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Age Is Just a Number: Adults Deserve the Same Access to Genetic Testing as Children

Clinical utility of multigene panel testing in adults with epilepsy and intellectual disability

Borlot F, De Almeida BI, Combe SL, Andrade DM, Filloux FM, Myers KA. *Epilepsia*. 2019;60(8):1661-1669. doi:10.1111/epi.16273.

Objective: To determine the diagnostic yield of a commercial epilepsy gene panel in adults with chronic epilepsy and accompanying intellectual disability, given that genetic evaluation is often overlooked in this group of patients. Methods: This is a cross-sectional study analyzing the results of epilepsy gene panels including up to 185 genes in adult epilepsy patients with intellectual disability, according to *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Patients with acquired structural brain abnormalities or known chromosomal abnormalities were excluded. Results: From approximately 600 patients seen from January 2017 to June 2018 at a single academic epilepsy center, 64 probands and 2 affected relatives (32 males, mean age = 31 years ± 10) were selected and clinically tested. Fourteen probands (14/64 = 22%; 4 males, mean age = 32 years ± 10) were found to have pathogenic or likely pathogenic variants in the following genes: *SCN1A*, *GABRB3*, *UBE3A*, *KANSL1*, *SLC2A1*, *KCNQ2*, *SLC6A1*, *HNRNPU*, *STX1B*, *SCN2A*, *PURA*, and *CHD2*. Six variants arose de novo, and the inheritance was not determined in 8. Nine probands (64%) had severe or profound intellectual disability, and 5 (35%) had autistic features. Eight patients (57%) had a diagnostic change from presumptive clinical diagnosis prior to genetic testing. Significance: We were able to demonstrate that a commercial epilepsy gene panel can be an important resource in clinical practice, identifying the etiology in 22% of adults with epilepsy and intellectual disability. The diagnostic yield is similar to previously reported pediatric cohorts. Larger samples would be required to evaluate the more prevalent genotypes among patients with adult epilepsy.

Commentary

At what point in the course of chronic epilepsy is finding the etiology no longer worthwhile? Is it fair to assume there comes a point where knowing the cause is no longer beneficial to the patient? If that time exists, is it the medical equivalent of waving the white flag?

Understanding the genetic basis of epilepsy has changed the way treatment is delivered, particularly for patients with epileptic encephalopathies. For the majority of people with seizures, regardless of severity, understanding the etiology of their epilepsy brings an end to the diagnostic odyssey that for many has included years of testing and uncertainties about the future. Multigene panels and whole-exome sequencing have primarily been used in pediatric populations where the downstream value of accurate diagnosis is likely highest and programs providing free testing make the early identification of syndromes where the course of treatment may be altered easier. Genetic testing has particularly high yield for children with early-life epilepsy and epileptic encephalopathies where the diagnostic hit rate can exceed 25%, approaching the yield of imaging and surpassing that of metabolic testing.[1,2] Unfortunately, for adults with chronic epilepsy of childhood onset, the bus has often left the station, and they are not afforded the same advances in gene testing. The question is whether that matters and the answer is we don't really know.

Increasingly, recognition of genetic epilepsies has become more than just making a diagnosis. Understanding the molecular etiology may lead to improved understanding of prognosis, a change in treatment, anticipatory guidance for the patient and family members, and ultimately improved outcomes. Indeed, Dravet syndrome is a prime example of how molecular diagnosis benefits patient care. Identifying Dravet syndrome in the setting of SCN1a mutation informs avoidance of medications known to exacerbate the epilepsy (ie, antiseizure medications with sodium channel mechanisms) and selection of medications most effective for the condition. In addition, multiple drugs have recently been approved for Dravet syndrome and diagnosis opens the door to additional research trials specific to this population. Even more compelling are precision treatments on the horizon utilizing antisense oligonucleotides, viral vector therapies, and drugs targeting the Nav 1.1 channel, promising the potential to truly modify the course of the disease. One

assumes earlier treatment will be associated with more favorable outcome, but there may still be benefits later in life. Dravet syndrome is not alone, as there are several conditions for which a molecular diagnosis may change therapeutic decision-making including GLUT-1 deficiency and sodium channelopathies such as SCN2a and SCN8a.

