# Epilepsy Genetics

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EPILEPSY BOARD REVIEW MANUAL

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Statement of Editorial Purpose

The Epilepsy Board Review Manual is a study guide for trainees and practicing physicians preparing for board examinations in epilepsy. Each manual reviews a topic essential to the current management of patients with epilepsy.

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Epilepsy Genetics

Christa W. Habela, MD, PhD, and Carl E. Stafstrom, MD, PhD

INTRODUCTION

The field of epilepsy genetics is expanding rapidly. New mutations in genes associated with epilepsy are being discovered on an almost weekly basis. Determining the genetic basis of epilepsy is no longer a topic of research interest only, but is becoming an increasingly important part of clinical practice.1,2 This article provides an overview of epilepsy genetics for epileptologists, emphasizing material that should be mastered in preparation for the epilepsy board examination. Complete coverage of all the genetic mutations that play a role in epilepsy is not possible in this brief review. Instead, we concentrate on basic concepts and definitions, discuss types of genetic tests, review the genetics of common epilepsies, and conclude with a discussion of practical clinical aspects including genetic counseling and ordering appropriate genetic tests. Some important epilepsies with a genetic basis, such as structural malformations and metabolic disorders, are covered in other articles in this series.

At least 70% of epilepsy is thought to have a genetic basis.3 However, monogenic, Mendelian disorders are rather uncommon in epilepsy, accounting for 1% to 2%.4,5 Instead, much of epilepsy with a genetic basis has a complex inheritance pattern, with several susceptibility genes thought to contribute to the pathophysiological hyperexcitability of the brain that underlies seizures. The existence of multiple diverse epilepsy syndromes supports the idea that etiologies are heterogeneous. Earlier investigations focused on ion channelopathies, but recent high-throughput screening methods have revealed that mutations in epilepsy commonly affect other aspects of neuronal function, including metabolism, synapse function, and network development. In that sense, there is emerging overlap between the genetic underpinnings of epilepsy, autism, and intellectual disability.

DEFINITIONS

Some familiarity with genetics concepts is assumed in this article. Basic aspects of human genetics and inheritance patterns are presented in a highly recommended review.6 Table 1 lists definitions of some common genetic terms.

Readers of this manual should be conversant with the definitions of seizures, epilepsy, and epilepsy syndromes. In accordance with the most recent International League Against Epilepsy nomenclature, the older terminology to describe epilepsy etiology has been replaced.7 Idiopathic epilepsies are now called genetic, reflecting modern knowledge about the contributions of genetics. The former term symptomatic has been supplanted by structural/metabolic, and the older term cryptogenic has been replaced by unknown. These changes in nomenclature reflect the remarkable increase in knowledge about gene mutations that cause epilepsy, as well as biochemical and radiologic advances. Of course, many structural/metabolic etiologies also have a genetic basis, so the categories overlap. Likewise, the older terms generalized epilepsy and focal epilepsy are discouraged in
### Table 1. Common Definitions in Genetics

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>allele</td>
<td>One of 2 or more versions of a gene at a given chromosome location (locus). An individual inherits 2 alleles for each gene, 1 from each parent.</td>
</tr>
<tr>
<td>aneuploidy</td>
<td>When the number of chromosomes is not a multiple of the haploid number (eg, state of having fewer or more chromosomes than normal).</td>
</tr>
<tr>
<td>copy number variant</td>
<td>Genomic alteration (deletion or duplication) that results in a cell having an abnormal number of copies of one or more segments of DNA.</td>
</tr>
<tr>
<td>dominant negative mutation</td>
<td>A mutation whose gene product adversely affects the normal, wild-type gene product within the same cell. Dominant negative mutations are often more deleterious than those producing no gene product (null mutations).</td>
</tr>
<tr>
<td>epigenetic</td>
<td>Heritable changes that do not affect the DNA sequence but influence gene expression.</td>
</tr>
<tr>
<td>expressivity</td>
<td>Variations in a phenotype among individuals with a particular genotype.</td>
</tr>
<tr>
<td>gain/loss of function</td>
<td>A mutation that confers new/enhanced activity or reduced/abolished protein function.</td>
</tr>
<tr>
<td>genome-wide association study</td>
<td>An analysis comparing the allele frequencies of all available polymorphic markers in unrelated patients with a specific symptom or disease and those of healthy controls to identify markers associated with a specific disease or condition.</td>
</tr>
<tr>
<td>haploinsufficiency</td>
<td>When an individual is heterozygous for a gene mutation at a particular locus, often due to deletion of the corresponding allele. The patient is clinically affected because a single copy of the normal gene does not produce enough protein for normal function.</td>
</tr>
<tr>
<td>haplotype</td>
<td>A set of closely linked genetic markers present on 1 chromosome that tend to be inherited together.</td>
</tr>
<tr>
<td>heteroplasmy</td>
<td>Presence of more than 1 type of mitochondrial DNA within a cell.</td>
</tr>
<tr>
<td>heterozygosity</td>
<td>If alleles at the same gene locus are different, the individual is heterozygous for that gene.</td>
</tr>
<tr>
<td>homozygosity</td>
<td>If 2 alleles at the same gene locus are the same, the individual is homozygous for that gene.</td>
</tr>
<tr>
<td>methylation disorder</td>
<td>Epigenetic alteration by which DNA methylation is abnormal, leading to altered gene expression.</td>
</tr>
<tr>
<td>mosaicism</td>
<td>Presence of 2 or more populations of cells with different genotypes in 1 individual who has developed from a single fertilized egg.</td>
</tr>
<tr>
<td>mutation</td>
<td>Any alteration in a gene (change in DNA sequence) from its natural state; may be disease-causing or benign (normal variant). Mutations can arise from DNA copying mistakes made during cell division, exposure to ionizing radiation, exposure to mutagenic chemicals, or viral infection. Germ-line mutations occur in eggs and sperm and can be passed on to offspring, while somatic mutations occur in body cells and are not passed on.</td>
</tr>
<tr>
<td>next-generation sequencing</td>
<td>Refers to genome-sequencing, genome-resequencing, transcriptome profiling (RNA-Seq), DNA-protein interactions (ChIP-sequencing), and epigenome characterization. Resequencing is necessary because the genome of a single individual will not indicate all of the genome variations among other individuals of the same species.</td>
</tr>
<tr>
<td>penetrance</td>
<td>The likelihood that a clinical condition will occur when a particular genotype is present.</td>
</tr>
<tr>
<td>polymerase chain reaction (PCR)</td>
<td>A technique whereby a single copy or a few copies of a segment of DNA is amplified by several orders of magnitude, generating up to millions of copies of a specific DNA sequence.</td>
</tr>
<tr>
<td>Sanger sequencing</td>
<td>A method of DNA sequencing based on the selective incorporation of chain-terminating dideoxynucleotides by DNA polymerase during in vitro DNA replication.</td>
</tr>
<tr>
<td>transcription factor</td>
<td>A protein that binds to specific DNA sequences, thereby controlling the rate of transcription of genetic information from DNA to messenger RNA. Transcription factors perform this function by promoting (activating) or blocking (repressing) the recruitment of RNA polymerase (the enzyme that performs the transcription of genetic information from DNA to RNA) to specific genes.</td>
</tr>
<tr>
<td>uniparental disomy (UPD)</td>
<td>When 2 copies of a chromosome or of part of a chromosome are inherited from 1 parent and no copies are inherited from the other parent. UPD may lead to the duplication of lethal recessive genes.</td>
</tr>
<tr>
<td>X-linked inactivation</td>
<td>When 1 of the 2 copies of the X chromosome present in females is silenced or inactivated.</td>
</tr>
</tbody>
</table>
the new nomenclature, while still acknowledging that seizure origin can be focal (within networks restricted to 1 hemisphere) or generalized (rapidly engaging both hemispheres). Mindful that classification systems will continue to evolve as new knowledge accrues, in this article the focal/generalized epilepsy terminology is retained as this distinction remains abundant in the literature.8

