**Novel Gene Discovery in the Epilepsies Using Diagnostic Exome Sequencing**

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**Objective:** Although diagnostic exome sequencing (DES) is transforming understanding and management of neurological diseases, the diagnostic rate reported by clinical laboratories analyzing only characterized genes has rarely exceeded 25–30%. DES simultaneously interrogates virtually all coding genes, providing unprecedented opportunities for novel gene discovery.

**Methods:** 314 unselected cases recently submitted to our lab with an indication of epilepsy underwent DES with analysis of characterized genes and, if negative, evaluation of variants in novel genes.

**Results:** Our diagnostic rate was 38.2% (120/314), with novel genes accounting for 12.5% (15/120) of positive cases. Additionally, 12.8% (5/39) of all uncertain/possibly positive cases involved novel genes. Altogether, these 20 cases represented 24 novel genes, with multiple novel genes found in three cases. Following our reporting of these genes, 37.5% (9/24) were subsequently reported in at least one publication with a median delay of 29.7 weeks and four (*COQ4, DNM1, IL21R, PURA*) were confirmed as dedicated disease genes in independent publications, on average within 20 weeks.

**Conclusions:** The inclusion of novel gene analysis as part of DES is of significant diagnostic value in the epilepsies. Novel gene interpretation for singleton cases is challenging and such findings cannot be definitively stated as causative. However, the 12.5% positive rate and the 37.5% corroboration rate in our cohort thus far demonstrate that overall clinical utility outweighs uncertainty for reporting novel findings. Novel gene reporting can both add to the growing body of evidence for Mendelian disease etiology in the epilepsies and aid in healthcare management of affected individuals.