Targeted Genetic Testing of Sixteen Epilepsy Genes with Known Therapeutic Associations: High Mutation Frequency Rate and Impact on Clinical Management

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Rationale: Recent advancements in clinical research have shown that particular genetic causes of epilepsy may be more or less responsive to certain types of therapy. Therefore, early diagnosis may lead to more customized and appropriate management.

Methods: In this study, we performed a retrospective analysis on the first 32 unselected individuals tested for either a standalone rapid (8-10 day turnaround time) targeted epilepsy panel of sixteen genes (ER) known to be associated with reported therapies and/or anti-epileptic drugs (AEDs), or with reflex to a comprehensive 100-gene epilepsy panel (EN). Known potential benefits of ordering ER rather than EN include rapid turnaround time and reduced number of genes in which variants of unknown significance (VUS) may be detected. The sixteen genes included on ER are: *ALDH7A1, FOLR1, KCNQ2, KCNQ3, KCNT1, MECP2, PCDH19, PNPO, POLG, PRRT2, SCN1A, SCN8A, SLC2A1, STXBP1, TSC1,* and *TSC2.* We also analyzed 35 positive EN standalone cases. Testing was performed using a combination of next generation sequencing (NGS), targeted microarray, and multiplex ligation-dependent probe amplification (MLPA) analyses. Ordering providers at Weill Cornell and Mount Sinai were also contacted to determine if positive results, found during ER testing, had resulted in a change to their patients' clinical management.

Results: We analyzed 9 ER cases and 23 ER reflex to EN cases for a total of 32 cases. We detected pathogenic mutations or likely pathogenic variants (VLP) in 5/32 (16%) total cases. 100% (5/5) of positive results were detected in one of the sixteen genes on the ER panel. Furthermore, of the 35 positive EN cases analyzed, 77% (27/35) were detected in one of the sixteen genes which are included on the ER panel. In total, 80% (32/40) of positive findings were detected in one of these sixteen genes. The three most commonly mutated genes were *SCN1A* (7 individuals), *PRRT2* (6 individuals), and *KCNQ2* (5 individuals). Mutations were found in multiple individuals in *PCDH19, ARX*, and *SLC2A1*. Of these six most commonly mutated genes, *ARX* is the only gene which is *not* included in the sixteen genes on the ER panel. Although ER results did not directly change the patients' clinical management at Mount Sinai or Weill Cornell, they did provide prognostic information and guidance as to which medications should be *avoided*, and allowed for formal genetic counseling which included: family planning, reproductive risk counseling, variable expressivity discussions, as well as formal referrals allowing patients to be followed in the event of new trials, treatments, or recommendations.

Conclusions: These data demonstrate that the frequency at which positive findings are detected in the sixteen genes included in the ER panel (80%) is substantially higher than the frequency at which positive findings are detected in other genes not included on the ER panel (20%). In addition to the previously described potential benefits of ordering ER, this high frequency of positive findings (80%) is another benefit that ordering providers should take into consideration when ordering first tier epilepsy panel genetic testing. In addition, as discussed, these sixteen genes are all known to be associated with reported therapies and/or AEDs, which means a positive result has the potential to directly impact clinical management. While positive results might not always result in treatments/AED modifications, they may allow the clinician to better understand and forecast a patients' prognosis, determine which medications to avoid, and appropriately refer to genetic counselors and/or specialized genetics clinics.