CURRENT TOPIC

Genetics of childhood epilepsy

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The epilepsies are a heterogeneous group of disorders with many causes. However, a genetic aetiology may be present in up to 40% of patients, and this proportion is even higher in epilepsy of childhood onset.[1]

The past decade has seen spectacular advances in our understanding of the genetics of epilepsy at a molecular level, and several comprehensive reviews are available.[2 3] It is apparent that epilepsy genes fall into several quite distinct classes including those in which mutations cause abnormal brain development, progressive neurodegeneration, disturbed energy metabolism, or dysfunction of ion channels. The discovery that several idiopathic mendelian epilepsies are caused by mutations in ion channels, including voltage gated potassium and sodium channels, is the most exciting advance because this might provide a clue to the cause of the more common idiopathic familial epilepsies.

In this short review, the focus is on those mendelian childhood epilepsies for which genes have recently been identified, and non-mendelian epilepsies for which mapping data are available.

Classification of genetic epilepsies
It is helpful to categorise genetic epilepsies according to the mechanism of inheritance involved and according to whether they are idiopathic (primary) or symptomatic.

Three major groups can be recognised according to the mechanism of inheritance:
(1) Mendelian epilepsies, in which a single major locus accounts for segregation of the disease trait in a family.
(2) Non-mendelian or "complex" epilepsies, in which the pattern of familial clustering can be accounted for by the interaction of several susceptibility loci together with environmental factors (or by the maternal inheritance pattern of mitochondrial DNA).
(3) Chromosomal disorders, in which a gross cytogenetic abnormality is present.

In the idiopathic (primary) epilepsies, recurrent seizures occur in individuals who are otherwise neurologically and cognitively intact, whereas in symptomatic epilepsies the seizures are usually one component of a complex neurological phenotype and a detectable anatomical or metabolic abnormality is present.

Over 160 mendelian phenotypes include epilepsy as a component of the phenotype. Although numerous, they are individually rare and probably account for no more than 1% of patients. Most are "symptomatic" and associated with major central nervous system abnormalities or recognisable metabolic disturbances. These include such major disorders as tuberous sclerosis, fragile X syndrome, neurofibromatosis, Angelman syndrome, and the so called progressive myoclonic epilepsies. However, there are a small but important number of "idiopathic" mendelian epilepsies, such as benign familial neonatal convulsions and benign familial infantile convulsions, autosomal dominant nocturnal frontal lobe epilepsy, and generalised epilepsy with febrile seizures plus.

The common familial epilepsies tend to display "complex" inheritance patterns. They include well characterised entities such as childhood absence epilepsy and juvenile myoclonic epilepsy.

Idiopathic epilepsies (table 1)
MENDELIAN IDIOPATHIC EPILEPSIES
Benign familial neonatal convulsions
First described in 1964, this autosomal dominant idiopathic generalised epilepsy occurs in

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Table 1   Genes implicated in idiopathic epilepsies

Epilepsy syndrome	Inheritance	Gene location	Gene	References
Mendelian inheritance				
Benign familial neonatal convulsions	AD	20q (EBN1)	KCNQ2	4, 5
		8q24 (EBN2)	KCNQ3	6, 7
Benign familial infantile convulsions	AD	19q	Unknown	8
Autosomal dominant nocturnal frontal lobe epilepsy	AD	20q13.2	CHRNA4	9, 10, 11
Generalised epilepsy with febrile seizures plus	AD	19q13	SCN1B	12
		2	Unknown	13
Non-mendelian inheritance				
Juvenile myoclonic epilepsy	Complex	15q14	?CHRNA7	14
		6p (EJM1)	Unknown	15, 16
Childhood absence epilepsy (and/or EEG trait)	Complex	8q24	Unknown	17
Juvenile absence epilepsy	Complex	?21q22.1	?GRIK1	18
Benign epilepsy with centrotemporal spikes	Complex	15q14	Unknown	19

EEG, electroencephalogram.

