

# Genetics of epilepsy

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**Genetic factors are suspected to have greater influence in idiopathic than symptomatic epilepsies. There are over 200 individually rare, mendelian disorders in which seizures form part of their phenotype. These diseases, however, are few and account for only 1% of all epilepsies. Hereditary disorders with epilepsy can hence be classified according to the mechanisms of inheritance as: Mendelian disorders in which epilepsy forms a part of the phenotype, idiopathic epilepsies with mendelian inheritance, epilepsies with complex inheritance and idiopathic epilepsies associated with cytogenetic abnormalities. The role of genetics is not only restricted to epilepsy type but also influences various aspects of pharmacotherapy. The knowledge gained from pharmacogenetics hopes to predict therapeutic drug response and adverse drug reactions (ADRs). It now appears that genetic mechanisms contribute to refractoriness of pharmacotherapies via pharmacodynamic and kinetic mechanisms. Research into genetic aspects of pharmacodynamic and kinetic responses of an individual and prediction of ADRs is going to be an important area of forthcoming research. Knowledge of this aspect of epilepsy is expected to provide not only innovative therapies but also help in the prevention of epilepsies.**

A hereditary component to epilepsy has been suspected since the time of Hippocrates. Sushruta too in the Indian system of medicine – Ayurveda, emphasizes the role of hereditary influences in epilepsy<sup>1</sup>. It is now known that the genetic factors have greater influences in idiopathic than symptomatic epilepsies. There are over 200 individually rare, mendelian disorders in which epilepsy forms part of their phenotype. These diseases, however, are few and account for only 1% of all epilepsy. These include neurocutaneous, neurodegenerative, inherited metabolic disorders and inherited malformations of cortical development. These have helped but not contributed much towards understanding the basic mechanisms of human epileptogenesis. On the other hand, epilepsies with predominantly a complex genetic predisposition are common and account for about 50% of all genetically based epilepsies<sup>2</sup>.

## Genetic analysis

The vast evidence in favour of the existence of mutant 'epilepsy genes' has been derived from studies of fami-

lies with a clustering of specific forms of epilepsy. In all these studies, individuals with epilepsy within the family have been correlated with the inheritance of a specific DNA marker or a mutant gene. In other words it involves the matching of a specific 'phenotype' (epilepsy type) with a specific 'genotype' (mutant gene). A variety of such candidate genes and specific genetic markers have now been identified, that can be assayed in small blood samples. The other clue, for identification, is defining specific epileptic syndromes that follow a hereditary pattern in the population<sup>3-5</sup>. The study of families with common phenotypes (homogenous pedigrees) by modern molecular biology techniques is essential to such progress (Figure 1). One approach for identifying potential gene mutations believed to cause human epilepsies is restriction fragment length polymorphism (RFLP) analysis. In this method, probes are used to analyse the DNA from families in which epilepsy is inherited. The other approach is to identify *candidate* epilepsy genes in animals, and search for their homologous counterparts in humans.

## Twinning and epilepsy

An important technique to address the genetics of complex disorders such as epilepsy is the study of twin samples. In one such large study of 253 twin pairs in whom one or both reported seizures, monozygous (MZ) pairs were more concordant for seizures than dizygous (DZ) pairs<sup>6</sup>. In 94% of the concordant MZ pairs and 71% of concordant DZ pairs, both twins had the same major epilepsy syndrome. This was significantly more among MZ pairs in generalized epilepsies (both idiopathic and symptomatic) than partial epilepsies. The higher frequency of concordant MZ pairs with the same major syndrome suggested that there are syndrome-specific genetic determinants rather than a broad genetic predisposition to seizures. Berkovic *et al.* were first to report that twins do not have an increased risk of seizures and suggested that perinatal factors had little bearing on the etiology of common epilepsies in the community<sup>7</sup>. A study done at our center also supported evidence de-linking factors associated with twin birth (perinatal) from the causation of epilepsy among twins<sup>8</sup>. In a recent analysis of discordant MZ twins occult acquired factors, such as prenatal insults or genetic abnormalities resulting from postfertilization genetic processes were the main causes of seizures<sup>9</sup>.

