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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,<sup>1</sup> with a lifetime cumulative incidence of 3%.<sup>2</sup> Genetic factors play a role in at least 40-50% of cases.<sup>3,4</sup> 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.<sup>8</sup>

Knowledge of genes in epilepsy has been gained by studying pedigrees in familial aggregation studies, twin studies, and genetic animal models.<sup>5,6</sup> Epileptic syndromes can be monogenic or polygenic, inherited in simple mendelian or complex inheritance patterns.<sup>7</sup> 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.<sup>7</sup> 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.<sup>9</sup> 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.<sup>10</sup> Three different mutations in the voltage-gated chloride channel CLCN2 Cl<sup>-</sup> have also been found in families with the JME phenotype.<sup>11</sup>

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

Channel Receptor	Gene	Locus	Mutation	Epileptic Syndrome
Potassium Channel	KCNQ2	20q13	Missense, truncation	BFNC, Myokymia
	KCNQ3	8q24	Missense	FS, CTE, GIE
	KCNA1	12p13	Missense	BFNC
Chloride Channel	CLCN2	3q26	Missense, truncation splicing	EA Type 1, IPE
				CAE, JAE, JME, Mutational grand mal epilepsy
GABA <sup>A</sup> Receptor	GABRA1	5q34	Missense	Myoclonic epilepsy
	GABRG2	5q34	Missense, truncation	GEFS+, JAE
Sodium Channel	CNS1A	2q24	Missense, nonsense, truncation, splicing	GEFS+, SMEI
	CNS2A	2q24	Missense	GEFS+, BFNC
	CNS1B	19q13	Missense	GEFS+, JAE
Acetylcholine Receptor	CHRNA4	20q13	Missense, Insertion	ADNFLE
	CHRN2	1p21	Missense	ADNFLE
Na/K Transporter (active transporter)	ATP1A2	1q21	Missense,	BFIC

BFNC: Benign familial neonatal convulsion, FS: Febrile Seizure, CTE: Centrotemporal Epilepsy, EA: Episodic Ataxia, IPE: Idiopathic Partial Epilepsies, CAE: Childhood absence epilepsy, JEA: Juvenile absence epilepsy, JME: Juvenile myoclonic epilepsy, JAE: Juvenile absence epilepsy with febrile seizure plus, SMEI: Severe myoclonic epilepsy of infancy, ADNFLE: Autosomal dominant nocturnal frontal lobe epilepsy

### Absence epilepsies 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<sup>A</sup> receptor have been identified.<sup>11,12</sup> 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 Z<sub>max</sub> of 3.6 at D8S502 in a five generation family from India.<sup>13</sup> Suggestive evidence of linkage to CACNG3 and the GABA receptor gene cluster on chromosome 15q has been obtained<sup>12</sup> and mutations were recently identified in CACNA1H in Chinese patients.<sup>14</sup>

### 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<sup>A</sup> receptors have been identified.<sup>11,12</sup>

### 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.<sup>15</sup> A

second locus EBN2 has been identified on chromosome 8q.<sup>16</sup> The genes for EBN1 and EBN2 were both identified as voltage-dependent potassium channels, KCNQ2 and KCNQ3.<sup>17,18</sup>

### **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.<sup>19</sup> Two French families with GEFS+ were then mapped to chromosome 2q24, and mutations were identified in SCN1A.<sup>20-22</sup>

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.<sup>23</sup> Generalized or partial febrile seizures are followed by afebrile 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.<sup>24</sup> The GEFS+ phenotype is also caused by mutations in other genes. In two GEFS+ families, mutations have been identified in the GABA<sup>A</sup> receptor  $\alpha$ -subunit gene, GABRG2.<sup>25,26</sup>

### **Autosomal-dominant juvenile myoclonic epilepsy**

GABA<sup>A</sup> 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.<sup>27</sup> 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<sup>A</sup> 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

### **Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)**

ADNFLE is a dominantly inherited disorder with high penetrance (70-80%),<sup>28,29</sup> characterized by seizures of short duration occurring during slow-wave sleep. There is a large amount of phenotypic variation seen in different families. Seizures can start as tremors, grunts or vocalizations, and are sometimes preceded by an aura. Seizures are mostly partial but can secondarily generalize, and usually appear in the first or second decade of life. A mutation has been found in the gene for the alpha 4 subunit of the neuronal acetylcholine receptor (CHRNA4).<sup>30,31</sup> Further loci have been found in genes encoding subunits of the nicotine acetylcholine receptor: alpha 3, alpha 5 and beta 4 (CHRNA3, CHRNA5, CHRNB4). Locus heterogeneity has been seen in genes encoding for the beta 2 subunit of the neuronal acetylcholine receptor (CHRNB2).<sup>30-34</sup>

### **Autosomal dominant partial epilepsy with auditory features (ADPEAF)**

This dominantly inherited epilepsy has been described in a few families. Almost 55% of cases have had auditory auras at onset. Chromosomal loci were identified at 10q22-24.<sup>35</sup> Partial seizure semiology manifested a lateral temporal lobe focus. EEG and SPECT scan pointed to an area of dysfunction in the lateral temporal lobes.

### **Familial partial epilepsy with variable foci**

This syndrome was described in a family with nocturnal seizures with epileptic foci from frontal, temporal and occipital lobes. This disease locus was mapped on chromosome 22q11-12.<sup>36</sup>

### **Benign epilepsy of childhood with centrotemporal spikes (BECTS)**

This condition starts between the ages of 3 and 13 years and stops spontaneously around 16 years of age. Seizure type can vary between brief motor, somatomotor, clonic, hemifacial or buccopharyngeal-laryngeal. It is usually sleep-related and responsible for anarthria. EEG shows abnormalities as the name explains; this condition is also called Benign Rolandic epilepsy. Linkage analysis has been found in the q14 region of chromosome 15. The alpha 7 subunit of the neuronal acetylcholine receptor (CHRNA7) is located in this region.<sup>37</sup>

### **Benign familial infantile convulsions (BFIC)**

Focal epilepsy starting in the first few months of life and having a good outcome has been described by Okumara<sup>38</sup> and Vigeveno<sup>39</sup> et al. Vanmolkot<sup>40</sup> has described a

genetic association between familial hemiplegic migraine and BFIC on the basis of mutations in the Na<sup>+</sup>/K<sup>+</sup> -type 2 ATPase pump (ATP1A2) in a family with patients getting migraine and also infantile convulsions between ages from 6 weeks upto 6 months.

The mode of inheritance has been uncertain in certain other epilepsies, including familial temporal epilepsy, Rolandic epilepsy and speech dyspraxia, childhood epilepsy with occipital paroxysms and primary reading epilepsy.

## 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<sup>41</sup> 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.

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