SHORT REPORT

A novel susceptibility locus at 2p24 for generalised epilepsy with febrile seizures plus

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Generalised epilepsy with febrile seizures plus (GEFS+) is a clinically and genetically heterogeneous epilepsy syndrome. Using positional cloning strategies, mutations in *SCN1B*, *SCN1A*, and *GABRG2* have been identified as genetic causes of GEFS+. In the present study, we describe a large four generation family with GEFS+ in which we performed a 10 cM density genome-wide scan. We obtained conclusive evidence for a novel GEFS+ locus on chromosome 2p24 with a maximum two point logarithm of the odds (LOD) score of 4.22 for marker D2S305 at zero recombination. Fine mapping and haplotype segregation analysis in this family delineated a candidate region of 3.24 cM, corresponding to a physical distance of 4.2 Mb. Linkage to 2p24 was confirmed ($p=0.007$) in a collection of 50 nuclear and multiplex families with febrile seizures and epilepsy. Transmission disequilibrium testing and association studies provided further evidence ($p<0.05$) that 2p24 is a susceptibility locus for febrile seizures and epilepsy. Furthermore, we could reduce the candidate region to a 2.14 cM interval, localised between D2S1360 and D2S2342, based upon an ancestral haplotype. Identification of the disease gene at this locus will contribute to a better understanding of the complex genetic aetiology of febrile seizures and epilepsy.

Febrile seizures (MIM 121210) represent the most common childhood convulsion disorder affecting 2–5% of children between the ages of 6 months and 5 years. Seizures are usually generalised tonic-clonic and of brief duration. They are by definition associated with fever and occur without evidence of intracranial infections or other definable causes. Typical febrile seizures remit spontaneously before the age of 5. Twin and family studies have shown that febrile seizures have a heritable component of about 70%.^{1,2} Most studies support a polygenic or multifactorial mode of inheritance.^{1–3} However, in some rare families, segregation of the febrile seizure phenotype is compatible with a monogenic inheritance model.^{2,3}

Although infantile febrile seizures are mostly benign, patients have an increased risk for epilepsy later in life. Generalised epilepsy with febrile seizures plus (GEFS+, MIM 604233) is a familial epilepsy syndrome that links febrile seizures with epilepsy.⁴ It encompasses a continuum of phenotypes with mild and severe forms of epilepsy. Most affected individuals present with typical febrile seizures or atypical febrile seizures, that is, febrile seizures that persist beyond 5 years of age. In addition, patients can have afebrile seizures including generalised tonic-clonic, absence, myoclonic, or atonic seizures. The most severe forms of epilepsy in the GEFS+ spectrum are myoclonic-astatic epilepsy and severe myoclonic epilepsy of infancy. GEFS+ has an

autosomal dominant inheritance pattern with reduced penetrance.

To date, eight chromosomal loci have been reported for febrile seizures and GEFS+: FEB1 at 8q13–q21, FEB2 at 19p13.3, FEB3 at 2q23–q24, FEB4 at 5q14–q15, FEB5 at 6q22–q24, GEFS+1 at 19q13.1, GEFS+2 at 2q21–q33, and GEFS+3 at 5q31.1–q33.1.^{5–13} Mutations in the $\beta 1$ subunit (*SCN1B*) and the $\alpha 1$ subunit (*SCN1A*) of the voltage gated sodium channel, and mutations in the $\gamma 2$ subunit of the GABA_A receptor (*GABRG2*), have been identified in GEFS+ families that are, respectively, linked to the GEFS+1, GEFS+2, and GEFS+3 loci.^{10,12–14}

In this report, we describe a large non-consanguineous family with febrile seizures and epilepsy (fig 1) that was compatible with GEFS+. The family comprised 11 patients in four successive generations and one affected spouse and was from Flanders, the Dutch speaking region of Belgium. All individuals were clinically assessed by means of a structured interview. For all patients, information was obtained about seizure type, duration, age at onset, frequency, and association with fever. The parents or the older siblings of the patients primarily provided clinical information, and all spouses were interviewed for familial occurrence of seizures to exclude possible bilineal inheritance. The detailed clinical characteristics of all patients are shown in table 1.

