GENETICS OF EPILEPSY

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The last decade has witnessed rapid advances in understanding the role of genetic factors in epilepsy. Mutations and chromosomal defects underlying many inherited symptomatic epilepsies have now been identified, and several genes have been associated with rare idiopathic epilepsies transmitted in a mendelian manner. However, the genetic factors underlying inherited susceptibility to idiopathic epilepsy remain to be identified.

CLASSIFICATION OF EPILEPTIC SYNDROMES

The International League Against Epilepsy (ILAE) *Classification of epileptic syndromes* (published in 1989) divides seizure disorders along two main axes. First, epilepsies are classified as idiopathic, symptomatic or cryptogenic, and second, they are either generalised or focal. Within this classification, genetic factors have conventionally been thought to play the largest role in the idiopathic generalised epilepsies. A genetically determined increased excitability of neuronal circuits provides an attractive explanation why otherwise normal individuals should develop unprovoked seizures without an identifiable focus of onset. This view has, moreover, been supported by the finding that concordance rates for idiopathic generalised epilepsy are elevated among first degree relatives, and more so among monozygotic twins. Similar arguments and evidence apply to febrile seizures, which do not count as an epilepsy syndrome as such. However, recent studies have shown that genetic factors also play an important role in cryptogenic epilepsy (seizure disorders where a syndromic diagnosis is not possible), and also contribute to several partial epilepsies. Also single gene defects have been identified in a small number of families with epilepsy inherited in an autosomal dominant fashion. These rare monogenic epilepsies have shed a new light on the mechanisms by which disorders of neuronal function can cause epilepsy. Major advances have also been made in establishing the cause of a number of rare but often severe symptomatic epilepsies.

This article will begin by considering a few genes responsible for symptomatic epilepsy, and then address recent progress in the genetics of idiopathic generalised and partial epilepsy. The principles outlined here provide a basis for advice to give to patients and relatives seen in an epilepsy or general neurology clinic. More detailed discussion of the genetics of epilepsy is available.¹

SYMPTOMATIC EPILEPSIES

Seizures are a variable feature of a very large number of congenital neurodevelopmental disorders. A detailed description is beyond the scope of this article, so only a few will be mentioned here, selected mainly because seizures can be a very prominent aspect of the disorder, and as a result such patients are seen in epilepsy clinics.

Neurocutaneous disorders

Tuberous sclerosis (TS) is a frequent cause of malignant childhood epilepsy, in particular West syndrome (hypsarrhythmia, mental retardation, and infantile spasms). Approximately half of patients with TS are familial cases, and the other half are sporadic. TS is caused by dominant mutations of one or other of two tumour suppressor genes (TSC1 and TSC2 located on 9q34 and 16p13.3, respectively). Neurofibromatosis type 1 is also occasionally associated with epilepsy, although with a far better prognosis than TS.

Malformations of cortical development

Malformations of cortical development (MCDs) are associated with refractory seizures and are often seen in association with variable degrees of mental retardation. However, subtle MCDs are sometimes picked up on magnetic resonance imaging in patients with apparently normal neurological function. They probably arise from both genetic and non-genetic mechanisms. Several genes have been identified in association with distinct patterns.² Recessively inherited mutations of LIS1 (chromosome 17p13.3), which codes for a microtubule associated protein, are a frequent cause of lissencephaly, which is associated with severe mental retardation and intractable epilepsy. Another gene associated with lissencephaly in males, XLIS (chromosome Xq22.3-q23), codes for a protein

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of unknown function, doublecortin. In heterozygous females, mutations of the same gene are associated with the milder phenotype of subcortical band heterotopia. Filamin A mutations have been reported in families with X linked bilateral periventricular nodular heterotopia, which causes focal epilepsy in females and is prenatally lethal in males. EMX2 mutations are associated with schizencephaly, an uncommon cause of focal epilepsy. Among other genetic causes of recessively inherited cortical malformation are mutations of genes coding for Fukutin (in association with Fukuyama congenital muscular dystrophy) and reelin. Some of the genes listed above are also involved in chromosomal defects associated with epilepsy and mental retardation.

Progressive myoclonic epilepsies

Most of the monogenic causes of progressive myoclonic epilepsy (PME) have been identified.³

Recessive inheritance

Unverricht-Lundborg disease or Baltic myoclonus—This usually presents in childhood with stimulus sensitive and spontaneous myoclonus, tonic-clonic seizures, ataxia, and mild cognitive decline. It is caused by mutations of the cystatin B gene (21q22.3), which codes for a protease inhibitor. The most common mutation is an unstable expansion of a repeated sequence of 12 nucleotides in the promoter region.

