Epilepsy

Epilepsy is a common neurological disorder that affects at least 0.8% of the population. It is defined by the occurrence of at least two unprovoked seizures occurring more than 24 hours apart. Seizures are the manifestation of abnormal hypersynchronous discharges of cortical neurons that can last for several seconds, minutes, or longer. The clinical presentation of seizures depends upon both the location of the epileptic discharges in the cortex and the extent and pattern of propagation of the electrical discharges in the brain.

Epilepsy can be an isolated neurological symptom, or it may occur as part of a more complex syndrome. There are many different causes of epilepsy, including genetic disorders, metabolic diseases, and structural brain abnormalities. However, in some cases, the cause of epilepsy is not known.

The International League against Epilepsy (ILAE) has described the underlying causes of epilepsy as the following.

• **Genetic:** “The concept of genetic epilepsy is that the epilepsy is, as best as understood, the direct result of a known or presumed genetic defect(s) in which seizures are the core symptoms of the disorder.”³ The genetic contribution must be evident by extensive and replicable molecular studies or familial studies, e.g., SCN1A gene has been demonstrated to be associated with generalized epilepsy with febrile seizures plus (EFS+).⁹

• **Structural/Metabolic:** There are also specific structural or metabolic disorders that have been proven in various studies to be associated with increased risk of epilepsy; the cause of epilepsy can be defined as structural or metabolic. The cause for such a disorder can be acquired (e.g., trauma, stroke, infection), genetic (e.g., malformations of cortical development) or both (e.g., West syndrome).

• **Unknown:** There are also cases where the underlying cause is yet unknown. Epilepsy may be caused by an unidentified genetic defect or acquired cause.
Clinical Presentation/Course

In many cases, seizures result in convulsions and loss of consciousness. Seizures may also manifest in other ways that affect personality, mood, memory, sensation, and/or movement.

Other possible seizure manifestations include:

- Blank stares
- Lip smacking
- Intermittent eye movements
- Jerking movements of the extremities

In some cases these may not be recognized as a seizure by patients, their family members, or even health care professionals. Seizures can be classified into various categories in Figure 1.

**FIGURE 1: Types of seizures**

![Chart showing distribution of seizure types](chart.png)

Diagnosis

The diagnosis of epilepsy is made based on via a number of factors, including a combination of personal health history, family health history, electroencephalogram (EEG) findings and genetic testing.
Clinical and Family History

The detailed clinical history may help confirm that the seizure events are in fact epileptic seizures, rather than non-epileptic events such as fainting, breath-holding, transient ischemic attacks, strokes, arrhythmias, or hypoglycemia, all of which can manifest similarly to epileptic seizures.

**FIGURE 2: Typical EEG abnormalities for different types of seizures**

A detailed clinical history also may help clarify potential triggers and diurnal patterns related to seizure events. The medical history will help to determine if the seizures are isolated or part of a larger syndrome. In addition to clinical history for the affected individual, a family medical history should be obtained, including any history of seizures and other neurodevelopmental disorders in any relatives. This information may help clarify the type of epilepsy in a family, including the mode of inheritance and the prognosis.

**Electroencephalogram (EEG)**

Children with a known or suspected diagnosis of epilepsy based on clinical and family history should undergo an EEG to help confirm the seizure type and to evaluate recurrence risk for future seizures. An EEG may also provide important information for making treatment decisions (Figure 2).
Physical Examination

In some cases, an individual with epilepsy may have other related neurological abnormalities, medical problems, or dysmorphic features that can be identified by physical examination. For example, many genetic syndromes involving epilepsy also cause developmental delay, hypotonia, birth defects, ataxia, dystonia, microcephaly or macrocephaly, dysmorphic facial features, or other features that can be noted in a physical examination.

Genetic Testing

A genetic etiology underlies epilepsy in approximately 40% of individuals. Genes have been identified that cause both generalized seizures and focal seizures, as well as unclassified epilepsy types such as infantile spasms. A genetic etiology is identified most often in individuals who have severe, early-onset seizures, seizures in conjunction with other neurodevelopmental symptoms, and/or in individuals whom seizures are refractory to treatment.

The genetic etiology of idiopathic generalized epilepsy (IGE) is frequently complex because it is due to a combination of multiple genetic factors that each confer a small risk for epilepsy and may be modified by environmental influences. Currently, approximately 2% of patients with IGE harbor an identifiable pathogenic variant in a single gene associated with Mendelian inheritance of epilepsy. However, the percentage of patients with inherited identifiable genetic forms of epilepsy is higher for specific epilepsy types such as infantile spasms, benign familial neonatal and neonatal-infantile seizures (BFNS and BFNIS), generalized epilepsy with febrile seizures plus (GEFS+), Lafora disease, and others.

