

# A Novel Mutation in Lafora Disease and Update on Pathophysiology and Future Treatments

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## Abstract

Lafora disease is a rare refractory epilepsy that results in death. This report highlights two cases of lafora disease and introduces a novel mutation in the patients. A review of the pathophysiology and future therapies is reviewed.

## Keywords

epilepsy, genetic epilepsy, progressive myoclonic epilepsy, lafora disease

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## Introduction

Lafora disease is a rare type of progressive myoclonic epilepsy characterized by refractory seizures, prominent myoclonus and early death. The prevalence has been best estimated to be roughly four cases per one million persons.<sup>1</sup> A once lethal disease may be on the brink of breakthrough with the rise of gene editing therapies. Basic animal models have shown promise in potentially curing the disease. This report highlights a novel mutation producing Lafora disease and summarizes recent advances in the understanding of its pathophysiology and treatment. An increased ability to recognize and differentiate Lafora disease from juvenile myoclonic epilepsy will allow for a faster time to diagnosis and consideration of novel targeted therapies.

## Case Report

A 16 year old young man (patient 1) presented to the pediatric intensive care unit with status epilepticus. The patient was diagnosed with juvenile myoclonic epilepsy at the age of 13 years. His seizures began with prominent myoclonus involving his distal upper and lower extremities. He initially experienced biweekly convulsions that progressed to daily treatment resistant generalized tonic clonic seizure clusters. His myoclonus was so severe that he was unable to feed himself with utensils and write with a pencil at school. Despite treatment with

vagus nerve stimulator, levetiracetam, valproic acid and scheduled clonazepam the patient continued to have seizures. He experienced significant cognitive decline over a 3 year period and began to have prominent visual hallucinations of insects crawling on walls. He withdrew from school due to his cognitive decline and inability to write. A review of his initial EEG was performed which revealed prominent occipital discharge (Figure 1). Magnetic resonance imaging of the patients brain was normal. The patient's 14 year old brother (patient 2) had a near identical clinical course beginning at age 12. He also experienced treatment resistant convulsions, visual hallucinations (seeing rainbows), prominent myoclonus and intellectual decline. This patients EEG also revealed occipital predominant discharges (Figure 2). A whole exome sequence was obtained for both siblings which revealed a compound heterozygous mutation responsible for Lafora disease.

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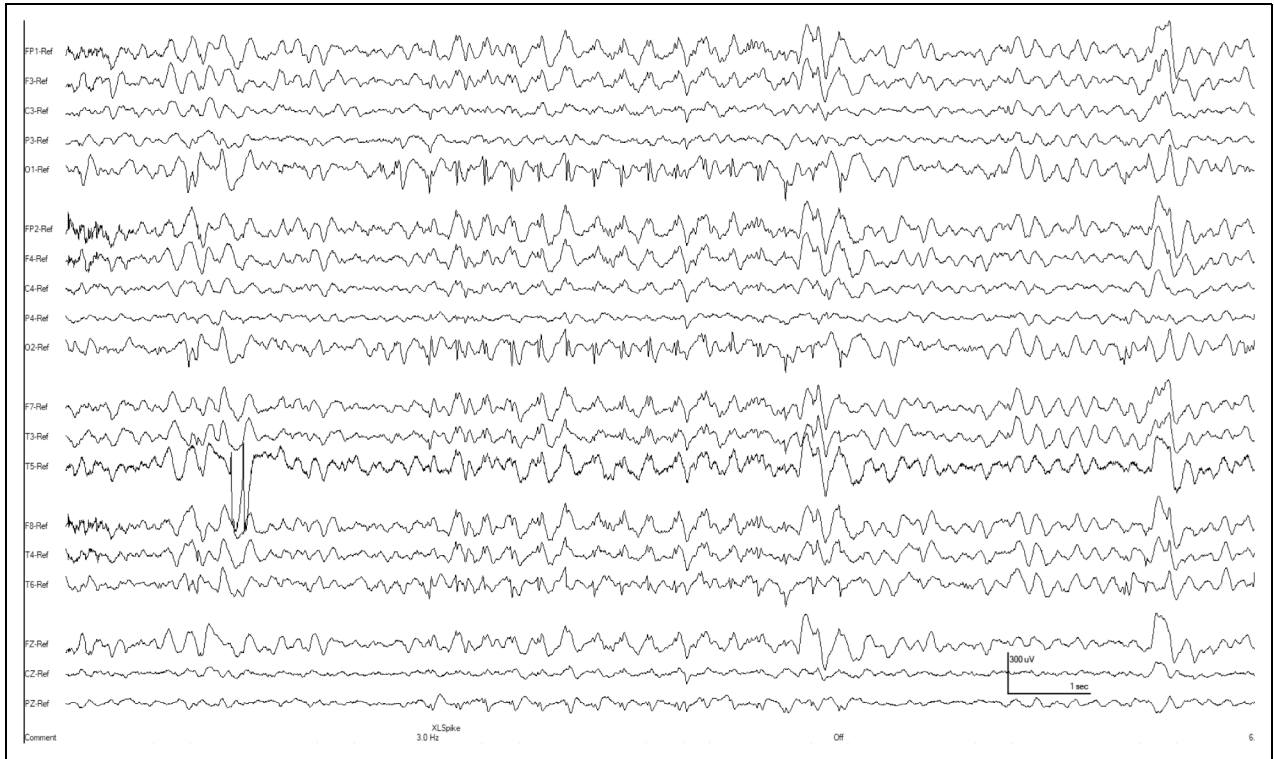


