

Whole-exome sequencing to disentangle the complex genetics of hippocampal sclerosis–temporal lobe epilepsy

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Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) is a common epilepsy syndrome accounting for approximately 20% of people with epilepsy.¹ It typically shows electroclinical features indicative of seizure onset in the mesial or limbic structures of the temporal lobe, i.e., epigastric/visceral, autonomic, psycho-affective, and sensorial symptoms, including déjà vu.¹ Awareness is generally preserved at onset, but loss of consciousness may also occur, with motionless stare and oro-alimentary, vocal, or gestural automatisms, eventually followed by a convulsive seizure. EEGs show anterior or mid-temporal epileptic abnormalities combined with focal slowing. Hippocampal sclerosis (HS) is demonstrable on coronal MRI sequences by a unilateral (or asymmetrical) decrease in hippocampal volume and an increase in signal on T2-weighted sequences. The neuropathologic hallmark of HS is a combination of atrophy and astrogliosis of the amygdala, hippocampus, uncus, parahippocampal gyrus, and the entorhinal cortex.¹ The diagnosis of MTLE-HS is crucial because it is often uncontrolled by antiseizure drugs but typically responsive to resective surgery.^{2,3}

The etiology of MTLE-HS remains largely elusive. Although generally perceived as an acquired disorder, a few familial cases have been reported,^{4–6} suggesting complex inheritance, similar to that widely accepted for genetic generalized epilepsies. Hitherto, this condition is an appropriate target for contemporary approaches to complex disorders, such as genome-wide association studies for common genetic variants or deep sequencing for rare variants. A relatively recent association study, including ~1,000 patients with MTLE-HS compared with ~7,500 controls, identified a robust association with a polymorphic marker in the sodium channel gene *SCN1A*.⁷

In this issue of *Neurology Genetics*[®], Wong et al.⁸ investigated the role of rare and de novo genetic variants in MTLE-HS by whole-exome sequencing (WES) performed in a small well-characterized cohort of Han Chinese patients from Hong Kong clinically homogeneous as to seizure semiology, ictal/interictal EEG recordings, and high-definition brain MRI studies. Age at onset of epilepsy was ≥2 years. As control, the authors used WES data from 692 Hong Kong Han Chinese participants with no history of developmental or neuropsychiatric disorders. Association studies of rare variants (frequency of minor allele <1% in population databases) were performed at gene or gene-set levels by comparing the total amounts of variation found in individual genes or in groups of clinically or functionally connected genes, respectively, in cases and controls. Moreover, in a subgroup of patients, of whom both parents were available, rare variant analysis of parent-proband trios was performed to uncover de novo variants not transmitted by either parent and potentially recessive mutations inherited by both parents.

Overall, WES data from 47 patients (26 females), including 23 trios, led Wong et al.⁸ to identify rare and de novo variants in a number of genes. Notably, compared to population controls, significant enrichment of rare variants was observed in *SEC24B*, a gene involved in vesicle trafficking and development, whereas gene-set association analysis showed variant enrichment

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in the fragile X mental retardation protein (FMRP)-related group of genes, which comprises hundreds of genes regulated by the FMRP protein, including the mammalian target of rapamycin (mTOR) pathway. In addition, analysis of trios revealed 21 de novo variants, many of which are known to be associated with different neuropsychiatric disorders. These results, however, while providing useful hints for future studies, should be considered with caution on a clinical/diagnostic ground because of the low statistical power of the cohort investigated. Indeed, the enrichment of variants revealed in *SEC24B*, based on 3/47 variants identified in the patients vs 1/652 in the controls, only indicates a statistical trend to be confirmed in studied of larger patient cohorts; variant enrichment in the FMRP gene set might reflect the higher number of genes making up this gene group as compared to the other gene sets investigated. Also, the conclusion that FMRP targets by its putative interaction with the mTOR pathway may play a pathogenic role in MTLE-HS sounds attractive, but it is speculative. However, the frequency of de novo mutations detected in the patients (21/23 trios) does not exceed that expected in the general population (approximately 1 de novo variant per individual). Some of them affect genes such as *ROBO4*, *NLGN3*, and *CEP170B*, which have been found to harbor variants in autism spectrum disorder, but their involvement in epilepsy awaits confirmatory studies.

Overall, no major hit emerged for MTLE-HS from this study, supporting the view that the genetic architecture underlying MTLE-HS is complex and that MTLE-HS and other neuropsychiatric disorders may have shared biology. The major limitation of this study is the relatively small cohort of investigated patients, particularly the small number of analyzed trios, which is unlikely to produce positive results, especially if considering the likely polygenic nature of the disease. Genetic epilepsies include over 30% of all epilepsy syndromes. Next-generation sequencing has proven to be effective in identifying mutations for mendelian, single-gene disorders.⁹ By contrast, this technique have showed so far limited success in the identification of variants causing more complex phenotypes where the phenotypes are more heterogeneous, and it is unclear whether they result from the action of a single gene, multiple genes, or a complex interaction between the genetic and environmental factors.

The increasing development of experimental tools and bioinformatics analysis for a large-scale evaluation of gene expression may help overcome this limitation to confirm the

preliminary findings emerging from this WES study. In a recent study, the group of E. Aronica examined the pathologic cellular pathways involved in different phases of epileptogenesis in human and animal hippocampus.¹⁰ This analysis revealed involvement of several key pathogenic pathways underlying epileptogenesis, including inflammation, gliosis and deregulation of the extracellular matrix. Better understanding of gene expression and regulation during the course of epileptogenesis in MTLE may eventually produce significant advances for the development of preventive treatment for this common chronic neurologic disease.

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