**INDICATIONS AND TECHNIQUES USED IN THE GENETIC EVALUATION OF EPILEPSY**

With the surge of available genetic testing options, both practical and ethical questions arise when considering whether to order genetic testing, and if so, what test to order (Table 2). There is now greater acceptance of the idea that epilepsies once considered “idiopathic” should be re-categorized as genetic, but there has not been a general consensus regarding the guidelines of when to initiate genetic testing. Certain comorbid conditions warrant genetic testing regardless of whether the patients have epilepsy, such as those with autism and intellectual disability not otherwise explained and those with multiple congenital malformations.9–11 In addition, the presence of additional findings such as movement abnormalities, dysmorphic features, and disorders of brain malformation imply a greater probability of a pathologic genetic abnormality. Individuals with severe and intractable epilepsies, early-onset epilepsies, and specific phenotypes known to be related to genetic mutations are more likely to benefit from testing from both diagnostic and therapeutic standpoints.12–14 There is increasing evidence for genetic contributions in both generalized and focal epilepsies.15,16

Modern techniques for clinical genetic testing include targeted sequence analysis of single genes and groups of genes, whole exome screening for mutations in protein-encoding regions of the genome, and chromosomal microarrays to identify copy number variants throughout the genome (Table 3).2,14,17 Each test has unique limitations and benefits and the test chosen should be based on the clinical history, family history, examination, and associated findings (Table 4). Prior to undertaking a genetic diagnostic evaluation, a detailed developmental history focusing on seizure onset, semiology, and progression should be obtained in addition to response to antiepileptic therapy. It is important to evaluate for associated developmental disabilities suggested by cognitive, behavioral, and physical delays or impairments. Specific attention should be paid to a history of regression in any of these domains as well as any temporal or situational exacerbations of seizures that may suggest a metabolic or systemic etiology. A detailed prenatal and birth history and history of past trauma should be elicited. General medical history should search for dysfunction in other organ systems that may suggest a multisystem process. Family his-

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**Table 2. Indications for Genetic Testing in a Patient with Epilepsy**

- Confirm a suspected genetic syndrome
- Define a gene mutation in a patient with epilepsy and a suspected genetic syndrome
- Determine a gene mutation in a patient with an epilepsy syndrome
- Evaluate for a gene mutation in a patient with an early-onset epileptic encephalopathy
- Evaluate for a gene mutation in a patient with a progressive myoclonic epilepsy
A comprehensive clinical evaluation may reveal a specific etiology for a patient’s epilepsy (ie, neonatal injury, structural abnormality, or trauma). If not, the clinician should determine if genetic testing is indicated. Broad screening tests such as microarrays and whole exome sequencing techniques are typically more useful when a gene mutation is suspected and there are other associated developmental disabilities, genetic inheritance patterns...
in the family, associated congenital anomalies, or severe intractable epilepsy not fitting a defined syndrome. More specific testing (eg, gene panel, single gene sequencing) is indicated when there is a strong suspicion of a specific genetic mutation based on clinical data. Genetic testing should be considered confirmatory, complementing the clinical assessment.

### TYPES OF GENETIC TESTING OF POTENTIAL UTILITY IN THE DIAGNOSIS OF EPILEPSY

#### Broad Screening Techniques

Chromosomal microarrays (CMAs) use fluorescent probe hybridization to detect duplications or deletions across the genome, otherwise known as copy number variations (CNVs). With a CMA, CNVs as small as 1Kb can be detected, but these can be up to mega bases in size. There are 2 commonly used CMAs in clinical practice: comparative genomic hybridization (CGH) and single-nucleotide-polymorphism (SNP) genotyping arrays. CGH arrays compare the amount of fluorescently labeled DNA from a patient sample that is bound to known DNA sequences to the amount of DNA from a healthy control that binds to the same DNA sequences. SNP arrays take advantage of multiple sites in the genome where 2 different alleles are present in the general population. The 2 different alleles are fluorescently labeled with different dyes and then hybridized with patient DNA. The total fluorescence and the fluorescence ratio of the 2 different dyes allows for analysis of homozygosity and heterozygosity as well as duplications or deletions. Although both types of arrays are equally effective in determining CNVs, SNP arrays can detect long regions of homozygosity that may indicate consanguinity or uniparental disomy, while CGHs cannot.

CMAs are capable of screening large segments of the genome when a particular gene is not suspected. This test examines both coding and non-coding DNA (regulatory elements) so is considered more comprehensive than techniques that screen only the coding regions of the genome. At the same time, the sensitivity of CMAs for identifying CNVs is orders of magnitude higher than karyotyping, while CMAs and karyotypes have similar efficacy in picking up mosaicism. There are several limitations of CMAs. First and foremost, CMAs will not detect point mutations or other relatively small changes in the DNA sequence in single genes, epigenetic changes such as methylation defects, balanced translocations, or ring chromosomes. Also, large regions of the genome are screened and therefore families need to be counseled that information not related to epilepsy may be obtained. Pertinent
examples include cancer risk genes and unrecognized consanguinity (in the case of SNPs).