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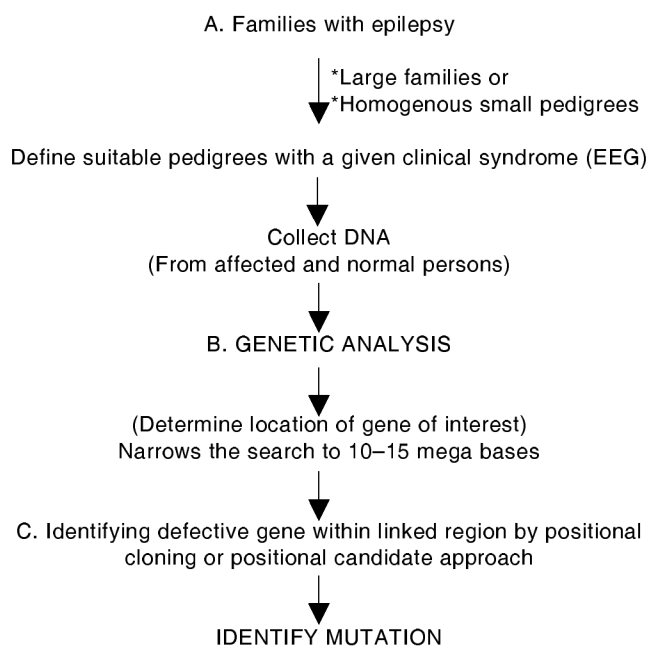


Figure 1. Key steps to finding genes.

The role of inheritance in epilepsy can hence be traditionally classified according to the mechanisms of inheritance to be as Mendelian disorders in which epilepsy forms a part of the phenotype, idiopathic epilepsies with mendelian inheritance, epilepsies with complex inheritance and idiopathic epilepsies associated with cytogenetic abnormalities.

## Genetics of idiopathic epilepsies

### *Idiopathic epilepsies with simple inheritance*

The inheritance of most idiopathic epilepsy syndromes is complex, few having a simple inheritance<sup>10</sup>. These are listed in Table 1 and some of them are discussed below. Benign familial neonatal convulsions (BFNC) was the first idiopathic epilepsy in which linkage analysis was successful in 1989. In 80% of cases seizures occur from about day 2 or 3 of life in otherwise normal neonates and recur every few days or weeks. About 11% have seizures later on in life. The seizures usually stop by 6 months of age. This autosomal dominant syndrome was initially linked to chromosome 20q (ref. 11). Subsequently discovery of a second linkage at 8q established a genetic heterogeneity<sup>12</sup>. In 1998 two novel potassium channel genes, *KCNQ2* and *KCNQ3*, were found at 20q and 8q loci respectively<sup>13</sup>. *KCNQ2* and *KCNQ3* are expressed in the brain. They contribute to the M current, which regulates the sub-threshold electrical excitability of neurons and determines their firing properties and responsiveness to synaptic inputs. The cause of the age dependence of BFNC may be due to specific developmental expression of these and

Table 1. Molecular genetics of idiopathic epilepsies

Epilepsy syndrome	Linkage	Gene
<i>Epilepsies with simple inheritance</i>		
Benign familial neonatal convulsions	20q	<i>KCNQ2</i>
	8q	<i>KCNQ3</i>
Benign familial infantile convulsions	19q	?
	16	?
Autosomal dominant nocturnal frontal lobe epilepsy	20q	<i>CHRNA4</i>
	15q	?
	1q	<i>CHRN2</i>
Familial partial epilepsy with auditory features	10q	?
	2q	?
Familial partial epilepsy with variable foci	22	
<i>Epilepsies with complex inheritance</i>		
Juvenile myoclonic epilepsy	6p	?
	15q	?
Idiopathic generalized epilepsy, unspecified	8q	?
	3p	?
Persisting absence with later myoclonic epilepsy	1p	?
Persisting absence with tonic clonic seizures	8q	?
Generalized epilepsy with febrile seizures plus	19q	<i>SCN1B</i>
	2q	<i>SCN1A</i>
Childhood absence and febrile seizures		<i>GABRG2</i>
	15q	?
Benign rolandic epilepsy	8q	?
Febrile seizures	19p	?
<i>Recently reported linkages</i>		
Infantile myoclonic epilepsy	16p	<i>AR</i>
Adolescent onset IGE	8	<i>CHRN3</i>

perhaps other potassium channel genes. Recently a substitution in the voltage sensor region of the potassium channel has also been described. This probably reduces the movement of the voltage sensor that precedes channel opening during voltage-dependent activation<sup>14</sup>.

