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Clinical letter

Lafora disease in a Malaysian with a rare mutation in the *EPM2A* gene

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1. Introduction

Mutations in the EPM2A gene encoding a dual-specificity phosphatase (Laforin) cause an autosomal recessive fatal disorder called Lafora disease (LD) classically described as an adolescent-onset stimulus sensitive myoclonus, epilepsy and neurologic deterioration [1]. Skin biopsy reveals Lafora bodies (LB), which are pathognomonic and not seen with any other progressive myoclonus epilepsies. Genetic testing is crucial to confirm the diagnosis as it reveals mutation in the *EPM2A* or *NHLRC1* gene. To date, at least 105 different mutations in the EPM2A gene and 84 mutations in NHLRC1 have been reported in the Lafora Progressive Myoclonus Epilepsy Mutation and Polymorphism Database (http://projects.tcag.ca/lafora) [2]. However, data on mutations from South East Asia, specifically among the ethnic Malay patients in Malaysia have never been reported.

2. Case report

A 26-year-old Malay gentleman presented with myoclonic epilepsy, progressive cognitive decline and unsteady gait since the age of 19. Six years into his illness, he became bed bound and fully dependent for his activities of daily living. He was the second child of four children from a non-consanguineous marriage. He had a normal childhood development history with no prior febrile seizure, head trauma or brain infection. He completed his secondary education with average grades.

In January 2018, he was hospitalised due to aggressive behaviour with acts of self-harm. His condition rapidly deteriorated with further cognitive decline and medically refractory epilepsy. He was obtunded, uncooperative with poor eye contact, only occasionally producing incomprehensible sound, and was smiling inappropriately. There was no focal neurological deficit on examination and ophthalmology assessment was normal. Neuropsychiatry assessment suggested postictal psychosis. He was subsequently intubated for status myoclonicus and required high doses of multiple antiepileptics to control his seizure, which included sodium valproate, levetiracetam, phenobarbitone, clonazepam, topiramate and perampanel. Brain computed tomography imaging did not show any significant abnormalities. His blood lactate levels were normal. Serial electroencephalograms (EEG) showed background slowing with the presence of multiregional spikes and generalised polyspikes [Fig. 1A]. In view of the constellation of symptoms and a positive family history, an adolescent onset neurodegenerative disease was suspected.

We proceeded with a skin biopsy from his left thigh, and histological examination showed the presence of intracytoplasmic inclusion bodies at the eccrine duct with positive Periodic acid-Schiff (PAS) stain [Fig. 1B] which strongly suggested the diagnosis of LD. The molecular analysis for the *EPM2A* or *NHLRC1* genes was performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103,

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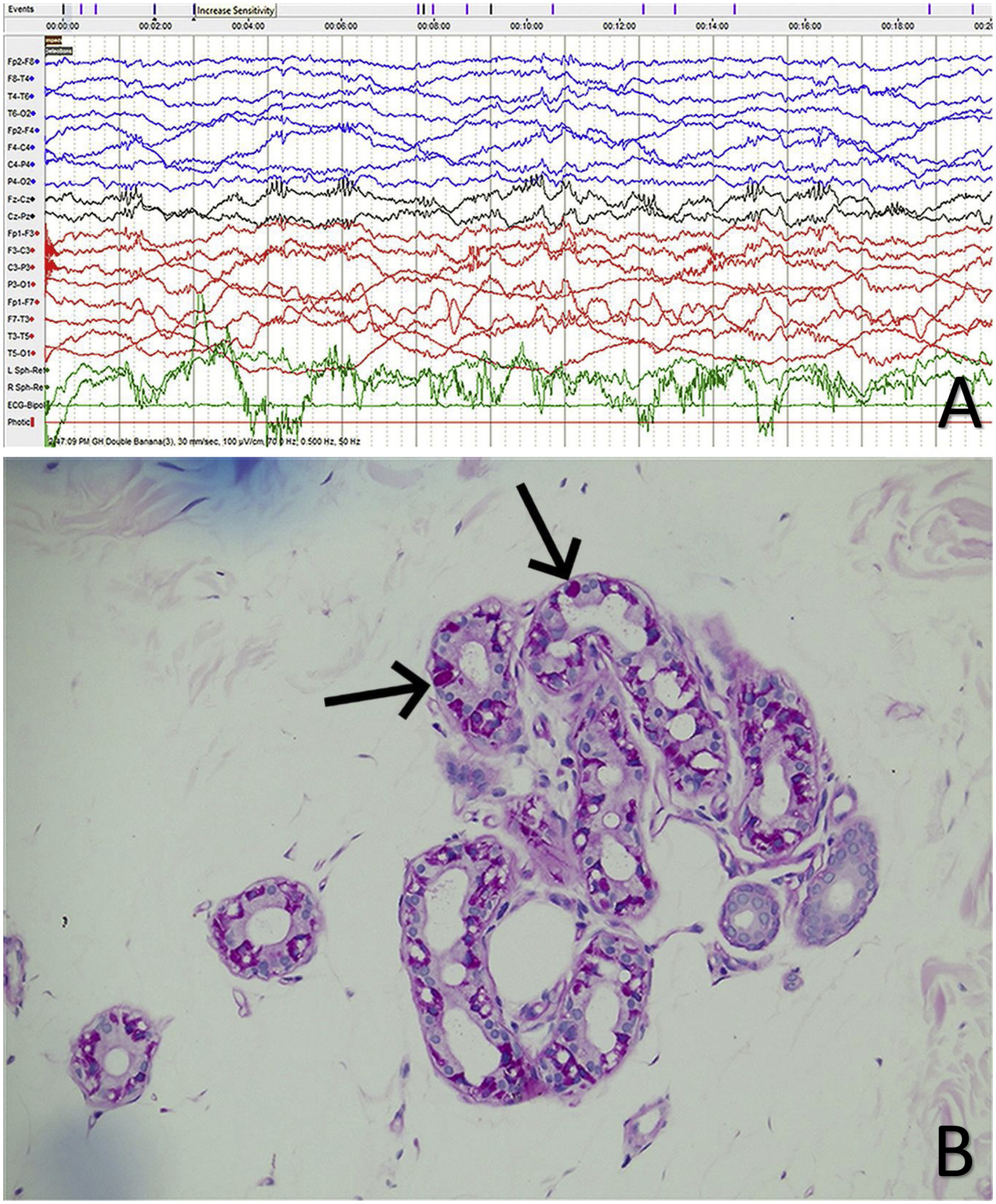