The limited use of genetic testing in adults is likely multifactorial. Essentially, all of the genetic epileptic encephalopathies have onset in childhood where the majority of research interest in diagnosis and treatment of these disorders exists. Unfortunately, this fails to acknowledge the undiagnosed adult patients who could benefit if afforded the same advances in treatment. For many of these conditions, early mortality has been the rule, thus many may consider testing low yield in older individuals. However, most of these conditions represent a phenotypic spectrum that is only now becoming more obvious as increasing numbers of individuals are diagnosed, thus we truly have no handle on the number of individuals with more favorable courses. Many adults with epilepsy and intellectual disabilities may no longer have strong advocates in the search for a diagnosis as they would have had as children, thus no voice to push for genetic testing. Finally, many question whether the outcome is altered in an adult who has suffered so many years with these conditions. This is a question that will remain unanswered if we don't identify adults living with these disorders now. Ultimately, the goal of care should likely be to decrease the burden of disease for every individual with epilepsy and having a precise diagnosis to provide the most effective care would be the obvious path to consider.

Borlot et al recently investigated the diagnostic yield of a commercially available epilepsy gene panel in an adult population with epilepsy and intellectual disabilities. The cohort was enriched with patients more likely to harbor a genetic etiology, excluding those with phenotypes consistent with classic chromosomal disorders and those with imaging findings that explained their condition. Of 64 eligible patients, 14 (21.8%) had pathogenic or likely pathogenic mutations and 8 (57%) patients had a diagnostic change from their working clinical diagnosis prior to testing. This finding is encouraging, as it demonstrates yield in adults is similar to that in pediatric populations. For some, the molecular diagnosis altered the course of therapy, though the impact on outcome was beyond the scope of this study. Four patients were identified with conditions where treatment might change, 3 with Dravet syndrome (one was noted to improve when sodium channel blocking antiseizure medications were stopped) and 1 with GLUT-1. Another was found to have Koolen-de Vries syndrome and now has the opportunity to connect with the small community of others with the same condition, the benefits of which are difficult to measure. However, for patients whose treatment was not changed based on diagnosis, learning the condition they have lived with for years was incorrect may have adverse consequences. One such case with a presumptive diagnosis of Angelman's was found to have ID31 (OMIM #616158). In the day of social media, many patients and families become strongly connected to a network of advocates for their condition and a loss of that identity is potentially harmful, but again difficult to measure. While it is worth recognizing the potential pitfalls of establishing a genetic diagnosis late in life, the potential value to patients in the end cannot be discounted.

It is worth noting that this study included only results that were pathogenic or likely pathogenic, thus the true number of patients who could have benefited from genetic testing may be higher. Defining the clinical meaning of variants of unknown significance can be challenging in adult populations where testing of first-degree relatives may be more difficult. The authors acknowledge that the disorders defined in this cohort were pediatric-onset epilepsies; thus, we would expect most will now be diagnosed earlier in the setting of increased genetic testing in children. While the number of adults who will benefit from testing may decline in the future as a result, genetic testing has value now. Likewise, as the phenotypic spectrum of many genetic epilepsies expands, milder presentations that may not have prompted testing as children could still benefit from diagnosis as an adult.

For so long, new tools in the evaluation and treatment of epilepsy have been field tested in adults and extrapolated to benefit children. Genetic testing is the pediatric equivalent of paying it forward. Adults with epilepsy of unknown cause deserve the same opportunities as children when it comes to molecular diagnosis and stand to benefit from the same advances in treatment. So, put away the white flag and continue looking for answers in those without one.

By M. Scott Perry

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