Generalized epilepsy with febrile seizures plus

Further heterogeneity in a large family

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Article abstract—*Background:* Generalized epilepsy with febrile seizures plus ($GEFS^+$) is a recently described benign childhood-onset epileptic syndrome with autosomal dominant inheritance. The most common phenotypes are febrile seizures (FS) often with accessory afebrile generalized tonic-clonic seizures (GTCS, FS^+). In about one third, additional seizure types occur, such as absences, myoclonic, or atonic seizures. So far, three mutations within genes encoding subunits of neuronal voltage-gated Na^+ channels have been found in $GEFS^+$ families, one in SCN1B (β_1-subunit) and two in SCN1A (α-subunit). *Methods:* The authors examined the phenotypic variability of $GEFS^+$ in a five-generation German family with 18 affected individuals. Genetic linkage analysis was performed to exclude candidate loci. *Results:* Inheritance was autosomal dominant with a penetrance of about 80%. A variety of epilepsy phenotypes occurred predominantly during childhood. Only four individuals showed the FS or FS^+ phenotype. The others presented with different combinations of GTCS, tonic seizures, atonic seizures, and absences, only in part associated with fever. The age at onset was 2.8 ± 1.3 years. Interictal EEG recordings showed rare, 1- to 2-second-long generalized, irregular spike-and-wave discharges of 2.5 to 5 Hz in eight cases and additional focal parietal discharges in one case. Linkage analysis excluded the previously described loci on chromosomes 2q21-33 and 19q13. All other chromosomal regions containing known genes encoding neuronal Na^+ channel subunits on chromosomes 3p21-24, 11q23, and 12q13 and described loci for febrile convulsions on chromosomes 5q14-15, 8q13-21, and 19p13.3 were also excluded. *Conclusion:* These results indicate further clinical and genetic heterogeneity in $GEFS^+$.

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Genetic analyses of Mendelian forms of epilepsy provide an excellent tool to study the etiology and pathophysiology of neuronal hyperexcitability in molecular detail. In particular, ion channel defects can cause inherited idiopathic epileptic syndromes, as has been found recently for autosomal dominant nocturnal frontal lobe epilepsy (ADFNLE),[1] benign familial neonatal convulsions (BFNC),[2-4] and generalized epilepsy with febrile seizures plus ($GEFS^+$).[5,6] Concepts derived from studies of these rare epileptic disorders may contribute to find new therapeutic strategies as has been shown recently for retigabine. This novel antiepileptic drug activates KCNQ K^+ channels, which are mutated in BFNC.[7]

$GEFS^+$ was first described in 1997 and 1999 by Scheffer et al.[8,9] as a syndrome featuring febrile convulsions and a variety of afebrile epileptic seizure types within the same pedigree showing autosomal dominant inheritance. Most common was the febrile convulsion syndrome (FS), often with febrile seizures persisting after the 6th year of life or in combination with afebrile generalized tonic-clonic seizures (called FS^+). The phenotypes FS and FS^+ were found in about two thirds of affected individuals. According to the additional seizure types occurring in the remaining third of the patients, phenotypes such as "FS^+ with absences," "FS^+ with myoclonic seizures," or "FS^+ with atonic seizures" were described. The most severe phenotype was myoclonic astatic epilepsy (MAE). Also, partial epilepsies occurred in rare cases ("FS^+ with temporal lobe epilepsy"). The penetrance was about 60%.

Voltage-gated sodium channels consist of one α- and at least one β-subunit. The α-subunit alone forms normally functioning channels when expressed in mammalian cells. It contains all main structural features such as the ion-conducting pore, voltage sensors, and the activation and inactivation

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gates. The β-subunits have only modulating properties. Several different α-subunits and three β-subunits expressed in skeletal muscle, heart muscle, and in the peripheral nervous system or the CNS have been described so far.[10-13]

The first genetic defect in GEFS$^+$ was found by Wallace et al.[5] The authors described linkage to chromosome 19q13 and identified a point mutation within the gene SCN1B encoding the β_1-subunit of the voltage-gated Na^+ channel. Recently, several groups found linkage to chromosome 2q21-33 in four GEFS$^+$ families,[14-17] where three genes encoding neuronal Na^+ channel α-subunits expressed in brain are located: SCN1A, SCN2A, and SCN3A.[11] For two of these families, mutations were detected in SCN1A.[6] Functional expression of SCN1B and SCN1A mutations revealed changes in sodium-channel fast inactivation and activation.[5,18] The gating changes are much more subtle than those found for a lot of mutations within the skeletal muscle Na^+ channel α-subunit gene SCN4A causing myotonia or periodic paralysis,[12] indicating that the brain reacts more sensitively to such alterations than skeletal muscle fibers.

