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Genes and Epilepsies

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Epidemiological studies from the South Asian region are scarce to determine the exact prevalence and incidence of epilepsy. The worldwide prevalence of epilepsy is 5 to 10 per 1000, making it the second most common cause of mental disability among young adults, with a lifetime cumulative incidence of 3%. Genetic factors play a role in at least 40-50% of cases. A high frequency of consanguinous marriages probably increases the tendency towards genetically inherited forms of epilepsy.

Over the last decade, a number of mutant genes have been identified that give us clues towards a better understanding and a more meaningful classification of inherited epilepsies. Molecular genetics research in ion channel diseases (so-called channelopathies) can be expected to lead to newer and better anti-epilepsy drugs with fewer adverse reactions and greater efficacy in seizure reduction. Appropriate prenatal counseling may also improve quality of life in patients with epilepsy.

Knowledge of genes in epilepsy has been gained by studying pedigrees in familial aggregation studies, twin studies, and genetic animal models. Epileptic syndromes can be monogenic or polygenic, inherited in simple mendelian or complex inheritance patterns. This article is an overview of identified gene loci and mutant ion channels in idiopathic generalized and partial epilepsies.

EPILEPTIC CHANNELOPATHIES

Epileptic seizure can be caused by excessive excitation, impaired inhibition, and faulty regulation of the membrane resting potential. Ion channels expressed in the brain are ideal candidates for mutational polymorphisms in a given family or population. Table 1 summarizes ion channels implicated in epilepsy.

IDIOPATHIC GENERALIZED EPILEPSIES (IGE)

The majority of idiopathic generalized epilepsies display a complex inheritance pattern. This common group of epilepsies constitutes mendelian (monogenic) as well as non-mendelian patterns of inheritance. Relatives of probands with IGE have a 5-8% risk of developing epilepsy. Two or more different IGE phenotypes are frequently found within a single pedigree; this suggests that there are susceptibility loci common to all IGEs. A common locus or group of loci may determine the seizure threshold, with additional loci contributing further phenotypic specificity.

NON-MENDELIAN IGE

Juvenile myoclonic epilepsy

JME has complex polygenic inheritance, and constitutes about 10% of IGE. Disease onset is usually between age 9-25 years, presenting with early morning myoclonus. Almost 90% have generalized tonic-clonic seizures and almost 20% have absence seizures with typical polyspike and slow wave complexes seen on EEG. Loci have been mapped to EJM1 on chromosome 6, which predisposes to JME. There has been advancement in linkage studies in 34 European families and linkage found in the region of CHRNA7 region in chromosome 15q14. Five missense mutations have recently been identified in EFHC1 in 6 of 44 families with JME. This gene maps to 6p12-p11 and encodes a protein with an EF-hand motif (a calcium-binding protein motif comprised of two helices joined by a loop) that may have a role in apoptosis. Three different mutations in the voltage-gated chloride channel CLCN2 CI-1 have also been found in families with the JME phenotype.
Absence epilepsy in children and adolescents

Absence epilepsies also have complex inheritance. Childhood absence epilepsy (CAE) starts in school-going children who typically have 10-200 episodes per day, precipitated by hyperpnea, taking the form of absences and atypical absences. EEG reveals typical 3 Hz spike and slow wave discharges. Juvenile absence epilepsy (JAE) is similar but starts around puberty with absences on awakening and with similar EEG findings. Mutations in the CLCN2 voltage-gated chloride channel and GABA\textsubscript{A} receptors have been identified.\textsuperscript{11,12}

A recent study provided evidence of linkage of CAE with tonic-clonic seizures and EEG 3-4 Hz spike and multi-spike slow-wave complexes to chromosome 8q24. Two-point linkage analysis assuming autosomal-dominant inheritance with 50% penetrance gave a Zmax of 3.6 at D8S502 in a five generation family from India.\textsuperscript{13} Suggestive evidence of linkage to CACNG3 and the GABA receptor gene cluster on chromosome 15q has been obtained\textsuperscript{12} and mutations were recently identified in CACNA1H in Chinese patients.\textsuperscript{14}

Epilepsy with GTCS on awakening

This form of epilepsy starts in adolescence, with seizures occurring on awakening. Factors that precipitate these forms of seizures are sleep deprivation, excessive alcohol consumption and forced waking. Early morning myoclonus and absences can occur signifying a continuum with JME, CAE, and JAE. Mutations in CLCN chloride channels and GABA\textsubscript{A} receptors have been identified.\textsuperscript{11,12}

MENDELIAN IGE

Benign familial neonatal convulsions (BFNC)

BFNC is a rare, autosomal dominant idiopathic epilepsy. Seizures can start in newborns from the third day of birth and can go on for 6-8 weeks. Seizures are mainly generalized, although they can have focal features as well. Seizures may recur later in life in up to 10% of cases. Locus to be identified by linkage analysis, designated EBN1, was found on chromosome 20q in a four-generation family with 19 individuals with BFNC.\textsuperscript{15} A

Table 1: Ion channels and receptors implicated in inherited epilepsies.

