THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

# Epilepsy Exome Panel

## Epilepsy Overview

Epilepsy is a heterogeneous neurological disorder characterized by recurrent paroxysmal seizure activity that is unprovoked by an acute systemic or neurological insult (1). The term "epilepsy" is an umbrella term under which many different disorders and conditions are included, which have a multitude of etiologies, outcomes and ages of onset (1). Epilepsy may be isolated, or may be a clinical feature of a syndrome with additional findings. Overall, the prevalence of epilepsy in children is estimated to be 5 cases per 1,000 (2).

## Seizure Types

Seizures observed in patients with epilepsy can be classified into multiple sub-types based on the clinical presentation, and the location and extent of the epileptic discharges in the brain. These sub-types include generalized tonic-clonic seizures, absence seizures, infantile spasms, myoclonic seizures, complex partial seizures and simple partial seizures (2). Some seizures may not fall into any of the currently defined classifications (2).

## Epilepsy Etiology

The etiology of epilepsy may be genetic, including genetic defects that lead to epilepsy as the only symptom (3). Other genetic disorders associated with congenital brain malformations or metabolic disorders can lead to a substantial risk of developing epilepsy as a secondary outcome (3). Epilepsy can also be due to many other acquired causes, including prenatal or birth injury, CNS infection, brain tumors, stroke and trauma (1, 2). The true etiology may not be identified in many cases.

## Clinical Utility of Genetic Testing for Epilepsy

Genetic testing for epilepsy can present challenges, due to the wide clinical and genetic heterogeneity that exists. Certain types of seizures can be associated with multiple genes, and conversely some genes can be observed in association with multiple sub-types of epilepsy. Despite this complexity, determining the molecular basis of disease using genetic testing can be useful in predicting prognosis and disease course, and in some cases, determining the underlying genetic defect can also inform treatment decisions including selection of medications (4). Utilizing exome sequencing technology for the Epilepsy Exome Panel test allows us to have a dynamic gene list that can be updated regularly as new genes are identified.

## The Epilepsy Exome Panel includes analysis of 538 genes

The Epilepsy Exome Panel involves analysis of exome sequencing data in a predefined set of 538 genes associated with epilepsy. These include genes known to be associated with epilepsy as the only feature, as well as genes associated with certain syndromes for which epilepsy is a commonly observed feature in affected individuals. Genes associated with metabolic or structural defects that predispose to epilepsy are also included.

*For a complete list of the 538 genes analyzed, please visit our website at dnatesting.uchicago.edu*

## Testing Analysis

Of the thousands of variants identified by exome sequencing, a list of rare variants that are located within a predefined set of 538 genes that have been associated with epilepsy is generated. The list of 538 genes has been carefully compiled based on a review of the available literature on the genetics of epilepsy. Most variants identified as part of exome sequencing will NOT undergo interpretation by a laboratory staff member. Only those variants identified that fall within a gene associated with epilepsy and are considered to be potentially relevant to the patient's condition are reviewed by a team of Board-Certified PhD geneticists, MD geneticists, and genetic counselors who will determine the likelihood of the variant being related to the patient's disorder.

## Test methods

Exome sequencing is performed using the Agilent SureSelect Clinical Research Exome kit that is designed to target the exome with greater coverage of known disease-associated genes. Sequencing is performed using the Illumina technology and reads are aligned to the reference sequence. Approximately 97-98% of exons in the genes of interest are targeted at a minimum depth of 10X in the diagnostic Epilepsy Exome panel. Our analytical pipeline presents variants on only the preselected 538 genes implicated in epilepsy. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. Please note that gaps in sequence data are not filled as part of this panel, and certain types of mutations such as mosaic mutations and large deletions may not be detected by exome sequencing analysis. In some cases, exome sequencing data may be used to detect larger copy number variations (CNVs) such as whole or partial gene deletions/duplications. The sensitivity of exome sequencing to detect intragenic deletions/duplications >20bp in size is not currently known.

## Parental Analysis

We strongly recommend sending samples from both biological parents (trio analysis), in addition to the proband's sample, in order to facilitate the interpretation of results. A separate parental report will not be issued.

## Reporting Results

Only variants that occur in genes within the pre-defined set of epilepsy-associated genes will be reported. As genes outside of this pre-defined gene set will not be interrogated, variants in the additional genes in the exome will not be reported. Secondary or incidental findings will not be interrogated nor reported in the Epilepsy Exome Panel. Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

## Required Forms

- Epilepsy Exome Panel Test Requisition Form
- Epilepsy Clinical Checklist
- Epilepsy Exome Consent Form

## Epilepsy Exome Panel (proband only)

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|---|---|
| Sample specifications: | 3 to10 cc of blood in a purple top (EDTA) tube |
| Cost: | $4000 |
| CPT codes: | 81415 |
| Turn-around time: | 6 weeks |

***Note: We do not bill insurance directly for this specific test***

## Epilepsy Exome Panel (Trio)

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|---|---|
| Sample specifications: | 3 to10 cc of blood in a purple top (EDTA) tube |
| Cost: | $5500 |
| CPT codes: | 81415 |
| Turn-around time: | 6 weeks |

***Note: We do not bill insurance directly for this specific test***

***Note: This test includes exome sequencing of the proband and both biological parents. Analysis is restricted to the genes included on the Epilepsy Exome Panel.***

***For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.***

## Re-analysis

As new gene discoveries and associations are reported in the literature, we can review past cases for findings in these genes. Re-analysis of exome sequencing data is available upon request.

## References:


1. Bromfield E. An Introduction to Epilepsy [Internet]. American Epilepsy Society: American Epilepsy Society, 2006.
2. Cowan LD. The epidemiology of the epilepsies in children. Ment Retard Dev Disabil Res Rev 2002: 8: 171-181.
3. Berg AT, Berkovic SF, Brodie MJ et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010: 51: 676-685.
4. Pong AW, Pal DK, Chung WK. Developments in molecular genetic diagnostics: an update for the pediatric epilepsy specialist. Pediatr Neurol 2011: 44: 317-327.