Here, we provide a detailed description of the clinical variability of GEFS$^+$ in another large family of German origin. In contrast to the previously reported families, many affected individuals did not experience febrile convulsions and some of the epileptic phenotypes fit well into the spectrum of idiopathic generalized epilepsies. Linkage analysis demonstrates further genetic heterogeneity in GEFS$^+$.

Methods. All but one patient (III-19, who was not available) or their parents gave informed consent to the clinical and genetic investigations. All procedures were in accordance with the Helsinki Convention and approved by the Ethics Committee of the University of Ulm. Clinical information was obtained from the history of the patients, their parents, or other relatives during visits in the clinic, at home or by telephone calls, and from medical records or direct interviews of physicians in hospitals and practices around Ulm. The pedigree is shown in figure 1. Two branches of the family came to our outpatient clinic for history taking, clinical examination, and EEG recordings (offspring of III-1 and III-2). Offspring of Individuals II-2 and II-8 as well as a few of the unaffected branches were visited at home. Classification was performed according to the Commission on Classification and Terminology of the International League Against Epilepsy[19,20] and to the nomenclature introduced by Scheffer et al.[8,9] for GEFS$^+$. Interictal EEG were recorded digitally in the neurologic clinic or in the pediatric clinic of the University of Ulm. EEG electrodes were attached according to the international 10–20 system. Previous interictal analogous paper-written EEG recordings (8 to 14 recording channels) from Individuals V-4, V-5, V-8, IV-19, III-14, and IV-40 were obtained from clinics and practitioners. For most EEG recordings of Individuals IV-5, IV-6, and III-19, only written reports but not the recordings themselves were available. Results of CT or MRI scans of the brain were obtained from medical records in most cases, but only a few images were available for inspection (Individuals V-8 and IV-19).

For genetic investigations, markers were used from the Human Screening Set/Version 8.8a (Pharmacia Biotech, Freiburg, Germany) and additional markers (Interactiva, Ulm, Germany) from the Genethon human linkage map.[21-23] DNA was extracted from leukocytes of peripheral blood samples by standard procedures. Microsatellite DNA polymorphisms were amplified by PCR with the following conditions in a final volume of 50 μL: 50 ng DNA, 30 pmol of each fluorescent primer, 15 mmol of deoxynucleoside triphosphate, 5 μL buffer (500 mmol KCl, 200 mmol Tris HCl, 25 mmol $MgCl_2$, 0.01% gelatin, pH 8.4), 0.2 μL Taq polymerase (Pharmacia Biotech). Samples were amplified in a thermocycler (Biometra, Goettingen, Germany) using the following conditions: 94 °C for 4 minutes; 35 cycles of 30 seconds at 94 °C, 45 seconds for annealing and 30 seconds at 72 °C, followed by a final extension period of 2 minutes at 72 °C. PCR products were loaded on a 6%-denaturating polyacrylamide gel for electrophoresis using an Alf Express automated sequencer (Pharmacia Biotech). Genotypes were scored relative to 95, 300, and 400 base-pair (bp) standards. Two-point linkage analyses were performed by the MLINK subroutine of the Linkage package program[24] using an autosomal dominant mode of inheritance with a disease allele frequency of 0.0001, a penetrance of 80%, a phenocopy rate of 0.03 for Patients IV-2

