■ Clinical commentary

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Epileptic Disorders

Epilepsy phenotypes associated with *MAP1B*-related brain malformations

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ABSTRACT – Recently, studies on whole-exome sequencing (WES) of large cohorts of people with periventricular heterotopia (PVH) have reported an association with loss-of-function variants in the *MAP1B* gene. However, neurological phenotypes of these patients remain poorly characterized. Four family members with seizures beginning in early childhood were evaluated. Integrated genomic analysis with WES and microarray was performed. Affected family members had various combinations of: febrile, fever-triggered and afebrile seizures; photo-sensitivity; comorbid mild developmental delays; obsessive-compulsive behaviors; and poor attention span. Neuroimaging showed PVH, corpus callosum abnormalities, and perisylvian polymicrogyria. A novel heterozygous frameshift variant in *MAP1B* was found in all affected family members. This report extends the clinical and neuroimaging phenotypes associated with *MAP1B* pathogenic variants. *MAP1B* variants may be considered in patients with febrile and afebrile seizures if characteristic neuroimaging, particularly PVH, is observed.

Key words: periventricular heterotopia; perisylvian polymicrogyria; genetic epilepsy

Periventricular heterotopia (PVH), a malformation of brain development, is associated with epilepsy in 85%-90% of patients, with seizure activity originating within the heterotopia and/or the overlying cortex [1]. Although PVH is genetically diverse, pathogenic variants in 10 genes account for about 25% of sporadic instances, with *FLNA* variants being most frequently reported [2-6]. Recently, exome sequencing of 202 individuals with sporadic PVH revealed loss-of-function variants in *MAP1B* to be associated with frontally predominant PVH and peri-sylvian polymicrogyria [6]. Other *MAP1B* loss-of-function variants have been reported in patients with developmental delay, intellectual disability, or autism spectrum [7-9]. However, there is a lack of data about neurologic manifestations of *MAP1B*-associated PVH. Here, we report a family with four affected members with epilepsy, comorbid behavioral disorders, and *MAP1B*-related brain malformations.

Case reports

Index patient

The index patient was a 2.3-year-old, left-handed girl, who started having seizures at around 3.5-months of age. Her seizures included full-body jerking, staring, upward rolling of the eyeballs, and unresponsiveness, for about five minutes, and falling asleep afterwards. These seizures occurred almost daily during any febrile illness, and less often (0-2/week) without fever.

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Her mother had recurrent gestational diabetes requiring insulin. She was delivered by emergency C-section at 37 weeks gestation during a maternal hypoglycemic episode and required intravenous fluids for 24 hours to help maintain her blood glucose levels.

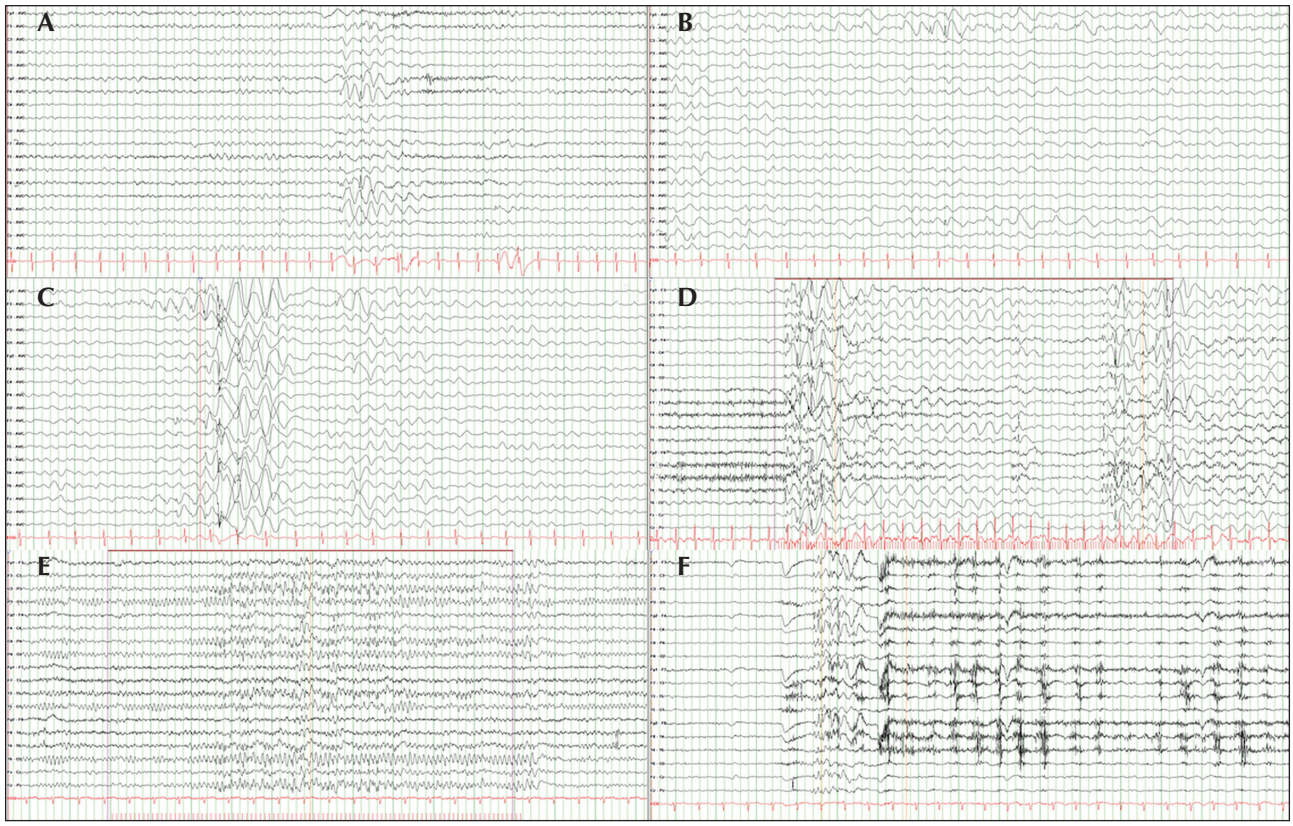
She had age-appropriate motor skills but mildly delayed language and personal/social domains, with 5-10 single words, and had began to combine words. She came across as a playful, interactive child, and identified accompanying family members. There were no cranial nerve or motor deficits.