The syndrome of benign familial infantile convulsions (BFIC) is an autosomal dominant epileptic disorder that is characterized by convulsions, with onset at age 3–12 months and a favourable outcome. Genetic heterogeneity with 19q (ref. 15) and chromosome 16 (peri-centromeric area) loci<sup>16,17</sup> exists. In families with the latter linkage, the affected individuals may have attacks of paroxysmal choreoathetosis (PCA) beginning by about 10 years of age. This is called the infantile convulsions and choreoathetosis (ICCA) syndrome. The exact gene is not yet recognized, but ion channel genes are suspected specially due to coexistence of the two BFIC and PCA.

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is characterized by epilepsy occurring anywhere from infancy to adult life, onset around 10 years being most common. The attacks mostly occur in sleep. Three mutations, one on chromosome 20q, 15q and the pericentromeric region of chromosome 1 have been described<sup>18–20</sup>. The latter locus is around a cluster of neuronal nicotinic subunits, which are mostly presynaptic

and regulate the release of neurotransmitters like glutamate and dopamine. Familial partial epilepsy with auditory features is an age-dependent syndrome with familial temporal lobe epilepsy. The classical hippocampal abnormality is not seen. It has been mapped to 10q. Candidate genes that may predispose the sensitivity to epilepsy in this region include those for adrenergic receptors, glutamate metabolism and a subunit of calcium-calmodulin protein kinase<sup>21</sup>. Familial partial epilepsy with variable foci can have seizure onset in childhood or adulthood. The first locus was mapped to 2q (ref. 22). This syndrome is characterized by mostly nocturnal seizures arising from frontal, temporal and occasionally occipital foci and has also been mapped to 22q. It is an autosomal dominant trait with incomplete penetrance<sup>23</sup>. The causative genes are still unknown.

#### *Idiopathic epilepsies with a complex inheritance*

Juvenile myoclonic epilepsy (JME) has been the most extensively studied epileptic syndrome without any definitive answers at the molecular level. This syndrome has the advantage of having a fairly homogenous phenotype with well-defined clinical and EEG features. JME and other forms of IGEs and abnormalities in EEG may also be found in clinically unaffected family members of probands. The lack of obvious exogenous factors in its etio-pathogenesis also makes it an ideal candidate for genetic studies. Although considered to be a single clinical syndrome, recent evidences suggest the existence of genotypic heterogeneity in JME because of phenotypic variability among probands and affected family members. Identification of its genes has been difficult probably because of the underlying genetic heterogeneity and analytical problems in disorders with complex inheritance.

Greenberg *et al.*<sup>24</sup> identified families through a patient of JME and genotyped markers throughout chromosome 6. Linkage analysis suggested heterogeneity. They also found evidence to suggest that JME may be predominantly maternally inherited and the HLA linked form is more likely to occur in families of European origin. The 6p locus itself has been variably located, either within the human leukocyte antigen region, just outside or quite distant from it. It appears likely that a variety of sets of genes may determine these phenotypes. Linkage to chromosome 6p was reported by a few other groups<sup>25</sup>. Another group found linkage to 15q and excluded the 6p locus in their families<sup>26</sup>.

In a large series, analysis of 369 probands with unequivocal clinical diagnosis of JME from the outpatient clinics of Neurosciences Center, AIIMS, New Delhi, India was very recently reported<sup>27</sup>. The basic clinical and EEG characteristics of the Indian probands were remarkably similar to those reported from other centers

of the world. Myoclonic jerks were noted in all 329 probands, 94% had generalized tonic clonic seizures. The one notable clinical difference among the Indian probands was a relatively reduced occurrence of absence seizures (9% versus 21%). The expression of JME in probands versus relatives was also slightly different. Myoclonic jerks as the only seizure type were seen in 26% relatives with JME as compared to 5% JME probands. This was probably because the relatives having only myoclonic jerks were diagnosed as JME as one of their relatives (the proband) had JME. None of the relatives diagnosed as JME had absence seizures or febrile convulsions (FC) while 5% of the probands had a history of febrile convulsions.

