Novel locus on chromosome 12q22–q23.3 responsible for familial temporal lobe epilepsy associated with febrile seizures

L Claes, D Audenaert, L Deprez, W Van Paesschen, C Depondt, D Goossens, J Del-Favero, C Van Broeckhoven, P De Jonghe

Key points
- Familial temporal lobe epilepsy and febrile seizures belong to the group of idiopathic epilepsies. They sometimes co-occur in families as the variable intra-familial expression of a presumably monogenic defect. Molecular genetic studies so far have provided evidence only for a digenic inheritance that implicates chromosomes 18qter and 1q25–q31 in a single pedigree.
- A 10 cM density genomewide scan was performed in an extended pedigree not linked with known loci for familial temporal lobe epilepsy and febrile seizures, and conclusive linkage with markers on chromosome 12q23 was obtained. Fine mapping and haplotype segregation analysis narrowed down the candidate region to a 10.35 cM (8.7 Mb) interval between D12S101 and D12S360.
- The chromosome 12q22–q23.3 locus represents a novel locus for autosomal dominant familial temporal lobe epilepsy with febrile seizures.

Familial idiopathic epilepsy and febrile seizures. These diseases with considerable clinical and genetic heterogeneity and an unclear inheritance pattern because of genetic and environmental factors. Families in which the disease segregates as an autosomal dominant trait with reduced disease penetrance have been identified occasionally. In some of these families, a single gene defect was identified as the cause of epilepsy. To date, mutations in 13 genes have been identified for distinct epilepsy types. Most genes encode subunits of ion channels. In addition, the gene remains to be identified for 21 mapped loci for epilepsy, which highlights the genetic heterogeneity of the idiopathic epilepsy syndromes.

Familial temporal lobe epilepsy (MIM 608096) was first described by Berkovic et al. and was recognised as a distinct epileptic syndrome by the International League Against Epilepsy. It is defined by familial occurrence of simple partial seizures, complex partial seizures, and secondarily generalised seizures of temporal lobe origin. Two genetically distinct autosomal dominant familial temporal lobe epilepsy syndromes have been reported. Autosomal dominant lateral temporal lobe epilepsy (MIM 600512), or autosomal dominant partial epilepsy with auditory features, was described first by Ottman et al., and recently, mutations in the leucine rich glioma inactivated 1 (LGI1) gene on chromosome 10q24 were identified. Auras that present as auditory and visual hallucinations are a clinical hallmark of this syndrome. The other variant of familial temporal lobe epilepsy is characterised clinically by onset in teenage years or early adulthood, absence of antecedent factors, low frequency of deja vu, and a usually good prognosis. This variant, which still can be heterogeneous genetically, is not mapped yet. In a large family with febrile seizures (MIM 121210) and familial temporal lobe epilepsy without hippocampal sclerosis, digenic inheritance with loci on chromosomes 1q25–q31 and 18qter was suggested. Finally, in a large pedigree with a mutation in SCN1A, a few affected mutation carriers had temporal lobe epilepsy, while others had febrile seizures.

Febrile seizures occur between six months and five years of age and affect 2–5% of all children. They are characterised by clonic, tonic–clonic, or atonic seizures that are provoked by fever but are without evidence of intracranial pathology. Sometimes febrile seizures extend beyond the age of five years, when they are designated febrile seizures plus. Association of febrile seizures and febrile seizures plus with a wide variety of afebrile seizures often is observed in patients with epilepsy. This syndrome was named generalised epilepsy with febrile seizures plus (MIM 604233). Although afebrile seizures in these families mostly are generalised, partial seizures, including temporal lobe epilepsy, also have been reported, which renders the designation of generalised epilepsy with febrile seizures plus less appropriate in these families.

Several loci for febrile seizures and generalised epilepsy with febrile seizures plus have been identified: FEB1 on chromosome 8q13–q21 (MIM 602476), FEB2 on chromosome 19p13.3 (MIM 602477), FEB3 on chromosome 2q24 (MIM 604403), FEB4 on chromosome 5q14–q15 (MIM 604352), FEB5 on chromosome 6q22–q24, GEFS+1 on chromosome 19q13.1 with mutations in SCN1B (MIM 600235), GEFS+2 on chromosome 2q24 with mutations in SCN1A (MIM 182389), and GEFS+3 on chromosome 5q31–q33 with mutations in GABRG2 (MIM 137164). We performed a 10 cM density genomewide scan in a five generation family affected by familial temporal lobe epilepsy and febrile seizures.

