



Genetic Testing in Epilepsy: What Should You Be Doing?

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With the burgeoning array of molecular tests available in the epilepsies, the clinician needs to know which tests to order for each patient. Epileptic encephalopathies are the most important clinical group for genetic testing with an increasing number of distinctive epilepsy syndromes being recognized. Identification of the causative mutation affects treatment as well as prognostic and genetic counseling.

Genetics of the Epilepsies

The genetic underpinnings of human disease are currently being elucidated; in no area is this more relevant than to the epilepsies. Recent major technologic advances offer the promise of identifying all the molecular defects that contribute to the genetic architecture of the epilepsies and will begin to unravel how various genes interact to produce a specific epilepsy syndrome. The added complexity of epigenetic factors is yet to be understood. However, deciphering these data is only in its elementary stages and not yet ready for use in the clinic.

Clinical genetic studies have set the scene for molecular discovery. Many epilepsies have a genetic component; this includes those that are largely genetic such as the genetic generalized epilepsies (GGE, previously called the idiopathic generalized epilepsies). Even epilepsies with a major acquired etiology may be influenced by genetic factors.

The GGE account for about 30% of all epilepsies and are the most challenging group to solve in the field of epilepsy genetics. This is because they follow complex inheritance, where multiple genes are likely to contribute with or without an acquired or environmental component. The GGE comprise a group of well-defined syndromes: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and generalized tonic-clonic seizures alone (previously called "on awakening"). The GGE broadly encompass other epilepsies with a genetic basis, where generalized spike-wave discharges occur such as the familial epilepsy syndrome of genetic epilepsy with febrile seizures plus (GEFS+). To date, little is known about the constellation of genes needed to result in GGE; that is, whether one requires two genes of moderate effect or ten genes of minor effect to produce an epilepsy phenotype. Perhaps either will do. This complex genetic inheritance pattern

is the reason why patients with GGE most frequently present without a family history of epilepsy.

As we are only beginning to identify susceptibility genes or alleles that predispose to the GGE, at present testing for such alleles is not clinically useful. The best example of a susceptibility variant is the recent observation that a recurrent microdeletion of chromosome 15q13.3 is found in 1% of patients with GGE (1). This finding is of considerably greater frequency than any of the previously described rare susceptibility genes. The identical 15q13.3 microdeletion has been found in 0.2% of patients with schizophrenia, 0.2% of patients with autism spectrum disorders as well as 0.02% of controls (2). Thus, the finding of the 15q13.3 microdeletion in an individual does not predict a phenotype; that individual has a 1 in 3 (33%) risk of developing GGE (3). Furthermore, if a patient has this microdeletion, we do not understand the other genetic components that result in the patient's epilepsy syndrome, as families typically have unaffected members who carry the same microdeletion (3). Finding the 15q13.3 microdeletion in an individual affects genetic counseling, but whether we really understand its significance as a predictive tool remains unclear.

In addition to the GGE, there are increasingly recognized focal epilepsies with a genetic basis. Some rare focal epilepsy syndromes are monogenic such as autosomal dominant nocturnal frontal lobe epilepsy, which is associated with mutations of three different subunits of the neuronal nicotinic acetylcholine receptor. Even in this distinctive clinical entity, fewer than 20% of families have had their molecular basis identified (4). It is thus arguable how useful molecular testing is at a clinical level given its expense and the relatively low mutation detection rate. However, where a causative mutation is identified, the etiology is understood and may reduce the need for further intensive investigations such as intracranial exploration for an epileptogenic focus. It also influences genetic counseling and enables earlier diagnosis. Other examples of more common focal epilepsy syndromes, such as the benign occipital epilepsies of childhood, follow complex inheritance, and



little is understood of the genetic and acquired determinants of these disorders.

In contrast to the common self-limited generalized and focal epilepsies, there are many severe monogenic epilepsy syndromes where molecular testing has a key role in clinical practice today. In no area is this truer than in the epileptic encephalopathies that predominantly begin in infancy and early childhood. Important examples include Dravet syndrome, Epilepsy limited to Females with Mental Retardation and specific infantile spasms phenotypes. In this setting, the finding of a causative genetic mutation, in contrast to a susceptibility variant or change, identifies the cause of the child's disorder. Most frequently, the mutation arises *de novo* in the child, and thus the family history is usually negative for seizure disorders. It is very important to test the parents for the change as the finding of a *de novo* mutation supports its likely pathogenicity and has significant implications for genetic counseling for the family. Identification of the molecular cause saves the child from further investigations, such as liver or skin biopsies, and may influence choice of anti-epileptic therapies and prognostic counseling. Of importance, it also gives the family an answer. They may previously have attributed the child's epileptic encephalopathy to another cause, such as vaccination, and a molecular etiology will allow them to move forward in dealing with their child's serious illness (5).

As more molecular causes are identified, it is likely that patients with common epilepsies may also have monogenic *de novo* mutations, providing an alternative explanation for the absence of a family history in some patients with GGE. It is not clear how frequently this will be the case, as we are only at the tip of the iceberg in our gene discovery for GGE.

