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Diagnostic Yield and Treatment Changes After Genetic Testing of Adults With Epilepsy

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Multigene Panel Testing in a Large Cohort of Adults with Epilepsy: Diagnostic Yield and Clinically Actionable Genetic Findings

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Background and Objectives: Although genetic testing among children with epilepsy has demonstrated clinical utility and become a part of routine testing, studies in adults are limited. This study reports the diagnostic yield of genetic testing in adults with epilepsy. Methods: Unrelated individuals aged 18 years and older who underwent diagnostic genetic testing for epilepsy using a comprehensive, next-generation sequencing-based, targeted gene panel (range 89-189 genes) were included in this cross-sectional study. Clinical information, provided at the discretion of the ordering clinician, was reviewed and analyzed. Diagnostic yield was calculated for all individuals including by age at seizure onset and comorbidities based on clinician-reported information. The proportion of individuals with clinically actionable genetic findings, including instances when a specific treatment would be indicated or contraindicated due to a diagnostic finding, was calculated. Results: Among 2,008 individuals, a diagnostic finding was returned for 218 adults (10.9%), with clinically actionable findings in 55.5% of diagnoses. The highest diagnostic yield was in adults with seizure onset during infancy (29.6%, 0-1 year), followed by in early childhood (13.6%, 2-4 years), late childhood (7.0%, 5-10 years), adolescence (2.4%, 11-17 years), and adulthood (3.7%, >/=18 years). Comorbid intellectual disability (ID) or developmental delay resulted in a high diagnostic yield (16.0%), most notably for females (19.6% in females vs 12.3% in males). Among individuals with pharmacoresistant epilepsy, 13.5% had a diagnostic finding, and of these, 57.4% were clinically actionable genetic findings. Discussion: These data reinforce the utility of genetic testing for adults with epilepsy, particularly for those with childhood-onset seizures, ID, and pharmacoresistance. This is an important consideration due to longer survival and the complexity of the transition from pediatric to adult care. In addition, more than half of diagnostic findings in this study were considered clinically actionable, suggesting that genetic testing could have a direct impact on clinical management and outcomes.

Commentary

The clinical utility of genetic testing for children with non-acquired epilepsy has been demonstrated, and testing is now ordered routinely in a growing number of pediatric neurology clinics. By contrast, genetic testing of adults with epilepsy is performed less often, possibly because some providers who mostly treat adults are less familiar either with it or with the epilepsy syndromes that begin in childhood. Additionally, genetic testing may not have been available when such adults began having seizures in childhood, and many years after seizure-onset epileptologists might forget to investigate a molecular etiology. Few studies on genetic testing of adults with epilepsy have been conducted. One such study examined 200 adults, the vast majority of whom had intellectual disability (ID).[1] Using gene panel testing, a genetic diagnosis was established in 46 (23%) of these adults. The genes *SCN1A*, *KCNT1* and *STXBP1* were found in 48% of positive cases. Moreover, gene-specific treatment changes were made in 11 of these adults, of whom 10 experienced an improved outcome.[1]

The current research[2] expands the adult literature. 2,008 adults with unexplained epilepsy and a mean age of 28.7 years who had undergone commercial genetic testing were retrospectively studied.[2] Genes were targeted and analyzed using next-generation sequencing (NGS) using blood or saliva. Single nucleotide variants, insertions and deletions, structural variants, and exon-level copy number variants were sought. Results were classified as benign or likely benign, variants of unknown significance (VUS), and pathogenic or likely pathogenic (P/LP). Only results of P/LP or VUS were reported to clinicians. A definitive molecular diagnosis was defined as either a single P/LP variant in a gene associated with autosomal dominant (AD) or X-linked inheritance

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or two P/LP variants (or a single homozygous variant) in genes associated with autosomal recessive inheritance. Nondiagnostic findings were defined as a VUS, one P/LP variant in an AR gene, and others. Negative findings were when no P/LP or VUS were reported.

The genetic results reported were compared to gender, age range at disease onset, age at seizure-onset, and the presence of intellectual disability (ID), developmental delay (DD), autism spectrum disorder, pharmacoresistant seizures, and family history of neurological disorders. Adults with ID/DD were not separated into groups with and without developmental and epileptic encephalopathy (DEE). To identify *de novo* variants, individuals reported to have AD or X-linked genes who had both parents subsequently tested were analyzed. Finally, the authors determined in what percentage of reports the results had the potential to change clinical treatment.

