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Short communication

A novel EPM2A mutation in a patient with Lafora disease presenting with early parkinsonism symptoms in childhood

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1. Introduction

Lafora Disease (LD) is an autosomal-recessive disorder first described as a fatal form of progressive myoclonic epilepsy. LD is a neurodegenerative disease caused by mutations in one of two genes: *EPM2A* encoding laforin or *NHLRC1* encoding malin; the mutations trigger loss-of-function of (respectively) glucogen phosphatase and E3 ubiquitin ligase [1]. Classical LD usually presents in adolescence; the symptoms include stimulus-sensitive myoclonus, tonic–clonic–absence epilepsy, and visual hallucinations [2]. Herein, we describe a child with molecularly diagnosed LD who developed early parkinsonism.

2. Case report

A 13-year-old girl was admitted to our clinic with seizures. She was the third child of first-degree consanguineous parents. She had two healthy sisters and a brother. Her early developmental milestones were unremarkable, but she had experienced a brief tonic–clonic seizure at the age of 10 years. At that time, she had been assessed in terms of epileptic status. However, as her neuroimaging, electroencephalographic, and laboratory findings were normal, no medication was prescribed.

Her major complaint was a generalized tonic–clonic seizure, 3–4 min in duration. She was very cooperative upon neurological examination. The cranial nerves were intact, and the muscle tonus was normal (thus, without weakness or any pyramidal symptom). She found it difficult to perform repetitive hand movements and exhibited resting tremor aggravated by motion. All serum blood test data exploring liver, kidney, and thyroid function, as well as the hemogram, were normal. We found no evidence of Wilson's disease; the serum copper and ceruloplasmin levels were within normal limits. Neither corneal nor fundus examination revealed any abnormality. Routine metabolic tests (tandem MS and blood and urine amino and organic acid levels) were not of assistance. Cranial magnetic resonance imaging (MRI) did not reveal any specific pathology. Electroencephalography revealed abnormal discharges; these were commonly generalized, high-amplitude spike complexes, especially in the bilateral fronto-temporal regions. She was prescribed valproic acid (750 mg/day). Six months later she was seizure-free, but her school performance, speech commencement, and saliva production control had decreased. On questioning, she delivered short tardy answers. She later experinced myoclonic seizures, visual hallucinations, and behavioral impairments. The seizures were not controlled by various combinations of anti-epileptic drugs (lamotrigine, levetiracetam, topiramate, and clonazepam). A repeat electroencephalogram revealed generalized high-amplitude spikes and multiple spike series with slow backgrounds. Electron microscopic examination of sweat gland biopsy material revealed ceroid-containing

