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A Novel Locus for Generalized Epilepsy With Febrile Seizures Plus in French Families

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Background: Generalized epilepsy with febrile seizures plus (GEFS+) is a familial autosomal dominant entity characterized by the association of febrile and afebrile seizures. Mutations in 3 genes—the sodium channel α1 subunit gene (SCN1A), the sodium channel β1 subunit gene (SCN1B), and the γ2 GABA receptor subunit gene (GABRG2)—and linkage to 2 other loci on 2p24 and 21q22 have been identified in families with GEFS+, indicating genetic heterogeneity.

Objectives: To localize by means of linkage analysis a new gene for GEFS+ in a large family with 11 affected members and to test the new locus in 4 additional families with GEFS+.

Design: Family-based linkage analysis.

Setting: University hospital.

Patients: Five French families with GEFS+ and at least 7 available affected members with autosomal dominant transmission. All the patients had febrile seizures and/or afebrile generalized tonic-clonic seizures or absence epilepsy.

Main Outcome Measures: We analyzed 380 microsatellite markers and conducted linkage analysis.

Results: In the largest family, a 10-cM-density genome-wide scan revealed linkage to a 13-Mb (megabase) interval on chromosome 8p23-p21 with a maximum pairwise logarithm of odds (LOD) score of 3.00 (at θ=0) for markers D8S1706 and D8S5530 and a multipoint LOD score of 3.23. A second family with GEFS+ was also possibly linked to chromosome 8p23-p21 and the region was narrowed to a 7.3-Mb candidate interval, flanked by markers D8S1706 and D8S549. We have not, so far, identified mutations in the coding exons of 6 candidate genes (MTMR9, MTMR7, CTSB, SGCG, SG22, and ATP6V1B2) located in the genetic interval.

Conclusions: We report a sixth locus for GEFS+ on chromosome 8p23-p21. Because no ion channel genes are located in this interval, identification of the responsible gene will probably uncover a new mechanism of pathogenesis for GEFS+.

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have been reported: febrile convulsions 1 gene (FEB1) on chromosome 8q13-q21,12 FEB2 on 19p13,13 and FEB5 on 6q22-q24.14

Herein, we ascertained 5 French families with GEFS+/without linkage to FS or GEFS+/loci previously reported. Conclusive linkage to chromosome 8p23-p21 was obtained in a large multigenerational family, and, in a second family, linkage to the same locus was suggested.

METHODS

FAMILIES

Five French families with at least 7 affected members for whom DNA was available were identified during a national campaign organized by the Association de Recherche sur la Génétique des Épilepsies and supported by the French Généthon Center. Simplified pedigrees of the families are given in Figure 1. All members of the families underwent clinical assessment using a detailed questionnaire. Information was also obtained retrospectively from medical records. Informed consent was obtained from all the participants or from their legal representatives.

GENOTYPING

Genomic DNA was isolated from blood lymphocytes using standard procedures. Genome scans for families 15173 and 12402 were performed at the Centre National de Genotypage. The set consisted of 400 fluorescent microsatellite markers (including 20 for chromosome X that were not tested because of a male-to-male transmission in each family) selected from the Généthon human linkage map that cover the entire human genome with a resolution of approximately 10 cM. Subsequent markers used for fine mapping were genotyped as previously reported.4

LINKAGE ANALYSIS

We calculated parametric pairwise logarithm of odds (LOD) scores using the MLINK program and multipoint LOD scores using the Allegro program, assuming an autosomal dominant trait with a disease allele frequency of 0.0001, penetrance of 0.60, equal recombination fractions in males and females, and equal frequencies for the alleles observed in the families. These variables were also used to calculate theoretical maximum LOD scores using the “affected only” method. At-risk individuals I:4 (67 years old), II:8 (40 years old), III:3 (21 years old), and III:6 (11 years old) of family 15173 and at-risk individuals I:2 (60 years old), I:6 (69 years old), II:3 (33 years old), II:5 (40 years old), and II:6 (38 years old) of family 12402 were clinically normal and were, thus, considered to be unaffected. All individuals who experienced 1 or more FSs or afebrile seizures were considered to be affected.