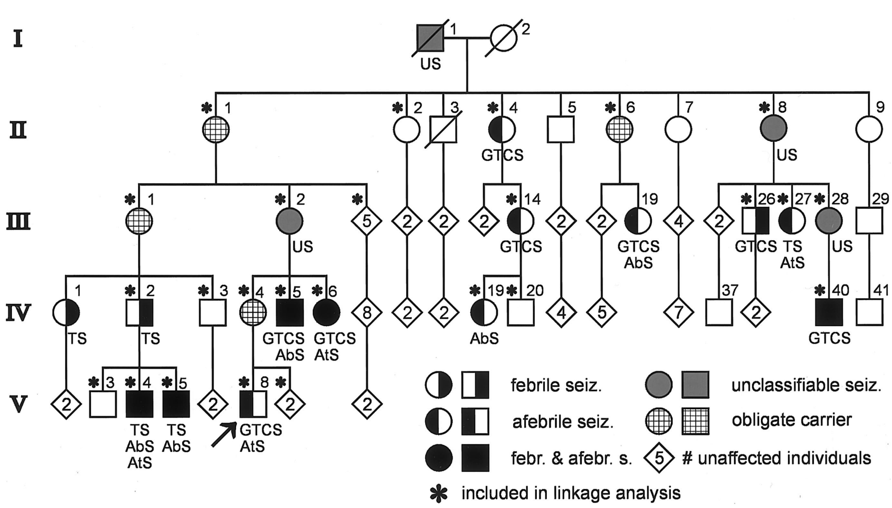

Figure 1. Simplified pedigree of the GEFS$^+$ family showing the different epileptic phenotypes. The index patient (V-8) is marked by an arrow. None of the spouses (who are not shown) had epilepsy or a history of epilepsy in his or her family. Circles indicate females; squares indicate males. GTCS = generalized tonic-clonic seizure; TS = tonic seizure; AtS = atonic seizure; AbS = absence seizure; US = unclassifiable seizure.

and III-26, having only febrile seizures, and a phenocopy rate of 0.01 for all other affected individuals (according to the prevalences of febrile seizures and epilepsy)[25-27] for lod score calculations. Obligate disease allele carriers were defined as nonaffected.

Results. *Clinical evaluation.* The complete pedigree of the five-generation family is shown in figure 1. Clinical information was obtained from all 92 direct descendants of Individual I-1 and the 34 nonconsanguineous individuals as described in the Methods section. Eighteen individuals experienced at least one febrile or afebrile seizure. All were regarded as affected for linkage analysis. Four individuals were designated as obligate carriers, including Individual II-1, who experienced seizures after a stroke at age 69 years. None of the 34 individuals nonconsanguineous to Individual I-1 (who are not shown in figure 1) had a history of seizures or a family history of seizures. The clinical information yielded an estimated penetrance of more than 80% (18 affected individuals of 22 probable gene carriers, including the four obligate carriers). Detailed case reports are given below. All important clinical information is summarized in the table.

Briefly, the epilepsy phenotypes in our pedigree can be described as follows: Three individuals had only one febrile convulsion presenting as generalized tonic-clonic (GTCS, 1) or tonic seizures (TS, 2) who were classified as FS. Five had febrile and afebrile GTCS (3) or TS (2), for four of them associated with afebrile absence seizures (AbS) (2) or atonic seizures (AtS) (1) or both (1). They were classified as FS^+ (1), FS^+ and AbS (2), FS^+ and AtS (1), or FS^+ and AbS and AtS (1). Two had AbS without FS, one associated with afebrile GTCS; both were classified as having childhood absence epilepsy (CAE). The other epilepsy phenotypes could not be classified: Three more had afebrile GTCS not associated with the sleep/wake cycle, one of them with AtS, and another individual had afebrile AtS and TS. For four individuals the obtained information was not sufficient to classify the seizure type (unclassifiable seizures [US]). Thus, at least 11 of the 18 affected individuals had afebrile seizures and at least six probably did not experience seizures associated with fever.

For all 12 patients for whom the definite onset of seizures was known, the mean age at onset was 2.8 ± 1.3 years (mean ± SD). A group of six patients who developed epilepsy had a typical age at onset between 1.5 and 2 years. One individual only had GTCS in adulthood with an age at onset of 24 years (III-14, not considered to calculate the mean value).

For all but one affected individuals the neurologic examination and development were normal or reported to be normal by relatives (V-8: isolated speech retardation). No other diseases were described for affected individuals that either would be of any importance concerning the clinical description of this familial epilepsy syndrome or that could have been the cause of epileptic seizures (Individual II-1 with the stroke was considered nonaffected).

A sleep EEG of the index patient (V-8) recorded 4 months after medication had been stopped showed one short episode of generalized, irregular spike-and-wave discharges and surprisingly, left-hemispheric focal spikes activated by sleep, presenting as a transverse dipole with a maximum negativity in the left parietal region (electrode P3, figure 2). These potentials resembled benign centrotemporal spikes of childhood. All other interictal EEG recorded in our clinic from the index patient and other individuals did not show epileptiform discharges or different abnormalities. However, for four other patients (V-4, V-5, IV-19, and III-14), interictal EEG obtained from other clinics or practitioners also showed short-lasting (1 to 2 seconds' duration), generalized, irregular spike-and-wave discharges at a frequency of 3 to 5 Hz but never focal epileptiform potentials. For three more patients (IV-5, IV-6, and III-19), generalized spike-and-wave discharges were reported, but the EEG were not available for inspection. None of the CT or MRI scans of the brain was abnormal except the one taken after a stroke. For some patients CSF and amino acid screening were obtained and reported to be normal. Treatment was generally uncomplicated, although some individuals received several different antiepileptic drugs (see table 1).

