■ Clinical commentary

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Epileptic Disorders

Temporal-parietal-occipital epilepsy in GEFS+ associated with *SCN1A* mutation

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ABSTRACT – Most families with genetic epilepsy with febrile seizures plus show a mutation in the sodium channel alpha 1 subunit gene, however, but there is much phenotypic heterogeneity and focal epilepsy remains relatively rare. Here, we report a family with electroclinical features indicative of temporal-parietal-occipital carrefour epilepsy with common occurrence of post-ictal migraine. We studied a four-generation family including nine affected subjects by means of EEG and MRI. Genetic testing was performed by targeted re-sequencing (gene panel). In most patients, seizure semiology included cognitive, autonomic, and emotional symptoms, eventually evolving towards sensory visual phenomena. Focal sensory vestibular seizures and changes in body perception were also reported in some cases. Post-ictal migraine was common, occurring in five out of the six (83%) epilepsy patients. A missense mutation (c.1130 G>A; p.R377Q) affecting the S5-S6 segment (pore region) of the sodium channel alpha 1 subunit was identified in all affected and four unaffected subjects. Temporal-parietal-occipital carrefour epilepsy is part of the genetic epilepsy with febrile seizures plus spectrum. The electroclinical features in this family support the involvement of a genetically impaired neural network. High prevalence of post-ictal migraine suggests the role of posterior brain areas in the clinical expression of this gene defect.

Key words: epilepsy; temporal-parietal-occipital; GEFS+; neural networks; post-ictal migraine; *SCN1A*

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Genetic epilepsy with febrile seizures plus (GEFS+) was first conceptualized in 1997 by Scheffer and Berkovic as a familial, autosomal dominant, epilepsy syndrome characterized by extensive phenotypic heterogeneity [1]. Up to 2017, when the spectrum was redefined, GEFS+ was considered as "generalized epilepsy with febrile seizures plus", according to the association with generalized epilepsy phenotypes [2]. However, when the association with focal epilepsies became more evident [2, 3], the need for the more comprehensive definition "genetic epilepsy with febrile seizures plus" arose.

Here we report a family with electroclinical features indicative of temporal-parietal-occipital (TPO) carrefour epilepsy and common post-ictal migraine. A missense mutation (c. 1130 G>A; p. R377Q) affecting the sodium channel alpha 1 subunit (*SCN1A*) was identified in all patients and four unaffected subjects.

Clinical features of the family

The proband (IV-6, *figure 1*) was referred to the epilepsy clinic because of febrile seizures (FS) from the age of 21 months. A family history of seizures was reported, including seven (64%) and two (25%) clinically affected males and females. All affected family members presented with FS. Six out of nine (67%) patients also developed epilepsy later in life (*table 1*, *supplementary material*). All of them had normal cognitive function.

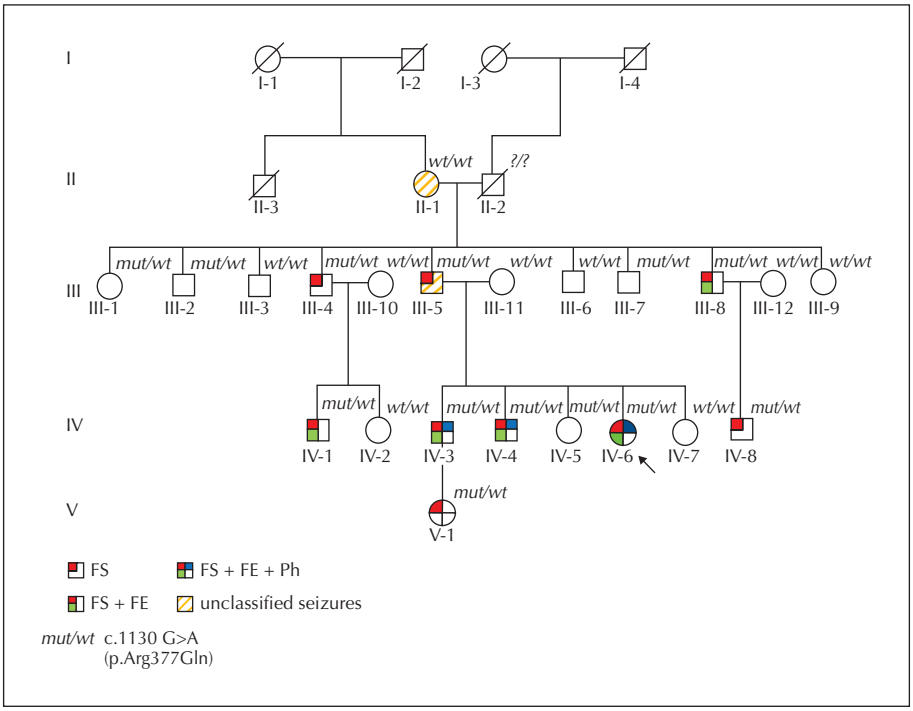
FS/FS+

Age at onset of FS ranged from 18 to 48 months (median: 21 months). Offset age ranged from 5 to 8 years (median: 7 years). For Patients IV-8 and V-1, lost to follow-up, we could only assess the development of FS during infancy. Patient III-4 initially had only FS that ended during childhood and afebrile seizures did not develop until the last evaluation. Parents of the three siblings (IV-3, IV-4, and IV-6) reported many seizures with head and gaze deviation. Moreover, all patients with FS, persisting up to 7-8 years of age, reported that FS were preceded by an aura, which also persisted in later afebrile seizures.