In summary, of the 11 patients, eight had seizures associated with fever, but none developed epilepsy later in life. The febrile seizures were generalised tonic-clonic. Most seizures were brief, but in two individuals (III.4 and III.10) they lasted for more than 30 min. The age at onset was very similar, ranging between 6 months and 2.5 years. The number of seizures varied between one and three except for individual II.5 who experienced 23 seizures associated with fever. Three patients had epileptic seizures without a history of febrile seizures. The epilepsy phenotype in those individuals was variable. Patient III.5 presented with generalised tonic seizures, while individual III.6 had only absences. For individual I.1, no detailed clinical data could be obtained.

Before initiating a genome-wide scan, we performed a simulation study using SLINK to estimate the power of this family.^{15,16} Two point logarithm of the odds (LOD) scores were calculated with MLINK software (version 5.1) from the LINKAGE package.¹⁷ All individuals with one or more febrile or epileptic seizures were considered affected. We assumed an autosomal dominant inheritance pattern with reduced disease penetrance and a disease frequency of 0.0001. We set the disease penetrance at 90% based upon calculations according to the method of Johnson *et al.*³ Since the frequency of febrile seizures in the population is 2–5%, we incorporated a 3% phenocopy rate. The data were analysed

Abbreviations: GEFS+, generalised epilepsy with febrile seizures plus; LOD, logarithm of the odds; NPL, non-parametric linkage; TDT, transmission disequilibrium test

Figure 1 Pedigree of the four generation Belgian-Dutch family with GEFS+. Closed box: man with epileptic seizures; closed circle: woman with epileptic seizures; vertical bar in empty box: man with febrile seizures; vertical bar in empty circle: woman with febrile seizures; forward slash: deceased. Haplotypes of chromosome 2p markers are shown under each symbol, a dash (-) indicates that genotypes were not obtained for the respective marker. To maintain confidentiality, the number of at risk individuals that were genotyped in the linkage analysis is indicated in a diamond. The disease haplotype is shaded. Haplotypes between brackets were inferred.

assuming equipotent marker alleles and gender average recombination rates. A maximum two point LOD score of 5.07 was generated, using an eight allele marker with equal allele frequencies.

We obtained peripheral blood from all participating individuals and extracted genomic DNA using standard methods. All participants or their legal representative signed a written informed consent form, and the Medical Ethical Committee of the University of Antwerp approved this study.

We performed a 10 cM genome-wide scan with the ABI Prism Linkage Mapping Set MD10 (Applied Biosystems, Foster City, CA) and genotyped 29 family members with 382 microsatellite markers distributed over the human genome. After amplification, PCR products were pooled and size fractionated on an ABI 3700 automated sequencer (Applied Biosystems). We used ABI Prism GeneScan and Genotyper version 3.7 software (Applied Biosystems) to determine allele sizes. For fine mapping, we analysed 16 additional

Table 1 Clinical data of patients in the four generation GEFS+ family

Patient	Gender	Age (years)	FS	ES	Onset age (months)	Seizure type	Duration (min)	No. of seizures
I.1	M	–	No	Yes	–	–	–	–
II.2	F	63	Yes	No	17	GTCS	2	3
II.3	M	62	Yes	No	18	GTCS	3–5	2
II.5	M	55	Yes	No	18	GTCS	5	23
II.8	F	57	Yes	No	17–24	GTCS	–	1
III.4	M	35	Yes	No	6	GTCS	2–30	3
III.5	M	37	No	Yes	9 years	GTS	1–2	3
III.6	M	24	No	Yes	9	Absences	5	1
III.9	M	16	Yes	No	30	GTCS	5	1
III.10	F	15	Yes	No	18	GTCS	>45	1
IV.1	M	14	Yes	No	15	GTCS	<1	2

ES, epileptic seizures; FS, febrile seizures; GTCS, generalised tonic-clonic seizures; GTS, generalised tonic seizures.

microsatellite markers selected from the Marshfield genetic map. Primer pairs for each marker were chosen with a proprietary algorithm implemented in the Multiplexer program (Goossens *et al*, unpublished data). For each marker, we calculated two point LOD scores and obtained a maximum LOD score of 4.22 for marker D2S305 at zero recombination (table 2), assuming the same genetic model as in the simulation study.