Lafora disease—Laforin is a tyrosine phosphatase (coded for on 6q24), homozygous mutations of which cause myoclonic epilepsy with onset in the second decade, associated with visual hallucinations and cognitive decline. The characteristic carbohydrate accumulations (Lafora bodies) seen on electron microscopy in skin, brain, muscle, and liver may result from aberrant interaction of laforin with glycogen.

Neuronal ceroid lipofuscinosis (NCL or Batten's disease)—This is another group of diseases causing progressive myoclonic epilepsy, which are variably associated with early visual impairment, cognitive decline, and spasticity. Several genes have been identified, which imperfectly correlate with the age of onset. These are:

- ▶ the palmitoyl-protein thioesterase gene (1p32), causing either infantile or juvenile-onset NCL
- ▶ the tripeptidyl peptidase 1 gene (11q15) and two other genes of unknown function (CLN5 gene on 13q21-32, and CLN6 gene on 15q21-23) associated with late infantile-onset NCL
- ▶ another gene coding for a protein of unknown function associated with a juvenile-onset form (CLN3 gene on 16p).

Sialidosis or cherry-red spot myoclonus—This storage disease is associated with loss of function mutations of the sialidase gene on 6p21.3.

Dominant inheritance

Dentatorubropallidolysian atrophy (DRPLA)—This is caused by a CAG expansion in a gene on 12p13.31.

Mitochondrial (maternal) inheritance

Myoclonic epilepsy with ragged red fibres (MERRF)—This disorder is frequently caused by missense mutations in the mitochondrial gene coding for lysine tRNA.

IDIOPATHIC EPILEPSIES: COMPLEX INHERITANCE

Although epilepsy only very rarely shows a mendelian pattern of inheritance (see below), first degree relatives of patients with idiopathic epilepsy have a roughly two- to threefold elevated risk of being affected.⁴ Twin studies in developed

Abbreviations

ADNFLE: autosomal dominant nocturnal frontal lobe epilepsy
ADPEAF: autosomal dominant partial epilepsy with auditory features
ADLTE: autosomal dominant lateral temporal lobe epilepsy
BNFC: benign neonatal febrile convulsions
DRPLA: dentatorubropallidolysian atrophy
GEFS+: generalised epilepsy with febrile seizures plus
ILAE: International League Against Epilepsy
JME: juvenile myoclonic epilepsy
MCD: malformation of cortical development
MERRF: myoclonic epilepsy with ragged red fibres
NCL: neuronal ceroid lipofuscinosis
PME: progressive myoclonic epilepsy
SMEI: severe myoclonic epilepsy of infancy
TS: tuberous sclerosis

countries have yielded monozygotic concordance rates greater than 40%, and estimates of heritability (the proportion of the variance attributable to shared genes) of about 70%.^{5,6} These estimates have generally been obtained without close attention to a syndromic diagnosis. Some family studies have reported that restricting attention to first degree relatives with the same syndrome greatly lowers the concordance rate. Conversely, adding a history of febrile seizures increases the concordance rate. However, when concordant monozygotic twins are examined, they are found to have remarkably similar epilepsy syndromes.⁵ These results have been interpreted as implying that, within affected families, a major gene confers the seizure susceptibility, possibly with low penetrance, but that in an individual member, the epilepsy phenotype (and whether epilepsy is present at all) results from an interaction with modifier genes.

In spite of the compelling evidence for genetic susceptibility factors, no single unambiguous chromosomal locus has emerged in broad searches among populations with idiopathic generalised epilepsy. Instead, a number of loci have been identified by restricting attention to subtypes of idiopathic epilepsy, especially epilepsies presenting in childhood.¹ For instance, several studies of juvenile myoclonic epilepsy (JME) have reported linkage disequilibrium with markers on chromosome 6p. By focusing on candidate genes (in particular ion channels, see below), another JME locus was found at 15q14, which contains the gene for a nicotinic receptor subunit. The same locus is associated with benign Rolandic epilepsy. However, the status of loci identified with these approaches is uncertain: mutations have yet to be discovered, and some studies that have examined apparently similar cohorts of patients and control populations have failed to confirm some loci. A plausible interpretation of these findings is that many epilepsy susceptibility genes, as well as modifier genes, exist, and that in different populations distinct permutations converge on a smaller number of common phenotypes.

What sort of genes might be responsible for the genetic predisposition to epilepsy? The best clue comes from rare families where epilepsy is transmitted as a mendelian trait.