Case reports. *Index patient V-8 (5 years).* At age 20 months, this patient's mother noticed that he lost muscle tone for a second without observing myoclonic jerks before. When sitting in a chair, his head might suddenly fall, standing or running, and he would collapse on his knees without an obvious reason. No postictal abnormalities were noticed. The seizures were classified as AtS. They occurred several times during a few days. At the same time after sleep deprivation, he had his first typical GTCS starting with an initial cry and generalized stiffening followed by clonic convulsive movements lasting 2 to 3 minutes. During that day, he had three more GTCS and was admitted to a pediatric hospital, where six more AtS were reported in the following days. All seizures occurred at various times of the day while the patient was awake. He was successfully treated with phenobarbital. Fever was not reported. He has remained seizure free up to now, although the medication had been stopped at age 4 years. Several interictal EEG recordings including a sleep EEG after the first GTCS did not show epileptiform discharges. After medication was stopped, a sleep EEG showed left parietal spikes (see above) and one 2-second period of generalized, irregular spike-and-wave discharges of 2.5 to 3 Hz (figure 2). An MRI scan of the brain at this time was normal and there was no evidence for partial epileptic seizures. Neurologic development was normal except for an isolated retardation of active speech with normal comprehension.

IV-5 (26 years). This patient's first seizure (GTCS lasting about 1 minute) occurred at 2 years of age early in the morning. He had three more GTCS during that day associated with fever, and within the next weeks a few more clearly afebrile GTCS during various times of the day. During one stay in a hospital, seizures with unconsciousness, oral automatisms, and staring of unknown duration were also reported (AbS). He was treated with primidone and later with valproate up to age 6 years. He had one more afebrile GTCS under treatment at 3 years of age. An interictal sleep EEG at age 2.2 years was reported to show generalized spike-and-wave discharges of 1 to 2 seconds' duration. Other interictal EEG studies were reported as normal.

IV-6 (19 years). The patient's mother reported that she fell backward, losing muscle tone in her knees, about two times a month when she was 18 to 24 months old (AtS). At

Table *Summary of important clinical information of the GEFS⁺ pedigree*

Individual/sex/ age, y	Febrile seizures: Age at onset/ end, y	Febrile seizures: Type of seizure, n	Afebrile seizures: Age at onset/ end, y	Afebrile seizures: Type of seizure, n	Classification of epilepsy
V-8/m/5 (index patient)	—	—	1.7/1.7	AtS, >10; GTCS, 4–5	Not classifiable
IV-5/M/26	2/2	GTCS, 4	2.1/3; 2.1/2.1	GTCS 4–5; AbS 4	FS^+ and AbS
IV-6/F/19	2/7	GTCS, 4–5	1.5/2	AtS, >10	FS^+ and AtS
III-2/F/55	Childhood	US, ?	Childhood	US, ?	Not classifiable
II-I/F/79	—	—	69/?	TS, 4–5	Not classifiable
V-5/M/4	2/?	TS, >10	2/?	TS, >10; AbS, >10	FS^+ and AbS
V-4/M/8	1.8/4.6	TS, 5	1.8/1.8 and 5/6.5	AtS, >10; AbS, 4–6	FS^+, AtS, and AbS
IV-2/M/35	4	TS, 1	—	—	FS
IV-1/F/39	3	TS, 1	—	—	FS
IV-19/F/24	—	—	6/10	AbS >10	CAE
III-14/F/49	—	—	24/38	GTCS, 5–7	Not classifiable
II-4/F/74	?	?	Childhood/40	GTCS, >10	Not classifiable
III-19/F/36	—	—	Childhood/?	AbS, ?; GTCS, 8–10	CAE
IV-40/M/4	1.5/2	GTCS, 3	2.5/?	GTCS, 4–5	FS^+
III-28/F/31	—	—	3	US, 1	Not classifiable
III-27/F/33	—	—	3/3.5	AtS, few; TS, 1	Not classifiable
III-26/M/37	3.5	GTCS, 1	—	—	FS
II-8/F/64	Childhood	US, ?	Childhood	US, ?	Not classifiable
I-I/M/deceased	Childhood	US, ?	Childhood	US, ?	Not classifiable

