AMERICAN EPILEPSY SOCIETY

New Insight Into the Genetic Causes of Epilepsy

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Washington, D.C., December 7, 2013 - Scientists screening the DNA of large cohorts for known and suspected epilepsy associated genes are finding that, while some genes are implicated in discrete phenotypes or forms of epilepsy, other genes are implicated in a wider range of phenotypes. Although ion channel genes are a common cause of epilepsy, the researchers also report a significant number of epilepsy patients with mutations in non-ion channel genes. The studies have important implications for treatment, prognosis and risk counseling.

Targeted resequencing of 101 genes

Epilepsy affects about three percent of the population and comprises a wide constellation of primary and syndromic neurological disorders. The epileptic encephalopathies (EE) are the most severe of the epilepsies, distinguished by multiple refractory seizures, cognitive deficit, and poor developmental outcome. *De novo* mutations in several genes are known causes of EE, but the genetic etiology of the vast majority of these encephalopathies is unknown.

An investigative team of researchers led by Dr. Heather Mefford, M.D., Ph.D., from the University of Washington, Seattle, and Dr. Ingrid Scheffer, MBBS, Ph.D, at the University of Melbourne, Australia, resequenced 101 known and candidate epilepsy genes in more than 600 patients with EE to identify the genetic causes underlying their conditions. The team demonstrates emerging trends in how mutations in some genes cause specific disorders, while mutations in others cause a wide range of neurodevelopmental phenotypes. Furthermore the investigators described six new EE genes, four of which are not involved in neurotransmission at the synapse, but rather may regulate expression of other genes. (Platform A.07 / Abstract 8750891 – *Targeted Resequencing of 101 Known and Suspected Candidate Epilepsy Genes in 600 Patients with Severe Epilepsies Identifies Recurrently Mutated Genes.*)

"Our study identifies pathogenic mutations in ~12% of our EE cohort, and has identified important new genes for this condition" says lead author, Gemma Carvill, Ph.D., of the University of Washington. "Understanding how these new EE genes cause epilepsy provides new avenues of research and, in the future, development of targeted therapies".

Molecular diagnostic testing of 1,600 individuals with epilepsy

In another report, GeneDx, a diagnostic laboratory in Gaithersburg, MD, presented results of diagnostic testing for up to 53 genes associated with major forms of primary and syndromic epilepsy in 1,600 patients to determine the etiology of their epilepsy. Overall, they found a

known or predicted pathogenic genetic abnormality in 261 cases (16%), while patients with infantile onset epilepsy had an even higher positive diagnostic rate of about 20%.

These results indicate that at least 20% of cases have a Mendelian genetic form of epilepsy. Although mutations in ion channel genes are a common cause of epilepsy, half of all pathogenic mutations were identified in non-ion channel genes including some very rare causes of epilepsy. In one-third of patients with a disease-causing mutation, molecular test results had immediate implications for patient treatment or management. (Platform A.08 / Abstract 1749369 – *New Insights into the Spectrum of Pathogenic Variation in Epilepsy Gained from 1600 Individuals.*)

According to Courtney Downtain, M.S., C.G.C., who presented the report, "Utilizing a multi-gene panel for epilepsy allowed us to identify disease-causing mutations in genes causing rare genetic forms of epilepsy, which were not primarily considered by the referring physicians. In addition, we are starting to appreciate the expanding phenotypic spectrum of many epilepsy-related genes. Our data demonstrate that mutations in many genes can result in similar clinical presentation, illustrating the utility of multi-gene panel testing."

Editors Note: Authors of this study will be available at a press briefing at 12:30 pm (EST), December 7, in the onsite pressroom, Room 209-A, Level 2 of the Walter E. Washington Convention Center. The call-in number for off-site journalists is 1-605-475-4000, passcode 521653#.

About epilepsy
The epilepsies affect 50 million people worldwide, including three million in the United States. The disorder can have a single specific, well-defined cause, such as a head injury, or manifest as a syndrome with a complex of symptoms. It is the third most common neurological disorder after Alzheimer's disease and stroke.

About the American Epilepsy Society (AES)
The American Epilepsy Society, based in West Hartford, Conn., seeks to advance and improve the treatment of epilepsy through the promotion of epilepsy research and education for healthcare professionals. The Society's annual meeting is the largest scientific meeting in epilepsy and each year attracts some 4,000 physicians, scientists and allied healthcare professionals from around the world.

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