There are also a number of well-established monogenic familial epilepsy syndromes for which the genes are known. The best example is benign familial neonatal seizures for which 60 to 70 percent of families have a potassium channel subunit gene mutation (*KCNQ2*, *KCNQ3*) (6). Given the striking familial pattern, clinical testing is helpful but not essential to making a diagnosis. A similar argument could be made for autosomal dominant epilepsy with auditory features where 50% of families have mutations of *LGII* (7). While detecting a mutation adds to the diagnosis, it is often expensive and may not change management or prognostic counseling (8).

Genetic Testing in Clinical Practice

Epileptic Encephalopathies (EE)

Copy Number Variation (CNV)

In recent years, the importance of copy number variation, where variable numbers of genes exist, such as deleted or duplicated genes, has come to be recognized as part of normal human variation. CNVs are more likely to be pathogenic if they are larger, but pathogenic CNVs vary considerably in their gene content from one critical gene to hundreds of genes. It is often unclear which gene is responsible for a specific phenotype. CNV testing by single nucleotide polymorphism (SNP) microarray or array comparative genomic hybridization (CGH) is also known as molecular karyotyping. It has essentially replaced routine karyotyping and become a key test for intellectual disability where 15 to 20 percent of patients have a causative CNV (9).

Emerging evidence suggests that molecular karyotyping should be routinely performed in the EE where approximately 8% of cases show a potentially significant CNV (H. Mefford and I. E. Scheffer, unpublished data, May 2011). Interpretation of the results is critical and needs the input of a geneticist. There are now many case reports of single cases or small series of patients harboring causative CNV.

SCN1A Encoding the Alpha-1 Subunit of the Sodium Channel

Dravet syndrome is a distinctive infantile onset epilepsy syndrome in which a normal infant presents at about 6 months with febrile status epilepticus that may be hemiclonic or generalized. Other seizure types develop between 1 and 4 years. Early development is normal and slows in the second year of life. More than 70% of patients have sequencing mutations of *SCN1A*, while 3% have causative CNV involving *SCN1A* (10). About half of the *SCN1A* mutations in Dravet syndrome cause truncation of the protein, while the other half are missense mutations (11). More than 90% of cases have a *de novo* mutation; however, parental germ line and somatic mosaicism are well described and need to be considered in estimating recurrence rates (12). In the setting of a baby presenting with their second episode of status epilepticus, particularly febrile status, *SCN1A* testing should be considered. The finding of a mutation would influence the clinician's management with regard to trying to achieve seizure control and selection of anti-epileptic agents, and importantly, genetic counseling for the family.

SCN1A testing in a family with GEFS+ is of academic interest rather than of clinical utility, as it would not change management (13). Few GEFS+ families have missense mutations of *SCN1A*. GEFS+ is characterized by phenotypic heterogeneity such that the *SCN1A* mutation is just one of several genes presumed to be contributing to the phenotypic variation in the family, and the finding of a mutation does not predict the phenotype.

We have recently shown that *SCN1A* mutations may cause other EE phenotypes such as migrating partial seizures of infancy and severe infantile multifocal epilepsy (14, 15).

PCDH19 Encoding Protocadherin 19

PCDH19 is the gene responsible for the striking disorder called Epilepsy limited to Females with Mental Retardation (EFMR) (16, 17). Since we first showed *PCDH19* to be the molecular cause of the original large American family with EFMR and four new families, EFMR has been found to be much more frequent than initially thought (16–18). Girls with EFMR typically present in infancy with febrile seizures that comprise focal or generalized tonic-clonic seizures that cluster with 10 or more seizures over a few days. Seizures may be highly refractory. Development is often normal with regression at seizure onset in some; intellect varies from normal in a third to severe intellectual disability. Autistic features are prominent in severely affected girls. The X-linked mode of inheritance is remarkable, as normal transmitting fathers are hemizygous carriers and will pass on EFMR to all their daughters, while half of the daughters of affected heterozygous mothers will inherit EFMR. We have recently described parental mosaicism of *PCDH19* (19). The mechanism underlying this fascinating inheritance pattern is thought to be cellular interference, where two populations of



cells (mutation positive and wild-type PCDH19) cannot form normal networks as PCDH19 has a key role in cell-cell adhesion (20).

PCDH19 became even more interesting when it was found to be mutated in girls with a Dravet-like picture (20). These girls differed in subtle ways from Dravet syndrome due to *SCN1A* mutations as they had a slightly later mean onset (9 months compared with 6 months), fewer absence and myoclonic seizures, and better developmental outcome. In some cases mutations were inherited. This finding suggests that these girls actually have EFMR rather than Dravet syndrome, a critical distinction for treatment, prognostic and genetic counseling.

Further studies have shown that over 10% of cohorts of girls with onset of seizures under 5 years of age have *PCDH19* mutations; many are de novo mutations and therefore do not have the characteristic family history seen in EFMR (21–23). Girls with normal intellect or intellectual disability who present with clusters of brief febrile seizures in infancy should be considered for *PCDH19* testing.

Other Genes for Epileptic Encephalopathies (EE)

In recent years, an increasing number of genes have been identified for specific EE. While this list is by no means complete, a range of genes should be considered depending on the correct clinical setting.