Her electroencephalography (EEG) showed bilateral multi-focal and diffuse epileptiform discharges, and photo-convulsive response (*figure 1A-D*). Her brain magnetic resonance imaging (MRI) showed gray matter heterotopia along the frontal horns of both lateral ventricles and left temporal horn; a thin corpus callosum; mild hypomyelination; mildly enlarged and somewhat distorted third and lateral ventricles; and suspected incomplete inversion of the left hippocampus (*figure 2A*).

She received levetiracetam since the onset of her seizures, which was ineffective. Topiramate and valproic acid completely controlled her afebrile seizures, and only two febrile seizures were reported at four months follow-up. However, she had a recent recurrence of seizures with sub-therapeutic levels of anti-seizure medications, raising concerns about adherence.

Full sibling

The full sibling of the index patient was a 4.6-year-old, ambidextrous male, who started having atypical febrile seizures at around 4.5 months of age,



■ **Figure 1.** EEG of the index patient (A-D) and half-sibling (E-F). The index patient was noted to have bursts of right fronto-temporal (A), left frontal (B), and diffuse bilateral (C) discharges (the example depicted in C shows a left frontal lead-in, but shifting asymmetry was observed). A photo-convulsive response (myoclonic jerk of upper body) was also seen (D). The half-sibling also showed a reproducible photo-paroxysmal response at 9 (E) and 20-Hz intermittent photic stimulation, along with diffuse bilateral polyspikes and slow-wave discharges (F) with shifting amplitude emphasis. All EEGs are shown at filter settings: high-pass of 1 Hz, low-pass of 70 Hz, notch of 60 Hz, and time base of 15 mm/sec. The sensitivity is 30 µV/mm (A-D), 10 µV/mm (E), and 20 µV/mm (F) respectively.

described as whole-body jerking, lasting 0.5-1 min, and often occurring in clusters. He had had about 10 seizure clusters, with the last around 3.2 years of age. He did not have afebrile seizures. He had compulsive and ritualistic behaviors including repetitive hand washing and arranging things (e.g. toy cars, according to their color).

