Genetic Testing for Epilepsy

DESCRIPTION

Epilepsy is a disorder characterized by unprovoked seizures. It is a condition that has many different types of seizures and varies in age of onset and severity. Classification is typically based on seizure type (e.g., simple partial, complex partial, generalized, convulsive, non-convulsive) or age of onset (i.e. neonatal, infancy, childhood, adolescent/adult). The most recent proposal by the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) proposes using terms with specific etiologic categories such as genetic, structural/metabolic, and unknown.

The common epilepsy syndromes, also known as idiopathic epilepsy, generally present in childhood, adolescence or early adulthood. They include generalized or focal in nature and may be convulsant (grand mal) or absence type. There is a lack of evidence on the clinical utility of genetic testing for the common genetic epilepsies

Epilepsy syndromes that present in infancy or early childhood are usually severe and characterized by seizures as the primary manifestation, without associated metabolic or structural brain abnormalities. Mutations in a large number of genes have been associated with early onset epilepsies. Specific clinical syndromes based on the ILAE classification and their associated genes are demonstrated in the following table:

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Associated Genes</th>
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<tbody>
<tr>
<td>Dravet syndrome (presents between 4 and 15 months with prolonged convulsive seizures; severe developmental delay)</td>
<td>SCN1A, SCN9A, GABRA1, STXBP1, PCDH19, SCN1B, CHD2, HCN1</td>
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<td>EFMR syndrome (epilepsy limited to females with mental retardation)</td>
<td>PCDH19</td>
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<tr>
<td>Nocturnal frontal lobe epilepsy (epileptic encephalopathy with continuous spike-and-wave during sleep)</td>
<td>CHRNA4, CHRNB2, CHRNA2, GRIN2A</td>
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<tr>
<td>GEFS+ syndrome (genetic epilepsy with febrile seizures plus)</td>
<td>SCN1A, SCN2A, SCN1B, SCN9A, GABRG2</td>
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<tr>
<td>Ohtahara syndrome (Early infantile epileptic encephalopathy with suppression burst)</td>
<td>KCNQ2, SLC25A22, STXBP1, CDKL5, ARX</td>
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<td>Landau-Kleffner syndrome (aphasia with convulsions)</td>
<td>GRIN2A</td>
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<td>West syndrome (the most common with onset within the first 2 years; hypersarrhythmia on interictal EEG, and developmental delay)</td>
<td>ARX, TSC1, TSC2, CDKL5, ALG13, MAGI2, STXBP1, SCN1A, SCN2A, GABA, GABRB3, DNM1</td>
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<tr>
<td>Glucose transporter type 1 deficiency syndrome</td>
<td>SLC2A1</td>
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Another area of interest for epilepsy research is the pharmacogenomics of anti-epileptic medications. It has been proposed that by identifying genetic markers in individuals who are likely to be refractory to common medications that a more efficient process for medication selection, and more effective control of symptoms could be developed. However, how genetic information might be used to tailor medication management is not yet well-defined.

While there are multiple commercial pre-curated genetic panels available, there are also companies that will allow a customized genetic test to be built for each individual (e.g. INVITAE at https://www.invitae.com ).

POLICY

This document has been classified as public information.
Genetic testing for epilepsy may be considered medically necessary if the medical appropriateness criteria are met (See Medical Appropriateness below).

Pre- and post- genetic counseling as an adjunct to genetic testing is considered medically necessary.

Genetic testing for epilepsy using expanded panels that include genetic mutations of questionable or unknown clinical significance is considered investigational.

See also: Responsive Neurostimulation for the Treatment of Refractory Partial Epilepsy

MEDICAL APPROPRIATENESS

Genetic testing for epilepsy diagnosis or medication management is considered medically appropriate if ALL of the following are met:

- Testing is for mutations associated with infantile and/or early childhood onset epilepsy syndromes (see Single-Gene Mutations Associated with Epileptic Syndromes table above) in which epilepsy is the primary symptom.

- Documentation of ALL of the following:
  - Onset of seizures at or before the age of 5 years
  - Symptoms cannot be explained clinically (e.g., by another syndrome, H&P, EEG, or MRI)
  - Seizure(s) is associated with ANY ONE of the following:
    - Affecting daily function
    - EEG showing interictal abnormalities

IMPORTANT REMINDERS

- Any specific products referenced in this policy are just examples and are intended for illustrative purposes only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available. These examples are contained in the parenthetical e.g. statement.

- We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits, or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

ADDITIONAL INFORMATION

For epilepsy pharmacogenomics, the body of evidence does not show consistent or strong relationships between genetic variants and response to medications. Therefore, the clinical utility of pharmacogenomics in epilepsy has not been demonstrated and genetic testing for anti-epileptic medication tolerance remains investigational.

No regulations are required by The U.S. Food and Drug Administration (FDA) for this type of testing. Genetic testing is considered laboratory-developed services and subject only to the general laboratory operational regulation under the Clinical Laboratory Improvement Amendments (CLIA) of 1988.

SOURCES

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