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Phenotypes and genotypes in epilepsy with febrile seizures plus

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Abstract

In the last several years, mutations of sodium channel genes, *SCN1A*, *SCN2A*, and *SCN1B*, and $GABA_A$ receptor gene, *GABRG2* were identified as causes of some febrile seizures related epilepsies. In 19 unrelated Japanese families whose probands had febrile seizures plus or epilepsy following febrile seizures plus, we identified 2 missense mutations of *SCN1A* to be responsible for the seizure phenotypes in two FS+ families and another mutation of *SCN2A* in one family. The combined frequency of *SCN1A*, *SCN2A*, *SCN1B*, *SCN2B*, and *GABRG2* mutations in Japanese patients with FS+ was 15.8%. One family, which had R188W mutation in *SCN2A*, showed digenic inheritance, and another modifier gene was thought to take part in the seizure phenotype. The phenotypes of probands were FS+ in 5, FS+ and partial epilepsy in 10, FS+ and generalized epilepsy in 3, and FS+ and unclassified epilepsy in 1. We proposed the term epilepsy with febrile seizures plus (EFS+), because autosomal-dominant inheritance in EFS+ might be rare, and most of EFS+ display a complex pattern of inheritance, even when it appears to be an autosomal-dominant inheritance. There is a possibility of simultaneous involvement of multiple genes for seizure phenotypes.

Keywords: Febrile seizures plus; Febrile seizure; Na^+-channel; $GABA_A$ receptor; Partial epilepsy; Severe myoclonic epilepsy of infancy

1. Introduction

The responsible genes for certain familial epilepsies have recently been identified. Genes identified as involved in febrile seizures related epilepsy are listed in Table 1. Mutations in the voltage-gated Na^+-channel $\alpha1$, $\alpha2$, and $\beta1$, and the gamma aminobutyric acid ($GABA_A$) receptor γ^2 subunits genes were found as a cause of some febrile seizures related epilepsies (Wallace et al., 1998, 2001a,b; Sugawara et al., 2001a,b, 2002; Escayg et al., 2000; Claes et al., 2001; Fujiwara et al., 2003; Ohmori

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Table 1
Responsible genes for febrile seizure related epilepsy

Disorder	Chromosome	Genes (product)	Reference
GEFS+1	19q13.1	*SCN1B* (Na^+-channel)	Wallace et al. (1998)
GEFS+2	2q24	*SCN1A* (Na^+-channel)	Wallace et al. (2001a) Sugawara et al. (2001a) Escayg et al. (2000)
SMEI	2q24	*SCN1A* (Na^+-channel)	Claes et al. (2001) Sugawara et al. (2002) Fujiwara et al. (2003)
Borderline SMEI	2q24	*SCN1A* (Na^+-channel)	Sugawara et al. (2002) Ohmori et al. (2002)
ICEGTC	2q24	*SCN1A* (Na^+-channel)	Fujiwara et al. (2003)
FS+ and partial epilepsy	2q23–q24.3	*SCN2A* (Na^+-channel)	Sugawara et al. (2001b)
GEFS+3	5q34	GABRG2 ($GABA_A$ receptor)	Baulac et al. (2001)
FS+ and absence	5q34	GABRG2 ($GABA_A$ receptor)	Wallace et al. (2001b) Kananura et al. (2002)
SMEI	5q34	GABRG2 ($GABA_A$ receptor)	Harkin et al. (2002)

et al., 2002; Baulac et al., 2001; Harkin et al., 2002).

2. Subjects and methods

In 1997, Scheffer and Berkovic originally used the term febrile seizures plus (FS+) to describe the phenotype of individuals who have febrile seizures extending beyond 6 years of age, with or without afebrile generalized tonic-clonic seizures (GTCS) (Scheffer and Berkovic, 1997).

In this study, we defined the term febrile seizures plus as follows. Individuals who demonstrate febrile seizures extending beyond 6 years of age with or without afebrile GTCS. Or, individuals under 6 years of age who demonstrate multiple febrile seizures and afebrile GTCS without epileptic discharges on EEG at the first afebrile seizure. Individuals with developmental delay or neurological abnormalities at the onset of febrile seizures were excluded.

We analyzed 19 unrelated Japanese families whose probands had febrile seizures plus or epilepsy following febrile seizures plus. Neurological examination, EEG, MRI, and analysis of sodium channel genes, *SCN1A*, *SCN2A*, *SCN1B*, and *SCN2B*, and $GABA_A$ receptor gene, *GABRG2* were performed in probands and available family members.

3. Results

The clinical and genetic characteristics of probands with FS+ families are shown in Table 2. There were 12 males and 7 females. The present ages ranged from 6 years and 2 months to 18 years. Ages at onset of febrile seizures ranged from 6 months to 4 years and 1 month. Ages of offset of febrile seizures ranged from 2 years and 3 months to 13 years and 1 month. Febrile seizures were frequent (more than 10 times) in 9, and afebrile GTCS were frequent in 5. MRI was examined in 13 patients and showed no abnormalities. Cases A and B had disease mutations in *SCN1A*, and case C had a disease mutation in *SCN2A*. There were no disease mutations in *SCN1B*, *SCN2B*, and *GABRG2*.

Ten subjects (from A to J) had partial seizures and focal epileptic discharges on EEG, and were diagnosed as having FS+ and partial epilepsy. Three subjects (from K to M) were diagnosed as having FS+ and generalized epilepsy, because they showed afebrile GTCS beyond 6 years of age with diffuse epileptic discharges. One subject (N) was diagnosed as having FS+ and unclassified epilepsy. Five subjects (from O to S) were diagnosed as FS+, because febrile seizures persisted beyond 6 years of age or afebrile GTCS was demonstrated. Most patients were treated with antiepileptic drugs, except for two patients. Fourteen patients have not had any seizures during the past 1-year. In the