CMAs are indicated when there is coexistent intellectual disability, developmental delay, congenital abnormalities in other organ systems, or autism. The diagnostic utility of genetic testing in these syndromes is well established, and consensus statements guide testing of patients when there is no perinatal, metabolic, structural, or endocrine abnormality to explain the clinical presentation.\textsuperscript{9,10} The diagnostic yield of CMAs in non-syndromic intellectual disability is approximately 10%, and in syndromic intellectual disability it is up to 30%.\textsuperscript{9,19–23} In comparison, the diagnostic yield of microarrays in epilepsy is 3% to 9% for genetic generalized epilepsy (GGE) alone,\textsuperscript{24,25} and 28% for GGE patients with intellectual disability.\textsuperscript{25}

Importantly, CNVs often do not follow Mendelian inheritance patterns and a CNV may either be pathologic (eg, \textit{MeCP2} duplication syndrome\textsuperscript{26}) or confer a certain risk that in the right setting leads to epilepsy or a neurodevelopmental disorder. This is particularly true in regions of the genome that contain low copy repeats, which predispose to recombination and result in syndromes with complex inheritance. In epilepsy, the importance of these regions is emphasized by the fact that the regions 15q11.2, 15q13.3, and 16p13.1 each account for up to 1% of GGE.\textsuperscript{25,27,28} In families where these CNVs are present, there may be individuals carrying the CNV who are severely affected with epilepsy. Other individuals in the same family and with the same CNV may only manifest mild neuropsychiatric symptoms or no symptoms at all. Although CNVs confer a certain risk for epilepsy, they are influenced by the individual’s genetic background and likely other factors. Therefore, changes discovered by CMA may be difficult to interpret and caution is required when discussing prognosis with a family.

\textbf{Whole exome sequencing} (WES) is a second broad screening technique. In contrast to CMA, where both coding and noncoding regions are analyzed, WES involves the sequencing of all protein coding regions in the genome. WES is based on the fragmentation of a patient’s genomic DNA followed by hybridization of those fragments to probes designed to capture protein coding sequences. The probes are based on public databases of current knowledge of the genome. Captured DNA is then amplified, which is followed by massively parallel sequencing. Variants are screened and filtered to distinguish between known population variation and those that are potentially pathologic. Potential positive results are confirmed by Sanger sequencing. Similar to CMA, interpretation of the information obtained is based on variation found in affected patients and unaffected parents. Therefore, testing usually requires DNA analysis of the patient as well as both parents (trios).

Coding regions comprise 1% of the entire human genome, yet it is estimated that 85% of disease-causing mutations occur in coding regions.\textsuperscript{29} This observation argues for WES as an efficient tool for diagnostic investigations of epilepsy, and multiple small studies and case reports support its use. Positive diagnostic information for patients with intractable epilepsy was found in 34.5% of patients in a small study comparing WES to karyotyping, single gene sequencing, and CMA.\textsuperscript{30} In a study of 10 patients with early-onset and difficult-to-treat GGE, 7 pathologic mutations were found by WES.\textsuperscript{31} Similarly, in a separate study, 7 of 9 patients received a diagnosis based on WES, with an eighth patient having a potential but unconfirmed pathologic mutation.\textsuperscript{32} In a larger study that focused on only patients with infantile spasms or Lennox-Gastaut syndrome, screening of 264 trios
resulted in the discovery of 329 de novo mutations, predominantly in regions of the genome with low tolerance to variability.\textsuperscript{33}

WES is indicated when there is a strong suspicion of a genetic syndrome (by associated features or family history) that is not readily identifiable clinically.\textsuperscript{34} For practical purposes, WES is usually considered after CMA has excluded large CNVs. WES should be considered a high-throughput screen for single gene defects when a particular gene is not suspected or commercial testing for that gene is not available. WES may be more useful in drug-refractory epilepsy, generalized epilepsy, or epilepsy associated with other neurodevelopmental disabilities. This recommendation is skewed because patients with more severe and difficult-to-treat epilepsy are more likely to undergo testing.

Important limitations are that WES will not capture duplications and deletions, rearrangements of the genome, or methylation defects. Massively parallel sequencing, the predominant sequencing technique used in WES, does not capture trinucleotide repeats as does Sanger sequencing, and disorders with trinucleotide repeats, such as fragile X syndrome, will have to be tested separately. Since WES examines coding regions only, disorders in which regulatory elements are critical will not be picked up. Whole genome sequencing is one way to circumvent this limitation, but this test is not yet used widely in the clinical setting. As our understanding of the genome evolves, so will our ability to interpret the implication of the results, including incidental findings. WES has a long turnaround time and high cost, although both are declining.

\textbf{Karyotyping.} One of the oldest, most inexpensive, and fastest genetic tests to obtain is the G-banded karyotype. This technique is based on the analysis of a photographic representation of the chromosomes in a single cell. Technically, like CMA and WES, karyotyping is a broad screening tool and is able to detect large regions of the genome that are duplicated, deleted, or rearranged. However, due to its very low resolution, with CNV detection at the 1 to 10 Mb level, karyotyping has largely been replaced by CMA. Karyotype analysis continues to be indicated when multiple congenital anomalies suggest a chromosome aneuploidy syndrome or ring chromosome disorder.\textsuperscript{35,36}

\textbf{Targeted Testing Techniques}

The techniques discussed in the previous section are useful in circumstances in which a particular gene or region of the genome is not suspected in the etiology for epilepsy and associated comorbidities. In cases where specific regions of the genome or genes are suspected, targeted testing is preferable.

\textbf{Fluorescent in situ hybridization (FISH) exposes chromosomes to a small DNA sequence that has a tag (usually a fluorescent molecule) attached to it. This probe sequence binds to its corresponding sequence on the chromosome. The DNA is then examined microscopically and the amount of probe bound to the genome provides information on CNV in that region. As a single probe is designed to look at only 1 segment of the genome, FISH requires a pretest suspicion of the involvement of a specific region of the genome and is not useful for large-scale screening. Rather, FISH is ideal for confirming CNV determined by CMA either in the patient or in family members that need to be tested to determine the significance of that change. Given that FISH allows the visualization of intact chromosomes, it is also informative for determining chromosome translocations and inversions. FISH will not detect small base pair changes within a gene, epigenetic changes, or trinucleotide repeats.}
Single gene sequencing. Like FISH studies, single gene sequencing is useful when a specific diagnosis is suspected. Sequencing, either by standard Sanger or next generation sequencing techniques, examines a patient's DNA for alterations in the sequence of a single gene that is believed to cause the phenotype. Due to the specificity of these tests as well as the practical considerations of cost and time involved in sequencing genes one at a time, this technique is usually indicated only as a molecular confirmation of a clinical diagnosis. An example is SCL2A1 sequencing in the case of a child with developmental delay, movement abnormalities, treatment-refractory epilepsy, and low cerebrospinal fluid glucose, to confirm the diagnosis of GLUT1 deficiency (See Genetic Epilepsies with Generalized Seizures section). Additionally, single gene sequencing is used for confirmation in the case of a mutation determined by WES. Single gene sequencing can be used to test family members to determine whether mutations are de novo or inherited. It is also useful in family testing when autosomal dominant or X-linked single gene causes of epilepsy are known to exist within a family.

