

The Genetics of Human Epilepsies

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Abstract

Introduction: Genetic causes contribute to many different forms of human epilepsies. Genetic analyses obviously represent a very powerful tool to study this highly heterogeneous pathology. The identification of the genes involved in various epileptic syndromes could prove useful in elucidating the basic mechanisms of epilepsies. This review summarises the recent progress that have been made in the localisation and/or identification of many epilepsy genes. **Methods:** The MEDLINE database as well as different other scientific sources were screened. **Results:** While the genes responsible for several progressive epilepsies have now been identified, it is unlikely that they play a role in the aetiology of true idiopathic epilepsies. Although the majority of idiopathic epilepsies are inherited as complex traits, most studies performed to date have led to the identification of several genetic loci underlying rare epileptic syndromes inherited in a Mendelian pattern. Four genes encoding neurotransmitter- or voltage-gated ion channel subunits have been identified in various idiopathic epilepsies. The epilepsies could thus be considered as one of many paroxysmal disorders that are due to mutations in ion channel genes. **Conclusion:** Effort is still needed to identify the genes responsible for the large variety of other epileptic disorders inherited as Mendelian traits and evaluate the role of these genes in the more common and polygenic forms. Defining the genetic bases of the latter will also require that exhaustive association and sib-pair studies to be performed. These studies may help understand the pathophysiology of human epilepsies, will lead to better genetic counselling in affected families, and represent the first step towards the discovery of new therapeutic targets and methods.

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Introduction

Epilepsies are one of the most common neurological disorders, affecting about 3% of individuals at least once in a lifetime.¹ It thus represents a major health care problem. Socio-economical and educational issues are well known. Current therapies are not satisfactory: anticonvulsants are effective only in a subset of individuals and do not cure the disease. In addition, toxic effects are frequent. Clinically, epilepsies are characterised by a predisposition to seizures, which are related to an abnormal and synchronous electrical activity of cerebral neurons, leading to paroxysmal clinical manifestations of different types: motor (convulsions), sensitive, psychic. They are classified according to both the seizure type (whether it is generalised or partial) and syndrome features (age of onset, severity, electroencephalographic aspects, response to anticonvulsants, precipitating factors etc.). It is also usual to distinguish between symptomatic epilepsies, arising from separate brain lesions or disorders, and idiopathic epilepsies, which are presumed to be of genetic origin. Genetic defects may represent about 40% of all the epilepsies.

An inherited contribution to the aetiology of idiopathic epilepsies has been suspected for a long time. Twin studies

clearly demonstrate a major genetic contribution to idiopathic epilepsies, especially those with generalised seizures. Genetic studies may help solve many issues that are encountered with human epilepsies. They of course will lead to better genetic counselling to families and to better clinical diagnosis. Advances in the genetics of epilepsy would also help revise current classifications.² Finally, new insights into the molecular mechanisms of epileptogenesis will lead to better understanding of pathophysiologies and normal brain functioning, as well as to the design of new therapeutic approaches.³

Animal models have been widely used. The role of several calcium channel subunits in various murine epilepsies has been demonstrated: the *tottering* phenotype (ataxia, absence and motor seizures) and the *lethargic* phenotype (ataxia, lethargic behaviour and motor seizures) are due to mutations in the α_1 and β subunit genes *Cch α 1a* and *Cch β 4*, respectively.^{4,5} The *stargazer* mutant, characterised by absence epilepsy, ataxia and head-tossing, is due to defects in a new neuronal calcium channel γ subunit gene, *Cacng2*.⁶ A sodium/proton exchanger is mutated in the slow-wave epilepsy mice.⁷ Many knock-out mice have also been generated; the lack of expression of

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different sorts of genes (ion channels, GABA, serotonin or glutamate receptors, etc.) can lead to epileptic seizures usually associated with other neurological abnormalities (ataxia, abnormal feeding behaviour, etc.).

Until recently, little progress had been made in the identification of the human genetic loci underlying the epilepsies, mostly because of their inherent complexity, at both the clinical and genetic levels. In most forms of human epilepsy, as in many other common human diseases such as autism, hypertension or diabetes, familial segregation does not fit with a simple Mendelian mode of inheritance.⁸ Interaction of several genes with each other as well as with environmental factors influence the disease. These interactions may differ from one epileptic syndrome to another, increasing the complexity of genetic analyses. By contrast, rare epileptic syndromes are inherited as monogenic traits, facilitating linkage analyses and the identification of epilepsy genes.

