More than half of all epilepsy is caused by genetic influences. There are three broad categories of epilepsy genetics: single gene disorders responsible for primary epilepsy syndromes, complex epilepsy phenotypes, and epilepsy susceptibility genes. The first category will be discussed in greater detail below with special attention to disorders of adult patients. For more detailed review of the other categories, the interested reader is referred to the review by Ferraro cited below.

**PRIMARY EPILEPSY SYNDROMES**

Monogenic epilepsies or primary epilepsy syndromes are those in which a single gene alteration is responsible for the phenotype. These mutations often lead to channelopathies or alterations in neurotransmitter receptor function, causing increased neuronal excitability. They are inherited as autosomal dominant traits with variable penetrance and follow Mendelian inheritance.

1. *Genetic (formerly generalized)* epilepsy with febrile seizures plus (GEFS+). GEFS+ includes a wide spectrum of phenotypic variability within the family including: febrile seizures, myoclonic seizures, atonic seizures, absence seizures, partial seizures, and status epilepticus. These patients often present with febrile seizures. Unlike cases with febrile epilepsy, however, the seizures do not show spontaneous remission after age five and often continue into adulthood. With time other types of seizures ensue and necessitate long-term treatment with antiepileptic drugs. Mutations involving the voltage gated sodium channel subunits (SCN1A, SCN1B and SCN2A), as well as GABA receptor subunits (GABRG2 and GABRD), account for less than 20 percent of cases. Mutational analysis for these genes is well established and commercially available through several companies. Genotyping does not predict the phenotypic severity, as both missense and truncation mutations may result in mild or severe manifestations. Moreover, the gene is only penetrant in 60
percent of cases, further complicating genetic counseling. The patients are developmentally normal, and the imaging studies do not show any discernible abnormalities in the cerebral cortex. In a mouse model harboring GABRG2 mutation, however, micro architectural changes in the cortex have been noted.

2. Autosomal Dominant Nocturnal Frontal Lobe epilepsy (ADNFLE). ADNFLE is characterized clinically by late adolescent onset of brief motor or hyperkinetic seizures occurring out of sleep and often in clusters. More severe phenotypes cause nocturnal convulsions. These cases are often misdiagnosed as parasomnias, night terrors or even hyperkinetic movement disorders. Mutations involving the subunits of nicotinic acetylcholine receptors, CHRNA4, CHRNA2 and CHRNB2, have been identified in a minority of affected families. The nicotinic acetylcholine receptors are widely expressed at the pre-synaptic glutaminergic and GABAergic terminals and facilitate neurotransmitter release. The exact mechanism of epileptogenicity in ADNFLE is elusive and may be caused by an increase in neuronal excitability due to altered modulation.

The transmission is autosomal dominant with 70 percent penetrance. Given the limitations of EEG recordings in these patients, including ictal recordings that are often obscured by movement artifact, DNA testing is of significant diagnostic value. The individuals show no evidence for developmental delay although some behavioral issues have been reported in 20 percent.

3. Juvenile myoclonic epilepsy (JME). JME is a very common idiopathic generalized epilepsy characterized by late adolescent onset of myoclonic or generalized seizures with an early morning predominance. JME is seen more frequently in women and has also been noted more commonly to result from maternal transmission. JME accounts for 12-30 percent of all cases of epilepsy. Multiple genes have been identified in patients with JME, which still account for a small percentage of affected individuals. The most common mutations in JME involve EFHC1 or myoclonin 1 gene. The function of myoclonin 1 is complex; it may influence the release of neurotransmitters via interacting with voltage gated calcium channels. Myoclonin 1 also seems to influence cortical development. High resolution MRIs have demonstrated increased thickness of the frontal medial gray matter in these patients.

While Myoclonin 1 mutations have been identified in about nine percent of JME patients, GABRA1 mutations are found only in a handful of families. A separate mutation directly affecting the beta subunit of the voltage gated calcium channels has been coded in a small number of patients with JME. CLCN2 gene coding for a chloride channel subunit has also been implicated in JME, although the overall evidence is weak.