The major limitation of single gene sequencing is that its usefulness is dependent on a single phenotype being linked to a single gene. Atypical presentations of known single gene mutations are common in epilepsy, suggesting that there are genotype-specific phenotypes. KCNQ2, which has long been associated with benign familial neonatal seizures, and SCN2A, a sodium channel gene implicated in benign familial infantile-neonatal seizures, have recently also been found in children with epileptic encephalopathies. Therefore, even in genetic epilepsies with ostensibly clear-cut clinical diagnostic criteria and assumed involvement of a specific gene, targeted single gene testing may be low yield, and a gene may be involved in multiple disorders with very different prognoses.

Epilepsy gene panels. Gene panels test for mutations in genes with known associations with a specific epilepsy phenotype. Such panels take advantage of next generation sequencing techniques used in WES, but sacrifice widespread genome coverage for greater coverage and specificity within specific genes. The ability to test multiple genes at a time decreases the cost and time involved and increases the sensitivity for finding a causative mutation. In one study, causative mutations were found in 16 of 33 patients with genetic epilepsy. Commerically available panels are typically more expensive than CMA and provide information on a limited number of genes, so the decision to proceed with this targeted test should be based on a high suspicion of involvement of a specific gene.

Importantly, gene sequencing, whether it is a single gene or a gene panel, does not provide information regarding gene duplications or deletions (single gene CNV), even if these occur in the gene being sequenced. Given that epilepsy resulting from single gene abnormalities can be due to mutations or to CNV in a gene, duplication and deletion analysis is indicated in most cases in which single gene sequencing and gene panel studies are undertaken. Single gene duplication and deletion analysis is similar to CMA in that it examines the genome for copy number changes. It differs in that it will look only at specified genes of interest. Although single gene duplication and deletion analysis can be accomplished with quantitative polymerase chain reaction (PCR)—based techniques, most commercially available testing is based on the same technology as that used in CGH microarrays. Fragmented patient DNA is fluorescently labeled using one tag and standardized
control DNA is labeled using a second tag. The DNA is then hybridized to an array containing DNA from the genes of interest. The relative amount of fluorescence from the patient sample compared to the control determines the copy number and, therefore, the presence of a deletion or duplication. This type of analysis is usually used in conjunction with single gene sequencing or sequentially when no sequence alterations of a gene of interest are found. Commercial labs offer this analysis in conjunction with gene sequencing panels. The test has limitations similar to those discussed for gene sequencing and gene panels.

Despite our increasing ability to offer multiple types of genetic testing with ever-decreasing financial burden, it is important to recognize that no test substitutes for comprehensive clinical assessment. Rather, the decision to undertake genetic testing should be made after careful consideration of the likelihood of finding a diagnosis and how such knowledge will affect the patient and family.

**PATHOPHYSIOLOGICAL MECHANISMS**

Considering the site of pathophysiology caused by a genetic mutation aids in understanding how that mutation can lead to neuronal hyperexcitability and seizures. Selected examples are highlighted here. Clinical summaries are provided for some of these disorders in subsequent sections. While seizures are conventionally conceptualized as occurring when there is a disruption in the brain’s excitation/inhibition balance, many recently described epilepsy genes invoke alternative or unknown mechanisms.

**SINGLE GENES**

**Ion Channels**

Given the pivotal role of ion channels in the regulation of neuronal membrane excitability, mutations in ion channel genes (channelopathies) would be expected to underlie some genetic epilepsies. Mutations causing epilepsy have been identified for each voltage-gated ion channel (sodium, potassium, calcium, chloride). Indeed, the first epilepsy ion channel gene mutation was reported in autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), in which a mutation of the gene coding for the ligand-gated nicotinic acetylcholine receptor (CHRNA4) was found. Potassium channel mutations were then identified in the genes KCNQ2 and KCNQ3, involved in benign familial neonatal epilepsies (BFNE). The iconic example of a sodium channelopathy is Dravet syndrome, due to a mutation in SCN1A that encodes the α1 subunit of the voltage-gated sodium channel, Na\(^{+}\). Mutation of the voltage-gated calcium channel α1 subunit gene, CACNA1A, leads to a syndrome of generalized seizures, episodic ataxia, and familial hemiplegic migraines. Though many genetic epilepsies have been found to be ion channelopathies, the early prediction that these would represent the majority of genetic epilepsies has not been borne out.

**Synapses**

Synapses are the primary mediators of neural communication between neurons, so their dysfunction would be an expected mechanism for seizure generation. Mutations in genes involved in synapse formation or function are being increasingly identified in the epilepsies, especially in epileptic encephalopathies. Possible sites of mutation that can engender seizures include neurotransmitter synthesis, release, receptor binding, and degradation. Mutation of the gene for syntaxin binding protein, STXBP1, causes severe infantile epileptic encephalopathy and intellectual impairment, including Ohtahara syndrome (See Early-Onset Epileptic Encephalopathies section).
**Epilepsy Genetics**

STXBP1 is critical for synaptic vesicle docking and neurotransmitter release.

**Signaling Pathways**

Disruption of molecular signaling represents another class of pathophysiological mechanism that leads to epilepsy. The mammalian target of rapamycin (mTOR) pathway is a key pathway regulating cell growth and differentiation, and is disrupted by *TSC1* or *TSC2* gene mutations, leading to tuberous sclerosis complex (TSC).44 Another example is the cyclin-dependent kinase-like gene, *CDKL5*, mutation of which causes a severe syndrome of epilepsy and intellectual impairment with some resemblance to Rett syndrome.45 *CDKL5* is a serine/threonine protein kinase that may be involved in neuronal maturation and migration, but its role in epileptogenesis is unclear.46

**Transcription Factors**

A transcription factor is a protein that binds to a specific DNA sequence and controls (promotes or represses) the rate of DNA transcription to messenger RNA. A large number of transcription factors have been identified among the genetic epilepsies. A relevant example is *ARX* (aristaless-related homeobox X), mutation of which can lead to several X-linked syndromes in boys who manifest epilepsy (including infantile spasms), intellectual disability, and abnormal genitalia.47 The most common *ARX* mutation is expansion of a polyalanine tract. The role of *ARX* in causing epileptic encephalopathies of infancy is probably related to loss of function of cortical GABAergic interneurons.48

**COMPLEX GENES**

In addition to the single gene disorders just described, many epilepsies are felt to be due to the complex interaction of multiple genes or susceptibility alleles with incomplete penetrance and phenotypic variability, gene-gene interactions, and environmental and epigenetic factors.49,50 CNVs are likely to play an increasing role in our understanding of epilepsy predisposition.