Monogenic Epilepsies

While they represent only a small proportion of all epilepsies, they have been extensively studied during the last years, using classical LOD scores statistical methods. At this stage, it is important to define two subgroups, whose pathophysiologies probably have little, or nothing, in common. Progressive epilepsies are characterised by mental deterioration and an often fatal evolution. Their degenerative nature clearly distinguish them from the other group, the so-called idiopathic epilepsies.

1. Progressive Epilepsies

These epilepsies are symptomatic of a severe disturbance of brain function. Identification of the disease genes and their functional analysis will help in genetic counselling, in discovering new therapeutic targets, and could also be used as tools to understand brain development. However, the mechanisms underlying these progressive epilepsies probably are very different from the basic process leading to true idiopathic epilepsies.

Progressive myoclonus epilepsy of the Unverricht-Lundborg type (EPM1): EPM1 is characterised by onset at age 6 to 15 years, stimulus-sensitive myoclonus, tonic-clonic seizures, and a progressive course throughout life. This rare recessive syndrome had been linked to chromosome 21q22 in Finish pedigrees.⁹ Point mutations within the cysteine proteinase inhibitor gene cystatin B have been found.¹⁰ However, most mutations occur within the 5' region of the gene, with expansion of a dodecamer repeat upstream of the transcription start site:¹¹⁻¹³ the copy number of this repeat is increased from 2 to 3 copies (normal alleles) to more than 60 copies. The pathological repeat expansion results in a reduction in cystatin B mRNA. Despite the discovery of the gene, the pathogenetic

mechanisms in EPM1 are not known yet.

Progressive myoclonus epilepsy of the Lafora type (EPM2): Lafora's disease is characterised by various epileptic seizures with common onset between 10 and 17 years, rapidly followed by constant myoclonus, dementia, and death within a decade. It is inherited as a recessive trait. Linkage was found at chromosome 6q23-q25 in nine families.¹⁴ The critical region had been narrowed down and the gene has now been identified:¹⁵ it encodes a protein tyrosine phosphatase that may act in the control of glycogen metabolism.

Progressive epilepsy with mental retardation (EPMR): This autosomal recessive disorder is characterised by generalised tonic-clonic seizures with onset at 5 to 10 years of age and progressive mental retardation beginning 2 to 5 years after the onset of seizures. The EPMR had been mapped to chromosome 8p¹⁶ and the interval narrowed down to 4 cM.¹⁷ EPMR was recently recognised as a new neuronal lipofuscinoses subtype (see below). The gene (CLN8) has been identified very recently¹⁸ and encodes a putative transmembrane protein.

Lipofuscinoses: Neuronal ceroid lipofuscinoses are autosomal recessive neurodegenerative disorders in which autofluorescent pigments accumulate in neurons and other cell types. They are characterised by loss of vision, progressive encephalopathy and myoclonic epileptic seizures. Several genes have been identified in the various subtypes.¹⁹ CLN1 (corresponding to the infantile form) encodes the palmitoyl protein thioesterase at chromosome 1p32. CLN2 (classic late-infantile) on chromosome 11p15 encodes a pepstatin-insensitive lysosomal peptidase. CLN3 (juvenile onset: Batten disease) is on chromosome 16p12 and encodes a membrane protein of unknown function. Two additional loci at chromosomes 13q22 (CLN5) and 15q21-q23 (CLN6) have been defined.

West syndrome: This classical form of epilepsy, associated with infantile spasms, mental retardation and hypsarrhythmia, occurs in early infancy and rarely is inherited as an X-linked recessive trait. Linkage to chromosome Xp11-pter has been obtained in these rare families.²⁰ The critical interval has been refined to a 7 cM region at Xp21-p22 in a large Canadian family.²¹

Cortical dysplasias: Abnormal cortical development could be involved in epileptogenesis.²² Certain cortical malformations are known to be genetically determined. Several genes have been identified. The gene responsible for X-linked bilateral periventricular nodular heterotopia is filamin 1 at Xq28. The Miller-Dieker syndrome, associating classical lissencephaly with malformation features, is caused by deletions of the LIS1 gene. Point mutations within the same gene have been found in patients with classical lissencephaly. In several families with X-

linked lissencephaly in hemizygous males, and subcortical band heterotopia in heterozygous females, mutations in the doublecortin gene on chromosome Xq22-q23 have been found.

