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Genetic Forms of Epilepsies and other Paroxysmal Disorders

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Abstract

Genetic mechanisms explain the pathophysiology of many forms of epilepsy and other paroxysmal disorders such as alternating hemiplegia of childhood, familial hemiplegic migraine, and paroxysmal dyskinesias. Epilepsy is a key feature of well-defined genetic syndromes including Tuberous Sclerosis Complex, Rett syndrome, Angelman syndrome, and others. There is an increasing number of singe gene causes or susceptibility factors associated with several epilepsy syndromes, including the early onset epileptic encephalopathies, benign neonatal/infantile seizures, progressive myoclonus epilepsies, genetic generalized and benign focal epilepsies, epileptic aphasias, and familial focal epilepsies. Molecular mechanisms are diverse, and a single gene can be associated with a broad range of phenotypes. Additional features, such as dysmorphisms, head size, movement disorders, and family history may provide clues to a genetic diagnosis. Genetic testing can impact medical care and counseling. We discuss genetic mechanisms of epilepsy and other paroxysmal disorders, tools and indications for genetic testing, known genotype-phenotype associations, the importance of genetic counseling, and a look towards the future of epilepsy genetics.

Keywords

Genetics; copy number variants; chromosomal microarray; early onset epileptic encephalopathies; progressive myoclonusepilepsies

Introduction

Genetic causes of epilepsy are increasingly recognized and overlap at times with other paroxysmal disorders including familial hemiplegic migraine, alternating hemiplegia of childhood, and paroxysmal dyskinesias. Mechanisms include genomic rearrangements (i.e. ring chromosomes, translocations, monosomies, and trisomies), copy number variants (CNVs, meaning deletions or duplications involving one or more genes), and single nucleotide alterations resulting in missense, frameshift, or nonsense mutations. CNVs and

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mutations can be present in the germline or somatic (post-zygotic) in origin. Examples of somatic mutations causing epilepsy syndromes include Sturge Weber syndrome and hemimegalencephaly, though somatic mosaicism of non-malformation related epilepsy genes is also reported.[1-5] Many single gene models of epilepsy have been identified both for lesional and non-lesional epilepsy, most notably the channelopathies (e.g., *SCN1A*-associated Dravet syndrome, or severe myoclonic epilepsy of infancy). Other mechanisms include modulation of synaptic vesicle docking and release (e.g., *STXBP1*), cell signaling (e.g., *CDKL5*), and transcription (e.g., *ARX*).[6-12] Methylation defects or uniparental disomy may also affect one region of DNA (e.g., Prader-Willi and Angelman syndromes), resulting in gain or loss of function of genes typically expressed only from the maternal or paternal copy, respectively.[13,14]

Genetic abnormalities can be inherited or arise *de novo*, and there are examples of inheritance from an asymptomatic or mildly affected parent with somatic mosaicism.[2,15-18] Complexities in inheritance patterns, such as incomplete penetrance, and the suspected presence of thus far not well-defined genetic and epi-genetic modifying factors likely explain the phenotypic diversity seen in epilepsy genetics, even within patients and families with the same mutation.[19] Additional complexities involve differences between loss of function and gain of function mutations within a gene, as well as interactions between genes that may modify phenotypes. One example of this is that haploinsufficiency of *SCN8A* is associated with movement disorders and intellectual disability but not epilepsy in mice and humans, whereas gain-of-function mutations are associated with epileptic encephalopathy.[20,21] Mouse models also suggest that *SCN8A* can modify the phenotype of *SCN1A* mutation associated epilepsy, and clinical data suggest that *SCN9A* mutations may be independently disease-associated or play a role as a modifier gene in patients with Dravet syndrome and *SCN1A* mutations.[22-25] Detailed functional analysis in both rodent and zebrafish models, as well as patient-derived induced pluripotent stem cells (iPS cells) expressing neuronal features, have been helpful in elucidating underlying mechanisms of mutations and will be critical to moving the field forward.[8,26-28]

As the complex genetics of epilepsy and associated paroxysmal disorders are unraveled through fast-paced research and clinical experience, we present a practical approach to clinical epilepsy genetics in 2014.

Tools for genetic testing in epilepsy and paroxysmal disorders

There are a number of genetic testing techniques that can be used to evaluate patients for genetic causes of epilepsy. Table 1 outlines these tests and provides suggestions of when they should be considered. Initial testing options include assessment for CNVs, single gene testing in well-defined syndromes, and gene panel testing. Careful choice of the appropriate testing and discussion of benefits and limitations with families are key. It is important to note that no one technology screens for all genetic mechanisms. Particularly when the first line of testing is not revealing of a genetic etiology, whole exome sequencing (WES) is proving to be an extremely valuable tool in both the research and clinical settings, though it has limitations as it does not identify CNVs, methylation abnormalities, or abnormalities in

non-coding regions, such as regulatory regions; furthermore, analysis is complex, and WES may be costly and time-consuming.[15,21,29-32]

Epilepsy in defined genetic syndromes

It is important to be able to recognize genetic syndromes in which epilepsy is a prominent feature, as the diagnosis may impact treatment and monitoring for other medical conditions (e.g., monitoring for long QT syndrome in Rett syndrome). Table 2 describes syndromes in which epilepsy is a prominent feature, and the epilepsy features of key syndromes are outlined below.

