The Road to Diagnosis: Shortening the Diagnostic Odyssey in Epilepsy

Epilepsy Currents
2019, Vol. 19(5) 307-309

DOI: 10.1177/1535759719871593
journals.sagepub.com/home/epi
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Diagnostic Exome Sequencing in 100 Consecutive Patients With Both Epilepsy and Intellectual Disability

Snoeijen-Schouwenaars FM, van Ool JS, Verhoeven JS, et al. *Epilepsia*. 2019;60(1):155-164. doi:10.1111/epi.14618. Epub December 7, 2018. PMID: 30525188.

Objective: Epilepsy is highly prevalent among patients with intellectual disability (ID), and seizure control is often difficult. Identification of the underlying etiology in this patient group is important for daily clinical care. We assessed the diagnostic yield of whole-exome sequencing (WES). In addition, we evaluated which clinical characteristics influence the likelihood of identifying a genetic cause and we assessed the potential impact of the genetic diagnosis on (antiepileptic) treatment strategy. Methods: One hundred patients with both unexplained epilepsy and (borderline) ID (intelligence quotient $\leq$85) were included. All patients were evaluated by a clinical geneticist, a (pediatric) neurologist, and/or a specialist ID physician. Whole-exome sequencing analysis was performed in 2 steps. In step 1, analysis was restricted to the latest versions of ID and/or epilepsy gene panels. In step 2, exome analysis was extended to all genes (so-called full exome analysis). The results were classified according to the American College of Medical Genetics and Genomics guidelines. Results: In 58 patients, the diagnostic WES analysis reported one or more variant(s). In 25 of the 100 patients, these were classified as (likely) pathogenic, in 24 patients as variants of uncertain significance, and in the remaining patients the variant was most likely not related to the phenotype. In 10 (40%) of 25 patients with a (likely) pathogenic variant, the genetic diagnosis might have an impact on the treatment strategy in the future. Significance: This study illustrates the clinical diagnostic relevance of WES for patients with both epilepsy and ID. It also demonstrates that implementing WES diagnostics might have impact on the (antiepileptic) treatment strategy in this population. Confirmation of variants of uncertain significance in (candidate) genes may further increase the yield.

Diagnostic Yield of Genetic Tests in Epilepsy: A Meta-Analysis and Cost-Effectiveness Study

Sánchez Fernández I, Loddenkemper T, Gaínza-Lein M, Sheidley BR, Poduri A. *Neurology*. 2019. Epub ahead of print. pii: 10.1212/WNL.0000000000006850. doi:10.1212/WNL.0000000000006850. PMID: 30610098

Objective: To compare the cost-effectiveness of genetic testing strategies in patients with epilepsy of unknown etiology. Methods: This meta-analysis and cost-effectiveness study compared strategies involving 3 genetic tests: chromosomal microarray (CMA), epilepsy panel (EP) with deletion/duplication testing, and whole-exome sequencing (WES) in a cost-effectiveness model, using "no genetic testing"" as a point of comparison. Results: Twenty studies provided information on the diagnostic yield of CMA (8 studies), EP (9 studies), and WES (6 studies). The diagnostic yield was highest for WES: 0.45 (95% confidence interval [CI]: 0.33-0.57; 0.32 [95% CI: 0.22-0.44] adjusting for potential publication bias), followed by EP: 0.23 (95% CI: 0.18-0.29) and CMA: 0.08 (95% CI: 0.06-0.12). The most cost-effective test was WES with an incremental cost-effectiveness ratio (ICER) of US$15 000/diagnosis. However, after adjusting for potential publication bias, the most cost-effective test was EP (ICER: US$15 848/diagnosis) followed by WES (ICER: US$34 500/diagnosis). Among combination strategies, the most cost-effective strategy was WES, then if nondiagnostic, EP, then if nondiagnostic, CMA (ICER: US$15 336/diagnosis); although adjusting for potential publication bias, the most cost-effective strategy was EP $\pm$ CMA $\pm$ WES (ICER: US$18 385/diagnosis). Although the cost-effectiveness of individual tests and testing strategies overlapped, CMA was consistently less cost-effective than WES and EP. Conclusion: Whole-exome sequencing and EP are the most cost-effective genetic tests for epilepsy. Our analyses support for a broad population of patients with unexplained epilepsy, starting with these tests. Although less expensive, CMA has lower yield, and its use as the first-tier test is thus not supported from a cost-effectiveness perspective.

Commentary

Significant advances in genomic technologies over the past 15 years have revolutionized gene discovery across a broad spectrum of human genetic disorders. Arguably, some of the greatest impacts have been in severe neurological and neurodevelopmental disorders, including the developmental and epileptic encephalopathies (DEEs),[1,2] where de novo, pathogenic variants account for a large proportion of affected individuals.[3,4] Genome-wide technologies, including chromosome microarray (CMA) and exome or genome sequencing, permit the identification of copy number and sequence variants across the genome without a prior hypothesis about candidate genomic regions or specific genes.