PARTICIPANTS AND MATERIALS
We previously reported a five generation family affected by familial temporal lobe epilepsy and febrile seizures but without hippocampal sclerosis. The Ethical Committee of the University of Antwerp approved this study and all participants signed informed consent forms. Samples of DNA were available from 53 family members. Detailed genealogical and clinical data have been described.
RESULTS

In a previous study, we excluded linkage to 13 epilepsy loci in this family, including the loci on chromosomes 1q25–q31, 18pter, and 10q and the loci for febrile seizures and generalised epileptic febrile seizures plus+ (except for the FEB5 and GEFS+3 loci, which were not discovered at the time of that study). We performed a genomewide scan for 53 family members to localise the disease gene in this family.

Two markers at 12p from the ABI Prism linkage mapping set gave a logarithm of odds score $>2$; a maximum logarithm of odds score $Z$ of 4.56 was obtained with D12S578 at recombination fraction $\theta = 0.05$ and a maximum $Z$ of 2.93 with D12S579 at $\theta = 0.10$. We analysed 13 additional short tandem repeat markers chosen from the Marshfield comprehensive genetic map and the UCSC genome browser. Sequences that contained short tandem repeats were retrieved from the UCSC genome browser, masked for repeats and used subsequently to generate a list of potential PCR primers using Primer3 (http://frodo.wi.mit.edu). From this list, primer pairs for each marker were chosen with a proprietary algorithm implemented in the Multiplexer program (Goossens et al., unpublished data). This resulted in a number of pools containing between four and 18 primer pairs that were amplified in a single tube reaction without extensive optimising. A maximum two point logarithm of odds score of 6.94 was reached at marker D12S1706 (table 1). The maximum multipoint logarithm of odds score was 7.87 at the same marker.

Segregation analysis identified a disease haplotype in all 22 patients, two obligate carriers, and five at risk family members (fig 1).

Two obligate recombinants (in members III-30 and IV-35) delineated the candidate region centromerically, and one recombination event (in member III-29) defined the candidate region telomerically. This mapped the disease gene for familial temporal lobe epilepsy and febrile seizures to a telomeric region of 1.3 cM between markers D12S101 and D12S578, which corresponds to a 8.7 Mb region (UCSC genome browser).

DISCUSSION

We performed a 10 cM density genomewide scan in a five generation pedigree in which familial temporal lobe epilepsy and febrile seizures were transmitted as an autosomal
dominant trait. We obtained conclusive linkage between markers D12S101 and D12S360 on chromosome 12q23. Most mutations that cause epilepsy identified to date affect genes that encode ion channels. The 8.7 Mb candidate interval that we identified (NT_019546) contains 50 genes, of which 30 are known and 20 are putative genes; none of these genes encode a classic ion channel. A potential functional candidate gene in this region is LOC121456, which is similar to SLC9A7.

Figure 1 Haplotype analysis of markers at chromosome 12q21.2–q24.1. ■ men with TLE; ● women with TLE; ● men with epilepsy; ■ women with epilepsy; / deceased family member; + family member who had febrile seizures; ? not known if family member had febrile seizures. To protect confidentiality, we used diamonds to indicate unaffected at risk individuals who were analysed in the genome scan; the number refers to the number of family members. The disease haplotype is boxed. Inferred haplotypes are between brackets. Family members are numbered according to the numbering in the article of Depont et al., in which detailed clinical data was reported.22
non-selective sodium potassium and proton exchanger. Other candidate genes in this region are VGLUT3 (vesicular glutamate transporter 3, MIM 607557), which is expressed in the brain and is responsible for glutamate uptake in intracellular synaptic vesicles, and Ntrn 4 and ASCL1 (achaete scute complex like 1, MIM 100790), which play a role in axon guidance and neuronal commitment and differentiation, respectively.

Our molecular genetic data confirmed that familial temporal lobe epilepsy with febrile seizures in this family represents a separate genetic entity, presumably caused by a monogenic gene defect. They also confirmed that familial temporal lobe epilepsy and febrile seizures represent the variable expression of this genetic defect, as all patients with only febrile seizures, with febrile seizures and afebrile seizures, or with only afebrile seizures carried the disease haplotype. The combination of febrile seizures or febrile seizures plus and generalised epilepsy is now known as generalised epilepsy with febrile seizures plus, and mutations in several genes have been shown to underlie this syndrome.\(^1\)\(^\text{21-26}\) Subsequent reports, however, showed that partial seizures also could be part of this syndrome: for example, mutations in SCN1A have been identified in families with febrile seizures and generalized epilepsy but also in families with febrile seizures and partial epilepsy.\(^21\)\(^\text{26}\) It has been suggested therefore to expand the spectrum of generalised epilepsy with febrile seizures plus to include partial seizures and to use the term autosomal dominant epilepsy with febrile seizures plus.\(^26\)

Identification of the gene involved in familial temporal lobe epilepsy and febrile seizures will contribute to the unraveling of the molecular mechanisms responsible for epilepsy and will assist the development of better and more effective therapies.

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