MONOGENIC EPILEPSIES: MENDELIAN INHERITANCE

Several families exhibiting epilepsy transmitted in a mendelian manner have recently been found to have mutations in single genes. They are all dominantly inherited and all but one of them code for ion channels, underlining the importance of

Table 1 Monogenic epilepsies and ion channels implicated in human epilepsy

Syndrome	Gene	Locus	Protein
1. Autosomal dominant inheritance			
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	CHRNA4	20q13.2-q13.3	Nicotinic ACh receptor subunit
"	CHRNA2	1p21	Nicotinic ACh receptor subunit
Benign familial neonatal convulsions (BFNC)*	KCNQ2	20q13.3	Potassium channel subunit
"	KCNQ3	8q24	Potassium channel subunit
Generalised epilepsy with febrile seizures plus (GEFS+)	SCN1A	2q24	Sodium channel subunit
"	SCN1B	19q13.1	Sodium channel subunit
"	GABRG2	5q31.1-q33.1	GABA _A receptor subunit†
Juvenile myoclonic epilepsy (JME)	GABRA1	5q34	GABA _A receptor subunit
Autosomal dominant partial epilepsy with auditory features (ADPEAF)‡	LGII	10q24	Leucine-rich, glioma-inactivated 1 (unknown function—not an ion channel)
2. Sporadic			
Severe myoclonic epilepsy of infancy (SMEI)	SCN1A	2q24	Sodium channel subunit
3. Other ion channel genes implicated in epilepsy§			
Febrile and afebrile seizures	SCN2A	2q23-q24.3	Sodium channel subunit
Episodic ataxia type 1 with partial epilepsy	KCNA1	12p13	Potassium channel subunit
Episodic ataxia type 2 with spike wave epilepsy	CACNA1A	19p13	Calcium channel subunit
JME	CACNB4	2q22-23	Calcium channel subunit¶

*1.5% risk of epilepsy continuing beyond infancy.

†Also associated with febrile seizures and absences.

‡Also known as autosomal dominant lateral temporal epilepsy.

§Mutations identified in small number of patients, so role in epilepsy less clear.

¶Also associated with generalised epilepsy with praxis-induced seizures.

this class of signalling protein in determining the excitability of neuronal circuits.^{7,8} Table 1 lists the genes that have been identified in monogenic epilepsies to date, as well as a few other ion channels that have been implicated in a small number of patients with epilepsy.

- The discovery of monogenic epilepsies has led to several surprises. Single gene mutations can cause both generalised and partial epilepsies.
- Even among the monogenic epilepsies, penetrance is sometimes incomplete—for example, carriers of nicotinic receptor mutations associated with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) do not always exhibit seizures.
- The phenotypes associated with some genes can be remarkably variable, even within a family where individuals have the same point mutation. Indeed, a major breakthrough came with the description of a new syndrome, generalised epilepsy with febrile seizures plus (GEFS+), which crosses almost all distinctions in the ILAE classification. GEFS+ encompasses (in various individuals and in various combinations) uncomplicated febrile seizures, febrile seizures persisting beyond childhood, and afebrile generalised tonic-clonic, absence, myoclonic, atonic, and temporal lobe seizures. Some patients have even been reported to suffer from myoclonic-astatic epilepsy, generally considered to be a malignant epilepsy. This remarkable variability is consistent with a strong effect of modifying factors even when a single dominant "epilepsy gene" is transmitted with high penetrance.
- Conversely, mutations of several different genes can converge on indistinguishable phenotypes. Thus, GEFS+ have been associated with mutations of three sodium channel genes and two GABA_A receptor genes. ADNFLE can arise from mutations of either of two nicotinic acetylcholine receptor subunits (α_4 and β_2), and benign neonatal febrile convulsions (BNFC) can arise from mutations of either of two potassium channel subunits (KCNQ2 and KCNQ3). Interestingly, the channel subunits implicated in some of these epilepsies are frequently associated with one another. Thus, $\alpha_4\beta_2$ heteromultimers form a commonly occurring type of nicotinic receptor in the frontal cortex and

thalamus, while KCNQ2-KCNQ3 heteromers are an important potassium channel modulated by muscarinic receptors.

How do ion channel gene mutations give rise to epilepsy? The most appealing explanation is that an alteration of ion channel function enhances neuronal excitability. This agrees with the finding that most of the sodium channel mutations associated with GEFS+ impair fast inactivation. That is, a proportion of sodium channels remains open in the face of continued depolarisation, instead of closing rapidly to facilitate repolarisation. In addition, it agrees with the finding that the KCNQ2/KCNQ3 mutations associated with BNFC reduce the size of the potassium current, and therefore can be predicted to destabilise membrane potentials. Moreover, the GABA_A receptor mutations also seen in some GEFS+ families appear to reduce maximal chloride current amplitude.