The information obtained from clinical and family histories, physical examination, and EEG can help a clinician determine whether genetic testing should be offered to a patient with epilepsy and which specific genetic test(s) may be appropriate.
Genetic Heterogeneity

The inheritance pattern can be autosomal dominant, autosomal recessive, or X-linked. Variants in a single gene may be associated with different types of seizures (clinical heterogeneity), and conversely, variants in different genes can cause the same epilepsy phenotype (genetic heterogeneity). In many cases, children with severe, early-onset seizures may harbor a de novo variant not inherited from either parent. The last decade has witnessed the discovery of many genes involved in epilepsy. Most of these genes are expressed in the brain and encode subunits of ion channels that play vital roles in stabilizing or propagating neuronal activity. Disruption of these genes in general induces neuronal hyperexcitability, thus causing seizures. As described above, there are many forms of epilepsy. A single gene may be associated with different forms of epilepsy, but one type of epilepsy may also result from defects in any one of a variety of genes. Examples of monogenic causes of epilepsy are pyridoxine-dependent epilepsy and neuronal ceroid lipofuscinoses (NCL). In some cases, copy number variations associated with neuropsychiatric disorders can be involved in epilepsy also. It is well known that the 1p36 microdeletion, Wolf-Hirshhorn, Miller-Dieker, Pallister-Killian, and Angelman syndromes include epilepsy as a major feature, but these disorders also involve various other clinical features as well.
Clinical Indications

1. Diagnostic testing in an individual with epilepsy
   a. Confirm a clinical diagnosis of a specific genetic syndrome or type of epilepsy
   b. Distinguish between syndromic and non-syndromic forms of epilepsy
   c. Establish the genetic cause of idiopathic epilepsy
   d. Provide information about prognosis
2. Assistance with selection of optimal treatment options
3. Predictive testing for asymptomatic family members of a proband with a known pathogenic variant associated with a genetic form of epilepsy
   a. Enable clinical monitoring, follow-up, and optimal treatment when symptoms develop in an individual with a positive result
   b. Reduce anxiety and forego clinical monitoring if result is negative
4. Prenatal diagnosis in at-risk pregnancies for known, pathogenic variants
5. Genetic counseling, recurrence risk determination, and family planning
<table>
<thead>
<tr>
<th>Test Options</th>
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<tbody>
<tr>
<td><strong>Test Name</strong></td>
</tr>
<tr>
<td>EpiXpanded Panel (Trio-based test)</td>
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<tr>
<td>Epilepsy Del/Dup Panel (95 Genes)</td>
</tr>
<tr>
<td>Comprehensive Epilepsy Panel (87 Genes)</td>
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<tr>
<td>Test Name</td>
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<td>---------------------------------</td>
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<tr>
<td>STAT Epilepsy Panel (22 Genes)</td>
</tr>
<tr>
<td>Infantile Epilepsy Panel (75 Genes)</td>
</tr>
<tr>
<td>Childhood Epilepsy Panel (58 Genes)</td>
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<tr>
<td>Progressive Myoclonic Epilepsy Panel (17 Genes)</td>
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**Test Options**

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Genes</th>
<th>TAT</th>
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<tbody>
<tr>
<td>Rett/Angelman Syndrome Panel (12 Genes)</td>
<td>CDKL5, CNTNAP2, FOXG1, MBD5, MECP2, MEF2C, NRXN1, SLC9A6,</td>
<td>4 weeks</td>
</tr>
<tr>
<td></td>
<td>TCF4, UBE3A, WDR45, ZEB2</td>
<td></td>
</tr>
<tr>
<td>Tuberous Sclerosis Panel (2 Genes)</td>
<td>TSC1, TSC2</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

Additional testing options are available, including targeted variant testing for a previously identified pathogenic or likely pathogenic variant. Appropriate test selection depends on the specific clinical history of a patient, including family and personal health histories as well as familial test results. Testing for most genes includes sequencing and deletion/duplication analysis via next-generation sequencing and/or exon array testing.
Sample Submission

Genetic testing can be performed on blood, oral rinse or extracted DNA samples. GeneDx test kits are available to ordering providers, and include sample collection items (such as mouthwash, collection tubes), the necessary sample submission paperwork, and a self-addressed return shipping label. Additionally all, test requisition forms are available for download from the GeneDx website: www.genedx.com/forms