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**GENETIC BASIS OF SPECIFIC EPILEPSY SYNDROMES**

Selected epilepsy syndromes with a genetic basis are listed in Table 5. In many cases, gene mutations have been detected in isolated individuals or small families, and it cannot be assumed that a single gene mutation accounts for all cases of a given epilepsy phenotype. Many of these epilepsies are presumed to have polygenic inheritance. Here we discuss a few syndromes of clinical and genetic interest. Further details about these disorders can be found in numerous publications.1,5,14,16,51

**GENETIC EPILEPSIES WITH GENERALIZED SEIZURES**

**Genetic Epilepsy with Febrile Seizures Plus (GEFS+)**

GEFS+ is defined as febrile seizures persisting beyond the age at which they usually stop (6 years) or accompanied by afebrile seizures (eg, GTC, absence, myoclonic). GEFS+ is an autosomal dominant epilepsy syndrome with reduced penetrance—different family members may express different seizure types (phenotypic heterogeneity). Therefore, GEFS+ differs from ordinary febrile seizures and represents a genetic predisposition to epilepsy. The outcome in GEFS+ is variable—seizures resolve in some children but persist in others. In some families, genetic defects have been identified in neuronal sodium channels52 and GABA receptors,53 suggesting genetic heterogeneity. The most common gene mutation involves the α1 subunit of the voltage-gated so-
dium channel, \textit{SCN1A}.\textsuperscript{54} Other sodium channel subunits (\textit{SCN2A}, \textit{SCN1B}) are involved in some families, and GABA\textsubscript{A} receptor genes (\textit{GABRD}, \textit{GABRG2}) have also been implicated. A genetic mutation has been identified in only about 10\% of GEFS+ families.

**Draevent Syndrome**

Draevent syndrome, previously called severe myoclonic epilepsy of infancy, is a rare epilepsy syndrome in which children present with seizures before 18 months of age.\textsuperscript{55} The initial seizure often occurs with a fever and has a hemiclonic semiology. Later, other seizure types occur (GTC, absense, focal, myoclonic) and the child's motor or cognitive development regresses, qualifying this syndrome as an epileptic encephalopathy. Seizures tend to be refractory to medications, although stribentol has shown some efficacy. Up to 80\% of patients with Draevent syndrome have a mutation in the \textit{SCN1A} gene, which are mostly sporadic, with haplo-insufficiency causing dysfunctional sodium channels. Therefore, the spectrum of \textit{SCN1A} mutations in epilepsy spans from mild (GEFS+) to severe (Draevent syndrome).\textsuperscript{56} It was previously thought that children with GEFS+ harbor a less severe missense \textit{SCN1A} mutation while those with Draevent syndrome have a more severe loss-of-function \textit{SCN1A} mutation, but exceptions are now recognized within each syndrome. The cel-

<table>
<thead>
<tr>
<th>Epilepsy Category</th>
<th>Syndrome</th>
<th>Gene Mutation</th>
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<tbody>
<tr>
<td>Genetic generalized epilepsies</td>
<td>Childhood absence epilepsy</td>
<td>GABRG2, GABRA1</td>
</tr>
<tr>
<td></td>
<td>Juvenile myoclonic epilepsy</td>
<td>EFHC1, GABRA1</td>
</tr>
<tr>
<td></td>
<td>GLUT 1 deficiency (De Vivo syndrome)</td>
<td>SLC2A1</td>
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<tr>
<td></td>
<td>GEFS+ (genetic epilepsy with febrile seizures plus)</td>
<td>SCN1A, SCN1B, GABRD</td>
</tr>
<tr>
<td></td>
<td>Draevent syndrome (severe myoclonic epilepsy of infancy, SMEI)</td>
<td>SCN1A</td>
</tr>
<tr>
<td></td>
<td>Doose syndrome (myoclonic-astatic epilepsy)</td>
<td>SCN1A</td>
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<tr>
<td></td>
<td>Epilepsy in females with mental retardation (EFMR)</td>
<td>PCDH19</td>
</tr>
<tr>
<td>Genetic focal epilepsies</td>
<td>Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)</td>
<td>CHRNA4, CHRNA2, CHRN B2</td>
</tr>
<tr>
<td></td>
<td>Familial lateral temporal lobe epilepsy</td>
<td>LGI1</td>
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<tr>
<td></td>
<td>Autosomal dominant partial epilepsy with auditory features (ADPEAF)</td>
<td>LGI1</td>
</tr>
<tr>
<td></td>
<td>Familial focal epilepsy with variable foci</td>
<td>DEPDC5</td>
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<tr>
<td></td>
<td>Benign childhood epilepsy with centrotemporal spikes (BCECTS, rolandic epilepsy)</td>
<td>GRIN2A</td>
</tr>
<tr>
<td>Early-onset epileptic encephalopathies</td>
<td>Ohtahara syndrome (early infantile epileptic encephalopathy, EIEE)</td>
<td>ARX, CDKL5, STXBP1</td>
</tr>
<tr>
<td></td>
<td>West syndrome (WS)</td>
<td>ARX, CDKL5, STXBP1</td>
</tr>
<tr>
<td>Progressive myoclonic epilepsies</td>
<td>Unverricht-Lundborg disease</td>
<td>Cystatin B, rest-inactivating 1 domain protein (PRICKLE1), scavenger receptor class b member 2 (SCARB2)</td>
</tr>
<tr>
<td></td>
<td>Lafora body disease</td>
<td>Laforin (EPM2A), malin (NHLRC1)</td>
</tr>
<tr>
<td></td>
<td>Neuronal ceroid lipofuscinosis</td>
<td>CLN1-3, CLN 5-8, CLN10</td>
</tr>
</tbody>
</table>
lular defect may be abnormal sodium channels in cortical interneurons, allowing increased firing of downstream excitatory pyramidal neurons that are released from inhibitory control.57–59 Other genes have also been implicated in Dravet syndrome, including SCN1B, GABRG2, and PCDH19. Patients with Dravet syndrome should not receive sodium channel blocking drugs (carbamazepine, oxcarbazepine, lamotrigine, lacosamide), which would further depress the function of remaining normal sodium channels.

