Although uncommon, the progression of febrile seizures (FS) early in life to mesial temporal lobe epilepsy with MTS is well-described; however, underlying mechanisms and predictors are poorly understood. Proposed mechanisms include prolonged FS at an early age damaging the hippocampus, initial hippocampal injury peri- or prenatally, or a hippocampal formation genetically predisposed to MTS triggered or activated by remote FS. Several rarer epilepsies featuring febrile seizures are caused by mutations in SCN1A, which encodes a brain-expressed sodium channel subunit targeted by many anti-epileptic drugs. We undertook a genome-wide association study in 1018 people with mesial temporal lobe epilepsy with hippocampal sclerosis and 7552 control subjects, with validation in an independent sample set comprising 959 people with mesial temporal lobe epilepsy with hippocampal sclerosis and 3591 control subjects. To dissect out variants related to a history of febrile seizures, we tested cases with mesial temporal lobe epilepsy with hippocampal sclerosis with (overall n = 757) and without (overall n = 803) a history of febrile seizures. Meta-analysis revealed a genome-wide significant association for mesial temporal lobe epilepsy with hippocampal sclerosis with febrile seizures at the sodium channel gene cluster on chromosome 2q24.3 [rs7587026, within an intron of the SCN1A gene, P = 3.36 x 10⁻⁹, odds ratio (A) = 1.42, 95% confidence interval: 1.26–1.59]. In a cohort of 172 individuals with febrile seizures, who did not develop epilepsy during prospective follow-up to age 13 years, and 6456 controls, no association was found for rs7587026 and febrile seizures. These findings suggest SCN1A involvement in a common epilepsy syndrome, give new direction to biological understanding of mesial temporal lobe epilepsy with hippocampal sclerosis with febrile seizures, and open avenues for investigation of prognostic factors and possible prevention of epilepsy in some children with febrile seizures.

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SCN1A and Febrile Seizures in Mesial Temporal Epilepsy

some 2q24 that includes SCN2A and SCN3A (5). SCN1A encodes a voltage-gated sodium channel alpha subunit. The alpha subunit of sodium channels forms the membrane pore. Each alpha subunit protein has four domains with six transmembrane segments connected by loops. The majority of SCN1A mutations cluster in the C-terminus and the pore loops in the first three domains of the protein (5,10). The pathophysiology of SCN1A mutations is a decrease in the activity of GABAergic inhibitory neurons. For example, most of the mutations that cause Dravet syndrome (SEMI) result in loss of function, whereas mutations that cause GEFS+ are missense, likely altering channel activity (3). However, about 5% of individuals with mutation-positive SEMI have a familial missense SCN1A mutation associated with a milder phenotype (i.e., GEFS+) in other family members (5).

The study by Kasperaviciute et al., is a multicenter, multinational genetic association study involving a large cohort of subjects with MTS with and without a history of FS. The aim of this study was to identify an association, if not a mechanism, of the most common focal-onset epilepsy when associated with early FS. A detailed meta-analysis demonstrated a target at the sodium channel gene cluster on chromosome 2q24.3 (rs7587026, within an intron of the SCN1A gene). Those subjects with early FS followed to nearly age 15 without developing hippocampal sclerosis HS did not possess the mutation. Although this study does not explain whether FS cause MTS, or whether pre-existing hippocampal abnormalities predispose to FS (2), it suggests that patients with MTS, with or without a history of FS possess different underlying pathogenetic mechanisms.

The study controls for the specificity of the association for MTS + FS rather than FS alone, since developing epilepsy following a history of FS is most often apparent by age 15 (4). No association of the rs7587026 with FS where patients did not develop epilepsy was found in comparison with controls from the same cohort. The authors reported observing a signal in MTS + FS not due to a history of FS alone. In addition, a dissociation was demonstrated where no significant relationship was detected in a group of patients with other partial epilepsies and a history of FS. The authors reported that their genetic association strategy did not differentiate between cell types (interneurons as proposed in Dravet syndrome vs principal neurons). Additionally, the authors did not address possible mechanisms underlying the specificity of hippocampal pathophysiology, or insight as to the critical age range of onset. Translational implications of this study include developing potential pharmacogenetic testing as a tool for individualized therapy. For example, mutations in the alpha-unit of the SCN1A gene have been associated with decreased efficacy of sodium channel blocking anti-epileptic medications. A single nucleotide polymorphism in SCN1A is associated with carbamazepine-resistant epilepsy. As a result, such individuals require higher maintenance dose of carbamazepine (9). Of note, children with SCN1A-related epilepsy may be at high risk of sudden unexpected death in epilepsy (SUDEP).

SCN1A has been closely connected with a number of other voltage-gated sodium channel genes (i.e., SCN1B, SCN2A, SCN3A). These genes may contribute both pathophysiologically and phenotypically to a number of the genetic epilepsies. Moreover, phenotypic expression of these other genes can overlap with those of SCN1A. This information suggests a heterogeneous group of genetic epilepsies. Nevertheless, this important well-organized multinational study contributes a better understanding of SCN1A-related mesial temporal lobe epilepsy with hippocampal sclerosis. Moreover, it provides a systematic approach that could inevitably lead to both prognosis and potential therapies in a subgroup of children with MTLE and a history of FS.

by Marvin A Rossi, MD, PhD

References

Disclosure of Potential Conflicts of Interest

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

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2. First Name  Marvin  Last Name Rossi  Degree MD, PhD

3. Are you the Main Assigned Author? Yes No

If no, enter your name as co-author:

4. Manuscript/Article Title: ISCN1A and Febrile Seizures in Mesial Temporal Epilepsy: An Early Signal to Guide Prognosis and Treatment?

5. Journal Issue you are submitting for: 14.4

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Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

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<th>Money to Your Institution*</th>
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* This means money that your institution received for your efforts on this study.
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* This means money that your institution received for your efforts.

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