otherwise well neonates, usually from the 2nd or 3rd day of life, usually remits by week 2–3, and has a favourable prognosis for neurological and intellectual development. Benign familial neonatal convulsions have been shown to be genetically heterogeneous. The first susceptibility locus, EBN1, was mapped in 1989 to chromosome 20q in a family of four generations with 19 affected individuals.[4] The gene, KCNQ2, was subsequently identified by positional cloning and was found to show significant homology to a voltage gated potassium channel gene, KCNQ1.[5] Six KCNQ2 mutations have subsequently been identified in affected family members. EBN2, the second locus for benign familial neonatal convulsions identified in 1993, has been mapped to chromosome 8q24 in a Mexican family of three generations with 14 affected members.[6] After a search of the expressed sequence tag database for homologues of KCNQ2, KCNQ3 was identified and subsequently localised to the EBN2 crucial region.[7] A missense mutation (G → T) in KCNQ3 has been characterised in affected members of the original EBN2 family.

Benign familial infantile convulsions
Also an autosomal dominant idiopathic generalised epilepsy, this was described originally in an Italian family and has an onset of seizures between 3.5 and 12 months of age. In the search for a gene, several candidate genes (including EBN1) were first excluded by linkage analysis in five Italian families. The gene for benign familial infantile convulsions was subsequently mapped to chromosome 19q.[8]

Autosomal dominant nocturnal frontal lobe epilepsy
With a typical childhood onset of nocturnal motor seizures preceded by an aura, this syndrome is often misdiagnosed as night terrors. The familial tendency is easy to miss because there is a pronounced variation in severity among family members and the penetrance is approximately 70%. A large pedigree in southern Australia including 27 affected individuals over six generations showed linkage to 20q13.2.[9] The gene for the α4 subunit of the neuronal nicotinic acetylcholine receptor (CHRNA4) was known to map to the same chromosomal region, and also to be expressed in the frontal cortex. As an excellent positional candidate gene, mutational analysis was undertaken, and a DNA sequence variant in CHRNA4 was found that co-segregated with the disease in the Australian family.[10] The mutation converts a serine to phenylalanine in the M2 transmembrane domain, known to be the crucial structure mediating ionic permeability. A second mutation in the M2 domain, resulting in insertion of a leucine residue, has now been found in a Norwegian family with autosomal dominant nocturnal frontal lobe epilepsy.[11] However, not all families with this syndrome are linked to mutations in CHRNA4.

Generalised epilepsy with febrile seizures plus
First described in 1997 in a large Australian family, "febrile seizures plus" refers to a childhood onset of multiple febrile seizures with afebrile seizures and febrile seizures continuing beyond 6 years of age.[19A] Other phenotypes include absences, myoclonic seizures, atonic seizures, and myoclonic astatic epilepsy. In a second pedigree with generalised epilepsy with febrile seizures plus, the gene was mapped to chromosome 19q13.[12] The gene for the β1 subunit of the voltage gated sodium channel, SCN1B, also maps to this region. Mutational analysis identified a C → G substitution in SCN1B that segregated with the disease This mutation results in reduced modulation of the sodium channel function by the β1 subunit and possible neuronal hyperexcitability. Recently, a new locus for generalised epilepsy with febrile seizures plus has been identified on chromosome 2q21-q33 in a large French family.[13]

NON-MENDELIAN "COMPLEX" IDIOPATHIC EPILEPSIES

Juvenile myoclonic epilepsy
With a large proportion of affected individuals having a positive family history, this idiopathic generalised epilepsy has received much attention as a candidate for linkage studies. However, it exemplifies the difficulties that arise when investigating a disease with complex inheritance and genetic heterogeneity. Evidence has emerged both for and against a locus on chromosome 6p, EJM1.[15 16] A candidate gene approach in 34 European families with juvenile myoclonic epilepsy found evidence of linkage in the CHRNA7 region on chromosome 15q14.[14] CHRNA7 encodes the α7 subunit of the neuronal nicotinic acetylcholine receptor and mutational analysis is currently under way.

Febrile convulsions
At least 10% of patients have a positive family history of febrile convulsions or other epilepsies. Segregation analysis has suggested both multigenic and single major locus models. Linkage heterogeneity has been established, with evidence of linkage to both chromosome 8q13–21 and chromosome 19p13.3.[20 21] The syndrome of generalised epilepsy with febrile seizures plus has already been discussed.

