Epilepsy is a highly complex disease and is one of the most common neurological conditions worldwide. Some 2,500 years after Hippocrates observed a hereditary tendency for epilepsy, researchers discovered the first causative gene, neuronal nicotinic acetylcholine receptor alpha 4 subunit (CHRNA4), in 1995.\(^2\) With the development and implementation of new genomic profiling technologies, the discovery of epilepsy-associated genes has increased rapidly in the past five years. It is currently estimated that 70 percent to 80 percent of epilepsy cases have a genetic component.\(^5\) Incorporating comprehensive genetic testing for epilepsy into clinical practice has enabled physicians to provide a proper diagnosis for many patients, resulting in a better understanding of prognosis, family counseling, and targeted treatment options.

Due to both the diverse spectrum of causative mutations, and the large number of genes and genomic regions associated with epilepsy, several molecular technologies are required to perform the most comprehensive genetic testing and produce the highest diagnostic yield. Genome-wide chromosomal microarray analysis (CMA) to detect copy number variants (CNVs) is generally the first line of testing for patients with unexplained epilepsy with co-morbid neurodevelopmental features.\(^3\) Current high-density oligonucleotide microarrays enable the detection of both large scale CNVs and small exon-level deletions and duplications in disease-associated genes. The diagnostic yield with CMA for individuals with epilepsy in association with intellectual disability or an autism spectrum disorder is estimated to be ~15 percent to 20 percent.\(^7\) CMA is also an appropriate first line test for individuals presenting with infantile spasms, with a diagnostic yield estimated at ~11 percent.\(^6\)

Target enrichment and next-generation sequencing (NGS) technologies, such as pre-specified candidate gene panels and whole exome sequencing, have revolutionized the field of epilepsy genetics during the last five years. These tests are used routinely in the clinic today and offer clinicians a variety of options depending on the patient’s phenotype.

The cost effectiveness and availability of target enrichment and NGS technologies have resulted in a multitude of commercial laboratories offering a wide range of epilepsy testing options. It is important for clinicians to realize that all tests are not created equal and that the detection rate will vary depending on not only the gene content of the panels ordered, but also the sensitivity and specificity of the technology and bioinformatics used for testing. These factors all impact the quality of the test.

**Improving the molecular diagnosis and treatment of epilepsy with complex genetic testing**

By Aaron Elliott, PhD, and Amanda Bergner, MS

The introduction of NGS and enhanced diagnostic testing options has enabled clinicians to better understand the complex genetic contribution to epilepsy and determine a causative diagnosis for patients, leading to an appropriate...
counseling and treatment plan. This was recently illustrated by research presented at the 2015 American Epilepsy Society Annual Meeting, which indicated that ~16 percent of epilepsy patients who underwent diagnostic sequencing harbored a mutation in a gene which had immediate treatment implications. As the number of clinicians who are comfortable utilizing complex genetic testing increases, the understanding of epilepsy genetics will increase rapidly, precipitating a paradigm shift in the diagnosis, management, and treatment of the disorder.

### REFERENCES


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**Figure 1. Epilepsy diagnostic testing strategy**

![Figure 1](image_url)