The Value of Novel Candidate Gene Analysis in Individuals with Epilepsy undergoing Exome Sequencing

4,200 characters (including spaces)

Authors:
Zöe Powis[1], Kirsten Blanco[1], Kelly D. Farwell[1], Deepali N. Shinde[1], Erica Smith[1], Amanda L. Bergner [1], Jing Wang[1], Sha Tang[1], Katherine L. Helbig[1]

Institution:
[1]Ambry Genetics, Aliso Viejo, CA

Introduction: Since 2011, clinical diagnostic exome sequencing (DES) has proven instrumental in providing molecular diagnoses for patients with wide-ranging, previously undiagnosed genetic diseases. Studies continue to highlight the usefulness of DES, particularly in patients with epilepsy, to yield a high diagnostic rate and to impact both genetic counseling and treatment. Novel candidate genes for patients with epilepsy continue to be elucidated. Herein, we report novel candidate gene findings and clinical characteristics of an unselected laboratory cohort of patients with epilepsy.
Methods: In an unselected sample of 461 patients with reported epilepsy referred for DES who then underwent subsequent novel candidate gene analysis (probands with informative family members in which novel genetic analysis was requested), the overall results categories were determined according to predefined diagnostic variant assessment criteria. 65 cases were excluded as pathogenic variations in characterized genes were identified. Where possible, available clinical information was reviewed, including seizure semiology, seizure onset, EEG reports, and available brain imaging reports, to determine epilepsy syndrome diagnoses according to established International League Against Epilepsy (ILAE) classification criteria.
Results: 35/396 (8.8%) cases had findings within 38 novel candidate genes; of these, one was determined to be *de novo*, 7 inherited and the rest uncertain due to non-biparental trios. Genes identified in 9/35 (25.7%) were later re-classified to characterized gene findings due to newly published literature, including *PURA*, *SON,* and *ZBTB18*. One negative case was later re-classified to having a finding in a novel gene (*RORB*) after re-analysis. Epilepsy diagnoses could be established for 24/35 patients with findings in novel candidate genes. Of these 24 patients, 16 (66.7%) had electroclinical features consistent with an epileptic encephalopathy.
Conclusion: In our cohort, potentially relevant novel candidate genes were identified in approximately 9% of patients with epilepsy referred for DES. Of these patients, two-thirds appeared to have an epileptic encephalopathy, which suggests that analysis and reporting of novel genetic etiologies may be particularly useful for this patient population. Of the reported novel candidate genes, 27% were subsequently confirmed by additional reported patients in independent peer-reviewed literature, indicating that systematic analysis of novel genetic etiologies according to established reporting criteria has clinical validity and can be applied on a diagnostic basis.