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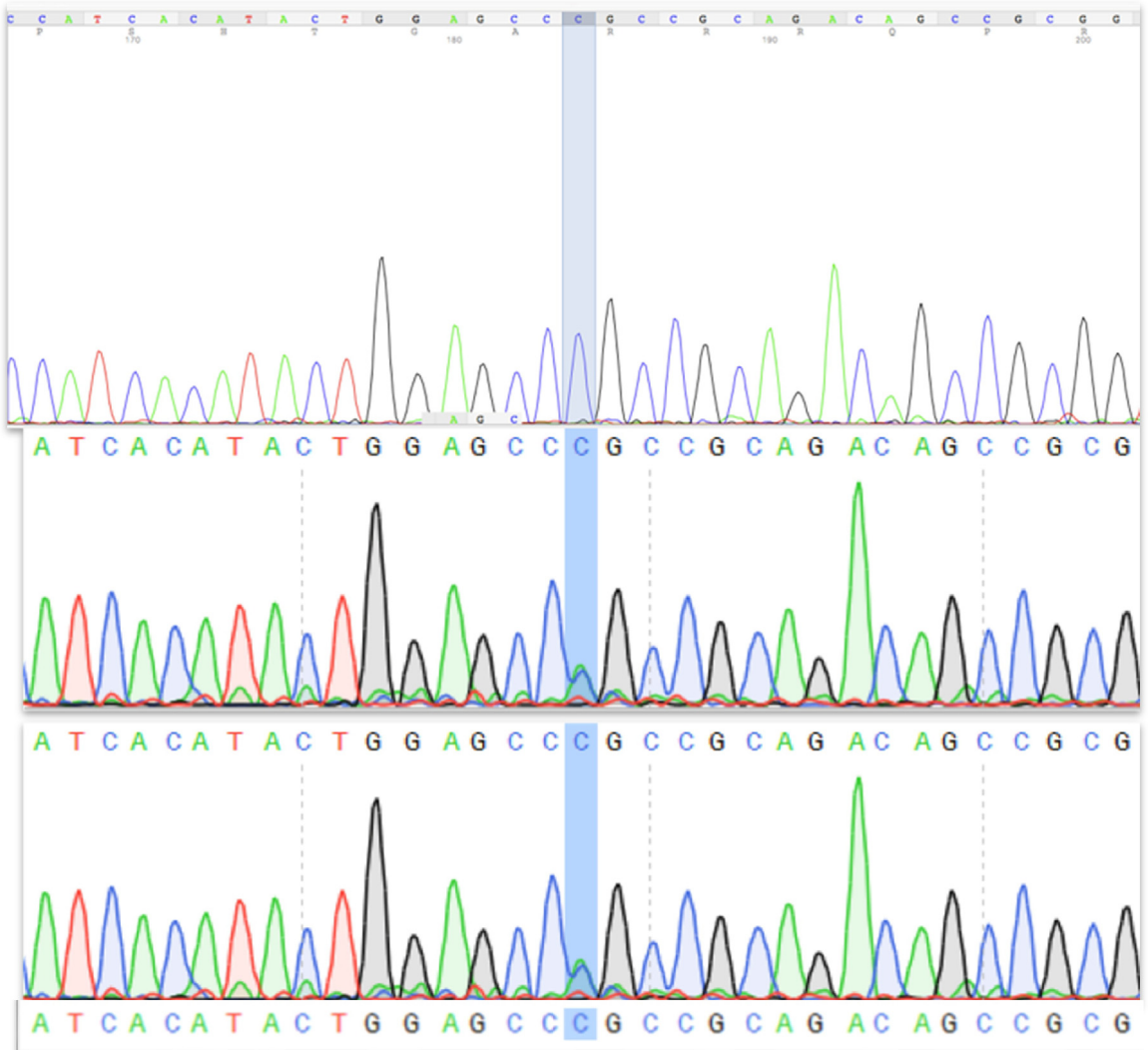

Fig. 1. The EPM2A sanger sequencing of the patient showed homozygous c.838T > G change in reverse read (top). The mother (middle) and father (bottom) were found to be heterozgyous carriers for the novel variant.

rectilinear and fingerprint inclusions as well as vacuoles containing lipofuscin. Genetic mutational analysis for neuronal ceroid lipofuscinosis (NCL) was negative. At the age of 14 years, she presented with continuous myoclonic jerking, dementia, mutism symptoms, and frequent falls when walking. Upper limb rigidity was also apparent. The late-childhood symptoms, including progressive myoclonic epilepsy and severe neurocognitive impairment, caused us to evaluate her LD status. *EPM2A* analysis revealed a new homozygous mutation (NM_005670.3; **c.838T > G;** pTrp280Gly) (Fig. 1). This missense variation is not recorded in either the EXAC or EVS database, but is predicted to be "damaging" by both the SIFT and Mutationtaster websites.

3. Discussion

LD is an autosomal recessive form of progressive myoclonic epilepsy. Classically, the disease develops in childhood (between the ages of 9 and 18 years [2]). Diagnosis is dependent on axillary skin biopsy and genetic analysis [2,3].

Our patient exhibited generalized tonic–clonic seizures that were controlled with AED for the first 2 years after the initial symptoms developed. However, the symptoms then worsened, accompanied by rapid neurocognitive regression. When she was aged 11 years, both tremor and a difficulty in commencement of spontaneous repetitive hand motion were apparent, and she later exhibited both bradykinesia and rigidity. To the best of our knowledge, only one LD patient has been described in the literature; that patient was aged 53 years and exhibited refractory epilepsy, neurocognitive impairment, and parkinsonism. Our present patient developed parkinsonism much earlier than did the previously reported patient.

In conclusion, we describe an LD patient with a novel *EPM2A* mutation presenting with early-onset parkinsonism and severe neurocognitive decline [4].

Conflict of interest

None.

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