed ataxia and intellectual disability. The PMPCA-related phenotype has been later expanded to include multisystem involvement consistent with mithocondriopathy[4] and occasional dystonia.[5–7] In all these cases, ataxia was the presenting and the most severe motor disturbance.

PMPCA encodes the alpha-subunit of mitochondrial processing peptidase (α-MPP), that cleaves nuclear-encoded mitochondrial precursor proteins upon their import into mitochondria.[8] Lowering of mitochondrial respiratory chain activity and impaired processing of frataxin have been demonstrated in *PMPCA*-mutated patients.[3,9]

We report on a patient with prominent dystonia of early onset who later developed cerebellar features, compound heterozygous for two *PMPCA* variants. The study methodology and patient's clinical features are reported in the supplemental online material.

The patient, second of three siblings, was born at term from a normal delivery to a non-consanguineous healthy Italian couple. Developmental milestones and cognition were unremarkable; he graduated in business management at age 26. No neurological disorders were reported in the family. His brothers had normal neurological examination and normal motor development. His mother's two siblings and other more distant relatives were all reportedly healthy.

At 8, his voice became low-pitched and hoarse; speech progressively became slurred. At 10, craniocervical dystonia presented with involuntary orofacial and cervical movements and postures to gradually spread involving the trunk and limbs. Treatment with levodopa, dopamine blockers, GABA agonists, VMAT2 inhibitors and botulin neurotoxin did not help; anticholinergic agents provided some relief. At age 18 the patient developed mild ataxic gait, seven years later dysphagia was reported.

We first saw the patient at age 24 (Video 1). Neurological examination revealed generalized dystonia, mainly involving the cranio-cervical district. Speech was severely affected, due to spasmodic dysphonia and severe dysarthria. Blepharospasm, jaw-opening and tongue protrusion dystonia induced by attempts to speak were noticed. There were abnormal neck postures with sagittal-shift, high-amplitude, patterned, torsional movements of the head and limbs and mild intentional tremor in the right arm. The patient walked unassisted, with a broad-based and dystonic gait, more severe on the right-hand side. In the right lower limb, there were knee extension and equinovarus foot posture that were accentuated by walking and attenuated when moving backward. There were no visual or hearing involvement. Ocular movements were unremarkable; there were no spasticity or parkinsonism. Sensory exam was normal.

At 29, his symptoms worsened. The patient progressively became anarthric and could not walk unassisted for long distances due to progression of gait ataxia. Deep tendon reflexes were brisk bilaterally. Cognition remained unaffected, and no behavioral abnormalities were reported. One year later he received a bilateral GPi-DBS implant without clinical improvements after eight months of continuous stimulation (Video 2).

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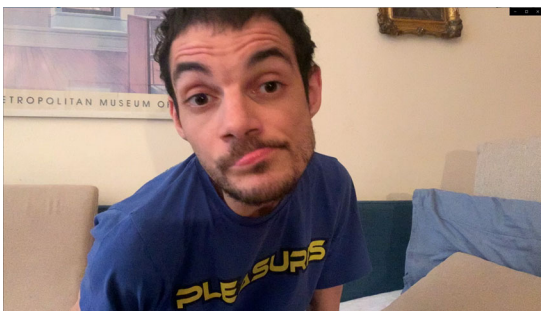
Video 1. This video shows the patient at 24 years. Dystonia is generalized, particularly severe at cranio-cervical level, but also involving the upper limbs. Speech is severely impaired. The clip shows involuntary orofacial movements, jaw-opening and tongue protrusion dystonia. At cervical level, there are abnormal postures and torsional movements relieved by a sensory trick (touching the chin with the left hand). Upper limb involvement is prevalent in the right arm with writer's cramp and evidence of mirror dystonia. Gait is broad-based with evident right foot dystonia accentuated by walking.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13749



Video 2. Video taken at home at age 29, 3 months after bilateral GPi implant. Dystonia has progressed. Facial grimaces are continuous, there is constantly flexed neck posture with head tilt to the right and rotational movements. Dystonic slowing is evident upon repetitive finger and foot tapping. There is bilateral dysmetria in the upper limbs. Sensory tricks (touching of the chin) provides inconstant relief. The patient is unable to write. Diffuse muscle atrophy is evident, with normal strength. The patient is able to stand-up unassisted and uses a walker due to severe gait ataxia. Standing posture is characterized by severe neck and trunk flexion. Gait is wide-based with cock-walk appearance.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13749

Brain MRI performed at age 20 showed marked cerebellar atrophy. Whole exome sequencing (WES) performed at age 29 identified two missense variants in the *PMPCA* gene (NM_015160.3: c.619G > A; p.Glu207Lys and c.751A > G; p.Met251Val); Sanger sequencing confirmed the presence of both variants and demonstrated that each segregated from one healthy heterozygous parent. Functional and modeling studies showed for both variants a reduction of protein levels and stability, supporting a re-classification from "variants of uncertain significance" to likely pathogenic (Fig. 1).

On Axis I, the patient had a progressive persistent isolated segmental dystonia of childhood onset.[10] Two years after onset, dystonia progressed to generalization, in adolescence became combined with ataxia and mild spasticity. On Axis II, there was structural evidence of cerebellar atrophy and genetic evidence of inheritance (compound heterozygous variants in the *PMPCA* gene).

Genotype–phenotype correlates are currently evolving for *PMPCA*-related disorders. Previous reports demonstrated that variants associated with a severe, multisystemic, phenotype do not impact on protein levels more than variants associated with milder phenotypes, and that protein levels and stability do not correlate with disease severity.[4,7,9]

The observation of isolated dystonia at onset and for approximately 10 years is a previously unreported feature in carriers of *PMPCA* gene variants. On the other hand, dystonia was occasionally observed in patients with the ataxic phenotype.