Figure 1. Average referential montage showcasing occipitally predominant spikes from patient 1.

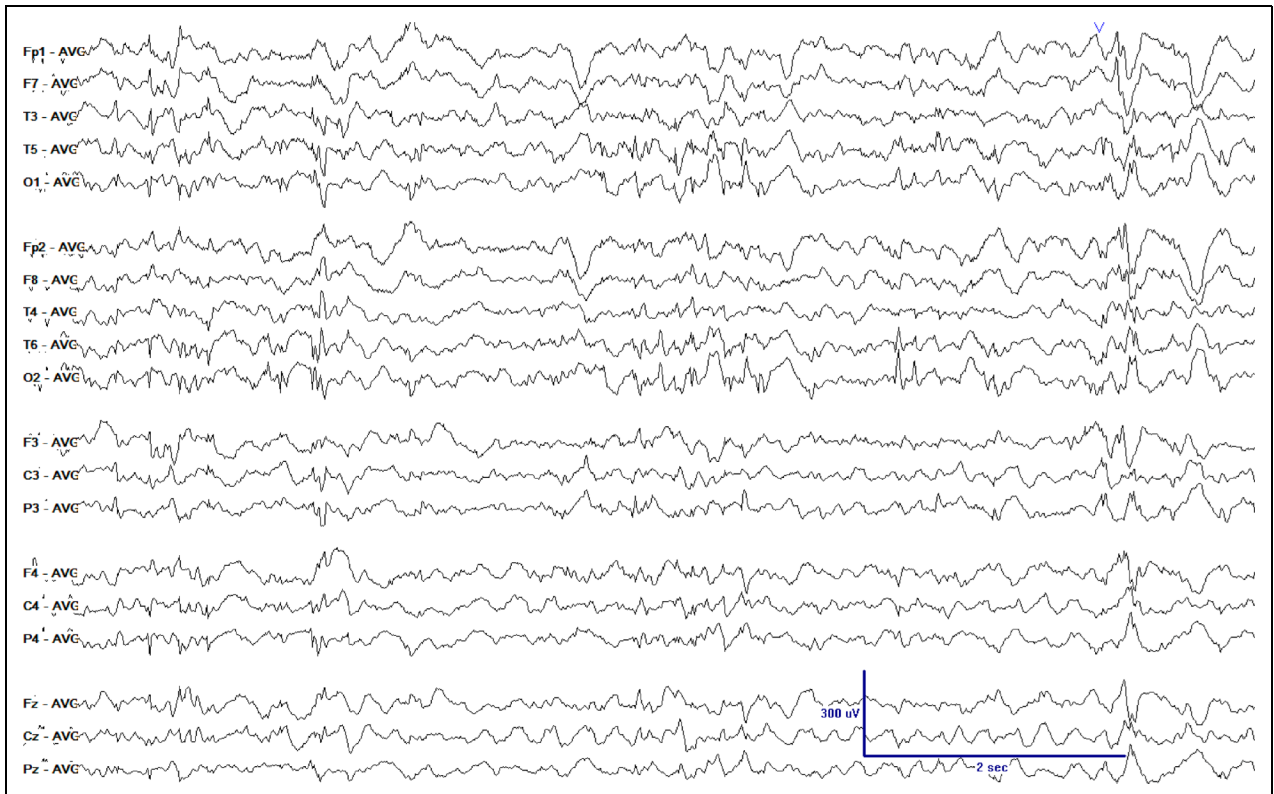


Figure 2. Average referential montage showcasing occipitally predominant spikes from patient 2.

## Results

Whole exome sequencing was obtained for the patient 1 and 2 which revealed a novel compound heterozygous mutation in *EPM2A* gene (c.721C>T, and c.624\_627dup) and clinical picture of Lafora Disease. Each parent was a carrier of one mutation.

The mutation c.721C>T causes a premature stop codon. The c.624\_627dup causes a frameshift mutation and premature protein termination resulting in a dysfunctional *EPM2A* gene.

## Discussion

Lafora disease is a severe type of progressive myoclonic epilepsy that remains challenging to diagnose due to its rarity. Patients have been reported to be diagnosed with JME when they in fact have a PME.<sup>2</sup> Thus, it is critical to be familiar with features of both in order to accurately diagnose and treat patients. Concerning features of a progressive myoclonic epilepsy include: cognitive impairment, treatment resistant juvenile myoclonic epilepsy, resting myoclonus and negative myoclonus.<sup>3,4</sup> Additionally, an EEG that shows occipital discharges as opposed to the classic 4–6 hz polyspike and wave discharges should be a red flag.<sup>5</sup>

This report highlights a novel mutation in c.624\_627dup which has not been reported in literature. The mutation in c.721C>T has been shown to cause a premature stop codon.<sup>4</sup> Both effect *EPM2A* and have been classified as pathogenic in both patients.

Lafora disease is caused by mutations in *EPM2A* and *NHLRC1* which encode laforin and malin, respectively.<sup>6–8</sup> Laforin and malin are molecules that serve to regulate glycogen. Lafora disease is caused by abnormal glycogen accumulation in the brain which results in Lafora body deposition.<sup>7,8</sup> Laforin and Malin both act on glycogen to ensure that it remains soluble in the CNS.<sup>1</sup> Lafora bodies are a result of glycogen that is insoluble.