However, this account is probably incomplete. De novo nonsense mutations of the sodium channel gene SCN1A (initially implicated in GEFS+) occur in a high proportion of patients with severe myoclonic epilepsy of infancy (SMEI). In contrast to the mutations associated with GEFS+, these mutations result in a non-functional channel subunit. This finding prompts the possibility that ion channel mutations can lead to epilepsy via indirect mechanisms—for example, by altering neuronal differentiation, migration and connectivity, all of which are known to be under the influence of transmembrane signalling mechanisms. Further supporting this hypothesis is the finding of the first monogenic epilepsy not caused by an ion channel mutation. Mutations of the LGII gene (leucine-rich, glioma-inactivated 1) have recently been found in families with a rare syndrome known as autosomal dominant partial epilepsy with auditory features (ADPEAF) or autosomal dominant lateral temporal lobe epilepsy (ADLTE). The normal function of this gene is not known, but mutations are also associated with gliomas, and there are hints that it may be involved in axonal guidance.

Other genes responsible for mendelian epilepsy have yet to be identified, but some large families with many affected members are currently under intense investigation. Whether the genes responsible for monogenic epilepsy in these rare families turn out to be susceptibility factors for sporadic idiopathic epilepsy remains to be determined.

PRACTICAL CONSIDERATIONS

DNA based diagnosis for the symptomatic epilepsies associated with neurodevelopmental disorders is beyond the scope of this article. Moreover, the rare families with mendelian epilepsy may already to be in contact with specialist neurogeneticists, and if they are not, they should be referred appropriately. This leaves the vastly more common situation encountered in an epilepsy clinic of a patient with sporadic epilepsy, who may or may not have a family history of epilepsy. A common question is whether and how much a diagnosis of epilepsy confers an elevated risk to a first degree relative. (When this question arises in the context of a young woman with epilepsy contemplating starting a family, it has to be distinguished from the teratogenic effects of antiepileptic drugs.) Heterogeneity in the type and cause of epilepsy precludes a simple answer. However, several studies have indicated an overall two- to threefold increase in risk over background, providing a starting point for discussion.⁴ The risk appears to be stronger with earlier onset of epilepsy, and may also be stronger in generalised than in localisation related epilepsies (although this is not a universal finding). Some studies have suggested that absence seizures are associated with an especially high risk to relatives. Other studies have suggested that the risk is similarly elevated whether the proband suffers from idiopathic or cryptogenic epilepsy. It is not clear from published data whether a syndrome in a sporadic patient coinciding with one of the epilepsies listed in table 1¹ confers an elevated risk.

Finally, the severity and type of epilepsy in a relative may differ extensively from that in the proband. The risk to relatives appears not to be significantly increased where the proband has a symptomatic epilepsy with an infective, traumatic or cerebrovascular aetiology. On the basis of this information, it is prudent to inform the patient suffering from idiopathic or cryptogenic epilepsy, whether generalised or partial, that there is a small but significantly increased risk to the next generation, and that this needs to be interpreted in the context of a background prevalence of epilepsy of approximately 0.5–1% and a lifetime prevalence in the general population of 3%.

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YNT-SCHERING FELLOWSHIP

Clinical training in multiple sclerosis

The YNT-Schering fellowship aims to promote high quality international clinical training in neurology. The fellowship focuses on advanced training in the diagnosis and management of patients with multiple sclerosis. The YNT-Schering fellowship is valued at 20 000 per candidate over six months and two fellowships will be available for 2003. Candidates should choose a specialist centre in another country with expertise in multiple sclerosis and arrange educational activities which would not otherwise be available to them. These may include clinical neurology and subspecialties. The host centre should have up-to-date brain imaging, laboratory, and electrophysiology facilities to enable the candidate to acquire the skills needed for establishing the diagnosis of MS according to the new McDonald criteria (*Ann Neurol* 2001;**50**:121–7). A letter of intent from the proposed host centre should be included with the application.

Applicants should be aged 35 years or less, and be affiliated to a neurological department as a neurology trainee with at least two years experience. They should be well motivated, intend to subspecialise in multiple sclerosis, and have a good professional curriculum vitae. The home centre should provide a letter stating how the experience acquired by the trainee would be implemented after their return. The period abroad must be recognised as counting towards official training. Activities aiming to establish future collaborations with the host centre will be encouraged.

The full application, including the candidates curriculum vitae, a description of the content and feasibility of the clinical rotation in the named host institution (maximum one page), and the supporting letters from the host/home centres mentioned above should be sent to Axel Petzold by 15 December 2002.

More information can be found on the YNT webpage. www.ynt-europe.com

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