Type of seizures: GTCS = generalized tonic-clonic seizure; TS = tonic seizure; AtS = atonic seizure; AbS = absence seizure, US = unclassifiable seizure. *Type of epilepsy*: FS = febrile convulsion syndrome; FS^+ = FS with afebrile GTCS; CAE = childhood absence epilepsy. *Antiepileptic drugs*: CBZ = carbamazepine; CLB = clobazam; CLN = clonazepam; ESX = ethosuximide; LTG = lamotrigine; PBT = phenobarbital; PHT = phenytoin; PRM = primidone; VPA = valproate. *Other*: GSW = generalized spike-and-wave discharges; ED = epileptiform discharges; AA = amino acid screening.

age 2 years, she had two GTCS in 1 day and short postictal drowsiness. When admitted to a hospital the same day, she developed fever due to an angina tonsillaris and had several more similar seizures. Hence, all GTCS were classified as febrile. She was treated with phenobarbital, and from age 4 to 15 years with valproate. With treatment, she had one more seizure at age 7 years associated with fever at night, when her mother found her unresponsive in her bed. From many interictal EEG recordings until age 19 years, two in sleep at ages 4 and 11 were reported with recurring generalized spike-and-wave discharges of 4 Hz.

II-1 (79 years). No seizures during childhood were reported in this patient. At age 69 years, she had a large, left-hemispheric stroke and had four seizures afterwards. Her daughter observed a symmetric stiffening of the whole body (10 to 20 seconds) without clonic convulsions and no signs of a focal onset (TS). She has been treated with phenytoin and has remained seizure free.

V-5 (4 years). At age 2 years, this patient had a series of seizures with generalized stiffening, elevation of the arms, tonic eye deviations, and little salivation lasting less than a minute (TS) during a febrile cold. After each seizure he was drowsy. He was admitted to a pediatric hospital, where he continued to have up to 11 TS per day for a period of 12 days (only initially with fever). In addition, 1- to 2-second episodes of staring without automatisms were reported (AbS). At this time, interictal EEG recordings were normal. He was treated with clobazam and phenobarbital. Later, clobazam was switched to ethosuximide. At age 3 years, an interictal EEG showed 3- to 4-Hz irregular, generalized spike-and-wave discharges lasting 1 to 2 seconds; therefore, the medication was switched to lamotrigine. One year later, when he was seen in our outpatient clinic, he had two more febrile seizures with only tonic components (10 to 20 seconds long) after sleep deprivation. Pre- and postictal EEG recordings at this time were normal.

V-4 (8 years). First febrile seizures were observed in this patient at age 2 years. His parents described a stiffening of the whole body, elevated arms, a tonic upward eye movement, oral automatisms, and short-lasting generalized shivering (maximal seizure duration of 1 minute; TS).

Treatment, period, age, y	Interictal EEG	Brain imaging	Neurologic examination/development	Other findings
PBT, 1, 7–4	2.5–3 Hz GSW, L parietal spikes	CT and MRI normal	Speech retardation	CSF normal; AA normal
PRM, VPA 2–6	GSW (unconfirmed)	Ultrasound and CT normal	Normal	—
PBT, 2–4; VPA, 4–15	4 Hz GSW (unconfirmed)	CT normal	Normal	AA normal
—	Normal (55 y)	—	Normal	—
PHT, 69–present	Left-hemispheric slowing, no ED	Large left-hemispheric stroke on CT	Global aphasia, right hemiparesis	—
CLB+PBT, 2–2.1; ESX+PBT, 2.1–3; LTG, 3–present	3–4 Hz GSW	CT normal	Normal	AA normal
PRM+CLN, 1.8–4; LTG, 5–present	3–4 Hz GSW	MRI normal	Normal	CSF normal
—	Normal (35 y)	—	Normal	—
—	—	—	Normal	—
ESX, 6–10; VPA, 10–15	4–5 Hz GSW	CT normal	Normal	—
VPA, 24–32; PHT, CBZ, 38–41	4–5 Hz GSW	CT normal	Normal	—
—	—	—	Normal	—
CBZ, 15–?	3 Hz GSW (unconfirmed)	CT normal	Normal	—
PBT, 2.5–present	Normal	MRI normal	Normal	—
—	—	—	Normal	—
—	—	—	Normal	—
—	—	—	Normal	—
—	—	—	Normal	—
—	—	—	Normal	—