4. Familial Temporal Lobe Epilepsy (FTLE). FTLE is an autosomal dominant epilepsy syndrome associated with simple partial, complex partial and secondarily generalized seizures subdivided into mesial and lateral forms. Familial Lateral Temporal Lobe Epilepsy (FLTLE) clinically presents as seizures associated with auditory phenomena. It is associated with mutations of LGI1, which may be involved in synaptic transmission via putative regulatory action upon K+ channels and AMPA receptors. Familial Mesial Temporal Lobe Epilepsy (FMTLE) is associated with typical medial temporal lobe auras and complex partial seizures. FMTLE has been linked to regions on chromosomes 4, 3q

<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>Associated Genes</th>
<th>Function/gene product</th>
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<tbody>
<tr>
<td>GEFS+</td>
<td>SCN1A, SCN2A, SCN1B, GABRD, GABRG2</td>
<td>Subunits of voltage gated sodium channel, GABA receptor subunits</td>
</tr>
<tr>
<td>JME</td>
<td>EFHC1, GABRA1, CACNB4, CLCN2</td>
<td>Cortical development, neurotransmitter release, GABA receptor subunits, Subunit of calcium channel, Subunit of chloride channel</td>
</tr>
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</tr>
<tr>
<td>FLTLE</td>
<td>LGI1, SCN1A, SCN1B</td>
<td>Regulation of K channel and AMPA receptors, Subunits of voltage gated sodium channel</td>
</tr>
<tr>
<td>FMTLE</td>
<td>Unknown</td>
<td>Unknown</td>
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“In this pattern of inheritance, which does not follow Mendelian rules, the involved genes are not disease causing mutations, rather DNA polymorphisms. Harboring several such susceptibility factors with synergistic effect, each producing a subtle alteration in the phenotype, may provide the genetic substrate for epilepsy, which may be exacerbated by certain environmental exposures.3”

and 12q, but causative genes have yet to be identified, potentially due to complex inheritance.4

**COMPLEX EPILEPSY PHENOTYPES**

Epilepsy may occur as part of the phenotype in complex genetic disorders. This group comprises a large list of inborn errors of metabolism, neuronal migration defects, mitochondrial diseases, Rett syndrome, glucose transporter defects, and disorders of fatty acid oxidation.3 These disorders may follow autosomal or mitochondrial patterns of inheritance. As a group, complex epilepsy syndromes are more prevalent than the simple monogenic forms of epilepsy described above. The monogenic syndromes are often inherited in an autosomal dominant manner and are associated with normal brain development; the complex epilepsy phenotypes may be caused by recessive, dominant, or maternal inheritance and encompass structural, neurologic or metabolic comorbidities.4

**EPILEPSY SUSCEPTIBILITY GENES**

Similar to many other neurological and psychiatric disorders, epilepsy may be caused by a combination of genetic influences and environmental factors. Examples of diseases caused by susceptibility factors include Alzheimer’s disease, Parkinson’s disease, schizophrenia, bipolar disorder, and even more common conditions such as hypertension and diabetes. In this pattern of inheritance, which does not follow Mendelian rules, the involved genes are not disease causing mutations, rather DNA polymorphisms. Harboring several such susceptibility factors with synergistic effect, each producing a subtle alteration in the phenotype, may provide the genetic substrate for epilepsy, which may be exacerbated by certain environmental exposures.3

**SUMMARY**

In the post genomic era, molecular testing for many forms of epilepsy has become commercially available. Knowledge of these conditions, options for DNA testing, and most importantly, interpretation of the test results are imperative for general neurologists. DNA testing, in addition to ending the diagnostic odyssey, may guide the treatment and also provide prognostic information. In most cases of genetic epilepsy, phenotypic variability is the rule rather than exception. As such, genetic counseling should be performed by individuals with adequate expertise in this field. ■

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