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EPILEPSY

Genetic variant in subtype of MTLE

A genome-wide association study has identified a link between single-nucleotide polymorphisms (SNPs) in the sodium channel gene SCN1A and mesial temporal lobe epilepsy with hippocampal sclerosis (MTLEHS) and febrile seizures. "The findings should give new direction to exploration of the cause of this syndrome," says Sanjay Sisodiya, Professor of Neurology at University College London, UK, who led the study.

MTLEHS is one of the most common forms of drug-resistant epilepsy. Moreover, resective surgery to remove the sclerosed hippocampal tissue is only effective in about half of patients who undergo such treatment. The syndrome often features severe comorbidities such as memory impairments and psychiatric disturbances. As Sisodiya notes, this syndrome is, therefore, an important epilepsy subtype to better understand if prognosis is to improve. Previous studies had suggested a possible genetic component to MTLEHS aetiology, but the cause of disease is unknown in most cases.

For the first part of their study, Sisodiya and co-workers investigated genome-wide association between MTLEHS and 531,164 SNPs in 1,081 MTLEHS cases compared with 7,552 controls. "We were interested to find common susceptibility variants that are shared among patients with MTLEHS and might point the way to understanding its biology," says Sisodiya. Patients with bilateral hippocampal sclerosis were excluded, and all cases and controls were of European descent. The team identified suggestive association for three SNPs on chromosome 2, in a region encompassing *SCN1A*. This gene encodes a brain-expressed sodium channel that is the most commonly mutated channel in epilepsy and an important target of antiepileptic drugs.

Next, the group stratified the data according to whether patients had a history of childhood febrile seizures. About 3% of children experience febrile seizures, some of whom go on to develop epilepsy. Such seizures have been reported in many—but not all—MTLEHS cases, and their role in this form of epilepsy has been unclear. "Some researchers suggest that febrile seizures damage the hippocampus and lead to MTLEHS," says Sisodiya, "whereas others think that the hippocampus in some children is in some way abnormal to begin with, and that febrile seizures then initiate a series of events that eventually lead to MTLEHS."

Importantly, the three MTLEHS-associated SNPs identified in the first part of the study only maintained genome-wide significance in the cohort with a history of febrile seizures, and were not associated with MTLEHS without febrile seizures. "The findings seem to fit nicely with the observation that many rare mutations in *SCN1A* cause epilepsies that feature febrile seizures," notes Sisodiya.

The findings were replicated in an independent validation cohort of 959 patients with MTLEHS and 3,591 population-matched controls. A weaker association was identified at this stage, however, highlighting the need for confirmation in larger samples.

The pathophysiological mechanism linking the *SCN1A* variant to disease remains to be established. On the basis of the location of the identified variants in or near the promoter region of the gene, Sisodiya and colleagues postulated that mechanisms related to gene expression might be at play. However, gene-expression analysis of resected middle temporal cortex tissue from 78 patients with MTLEHS and 78 neurologically normal individuals did not reveal any differences in *SCN1A* expression. One possible explanation for this negative finding could be that effects of the *SCN1A* variant depended on brain region or cell type.

"There are many avenues to explore," says Sisodiya. "We need to understand how this association comes about, and what the underlying mechanisms are. The aim is to determine whether, in some cases, the development of MTLEHS can be prevented."

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