Fig. 1. A. EEG 10–20 system, double banana montage, 100 u V/cm, 30 mm/second, high frequency filter (HFF) 70 Hz, low frequency filter (LFF) 0.5 Hz. Diffused slowing with generalised polyspikes (predominantly bilateral frontocentral regions) and multiregional spikes. B. Light microscope x200. Eosinophilic round inclusion in the cytoplasm of the eccrine glands. Periodic acid Schiff (PAS) highlights the Lafora bodies (arrows).

#05D2040778) using their Epilepsy Panel. Genomic DNA was enriched for targeted regions using a hybridization-based protocol and sequenced using Illumina technology. Gene deletions and duplications were called using an in-house algorithm and confirmed with array comparative genomic hybridization. The results showed compound heterozygous mutations in the *EPM2A* gene- a whole gene deletion and a rare missense mutation in exon 4, c.758A > T, p.(His253Leu) (NM_005670.3). The patient had two brothers with similar adolescent onset cognitive decline and myoclonic jerks. One younger brother, now aged 21 carried the same two mutations. The other brother passed away

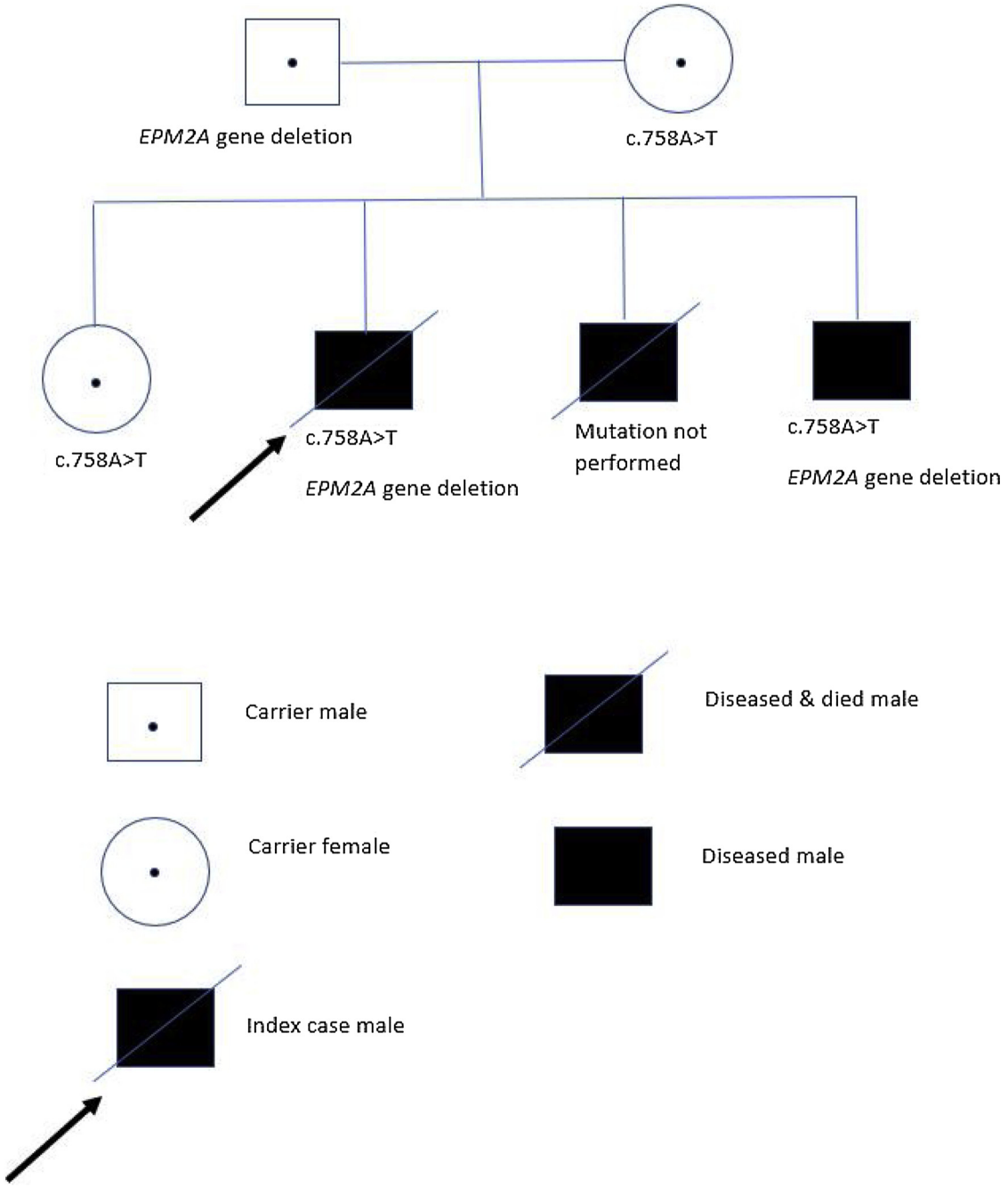

Fig. 2. Family pedigree.

due to drowning at 24 years old before genetic testing could be performed. We were unsure if this was seizure-related. His father was a heterozygous carrier of *EPM2A* gene deletion. His mother and asymptomatic elder sister were heterozygous carrier of the c. 758A > T mutation [Fig. 2].

Despite multiple antiepileptics, his condition continued to deteriorate, and he succumbed to his illness eight months after hospitalization.

3. Discussion

Our patient had a classical presentation of LD as described by Ganesh et al with adolescent-onset stimulus sensitive grand mal, absence and myoclonic seizures followed by dementia and neurologic deterioration. The disease is associated mainly with mutations in exon 4 of the *EPM2A* gene [1].The gross, heterozygous whole gene deletion mutation was classified as pathogenic and has been reported in only three patients thus far [2]. Unfortunately, the boundaries