Childhood absence epilepsy
Childhood absence epilepsy is a syndrome in which absence seizures (of any type except myoclonic absences) occur with an onset between 2 and 12 years of age and a typical electroencephalogram (EEG) showing bilateral, synchronous, symmetrical discharges of 2.5–4 Hz spike wave or polyspike wave complexes on a normal background. The genetic basis of childhood absence epilepsy is now well established, being supported by both family studies and animal models. Childhood absence epilepsy does not appear to follow a mendelian pattern of inheritance resulting from a single gene defect, although autosomal dominant inheritance has been shown for the EEG trait of bilaterally symmetrical 3 Hz spike and slow

wave complexes.[22] The phenotype of childhood absence epilepsy and tonic–clonic seizures with EEG 3–4 Hz spike and multispike slow wave complexes in a large Indian family has now been linked to chromosome 8q24.[17]

Six single locus mouse models for human spike wave epilepsy have been characterised. Disease causing mutations have now been described for five of the mutants. The tottering, lethargic, and stargazer genes encode voltage gated calcium channel subunits, the slow wave epilepsy mutant involves the Na^+/H^+ exchanger gene, and the mocha gene encodes an adapter related protein δ subunit gene.[23–27] The homologous genes in humans provide some excellent candidates for a positional candidate approach to childhood absence epilepsy.

Juvenile absence epilepsy
Juvenile absence epilepsy has an onset between 12 and 26 years, with a lower seizure frequency than childhood absence epilepsy and a more common association with generalised tonic–clonic seizures. Familial clustering of juvenile absence epilepsy with childhood absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalised tonic–clonic seizures on awakening suggests a shared genetic predisposition of these idiopathic generalised epilepsies. Allelic association of juvenile absence epilepsy with a glutamate receptor gene (GRIK1) polymorphism has been demonstrated in 20 families.[18]

BENIGN EPILEPSY WITH CENTEROTEMPORAL SPIKES
This syndrome, also known as benign rolandic epilepsy, is the most common idiopathic epilepsy syndrome in childhood. A study of 22 families with benign epilepsy with centerotemporal spikes found evidence of linkage to chromosome 15q14 with genetic heterogeneity.[19] The same chromosomal area has been linked to juvenile myoclonic epilepsy (see above).

Symptomatic epilepsies
PROGRESSIVE MYOCLONIC EPILEPSIES
Progressive myoclonic epilepsies account for about 1% of all epilepsies occurring in childhood and adolescence. They are characterised by evolving myoclonias, seizures (myoclonic, tonic–clonic, and partial) and neurological deterioration involving cerebellar and higher neurological function.

Mendelian progressive myoclonic epilepsies
(1) *Unverricht–Lundborg disease* (Baltic myoclonus, Mediterranean myoclonus) is an autosomal recessive progressive myoclonic epilepsy with a high prevalence in Finland (one in 20 000 births), which has been mapped to chromosome 21q22.3.[28] The gene, CSTB (or EPM2), was identified by a positional cloning approach, and encodes cystatin B, a cysteine protease inhibitor.[29] About 14% of patients have mutations within the coding region of the gene. An unstable repeat expansion of 12 base pairs in the 5' untranslated region is found in most cases.[30] Instead of the normal two to three copies, more than 60 repeats are found in the mutant alleles, resulting in disrupted transcription and reduced amounts of cystatin B mRNA. In mice with myoclonic seizures and ataxia, in which the cystatin B gene has been knocked out, there appears to be a link between reduced cystatin B and apoptotic cerebellar cell death.[31]

(2) *The neuronal ceroid lipofuscinoses* are a group of at least 10 neurodegenerative disorders characterised by the accumulation of autofluorescent lipopigment in neurons and other cell types. All the childhood onset types exhibit autosomal recessive inheritance. They are the most common cause of childhood neurodegenerative disease and are all characterised by seizures and progressive cognitive, motor, and visual deterioration. The subtypes exhibit differing age of onset, clinical course, and histological features, with the most common form being juvenile neuronal ceroid lipofuscinosis. Six genes have been mapped and four cloned, with at least two more to be identified (table 2).[32–41]

(3) *Lafora disease* is diagnosed by the presence of characteristic polyglucosan inclusions (Lafora bodies) on skin biopsy. This autosomal recessive progressive myoclonic epilepsy is characterised by an onset in adolescence with a rapid neurological and cognitive decline towards death. After mapping of the disease locus to 6q24, the gene, EPM2A, was identified by a positional cloning approach.[42] This encodes laforin, a protein tyrosine phosphatase that regulates intracellular concentrations of phosphotyrosine.

