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EPM2A in-frame deletion slows neurological decline in Lafora Disease

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Keywords

Lafora Disease; laforin; progressive myoclonus epilepsy

Lafora Disease is an autosomal recessive progressive myoclonus epilepsy with onset in teen age and death within 10 years. By age 20, patients are commonly debilitated with near-constant myoclonus associated with atypical absences interrupting every thought and spoken sentence, have significant cognitive decline and are wheelchair bound. The disease is caused by mutations in either the *EPM2A* gene encoding the laforin glycogen phosphatase or the *EPM2B* gene coding for the malin ubiquitin E3 ligase [1]. Here, we describe a patient with delayed and decelerated neurological decline, due to a novel homozygous in-frame deletion in *EPM2A* replacing 9 amino acids with a single glycine.

CASE

This 20 year-old male experienced a first generalized tonic-clonic seizure at age 16 following a history of myoclonus from age 14. The generalized seizures occurred weekly, and myoclonus became highly stimulus sensitive. Absence seizures with eyelid myoclonia, atypical absences, and myoclonic atonic seizures emerged. Seizures were refractory despite trials of valproic acid, lamotrigine, levetiracetam, clonazepam, the ketogenic diet, cannabidiol and PRN lorazepam, responding only to intranasal midazolam. Brivaracetam 50-100 mg bid helped decreased seizure frequency.

Electroencephalography revealed a background of theta slowing with generalized, photosensitive 4-6 Hz spike and polyspike-slow wave discharges, with occipital polyspikes (Figs. 1A, B). Magnetic Resonance Imaging at 16 years was normal, although follow-up 1.5

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years later revealed diffuse cortical volume loss (Fig. 1C). An epilepsy gene panel identified a homozygous mutation in the *EPM2A* gene (c.98_121DEL, p.Glu33_Arg41delinsGly).

One year following onset, the patient ceased playing lacrosse and guitar. He experienced episodic visual loss and hallucinations of frightening people. Anxiety and gait ataxia emerged. He succeeded in graduating from Grade 12 with an educational assistant at age 19. Presently, despite ongoing myoclonus, dysdiadochokinesia and dysmetria, he ambulates independently. He performs self-care activities and manages medications with supervision, although he requires assistance with higher order instrumental activities of daily living. He uses a cell phone to call friends and surf the internet. He converses with his family, only occasionally struggling with comprehension. His neurological status has been stable for over 3 years, which is a highly atypical pattern for Lafora disease, especially in early adulthood.

DISCUSSION

The patient's in-frame *EPM2A* mutation likely causes major reduction in laforin quantity or function, or both, as he does have Lafora disease. However, the unusual stabilization of the disease suggests that some quantity and function of laforin are preserved.

Laforin has two well-established domains, an N-terminal carbohydrate binding domain with which it binds glycogen and a C-terminal phosphatase domain which dephosphorylates glycogen. The interaction of the carbohydrate binding domain with glycogen is through the evolutionarily highly conserved amino acids W32, K87, W99, and D107 [2]. Our patient's mutation replaces a 9-amino acid loop region between W32 and K87 with a glycine (Fig. 1D and E). Homology modeling [3] of laforin with the patient's mutation overlayed on the crystallographically-defined structural model of normal laforin predicts that the mutation does not alter laforin's contact with glycogen at K87, W99 and D107. It however slightly angles W32 toward the glucose molecule, with the greatest distance between homologous atoms of 0.93 Å (Fig. 1F). Missense mutations of W32 and K87 are established causes of typical Lafora disease, while mutations in W99 and D107 have not been reported to date [2, 4]. Our patient's mutation potentially disturbs the contact between W32 and glycogen and partially destabilizes the protein's structure. This potential disturbance is sufficient to cause Lafora disease but not the disease's full-unfolding phenotype.

Genotype-phenotype correlations in unique patients such as this young man with Lafora disease inform gene product function. This in turn helps clarify basic mechanisms of disease and normal brain function.