Please note that all testing must be performed under the guidance of a healthcare provider. For more information on the sample submission process, please visit our website: www.genedx.com/supplies or email us at: zebras@genedx.com
Genetic Test Results

Nearly all test results fall into one of four categories:

1. Positive (pathogenic variant(s) identified)
2. Likely pathogenic variant(s) identified
3. Variant(s) of uncertain significance (VUS) identified
4. Negative (no variants of clinical significance identified)

GeneDx test reports contain detailed information about a specific genetic result and, if available, medical management options. Genetic counseling is recommended prior to genetic testing to understand the benefits and limitations of testing and after genetic testing to discuss the implications of the genetic test results. Genetic counseling services across the country can be found at www.nsgc.org

Positive Result

A positive result indicates a pathogenic (disease-causing) genetic variant (change) was identified in a specific disease gene. This finding confirms an underlying genetic cause for the patient’s symptoms and provides a diagnosis of a specific genetic disorder or indicates an increased risk for developing a genetic disorder. Knowledge of the specific pathogenic variant(s) provides valuable information to the patients, their healthcare providers and family members because it helps to determine the recurrence risk and to develop an appropriate medical management plan. A medical management plan may include lifestyle modifications, ongoing screening, preventative medications and measures, and/or surgical/medical device interventions. Furthermore, a positive genetic test result allows targeted testing of at-risk relatives to determine if any of them carry the pathogenic variant(s) as well as to address the recurrence risk of the disorder in future offspring.
Likely Pathogenic Result
A likely pathogenic result indicates the presence of genetic variant(s) in a specific disease gene for which there is significant, but not conclusive, evidence that the variant(s) are disease-causing. This finding strongly suggests an underlying genetic cause of the patient’s disorder or indicates an increased risk for developing a genetic disorder. With this type of result, medical management options and testing of family members are often similar as described above for a positive result.

Variant of Uncertain Significance (VUS)
A variant of uncertain significance (VUS) result indicates an inconclusive outcome of a genetic test. A VUS is a change in a gene for which the association with disease cannot be clearly established. The available information for the variant is either insufficient or conflicting, and it cannot be determined at this time whether the variant is associated with a specific genetic disorder or if the variant is a unrelated (benign) variant unrelated to the patient’s disorder.

In the case of a VUS test result, all medical management recommendations should be based on clinical symptoms, and past personal and family history. Predictive genetic testing of family members for a VUS is not indicated. Nevertheless, in some circumstances, it can be useful to test other family members through our Variant Testing Program to gain more evidence about the variant itself and its possible association with disease. Over time, additional clinical evidence may be collected about certain VUS, which could ultimately lead to the reclassification of the variant and test result.

Negative Result
A negative result indicates that the genetic test did not identify reportable, medically relevant variant(s) in any of the genes tested. Therefore, the cause for the patient’s disorder or family history remains unknown. Although the patient’s disorder may be caused by non-genetic factors, a negative genetic test result does not completely rule out an underlying genetic cause. For example, the patient’s disorder may be due to unidentified genetic changes in gene regions or genes not included in the initial test. Depending on the patient’s personal and family health history, additional genetic testing may be indicated for the patient or another family
member. A genetic specialist or other healthcare providers can determine if further genetic testing is appropriate.

In case of a negative genetic test result, all medical management recommendations should be based on clinical symptoms in addition to past personal and family history. Predictive genetic testing of family members is not available.

When an individual tests negative for a familial pathogenic variant that was previously identified in another affected family member, this is considered a ‘true’ negative test result. In most cases, this means that the individual has no greater risk for developing the specific genetic disorder that runs in the family than anyone in the general population.

**Medical Management**

The treatment of epilepsy depends upon the type of seizure, age of the patient, and other factors. Knowledge of the genetic etiology of epilepsy may guide selection of the most appropriate treatment options in some cases. A number of antiepileptic medications are used in the treatment of epilepsy. The specific type and etiology of seizures may influence the selection of antiepileptic medication for each patient.