of this event are unknown as the deletion extends beyond the assayed region for this gene and therefore may encompass additional genes. A second heterozygous mutation in our patient, c.758A > T has not been previously reported in the "Lafora Progressive Myoclonus Epilepsy Mutation and Polymorphism Database" but was found in Exome Aggregation Consortium (ExAC) database and Genome Aggregation Database (gnomAD) at a frequency of 0.000008332 and 0.000004017, respectively. However, the variant was not detected in 100 genomes of Singapore Malays retrieved from the SingaporeSequencingMalayProject(SSMP) (http://phg.nus.edu.sg/StatGen/public_html/SSMP/SSMP_index.html).

In silico prediction for c.758A > T, p. (His253Leu) mutation showed conflicting results; pathogenic for MutationTaster and PROVEAN but benign for FATHMM-XF and Condel. Using its

automated setting, InterVar classification system suggested this mutation as 'Uncertain significance', but when considering the presence of another pathogenic mutation in trans InterVar classification changed to 'Likely pathogenic'.

Mutation segregation analysis showed these two mutations to segregate in the symptomatic siblings. Pathogenicity of this mutation may be made clearer if found in other unrelated patients as well.

Several authors have reported high false negative rate of skin biopsy [3,4]. However, skin biopsy remains a useful diagnostic tool in patients negative for mutation screening and in countries with no access to advance genetic testing.

4. Conclusion

We have reported a Malaysian of Malay ethnicity with Lafora disease. To our knowledge, this is the first reported case of Lafora disease with the rare mutation c.758A > T, p. (His253Leu) associated with a whole gene deletion. This finding may widen and enhance our understanding towards the complex genetic heterogenicity of Lafora disease.

Consent

Informed consent was obtained from patient's father.

Declaration of interests

None

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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