None of the previously reported loci showed evidence of linkage, and no other markers from the genome-wide panel gave a LOD score above 3 (data not shown). After analysis of recombination events in patients, we delineated a candidate region of 3.24 cM, localised between markers D2S1360 and D2S2201 (fig 1), corresponding to an estimated physical distance of 4.2 Mb. The telomeric boundary was defined by the recombinant haplotype in II.5 and his son III.6. A recombination in III.9 delimited the centromeric boundary. All patients except IV.1 shared the haplotype segregating with the disease. His unaffected mother also did not inherit the disease haplotype, indicating that individual IV.1 was likely a phenocopy and that his febrile seizures were unrelated to the genetic aetiology in the family. This is not unusual in GEFS+ families, and in part reflects the high frequency of febrile seizures (2–5%) in the general population. It is also of interest that none of the unaffected at risk family members carried the disease haplotype, indicating that the GEFS+ phenotype is fully penetrant in this pedigree. This is rather exceptional as GEFS+ or febrile seizures usually show a disease penetrance varying between 60% and 90%.

After establishing linkage at chromosome 2p24, an additional group of 50 families with febrile seizures and/or epilepsy (table 3) was analysed. All families were of Belgian-Dutch origin. The group comprised a total of 291 individuals of whom 142 were patients. The proband of each family presented with seizures that were associated with fever. For each proband, at least one of the parents was available and provided clinical

Table 3 Characteristics of the febrile seizures and/or the epilepsy families

	2 generation (1 affected offspring)	2 generation (≥ 1 affected offspring)	3 or more generation (≥ 2 patients)
No. of families	11	8	31
No. of individuals analysed	31	36	224
No. of patients	21	20	101
Phenotype of patients			
FS	17	15	87
FS+ES	4	1	6
ES	0	5	8

ES, epileptic seizures; FS, febrile seizures.

Table 4 Non-parametric linkage analysis

Marker	Distance (cM)	NPL score	p value
D2S1360	38.33	2.25	0.011
D2S305	38.87	2.42	0.007
D2S2233	39.93	2.43	0.007
D2S2342	40.47	2.16	0.013
D2S2201	41.57	1.79	0.032

NPL, non-parametric linkage. Positions of the markers were obtained from the Marshfield genetic map.

information about seizure frequency and association with fever. Parents were interviewed to identify a possible positive history for febrile seizures in other family members. If other patients in the family were available, the patients and/or their parents were contacted and interviewed. Additional patients were considered affected if they had at least one unprovoked febrile and/or

Table 2 Two point LOD scores for markers at 2p24

Marker	Distance (cM)	LOD scores at recombination fraction θ of						
		0.00	0.01	0.05	0.10	0.20	0.30	0.40
D2S168*	27.06	1.17	1.29	1.56	1.66	1.53	1.16	0.63
D2S2200	27.60	1.17	1.26	1.43	1.46	1.28	0.93	0.49
D2S1360	38.33	3.10	3.15	3.18	3.04	2.51	1.78	0.94
D2S305*	38.87	4.22	4.15	3.87	3.51	2.73	1.87	0.96
D2S2233	39.93	3.03	2.99	2.79	2.52	1.90	1.23	0.55
D2S2342	40.47	3.57	3.51	3.25	2.92	2.23	1.52	0.77
D2S2201	41.57	1.65	2.56	2.98	2.94	2.49	1.81	0.98
D2S2168	45.30	1.04	1.95	2.36	2.32	1.92	1.33	0.67
D2S165*	47.43	–1.04	–0.10	0.45	0.59	0.58	0.44	0.24

Positions of the markers were obtained from the Marshfield genetic map.

*Microsatellite marker from the 10 cM genome-wide scan panel.