Tuberous Sclerosis Complex—For Tuberous Sclerosis Complex, gene testing (sequencing as well as deletion/duplication testing) for *TSC1* and *TSC2* is helpful especially in unclear cases at onset, as it allows for confirmation of the diagnosis and appropriate clinical monitoring and treatment. It also helps with genetic counseling for the patient and family. Epilepsy occurs in approximately 85% of patients with Tuberous Sclerosis Complex, and >1/3 of patients will have infantile spasms (IS).[33] Refractory epilepsy occurs in >50% of cases for at least a period of time, including ~75% of patients with IS and ~40% of patients without IS. [33,34] Vigabatrin is particularly effective for IS in TSC.[35,36] The TSC1-TSC2 complex normally inhibits the mammalian target of rapamycin (mTOR) signaling pathway. Mutations lead to dysregulation that results in overgrowth, which is the cause of the multiple organ system lesions including CNS. Inhibitors of the mTOR pathway are potential mechanism-specific treatments. Although they are established treatment for subependymal giant cell astrocytomas, there is thus far only a single Phase I/II open label study for epilepsy showing promise with a 60% response rate.[37]

Rett syndrome and variant/overlapping disorders—Epilepsy is a feature of classical Rett syndrome as well as its variant forms (preserved speech variant, early seizure or Hanefeld variant, and congenital variant). *MECP2* mutations or deletions are the cause of at least 95% of classical Rett syndrome cases, most preserved speech variant cases, and some congenital variant cases.[38] Mutations in the genes *CDKL5* and *FOXG1* cause well-defined disorders often with Rett-like features, and the minority of patients with mutations in these genes meet criteria for the early seizure variant and the congenital variant, respectively.[9,12,39] Less than 25% of girls with CDKL5 mutations and no boys with CDKL5 mutations met criteria for atypical Rett syndrome in one series, largely due to lack of regression.[12] In the case of FOXG1 mutations, there is not typically a period of normal development, which is an exclusion criteria for Rett syndrome.[38-40] Epilepsy in classical Rett syndrome typically has onset in childhood, between 2 and 20 years, with the highest frequency of seizures in the 7-12 year age group.[41-46] Girls with typical Rett syndrome have a variety of seizure types but rarely if ever infantile spasms. Epilepsy wanes over the teenage years. The prevalence is approximately 80%, and drug resistance is similar to or slightly less than the general epilepsy population.[42-45] In contrast, patients with pathogenic *CDKL5* mutations have epilepsy onset typically before 6 months of age, 90% before 3 months of age.[9,12] Epileptic spasms and seizures with multiple phases such as the hypermotor-tonic-spasm sequence are commonly reported and are typically drug-resistant.[9,47] EEG is often normal or nearly so early in the disease course and deteriorates over time. Hypsarrhythmia

may be seen with infantile spasms. *CDKL5* is on the X-chromosome; mutations are most often identified in girls, but boys have been reported as well.[9,12] The epilepsy phenotype of patients with *FOXG1* mutations and deletions is less well-defined, with onset ranging from 3 months to 14 years.[39,40] In contrast, *FOXG1* duplications are known to cause infantile spasms, but not Rett-like features.[48]

Angelman syndrome—Angelman syndrome is caused by deletion of the maternal copy of 15q11-q13, a methylation abnormality in the same region (most often from paternal uniparental disomy and less often from an imprinting defect), or a *UBE3A* mutation.[13,49] Angelman syndrome is associated predominantly with generalized epilepsy, though focal seizures can also be seen.[50-52] The most frequent seizure types described include myoclonic, atonic, generalized tonic clonic, and absence.[50-52] There is a tendency towards status epilepticus, especially non-convulsive or myoclonic status epilepticus.[51-53] EEG typically shows a pattern of intermittent rhythmic theta or delta, notched at times, as well as slow posterior dominant rhythm for age and interictal generalized and/or focal epileptiform discharges.[52,54] The rhythmic theta and delta appear to be quite sensitive though not specific to Angelman syndrome, and serve as an important biomarker.[54] Patients are frequently tremulous and it may be difficult to distinguish epileptic versus nonepileptic movements. A phenotypic overlap syndrome with Angelman is X-linked Christianson syndrome, caused by mutations of the solute carrier SLC9A6 gene which encodes for a sodium-hydrogen exchanger and is associated with early onset seizures including status epilepticus.[55]

Defined syndromes associated with chromosomal abnormalities—There are numerous defined genetic syndromes associated with copy number variants (CNVs) for which epilepsy is a common feature.[56] These include the 22q11.2 deletion syndrome, 22q11 duplication syndrome, 1p36 deletion syndrome, terminal 6q deletion syndrome, Mowat-Wilson syndrome (*ZEB2* deletion, 2q22.3), Wolf-Hirschhorn syndrome (4p16.3 deletion), Kleefstra syndrome (9q34.3 deletion), and Phelan-McDermid syndrome (22q13.3 deletion), among others.[57-64] In addition, there are several recurrent genomic “hotspots” where CNVs predispose to genetic generalized or idiopathic focal epilepsies (e.g. 15q11.2, 15q13.3, 15q11-q13, 16p11.2, 16p13.11, 1q21.1).[65-69] CNVs occur in these regions due to non-allelic homologous recombination between flanking segmental duplications. More complex chromosomal disorders with associated epilepsy include ring chromosomes (14 and 20 are well described), isodicentric chromosome 15, and a variety of unbalanced translocations.[70-73] In some cases the association of specific CNVs or chromosomal rearrangements with epilepsy is less clear, such as in the case of Xp22.31 CNVs.[74-77] The combination of epilepsy phenotype and other features such as dysmorphic features or congenital abnormalities may aid in clinical diagnosis of a specific syndrome. In many cases, these syndromes are identified by chromosomal microarray, and if there is suspicion for a complex chromosomal rearrangement then via karyotype or FISH studies as well.

