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Febrile seizures (FS) affect 3% of children aged 6 months to 6 years and have a strong genetic component with recurrence risk ratios of 3–5 in first-degree relatives. In rare families with autosomal dominant FS, mutations in the sodium channel alpha 1 subunit gene, SCN1A, have been identified. However, FS usually show complex inheritance with a polygenic basis. The search for susceptibility variants has been slow, so the recent report of a common splice site single nucleotide polymorphism (SNP) in SCN1A (IVS5N + 5 G>A, rs3812718) is notable. Two patient groups were studied: the first, adults with focal epilepsy with and without a history of FS (n = 90 and 486 respectively); the second, children with FS (n = 144). Patients homozygous for the A allele were reported to have a genotype relative risk of ~3.0 for FS. The rs3812718 SNP is a plausible candidate for FS as it influences relative expression of neonatal and adult transcripts of SCN1A, which plays a key role in membrane excitability.

To confirm the association between rs3812718 and FS, independent replication studies are vital. We tested the primary hypothesis of the original study, that an AA genotype at this SCN1A polymorphism confers increased risk of FS. For this, we recruited 558 unrelated Australian (predominantly Caucasian) patients with epilepsy clinics at 2 tertiary hospitals in Melbourne. The criteria for a diagnosis of FS were identical to that of the original study. Patients with an afibrile seizure history prior to the onset of FS were excluded. The genotyping methodology has been described previously. Approval was obtained from the Human Research Ethics Committees of Austin and Melbourne Health.

The cohort of 558 patients comprised 76 (14%) cases with and 482 (86%) without a history of FS. A total of 382 (68%) patients had idiopathic generalized epilepsies; 137 (25%) had focal epilepsies; 12 (2%) had both idiopathic generalized and focal epilepsies; 17 (3%) had unclassified epilepsy; and 10 (2%) had only ever experienced FS.
To ensure statistical consistency with the original findings, we utilized the Armitage trend test. No other SCN1A polymorphisms were examined.

**Results.** Our Australian study did not replicate the association reported between the AA genotype of the rs3812718 SCN1A SNP and increased risk of FS despite using identical FS classification, statistical methodology, and a similar sample size (table). We tested the primary hypothesis of the original study in a cohort of mixed idiopathic generalized and focal epilepsy patients who had a confirmed history of FS. We then performed a secondary post hoc analysis to more closely replicate the population of the original study. We compared our focal epilepsy and FS group (including n = 10 pure FS cases) with our focal epilepsy control group (table). Finally, we compared the Australian FS group (n = 76) with the European control group (n = 701) as described in the original article. On all occasions the results were negative; however, we did not have the sample size required to test the hypothesis in a pure FS group.

Because our Australian cohort consisted of predominantly patients with generalized epilepsy, we also evaluated a pure focal epilepsy cohort from the EPIGEN consortium, which is in complete linkage disequilibrium with rs3812718 (\(r^2 = 1\)) in Western European populations, was studied. Focal epilepsy patients (n = 1,589) from the United Kingdom, Ireland, Belgium, and the United States showed no difference between those with (n = 232) and those without a history of FS (n = 1,357) (\(p = 0.9\), odds ratio AA vs GG homozygotes = 1.0, 95% confidence interval 0.7–1.5) or focal epilepsy with FS vs population controls (n = 1,806) (\(p = 0.3\), odds ratio AA vs GG = 1.2, 95% confidence interval 0.8–1.8).

Our failure to replicate the original findings raises the possibility that the original observation was a false positive.

*Members of the EPIGEN Consortium are listed in the appendix.

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**Table** IVSN + 5 G>A (rs3812718) genotypic frequencies in an Australian population

<table>
<thead>
<tr>
<th>Test</th>
<th>Genotype</th>
<th>Case, n (%)</th>
<th>Control, n (%)</th>
<th>p Value</th>
<th>(OR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FS with all epilepsy (n = 76) vs no FS with all epilepsy (n = 482)</strong></td>
<td>AA 27 (35)</td>
<td>152 (32)</td>
<td>0.41</td>
<td>1.13, 0.7–2.6</td>
<td></td>
</tr>
<tr>
<td>AG 34 (45)</td>
<td>218 (45)</td>
<td>1.23, 0.7–2.2</td>
<td></td>
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</tr>
<tr>
<td>GG 15 (20)</td>
<td>112 (23)</td>
<td>1.16, 0.6–2.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Focal with FS and FS only (n = 23) vs focal without FS (n = 124)</strong></td>
<td>AA 10 (43)</td>
<td>33 (27)</td>
<td>0.24</td>
<td>1.18, 0.8–5.9</td>
<td></td>
</tr>
<tr>
<td>AG 8 (35)</td>
<td>61 (49)</td>
<td>1.15, 0.4–3.4</td>
<td></td>
<td></td>
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<tr>
<td>GG 5 (22)</td>
<td>30 (24)</td>
<td>0.79, 0.2–2.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FS with all epilepsy (n = 76) vs European controls (n = 701)</strong></td>
<td>AA 27 (35)</td>
<td>187 (27)</td>
<td>0.15</td>
<td>1.57, 0.8–3.0</td>
<td></td>
</tr>
<tr>
<td>AG 34 (45)</td>
<td>351 (50)</td>
<td>1.23, 0.7–2.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG 15 (20)</td>
<td>163 (23)</td>
<td>1.05, 0.6–2.0</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*First OR (AA vs GG); second OR (AA + AG vs GG); third OR (AG vs GG).†Combining focal epilepsy patients with FS (n = 13) and the pure FS cases (n = 10).‡Patients who had both generalized and focal epilepsies (n = 12) were excluded from this analysis.

CI = confidence interval; FS = febrile seizures; OR = odds ratio.
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APPENDIX

The EPIGEN Consortium contribution to this work was coordinated by Dr. S.M. Sisodiya. The Consortium additionally comprises the following: C. Depondt, M. Pandolfo (Department of Neurology, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium); G. Cavalleri, N. Delanty, S. Alhusaini (The Department of Clinical Neurological Sciences and Molecular and Cellular Therapeutics, RCSI Research Institute, Royal College of Surgeons in Ireland); C. Doherty (Division of Neurology, Beaumont Hospital, Dublin, Ireland); E.L. Heinzen, D.B. Goldstein, R. Radtke, T.J. Urban (Institute for Genome Sciences and Policy, Center for Human Genome Variation, Duke University, Durham, NC); C. Catarino, D. Kasperaviciute, S.K. Tate (Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, UK). C.D., M.P., N.D., S.A., C.D., R.R., C.C., S.M.S., and S.K.T. participated in the collection of the EPIGEN data. G.L.C., E.L.H., D.B.G., T.J.U., and D.K. analyzed the EPIGEN data. The Australian authors (S.P., I.E.S., T.J.O., and S.F.B.) were not part of the EPIGEN consortium.

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