Six per cent of all persons with JME had myoclonic jerks as the only seizure type. The issue of JME presenting as only myoclonic jerks has been discussed in detail and it has been suggested that those cases having only myoclonic jerks and a first degree relative with definite JME, should be classified as 'affected' for molecular studies, as it may be incorrect to diagnose JME in everyone who gets a few jerks once in a while<sup>28</sup>. A small fraction of our JME patients (12%) required another AED besides valproic acid (VPA) and this might be another aspect of the syndrome that needs to be looked into. A photoparoxysmal response was seen in 9% of the probands. All patients with EEG photosensitivity had eventually responded only to VPA. EEG photosensitivity and response to VPA appear to segregate together in Indians and could be another evidence to support heterogeneity in JME<sup>29</sup>.

In a study of IGEs including JME, epilepsy with only GTCS occurring randomly during the day (random grand mal) or on awakening (awakening grand mal), and juvenile absence epilepsy (JAE), an evidence of linkage to chromosome 8 in adolescent onset IGE (AOIGE) was present in families in which JME was not present<sup>30</sup>. Localization to the beta 3-subunit of the nicotinic acetylcholine receptor (CHRN3), makes this gene a possible candidate for the specifications of AOIGE. The linkage of JME to this region was excluded. These results further indicate a genetic heterogeneity within IGEs. A genome scan in 91 families ascertained through a proband with adolescent-onset IGE was done. The IGEs included juvenile myoclonic epilepsy (JME), juvenile absence epilepsy (JAE), and epilepsy with generalized tonic clonic seizures (EGTCS). The linkage results supported an oligogenic model for IGE, with strong evidence for a locus common to most IGEs on chromosome 18. The other loci that may influence specific seizure phenotypes for different IGEs were a previously identified locus on chromosome 6 for JME. A locus on chromosome 8 influencing non-JME forms of IGE and two newly discovered loci for absence seizures have been reported on chromosome 5. These data suggest that the genetic classification of different forms of

IGE is likely to cut across the clinical classification of subforms of IGE. The authors hypothesized that interactions of different combinations of these loci produce the related heterogeneous phenotypes seen in IGE families<sup>31</sup>.

Benign adult familial myoclonic epilepsy (BAFAME) is an AD idiopathic epilepsy syndrome characterized by adult onset, non-progressive course tremulous finger movements, myoclonus, and epileptic seizures. Linkage analysis localized the gene to 8q (refs 32, 33). This region contains the KCNQ3 potassium channel subunit gene.

Generalized epilepsy with febrile seizure plus (GEFS) is another hereditary IGE syndrome with heterogeneous phenotypes and a complex inheritance<sup>34</sup>. In some pedigrees an autosomal dominant pattern is obvious. Mutation of the gene for beta 1 subunit of voltage-gated sodium channel (SCN1B) has been reported with mapping on to 19q (ref. 35). A subsequent disruption of a critical disulphide bridge in the beta-1 subunit, which in turn interferes with the ability of the unit to modulate sodium channel gating may result in epilepsy. Very recently, 2 new mutations have been described – one linked to chromosome 2q (ref. 36). This is in the region of the gene encoding the neuronal voltage-gated sodium channel (SCN1A). The other is a unique mutation in the GABA (A) receptor gamma2-subunit gene (GABRG2) that provides the first genetic evidence that a GABA(A) receptor is directly involved in human idiopathic epilepsy<sup>37</sup>.

Benign rolandic epilepsy is an age-dependent syndrome with predilection to a particular epoch in life. It also has a complex inheritance. Linkage studies are difficult, as large pedigrees are difficult to find. A linkage to chromosome 15q has been recently reported for the centrotemporal epileptiform abnormalities<sup>38</sup>. An AR syndrome mapped to chromosome 16 has been identified in which patients are affected by rolandic-type motor seizures, writer's cramp (both right handed) and exercise-induced dystonia<sup>39</sup>.