SEQUENCING

A mutation search by means of direct sequencing was performed in the coding exons and flanking splice sites of 6 candidate genes (MTMR9 [OMIM 606260], MTMR7 [OMIM 603562], CTSB [OMIM 116810], SGCZ [OMIM 608113],

FIGURE 1. Pedigrees of the 5 families with generalized epilepsy with febrile seizures plus. AS indicates afebrile seizure; FS, febrile seizure.
The genomic organization of the candidate genes and the primer sequences were obtained from the University of California Santa Cruz Web site (http://genome.ucsc.edu/) and are available on request. Polymerase chain reaction products were sequenced on both strands on an ABI3730 automatic sequencer using the Big Dye Terminator Cycle sequencing kit (Applied Biosystems, Foster City, California).

RESULTS

CLINICAL CHARACTERISTICS

Family 15173

We identified a 3-generation kindred with 22 family members: 11 affected individuals with a history of at least 1 FS, 3 of whom also had afebrile seizures, 2 unaffected obligate carriers, 5 unaffected individuals, and 5 married-in individuals (Table 1 and Figure 2). No blood sample was available for patient II:7, who experienced 1 FS.

The FSs began at age 8 months to 1.5 years and persisted beyond age 6 years in 4 patients (II:1, 11 years; II:4, 11 years; and III:7, 6.5 years). The number of FSs was particularly high in 3 patients in generation II despite the prescription of antiepileptic drugs (20 episodes of FS in patient II:1 and 15 in patient II:3). In addition, individual II:4 had an association of FSs and afebrile seizures; he experienced a total of 50 seizures between ages 1 to 11 years. Two individuals had complex FSs: II:4 had 1 prolonged FS followed by transitory hemiplegia at 1 year of age and another prolonged FS without a motor deficit 6 months later, and III:7 had several FSs lasting more than 30 minutes, 1 of which was followed by transitory hemiplegia.

Three individuals (II:1, II:4, and III:5) also had afebrile seizures. Individual II:1 had 1 generalized tonic-clonic seizure (GTCS) during a period of sleep deprivation and alcohol intake, another during treatment with an antidepressant drug. Interictal electroencephalography (EEG) showed rare generalized spike waves in this patient. Individual II:4, after the period (1-11 years) of mixture of FSs and afebrile seizures, was completely seizure-free until age 40 years, when he had an afebrile GTCS in a context of stress and sleep deprivation. An EEG was not available. None of these patients was receiving antiepilep-
tic drugs when examined. For individual III:5, GTCSs and absences began during adolescence. Interictal EEG showed rare generalized spike waves. All affected family members have had normal psychomotor development, and even individuals with a high number of or complex FSs have had good school performance.

Family 12402

In this second 4-generation family, 11 individuals were affected (data were available for only 10 individuals) (Table 1 and Figure 3). Four individuals were dead at the time of this study; DNA was, therefore, available for only 7 individuals. Six of these 7 patients had FSs, with ages at onset ranging from 9 to 24 months. All FSs stopped before or at age 6 years except in 1 patient (I:8) who had his last FS at age 8 years. He also had the highest number of episodes (>10 FSs). The FSs were simple in 4 patients, consisting of brief GTCS, but in 2 patients (I:4 and II:7) they lasted up to 15 to 20 minutes (complex FSs).

Two patients (II:2 and II:4) also had absence epilepsy, with late childhood onset and a 3-Hz spike wave pattern recorded by means of EEG. In addition, in patient I:4, afebrile GTCS occurred during the same period as FSs and stopped by age 9 years. Three family members who died before the study had epilepsy with no reported FSs: the first had absence epilepsy (I:10), and the other 2 had temporal lobe seizures beginning in adolescence (I:11 and II:9). The cause of death was undetermined for patient I:11.