Afterward, he was little drowsy. Four such seizures occurred within 24 hours. One to 2 weeks later he often collapsed in his knees or his head fell suddenly (AtS). This happened up to 10 times a day and stopped after 1 week, when he was treated with primidone and clonazepam. After 2 years without seizures, the medication was discontinued. At age 4 years, he had one more febrile TS. At age 5 years, he developed afebrile seizures of different semiology: he became cyanotic, stared, and showed oral automatisms. Once, on a bicycle, he continued to ride with lower speed, becoming cyanotic and unconscious, but did not fall. These seizures lasted maximally for 30 seconds (AbS). Since then, he has been treated with lamotrigine and has had one more AbS at age 6 years. One interictal EEG at 3 years (of 20 between 2 and 8 years of age) showed 3- to 4-Hz irregular, generalized spike-and-wave discharges of 1 to 2 seconds' duration.

IV-2 (35 years) and IV-1 (39 years). For IV-2, one febrile seizure was reported at 3 to 4 years of age with high fever. His mother observed a loss of consciousness and a tonic upward eye movement (TS). For IV-1, one febrile seizure was reported with the age of 3 years, when her aunt noticed a tonic eye deviation and short-lasting stiffening (TS).

IV-19 (24 years). At age 6 years, this patient's parents noticed 5- to 10-seconds-long periods of unconsciousness with staring and oral automatisms, when for example she continued to walk or interrupted her meal (AbS). The patient herself reported to remember some of the seizures as trancelike episodes, being unable to do anything. Under treatment with ethosuximide, she used to have three to four AbS per week, and later sometimes several per day, until she was 10. She was later treated with valproate until age 15 and has had no further seizures. The only abnormal interictal EEG at 13 years showed a 2-second period of 4- to 5-Hz irregular, generalized spike-and-wave discharges. .

III-14 (49 years). This patient had no seizures during childhood. Her first typical GTCS occurred at age 24 years, when she was pregnant. With valproate treatment, she used to have about one GTCS every year for about 8 years that was not related to the sleep-awake cycle. Treatment was stopped at age 32 years. At age 38 years, one further GTCS occurred when she had a high fever; an interictal EEG showed 1- to 2-seconds periods of 4-Hz irregular, generalized spike-and-wave discharges. She was treated with phenytoin and later carbamazepine for another 3 years and has remained seizure free.

II-4 (74 years). This patient's older brother and sister observed a seizure at about 5 years of age, when the patient fell backward from a wall. They remembered her

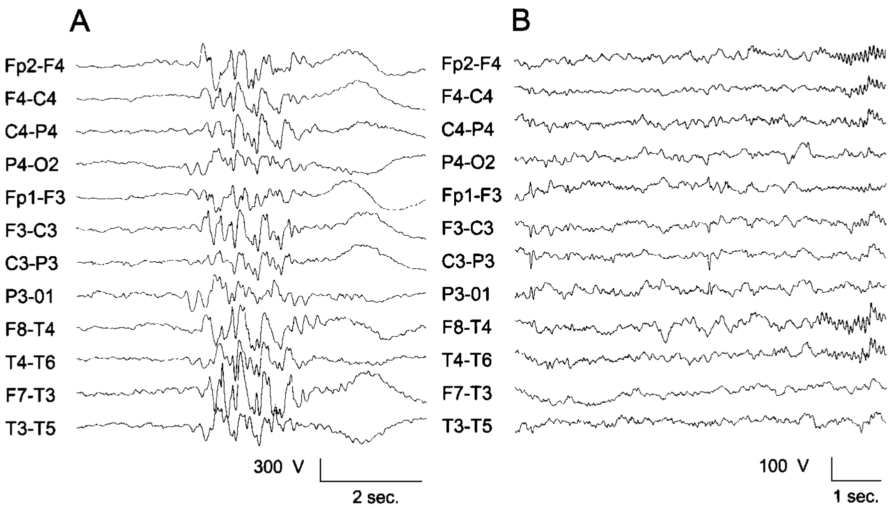

Figure 2. Interictal EEG recordings from the index patient. (A) Irregular, generalized spike-and-wave discharges. Similar epileptiform potentials were also observed in seven other affected individuals. (B) Focal left-hemispheric epileptiform discharges presenting as a dipole with a maximum negativity at electrode P3 and a maximum positivity at F3. Such potentials were only seen in one sleep-EEG of the index patient. Electrodes were placed according to the international 10–20 system and EEGs were recorded digitally.

lying on the ground with clonic convulsions of the arms and hypersalivation lasting 2 to 3 minutes (GTCS). She probably had more GTCS after she left school, and further GTCS occurred at age 30 to 40 years (witnessed by her daughter). No one remembered associated fever.

