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Genetic Generalized Epilepsies

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Abstract

The genetic generalised epilepsies (GGE) are mainly genetically determined disorders. Although inheritance in most cases appears to be complex, involving multiple genes, variants in a number of genes are known to contribute. Pathogenic variants of *SLC2A1* leading to autosomal-dominant GLUT1 deficiency account for up to 1% of cases, rising to 10% of those with absence seizures starting under 4 years. Copy number variants are found in around 3% of cases, acting as risk alleles. Copy number variation is much more common in those with co-morbid learning disability. Common variant associations are starting to emerge from genome-wide association studies but do not yet explain a large proportion of GGE. Although currently genetic testing is not likely to yield a diagnosis for most patients with GGE, it can be of great importance in specific clinical situations. Providers should consider the individual patient's history in determining the utility of genetic testing.

The worried parents

A mother presents with her infant son. She has had epilepsy since her teenage years with both absence seizures and convulsions that respond to medication. She asks if her child will develop epilepsy like her.

A father presents with his 6 year old daughter. The daughter has had difficult to control absence seizures since before her third birthday as well as the occasional convulsion. He requests advice about treatment and risks to further children.

What would you say to each parent?

The genetic generalised epilepsies (GGE), also known as idiopathic generalised epilepsies, make up around a quarter of all epilepsies [1]. They show a combination of generalised spike and wave discharges on EEG occurring at over 2.5 Hz and otherwise normal intellect and brain imaging [2]. There are three common seizure types seen. Typical absence seizures show brief (5-20s) bursts of regular spike and wave, accompanied by sudden onset and offset of lost awareness. There may be subtle facial myoclonus and drifting open of closed eyes but postural tone is largely unaffected. Myoclonic seizures are brief jerks, usually of the axial or upper limb muscles, accompanied by a spike or poly-spike wave discharge on the EEG. Generalised tonic-clonic seizures (GTCS) are the third, common seizure type in GGE.

The classical sub-syndromes of GGE are divided based on the combination of seizure types and the age of onset. In childhood absence epilepsy (CAE) typical absence seizures usually begin between 4 and 8 years of age, with multiple absences a day. For juvenile absence epilepsy (JAE), the onset is later (usually after 11 years) and absences are less frequent while GTCS are often seen as well. Juvenile myoclonic epilepsy (JME) with onset in adolescence has prominent myoclonic seizures, often intermixed with GTCS and sometimes absence. Generalised tonic clonic seizures can also be seen as the sole seizure type in GGE, often occurring first thing in the morning; GTCS alone or GTCS on awakening (GTCSA).

Although these sub-syndromes are broadly accepted, the diagnostic classification for epilepsy does not draw clear lines between them and the limits, particularly of CAE, are a matter of active debate. There are also cases which fit the broad definition of GGE but not the classical age at onset, for instance adult-onset GGE and some early onset absence epilepsies (EOAE) where seizures start before 4 years of age [3, 4]. There are also situations where the epilepsy is

consistent with GGE but intellectual impairment or autism is also present, and which fall outside the strict definition of GGE but are important as the genetic causes appear to overlap [5].

The Genetics of GGE

Genetic generalised epilepsy, as the name suggests, is a disease where a predominant genetic contribution is suspected. Twin studies comparing monozygotic (MZ or identical) twins with dizygotic (DZ or fraternal) twins are useful for estimating the contribution of genetics to a disease on a population level [6]. MZ twins share all of their genome while DZ twins are siblings, therefore sharing half. Being twins, both groups have very similar environments, hopefully excluding environmental effects to compare the importance of inheritance.

Concordance, the rate at which a second twin is affected given disease in the first, can be compared between DZ and MZ twins. Multiple sclerosis, a disease with strong environmental as well as genetic contributions, shows an MZ concordance of 30% and a DZ concordance of 4% [7]. Seizures as a whole show MZ vs. DZ concordance of 62% vs 18% while genetic generalised epilepsy shows 76% vs. 33% [8]. This is consistent with a largely, although not necessarily exclusively, genetic disease.

Overall the rate of epilepsy in siblings of patients with GGE is around 8% [9]. This is lower than the 25% expected of a recessive or 50% expected of a dominantly-inherited trait. Family histories, when present, tend to be sparse [10]. This suggests that, in most cases, multiple gene variants are needed to produce GGE. However, as of 2017, there are no accepted models yet on how such a presumed polygenic inheritance occurs on a genetic level, including the type of variants and the associated genes.

This leaves GGE as a genetic but not necessarily inherited or familial disorder. This complexity, as well as the cultural impact of diagnosing heritable disease in many places, has prompted the ILAE to maintain idiopathic generalised epilepsy as an alternate term for the classical GGE syndromes[11].

Gene variants contributing to complex disease can either be individually low impact and common, or individually high impact but rare. Both kinds of variants have been identified in GGE, although only a minority of the gene changes needed to explain GGE overall have been found.