Absence epilepsy in this family was of late onset (I:10, 7 years; II:2, 10 years; and II:4, 16 years) and highly photosensitive. No lesions were observed by means of magnetic resonance imaging (MRI) in patients with temporal lobe epilepsy. Psychomotor development was normal in all affected family members. Performance in school of patient II:2 declined from age 12 years; she was oriented toward a profession at age 16 years.

Families 16923, 17516, and 15635

In family 16923 (8 affected individuals), FSs were simple, infrequent (n=1-4), and stopped before age 6 years. Two patients had afebrile GTCS at ages 3 and 6 years and were fully controlled with antiepileptic drug monotherapy. In family 17516, 10 patients had FSs, which were simple, recurred 2 to 3 times except in 1 patient (n=8), and stopped before 6 years of age. Three patients had afebrile GTCS that occurred once in 1 patient (age at oc-
LOD scores to determine which families were sufficient seizures in adolescence. Their brain MRIs were normal. They were not pharmacoresistant at the time of this study and were 17 and 20 years of age. Their mother had isolated FSs. All affected members of these 3 families had normal psychomotor development.

**LINKAGE ANALYSIS**

**Exclusion of Known FS and GEFS+ Loci**

We first examined whether any of the 5 families presented linkage to previously reported loci for GEFS+ and FS. Negative pairwise LOD scores were obtained in all 5 families, excluding the following loci as the cause of the disease: 19q13 (SCN1B), 2q24 (SCN1A), 3q24 (GABRG2), 2p24 (GEFS+), 2q13 (GEFS+), 8q13–21 (FEB1), 19p13 (FEB2), and 6q22–24 (FEB5) (data not shown).

We then calculated the maximal theoretical pairwise LOD scores to determine which families were sufficiently informative to map a new gene. Using the affected only method, at Θ=0.0, family 15173 (DNA available for 10 affected members) had a Z\(_{\text{max}}\) of 3.06, family 12402 (DNA available for 7 affected members) had a Z\(_{\text{max}}\) of 1.7, family 16923 (DNA available for 8 affected members) had a Z\(_{\text{max}}\) of 2.7, family 15635 (DNA available for 7 affected members) had a Z\(_{\text{max}}\) of 1.8, and family 17516 (DNA available for 7 affected members) had a Z\(_{\text{max}}\) of 1.8.

**Genomewide Scan in Family 15173**

A genome scan of all autosomes was conducted with 380 microsatellite markers in family 15173, the only family in which the theoretical maximal pairwise LOD score reached the threshold value of 3.00 in linkage analyses. Calculation of pairwise LOD scores revealed 20 of 380 noninformative markers, which were excluded by means of haplotype reconstruction (data not shown). In addition, positive pairwise LOD scores were obtained for 6 markers (D10S208, D15S130, D16S423, and D18S61 and the 2 adjacent markers D8S3531 and D8S550). Fine mapping with additional markers (D10S183, D10S199, D15S331, D15S207, D16S3030, D16S3134, and D18S1125, and D18S386) excluded the regions on chromosomes 10, 15, 16, and 18. In contrast, genotyping of 14 additional markers (D8S264, D8S262, D8S1742, D8S277, D8S1706, D8S3531, and D8S550).
D8S351, D8S503, D8S552, VNTR22TG, D8S602, D8S639, D8S262, VNTR25CA, and D8S258) confirmed linkage on chromosome 8p23-p21. Maximal pairwise LOD scores were 3.00 at \( \Theta = 0.0 \) for D8S351 and D8S550 calculated using the affected only method (Table 2). The scores recalculated with inclusion of all at-risk individuals yielded pairwise LOD scores slightly below 3.00 (Table 2) because of incomplete penetrance. Under these conditions, multipoint analysis with 15 markers generated a maximal LOD score of 3.23 in the interval flanked by D8S351 and VNTR25CA; the remaining genome was excluded (data not shown).