III-19 (36 years). This patient's sister recalled typical AbS with a 10-second period of unconsciousness and staring when the patient was about 5 or 6 years old. At age 15 years, she had her first GTCS and has continued to have rare GTCS until now. She was treated not continuously with carbamazepine.

IV-40 (4 years). This patient's mother reported about three febrile GTCS between 1.5 and 2 years of age, and four or five afebrile GTCS around age 2.5 years. The patient was treated with phenobarbital, and remained seizure free.

III-28 (31 years), III-27 (33 years), and III-26 (37 years). For III-28, her parents reported one episode at age 3 years, when she was lying in her parents' bed in the morning being acutely unresponsive for an unknown period (US). For III-27, her parents reported a few afebrile atonic seizures at age 3 years. Her brother remembered one seizure with rhythmic head movements (classified as recurring TS). III-26 had one typical febrile GTCS at the age of 3 to 4 years.

III-2 (55 years), II-8 (64 years), and I-1 (deceased). These patients were remembered by relatives to have had seizures during childhood. Nothing is known about associated fever or about the semiology (US).

Linkage analysis. Genetic linkage studies were performed for the known loci on chromosome 19q13 (GEFS1),[5] the location of SCN1B,[28] and on chromosome 2q21-33 (GEFS2/FEB3),[14–17] the location of SCN1A,[29] SCN2A,[30,31] SCN3A,[31,32] and SCN9A[33] using markers given in the supplementary material on the *Neurology* Web site (go to www.neurology.org and scroll down the Table of Contents to find the title link for this article). Linkage was excluded using both haplotype and two-point lod score analysis (additional material related to this article can be found on the *Neurology* Web site; go to www.neurology.org). A few markers on chromosome 2 were not informative enough to exclude linkage by lod score analysis, but different haplotypes of affected individuals with a GEFS$^+$ phenotype definitely excluded this locus (figure 3). Other genes encoding known subunits of voltage-gated Na^+ channels expressed in the central or peripheral nervous system are located on chromosome 3p21-24 (SCN10A and SCN11A),[34,35] 11q23 (SCN2B and SCN3B),[36,13] and 12q13 (SCN8A).[37] Other loci for febrile convulsions are on chromosomes 8q13-21 (FEB1),[38] 19p13.3 (FEB2),[39] and 5q14-15 (FEB4).[40] Those loci were also excluded by two-point lod scores (additional material can be found on the *Neurology* Web site; go to www.neurology.org).

Discussion. The pedigree presented here fits well into the GEFS$^+$ spectrum with regard to the autosomal dominant mode of inheritance, the previously described phenotypes of FS, FS$^+$, and FS$^+$ associated with absences or atonic seizures, the age at onset, and the benign appearance of this syndrome. However, our family differs in some aspects from previous descriptions. We would like to discuss the following points concerning these differences and the classification of seizure types as follows:

1. Six of the 18 affected individuals did most probably not experience febrile seizures, only one (IV-6) presented with febrile seizures occurring beyond the upper age limit of 6 years, and only three presented definitely without afebrile seizures. Thus, the clinical spectrum was shifted toward more frequent afebrile seizures compared with previously published pedigrees.[8,9,14-16] The phenotypes FS, FS$^+$, and FS$^+$ with other seizure types as defined by Scheffer and Berkovic[8] only applied to eight individuals. Two individuals had childhood absence epilepsy, which has not been described in GEFS$^+$ pedigrees so far (see the table).
2. Four individuals presented with febrile TS instead of GTCS, which is the only febrile seizure type that occurred in the families described up to now. It might be difficult to differentiate exactly between TS and GTCS in early childhood. In our cases (V-4, V-5, IV-1, and IV-2), the shorter duration, the absence of clonic convulsive movements, and typical clinical signs such as the elevation of the upper extremities prompted us to classify the observed seizures as tonic.
3. From a clinical point of view, it is most probable

