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Short Communication

A novel exon 3 mutation in a Tunisian patient with Lafora's disease

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ABSTRACT

We report a Tunisian patient born from consanguineous marriage affected with progressive myoclonus epilepsy and cognitive decline, consistent with the diagnosis of Lafora disease. Genetic analysis showed a novel c.659 T>A mutation on exon 3 of the *EPM2A* gene, converting a leucine to a glutamine residue at amino acid position 220 (p.Leu220Gln), in the dual-specificity phosphatase domain.

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1. Introduction

Lafora disease (LD) is an autosomal recessive disease, frequent in Mediterranean countries, characterized by epilepsy, myoclonus, dementia and periodic acid-Schiff-positive intracellular inclusion bodies [1]. LD is caused by mutations in the *EPM2A* or *EPM2B/NHLRC1* genes localized on 6q24 and respectively encoding Laforin and Malin [2,3]. The EPM2 gene expands 4 exons and more than 30 different mutations have been reported [4,5]. We report a novel mutation in a Tunisian family with a phenotype of Lafora disease.

2. Case report

A 16-year-old female patient was referred to the neurological department of Charles Nicolle Hospital, Tunis, at age of 14, for seizures and cognitive decline. She originated from Tataouine (south of Tunisia), was born to third degree related parents. Her medical history showed no problems at birth and psychomotor development was normal until the beginning of adolescence. In her family history, a sister, dead at age of 22, presented cognitive decline and intractable epilepsy beginning at the age of 14.

From the age of 12, the patient's parents noted erratic jerks of arms. Electroencephalography (EEG) findings at that time were unremarkable (Fig. 1A). One year after, she had experienced monthly tonic–clonic seizures, visual hallucinations and a decline in her school performance. EEG revealed slow background activity, irregular generalized spike-waves and polyspike-waves enhanced by photic stimulation (Fig. 1B). Laboratory evaluations, ophthalmologic examination and brain imaging were normal. Despite adequate anti-epileptic treatments, the patient continued to have seizures and her mental decline continued. Her last visit to our department was at age of 16 with very frequent seizures. Neurological examination showed impaired cognition, dysarthria and ataxia. EEG showed long bursts of diffuse slow waves enhanced by photic stimulation (Fig. 1C; D). LD was suspected on the basis of the electroclinical picture. Microscopic examination of the axillary skin biopsy did not reveal Lafora bodies.

Genetic analysis, after informed consent, showed that the patient was homozygous for a novel c.659 T>A mutation on exon 3 of the *EPM2A* gene (Fig. 2). It was predicted to convert a leucine to a glutamine residue at amino acid position 220 (p.Leu220Gln), in the dual-specificity phosphatase domain. The parents were heterozygous for this mutation.

3. Discussion

Our patient had a typical clinical presentation of LD on the basis of the family history, age at onset, typical appearance of symptoms, rapid worsening of cognitive function and typical EEG features. The genetic finding in our patient confirmed the diagnosis of LD and provided two main results. First, the mutation involving the *EPM2A* was unexpected. Indeed, *EPM2A* mutations have been considered not frequent in Mediterranean countries in comparison to *NHLRC1* mutations [5]. The second finding was the novel mutation of *EPM2A* never reported in the genetic database of LD [4,6]). This amino acid, converting a leucine to a glutamine residue, is highly conserved among species [4]. This mutation was not found in ethnically matched control individuals [4].