Epilepsy syndromes

There is an increasing number of identified genetic causes of defined epilepsy syndromes, with a heterogeneous mixture of mechanisms including but not limited to channelopathies (e.g. *SCN1A*-associated Dravet syndrome, *KCNQ2*-associated benign neonatal seizures or

early onset epileptic encephalopathy).[78,79] Other mechanisms include modulation of synaptic vesicle docking and release (e.g., *STXBP1, SPTAN1*), cell signaling (e.g., *CDKL5, PLCB1*), cell-cell adhesion (e.g., *PCDH19*), transcription (e.g., *ARX*), DNA repair (*PNKP*), mitochondrial glutamate symporter (e.g., *SLC25A22*), and enzymes involved in metabolic pathways (e.g., *PNPO*).[3,8-10,80-84] Even within well-defined electroclinical syndromes such as infantile spasms (West syndrome) and migrating partial seizures in infancy (MPSI), the genetic mechanisms are diverse.[81,85-92] Genotype-phenotype correlations often require refinement as new cases are reported, and some non-epilepsy features may emerge as associated with a given gene. For example, within the early onset epilepsies, microcephaly is seen with *FOXG1* deletions and in homozygous or compound heterozygous mutations in *PNKP* or *SLC25A22*.[39,40,80,93] Movement disorders are a prominent feature in patients with mutations in *FOXG1*, *STXBP1*, *SLC2A1*, and *PRRT2*.[39,40,94-96] The combination of epilepsy and movement disorder phenotypes, physical examination features, MRI imaging, EEG findings, as well as family history may lead to a specific gene diagnosis or point towards a subset of genes with similar clinical presentations. Suspected inheritance pattern can also provide clues with regards to which genes are most likely implicated, and in cases of consanguinity chromosomal microarray to identify regions of homozygosity can be helpful in narrowing down the possible genetic etiology.

Early onset epileptic encephalopathies (EOEE)

The EOEEs include Ohtahara syndrome (OS), early myoclonic encephalopathy (EME), non-specific early onset epileptic encephalopathy with burst suppression (EOEE-BS), MPSI, Dravet syndrome, and infantile spasms. With the exception of Dravet syndrome, which is most often associated with a mutation in *SCN1A*, the other syndromes are heterogeneous in etiology.[85,97-99] Even within Dravet syndrome, other genes have been found to cause a similar clinical syndrome, particularly early in the course of disease (*PCDH19*, *SCN1B*, *GABRG2*, *STXBP1*, *GABRA1*).[100-104] OS is frequently associated with structural brain malformations but has also been associated with *de novo* heterozygous deletions or point mutations of the genes *STXBP1*, *SPTAN1, SCN2A*, and *KCNQ2* and in inherited homozygous (or compound heterozygous) mutations in the genes *SLC25A22*, *ALDH7A1,* or *PNPO* amongst others as outlined in Table 3.[10,80,83,105-110] EME is often associated with metabolic etiologies, which are typically genetic in origin, but overlaps significantly with OS and can be caused by the same genetic etiologies.[98,107,111] MPSI is also associated with a growing list of genes including *de novo* dominant mutations in potassium and sodium channels *KCNT1, SCN1A*, and *SCN2A* and inherited recessive mutations in *PLCB1, TBC1D24, SLC25A22*, and *QARS,* genes that encode a phospholipase C isoform, a GTPase-interacting protein, a mitochondrial glutamate transporter, and a tRNA synthetase, respectively.[81,86-92] Similarly infantile spasms (IS) have a quite diverse range of underlying genetic mechanisms.[19,85,98,112]

Well-established genes associated with the EOEEs are listed in Table 3, and the list is growing. A genetic etiology for EOEEs can be established in ~15-20% of cases.[30,113] As more specific genetic etiologies are identified, the phenotypic spectrum may expand for each gene. Not included in the table are the genes for metabolic disorders, such as urea cycle disorders, organic acidurias, amionoacidopathies other than NKH/glycine encephalopathy,

and mitochondrial disorders other than *SLC25A22*. These are typically identified through standard clinical screening methods.

In general for EOEEs, the first step is to evaluate for a structural or metabolic etiology. Then consider genetic testing. If the patient fits the phenotype of a specific gene, then it is time- and cost-effective to start with testing that gene. If the patient's presentation is not suggestive of a specific etiology, then one should consider sending a panel of genes associated with early onset epilepsy. A chromosomal microarray may be helpful to identify potentially pathogenic CNVs that may include the specific genes of interest or encompass epilepsy-associated regions.[114-116] Finally, whole exome sequencing may add additional yield if epilepsy gene panels are negative, as the list of epilepsy associated genes is always expanding. The advantages of starting with a panel are that there is focused coverage on the genes of interest, and some panels include both sequencing and deletion/duplication testing whereas whole exome sequencing does not currently identify CNVs over epilepsy genes/exons well.