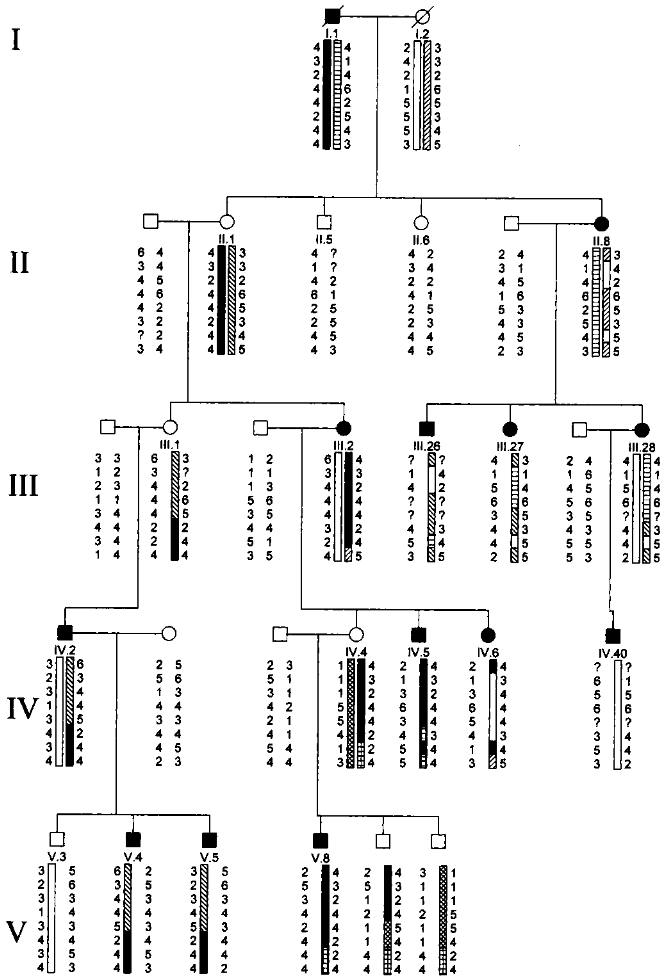

Figure 3. Haplotype analysis on chromosome 2q21-33. Reduced pedigree showing the completely different haplotypes on chromosome 2q21-33 for two branches of the family with a definite GEFS$^+$ phenotype. Circles indicate females; squares indicate males. The following markers are shown: D2S1334, D2S1399, D2S1353, D2S2330, D2S2261, D2S1391, D2S128, D2S434. This analysis clearly excludes the GEFS2/FEB3 locus in our family.

that all affected individuals from the pedigree presented here have primary generalized epileptic seizures, as there were no signs for a focal onset and all but one of the pathologic EEG recordings showed generalized epileptiform discharges. However, particularly in the absence of ictal EEG and video recordings, a focal type of epilepsy cannot be ruled out with certainty. At least some of the epileptic seizures could also be generated by a focal frontal or parietal onset with a fast bilateral synchrony. Indeed, one EEG recording of the index patient showed left-hemispheric parietal epileptiform discharges. Conversely, these discharges—activated on falling asleep—resembled those classified as benign centrotemporal spikes of childhood, and this patient also showed speech retardation, which can be associated with such benign epileptiform discharges.[41] Because such EEG alterations are common in childhood (2% of children),[42] they may not be a sign of the familial epilepsy syndrome presented here but could be coincident. Altogether, a generalized epileptic syndrome favored by an autosomal dominantly inherited mutation seems to be most probable for our family.

Our linkage data clearly exclude the previously described loci for GEFS$^+$ on chromosomes 19q13 and 2q21-33, demonstrating further genetic heterogeneity of this syndrome. In addition, we excluded all other loci for known genes encoding subunits of voltage-gated Na^+ channels expressed within the nervous system and the previously described loci for febrile seizures. Hence, the mutation causing epilepsy in our family must predict mutation of a thus far unknown Na^+ channel subunit or of a completely different protein, or perhaps another ion channel.

The family had five branches with affected individuals. Three of them presented with a quite homogeneous picture of epileptic syndromes: the offspring of III-1 presented with febrile or afebrile TS, in some cases combined with atonic and absence seizures; the offspring of III-2 presented with febrile and afebrile GTCS combined with atonic and absence seizures; and the offspring of II-4 presented without febrile seizures. The three individuals of the latter branch could be classified as having different forms of idiopathic generalized epilepsy. A speculative but possible reason for this observation could be a different genetic background within those branches causing groups of phenotypic variability. Theoretically, it may also be possible that the idiopathic generalized epileptic syndromes in the offspring of II-4 are not part of GEFS$^+$, but caused by mutation(s) in different gene(s). In this regard, it is important to note that none of the exclusions of chromosomal locations by linkage relied on exclusively different haplotypes of this part of the family.

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