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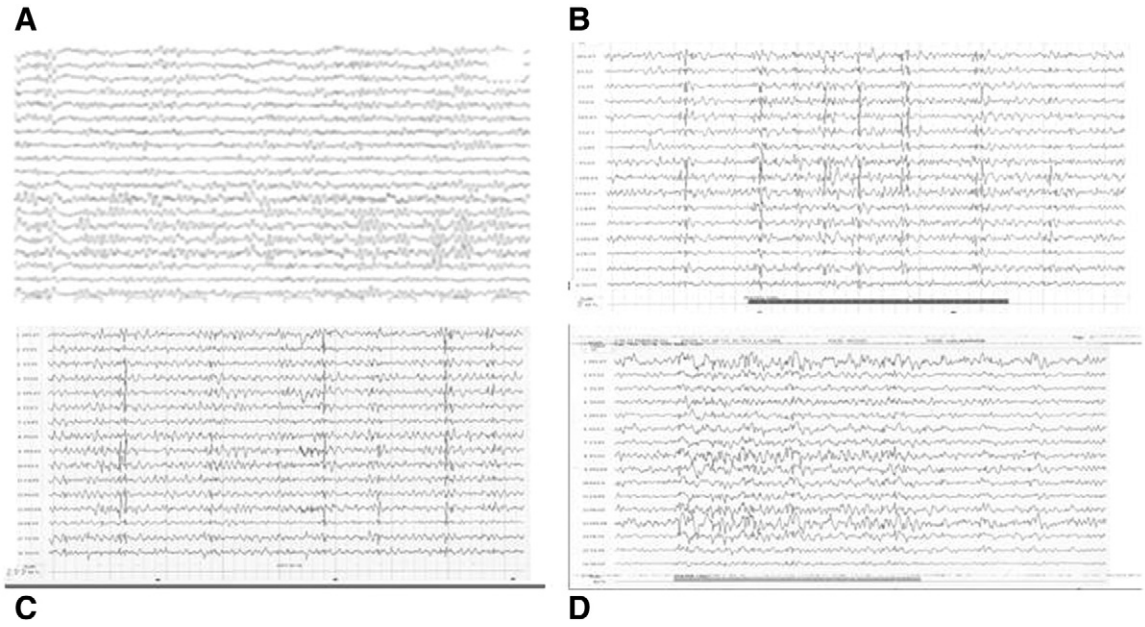


Fig. 1. EEG changes in a patient with Lafora disease. (A) At onset (age 12 years) EEG showed slightly slowed background activity. (B) one year later (age 13 years), irregular generalized spike-waves and polyspike-waves enhanced by photic stimulation. (C) At age 14 years, generalized spike-waves and slow background activity. (D) Her last visit (age 16 years), EEG recordings show long bursts of diffuse slow waves.

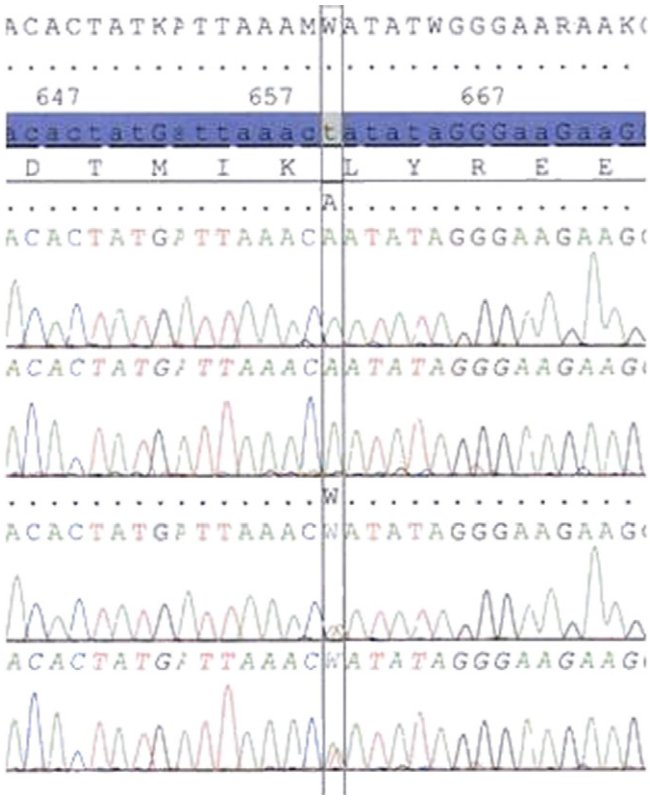


Fig. 2. Genetic analysis of Lafora disease. A homozygous c.659 T>mutation was found on exon 3 of EPM2A patient gene. Parents were heterozygous.

4. Conclusion

This first *EPM2A* mutation reported in a Tunisian family will bring additional data to the genetic epidemiology of LD. Our finding together with the other new mutations recently described will help to complete the pathogenetic understanding of the disease and certainly develop new therapeutic gene replacement trials.

Informed Consent/Ethics of Experimentation

We received prior approval by the appropriate institutional review body. Informed consent was obtained from each subject or patient.

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