**Epilepsy Genes with Treatment Implications**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Disorder/Syndrome</th>
<th>Treatment Implications</th>
<th>Panels</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALDH7A1</td>
<td>Pyridoxine-dependent epilepsy Folinic-acid responsive seizures</td>
<td>Supplemental vitamin B6 and/or folinic acid treatment</td>
<td>Comprehensive, Infantile, STAT, EpiXpanded &amp; Epi Del/Dup panels</td>
</tr>
<tr>
<td>CSTB</td>
<td>Unverricht-Lundborg disease</td>
<td>Avoid sodium channel blockers and GABAergic drugs, which can increase myoclonus, dementia, and ataxia</td>
<td>Comprehensive, Childhood, Progressive Myoclonic Epilepsy, EpiXpanded &amp; Epi Del/Dup panels</td>
</tr>
<tr>
<td>EPM2A, EPM2B, (NHLRC1)</td>
<td>Lafora disease</td>
<td>Avoid phenytoin, lamotrigine, carbamazepine, and oxcarbazepine</td>
<td>Comprehensive, Childhood, Progressive Myoclonic Epilepsy, EpiXpanded &amp; Epi Del/Dup panels</td>
</tr>
</tbody>
</table>
## Epilepsy Genes with Treatment Implications Cont.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Disorder/Syndrome</th>
<th>Treatment Implications</th>
<th>Panels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FOLR1</strong></td>
<td>Cerebral folate deficiency</td>
<td>Supplemental folic acid treatment</td>
<td>Comprehensive, STAT, Infantile, Childhood, Progressive Myoclonic Epilepsy, EpiXpanded &amp; Epi Del/Dup panels</td>
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<tr>
<td><strong>GAMT, GATM</strong></td>
<td>Creatine deficiency syndromes</td>
<td>Oral creatine (GAMT, AGAT)</td>
<td>Comprehensive, Infantile, Childhood, EpiXpanded &amp; Epi Del/Dup panels</td>
</tr>
<tr>
<td><strong>KCNQ2</strong></td>
<td>KCNQ2-related disorders</td>
<td>Carbamazepine and phenytoin</td>
<td>Comprehensive, STAT, Infantile, EpiXpanded &amp; Epi Del/Dup panels</td>
</tr>
<tr>
<td><strong>KCNT1</strong></td>
<td>KCNT1-related disorders</td>
<td>Cardiac Screening. Consider treatment with quinidine</td>
<td>Comprehensive, STAT, Infantile, Childhood, EpiXpanded &amp; Epi Del/Dup panels</td>
</tr>
<tr>
<td><strong>PNPO</strong></td>
<td>Pyridoxal 5’-phosphate dependent epilepsy</td>
<td>Supplemental pyridoxal 5-phosphate (PLP)</td>
<td>Comprehensive, STAT, Infantile, EpiXpanded &amp; Epi Del/Dup panels</td>
</tr>
<tr>
<td><strong>POLG</strong></td>
<td>Alpers-Huttenlocher and other POLG-related disorders</td>
<td>Avoid valproic acid, which can induce or accelerate liver disease</td>
<td>Comprehensive, STAT, Infantile, Childhood, EpiXpanded &amp; Epi Del/Dup panels</td>
</tr>
<tr>
<td><strong>SCN1A</strong></td>
<td>Dravet syndrome and other SCN1A-related disorders</td>
<td>Valproate, clobazam, stiripentol, levetiracetam, topiramate, and avoid phenytoin, carbamazepine, and lamotrigine</td>
<td>Comprehensive, STAT, Infantile, Childhood, EpiXpanded &amp; Epi Del/Dup panels</td>
</tr>
<tr>
<td><strong>SLC2A1</strong></td>
<td>Glucose transporter type 1 deficiency syndrome</td>
<td>Seizures typically respond to a ketogenic diet</td>
<td>Comprehensive, STAT, Infantile, Childhood, EpiXpanded &amp; Epi Del/Dup panels</td>
</tr>
<tr>
<td><strong>TSC1, TSC2</strong></td>
<td>Tuberous sclerosis complex</td>
<td>Vigabatrin for infantile spasms</td>
<td>Comprehensive, STAT, TSC, Infantile, Childhood, EpiXpanded &amp; Epi Del/Dup panels</td>
</tr>
</tbody>
</table>
Implications for Family Members

Regardless of the result, patients should share their test report with their blood relatives, who can then discuss the results with their healthcare providers. Sharing a copy of the test result with family members and healthcare providers will help to determine if additional testing is necessary and will ensure that the proper test is ordered for relatives, if indicated.

For positive or likely pathogenic test results in autosomal dominant conditions, first-degree relatives (including parents, siblings, and children) have a 50% chance to have the same variant. The risk for other family members to carry the variant depends on how closely related they are to the person with a positive or likely pathogenic test result. It is important to remember that for most of these genes, not all people who inherit a pathogenic or likely pathogenic variant will experience seizures due to reduced penetrance.

In cases where the gene is associated with an autosomal recessive condition, an individual inherits two pathogenic variants, one from each parent. Siblings of the individual with seizures have a 25% chance to inherit both pathogenic variants and develop epilepsy.