Benign familial neonatal/infantile seizures—The genetic causes of benign familial neonatal/infantile seizures include *KCNQ2*, *KCNQ3*, *SCN2A*, and *PRRT2* (Table 4).[95,117-119] Of these, *KCNQ2* and *SCN2A* have more recently been associated also with more severe early onset epileptic encephalopathies as above.[89,106,107,109,110,117-120]

Progressive myoclonus epilepsies—Multiple genes are identified and clinically testable in the progressive myoclonus epilepsies (PME).[121-124] In addition to the genetic causes (Table 5), the differential diagnosis for PME also includes the genetic disorder sialidosis and mitochondrial disorders, typically identifiable by ophthalmologic examination and metabolic markers rather than single gene testing. Genetic testing for myoclonic epilepsy associated with ragged-red fibers (MERRF) can be done via mitochondrial gene sequencing or targeted mutation analysis. Genetic testing is recommended if a PME is suspected, as it would significantly affect prognosis for the patient. Clinical features and serum markers may guide testing in a stepwise manner. Some cases remain undiagnosed despite extensive testing, suggesting thus far unidentified genetic etiologies.[124]

Genetic generalized epilepsies and benign focal epilepsies—As above, CNVs in a number of recurrent genomic "hotspots" predispose to genetic generalized or idiopathic focal epilepsies (e.g. 15q11.2, 15q13.3, 15q11-q13, 16p11.2, 16p13.11, 1q21.1).[65-69] Mutations in *SLC2A1* (Table 3) are associated with glucose transporter 1 deficiency. Though typically early onset with a combination of infantile onset seizures, cognitive impairment, and a movement disorder, *SLC2A1* can be associated with early onset absence seizures and other genetic generalized epilepsies such as typical childhood absence epilepsy or juvenile myoclonic epilepsy, especially familial cases.[96] The presence of paroxysmal dyskinesia in the family and/or response to ketogenic diet may be a clue.[96] There are some genes identified as likely susceptibility factors for generalized epilepsies including *CACNA1H, CACNB4, CHRNA7, CLCN2,* and *EFHC1*.[66,125-128] *CACNA1A* is a gene associated with epilepsy and episodic ataxia, with an absence phenotype in mice, but the epilepsy is more heterogeneous with focal and generalized seizures in reported patients.[129,130] In addition to *SCN1A* and *PCDH19,* mutations or deletions in *SCN1B, SCN2A,* and *GABRG2* are

associated with GEFS+ (Genetic epilepsy with febrile seizures plus).[18,100,117,118] Genetic testing for Benign Rolandic Epilepsy (BRE) and other benign focal epilepsies is not typically indicated.

Familial focal epilepsies—There are increasingly identified genetic causes of the familial focal epilepsies, though in many cases the yield has not been high. Testing for mutations in the acetylcholine receptor genes *CHRNA4, CHRNB2*, and *CHRNA2* in the case of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) has a yield of ~20% with a positive family history compared to <5% with a negative family history, and the majority of mutations are found in *CHRNA4*.[131] Mutations in the potassium channel *KCNT1* were also recently identified in association with ADNFLE as well as the more severe phenotype of MPSI.[132] The finding of more severe phenotypes may justify genetic testing in ADNFLE despite the low yield, in order to provide appropriate counseling. Genetic testing for autosomal dominant partial epilepsy with auditory features may reveal a mutation in *LGI1* (leucine-rich, glioma inactivated 1) though if the family history is not strongly suggestive it is less likely to do so, and knowledge of mutations in this gene at this point may not significantly impact management.[131,133] Mutations in *SYN1* (coding for a synapsin, implicated in synaptic transmission and plasticity) have been identified in association with X-linked autism and/or epilepsy including in a large French-Canadian family, but indications for testing are not fully developed.[134] Recently identified genetic associations for focal epilepsies include *DEPDC5* mutations in familial focal epilepsy with variable foci with or without focal cortical dysplasias, as well as less commonly in other focal epilepsy syndromes including ADNFLE, familial temporal lobe epilepsy, and rolandic epilepsy.[135-138] *DEPDC5* codes for an mTOR pathway regulator, and cortical malformations are hypothesized to occur via a second genetic hit.[139] Homozygous mutations in *CNTNAP2* are associated with cortical dysplasia-focal epilepsy syndrome, and there is some suggestion but no definitive evidence that heterozygous mutations may be associated with a spectrum of neurodevelopmental disorders and epilepsy.[140]

Epileptic aphasias—Mutations in the gene *GRIN2A*, coding for the NR2A subunit of the NMDA receptor, have been recently identified in association with Landau-Kleffner-syndrome (LKS), epileptic encephalopathy with continuous spike and wave during slow-wave sleep syndrome (CSWSS), atypical rolandic epilepsy with speech impairment, and less often typical benign rolandic epilepsy.[141-143] *GRIN2A* mutations are also described in a case of early onset epileptic encephalopathy and several patients with less specific epilepsy syndromes and learning problems and/or intellectual disability of variable severity.[144] The epileptic aphasia syndromes are proving to be the most common phenotype however.

Epilepsy in association with features that suggest a genetic syndrome

If there are dysmorphic features or congenital anomalies that do not fit a well-described syndrome, consider initiating genetic testing with a broad screen such as chromosomal microarray and referring to a pediatric geneticist.

