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

Pasquale Striano, MD, PhD, and Carlo Nobile, PhD

Neurol Genet 2018;4:e241. doi:10.1212/NXG.0000000000000241

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., epigatric/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 \(\sim1,000\) patients with MTLE-HS compared with \(\sim7,500\) controls, identified a robust association with a polymorphic marker in the sodium channel gene \(SCN1A\).\(^7\)

In this issue of Neurology Genetics\(^8\), 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 \(\geq2\) 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...
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 com-
pared 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 (ap-
proximately 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
MTHE-HS is complex and that MTLE-HS and other neu-
ropsychiatric disorders may have shared biology. The major
limitation of this study is the relatively small cohort of in-
vestigated 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 pheno-
types 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 bio-
informatics analysis for a large-scale evaluation of gene ex-
pression may help overcome this limitation to confirm the
preliminary findings emerging from this WES study. In a re-
cent study, the group of E. Aronica examined the pathologic
cellular pathways involved in different phases of epilepto-
genesis 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 un-
derstanding 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.

Study funding
No targeted funding reported.

Disclosure
P. Striano has served on the scientific advisory board of the
Italian Agency of the Drug (AIFA) and received honoraria
from Kolfarma s.r.l., UCB pharma, and Eisai Inc., and research
support from the Italian Ministry of Health. C. Nobile re-
ceived research support from the Telethon Foundation
(Grant no. GGP15229) and the Genetics Commission of the
Italian League Against Epilepsy. Full disclosure form in-
formation provided by the authors is available with the full
text of this article at Neurology.org/NG.

References
1. Blumcke I, Aronica E, Miyata H, et al. International recommendation for a compre-
  hensive neuropathologic workup of epilepsy surgery brain tissue: a consensus task
  force report from the ILAE Commission on Diagnostic Methods. Epilepsia 2016;57:
  348–358.
2. Androsova G, Krause R, Borghei M, et al. Comparative effectiveness of antiepileptic
drugs in patients with mesial temporal lobe epilepsy with hippocampal sclerosis.
Epilepsia 2017;58:1734–1741.
3. Wibbe S, Blume WT, Girvin JP, et al. Effectiveness and efficiency of surgery for
  temporal lobe epilepsy study group. N Engl J Med 2001;345:311–318.
4. Briellmann RS, Torn-Broers Y, Jackson GD, Berkovic SF. Seizures in family members
  of patients with hippocampal sclerosis. Neurology 2001;57:1800–1804.
5. Kobayashi E, D’Agostino MD, Lopes-Cendes I, et al. Hippocampal atrophy and T2-
  weighted signal changes in familial mesial temporal lobe epilepsy. Neurology 2003;60:
  405–409.
6. Striano P, Gambardella A, Cippolla A, et al. Familial mesial temporal lobe epilepsy
  (FMTLE): a clinical and genetic study of 15 Italian families. J Neuro 2008;255:
  16–23.
7. Kasperaviciute D, Catarino CB, Matarin M, et al. Epilepsy, hippocampal sclerosis and
  febrile seizures linked by common genetic variation around SCN1A. Brain 2013;136:
  3140–3150.
8. Wong JK, Hongsheng G, Maxwell K, et al. Rare variants and de novo variants in
  mesial temporal lobe epilepsy with hippocampal sclerosis. Neurol Genet 2018;4:
  e245.
9. Orsini A, Zara F, Striano P. Recent advances in epilepsy genetics. Neurosci Lett 2018;
  667:4–9.
10. Korotkov A, Mills JD, Gorter JA, van Vliet EA, Aronica E. Systematic review and meta-
    analysis of differentially expressed miRNAs in experimental and human temporal lobe
    epilepsy. Sci Rep 2017;7:11592.
Whole-exome sequencing to disentangle the complex genetics of hippocampal sclerosis–temporal lobe epilepsy
Pasquale Striano and Carlo Nobile
Neurol Genet 2018;4;
DOI 10.1212/NXG.0000000000000241

This information is current as of June 11, 2018

Updated Information & Services
including high resolution figures, can be found at:
http://ng.neurology.org/content/4/3/e241.full.html

References
This article cites 10 articles, 1 of which you can access for free at:
http://ng.neurology.org/content/4/3/e241.full.html##ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
All Epilepsy/Seizures
http://ng.neurology.org/cgi/collection/all_epilepsy_seizures
Association studies in genetics
http://ng.neurology.org/cgi/collection/association_studies_in_genetics
Hippocampal sclerosis
http://ng.neurology.org/cgi/collection/hippocampal_sclerosis

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://ng.neurology.org/misc/about.xhtml#permissions

Reprints
Information about ordering reprints can be found online:
http://ng.neurology.org/misc/addir.xhtml#reprintsus