Single genes and GGE

As with any disease with complex inheritance a proportion are caused by variants in single genes. Variants in the GABA receptor subunit gene *GABRG2* can cause childhood absence epilepsy but do not appear to be a common cause in GGE overall [12]; similarly variants in *GABRA1* rarely cause monogenic GGEs[13]. More important overall is *SLC2A1*, which codes for a glucose transporter, GLUT1. The brain is critically dependent on glucose for metabolism and GLUT1 is the sole transporter of glucose across the blood-brain barrier. Loss of function of one of the two copies of this gene leads to GLUT1-deficiency, a condition initially described as a severe metabolic encephalopathy including intractable epilepsy, complex motor dysfunction and intellectual disability [14].

Milder GLUT1-deficiency, initially recognised via familial cases, causes a combination of movement disorder and epilepsy with prominent absence seizures, along with intellect that is often normal [15]. The movement disorder in GLUT1-deficiency is unusual, with prolonged exercise leading to dystonia and chorea largely confined to the limbs doing the exercise (paroxysmal exertional dyskinesia) [16].

GLUT1-deficiency is seen in 10% of those with typical absence seizures starting under 4 years of age and around 1% of people with typical GGE overall [17-19]. With a narrow definition of EOAE that excludes not only those with intellectual impairment but also those who have ever had GTCS, myoclonic seizures or photosensitivity on EEG, the rate of GLUT1-deficiency in EOAE is probably closer to the 1% seen in GGE overall [4].

GLUT1-deficiency is also remarkable in having a specific remedy in the ketogenic diet. Ketones utilise a different transporter so that the ketogenic diet bypasses the metabolic defect, leading to excellent seizure control in even the most severe cases and likely improvement in intellectual function, making a diagnosis of mild GLUT1-deficiency clinically important [20, 21].

Single gene GGE mimics

In addition, some genetic disorders can be mistaken for GGE. This is particularly true where GGE is refractory to treatment. The epilepsy associated with most neuronal migration disorders is either focal or sufficiently severe to qualify as an epileptic encephalopathy. Sub-cortical band heterotopia however, particularly with x-linked inheritance in women due to variants of the gene *DCX* , can occasionally present with GTCS and generalised spike and wave discharges over 2.5Hz with normal intellect, although clearly not with normal imaging on close examination of MRI [22, 23].

The progressive myoclonic epilepsies (PME) are a group of degenerative disorders characterised by myoclonic and convulsive seizures, action myoclonus, tremor, ataxia and often cognitive decline, all combined with EEG showing generalised spike and wave[24]. The commonest identified cause of PME is Unverricht-Lundborg disease, a recessive disease due to variants in the gene *cystatin B* [25]. The presentation in Unverricht-Lundborg disease particularly, but in other PME as well, can mimic juvenile myoclonic epilepsy with GTCS starting around 6-12 years old along with myoclonus and EEG evidence of generalized spike and wave [26]. It is not until ataxia and action myoclonus appears later that the diagnosis becomes clear. In rare, mild cases of Unverricht-Lundborg disease the clinical features can continue to mimic juvenile myoclonic epilepsy until at least middle age[27].

Complex genetics: Copy Number Variants

Deletions and duplications of chromosomal segments, also referred to as copy number variants (CNV), are important contributors to the genetics of neurodevelopmental disorders with complex inheritance, including GGE [28]. Recurrent deletions on chromosome 15 (15q13.3, 15q11.2) and chromosome 16 (16p13.11) are all associated with GGE, with around 3% of people with GGE being carriers for one of these three deletions [28, 29]. Despite encompassing multiple genes, these CNV are also seen in unaffected members of the general population, albeit rarely, and therefore act as risk factors rather than causative alleles. In any

given family, unaffected carriers and family members with epilepsy who are not carriers for the CNV may be identified, supporting the role of the CNV as a genetic risk factor rather than a Mendelian cause of disease [5, 30]. The odds ratios suggest that approximately one carrier in three with the strongest risk allele (15q13.3) will develop GGE.

Although GGE is defined by the absence of other significant brain disease, these CNV were first described in other neurodevelopmental disorders; including autism spectrum disorders, intellectual disability and schizophrenia [31-33]. These CNV appear to raise risk for multiple disorders not just in relatives but in the same individual. Those with GGE-like epilepsy and co-morbid intellectual disability are significantly more likely to be carriers for such a recurrent CNV than those with either GGE or intellectual disability alone [5, 34]. Overall, although these CNV are risk factors for epilepsy, they are also risk factors for much more disabling neurodevelopmental conditions and, when these CNVs are found, genetic counselling needs to take that into account.

Complex Genetics: Sequence variants

For discovering common variants contributing to complex disease, the established approach is the genome-wide association study (GWAS) [35]. For a GWAS, large groups of cases with the disease of interest are collected along with a similarly large group of control individuals. Common single nucleotide polymorphisms (SNPs) are then genotyped across the genome and the frequency of each SNP compared between cases and controls. As there are several million common SNPs, this requires controlling for multiple comparisons.