Genetic Counseling

Prior to genetic testing, patients should speak with their healthcare provider and/or a genetics specialist about their personal and family health history. Healthcare providers should discuss the benefits and limitations of testing, as well as possible test results. These conversations help to determine if the patient is an appropriate candidate for testing, facilitate the ordering of appropriate test(s) and ensure that the patient has agreed to the proposed genetic testing (written informed consent).

If pathogenic variant(s) have already been identified in a family member, testing of the specific variant(s) is appropriate. If no pathogenic variant(s) are known in a family with a specific genetic disorder, an affected family member with the highest likelihood of a positive test outcome (an individual manifesting associated clinical symptoms) is ideally the best person for initial testing within a family. In instances when an affected family member is not available, testing of an unaffected family member may be
considered, although a negative test result will not guarantee that the unaffected individual does not have an increased risk to develop the clinical symptoms that are present in the family.

Once a patient makes the decision to undergo genetic testing, post-test genetic counseling is recommended to understand the implications of the results, including a discussion of the appropriate medical management based on both the test results and the patient’s medical and family history. Genetic counseling services across the country can be found at www.nsgc.org

**Insurance Coverage and Cost for Genetic Testing**

GeneDx accepts all commercial insurance plans and is a Medicare provider. Additionally, GeneDx is a registered provider with several Medicaid plans. If a patient does not have health insurance coverage or cannot afford to pay the cost of testing, GeneDx offers a financial assistance program to help ensure that all patients have access to medically necessary genetic testing.

For more information on the paperwork that is required by some insurance carriers, as well as additional details on patient billing and our financial assistance program, please visit our website: www.genedx.com/billing

**Genetic Information Nondiscrimination Act**

The Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, is a federal law that protects Americans from discrimination by health insurance companies and employers based on their genetic information. However, this law does not cover life insurance, disability insurance, or long-term care insurance. GINA’s employment protections do not extend to individuals in the U.S. military, federal employees, Veterans Health Administration and Indian Health Service. Some of these organizations may have internal policies to address genetic discrimination. For more information, please visit: http://genome.gov/10002328
This individual is heterozygous for a partial deletion of the STXBP1 gene, which is consistent with the diagnosis of neurodegeneration with brain iron accumulation (NBIA) in this individual. The WDR45 gene encodes one of the WD repeat proteins, which form multi-protein complexes involved in signal transduction, transcriptional regulation, autophagy and cell cycle control (Haack et al., 2012). De novo pathogenic variants in the WDR45 gene have been identified in patients with early infantile epileptic encephalopathy (Haack et al., 2012; Saitsu et al., 2013). Approximately 50% of patients with NBIA have a de novo dominant mutation in the WDR45 gene (Haack et al., 2012; Saitsu et al., 2013). A novel pathogenic variant was identified in the WDR45 gene: p.Gln16Ter (CAA>TAA): c.46 C>T in exon 3 (NM_007075.3). For this gene, 93.40% of the 6,500 European and African American ancestry individuals in the NHLBI Exome Sequencing Project have a non-pathogenic variant. Although this pathogenic variant has not been reported previously, it is likely to be the cause of the clinical phenotype in this individual. Genetic counseling is recommended to discuss the implications of this test report, specifically including the risk of recurrence for this family and testing options for other at-risk family members.
Resources

GeneDx neurology page: www.genedx.com/neurology

GeneReviews, a database of genetic diseases:
    www.geneclinics.org

National Society of Genetic Counselors, to help you find a counselor near you: www.nsgc.org

American Epilepsy Society: www.aesnet.org

Epilepsy Foundation: www.epilepsyfoundation.org
References


About GeneDx

GeneDx was founded in 2000 by two scientists from the National Institutes of Health (NIH) to address the needs of patients diagnosed with rare disorders and the clinicians treating these conditions. Today, GeneDx has grown into a global industry leader in genomics, having provided testing to patients and their families in over 55 countries. Led by its world-renowned clinical genomics program, and an unparalleled comprehensive genetic testing menu, GeneDx has a continued expertise in rare and ultra-rare disorders. Additionally, GeneDx also offers a number of other genetic testing services, including: diagnostic testing for hereditary cancers, cardiac, mitochondrial, and neurological disorders, prenatal diagnostics, and targeted variant testing. At GeneDx, our technical services are backed by our unmatched scientific expertise and our superior customer support.

Our growing staff includes more than 35 geneticists and 140 genetic counselors specializing in clinical genetics, molecular genetics, metabolic genetics, and cytogenetics who are just a phone call or email away to assist you with your questions and testing needs. We invite you to visit our website: www.genedx.com to learn more about us.