

## Partial epilepsy with febrile seizure plus: A subtype of GEFS+ or SME?

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**Objective:** Febrile seizures (FS) are the most common convulsive events in humans. It can be a benign disorder occurring only in infancy or childhood between 3 months and 6 years. It also may be part of epilepsy syndromes such as generalized epilepsy with febrile seizure plus (GEFS+) and severe myoclonic epilepsy of infancy (SME or SMEI). GEFS+ is a recently recognized form of inherited childhood-onset epilepsy with heterogeneous epilepsy phenotypes, including tonic-clonic, myoclonic, atonic, absence, and partial seizures.<sup>1</sup> Individuals with partial seizure accounted for about 10% in GEFS+. Mutations in *SCN1A*, *SCN2A*, *SCN1B* and *GABRG2* genes have been identified in families with GEFS+.<sup>2</sup> SME is an intractable epileptic encephalopathy, which is often considered to be the most severe phenotype of the GEFS+.<sup>3</sup> Partial seizures can be observed in 43%-78.6% of SME patients. Prolonged partial febrile seizures in the first year of life are usually followed by intractable epilepsy and mental handicap. SME borderland (SMEB) may miss some key features of SMEI phenotype such as myoclonus. More than 150 mutations in *SCN1A* gene have been identified in children with this disorder, which account for 30% to 90% SME (SMEI and SMEB) patients tested.<sup>4</sup> Most of the cases are sporadic with *de novo* mutations. Clinically, patients of febrile seizure with later onset partial epilepsy, which we prefer to name as partial epilepsy with febrile seizure plus (PEFS+), are more common. It is usually difficult to differentiate the patients of PEFS+ from the patients with partial seizures in GEFS+ or SME (especially SMEB). It is suspected that some of the patients with PEFS+ may have the same genetic basis as GEFS+ or SME. The present study is to identify the genetic basis of sporadic cases with PEFS+.

**Methods:** We retrospectively studied 4 patients with PEFS+. Their clinical manifestations, including family history, seizure frequency, seizure type, antiepileptic drugs (AEDs) treatment response, EEG recording, and neuroimaging (MRI) materials were reviewed. The focus was the correlation between seizure frequency and the response to AEDs. DNA was gotten from blood samples of the 4 patients and their parents. Mutations in *SCN1A*, *SCN2A*, *SCN1B* and *GABRG2* were screened by PCR amplification and denaturing high performance liquid chromatography (DHPLC) analysis and were identified by subsequent sequencing. Parental DNA was examined to ascertain the origin of the mutation.

**Results:** There were 3 males and one female patient. The ages ranged from 8 years to 13 years. Ages at onset of febrile seizures ranged from 6 months to 10 months. Ages of offset of febrile seizures ranged from 2 years and 6 months to 7 years. All patients had partial seizure and the most frequently observed seizure types were complex partial seizure (CPS) and secondarily generalized tonic-clonic seizure (sGTCS), which occurred either before or after the offset of febrile seizures. Interictal recording showed localized or local dominant paroxysm of spike-and-slow/polyspike-and-slow waves discharges. All patients had experience of seizure aggravating by lamotrigine. For the genetic analysis, we detected two different mutations in sodium channel gene *SCN1A* in two patients. One male patient had moderate intellectual disability with no family history of seizure. Brain MRI showed the signal change of the left temporal lobe and the left mesial temporal dystrophy. In this patient we detected one novel mutation of T→A transversion at nucleotide 5295 resulting in the substitution of phenylalanine 1765 by leucine (F1765L) in the D4/S6. Phenylalanine at this position is highly conserved in voltage-gated sodium channel subunits in the CNS of all species. This patient showed refractory to many AEDs and the seizure was finally controlled by the combination of valproate (VPA) and topiramate (TPM).

One female patient had family history of febrile seizure (Her aunt had febrile seizure in childhood). IQ was 73 and brain MRI was normal. In this patient we detected one G→A transition at nucleotide 2837 resulting in the substitution of arginine 946 by histidine (R946H) in D2/S5-S6 which has been reported in a patient with SME.<sup>5</sup> Although refractory to AEDs at early years, she had been seizure-free for 2 years after the use of combination of VPA and TPM. Both missense mutations resulted in the amino acid substitutions in the “pore-forming” region of voltage-gated sodium (Na<sup>+</sup>)-channel 1 subunit, which may have impact on the function of Na<sup>+</sup> channel. Both mutations could not be detected in their parents. Molecular study of *SCN2A*, *SCN1B* and *GABRG2* did not reveal any mutation. The other two patients, who had no mutations of any genes we detected, also had good treatment response to the combination of TPM and VPA.

*Conclusion:* More attention should be given to the genetic factor of the patients with FS plus partial seizure, including sporadic patients. We proposed the term partial epilepsy with febrile seizure plus (PEFS+), which may have the same genetic basis as GEFS+ or SME. Some AEDs, such as Na<sup>+</sup>-channel blocker, may aggravate seizures in these patients even without *SCN1A* missense mutations. More patients should be detected before we may find the relationship between the PEFS+ and gene mutations. Awareness of its existence may be important in genetic consultation and clinical treatment, which may have great importance to sporadic patients.

## References

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