Epilepsy phenotypes

Six patients suffered with afebrile seizures, typically featuring a stereotyped aura including *déjà-vu* experience, epigastric discomfort, and a feeling of fear. In Patients IV-3, IV-4, and IV-6, whenever prolonged, the initial aura could be followed by a second phase characterized by vertiginous sensations and the appearance of an "intense, achromatic, unpleasant, flickering" of light in the right visual hemifield in Patients IV-3 and IV-4, and in the central visual field in Patient IV-6. These episodes were often triggered by television or pattern stimulation and could be followed by brief absences (lasting for 3-6 minutes) associated with eyelid myoclonia. Ipsilateral head and gaze deviation were reported in Patients IV-3 and IV-4. Focal to bilateral tonic-clonic seizures occurred occasionally in Patients IV-3 and IV-4, as well as in Patient IV-1, whose seizures were mainly limited to the *déjà-vu* experience. None of the subjects reported prolonged (>5 minute) seizures or clusters.

Post-ictal migraine was constantly present, even in events consisting of aura only. Post-ictal vomiting, instead, was limited to focal to bilateral tonic-clonic seizures. Patient IV-4 also experienced focal seizures at night or upon awakening, consisting of 'intense light'. Patient III-8 reported initial epigastric discomfort, followed by the appearance of lights in the visual



■ **Figure 1.** Pedigree of the family. FS: febrile seizures; FE: focal epilepsy; Ph: photosensitivity.

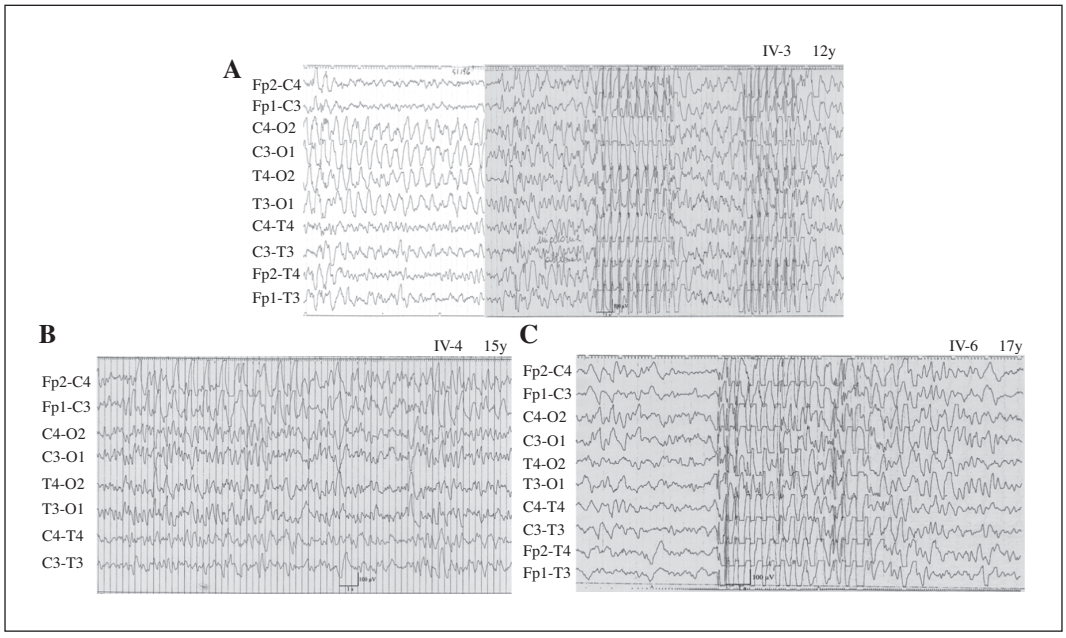
field or perception of an image of his own body. He never reported post-ictal migraine. Patient III-5 experienced afebrile nocturnal, tonic-clonic seizures, however, a focal origin of these seizures in the temporal-occipital area [4], with secondary generalization, could not be excluded based on the occurrence of post-ictal migraine.
Among patients who developed epilepsy, 3/6 (50%) achieved remission in adolescence/post-adolescence without treatment. The remaining three patients started a variable combination of anti-epileptic drugs (AEDs), including levetiracetam (LEV), lamotrigine (LGT), zonisamide (ZNS), valproate (VPA) and clobazam (CLB). Only Patient IV-6 achieved remission, whereas Patients IV-3 and IV-4 were under treatment at the time of the last evaluation due to poor adherence.