In addition, there are an increasing number of identified genetic causes of epilepsy with brain malformations with or without other syndromic features. Please refer to the review of brain malformations and migrational defects.[145]

Genetic causes of alternating hemiplegia of childhood, familial hemiplegic migraine, paroxysmal movement disorders, and overlap with epilepsy

Alternating hemiplegia of childhood is a rare disorder characterized by recurrent episodes of hemiplegia lasting minutes to days along with abnormal eye movements, involuntary movements, hypotonia, and seizures with onset in infancy. Genetic causes include mutations in the sodium-potassium ATPase α2 and α3 subunits *ATP1A2* and *ATP1A3*.[146-150] *ATP1A3* is also associated with rapid-onset dystonia-parkinsonism syndrome. *ATP1A2* mutations are described mainly in familial and not sporadic cases, whereas *ATP1A3* are often sporadic. One evaluation of genotype-phenotype correlations showed that a specific mutation Glu815Lys in *ATP1A3* is associated with a more severe phenotype.[148]

Familial hemiplegic migraine is caused by mutations in 3 known genes, *CANCA1A*, *ATP1A2*, and *SCN1A,* all with different mechanisms of action.[151,152] In each of these, epilepsy can be a comorbid feature.[127,151-153] *CACNA1A* mutations also cause episodic ataxia type 2, notably responsive to acetazolamide, and spinocerebellar ataxia.[127,151,152] Mitochondrial processes including mutations in *POLG* and *C10orF2* (Twinkle) are other examples of genetic disorders with overlapping symptoms including migraine and epilepsy.[151] There is strong evidence of a genetic predisposition to migraine with and without aura, but mechanisms are likely more complex and less likely single gene mendelian disorders.[152]

A number of genetic disorders are characterized by phenotypes including an overlap of movement disorders and epilepsy, and the combination with a patient or family can provide clues to the diagnosis. The genes most closely associated with a combination of movement disorder and epilepsy phenotypes are *PRRT2*, *SLC2A1*, *FOXG1*, and *STXBP1*.[39,40,94-96,154] With *PRRT2* and *SLC2A1* paroxysmal kinesiogenic dyskinesia is common, most often occurring in later childhood/adolescence or even adulthood compared to the early onset epilepsy.[95,96] The epilepsy phenotypes differ though with *PRRT2* mutations typically associated with benign infantile seizures whereas *SLC2A1* is typically associated with a more severe epileptic encephalopathy but can occur with milder epilepsy phenotypes also.[95,96] In the case of *FOXG1* and *STXBP1* mutations, the movement disorder is characterized by dyskinesias predominantly, with onset in conjunction with epilepsy in infancy/early childhood.[6,39,94,154] *FOXG1* mutations cause a neurodevelopmental syndrome including post-natal microcephaly, hypotonia, developmental delay, abnormal brain MRI, epilepsy and a movement disorder.[39,40] The movement disorder is characterized by dyskinesia with mixed features of athetosis, chorea and dystonia as well as stereotypies beginning in early childhood.[39,40] *STXBP1* mutations cause Ohtahara syndrome or similar early onset epileptic encephalopathies. In addition to epilepsy patients develop a prominent dyskinetic movement disorder and often have spasticity and tremors. Movements including axial contractions can be difficult to differentiate from seizures at times.[6,10,94,154]

A summary of the genetic etiologies of these paroxysmal disorders and overlap with epilepsy is provided in Table 6.

When does one perform genetic testing for epilepsy or other paroxysmal disorders?

The decision to perform genetic testing in epilepsy depends on a number of factors. These include the likelihood of finding a genetic etiology according to the clinical phenotype as well as the clinical impact that the findings will have for the patient and family. Benefits may include further information on clinical features of the syndrome that may require monitoring, providing an explanation for the family, providing a sense of prognosis based on other patients with the same genetic disorder, improved genetic counseling, and in some cases direct impact on treatment.[19,131,155] Anecdotally, we have found that many families worry that they or their doctors did something wrong that led to their child's epilepsy, and having a genetic diagnosis can alleviate those fears. In situations where genetic testing will not clearly affect medical management, the decision of whether or not to pursue genetic testing depends on a balance of clinical suspicion and benefit to the patient/family.

Genetic testing for potentially treatable conditions or those for which medication choices would change with treatment—Treatable genetic causes of epilepsy include those involving a metabolic pathway that is treatable (e.g., creatine disorders, glucose transporter 1 deficiency, vitamin-responsive epilepsies, serine deficiency disorders, amino acidopathies and mitochondrial disorders). Inherited metabolic disorders are discussed in more detail elsewhere.[83,96,111,156-161]

Currently the impact of genetic diagnosis on treatment is illustrated by the following examples:

1. Use of vigabatrin for infantile spasms in patients with TSC.[35,36]
2. Avoidance of AEDs that block sodium channels in patients with sodium channel mutations such as *SCN1A*. For example, lamotrigine often worsens seizures in patients with Dravet syndrome and *SCN1A* mutations.[162,163]
3. Testing of patients of East Asian descent for *HLAB*1502*, and if positive avoidance of carbamazepine, oxcarbazepine, phenytoin, and lamotrigine due to increased risk for Stevens Johnson syndrome.[164]
4. Specific treatments are indicated for glucose transporter 1 deficiency (ketogenic diet), pyridoxine dependent/folinic acid responsive epilepsy (pyridoxine + folinic acid), pyridoxal-5-phosphate dependent epilepsy (pyridoxal-5-phosphate), creatine disorders (creatine), serine deficiency disorders (L-serine), and mitochondrial disorders (treatment recommendations vary).[83,96,111,156-161]

There is hope for more gene specific treatments in the future. For example, retigabine, a potassium channel modulator, has been tried anecdotally in the case of *KCNQ2* mutations and there is one case report of efficacy in a patient with ring chromosome 20, but there is not yet definitive evidence on efficacy.[165] Similarly there is early optimism that mTOR inhibitors may be beneficial for epilepsy in TSC.[37]

Genetic counseling in epilepsy

With the rapidly expanding field of epilepsy genetics, involvement of genetic counselors and physicians knowledgeable in the field is increasingly important. They can help guide a step-wise approach to diagnosis and educate families about types of genetic testing and risks and benefits to the testing. When a genetic diagnosis is made, genetic counseling is critical to give the family a sense of prognosis, potential impacts on treatment and an understanding of modes of inheritance that can be helpful for family planning.[155,166] Programs in epilepsy genetics and neurogenetics have been developed at various centers and are one approach to a team effort between physicians and counselors for patient evaluation, treatment and counseling.