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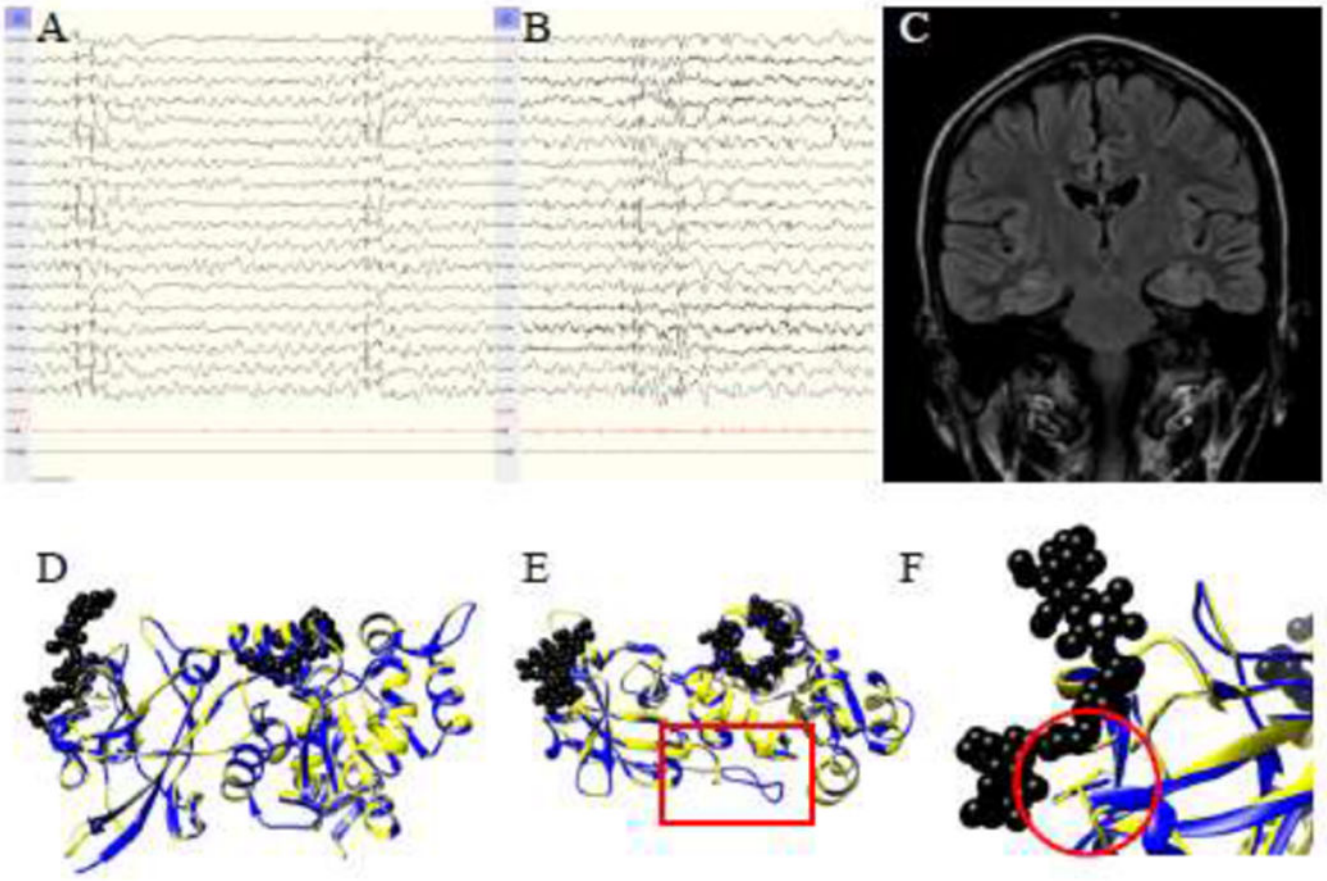

Figure 1.

(A) EEG: Generalized 4-6Hz spike and polyspike and slow wave discharges on a background of diffuse theta slowing. Superimposed generalized paroxysmal fast activity with bi-occipital predominance. (B) EEG: Burst of generalized polyspikes during a cluster of myoclonic jerks. The patient was 17 years of age at the time of this EEG. (C) Coronal FLAIR at the level of hippocampi showing diffuse cortical atrophy out of keeping with patient's age. (D) Homology model of patient mutation in laforin (yellow) overlayed with laforin structure (blue, PDB ID 4RKK). Maltohexaose molecules in black. (E) The region of the patient deletion is highlighted in the red box where the loop is truncated. (F) Conserved carbohydrate binding module residues displayed in stick model overlay well between the homology model and the experimentally determined structure. The largest deviation is 0.93A in aromatic ring of W32.