Non-mendelian "complex" progressive myoclonic epilepsies
Myoclonic epilepsy and ragged red fibres (MERRF) is a mitochondrial disorder that is diagnosed histologically by the presence of

Table 2   Genes implicated in neuronal ceroid lipofuscinoses (NCL)

NCL type	Inheritance	Gene location	Gene	Gene product	References
Infantile	AR	1p32	CLN1	Palmitoyl protein thioesterase (PPT)	33
Classic late infantile	AR	11p15	CLN2	Lysosomal pepstatin insensitive protease	34
Finnish late infantile	AR	13q21–32	CLN5	Novel membrane protein	35
Variant late infantile	AR	15q21–23	CLN6	Unknown	36
Turkish variant late infantile	AR	Unassigned	CLN7	Unknown	37
Late infantile with GRODs	AR	1p32	CLN1	PPT	38
Juvenile	AR	16p12	CLN3	Novel membrane protein	39
Variant juvenile with GRODs	AR	1p32	CLN1	PPT	40
Progressive epilepsy with mental retardation	AR	8p23	CLN8	Novel membrane protein	41

GROD, granular osmiophilic deposits.

ragged red fibres (subsarcolemmal accumulation of mitochondria) on skeletal muscle biopsy. Dementia and sensory symptoms, particularly deafness, can occur several years before the onset of seizures, myoclonus, and ataxia. A study of the mitochondrial DNA of four patients with this syndrome from three different families found a heteroplasmic A → G mutation (varying proportions of mutant DNA between individuals) in position 8344.[43] This mutation, as well as a second mutation found in the same gene, causes premature termination of translation of mitochondrial mRNAs, reduced polypeptide synthesis, and reduced activity of respiratory chain complexes I and IV in skeletal muscle.[44 45]

Discussion

Most progress has been made in the analysis of mendelian epilepsies, which are more susceptible to the powerful gene cloning approaches developed in the past decade. This has allowed new classifications based on molecular genetics and has led to new DNA based diagnostics. However, these account for a very small proportion of children with epilepsy and the therapeutic impact is limited at present. The major challenge in the future is the identification of susceptibility genes for the common familial epilepsies, such as childhood absence and juvenile myoclonic epilepsy. The confounding factors are not inconsiderable. What exactly is the relation between a particular combination of genes (the genotype) and an epilepsy syndrome (the phenotype)? Can a particular phenotype arise from more than one genotype (genetic heterogeneity), and can the same genotype be expressed differently among family members (genetic variability). How many susceptibility genes are there, how important is the contribution of any single gene, and what role do environmental factors play? Recent successes in complex diseases such as insulin dependent diabetes mellitus and Alzheimer's disease demonstrate that the problems are not intractable. These projects require hundreds of families to reveal small genetic contributions to the disease, and cooperation among clinicians and molecular geneticists is essential. Progress in sequencing the human genome together with the identification of common DNA sequence variations between individuals will make an important contribution. As in other complex diseases, knowledge of the genetic basis of the rare forms of epilepsy certainly provide insights into the causes of the common familial epilepsies. Ultimately, success will provide a greater understanding of the physiological defect underlying a particular epilepsy, such as disruption of ion channel function, which should result in improved diagnosis and the development of new targets for antiepileptic drugs.

It is probably not too fanciful to suggest that within the next decade the molecular basis of the common familial idiopathic epilepsies will be understood and that a revolution in the management of childhood epilepsy will ensue. DNA from a buccal swab will be analysed using a microarray (chip) designed to test for common mutations in, say, 50 ion channel genes. A precise molecular diagnosis will be made and an antiepilepsy drug prescribed that will be designed specifically for the particular electrophysiological dysfunction present. The EEG might become a redundant investigation, albeit of historical interest.

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