**GLUT1 Deficiency**

Deficiency of the gene for the facilitated glucose transporter type 1, GLUT1, also known as De Vivo syndrome, presents with variable symptoms including seizures, developmental delay and a movement disorder.60 A mutation in the glucose transporter gene SLC2A1 (solute carrier family 2 member 1) results in the inability to transport glucose into the cerebrospinal fluid in sufficient quantity to support normal neuronal function, causing deficient energy availability. Energy for brain function can be restored partially by the ketogenic diet, which uses ketones for energy, bypassing the glucose transport defect. Importantly, ketogenic diet treatment results in a significant decrease or even resolution of seizures and may attenuate developmental delays.61

**Epilepsy in Females with Mental Retardation (EFMR)**

EFMR is an epilepsy syndrome limited to females in which generalized or focal seizures resembling those in Dravet syndrome (febrile or afebrile) occur in clusters, beginning by 3 years of age. Affected girls also demonstrate mild to severe cognitive impairment. Protocadherin 19 (PCDH19, located on the X chromosome), a cell-cell adhesion molecule, is deficient in EFMR, leading to abnormal cellular network formation.62 The inheritance pattern of EFMR is unusual—about half of the PCDH19 mutations occur de novo and the other half are inherited from healthy fathers. Therefore, heterozygous females with a PCDH19 mutation are affected, while hemizygous males do not incur the disease.63

**GENETIC EPILEPSIES WITH FOCAL SEIZURES**

**Benign Childhood Epilepsy with Centrotemporal Spikes (BCECTS or Rolando epilepsy)**

BCECTS is a well described syndrome in which focal motor seizures affect mainly the face and neck, with preserved awareness; seizures occasionally spread to involve the ipsilateral extremities or generalize. Seizures are often nocturnal. Seizure onset is between 5 and 12 years of age in otherwise normal children and seizures typically remit in the early teen years. A genetic basis has been long suspected based on familial occurrence of either the full BCECTS syndrome or EEG manifestations (high-amplitude spikes over the centrotemporal region) in siblings during the vulnerable age range.64 Recently, mutations in the gene GRIN2A have been implicated in BCECTS.65 GRIN2A encodes the α2 subunit of the N-methyl-D-aspartate (NMDA) glutamate receptor subtype, which may be involved in the mutated condition.66 Interestingly, 2 other epilepsy syndromes with unknown cause (Landau-Kleffner syndrome, continuous spikes and waves during slow-wave sleep) have also been associated with GRIN2A mutations.67 In one intriguing case study, a de novo mutation in this gene containing an NMDA receptor subunit caused intractable seizures that were improved with use of the NMDA receptor antagonist memantine.66

**Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE)**

ADNFLE is characterized by frontal lobe seizures during sleep.68 The seizures often have a
hyperkinetic character with nonrhythmic thrashing movements as often seen in frontal lobe epilepsy. ADNFLE was the first epilepsy in which a mutation in an ion channel gene was discovered. In many affected families, mutations have been noted in the CHRNA4, CHRNA2, and CHRNβ2 genes of the neuronal nicotinic acetylcholine receptor.69

Familial Mesial Temporal Lobe Epilepsy (FMTLE) and Autosomal Dominant Lateral Temporal Lobe Epilepsy (ADLTE)

Familial temporal lobe epilepsy has autosomal dominant inheritance and 2 types are recognized—mesial and lateral. Both types are relatively benign in terms of seizure severity and medication responsiveness. The lateral type, also known as autosomal dominant partial epilepsy with auditory features (ADPEAF), is characterized by visual and auditory hallucinations; approximately 50% of families have mutations in the gene LGI1 (leucine-rich glioma-inactivated 1), which is involved in neuronal growth and migration and signal transduction pathways. LGI1 produces a secreted protein that inactivates potassium currents and prolongs neuronal depolarization. The mesial form is less well defined and likely has a complex genetic basis.1 FMTLE may present with ictal déjà vu, fear, or gastric symptoms. A possible relationship of FMTLE to prior febrile seizures or hippocampal sclerosis is debated.

Benign Familial Neonatal Epilepsy (BFNE). BFNE is a neonatal epilepsy syndrome in which seizures begin in the first week of life. Seizures are focal clonic or focal tonic, often accompanied by apnea. They usually stop after a few days or weeks. Except for seizures, the infants are normal and evaluation fails to detect an etiology. The key to the diagnosis is a family history of newborn or infantile seizures that resolved. The prognosis of BFNE is good, although approximately 10% to 15% of affected infants continue to have seizures beyond the neonatal period, even into adulthood.70 BFNE has been linked to 2 genes, KCNQ2 on chromosome 20q and KCNQ3 on chromosome 8q. In addition to BFNE, KCNQ2 mutations have recently been reported to underlie a syndrome of epileptic encephalopathy.71,72 KCNQ2 and KCNQ3 code for voltage-gated potassium channel subunits that regulate the M-current, a muscarine-activated neuronal current that turns off potassium channels.73 The M-current stabilizes resting membrane potential; its dysfunction leads to increased neuronal excitability and seizures. It is not known why seizures in BFNE affect neonates then resolve, since the genetic defect is present throughout life. Theoretically, restoring potassium channel function, even partially, could alleviate some of the manifestations of KCNQ2 and perhaps other potassium channelopathies. In this regard, the recently available drug ezogabine (retigabine) is a potassium channel opener that improves potassium flux.74

Benign familial infantile epilepsy (BFIE). The gene PRRT2, coding for a proline transporter, has been found to cause the syndrome of BFIE.75 BFIE appears in otherwise normal infants during the first several months of life but beyond the neonatal period. Seizures typically abate by 2 years of age, but some affected patients develop a movement disorder (paroxysmal dystonia or choreoathetosis) around adolescence. Sodium channel blockers such as carbamazepine or oxcarbazepine often suffice for seizure control until the child outgrows the seizure propensity.

Familial focal epilepsy with variable foci (FFEVF). This autosomal dominant epilepsy syndrome was originally described in families presenting with focal seizures emanating from the
frontal or temporal lobe. It is now apparent that the responsible gene, \textit{DEPDC5} (disheveled, Egl-10, pleckstrin domain-containing protein 5) links a wide spectrum of epilepsies ranging from benign to severe; some patients have brain malformations and intellectual/psychiatric impairment and others do not. \textit{DEPDC5} is an mTOR inhibitor, emphasizing the importance of this critical signaling pathway in epilepsy etiogenesis.

\textbf{EARLY-ONSET EPILEPTIC ENCEPHALOPATHIES}

\textbf{Ohtahara Syndrome (OS)}

Also known as early infantile epileptic encephalopathy (EIEE), OS is a severe epileptic encephalopathy with severe seizures in the form of tonic spasms appearing in the first days or weeks of life. The EEG shows a characteristic burst-suppression pattern. The etiology is most often a structural brain anomaly, but several gene mutations have been associated with OS. Infants with OS have been shown to have mutations in \textit{STXB1} (involved in cellular differentiation especially of GABAergic synapses) or \textit{ARX} (homeobox gene that regulates cellular differentiation and migration). Mutation of the sodium channel gene \textit{SCN2A} has also been reported in OS, expanding the potential causative mechanisms for this epileptic encephalopathy. Infants with OS have a poor prognosis, and if they survive, OS often evolves into West syndrome or Lennox-Gastaut syndrome. The related syndrome of early myoclonic encephalopathy (EME) overlaps OS in that the severe seizures occur in infancy and have a burst-suppression pattern, but the seizures in EME are typically myoclonic and EME more often has a metabolic etiology.