Conclusion and Future perspectives

This field is rapidly evolving. Many more genes are likely to be identified. While whole exome sequencing is already becoming a key diagnostic tool,[21,30] whole genome sequencing may soon be common practice as well. As the genetics of epilepsy and paroxysmal disorders is unraveled there is hope for more gene and pathway specific treatments, which is the ultimate goal to improve patient quality of life.

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Table 1

Toolkit for genetic testing in epilepsy[19]

Testing method	Description	Suggestions of when to use this test
Chromosomal microarray	Uses either single nucleotide polymorphism (SNP) array or array-comparative genomic hybridization (using oligonucleotide probes). Evaluates targeted regions throughout the chromosomes for CNVs.	Especially when epilepsy is seen in association with developmental delay, autism, and/or dysmorphisms. Can also be helpful in other idiopathic epilepsy syndromes.
Single gene sequencing	Evaluates for sequence alterations and whether they cause amino acid changes.	When a specific genetic abnormality is suspected. For example, test *SLC2A1* when glucose transporter 1 deficiency is suspected.
Single gene duplication/deletion analysis	Evaluates for CNV in a targeted gene.	When sequencing is negative and you are suspicious for an abnormality in a specific gene. More sensitive than microarray in this case.
Targeted mutation analysis	Sequencing looking for a specific mutation.	• Parental testing to help determine significance of a mutation of unknown significance. • Carrier testing.
Panels of genes associated with a disorder	Sequencing +/− duplication/deletion testing for a panel of genes of interest. Typically using next generation sequencing.	In disorders with many associated genes, such as the EOEEs.
Methylation studies	Evaluates for methylation abnormalities in a specific chromosomal region.	Suspected methylation disorder, e.g., Prader-Willi and Angelman syndromes.
Fluorescent in situ hybridization (FISH)	Fluorescently labeled probes identify specific chromosomal regions.	• Confirmation of a deletion/duplication. • Evaluate for deletion of a specific region (i.e. 22q11)
Karyotype	A photographic representation of all of the chromosomes in a single cell, arranged in pairs based on size and banding pattern.	Consider in patients with dysmorphisms or multiple congenital anomalies. May be helpful in the case of large CNVs to evaluate for re-arrangements.
Whole exome or whole genome sequencing	Evaluate for sequence changes and CNVs throughout the exome (coding sequencing only) or genome.	• Consider when known clinical testing is not revealing and a genetic diagnosis is strongly suspected.

EOEEs = early onset epileptic encephalopathies.

Table 2

Key genetic syndromes with frequently associated epilepsy (not comprehensive):[19]

Syndrome	Genetics	Brief summary	EEG features
Classical Rett syndrome	*MECP2* deletions or mutations (Autosomal dominant, most *de novo*) *Early onset seizure variant is associated with *CDKL5* mutations/deletions. *Congenital variant is associated with *FOXG1* mutations/deletions.	Progressive microcephaly, loss of purposeful hand skills, stereotypic hand movements, partial/complete loss of language, gait abnormalities. Majority develop epilepsy in childhood.	Frontocentral theta slowing. Loss of phase II sleep features. Focal or multifocal epileptiform activity.
Angelman syndrome	Maternal deletion (majority) or uniparental disomy of 15q11-q13, methylation defect of this region (deletion of the imprinting center), or *UBE3* mutation or deletion (inheritance pattern varies by defect)	Severe DD or ID, severe speech impairment, gat ataxia and/or tremulousness of limbs, unique behavior of inappropriate happy demeanor. Microcephaly and seizures common.	Intermittent rhythmic delta. Epileptiform activity.
Tuberous sclerosis complex	Mutation or deletion of *TSC1* or *TSC2* (Autosomal dominant)	DD, typical skin findings, epilepsy, +/− autism. Also often involves renal, cardiac, and other organ system involvement.	Multifocal epileptiform activity +/− slowing, associated with tubers. Not specific.
Hypomelano-sis of Ito	Heterogeneous, frequently with mosaic chromosomal abnormalities/rearrangements including translocations, abnormal ploidy, trisomies, CNVs or mosaicism for sex chromosomes. Most found in cells from the skin lesions.	Hypopigmented skin lesions (whorls, streaks, patches) following the lines of Blaschko +/− extracutaneous manifestations. ID and epilepsy common. Often associated with malformations including hemimegalencephaly, pachygyria, cortical dysplasia, heterotopias, or others.	Not specific.
Menkes disease	Mutation or deletion of *ATP7A* (X-linked recessive)	Males with hypotonia, failure to thrive and seizures with onset at ~1-3 months. Typical sparse, coarse, twisted, lightly pigmented hair. Low copper/ceruloplasmin.	Epileptiform activity and seizures initially posterior predominant. May develop hypsarrhythmia. Late multifocal epileptiform activity and slowing
1p36 deletion syndrome	Deletion in the 1p36 region.	DD, ID, hypotonia, craniofacial abnormalities, congenital heart defects, precocious puberty, obesity. Epilepsy in ~50-60%. Spasms and apneic seizures are common.	Multifocal and/or generalized spikes and slowing. Some develop hypsarrhythmia.