Haplotype reconstruction showed that all patients shared a common haplotype encompassing markers D8S351 (chromosome 8: 8 714 310-8 914 565) to VNTR25CA (chromosome 8: 19 887 367-19 887 416) (Figure 2). The boundaries of this interval were defined by a recombination between markers D8S1706 and D8S351 in patient III:9 and a recombination between markers VNTR25CA and D8S258 in patient II:1. This genetic interval (D8S1706-D8S258) corresponds to a 13-Mb (megabase) large region located on chromosome 8p23.1-p21.3, according to the University of California Santa Cruz Genome Browser (http://genome.ucsc.edu/).

### Table 2. Pairwise LOD Scores for 15 Markers on Chromosome 8p23-p21 From Telomere (Top) to Centromere (Bottom) for Family 15173 and Family 12402

<table>
<thead>
<tr>
<th>Marker</th>
<th>( \Theta = 0 )</th>
<th>( \Theta = 0.01 )</th>
<th>( \Theta = 0.05 )</th>
<th>( \Theta = 0.10 )</th>
<th>( \Theta = 0.20 )</th>
<th>( \Theta = 0.30 )</th>
<th>( \Theta = 0.40 )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AO</td>
<td>AR</td>
<td>AO</td>
<td>AR</td>
<td>AO</td>
<td>AR</td>
<td>AO</td>
</tr>
<tr>
<td>D8S262</td>
<td>-9.61</td>
<td>-3.56</td>
<td>-3.45</td>
<td>-2.85</td>
<td>-1.50</td>
<td>-1.70</td>
<td>-0.77</td>
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<td>D8S1742</td>
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<td>-0.27</td>
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<td>0.31</td>
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<td>D8S277</td>
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<td>1.16</td>
<td>1.14</td>
<td>1.03</td>
<td>1.03</td>
<td>0.90</td>
<td>0.90</td>
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<td>D8S1706</td>
<td>-3.03</td>
<td>0.95</td>
<td>0.68</td>
<td>1.14</td>
<td>1.39</td>
<td>1.38</td>
<td>1.44</td>
</tr>
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<td>D8S258</td>
<td>3.00</td>
<td>2.83</td>
<td>2.55</td>
<td>2.52</td>
<td>2.73</td>
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<td>2.02</td>
<td>1.84</td>
<td>1.82</td>
<td>1.48</td>
<td>1.58</td>
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<tr>
<td>D8S550</td>
<td>3.00</td>
<td>2.57</td>
<td>2.95</td>
<td>2.52</td>
<td>2.73</td>
<td>2.33</td>
<td>2.46</td>
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<tr>
<td>D8S552</td>
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<td>1.28</td>
<td>1.74</td>
<td>1.25</td>
<td>1.59</td>
<td>1.14</td>
<td>1.38</td>
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<tr>
<td>VNTR22TG</td>
<td>2.63</td>
<td>2.28</td>
<td>2.58</td>
<td>2.24</td>
<td>2.39</td>
<td>2.07</td>
<td>2.14</td>
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<tr>
<td>D8S549</td>
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<td>2.16</td>
<td>2.32</td>
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<td>2.15</td>
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<td>1.92</td>
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<td>D8S602</td>
<td>2.93</td>
<td>2.30</td>
<td>2.88</td>
<td>2.27</td>
<td>2.67</td>
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<td>D8S639</td>
<td>2.67</td>
<td>2.44</td>
<td>2.62</td>
<td>2.40</td>
<td>2.43</td>
<td>2.23</td>
<td>2.18</td>
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<tr>
<td>D8S261</td>
<td>1.77</td>
<td>1.40</td>
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<td>1.38</td>
<td>1.62</td>
<td>1.29</td>
<td>1.46</td>
</tr>
<tr>
<td>VNTR25CA</td>
<td>2.97</td>
<td>2.72</td>
<td>2.91</td>
<td>2.68</td>
<td>2.70</td>
<td>2.48</td>
<td>2.43</td>
</tr>
<tr>
<td>D8S258</td>
<td>-2.95</td>
<td>0.90</td>
<td>0.85</td>
<td>1.06</td>
<td>1.36</td>
<td>1.27</td>
<td>1.42</td>
</tr>
</tbody>
</table>

**Abbreviations:** AO, “affected only” method; AR, all at-risk individuals; LOD, logarithm of odds.

* Maximum LOD scores.
combination between markers D8S552 and VNTR22TG in patient II:2. This haplotype encompassed a region of 7.3 Mb that overlapped with the haplotype segregating in family 15173, suggesting that both families are linked to the same locus on chromosome 8p23-p21 (Figure 3). However, the allele combinations differed in the 2 families, excluding a common ancestor.