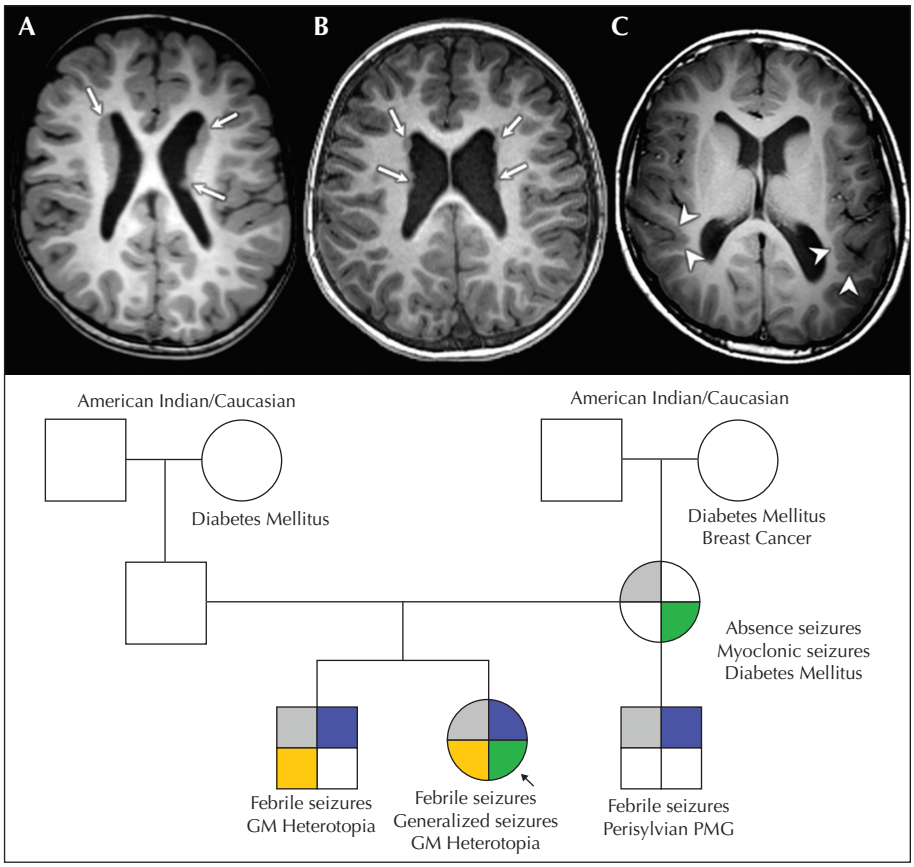
He was large for gestation and was delivered by emergency C-section at 42 weeks gestation, due to threatened scar dehiscence and maternal hypoglycemia. He had respiratory difficulty at birth which required supplemental oxygen for 24 hours and nursing care for six days. He was developmentally age-appropriate and had a normal neurological exam.

His EEG showed a mildly slow background but no epileptiform abnormalities. His brain MRI showed multiple sub-ependymal gray matter heterotopia, mild volume loss with enlargement of the lateral ventricles and thinning of the corpus callosum, which was more pronounced posteriorly (*figure 2B*). He has remained seizure-free for the last 2.5 years on levetiracetam.

Maternal half-sibling

The maternal half-sibling of the index patient was a 12.8-year-old, right-handed male, who started having apparently generalized tonic-clonic seizures around two years of age, during febrile illnesses, consistent with both typical and atypical (prolonged, multiple) febrile seizures. The last seizure occurred before his 12th birthday. He did not have afebrile seizures. He also had migraine, and comorbid attention deficit and obsessive/compulsive behaviors.

He was delivered by emergency C-section at 39 weeks gestation, for a maternal hypotensive episode on attempting epidural anesthesia. However, he did not require any resuscitation or support. He was age-appropriate in all



■ **Figure 2.** Brain magnetic resonance imaging (upper panel) of the index patient (A), full sibling (B), and maternal half-sibling (C). Note the periventricular heterotopia (white arrows), thinning of posterior corpus callosum (B), and perisylvian polymicrogyria (arrowheads). Pedigree diagram is shown in the lower panel, with different colors representing heterozygosity for the pathogenic variant (c.6385delG, gray), generalized seizures (green), febrile seizures (blue), and gray matter heterotopia (yellow).

developmental domains and was in seventh grade with above-average scholastic performance. He had a normal neurological examination.
His EEG showed diffuse epileptiform discharges with bi-frontal amplitude emphasis, often occurring in 4-Hz bursts and lasting up to two seconds, and a photo-paroxysmal response (*figure 1*). His brain MRI showed bilateral peri-sylvian polymicrogyria (*figure 2C*).
He was first started on levetiracetam, which caused aggression and mood swings, but subsequent ethosuximide controlled his seizures. He continues to remain seizure-free for the last nine months.