\textbf{West Syndrome}

West syndrome is an epileptic encephalopathy characterized by the triad of epileptic spasms (flexor or extensor), an interictal EEG pattern (hypsarrhythmia), and intellectual disability. When occurring during the first year of life, the syndrome is called infantile spasms, which has a peak age of onset between 4 and 6 months. Spasms often occur in clusters, often during sleep transitions. Hypsarrhythmia is a disorganized, “chaotic” pattern of very high-voltage slow waves and spikes over multiple cortical areas. The classic ictal EEG pattern is generalized voltage attenuation (“electrodecrement”) accompanying the clinical spasm.

Most cases of West syndrome have an identifiable cause, such as hypoxia-ischemia, intracranial hemorrhage, central nervous system infection, developmental brain anomaly, or inborn metabolic error. More than 200 etiologies are now identified, with genetic causes being increasingly recognized. Not unexpectedly, given the immense diversity of West syndrome etiologies, genes regulating cell differentiation, migration, and synapse formation have been found in the syndrome, including several mentioned above (\textit{ARX}, \textit{STXB1}, \textit{CDKL5}), as well as genes involved in lesional genetic syndromes (\textit{TSC}, \textit{DCX}). Among genetic causes, TSC has an especially high incidence of infantile spasms (up to 50% of TSC patients). Adrenocorticotropic hormone (ACTH) and corticosteroids are the primary drugs used to treat infantile spasms. The anticonvulsant mechanism of ACTH is not known; it may work via the hypothalamic-pituitary axis or directly affect neuronal membrane excitability. Vigabatrin, a GABA transaminase inhibitor, is highly effective for spasms in children with TSC. West syndrome has a poor prognosis. At least two-thirds of affected children have intellectual disability. With age, the seizures often change from spasms to other seizure types.
Other

Mutations in other potassium genes (eg, \textit{KCNT1} and \textit{KCNT2}) are also associated with epileptic encephalopathy. In one report, the antiarrhythmic drug quinidine was effective in a young child with migrating partial seizures of infancy (MPSI; gain-of-function mutation in \textit{KCNT1}).\textsuperscript{82} Therefore, MPSI and perhaps other potassium channelopathies or other genetic epilepsies could be responsive to antiarrhythmic agents.

**PROGRESSIVE MYOCLONIC EPILEPSIES (PME)**

PMEs are a group of rare disorders with an overlapping phenotype that includes myoclonic seizures, neurologic deterioration, and often, a movement disorder. Examples include Unverricht-Lundborg disease, Lafora disease, neuronal ceroid lipofuscinosis (with at least 8 subtypes, each with a different genetic basis), as well as metabolic disorders such as sialidosis and mitochondrial encephalopathies such as mitochondrial encephalomyopathy with ragged red fibers (MERRF). PMEs are diagnosed by clinical features and biochemical evaluation; genetic testing can be confirmatory. Multiple genes have been identified for the PMEs (Table 5). Detailed discussion of these disorders is available in recent reviews.\textsuperscript{83,84}

**GENETIC DISORDERS WITH EPILEPSY AS A PROMINENT COMPONENT**

**Tuberous Sclerosis Complex**

TSC is a multisystem disorder caused by mutation of either \textit{TSC1} or \textit{TSC2}. These 2 genes form a dimeric complex upstream from the mTOR, which normally regulates and constrains cell growth and proliferation. Loss-of-function mutation of either \textit{TSC1} or \textit{TSC2} releases mTOR-mediated inhibition on cell growth, resulting in the formation of benign tumors that occur in several organs (eg, brain, skin, heart, kidneys). Testing is available for \textit{TSC1/2} deletions/duplications, and the genes can be sequenced as well, providing prognostic information. Individuals harboring a \textit{TSC2} mutation tend to have more severe disease than those with a \textit{TSC1} mutation. Although TSC is inherited in an autosomal dominant manner, up to 75\% of cases represent new mutations.

Signs and symptoms in TSC are related to the number and type of brain malformations. Two types of pathology occur in the brains of individuals with TSC. Tubers are hamartomas, collections of immature neural and glial cells located in the cerebral cortex where they create seizure foci; tubers do not grow or become malignant. The second neuropathologic finding in TSC is subependymal nodules (SEN), composed of enlarged, abnormal glial and neural cell precursors. SEN are found along the ventricular surface and can grow and transform into subependymal giant cell astrocytomas (SEGA). SEGA can obstruct cerebrospinal fluid flow and cause acute hydrocephalus; however, as opposed to cortical tubers, SEN/SEGA do not cause seizures. Epilepsy occurs in most individuals with TSC. Seizures are often refractory to medications and can have multifocal onset, reflecting tuber locations.\textsuperscript{85} Infantile spasms are also common, accounting for about one third of infantile spasm cases.\textsuperscript{86} Infantile spasms in TSC are responsive to the GABA transaminase inhibitor vigabatrin. Clinical trials are underway to evaluate the effectiveness of rapamycin analogs such as everolimus,\textsuperscript{87} which would be hypothesized to reduce unbridled mTOR activity.\textsuperscript{88}

**Rett Syndrome**

This X-linked dominant disorder, predominantly affecting girls (lethal in boys in utero), is marked by progressive psychomotor retardation, diminished hand use/stereotypies, acquired microcephaly, and
epilepsy with multifocal seizures that often become intractable. Rett syndrome is caused by mutation in MeCP2, coding for methyl CpG binding protein 2, a repressor of gene expression. Epilepsy is present in almost all affected patients. Seizures are typically focal-onset, are most severe during early childhood, and wane during the teen years. Some children with early-onset epileptic encephalopathy have been considered to have a Rett syndrome variant, such as a syndrome caused by mutation of CDKL5. However, children with CDKL5 mutations develop severe seizures earlier than patients with Rett syndrome (first year of life), there is no period of normal development, and although girls are disproportionately more affected than boys, this gene is responsible for the genetic defects in up to 5% of boys with early-onset epileptic encephalopathies.