The infantile spasm syndrome, although distinct phenotypically, is etiologically heterogeneous. Linkage to Xp21-Xp22 regions has been cited. Data now supports a multifactorial model involving polygenic determination of susceptibility. Additional environmental factors such as anoxia, birth trauma, or immunization are triggers for the manifestation. Reports of occurrence of this syndrome in monozygotic twins and in multiple sibships helped in localizing this to the Xp21-22 region<sup>40</sup>. Another recessive idiopathic myoclonic epilepsy starting in early infancy as myoclonic seizures, febrile convulsions, and tonic-clonic seizures was mapped by linkage analysis to 16p. This is the first report of an idiopathic epilepsy inherited as an autosomal recessive trait<sup>41</sup>. Interestingly the voltage-dependent chloride channel gene is also located near this region.

Childhood absence epilepsy (CAE) is said to account for 5 to 15% of idiopathic generalized childhood epilepsies. There are at least 3 sub-types of this syndrome. The first accounts for approximately 40 to 60% of CAE patients, is characterized by absence seizures as the sole phenotype and remits spontaneously during adolescence. The second, which accounts for another 40% of CAE patients, persists into adolescence and adulthood, during which patients develop tonic-clonic seizures. The third accounts for a smaller percentage (10%) of CAE patients and is characterized by the development of tonic-clonic and myoclonic seizures during adolescence, after the onset of absences in childhood. The chromosomal locus of the persisting form of childhood absence epilepsy has been reported on 8q (ref. 42). A mutation in a gene encoding a GABA (A) receptor subunit in a large family with CAE and febrile seizures (FS) has been recently reported<sup>43</sup>. GABRB3 mutation is also documented<sup>44</sup>.

### Genetics of febrile seizures

Febrile seizures (FS) is the commonest form of convulsive disorder occurring in 3–5% of children from 3 months to 5 years of age. In large families, the FS susceptibility trait is inherited by the AD pattern with reduced penetrance<sup>45,46</sup>. In other families, the inheritance appears to be multifactorial. Recent linkage studies provide evidence that regions of chromosome 8 and 19 contain febrile convulsions (FC) susceptibility genes<sup>47,48</sup>. Febrile seizures and convulsions may be caused by a mutation in several genes. Four loci FEB1 on 8q, FEB2 on 19p, FEB3 on 2q (ref. 49) and FEB4 on 5q (ref. 50) have been identified.

Rich *et al.*<sup>51</sup> performed complex segregation analysis of 467 nuclear families ascertained through probands with febrile convulsions, this rejected a single major locus model. However when segregation was done on the basis of frequency of febrile convulsions in the probands, significant heterogeneity was noted. A polygenic mode was seen in families of probands with a single febrile convulsion. In families of probands with multiple FC, a single-major locus mode was dominant. In other families the inheritance appears to be multifactorial.

### Genetics of familial mesial temporal lobe epilepsy

Twenty-two unrelated families with at least two individuals with mesial temporal lobe epilepsy (MTLE) were identified by clinical and EEG findings in a large study<sup>52</sup>. Ninety-eight individuals with history of seizures were evaluated. Sixty-eight patients fulfilled the diagnostic criteria for MTLE. The authors concluded that familial MTLE is a clinically heterogeneous syn-

drome. Hippocampal atrophy was observed in 57% of patients, including those with benign course or seizure remission, indicating that the relationship between hippocampal atrophy and severity of epilepsy might be more complex than previously suspected. In addition, these findings indicated the presence of a strong genetic component determining the development of mesial temporal sclerosis in these families.

### Genetics of status epilepticus

The role of genetics in status epilepticus (SE) has already been demonstrated in some rare epilepsy syndromes associated with prolonged seizures. A mitochondrial cytopathy presenting as hereditary sensory neuropathy and progressive external ophthalmoplegia, ataxia, and fatal myoclonic SE has been described in six patients from three separate families<sup>53</sup>. A very unusual chromosomal anomaly known as ring chromosome 20 has been associated with a characteristic form of nonconvulsive SE in a small number of patients<sup>54</sup>. Corey *et al.* studied data from a twin registry that provided very compelling evidence in support of a genetic basis for SE. The concordance rate for SE was higher in the monozygotic twins than in the dizygotic twins<sup>55</sup>.