For example, spasms beginning in infancy should make one consider *ARX* in boys and *CDKL5* in girls (24). Three stages for the course of the epilepsy in girls with *CDKL5* mutations have been described and include an unusual, distinctive seizure type called hypermotor-tonic-spasms sequence (25, 26).

STXBP1 mutations were first found in one-third of patients with Ohtahara syndrome and later shown to be causative in early-onset EE, typically with onset under 6 months of age (27, 28). Ohtahara syndrome has also been associated with mutations in *ARX* (29) and in *SLC25A22* encoding a mitochondrial glutamate carrier (30).

A number of genes have been identified for small numbers of cases with early-onset EE including *SPTAN1* encoding α -II spectrin, which causes West syndrome with cerebral hypomyelination (31), and *PLCB1* encoding phospholipase C- β 1 beginning with tonic seizures evolving to infantile spasms (32). Recently homozygous 15q13.3 deletions have been implicated in causing EE (33).

An important infantile onset EE is GLUT1 encephalopathy, which has historically been diagnosed on the basis of hypoglycorrachia (34, 35). GLUT1 encephalopathy is due to *SLC2A1* mutations, the gene encoding the glucose transporter 1 that transports glucose across the blood brain barrier and into glia (36). Recent work suggests that the spectrum of GLUT1 deficiency is broader than the well recognised severe encephalopathy.

Genetic Generalized Epilepsies

GLUT1 Deficiency Encoded by SLC2A1

The only gene that is currently important to test in the clinical domain of the GGE is *SLC2A1*. We recently found that it was responsible for 10% of patients with early-onset absence epilepsy, where onset occurs under 4 years of age (37). Our auto-

somal dominant families expanded the phenotypic spectrum by showing that the predominant seizure type was absence seizures beginning at all ages; focal seizures occurred in some family members (38). A strong clue is the presence of paroxysmal exercise-induced dyskinesia in family members (39). More recently we have shown that 5% of patients with the syndrome of epilepsy with myoclonic-atic seizures, delineated by Doose, have GLUT1 deficiency (40). The reason that testing should be considered is that the ketogenic diet is a treatment for GLUT1 deficiency and provides an alternative therapy that may result in seizure control and potentially improve cognitive outcome.

A number of other genes, particularly encoding ion channel subunits, have been found in rare families with GGE. At present, these are not sufficiently common to recommend testing.

The Way Forward

In the last couple of years, new molecular technologies have provided previously unimagined, rapid and tantalizing approaches that allow the decoding of each human being's DNA. We now have access to an enormous dataset obtained by the sequencing of a person's whole exome (about 30 million base pairs, and about 1% of the human genome), meaning every base pair of all 180,000 exons, the part of each gene that encodes the protein product (41). Over 90 times the dataset can be produced by sequencing the whole genome, which includes all the regulatory genetic sequences and non-coding DNA; the purpose of the latter is currently poorly understood (42). This novel technology is yielding inconceivable datasets fueling a huge explosion in bioinformatics to interpret such unwieldy amounts of information. The mission is to find the "needle in the haystack" or the genetic mutation causing or contributing to a specific epilepsy syndrome.

From whole exome sequencing of an individual, one might find over 1,300 variants that are not identified in human databases of normal human variation and could potentially be pathogenic (41). Scrutiny of each variant is then necessary to see if it changes the amino acid to a different amino acid in the protein sequence. If so, does it result in an amino acid with altered properties that could affect protein function? This is just the start of the complex process of understanding the relationship of the genetic mutation to the epilepsy syndrome; other factors involve whether this change was inherited from an affected or unaffected parent, whether the person's epilepsy is likely to be polygenic or monogenic, and whether other individuals with a related epilepsy phenotype also have mutations of the same gene.

So what does this mean to the epilepsy clinician? At present, whilst very exciting at a research and neurobiological level, these technologies are not useful in clinical practice. It is not worth investing in whole exome or whole genome sequencing of your patients despite the relatively low cost (\$2,000–\$5,000 often delivered with a basic bioinformatic analysis thrown in) as you will be faced with an uninterpretable set of genetic variants and have considerable difficulty explaining the findings to your patients. Nevertheless, patients may seek these data independently through a range of online buy-your-own-genome analysis companies.



At present, genetic testing is indicated for specific disorders, as outlined above, where the finding of a genetic mutation may save further potentially invasive investigations into the underlying cause and may influence patient management and genetic counseling. One day, when each individual's genome is readily available, potentially from the time of conception or after delivery, the identification of deleterious molecular changes will be more accessible, but their interpretation will remain complex.

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Disclosure of Potential Conflicts of Interest

Section #1 Identifying Information

1. Today's Date: 14 April 2011
2. First Name: Ingrid Last Name: Scheffer Degree: MBBS PhD FRACP
3. Are you the Main Assigned Author? Yes No
 If no, enter your name as co-author _____
4. Manuscript/Article Title: ___ Genetic Testing in Epilepsy: What should we be doing? _____
5. Journal Issue you are submitting for: 11.4

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