Family history

Family history was consistent with an autosomal dominant genetic epilepsy with variable expressivity affecting the index patient, her full brother, maternal half-brother, and mother (*figure 2*). Similar epilepsy phenotypes, behavioral comorbidities, and brain MRI abnormalities were noted in the three family members. In addition, the mother reported absence and myoclonic seizures during her childhood, although no records or neuroimaging were available. Mother and her extended family were also reported to have type 2 diabetes. Consanguinity was denied both for index patient and maternal half-sibling. Ethnicity was reported to be American Indian and unspecified Caucasian.

Genetic analysis

Integrated genomic analysis was performed on the family, and whole-exome sequencing was performed on the proband, affected brother, affected half-brother, affected mother, and unaffected father. Saliva samples were collected from the family. Genomic DNA was extracted by Chemagic MSM I system (Perkin Elmer Inc., Waltham, MA). Extracted DNA was enriched using Agilent SureSelect All Exon V2 and sequenced (76 base paired end) on the Illumina HiSeq 2500 sequencer (Broad Institute, Harvard University) through Clinical Research Sequencing Platform. Sequenced data were aligned to the hg19 NCBI human reference sequence and analyzed using Ingenuity Variant Analysis software (Qiagen, Hilden, Germany), using specific filters to identify clinically relevant variants. Mutation nomenclature is based on the recommendation by the American College of Medical Genetics, such that nucleotide +1 corresponds to the A of the ATG translation initiation codon. Also, chromosomal microarray was performed on the proband, using the Infinium Assay with the Illumina CytoSNP-850Kv1.1 BeadChip platform. Linear positions of abnormalities are listed according to the Human Genome Build (GRCh37: Feb. 2009(hg19)).

Exome analysis revealed a novel heterozygous frameshift variant in *MAP1B* (NM_005909.4), c.6385delG (p.Ala2129Profs*107) in all the affected family members which was confirmed by Sanger sequencing. The identified variant, c.6385delG (p.Ala2129Profs*107), has not previously been reported in the literature nor has it been reported in any general population databases, such as the 1000 Genomes, the Exome Sequencing Project, or the gnomAD database. This variant is located in exon 5 of the total seven exons and is expected to subject to nonsense-mediated mRNA decay. Chromosome microarray did not reveal any abnormality.

Discussion

We describe four family members with epilepsy, other neuro-behavioral comorbidities, and a novel pathogenic variant in *MAP1B* associated with PVH and peri-sylvian polymicrogyria.
PVH is a malformation of cortical development, associated with a clinical spectrum from asymptomatic (neuroimaging only) individuals to drug-resistant epilepsy and intellectual disability. The neurological phenotypes of *MAP1B*-associated PVH are not described sufficiently. Heinzen *et al*. [6] reported seizures, cognitive impairment, and dysmorphic features to be variable across their four patients. Three of their four *MAP1B* variants were transmitted from an unaffected parent. In another study including nine *MAP1B* loss-of-function variant carriers with PVH, only one had a diagnosis of epilepsy [7]. Although recently a child with *MAP1B*-associated PVH was reported to have global developmental delay, seizures, microcephaly, short stature and dysmorphic features, the phenotype was confounded by prenatal alcohol exposure [8]. In contrast, we provide a detailed description of phenotypes in four members of a family with febrile and afebrile seizures, photosensitivity, and behavioral comorbidities. Although the co-existence of febrile and afebrile seizures in different members of the family raises concerns for the genetic epilepsy with febrile seizures plus spectrum, the neuroimaging was inconsistent [10].
In an aforementioned study, frontal dominant PVH with bilateral and symmetric nodules was reported in three patients, and two additionally had peri-sylvian/insular polymicrogyria [6]. However, we found the neuroimaging to be more variable in our patients (*figure 2*). Two of our patients had bilateral, but asymmetric, PVH along frontal and temporal horns. Also, both of these patients had a thin corpus callosum, which was thinner posteriorly in one case. One of our patients (half-sibling) did not have PVH but showed bilateral peri-sylvian polymicrogyria. Our finding of corpus callosum thinning in two patients

and hypomyelination in one patient is consistent with a *MAP1B* null mouse model (MAP1Bdelta93), in which heterozygotes had agenesis of the corpus callosum with dysmyelinated axonal bundles of cortical neurons [11]. Recently, another child with PVH, dysgenesis of the corpus callosum, and a *de novo* *MAP1B* nonsense variant has also been reported [8]. Our report provides a detailed description of the electroclinical features of the epilepsy associated with *MAP1B* variants. From a clinical standpoint, if future larger reports substantiate our observations, it may be pertinent to suspect *MAP1B* variants in patients with febrile and afebrile seizures, having any combination of PVH, peri-sylvian polymicrogyria, and corpus callosum abnormalities. ■

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