DD= developmental delay; ID = intellectual disability

Table 3

Non-malformation-associated epilepsy genes identified in EOEE

GENE	FULL GENE NAME	Locus	Phenotype
ALDH7A1	ALDEHYDE DEHYDROGENASE 7 FAMILY, MEMBER A1 (enzyme in pipecolic acid pathway)	5q23.2	EOEE, EOEE-BS, or OS , Pyridoxine-dependent epilepsy
ATP7A	COPPER-TRANSPORTING P-TYPE ADENOSINE TRIPHOSPHATASE	Xq21.1	EOEE, Menkes syndrome
ARX	ARISTALESS-RELATED HOMEOBOX, X-LINKED (transcriptional repressor and activator)	Xp21.3	EOEE, EOEE-BS, OS, or IS, especially if corpus callosal and/or genital abnormalities, can be associated with lissencephaly
CDKL5	CYCLIN-DEPENDENT KINASE-LIKE 5 (serine-threonine kinase)	Xp22.13	EOEE, often IS, rare EOEE-BS. Especially if microcephaly, hypotonia, Rett-like features.
GAMT *GATM* *SLC6A8*	GUANIDINOACETATE METHYLTRANSFERASE L-ARGININE;GLYCINE AMIDINOTRANSFERASE SOLUTE CARRIER FAMILY 6, MEMBER 8	19p13.3	EOEE, Creatine deficiency, epilepsy most prominent in GAMT mutations
GLDC *AMT*	GLYCINE DECARBOXYLASE AMINOMETHYLSTRANSERASE (enzymes for cleavage of glycine)	9p24.1 3p21.31	EME, Non-ketotic hyperglycinemia (NKH)/glycine encephalopathy
KCNQ2	POTASSIUM CHANNEL, VOLTAGE-GATED, KQT-LIKE SUBFAMILY, MEMBER 2 (potassium channel)	20q13.33	Benign familial neonatal seizures or EOEE
KCNT1	POTASSIUM CHANNEL, SUBFAMILY T MEMBER 1 (sodium-activated potassium channel)	9q34.3	MPSI
MAGI2	MEMBRANE-ASSOCIATED GUANYLATE KINASE INVERTED-2 (synaptic scaffolding protein)	7q11.23-q21.1	EOEE or IS
PCDH19	PROTOCADHERIN 19 (cell-cell adhesion molecule)	Xq22.1	Dravet, epilepsy with ID in females
PLCB1	PHOSPHOLIPASE C, BETA-1 (enzyme involved in cellular signaling)	20p12.3	OS, IS, MPSI
PNKP	POLYNUCLEOTIDE KINASE 3'PHOSPHATASE (enzyme involved in DNA repair)	19q13.33	OS, IS. Especially with microcephaly.
PNPO	PYRIDOXAMINE 5-PRIME-PHOSPHATE OXIDASE (rate limiting enzyme in vitamin B6 synthesis)	17q21.32	EOEE, EOEE-BS, or OS, Pyridoxal-5'-phosphate-dependent epilepsy (PLP-DE)
POLG	DNA POLYMERASE GAMMA (role in mitochondrial replication)	15q26.1	EOEE, Alpers syndrome
QARS	GLUTAMINYL-tRNA SYNTHETASE	3p21.31	MPSI
SCN1A	SODIUM CHANNEL, NEURONAL TYPE I, ALPHA SUBUNIT (subunit of voltage gated sodium channel)	2q24.3	GEFS+, Dravet syndrome, MPSI
SCN2A	SODIUM CHANNEL, VOLTAGE-GATED, TYPE II (sodium channel)	2q24.3	Benign familial neonatal/infantile convulsions, GEFS+, EOEE +/− BS, MPSI
SLC25A22	SOLUTE CARRIER FAMILY 25 (MITOCHONDRIAL CARRIER, GLUTAMATE), MEMBER 22 (mitochondrial glutamate/H+ symporter)	11p15.5	OS, EOEE, MPSI. Especially with microcephaly and in the case of consanguinity.
SLC2A1	SOLUTE CARRIER FAMILY 2 (FACILITATED GLUCOSE TRANSPORTER), MEMBER 1	1p34.2	EOEE. GLUT1 deficiency. Early onset absence seizures or other genetic generalized epilepsies, often with developmental delay.
SPTAN1	SPECTRIN, ALPHA, NONERYTHROCYTIC 1 (cytoskeletal protein)	9q34.11	OS?, WS
STXBP1	SYNTAXIN-BINDING PROTEIN 1 (modulator of synaptic vesicle release)	9q34.11	EOEE, OS , especially if movement disorder and severe DD

GENE	**FULL GENE NAME**	**Locus**	**Phenotype**
TBC1D24	TBC1 DOMAIN FAMILY, MEMBER 24 (Tre2-Bub2-Cdc16 (TBC) domain-containing RAB-specific GTPase-activating protein, coordinates transport of intracellular vesicles)	16p13.3	MPSI, infantile myoclonic epilepsy, focal epilepsy and ID

EOEE = early onset epileptic encephalopathy; BS = burst suppression; GEFS+ = generalized epilepsy with febrile seizures plus; MPSI = migrating partial seizures of infancy; OS = Ohtahara syndrome; IS = Infantile spasms

Table 4

Genes associated with benign familial neonatal/infantile seizures.