Table 5 Allelic association analysis for five markers at 2p24

Marker	P _{overall}	Alleles	Proband		Control		p
			n	%	n	%	
D2S1360	0.656	2	10	10	22	11.2	0.748
		3	6	6	16	8.2	0.502
		4	26	26	61	31.1	0.360
		5	10	10	19	9.7	0.933
		6	9	9	15	7.7	0.688
		7	10	10	19	9.7	0.933
		8	7	7	12	6.1	0.771
		9	6	6	13	6.6	0.834
		Other	16		19		
D2S305	0.262	2	10	10	23	11.7	0.654
		3	9	9	18	9.2	0.959
		4	12	12	35	17.9	0.192
		6	46	46	67	34.2	0.048*
		7	12	12	22	11.2	0.843
		Other	11		31		
D2S2233	0.048*	2	10	10	36	18.4	0.060
		4	13	13	43	21.9	0.063
		5	9	9	18	9.2	0.959
		6	13	13	26	13.3	0.949
		7	32	32	42	21.4	0.047*
		8	12	12	11	5.6	0.052
		9	7	7	14	7.1	0.964
		Other	4		6		
D2S2342	0.897	2	46	46	87	44.4	0.792
		5	15	15	33	16.8	0.685
		6	27	27	48	24.5	0.639
		Other	12		28		
D2S2201	0.476	1	6	6	9	4.6	0.601
		5	8	8	17	8.7	0.844
		7	6	6	15	7.7	0.600
		8	64	64	112	57.1	0.256
		9	7	7	12	6.1	0.771
		Other	9		31		

Only alleles with an observed frequency >5% in the patients were included in the analysis.
 *p<0.05, statistically significant.

afebrile seizure. Mutations in *SCN1A*, *SCN1B*, and *GABRG2* were excluded by mutation analysis of genomic DNA of each proband¹⁸ (Audenaert *et al*, unpublished data).

To examine linkage to 2p24, we genotyped these families for three markers localised within the candidate region and

two flanking markers, spanning a region of 3.24 cM. We calculated multipoint non-parametric linkage (NPL Z_{all}) scores and associated p values, using the total stat command in the Genehunter program (<http://linkage.rockefeller.edu/soft/gh>). Eleven families consisted of only one affected

Table 6 Two marker sliding window analysis

Haplotype markers	P _{overall}	Alleles	Proband		Control		p
			n	%	n	%	
D2S1360–D2S305	0.681	H-2-6	5	5	7	3.8	0.556
		H-4-6	11	11	17	9.2	0.517
		H-4-7	5	5	7	3.8	0.556
		Other	79		165		
D2S305–D2S2233	0.008*	H-4-7	4	4	7	3.8	0.854
		H-6-6	5	5	10	5.4	0.970
		H-6-7	17	17	12	6.5	0.003*
		H-6-8	4	4	2	1.1	0.085
		Other	70		165		
D2S2233–D2S2342	0.114	H-4-2	5	5	12	6.5	0.695
		H-6-2	9	9	13	7.1	0.463
		H-7-2	15	15	18	9.8	0.133
		H-7-5	4	4	3	1.6	0.186
		H-7-6	8	8	11	6.0	0.428
		H-8-6	4	4	3	1.6	0.186
		H-9-2	4	4	6	3.3	0.672
		Other	51		130		
		H-2-8	25	25	42	22.8	0.487
D2S2342–D2S2201	0.775	H-2-9	5	5	2	1.1	0.033*
		H-5-8	7	7	18	9.8	0.523
		H-6-8	16	16	27	14.7	0.608
		Other	47		107		

Only haplotype alleles with an observed frequency >4% in the patients were included in the analysis.
 *p<0.05, statistically significant.

offspring and were omitted from the NPL analysis. A maximum multipoint NPL Z_{all} score of 2.43 ($p = 0.007$) was obtained at D2S2233 (table 4). The information content of the markers was higher than 80% throughout the 3.24 cM region. These results indicated that the locus at 2p24 is involved in the genetic aetiology underlying the susceptibility for febrile seizures and epilepsy in these families.