**Fragile X Syndrome (FXS)**

FXS is caused by a mutation in the fragile X mental retardation 1 (FMR1) gene on the long arm of chromosome X, leading to specific dysmorphic features (large ears, long face, macro-orchidism) and intellectual disability. FXS is the most common cause of inherited intellectual impairment. It arises when a CGG-repeat tract in the 5' noncoding region of FMR1 exceeds 200 repeats, at which point the gene becomes hypermethylated and transcriptionally silent. Epilepsy occurs in up to 20% of individuals with FXS and tends to be mild, resembling BCECTS with regard to both seizure semiology and EEG findings. FMR1 is hypothesized to play a role in dendritic metabotropic glutamate receptor-mediated neurotransmission that underlies learning and memory.

**Angelman Syndrome**

Angelman syndrome, involving dysmorphisms (wide mouth, angular features), ataxic puppet-like movements, and epilepsy, arises from deficient expression of the maternal copy of the ubiquitin protein ligase E3A gene (UBE3A). There are several possible mutation mechanisms: deletion of maternal 15q11-q13, methylation defect of 15q11-13 caused by paternal uniparental disomy, or point mutation in UBE3A. The majority of children with Angelman syndrome have epilepsy with generalized seizures (absence, atonic, myoclonic, GTC) predominating over focal seizures; nonconvulsive status epilepticus is not uncommon. There is a fairly characteristic EEG signature of high-amplitude rhythmic slowing anteriorly (2–3 Hz) and posteriorly (4–6 Hz), both of which can show notches. The most sensitive diagnostic test is methylation analysis of 15q11-13; if abnormal, further testing is needed to determine if the defect is a deletion, uniparental disomy, or imprinting abnormality. If methylation testing is negative, UBE3A sequencing is recommended.

**OTHER**

**Febrile Seizures**

Febrile seizures are provoked by fever so are not considered to be epilepsy, but they are worth mentioning here because of their strong genetic basis and high incidence (up to 5% in 6-month to 5-year range). Familial occurrence of febrile seizures has been reported in 10% to 46% of studies; there is a higher concordance in monozygotic twins than dizygotic twins. Linkage studies have identified 11 different chromosomal loci, FEB1–FEB11. Familial immune response genes may modulate fever-related brain hyperexcitability in febrile seizures.
serves the purpose of obtaining informed consent for testing and preparing the family for possible results. Depending on the type of genetic test and the clinical complexity, genetic counseling will be more or less involved and time intensive. Involvement of a genetic counselor should always be considered, especially when a provider does not feel prepared to discuss the implications of test results. Additionally, the involvement of a medical geneticist may be indicated to determine the most appropriate testing based on phenotype as well as for management beyond treatment of seizures. This is particularly true when multiple organ systems are involved, there is concern for an inborn error of metabolism, or a severe degenerative phenotype is present.

At a minimum, when initiating broad screens such as WES and CMA, there are several possible outcomes about which the patient or family should be aware: (a) a diagnosis will be found, (b) a diagnosis will not be found, (c) an abnormality of unknown significance will be discovered, or (d) an abnormality unrelated to the diagnosis in question will be discovered. The latter 2 possibilities will be especially concerning if a family is not prepared. A pertinent example is finding a gene related to cancer susceptibility that does not affect a family now, but may affect them in the future and the knowledge of this mutation may not change the course. When a SNP array is used, the family will need to be counseled that consanguinity could be detected.

It is not possible to accurately advise about the clinical implications of every possible abnormality (pathologic or incidental) that may be found with WES or CMA. More targeted testing should involve counseling related to the gene mutations or chromosomal CNVs that are being tested. For all genetic testing, it is important that the family is knowledgeable about some general principles of genetic disease, especially that genetic disease cannot be cured but knowing the diagnosis may affect treatment decisions. Counseling may help to provide prognosis which, in turn, may provide better access to services and prepare the family for future outcomes. Also, if other organ systems are known to be involved, appropriate screening and surveillance can be undertaken. Finally, abnormalities found in a patient may have implications for other living relatives and future children within that family.

**TREATMENT IMPLICATIONS**

Despite the progress in identifying genetic mutations in epilepsy and their pathophysiological

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### Table 6. Examples of Genetic Diagnosis Affecting Treatment Choice

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene Mutation</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>GLUT1 deficiency</td>
<td>SLC2A1</td>
<td>Ketogenic diet</td>
</tr>
<tr>
<td>Dravet syndrome</td>
<td>SCN1A</td>
<td>Avoid sodium channel blockers</td>
</tr>
<tr>
<td>Benign familial neonatal epilepsy</td>
<td>KCNQ2</td>
<td>Potassium channel opener</td>
</tr>
<tr>
<td>Benign familial infantile epilepsy</td>
<td>PRRT2</td>
<td>Carbamazepine or oxcarbazepine</td>
</tr>
<tr>
<td>Tuberous sclerosis complex</td>
<td>TSC1, TSC2</td>
<td>Vigabatrin, rapamycin analogs</td>
</tr>
<tr>
<td>Epileptic encephalopathy</td>
<td>GRIN2A</td>
<td>Memantine (possibly)</td>
</tr>
<tr>
<td>Pyridoxine-dependent epilepsy</td>
<td>ALDH7A1, PNPO</td>
<td>Pyridoxine</td>
</tr>
<tr>
<td>Epilepsy in persons of south Asian descent or Han Chinese</td>
<td>HLA-B*1502</td>
<td>Avoid carbamazepine, oxcarbazepine</td>
</tr>
</tbody>
</table>
consequences, at present there is only a limited list of clinical situations in which a specific genetic mutation leads to a specific treatment option or alternative. Several of these treatment-specific disorders are discussed above and are summarized in Table 6. This list is bound to increase over time. Many authorities anticipate that personalized genomics and therapeutics will emerge for many genetic disorders.

In addition to the genetic syndromes described above, many disorders in metabolic pathways are associated with epilepsy.95 Details are found elsewhere. An example of treatable metabolic disorders is pyridoxine-dependent epilepsies due to mutations of the genes ALDH7A1 or PNPO, where exogenous administration of pyridoxine can provide the deficient substrate needed to improve function.96
Finally, individuals harboring the haplotype HLA-B*1502 are at particular risk for developing severe cutaneous reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) when exposed to carbamazepine or oxcarbazepine. Obviously, those drugs should be avoided in populations at risk, including Asians. At risk individuals can be tested for the haplotype.

**ALGORITHM FOR ORDERING GENETIC TESTS**

We conclude this article with an algorithm to serve as a guide for ordering genetic tests in patients with epilepsy (Figure). Details of the tests are provided in previous sections. As in all clinical medicine, the clinical history should inform all testing decisions. In this rapidly evolving field, recommendations will change over time. The partnership between the epilepsy specialist, geneticist, and family is foremost in choosing whether to pursue genetic testing and which tests will be most helpful in clinical management.

**ACKNOWLEDGMENT**

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