Title:

Genetic Testing for Epilepsy in Adults

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Description:

Introduction: The field of epilepsy genetic testing is expanding, particularly in relation to childhood onset disease. Studies of epilepsy genetic testing demonstrate a high diagnostic yield and impact on treatment and counseling. Previous studies have shown that adult healthcare providers are significantly less likely to order genetic testing. Little is known about genetic testing in adult patients with epilepsy. Herein, we report the characteristics and detection rates of a cohort of adult patients with epilepsy

Methods: We reviewed an unselected cohort of 334 adults referred for epilepsy genetic testing at one commercial laboratory who underwent epilepsy multigene panel testing (MGPT) ranging from 16 to 96 genes, and/or diagnostic exome sequencing (DES). All probands with DES underwent characterized gene analysis, and if negative, novel candidate gene analysis (if an informative family trio was provided and novel genetic analysis was requested). The overall results categories were determined according to

predefined diagnostic variant assessment criteria. Statistical analysis was performed using Fisher's exact test.

Results: From 334 probands, 109 MGPT tests and 234 DES tests were performed. 8 probands reflexed from MGPT to DES; 2 cases VUS, 1 carrier and the remainder negative. One patient underwent two MGPT tests. All patients undergoing DES had syndromic epilepsy, 16 patients undergoing MGPT had isolated epilepsy. One case of isolated epilepsy was positive for a pathogenic alteration in *SCN1B*.

Overall, testing was ordered mostly by geneticists (53.6%) and neurologists (43.1%), with geneticists more likely to order DES and neurologists more likely to order MGPT ($p<0.001$). 2 patients undergoing DES did not have any previous genetic testing, 58 patients undergoing MGPT did not have any previous genetic testing.

Of 334 probands, 54 (19.2%) had Positive/Likely Positive results and 86 (24.9%) had uncertain/inconclusive findings in characterized genes. Out of 105 cases in which uncharacterized or novel gene analysis was performed on DES 4 (3.8 %) had novel candidate findings. 7 MGPTs had carrier results (6.4%). Overall, 182 (54.5%) cases were negative. MGPT had more uncertain/inconclusive results and DES had more negative results ($p<0.0001$). The detection rate in characterized genes for childhood onset and adult onset epilepsy were both 17.8%.

Positive MGPT results were found in 20 genes including two cases in *SCN1A*. 9 positive cases also had VUS or carrier findings in 9 additional genes. Positive/likely positive findings in DES cases were also found in 20 genes found on panel testing including multiple cases in various genes (*SCN1A* (5), *MECP2* (4), *MEF2C, SLC2A1 and WDR45* (2 cases each)). 6 cases had findings in two genes.

Conclusion: While adults with epilepsy are less likely to have genetic testing offered, our results show that patients have similar diagnostic yields to pediatric cohorts and may still benefit, not only to test at risk family members but also for personal therapeutic management. For example, individuals with positive results in *KCNQ2, MECP2, SCN1A,* and *SLC2A1* have recommended personalized treatments and medications to utilize or avoid. Testing of adults may be utilized not only for reproductive risks but also for personalized precision medicine.

Our results also demonstrate the complexity of genetic testing for adults with epilepsy as most patients had a range of additional clinical findings, and showed a wide spectrum of seizure types. Genetic testing for epilepsy continues to be challenging, but testing of adults is an area in which even less is known. The continual discovery of new genetic etiologies for epilepsy can aid in treatment but also underscores the complexity of genetic testing. Additional studies are needed to expand what is known about epilepsy testing of adults and its clinical utility.

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Whole exome sequencing

Primary Topic Focus:
Molecular Genomics/Exome Sequencing

Files:

12156_chart_Adults_Epilepsy_Demographis_figure_ACMG.docx

Learning Objective 1:	Describe the characteristics and detection rates of genetic testing in a cohort of adult patients with epilepsy