Genes with therapeutic associations responsible for majority of epilepsy mutations

Weltmer EC, Yussuf A, Newman H, Carter T, Wang J

INTRODUCTION

Precision medicine in epilepsy involves identifying a specific genetic epilepsy syndrome and, when available, applying a specific treatment. Testing via a rapid, targeted panel of genes with therapeutic associations may expedite diagnosis and tailor management. For example, clobazam and valproic acid may be used as first-line medications for *SCN1A*-related seizure disorder, while sodium channel-blocking anticonvulsants may be avoided; anti-epileptic drugs may even be avoided all together in favor of the ketogenic diet for *SLC2A1*-related seizure disorder. In addition, since understanding of these associations is still ongoing, testing via a comprehensive epilepsy gene panel may still provide valuable information in the short term for prognosis and recurrence risk. We compared the diagnostic effectiveness of a targeted panel of 16 epilepsy genes with therapeutic associations to a comprehensive panel of 100 epilepsy genes.

METHODS

We reviewed the first 65 cases submitted to our laboratory for either a standalone panel (ER) of 16 epilepsy genes (*ALDH7A1, FOLR1, KCNQ2, KCNQ3, KCNT1, MECP2, PCDH19, PNPO, POLG, PRRT2, SCN1A, SCN8A, SLC2A1, STXBP1, TSC1, TSC2*) with therapeutic associations or for ER with reflex to a comprehensive 100-gene epilepsy panel (EN), and 428 cases submitted directly for EN. EN included all 16 ER genes plus an additional 84 genes associated with epilepsy. We determined mutation and VUS rates per panel and per gene.

RESULTS

Twelve cases were submitted for ER, 53 for ER with reflex to EN. Of these 65 cases, 9 (14%) were positive for a pathogenic mutation; 8/9 (89%) mutations were in one of the 16 ER genes. Of the EN cases, 46/428 (11%) were positive; 31/46 (67%) mutations were in an ER gene. The 55 total mutations were distributed among 20 genes, 7 of these genes were on the ER panel. The most frequently implicated genes, all on the ER panel, were *SCN1A* (13 mutations), *KCNQ2* (9 mutations), *PRRT2* (7 mutations) and *PCDH19* (5 mutations). Five genes (including *SLC2A1* and *TSC2* on ER panel) had 2 mutations each and the remaining 11 mutations were each in a different gene (including *SCN8A* on ER panel). With the exception of the c.649dupC common mutation in *PRRT2*, which was identified in 5 unrelated patients, each mutation was seen in only one patient. In addition, a total of 467 VUS in 82 genes (16 on ER panel) were detected among the total cohort of (493) patients. 83/467 (18%) of VUS were found in an ER gene. In addition to the overall positive rate of 11% (55/493 patients), 54% (264/493) of patients received a VUS report, and 35% (174/493) of patients received a negative report.

CONCLUSIONS

The majority (39/55; 71%) of epilepsy mutations were found in genes with therapeutic associations. Although the additional genes on the comprehensive 100-gene panel were responsible for nearly 30% of mutations and patient diagnoses, these additional genes were also responsible for the majority (384/467; 82%) of VUS. A tiered approach to testing, beginning with a targeted panel of management-associated genes and then reflexing to a more comprehensive panel, may be efficient for many patients. This approach takes advantage of a high epilepsy diagnostic yield in a short amount of time (2 weeks), while maintaining the option to pursue other genetic causes of epilepsy with minimal time in between. In addition, the potential for uncertain results is minimized when the management-associated panel is pursued first. Continued research into the genetic causes of epilepsy and potential targets for therapy are critical to increasing access to precision medicine in epilepsy management.