To confirm this finding, we performed for each of the five markers at 2p24 a transmission disequilibrium test (TDT) with the probands of the 50 families, using the Genehunter tdt command. This showed that allele 6 at D2S305 was transmitted significantly more to the patients compared to other alleles at D2S305 ($p = 0.022$; allele 6 was transmitted 29 times and not transmitted 14 times).

As a next step, we performed an association study and compared the allelic distribution between probands of the 50 families and 98 Belgian-Dutch population control individuals. Overall p values were calculated using CLUMP (<http://linkage.rockefeller.edu/soft/clump.html>). The overall allelic distribution of the markers was not significantly different between patients and controls, except for D2S2233 (table 5; $p_{overall} = 0.048$). Using the χ^2 statistic, we compared allele frequencies between patients and controls. We found significant allelic association with febrile seizures at D2S305 and D2S2233 (table 5): allele 6 at D2S305 ($P_{allele6} = 0.048$; OR 1.64; 95% CI 1.00–2.68) and allele 7 at D2S2233 ($P_{allele7} = 0.047$; OR 1.73; 95% CI 1.00–2.96).

These findings were further supported using sliding window analysis of two marker haplotypes. To obtain observed haplotypes, we genotyped the 50 probands with their parents and 49 triads of Belgian-Dutch population control individuals. Genehunter generated the most likely haplotypes of patients and control individuals. Using CLUMP, we compared the overall allelic distribution of the two marker haplotypes and found a highly significant overall p value at D2S305–D2S2233 (table 6; $p_{overall} = 0.008$). We calculated the contribution of each haplotype to the overall p value using the χ^2 statistic, and found that H-6-7 at D2S305–D2S2233 was significantly overrepresented in patients (table 6; $p_{H-6-7} = 0.003$; OR 2.94; 95% CI 1.34–6.43). These results demonstrated that a common haplotype at chromosome 2p24, H-6-7, contributed to developing febrile seizures in the Belgian-Dutch population. Furthermore, the disease haplotype in the large linkage family also contained the H-6-7 allele at D2S305–D2S2233 (fig 1). This allowed us to further refine the candidate region at 2p24 to a 2.14 cM interval localised between D2S1360 and D2S2342, based upon ancestral recombination events. A p value less than 0.05 was also obtained for H-2-9 at D2S2342–D2S2201. However, the frequency of this haplotype allele in the control group (table 6; 1.1%) was too low to provide conclusive evidence.

The chromosome 2p24 locus for febrile seizures contains 14 known and six putative genes. So far, the three genes involved in GEFS+, that is, *SCN1B*, *SCN1A*, and *GABRG2*, encode subunits of voltage gated or ligand gated ion channels. Therefore, one of the most attractive candidate genes in this locus is *KCNK3* (voltage gated potassium channel, subfamily S, member 3). It encodes a subunit of the voltage gated potassium channel of the delayed rectifier type and is abundantly expressed in the brain.¹⁹ Further characterisation of *KCNK3* and other genes at the chromosome 2p24 locus might lead to identification of the actual susceptibility alleles in the Belgian-Dutch population and the causal variant in our linkage family.

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ELECTRONIC-DATABASE INFORMATION

The following websites have been mentioned in this report: Center for Medical Genetics, Marshfield Medical Research Foundation, <http://research.marshfieldclinic.org/genetics/>; Laboratory of Statistical Genetics, Rockefeller University, <http://linkage.rockefeller.edu> (for Genehunter and CLUMP); Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim/> (for febrile seizures, and generalised epilepsy with febrile seizures plus); VIB Genetic Service Facility, <http://www.vibgeneticservicefacility.be>.

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CORRECTION

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In the Letter to JMG titled, a genome screen of families at high risk for Hodgkin lymphoma: evidence for a susceptibility gene on chromosome 4 (*J Med Genet* 2005;**42**: 595-601) figure 1 was incorrect. The curves are missing from Chromosomes 16 and 19. A full corrected figure 1 is available on the JMG website at <http://www.jmedgenet.com/supplemental>.