Instrumental findings

EEG recordings were available for the three siblings (*figure 2*). At least one of the EEGs showed paroxysmal activity (PA), namely, spikes, spike-wave or sharp-and-slow-wave complexes, extending bilaterally over the temporal-parietal-occipital areas. EEG changes tended to be synchronous or asynchronous in Patients IV-3 and IV-4 and often extended anteriorly over the frontal regions. All the three siblings who reported seizures elicited by visual stimuli showed photosensitivity to intermittent photic stimulation (IPS). Brain MRI was unremarkable in all patients.

Molecular genetic analysis

Genomic DNA was isolated from 1 mL of peripheral blood using QIAamp DNA Blood Midi (Qiagen) and sheared by sonication. DNA samples were enriched with Ion AmpliSeq Custom Panel containing 36 genes. Libraries were loaded into Ion Torrent Personal Genome Machine (PGM) System (ThermoFisher) for sequencing. Using CLC Genomics Workbench 7.5.1 (Qiagen), reads were mapped to the reference human genome sequence (GRch37/hg19). Single-nucleotide variants (SNVs) and short deletions or insertions (indels) were identified using the same software with the probabilistic variant calling plugin. Variants were filtered according to genetic criteria for a very rare, highly penetrant autosomal dominant trait, based on: 1) heterozygosity; 2) MAF ≤0.0001, not reported for dbSNP147; 3) non-synonymous or affecting a splice site. Validation and parental origin of the variant were assessed by Sanger sequencing.
We identified a heterozygous G to A transition at nucleotide 1130, resulting in the substitution of



■ **Figure 2.** Interictal EEG recordings of affected individuals IV: 3, IV:4, and IV: 6 (grey: during IPS). (A) EEG of Patient IV-3 (12 years) showing interictal posterior delta rhythm and diffuse, high-amplitude, polyspike-wave and spike-wave complexes associated with eyelid myoclonia, during IPS. (B) Interictal EEG of Patient IV-4 (15 years) showing anterior and posterior sharp waves and sharp-and-slow-wave complexes evoked by IPS. (C) EEG of Patient IV-6 (seven years) showing diffuse spike-and-wave complexes evoked by IPS.

arginine 377 by glutamine (p. R377Q) corresponding to the DI/pore-forming region of NaV1.1. The mutation was detected in 13 (68%) family members, of whom four (31%) were clinically unaffected (69% penetrance) (*figure 1*).

Discussion

The GEFS+ spectrum has been refined over recent years to include focal epilepsies [2]. Epilepsies arising from mesial and lateral temporal (i.e. epilepsy with auditory features- EAF) and frontal lobes are recognized within the GEFS+ spectrum [1-3].

We report a family with FS+ and focal epilepsy mainly involving the TPO network. The concept of neural networks in epilepsy is nowadays largely used within the framework of presurgical work-up. Seizures can originate from any area of the network and secondarily propagate outside of this network [5, 6]. In the absence of ictal EEG in our patients, the TPO location of epilepsy was supported by an anatomo-functional hypothesis of seizure propagation in the four subjects with the best described semiology, including *déjà-vu*, epigastric discomfort, and a feeling of fear, as well as post-ictal migraine reported in five individuals. That indicates temporal onset and spread to the occipital cortex, however, this hypothesis is not compatible with the other ictal manifestations (*e.g.*, vertigo, head and gaze deviation, change in body perception). However, the TPO junction has been described to be involved in vestibular information processing [7, 8], which is in line with the vertiginous sensations predominating in our patients. A predominance of the right hemisphere in vestibular information processing has also been reported [8, 9]. Moreover, Patient III-8 also experienced changes in body perception, corroborating theories suggesting an overlap of mechanisms underlying body representation and vestibular function [10]. Ultimately, the primary visual cortex was also shown to be involved (*table 1, supplementary material*). EEG recordings demonstrated interictal abnormalities localized predominantly over the TPO areas. Inconstant spread of PA towards the frontal regions confirms the possibility of discharge propagation outside of the primary network.

Our patients demonstrated a form of non-lesional TPO carrefour epilepsy. This epilepsy has already been described, but has never been associated with an obvious genetic link [8]. Here, we identify a heterozygous p. R377Q missense mutation in *SCN1A* segregating with the dominant phenotype. This mutation has been previously reported in GEFS+ [11]. Although no functional studies are available, the mutation localizes within the S5-S6 segment, which represents the DI pore-forming region of *SCN1A* and is believed to affect channel activity.

Post-ictal migraine occurred in all but one of the affected individuals with afebrile seizures, supporting the involvement of posterior brain areas in the pathophysiology of epilepsy in this family.

In conclusion, TPO carrefour epilepsy with photosensitivity may be part of the GEFS+ spectrum. The identification of a genetic link between *SCN1A* and the altered network suggests that TPO carrefour epilepsy may be inherited. Moreover, the relevance of post-ictal migraine in our series may also provide useful insight into the functions of posterior brain areas. ■

Supplementary data.
Supplementary table is available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) What types of seizures are more frequent within the GEFS+ spectrum?

(2) The TPO junction involves the processing of what system?

(3) Which cerebral lobes are usually involved in focal epilepsies with post-ictal migraine?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".