### Genetics of syndromes manifesting with seizures

There are a number of conditions with a simple inheritance in which seizures are part of a phenotype of varied manifestations. Most of these are associated with significant neurological morbidity and are unlikely to be relevant to the causation of idiopathic epilepsies.

#### *Unverricht–Lundborg disease*

This is a progressive myoclonus epilepsy (EPM1) with onset of seizures occurring between 6 and 13 years of age. Myoclonus begins 1 to 5 years later and eventually dementia develops. Cerebellar signs are present late in the course, which usually is 10 to 20 years in duration. A mutation in the cystatin B gene results in this syndrome<sup>56</sup>. It is inherited as a recessive trait and appears to be due to the result of decreased amounts of cystatin B (also called Stefin B). This is a small protein that is a member of the superfamily of cysteine protease inhibitors. Though widely distributed, it is localized mostly intracellularly. It probably acts as a protector against the proteases of the cathepsin family leaking from lysosomes. Despite the ubiquitous expression of this protein, it is not understood why mutation of the gene encoding cystatin B causes the symptoms of EPM1. Linkage to markers in the distal part of chromosome 21 has been found.

#### *Lafora disease (EPM2A)*

Onset of this disease is marked by grand mal seizures and/or myoclonus at about age of 15 years. Rapid and severe mental deterioration ensues, often with psychotic features. The affected seldom survive for more than 10 years. Histologic study of the brain shows Lafora bodies (which may also be demonstrable on muscle and liver biopsy). Intracellular Lafora bodies suggesting amyloid are found in the brain and similar inclusions can be seen in the cells of the heart and liver. The Lafora material has the properties of an acid mucopolysaccharide and is a polyglucosan in nature. A region on chromosome 6q was identified by linkage for EPM2A; this encodes for a protein indicative of a protein-tyrosine phosphatase (PTP). Tyrosine phosphatase mutations probably cause deleterious effects in the putative gene product, named 'laforin', which is a cell membrane and endoplasmic reticulum-associated protein that it is a functional PTP<sup>57</sup>. The gene inactivated in this disorder<sup>58</sup> may be important in the control of glycogen metabolism, thus accounting for the glycogen-like intracellular inclusion bodies (Lafora bodies).

#### *Sialodosis type 1 or cherry-red spot myoclonus*

This results from a mutation in the gene encoding glycoprotein specific alpha neuraminidase on chromosome 6p (ref. 59). *Neuronal ceroid lipofuscinosis* manifests with seizures, motor disturbances, visual impairment and dementia. Several genetically distinct subgroups have been identified with different age of presentation and the appearance of the intracellular lipopigment. The gene for the infantile form CLN1 is located on chromosome 1p and encodes palmitoyl-protein thioesterase, a lysosomal enzyme involved in lipid modification of protein<sup>60</sup>. The gene for the classic late infantile form CLN2, maps to 11p, mutations in the gene encoding a pepstatin-insensitive lysosomal peptidase have been identified<sup>61</sup>. The juvenile type (Batten disease) CLN3 localizes to 16p and codes for a protein whose function is not yet known but is probably a lysosomal membrane protein<sup>62</sup>. The Finnish variant, CLN5 is a subtype of the late infantile form maps to chromosome 13q and the gene codes for a polypeptide of unknown function<sup>63</sup>. A neuroserpin mutation associated with progressive myoclonus epilepsy has also been reported<sup>64</sup>.

#### *MERRF*

This is a prototype of a mitochondrial disorder. An adenine to guanine transition mutation at nucleotide pair 8344 in the mitochondrial DNA (mtDNA) has been identified<sup>65</sup>. However, the mutation is not present in about 20% of cases, suggesting genetic heterogeneity.

The PMEs provide a paradigm for a common phenotypic expression, for multiple defects such as, (a) those occurring at the molecular level resulting in myoclonic seizures, (b) defects in neuronal energy production [MERRF], (c) those due to neuronal degeneration from storage [sialodosis, CLN3, EPM2] and (d) proteolytic mechanisms [EPM1].

