Roles for Genetic Testing in Epilepsy

Written by Phil Vinall

Epilepsy medicine is beginning to use targeted therapy based on genetic testing. David B. Goldstein, MD, Duke University School of Medicine, Durham, North Carolina, USA, discussed some of the work being performed by researchers at Epi4K – Gene Discovery in Epilepsy, a center funded by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health. Epi4K researchers use the most modern genetic technologies from throughout North America, Europe, and Australia in screening >4000 patient genomes for mutations that potentially influence the risk for epilepsy [Epi4K Consortium. *Epilepsia* 2012].

The first project Dr. Goldstein discussed was the epileptic encephalopathies project, in which 264 patients with infantile spasms and Lennox-Gastaut syndrome were sequenced to identify genetic causes of these syndromes [Epi4K Consortium. *Nature* 2013]. The parents of a subset of study participants were also sequenced to identify cases in which patients harbored de novo or rare pathogenic mutations. The design of the study was to perform whole-exon sequencing on probands and their parents. In the first study, investigators examined 264 trios with either infantile spasms or Lennox-Gastaut syndrome to identify risk. The average number of de novo mutations was about 1 for the protein-encoding part of the genome. Using a likelihood analysis to test for the presence of risk factors, no significant evidence of risk factors was found in any of these mutations.

To determine which mutations might most likely influence disease, Dr. Goldstein's team next developed an intolerance-scoring system that assesses whether genes have relatively more or less functional genetic variation in the human population than expected on the basis of the apparently neutral variation found in the gene. Genes with less common functional variation than predicted imply genes with mutations that do something harmful. The intolerance-ranking system was then used to interpret personal genomes and identify pathogenic mutations [Petrovski S et al. *PLoS Genet* 2013].

The authors found statistical evidence of risk factors of disease among the 4264 intolerant genes identified and estimated that 90 genes might carry mutations that influence risk. Having 1 of these mutations increased the risk for epileptic encephalopathy 80-fold. Thus, certain genetic mutations were thought to have a major impact on risk.

Next, the mutation rate of each gene was calculated using the trinucleotide mutation rate matrix, which is a test for excess mutation in individual genes as a function of their mutation rates and sizes. Applying this analysis to all the genes in the data set that had multiple mutations, 5 genome-wide significant genes (*SCN1A*, *STXBP1*, *GABRB3*, *CDKL5*, and *ALG13*) that confer risk for encephalopathy were identified. This small study detected causal de novo mutations in about 10% of patients. These causal mutations are very rare but clearly organized into specific biological processes.

Almost every patient has an underlying different mutation, which makes it very difficult to stratify patients genetically for treatment. However, these mutations tend to merge into a much smaller number of biological pathways, making it possible to use treatment options tailored to the disregulated biological pathway. This is highlighted by the finding in the aforementioned data that showed that 6 of 264 patients had *GABA* receptor mutations, and 7 of 264 had mutations influencing vesicle trafficking.

These findings are now being put to use in a gene-sequencing clinic in children with presumed genetic conditions but no diagnoses. In a case discussed by Dr. Goldstein, a patient came to this clinic with an unrecognized neurologic condition. Whole-exome sequencing was performed, and mutations in *KCNT1* were identified. Mutations in *KCNT1* have been implicated in autosomal dominant nocturnal frontal lobe epilepsy and epilepsy of infancy with migrating focal seizures. *KCNT1* mutations cause marked increases in the gain of function in the potassium channel associated with these conditions. Exposure to quinidine has been found to significantly reduce this gain of function for all mutations studied [Milligan CJ et al. *Ann Neurol* 2014], and as a result, patients identified as quinidine sensitive experience decreased rates of seizures following quinidine treatment. This example of the patient with a *KCNT1* mutation illustrates how performing genetic sequencing can then potentially identify ways to specifically tailor treatment and hopefully optimize outcomes.

Dr. Goldstein is also involved with creating the Epilepsy Genetics Initiative, with the aim to establish a data repository of clinical exome and genome sequences. These data will be reanalyzed every 6 months for novel genetic changes, and new results will be communicated back to patients through their doctors. The data will also be made available so as to advance epilepsy research.

Precision medicine in the epilepsies needs comprehensive efforts to provide genetic diagnoses for all unexplained cases, a focus on both *in vitro* and *in vivo* modeling of the effects of those mutations, and the establishment of a translational paradigm to clinically evaluated targeted treatments.