Table 3. Candidate Genes Explored in the 8p23-p21 Interval

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Position in Bases at Chromosome 8</th>
<th>Protein</th>
<th>Potential Role in Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SG223</td>
<td>8 212 676-8 276 667</td>
<td>Tyrosine-protein kinase</td>
<td>Homology with rat prgamma of Rnd2, which is involved in the migration of pyramidal neurons[15]</td>
</tr>
<tr>
<td>MTMR9</td>
<td>11 179 410-11 223 064</td>
<td>Myotubularin-related protein 9</td>
<td>Brain binding partner of MTMR7[16]</td>
</tr>
<tr>
<td>CT5B</td>
<td>11 739 236-11 744 571</td>
<td>Cathepsin B</td>
<td>Uregulated after seizures provoked by hippocampal kindling[17]</td>
</tr>
<tr>
<td>SG2Z</td>
<td>13 991 744-15 140 163</td>
<td>Sarcoglycan zeta</td>
<td>Abundant in the brain[18]</td>
</tr>
<tr>
<td>MTMR7</td>
<td>17 203 534-17 250 961</td>
<td>Myotubularin-related protein 7</td>
<td>Brain binding partner of MTMR9[16]</td>
</tr>
<tr>
<td>ATP6V1B2</td>
<td>20 098 984-20 123 487</td>
<td>ATP synthase subunit B</td>
<td>High levels of expression in the brain[19]</td>
</tr>
</tbody>
</table>

\[The MTMR7 and ATP6V1B2 genes are located outside of the common interval of both families but were initially screened because they were included in the interval segregating in family 15173.\]

We recruited 5 French families with a phenotype compatible with GEFS\[\]. The disorder segregated as an autosomal dominant trait with incomplete penetrance in all families. Most patients in the 5 families experienced simple FSs (93%) and some afebrile seizures (34%), mostly GTCSs or absence seizures. None of the families were linked to the previously reported GEFS\[\] and FS loci.

A 10-cM-density genomewide scan in the most informative family (15173) revealed a unique region with significant maximum pairwise LOD scores of 3.00 and multipoint LOD scores of 3.23 on chromosome 8p23-p21, which strongly suggests that we have identified a new locus for GEFS\[\]. Because all other regions of the genome were excluded, we believe that the responsible gene is probably localized in this interval. Furthermore, when the 4 other families were then tested for linkage to this novel locus, we obtained evidence of probable linkage in 1 family (12402) to a region of 7.3 Mb that overlapped the locus on chromosome 8p23-p21 in family 15173. Although a linkage in family 12402 might have been obtained by chance, the absence of any other positive region is in favor of a conclusive linkage. Furthermore, all affected family members shared the same haplotype, and no novel copies were identified. Although 4 unaffected individuals (including 2 obligate carriers) in family 15173 and 5 (including 2 obligate carriers) in family 12402 also carried the haplotype associated with the disease, this illustrates an incomplete penetrance of GEFS\[\] associated with 8p23-p21. This would not be unusual because reduced penetrance of 60% has previously been reported in families with GEFS\[\] and it was estimated to be 64% in a collection of families with FSs.\[20\] The present data suggest that this locus is involved in 2 of the 5 families tested, suggesting that it might not be a rare locus.