2. Idiopathic Epilepsies with the Gene Identified

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE): Seizures are mainly of the motor type and occur at night. They usually begin in childhood. Linkage to chromosome 20q13 had been obtained in a single large Australian pedigree²³ and then confirmed in another pedigree from Norway.²⁴ In both cases, mutations within the coding sequence of the CHRNA4 gene have been found.^{24,25} This gene encodes the neuronal nicotinic acetylcholine receptor $\alpha 4$ subunit, and both mutations led to alterations within the second transmembrane domain of the protein, supposed to form the ion-conductive pore of the receptor. Since then, additional analyses have been performed. Some families clearly are not linked to chromosome 20q13 (unpublished data), proving genetic heterogeneity. A second locus has been reported at chromosome 15q24,²⁶ a region where several genes encoding subunits of nicotinic cholinergic receptors are located.

Functional studies using *Xenopus* oocytes have shown that both mutations known to date lead to physiological and pharmacological alterations, including a reduction of calcium flux through the receptor. This could lead to synaptic disinhibition via a decrease in the release of neurotransmitters from presynaptic terminals, which in turn would trigger epileptic seizures.

Benign neonatal familial convulsions (BNFC): Seizures usually begin in the first days of life and remit by six months of age. Epileptic seizures recur later in life in 15% of patients. The disorder is transmitted as an autosomal dominant trait. Linkage to chromosome 20q13 was established in several pedigrees.^{27,28} Genetic heterogeneity has been shown, with linkage of additional families, to chromosome 8q24.²⁹ In both cases, the genes, KCNQ2 and KCNQ3, have been identified and encode potassium channel subunits.³⁰⁻³² Both genes are homologous to each other, and to KCNQ1, a gene that is responsible for cardiac long QT syndrome.³³ KCNQ2 and KCNQ3 products apparently can associate to form heteromers.^{34,35} Co-expression in *Xenopus* oocytes of mutant KCNQ2 with wild-type KCNQ2 and KCNQ3 led to reduction of currents. A moderate loss of KCNQ2/KCNQ3 heteromer function could be sufficient to cause neuronal hyperexcitability.³⁴

Generalised epilepsy with febrile seizures plus (GEFS+): These families are characterised by febrile convulsions associated with different types of seizures occurring in the absence of fever. Linkage to chromosome 19q has been shown in one large pedigree, and a point-mutation in

SCN1B, which encodes the β chain of a sodium channel was found.³⁶ The mutation changed a cysteine to a tryptophan. This would lead to disruption of a putative disulphide bridge which could play a critical role in the structure of an immunoglobulin-like fold in the extracellular domain. Preliminary oocytes experiments showed that co-expression of the mutant $\beta 1$ subunit with the α subunit resulted in sodium channels that inactivated slower than when the α -subunit was expressed alone, while inactivation was even more rapid when wild-type $\beta 1$ subunit was used.

3. Idiopathic Epilepsies whose Gene is not Identified

Other febrile convulsions: In addition to SCN1B, two other genetic loci (FEB1 and FEB2, respectively) had been found, at chromosome 8q21³⁷ and 19p.³⁸ Another locus (FEB3) has been defined very recently. Families harbouring the GEFS+ phenotypes have been linked to chromosome 2q in two recent and independent studies;^{39,40} moreover, pure febrile convulsions have been linked to the same region at 2q23-q24.⁴¹

Benign infantile familial convulsions: Two loci are known to date. One locus is on chromosome 19q12-q13,⁴² a region that contains several candidate genes. These include SCN1B itself, as well as several potassium channel genes.⁴³ Genetic heterogeneity has been shown, with chromosome 19q being excluded in one Italian family with 18 affected individuals.⁴⁴ The other locus is at chromosome 16p12-p11^{45,46} and concerns five families with infantile convulsions associated with choreoathetotic dyskinesia (ICCA syndrome). It remains to be seen whether other families with either pure infantile convulsions, or pure dyskinesia, may be linked to chromosome 16 as well. Interestingly, one homolog of the murine *stargazer* gene,⁶ responsible for a phenotype associating absence epilepsy, ataxia and head tossing, lies at 16p12 and encodes the γ chain of a new calcium channel.

Benign adult familial myoclonic epilepsy: This autosomal dominant syndrome is characterised by adult-onset tremulous finger movement, myoclonus, and epileptic seizures. The gene has been assigned to chromosome 8q23-q24 by linkage analysis in several Japanese families.^{47,48} The critical interval apparently neither overlaps that of childhood absence epilepsy,⁴⁹ nor contains the KCNQ3 gene responsible for neonatal convulsions.³¹ Several epilepsy genes could thus lie at 8q24. Interestingly, new potassium channel genes have been mapped to this genomic area⁴³ and represent strong candidates for these diseases.