One of the first genome-wide technologies implemented in epilepsy was CMA to detect deletions and duplications, also known as copy number variants (CNVs), and numerous studies have consistently shown that de novo copy number changes are causative in 5% to 10% of DEE.[5-7] Across broad neurodevelopmental disorders including intellectual disability (ID) and autism with or without epilepsy, the diagnostic yield of CMA is even higher.[8] Chromosomal microarray moved into the clinical setting shortly after successes in the research lab and has been recommended as a first-line test in the workup of neurodevelopmental disorders,[8] including epilepsy.

The development of "next-generation" or massively parallel sequencing (MPS) has had the greatest impact on gene discovery. Massively parallel sequencing facilitates rapid and cost-effective sequence analysis of multiple genes simultaneously, and since its introduction, there has been an explosion of gene discovery in the DEEs.[2] Common approaches that employ MPS are targeted sequencing, in which multiple genes (ranging from dozens to hundreds) are sequenced simultaneously, and exome sequencing, a more comprehensive and unbiased approach in which all ~20 000 human genes are sequenced. Notably, the same approaches applied in the research setting for gene discovery moved rapidly into clinical laboratories for diagnosis, and today, there are dozens of tests available that test a few to hundreds of epilepsy-related genes simultaneously (gene panels) as well as clinical exome sequencing.

With an increasing menu of genetic testing options, choosing a test in the clinical setting can be confusing. Which test will have the highest yield? Which test is most cost-effective? Which test will have the fastest turnaround time? Will the results affect medical management? Two recent studies, among others, begin to address these questions by evaluating the diagnostic yield and cost-effectiveness of various genetic testing strategies in individuals with epilepsy.

Sanchez Fernandez and colleagues compared the diagnostic yield of the 3 most commonly employed genetic tests: CMA, epilepsy gene panels, and exome sequencing. In addition, they evaluated the cost-effectiveness of each platform individually and in combination. To address these questions, they analyzed previously published data from 20 studies and found the overall yield of CMA to be 8%, while epilepsy gene panels came in at 23% and exome sequencing solved an average of 45% of cases. They then used the incremental cost-effectiveness ratio metric to determine that gene panels are the most cost-effective single test (US$15 848 per diagnosis); it is important to note that the gene panels in each study they evaluated varied in the number and combination of genes sequenced, and an optimal panel was not identified. When more than one test is required to make the diagnosis, they found that the most effective strategy is to use an epilepsy gene panel, followed by CMA, followed by exome (US$18 385 per diagnosis); this is a departure from what is often recommended as a standard workup, which is to start with CMA, then gene panel, and finally exome.

In another study, Snoeijen-Schouwenaars and colleagues investigated the diagnostic yield of exome sequencing in 100 individuals with epilepsy and ID; they sequenced the parents when possible to facilitate efficient segregation analysis and aid variant interpretation. The authors performed a tiered analysis of the data, first evaluating a panel of epilepsy genes, ID genes, or both, depending on the primary phenotypic features of the patient. Notably, they did not perform CMA, as they note that CNVs can increasingly be predicted from MPS data. The first-tier analysis yielded 18 pathogenic variants and 10 variants of uncertain clinical significance (VUS). Further analysis of the whole exome identified 7 additional pathogenic variants and 14 VUS. Thus, the overall diagnostic yield of "panel" testing was 18% with a clear diagnosis and up to 28% if VUS are included; trio exome analysis had a yield of 25% pathogenic variants with an additional 24% VUS. These results are consistent with other studies using exome sequencing to evaluate individuals with epilepsy and other neurodevelopmental features.[9-12]

These are just 2 recent examples of many studies that aim to establish the yield, cost-effectiveness, and clinical utility of genetic testing in epilepsy. For example, Howell and colleagues[13] evaluated diagnostic strategies in a population-based cohort of infants who present with epilepsy. They also found that gene panel sequencing is a cost-effective test, especially if done early in the diagnostic workup. Another study[11] analyzed the cost-effectiveness of exome sequencing compared to a fairly comprehensive first-tier workup (including imaging, metabolic screening, CMA, gene panel) and found that exome sequencing early in the diagnostic process offers a cost savings.

The landscape of genetic testing continues to evolve, but it is clear that MPS-based diagnostic tests are high yield and cost-effective for the genetic diagnosis of epilepsy. Although the findings of each study differ slightly, exome sequencing clearly has the highest diagnostic yield, though may not be the most cost-effective depending on the clinical setting. As technology and analysis strategies to detect CNVs improve, CMA may be eliminated from the diagnostic workup and cost-effectiveness models. Other important considerations for the individual patient are the acuity of illness (acutely ill infants may benefit from a more comprehensive test and decreased turnaround time) and insurance coverage, which is nearly impossible to model in a complex private payer medical system. These studies provide a strong foundation for continued analysis of the

diagnostic approach to genetic diagnosis of epilepsy and support streamlined testing in this population.

By Heather C. Mefford

ORCID iD

Heather C. Mefford https://orcid.org/0000-0001-7188-522X

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