### *Inherited developmental cortical malformations*

Familial subcortical band heterotopia is due to a brain-specific gene mutated in Xq and this results in double cortin dysfunction, which is responsible for neuronal migration. This results in a double cortex syndrome in heterozygous females and in an X-linked dominant lissencephaly in hemizygous males<sup>66</sup>. Familial periventricular heterotopia is inherited as dominant trait and was mapped to Xq by linkage analysis in one family. Males with the gene mutation die during early embryogenesis. Remarkably, most females with the disorder show normal intelligence but suffer from seizures and various extra-CNS manifestations, especially relating to the vascular system such as patent ductus arteriosus and coagulopathy. The neurons that fail to migrate into the developing cerebral cortex, remain as nodules that line the ventricular surface. They presumably represent those cells that carry the mutation due to X inactivation. The gene codes for filamin-1, which encodes an actin-crosslinking phosphoprotein that transduces ligand-receptor binding into actin reorganization that is required for migration of many cell types<sup>67</sup>.

### **Channelopathies and epilepsy**

Epilepsy susceptibility genes are voltage-gated and ligand-gated ion channels. A recently recognized etiology of epilepsy in the developing and mature central nervous system is due to inherited disorders of these voltage-gated ion channels<sup>68</sup>. Two human epilepsy syndromes, BFNC and GEFS+ represent K<sup>+</sup> and Na<sup>+</sup> channelopathies. Other newly-defined syndromes have also been mapped to chromosomal regions that are rich in ion channel genes. Table 2 lists the epilepsies identified as channelopathies in humans and mouse models. The *potassium channel* contributes to the native M current (muscarinic current) found in many neurons, including hippocampal pyramidal neurons. This current controls membrane excitability by being the only sustained current in the range of action potential initiation. Disruption of M-current function via mutations in either KCNQ2/Q3, as found in BFNC, may lead to a decrease in inhibitory electrical activity in the brain and result in seizures. The *sodium channel* mutations may in turn produce abnormal depolarization and may lower seizure threshold in the brain. The expression of these channels

is seen selectively in the mRNA of neurons within limbic regions susceptible to epilepsy. *Calcium channels* on the other hand, are important in modulation of membrane excitability, transmitter release and gene expression – mutations could hence alter these functions<sup>69</sup>. A report of a mother and son both having continuous motor unit activity (CMUA) and associated with epileptic seizures disclosed a G724C point mutation in the potassium channel *KCNA1* gene<sup>70</sup> implicating a common cause for the same. The ring-chromosome 20-(r20) syndrome is an infrequent chromosopathy, which is associated with epileptic seizures, behaviour disorders and mental retardation. Two genes related to epileptic channelopathies (*CHRNA4* and *KCNQ2*) have been described on the same chromosome, suggesting the hypothesis that this may be an epileptic channelopathy<sup>71</sup>.

### **Animal models**

A significant contribution to the understanding of epilepsy mechanisms has come from animal models. Many animal models are well characterized in seizure morphology, EEG features, neuropathology and response to AEDs. Spontaneous epileptic mutants are found among diverse species, from rodents to primates. Some of these involve a single gene (trotting and lethargic) or multiple genes (genetically epilepsy-prone rats). In these the epilepsy phenotype was a starting point to discover the genes responsible for cortical hyperexcitability. In the past few years genetically engineered transgenic mice have allowed the reverse approach, i.e. by altering a specific gene, one can evaluate its contribution to the epilepsy phenotype. A number of such models have now emerged<sup>72</sup>.

**Table 2.** Channelopathies and epilepsy

Channels	Chromosome	Epilepsy phenotype
<i>K<sup>+</sup> channels</i>		
KCNQ2	20q	EBN1, BFNC
KCNQ3	8q	EBN2, BFNC
KCNQ1	12p	EAI, partial epilepsy
KCNA1		FCMUAE n3
KCNA1	6 (mouse)	Tonic/clonic seizures
<i>Na<sup>+</sup> channels</i>		
SCN1B	19q	GEFS+
SCN1A	2q	GFES+
<i>Ca<sup>++</sup> channels</i>		
CACNB4		Epilepsy and episodic ataxia
CACNALA	8 (mouse)	Gen. spike wave absence
CACNB4	2 (mouse)	Gen. spike wave absence
CACNG2	15 (mouse)	Gen. spike wave absence
CACNA2D	5 (mouse)	

