ASHG Abstract

Diagnostic Exome Sequencing as the Foundation of Building Pharmacogenomics Based Therapeutic Models for the Treatment of Ion Channel Epilepsy

Gandomi SK[1], Waller K[1], Farwell Gonzalez K[1], Shahmirzadi L[1], Baxter RM[1], Tippin-Davis B[1], Tang S[1]

1.) Ambry Genetics

Diagnostic exome sequencing is currently the most comprehensive clinical genetic testing option available to patients with neurological disorders. Historically, individuals presenting with features suggestive of an underlying genetic syndrome had limited options in the diagnostic process, especially in regards to their subsequent management. With the recent advancement of Next Generation sequencing techniques, and the rapid growth in clinical utility of diagnostic exome sequencing (DES) in the clinical neurology setting, the diagnostic and treatment options available for epilepsy patients is progressively changing. Here we present our institution's DES data to show the effectiveness of DES in diagnosing ion channel related epilepsy, which therefore lays the foundation for potential pharmacogenomic treatment protocols in the near future.

In the first 496 cases sent to our institution for DES, 131 (27.93%) patients were diagnosed with epilepsy as a major clinical feature upon referral. Approximately 43 (32.8%) of these patients were found to have positive, pathogenic alterations, and an additional 11 (8.4%) patients were found to have "likely positive" alterations in a variety of genes. In both of these cohorts combined (n=54), 1 patient had an alteration in a calcium-activated chloride channel gene (*ANO3*), 3 patients had alterations in sodium channel genes (*SCN3A, SCN1A*), and 3 additional patients had alterations in potassium channel genes (*KCNQ2, KCNC3*).

As the current literature suggests, there are rapidly increasing therapeutic possibilities for epilepsy, especially for disorders involving major ion channels such as *SCN1A*. We anticipate the continued and increased use of DES in identification of pathogenic alterations for patients with ion channel-related epilepsy, and recommend the integration of DES technology into research and clinical settings for the long-term development of targeted therapies.