100 or more genes were tested in over 98% of adults. A definitive molecular diagnosis occurred in 218 patients (10.9%) overall, but several factors were found that increased the yield. Not surprisingly, there was a trend toward a greater yield as the number of genes analyzed grew over the years. A definitive result was reported for 61 genes (most common were *SCN1A* and *MECP2*). The diagnostic yield was greatest in patients whose seizures began during infancy (29.6%), and among those patients the genes found were ones mostly associated with either full penetrance or early-onset syndromic diseases (e.g., *SCN1A*, *PCDH19*). In contrast, definitive diagnoses in patients with adult-onset seizures largely were for genes associated with reduced penetrance and variable expressivity (e.g., *FLNA*, *LGI1*). Comorbid ID/DD also conferred a high rate of definitive results: 19.6% in females and 12.3% in males ($P = .037$). In those females, the X-linked genes *MECP2* for Rett syndrome and *PCDH19* for DEE-9 were commonly reported. 30 patients who had a definitive molecular diagnosis later had both parents tested, and, of those, 25 patients (83.3%) had *de novo* variants. Finally, of the 218 patients with definitive results, 121 (55.5%) had diagnostic findings in 1 of 22 genes indicating a "clinically-actionable" specific treatment: 99 patients with indications for an antiseizure medication (ASM) and 64 for possible surgery.

The large percentage of *de novo* variants found in the group with definitive molecular results suggests that when genetic testing is performed for patients with epilepsy and ID/DD who present for care at any age (even those with no identifiable family history or other etiology) there is a high likelihood of establishing a new genetic diagnosis. It also emphasizes the importance of including parents in testing when a definitive molecular diagnosis is determined. Logistically, the latter becomes more difficult in older adult patients because their parents may be deceased or unavailable.

One must be careful not to overinterpret VUS because while some may be upgraded to P/LP variants in the future most are eventually downgraded to benign variants. Additionally, negative results do not signal the lack of a genetic etiology. It is also important to remember that when an NGS panel result is negative, other assays could still indicate the correct diagnosis, e.g., chromosomal microarrays, whole exome sequencing, karyotyping, and mitochondrial DNA sequencing.

This study did not specifically examine how test results changed treatments or, if so, what was the clinical outcome. Nevertheless, the finding that most of the results pointed to specific ASM, surgical or metabolic treatments for epilepsy (and, in a small number, a specific treatment for another disorder) supports the conclusion that genetic testing now has a favorable benefit/cost ratio.

The 1990s was declared the Decade of the Brain by the United States Congress. During that decade a handful of epilepsy gene loci were discovered using pedigree analysis and some of us were optimistic that it would not be long until genetic test results would inform precision ASM prescribing. In actuality, the subsequent discovery of hundreds of genes (more than 400 for the DEEs alone[3]) and myriad mutations within many of those genes led some of us to worry that personalized medicine may not be possible in this field. The message from the current paper[2] is that, more than 30 years after the start of the Decade of the Brain, mechanism-based treatments for some adults with unexplained epilepsy can be informed by NGS.

The American Board of Internal Medicine Foundation's ongoing *Choosing Wisely*® initiative asks clinicians to consider benefit/cost ratios before ordering tests. With respect to epilepsy, the cost-effectiveness of genetic testing of children has been assessed.[4,5] The current study[2] supplements the pediatric literature by determining that the highest yield among adults is in patients whose epilepsy began at a very young age or who have ID/DD (especially females).

A new systematic review and meta-analysis of reports on genetic testing in the epilepsies found that the diagnostic yield depended upon the test modality: 48% for genome sequencing, 24% for exome sequencing, 19% for multigene panels, and 9% for comparative genomic hybridization - chromosomal microarray.[6] Similar to the current study,[2] the diagnostic yield was highest among patients with DEEs.[6] It determined that among patients who received a genetic diagnosis treatment changes were reported in 12-80%. These changes included these potential new avenues of treatment: 1) avoiding, starting or stopping specific ASMs, 2) ketogenic diet, 3) clinical trials or 4) surgery.[6] Additional benefits to establishing a genetic diagnosis were to inform prognosis, end the diagnostic odyssey for the family, reduce parental guilt, direct access to support groups, give estimates of recurrence risks and allow for genetic counseling.[6]

There has been an explosion in the understanding of epilepsy genetics and in the diagnostic yield of clinical genetic testing. The benefit-to-cost ratio is now large enough to indicate that genetic testing should be considered in carefully selected children as well as adults. 35 years ago, clinicians quickly saw the value of MRI and incorporated it into their diagnostic repertoire. Let us now embrace the use of genetic testing in a similar, yet thoughtful, manner.

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Supplemental Material

Supplemental material for this article is available online.

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