<table>
<thead>
<tr>
<th>Channel Receptor</th>
<th>Gene</th>
<th>Locus</th>
<th>Mutation</th>
<th>Epileptic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium Channel</td>
<td>KCNQ2</td>
<td>20q13</td>
<td>Missense, truncation</td>
<td>BFNC, Myokymia</td>
</tr>
<tr>
<td></td>
<td>KCNQ3</td>
<td>8q24</td>
<td>Missense</td>
<td>FS, CTE, GIE, BFNC</td>
</tr>
<tr>
<td></td>
<td>KCNA1</td>
<td>12p13</td>
<td>Missense</td>
<td>EA Type 1, IPE</td>
</tr>
<tr>
<td>Chloride Channel</td>
<td>CLCN2</td>
<td>3q26</td>
<td>Missense, truncation splicing</td>
<td>CAE, JAE, JME, Mutational grand mal epilepsy</td>
</tr>
<tr>
<td>GABA\textsubscript{A} Receptor</td>
<td>GABRA1</td>
<td>5q34</td>
<td>Missense</td>
<td>Myoclonic epilepsy</td>
</tr>
<tr>
<td></td>
<td>GABRG2</td>
<td>5q34</td>
<td>Missense, truncation</td>
<td>GEFS+, JAE</td>
</tr>
<tr>
<td>Sodium Channel</td>
<td>CN51A</td>
<td>2q24</td>
<td>Missense, nonsense, truncation, splicing</td>
<td>GEFS+, SMEI</td>
</tr>
<tr>
<td></td>
<td>CN52A</td>
<td>2q24</td>
<td>Missense</td>
<td>GEFS+, BFNC</td>
</tr>
<tr>
<td></td>
<td>CN51B</td>
<td>19q13</td>
<td>Missense</td>
<td>GEFS+, JAE</td>
</tr>
<tr>
<td>Acetylcholine Receptor</td>
<td>CHRNA4</td>
<td>20q13</td>
<td>Missense, Insertion</td>
<td>ADNFLE</td>
</tr>
<tr>
<td></td>
<td>CHRN82</td>
<td>1p21</td>
<td>Missense</td>
<td>ADNFLE</td>
</tr>
<tr>
<td>Na/K Transporter (active transporter)</td>
<td>ATP1A2</td>
<td>1q21</td>
<td>Missense, truncation</td>
<td>BFNC</td>
</tr>
</tbody>
</table>

second locus EBN2 has been identified on chromosome 8q. The genes for EBN1 and EBN2 were both identified as voltage-dependent potassium channels, KCNQ2 and KCNQ3.

**Generalized epilepsy with febrile seizures plus (GEFS+) and severe myoclonic epilepsy of infancy (SMEI)**

GEFS+ is an autosomal dominant epilepsy. The phenotype comprises childhood onset of multiple febrile seizures persisting beyond the age of 6 years, along with absences, myoclonic seizures, atonic seizures, and rarely, myoclonic-astatic epilepsy. A large Australian GEFS+ family was mapped to chromosome 19q13.1, and a point mutation identified in SCN1B. Two French families with GEFS+ were then mapped to chromosome 2q24, and mutations were identified in SCN1A.

De novo mutations in SCN1A have subsequently been identified in patients with severe myoclonic epilepsy of infancy (SMEI). SMEI was first described in 1978 by Dravet and is characterized by early normal development before the onset of seizures in the first year of life. Generalized or partial febrile seizures are followed by febrile seizures, including myoclonic, absence, tonic-clonic and partial seizures. Many patients with SMEI have a family history of seizures consistent with the spectrum of seizure phenotypes seen in GEFS+, suggesting that SMEI is the most severe phenotype in the GEFS+ spectrum. The GEFS+ phenotype is also caused by mutations in other genes. In two GEFS+ families, mutations have been identified in the GABAA receptor A- subunit gene, GABRG2.

**Autosomal-dominant juvenile myoclonic epilepsy**

GABA A receptors are the major site of fast synaptic inhibition in the brain, and dysfunction of this receptor has long been suspected in the development of epilepsy. A mutation of GABRA1 has recently been described in a large French-Canadian kindred with autosomal dominant segregation of a phenotype consistent with juvenile myoclonic epilepsy. All affected individuals had myoclonic and generalized tonic-clonic seizures with generalized polyspike-and-wave discharges on EEG. A genome scan provided evidence of linkage to chromosome 5q34 encompassing a cluster of GABA A receptor subunit genes: GABRB2, GABRA1, and GABRG2.

**IDIOPATHIC PARTIAL EPILEPSIES**

Localization-related epilepsy syndromes that occur in the absence of insult have been genetically recognized by familial aggregation and twin studies.
The mode of inheritance has been uncertain in certain epilepsy with occipital paroxysms and primary reading epilepsy. There are around 12 mutant genes that have been identified focal EEG abnormalities as the commonest, syndromes are commoner than once thought, or does idiopathic partial epilepsy have high prevalence in one or more subsets of the population.

CONCLUSION

Idiopathic epilepsies are the commonest category of epilepsy identified, mainly comprising generalized seizures. It is also interesting to note that gene loci have been identified for the idiopathic partial epilepsies. In contrast to this, a pediatric EEG database at our institution has identified focal EEG abnormalities as the commonest, representing 71.4% of abnormal EEGs between the ages 1-14 years. This study raises the still unresolved question whether symptomatic localization-related epilepsy syndromes are commoner than once thought, or does idiopathic partial epilepsy have high prevalence in one or more subsets of the population.

There are around 12 mutant genes that have been identified and implicated in idiopathic epilepsy. Multiple phenotypic expression in the same family suggests polymorphism, with other genes possibly implicated in phenotypic expression. Alternatively, there may be a high probability of influence from environmental factors. Although genes play an important role in the pathogenesis of epilepsy, genetic analysis is not recommended in sporadic cases. It sought only in families with a strong family history of epilepsy. It is expected that with time more genetic mutations and loci will be identified in the idiopathic epilepsies with complex inheritance.

REFERENCES

8. Prasad AN, Prasad C, Salfstrom CE. Recent advances in the genetics of epilepsy: insights from human and animal studies. Epilepsia 1999; 40:1329-52