Patients with Lafora disease experience refractory epilepsy, visual hallucinations and progressive dementia which is believed to be secondary to the accumulation of glycogen and subsequent inflammation.<sup>1</sup> Patients are often refractory to multiple medications and die from the disease within 10 years of onset.<sup>1</sup> The most common cause of death is status epilepticus and respiratory failure.

Recent advances in animal models have shown promise for patients with Lafora disease. Research has identified a better response to perampanel in patients with Lafora disease compared to other seizure medications.<sup>8–12</sup> The exact mechanism of perampanel in the control of seizures in LD remains unknown. Metformin has been designated as an orphan drug for the treatment of Lafora disease.<sup>1</sup> In animals models metformin has been shown to slow the progression of Lafora disease by impacting gluconeogenesis, thereby decreasing systemic glycogen.<sup>2,8</sup> Human cases describing the response to metformin are lacking. Patient 2 in our case was started on perampanel and

metformin with seizure diary indicating a decrease in convulsions from daily to weekly.

Arguably the most exciting breakthrough with Lafora disease has come through advances in gene therapy. Landmark research in animal models demonstrate the ability to stop the Lafora disease phenotype by decreasing the activity of glycogen synthase.<sup>13</sup> Animals models have shown that introducing a mutation to produce half of the working glycogen synthase enzyme is adequate to provide necessary glycogen for survival without causing Lafora disease. Plans for a human safety trial are currently underway.<sup>8</sup>

## Conclusion

Lafora disease is a rare progressive myoclonic epilepsy that historically has resulted in death within 10 years of diagnosis. The ability to recognize and diagnose Lafora have never been as important with the rise of breakthrough treatment strategies.



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