We described in detail the clinical features of the 2 families, 15173 and 12402, linked to the new locus on chromosome 8p23-p21. In family 15173, all affected individuals experienced FSs, and 3 of 11 also experienced...
Afebrile seizures co-occurred with FSs in at least 1 patient. Complex FSs were observed in only 1 of 27 patients (4%) from families excluded for this in 53% of patients from families linked to chromosome Furthermore, there was a high rate of recurrence of FSs to be a family with epilepsy and FSs rather than typical epilepsy (Table 3). So far, no causal mutations have been reported in families with GEFS*. Two families corresponded to the description of the familial GEFS* context.

In the literature, phenotype-genotype correlations have been reported in families with GEFS*. For example, the proportion of patients with FS+ was higher in families with SCN1A mutations than in families with GABRG2 mutations.23 In the present study, families with linkage to the 8p23-p21 locus had a higher proportion of patients with FS+ than did families without linkage (28% vs 7%). Furthermore, there was a high rate of recurrence of FSs in 53% of patients from families linked to chromosome 8p23-p21, whereas frequent recurrence was reported in only 1 of 27 patients (4%) from families excluded for this locus. Complex FSs were observed in only 2 families linked to chromosome 8p23-p21 (4 of 17 patients). Afebrile seizures co-occurred with FSs in at least 1 patient per family except for family 15635. Because none of the patients had FS+ in this family, it was considered to be a family with epilepsy and FSs rather than typical GEFS+.

The new locus contains approximately 80 known genes, none of which are known or predicted to encode ion channels, neurotransmitter receptors, or proteins homologous to others involved in epilepsy. Twenty of the genes encode defensins and were not considered as candidates for epilepsy. Thirty genes encode unknown proteins. To identify the causative gene, we sequenced the coding regions and flanking splicing sites of genes encoding proteins expressed in brain or with a putative role in epilepsy (Table 3). So far, no causal mutations have been identified in the coding regions of the following genes: CTSB, SGCG, SG223, MTMR9, MTMR7, and ATP6V1B2. We hope that elucidation of the function of the unknown proteins encoded by genes located in the interval will provide new candidates to screen for FSs and epilepsy. In parallel, we will search for rearrangements that are reported to be frequent in the 8p23 region.24,25 Identification of additional families with GEFS+ linked to the 8p23-p21 region will reinforce linkage to this new locus, the sixth to be identified for this disorder. This might also narrow the candidate interval and consequently decrease the number of candidate genes to explore. So far, 3 genes have been implicated in GEFS+; SCN1A, SCN1B, and GABRG2. Except for leucine-rich glioma inactivated 1 (LGI1) and EF-hand domain (C-terminal) containing 1 (EFHC1), all other genes involved in idiopathic monogenic epilepsies encode ion channel or neurotransmitter receptor genes.26 It is, thus, interesting that the novel locus reported herein does not contain genes with functions similar to those already implicated in epilepsy. Identification of the responsible gene in 8p23-p21 might bring to light a new mechanism involved in epileptogenesis.

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: S. Baulac, Gourfinkel-An, Dulac, M. Baulac, LeGuern, and Nabbout. Acquisition of data: S. Baulac, Gourfinkel-An, Couarch, Kaminska, and Nabbout. Analysis and interpretation of data: S. Baulac, Gourfinkel-An, Depienne, and LeGuern. Drafting of the manuscript: S. Baulac, Gourfinkel-An, Couarch, LeGuern, and Nabbout. Critical revision of the manuscript for important intellectual content: S. Baulac, Gourfinkel-An, Depienne, Kaminska, Dulac, M. Baulac, LeGuern, and Nabbout. Obtained funding: S. Baulac, M. Baulac, and Nabbout. Administrative, technical, and material support: Couarch, Kaminska, and Dulac. Study supervision: S. Baulac, Gourfinkel-An, and LeGuern.

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REFERENCES


Announcement

Trial Registration Required. In concert with the International Committee of Medical Journal Editors (ICMJE), Archives of Neurology will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorial by DeAngelis et al in the January issue of Archives of Dermatology (2005;141:76-77). Also see the Instructions to Authors on our Web site: www.archneurol.com.