A recent combined analysis of multiple GWAS for GGE and focal epilepsy suggests a number of common loci for GGE [36]. For epilepsy as a whole, common variant associations were shown with SNPs in the sodium channel subunit *SCN1A* and the cell interaction molecule, protocadherin 7 (*PCDH7*). Both of these genes are biologically plausible candidates. Pathogenic variants in *SCN1A* are well known to cause epilepsy, underlying most of the epileptic encephalopathy Dravet syndrome and also occurring in the familial syndrome of genetic epilepsy with febrile seizures-plus [37, 38]. Although *PCDH7* has not previously been

associated with epilepsy another member of the gene family, *PCDH19*, is associated with an X-linked, female-limited epilepsy [39].

For GGE alone, common variants in the gene *VRK2* showed association. This gene has not previously been associated with epilepsy outside of GWAS and is a protein kinase involved in signal transduction and apoptosis. Interestingly, one of the SNPs forming the association signal in this gene has one allele that predisposes to GGE while being simultaneously protective against schizophrenia; the opposite effect of the microdeletions discussed above [40]. The evidence for these common variants as genetic risk factors is not yet definitive and requires replication.

Recently, a whole exome analysis of 640 cases of GGE with a family history revealed an excess of ultra-rare variants in cases compared to controls, although no individual genes reached significance with this sample size. Remarkably, there was an excess of variation in genes known to cause epileptic encephalopathies [41] including *SCN1A*, *GABRG2*, *ATP1A3*, and *KCNQ2*.

Conclusion

Although the genetics of GGE is a rapidly moving and expanding field, the puzzle is far from solved. While GWAS findings are statistically robust and the variants are frequently found in people with GGE, each of these SNP associations is of very small magnitude, with odds ratios less than 1.3. The effect of each GGE-associated SNP, and indeed the likely overall effect of all common variation, explains only part of the genetic contribution to GGE.

For gene changes such as *SLC2A1* pathogenic variants leading to GLUT1-deficiency, each variant is of high impact but only about 1% of those with GGE are carriers for any of these known genetic changes. For early-onset absence epilepsy, testing for GLUT1-deficiency with a lumbar puncture or sequencing has both a significant yield and treatment implications. Where GGE is combined with intellectual disability either in the individual or in a close

relative, a chromosomal microarray looking for CNV is indicated. This test is, however, indicated in developmental disability more broadly and the presence of GGE does not significantly alter that. Although massive genome sequencing projects are underway that will likely transform our understanding, at the moment, genetic testing to predict recurrence of GGE in family members is indicated only in specific clinical scenarios.

The worried parents revisited

You sit down and listen to the first mother's concerns that she may pass on her epilepsy to her son. You explain that he has about an 8% risk of having seizures by age 20. It is far more likely that he will not have seizures and, should they occur, it is likely they will be easy to control. You further explain that there is currently no genetic test that can accurately predict if her next child will develop epilepsy.

In the second case, you quickly realise that this absence epilepsy is of unusually early onset. On careful questioning, the father reveals that he had experienced prolonged cramping and jerking of the legs with playing sport at school that you realize might indicate paroxysmal exertion dyskinesia. You therefore suspect GLUT1-deficiency and discuss investigation with lumbar puncture and genetic testing. If positive, this will lead to different therapeutic options such as the ketogenic diet, and this may improve her daughter's seizure control. It will also alter your counselling advice as further children have a 50% risk of inheriting the variant and about a 40% chance of having seizures.

Key Points

1. Genetic generalized epilepsies are presumed to be largely genetic disorder with complex inheritance
2. GGE is associated with different types of genetic variants – single gene disorders, copy number variants and common variants

3. GLUT1-deficiency is a potentially treatable genetic cause of GGE, and should be considered in early onset absence epilepsy, or in patients with epilepsy and paroxysmal exercise-induced dystonia.

4. Genetic testing for GGEs, with the exception of specific clinical scenarios, is currently best done in a research setting.

MCQ test

1. Which of the following seizures types is not seen in the Genetic Generalized Epilepsies?

a. Absence seizures
b. Generalized tonic-clonic seizures
c. Myoclonic seizures
d. Focal aware seizures

2. You see a 4 year old boy with absence seizures, and you realize his absences started at age 3 years of age. In addition, his cousin has epilepsy, as well as episodes described as "funny limb movements" with preserved consciousness. Given this history, you would consider genetic testing for:

a. SLC2A1 pathogenic variants
b. Microdeletions in chromosome 15
c. Cystatin B pathogenic variants
d. PCDH19 pathogenic variants

3. A 26 year old man with previously diagnosed with Juvenile Myoclonic Epilepsy (JME) at age 18 presents with ongoing myoclonus. Although valproate has controlled GTCS he continues to have frequent morning myoclonus and has now developed jerks with use of his arms as well as a tremor and clumsiness. Is there an alternate diagnosis that should be considered?

a. Juvenile absence epilepsy
b. Ataxia telangiectasia
c. Dravet syndrome
d. Unverricht-Lundborg disease

Test yourself on what you've just read. Try our online MCQs at http://www.geneticliteracy.info/gl-test3; answers are immediately provided online.

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