This patient's phenotype was not evocative of mitochondrial disease and did not reveal any intellectual deficiency or psychomotor delay. GPi DBS was inefficacious during the first 8 months of continuous stimulation; a longer observation is needed to affirm clinical outcome following this procedure.

PMPCA-related dystonia is an intriguing phenotype to be taken into consideration.

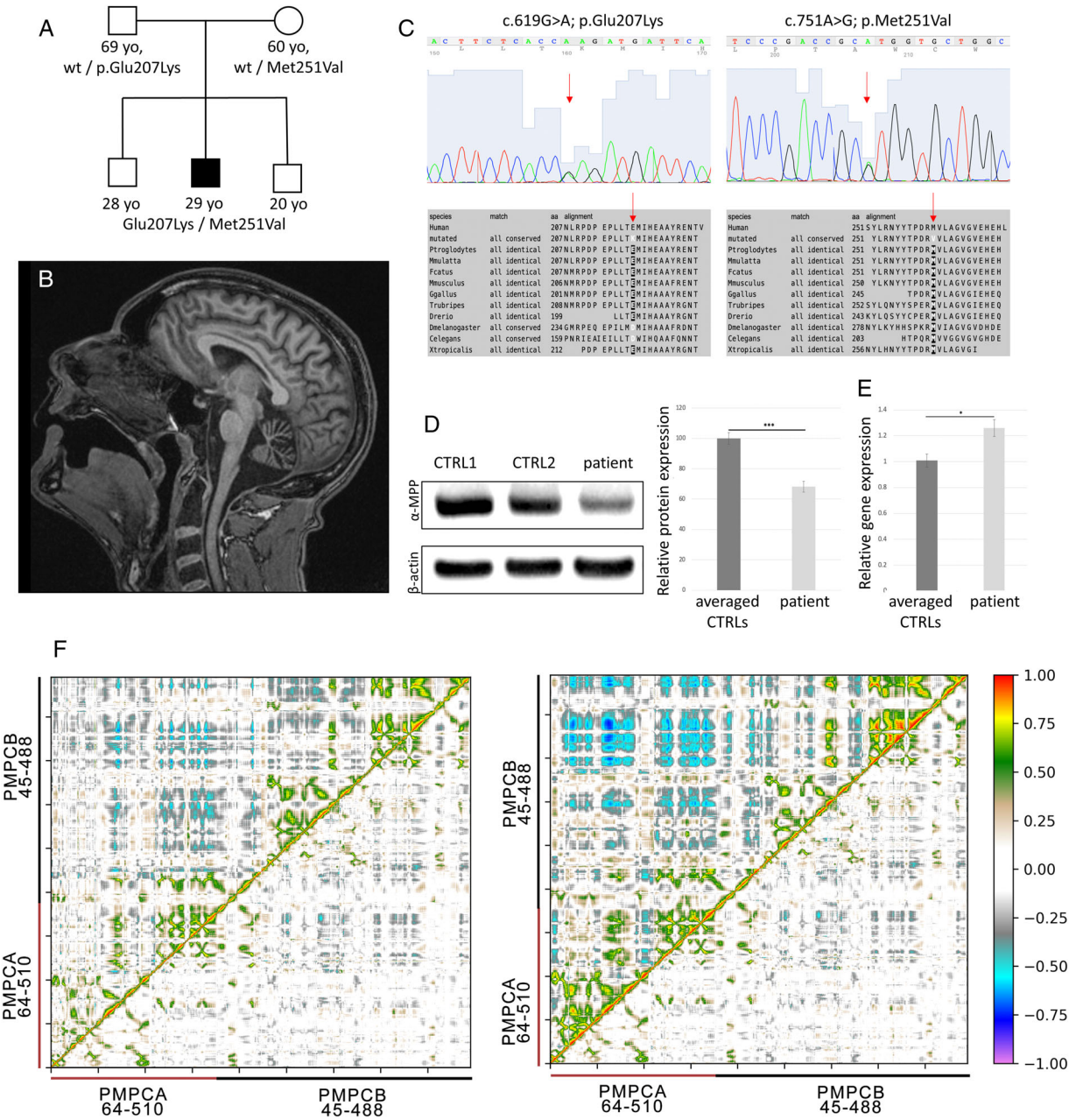


Figure 1. Imaging, genetic, and functional studies data. (A) pedigree of the family; (B) T_1-weighted sagittal MRI of the proband showing brainstem and cerebellar atrophy; (C) electropherograms and conservation of *PMPCA* variants among species; (D) western blotting and related densitometric analysis showing significantly reduced levels of PMPCA protein expression in patient's fibroblasts compared to two unrelated controls; (E) quantitative RT-PCR showing mildly but significantly increased levels of *PMPCA* gene expression in patient's fibroblasts compared to two unrelated controls; (F) DCCM plots of WT (lower triangular) and PMPCA mutants (upper triangular). Left panel refers to p.Glu207Lys, right panel to p.Met251Val variant. Red and violet colors represent perfect direct and inverse correlations between distinct protein regions, intermediate colors represent lower correlation values.

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.

T.D.S.: 1A, 1C, 3A, 3C
V.S.: 1C, 2B
T.B.: 1B, 1C
M.L.: 1B, 1C
C.C.: 1C
T.M.: 1B, 1C
E.M.V.: 1A, 1B, 3B
A.A.: 1A, 1B, 3B.

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work, as all clinical activities were observational and carried out according to good clinical practice rules. Informed consent was obtained for reproducing video images. 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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Supporting Information

Supporting information may be found in the online version of this article.

Data S1. Supporting information.