GENE	FULL GENE NAME	Locus	Phenotype
KCNQ2	POTASSIUM CHANNEL, VOLTAGE-GATED, KQT-LIKE SUBFAMILY, MEMBER 2	20q13.33	Benign familial neonatal seizures or EOEE +/− BS
KCNQ3	POTASSIUM CHANNEL, VOLTAGE-GATED, KQT-LIKE SUBFAMILY, MEMBER 3	8q24.22	Benign familial neonatal seizures
SCN2A	SODIUM CHANNEL, VOLTAGE-GATED, TYPE II, ALPHA SUBUNIT	2q24.3	Benign familial neonatal/infantile convulsions, GEFS+, or EOEE +/− BS
PRRT2	PROLINE-RICH REPEAT PROTEIN 2	16p11.2	Benign familial infantile seizures (BFIS) Infantile convulsions with choreoathetosis syndrome (ICCA)

BS = burst suppression; EOEE=early onset epileptic encephalopathy; GEFS+ = genetic epilepsy with febrile seizures plus. Note that both *KCNQ2* and *SCN2A* have more recently been associated with early onset epileptic encephalopathies in addition to the milder phenotype of benign neonatal/infantile seizures.

Table 5

Genes associated with Progressive myoclonus epilepsies.

GENE	FULL GENE NAME	Locus	Phenotype
CSTB	CYSTATIN B	21q22.3	Unverricht-Lundborg disease
PRICKLE1	REST-INTERACTING LIM DOMAIN PROTEIN	12q12	Unverricht-Lundborg-like PME
SCARB2	SCAVENGER RECEPTOR CLASS B, MEMBER 2	4q21.1	Unverricht-Lundborg-like PME
EPM2A	LAFORIN	6q24.3	Lafora disease
NHLRC1 (EPM2B)	MALIN	6p22.3	Lafora disease
PPT1/CLN1, TPP1/CLN2, CLN3, CLN5, CLN6, MFSD8/CLN7, CLN8, CLN10	PALMITOYL-PROTEIN THIOESTERASE 1, TRIPEPTIDYL PEPTIDASE, BATTENIN, CEROID LIPOFUSCINOISIS, NEURONAL, 5-8 AND 10	1p34.2 11p15.4 16p11.2 13q22.3 15q23 4q28.2 8p23.3 11p15.5	Neuronal ceroid lipofuscinosis, multiple subtypes.

Table 6

Genetic causes of movement disorders, familial hemiplegic migraine, alternating hemiplegia of childhood, and overlap with epilepsy

Gene	Movement disorder	Epilepsy	Familial hemiplegic migraine	Cognitive features
PRRT2	• **Paroxysmal kinesiogenic dyskinesia (onset childhood or adolescence)** • Paroxysmal non-kinesiogenic dyskinesia or paroxysmal exercise-induced dyskinesia (less common) • Paroxysmal torticollis (rare) • Episodic ataxia (rarely)	• **Benign familial infantile seizures (BFIS)** • **Infantile convulsions with choreoathetosis syndrome (ICCA)** • Febrile seizures and childhood absence epilepsy (rare reports)	• Rare reports	• Typically normal • Intellectual disability (rare)
SLC2A1	• **Paroxysmal kinesiogenic dyskinesia (most common)** • **Dystonia** • **Ataxia** • **Chorea** • **Spasticity**	• **Infantile seizures** (variety of seizure types) • Early onset childhood absence epilepsy • Other genetic generalized epilepsies (less common)	• No	• **Intellectual disability** (common) • Attention deficits (common)
STXBP1	• **Dyskinesias** (common) • **Tremors (increase** with voluntary movements) • **Non-epileptic myoclonus** • **Choreiform movements** • **Axial contractions resembling spasms** • Stereotypies • Rigidity • Spasticity	• Ohtahara syndrome • Early myoclonic epilepsy • Other early onset epileptic encephalopathy	• No	• Severe intellectual disability and developmental delay
FOXG1	• Dyskinesias (mixed athetosis, chorea, dystonia)	• Yes, common with onset age 3 months – 14 years *Duplications only associated	• No	• Global developmental delay/ Intellectual disability

Gene	Movement disorder	Epilepsy	Familial hemiplegic migraine	Cognitive features
	• Stereotypies	with infantile spasms.		
CACNA1A (α_1-subunit of a voltage-dependent P/Q Ca^{2+} channel)	• Episodic ataxia type 2 • Spinocerebellar ataxia	• Absence seizures (rare with FHM)	• Yes, common	• Not described
SCN1A (αl-subunit of a neuronal voltage-gated Na channel)	• Not described	• Dravet syndrome, GEFS + • Febrile seizures • Focal seizures	• Yes, uncommon	• Variable
ATP1A2 (α2-subunit of a Na/K pump)	• **Atypical Alternating hemiplegia of childhood, atypical**	• **Yes – febrile seizures, BFIS, focal seizures and GTCs including status epilepticus**	• **Yes, common** • Also basilar and common migraine	• Intellectual disability in some
ATP1A3 (α2-subunit of a Na/K pump)	• **Alternating hemiplegia of childhood**	• **Yes, including status epilepticus**	• No	• Developmental delay, variable severity