## Epilepsy and pharmacogenetics

No two people respond to a given drug in the same manner. This is because of inherited differences to drug sensitivity. Pharmacogenetics aims to predict therapeutic drug response and adverse drug reactions. It is now clear that genetic mechanisms contribute to refractoriness via pharmaco-dynamic and kinetic mechanisms<sup>73</sup>. The difference in the pharmacodynamic response to antiepileptic drugs (AEDs) might be influenced by the genetic differences in receptor subunits. This is evident by studies showing that the response to benzodiazepines can be genetically modified<sup>74</sup>. Pharmacokinetic mechanisms might also act to influence drug resistance in epilepsy. Multidrug resistance (MDR) essentially means resistance to some structurally and functionally unrelated agents. The human *MDR-1* gene encodes an integral membrane protein, P-glycoprotein, the function of which is energy-dependent transport of molecules across membranes. Increased expression of this protein has been demonstrated in the brain of some patients with medically intractable epilepsy, indicating that MDR proteins may play a role in determining the pharmacokinetic profile of AEDs in the blood-brain barrier<sup>75</sup>.

There is intense interest on research in functional polymorphisms that could confer refractoriness to AEDs. In addition to response to drugs, certain ADRs may also have a genetic basis. Allergic sensitivity to toxic arene oxide is a possible mechanism, also a functional epoxide hydrolase defect has been noted to be responsible for the fatal anticonvulsant hypersensitivity syndrome<sup>76</sup>. The potential for this defect to be genetically linked is increased by the finding of familial aggregation of phenytoin hypersensitivity<sup>77</sup> and concordance of carbamazepine hypersensitivity in MZ twins<sup>78</sup>. The teratogenic effects of AEDs also offer scope for pharmacogenetics to stratify offspring risk on the basis of genetic susceptibility<sup>79</sup>. An experimental mouse model to this effect has been studied and offers evidence that offspring liability to valproate toxicity is genetically determined<sup>80</sup>.

## Genetic counselling and epilepsy

What does a neurologist do when confronted with a family of one or more persons with epilepsy? The responsibility for explaining the patient and family is the onus of the clinician. The risk of a person to have a child with epilepsy clearly depends on the type of the epileptic syndrome. It is also determined to some extent by the sex of the parent with epilepsy (the risk has been reported to be greater when the mother is affected), the age of development of epilepsy (being greater at a younger age), the occurrence of epilepsy in the other

parent or another sibling, and the presence of EEG abnormalities in the child at risk. The risk of the siblings developing epilepsy again depends on the type of epilepsy and other factors like age at onset, whether more than one family member is affected. A female preponderance in transmission of seizure liability is the result of a complex of genetic interactions that include the generalized alpha-EEG<sup>81</sup>. The risk of siblings developing epilepsy is about 4% in GE and of any non-febrile seizure at 6–12%, although about 50% may show generalized spike and wave abnormalities on their EEG at some point of time. The risk increases if a parent is also affected. In partial seizures, the risk of non-febrile seizures developing in siblings is about 3–5% by the age of 40 years. In siblings of children with benign childhood epilepsy with centrotemporal spikes the chance of seizures is about 15%. The advantage of the identification of genetic etiology is manifold – it allows earlier diagnosis, permits identification of affected versus unaffected persons within the pedigree, facilitates family planning, and enhances the search for new therapy<sup>72</sup>. An epileptologist looking at familial epilepsies should also ponder on quality of life issues involving clinical research and look at the family as a whole<sup>82</sup>.

## Conclusions

The last decade has witnessed an explosive pace in the identification of human epilepsy genes. Clinical neurologists continue to refine the clinical spectrum of various presentations, look at pedigrees and proceed with molecular tools. Research into genetic aspects of pharmacodynamic and kinetic responses of an individual and prediction of ADRs are going to be the areas of forthcoming research. All these endeavours are to provide innovative therapies for persons with epilepsies suited to their genetic type and for prevention of these disorders in the future.

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