Partial epilepsies: The inherited nature of partial epilepsies has long been neglected.⁵⁰ Evidence now exists, that several types of partial epilepsies can be due to genetic defects.

Partial epilepsies with auditory features have been linked to chromosome 10q in one large family.⁵¹ Confirmation of linkage recently has been obtained in one family with temporal lobe epilepsy.⁵² Interestingly, seizures were of various type within the former family, and some patients, although displaying epileptic seizures, did not bear the disease haplotype, suggesting the existence of either sporadic cases or other genetic influence within the family.

Several families with rolandic epilepsy and specific EEG abnormalities (BECTS) were studied using an autosomal dominant model and an "affected members only" statistical analysis. Linkage was found at chromosome 15q14.⁵³ One consanguine family with rolandic epilepsy and dyskinesia features inherited as a recessive trait, has been linked to chromosome 16.⁵⁴ The critical region overlaps that of the ICCA syndrome.^{45,46} Whether the gene is the same or not remains to be determined, but this colocalisation could be coincidental by chance.

Familial partial epilepsy with variable foci (FPEVF) is a newly recognised syndrome whose frequency could be underestimated. Seizures in one large Australian family were of different anatomical origin, involving the frontal, temporal, occipital or centroparietal lobes. Linkage has been suggested (LOD score of 2.74 at $\theta=0$ with marker D2S133) on chromosome 2q.⁵⁵

Polygenic Epilepsies: Problems and Future Prospects

As stated above, most epilepsies are not inherited as monogenic traits. This is the case for idiopathic generalised epilepsies (IGE), which comprise several different syndromes: generalised tonic-clonic seizures, absence epilepsy of childhood (CAE), juvenile absence epilepsy, and juvenile myoclonic epilepsy (JME).

JME is a frequent subtype of IGE with onset in adolescence. While clearly genetically determined, mode of inheritance remains unclear. Several models have been proposed and contradictory genetic data have been published, with linkage to chromosome 6p21-p11 being affirmed or excluded.⁵⁶ Moreover, one locus for JME has been located on chromosome 15q14 using non-parametric methods.⁵⁷

Similarly, most febrile convulsions are inherited as complex traits. However, some families clearly display Mendelian mode of inheritance (see above), facilitating genetic analyses. The genes that are involved in the monogenic forms obviously will represent good candidates to be tested in the majority of febrile convulsions that are inherited in a more complex way. This strategy could be complementary to more exhaustive complex genetic analyses, such as sib-pair studies. In the case of epilepsies, the relative risk λ_s , which is a good indicator of the putative power of sib-pair analyses, is 7.5 only in IGE. By

comparison, λ_s is ≈ 100 in autism, and 15 in diabetes type I. The lower the λ_s , the higher the number of sib-pairs needed to reach statistical significance. This is an important issue, as recruiting patients with familial history seem to be a hard task in the case of epilepsies.⁵⁸ Few studies have been successfully performed with the use of nonparametric statistical methods. One example illustrates the difficulty of such analyses in the case of IGE. Zara et al⁵⁹ have employed an affected pedigree member analysis to obtain linkage of IGE to chromosome 8q24. However, this region has been excluded in another study.⁶⁰ By contrast, CAE, a subset of IGE, have also been linked to 8q24,⁴⁹ using both nonparametric and parametric models. At least three potassium channel genes are situated at 8q24,⁴³ including KCNQ3 itself. Checking directly the possible involvement of these genes in the various forms of epileptic syndromes that could be linked to 8q24 should help solve these controversial issues.

Candidate gene strategies could thus be employed as an alternative approach. Many classes of genes could be implicated in epilepsies. Numerous association studies have been performed on genes with various functions, but no association has been clearly demonstrated yet. One should probably focus first on the genes that are the most obvious candidates, i.e. those encoding ion channels. The systematic identification of single nucleotide polymorphisms (SNPs) across the genome, together with the use of DNA chips, will make it feasible to perform large-scale association studies with SNPs specific to all putative candidate genes for the epilepsies.

Epilepsies as Other Paroxysmal Syndromes: Ion Channel Disorders?

The clinical and epidemiological relationships between epilepsies and other paroxysmal disorders such as migraine or dyskinesia are well known. As a matter of fact, several families present with epileptic syndromes variably associated with other paroxysmal cerebral disorders. Families with epilepsy and hemiplegic migraine,^{61,62} epilepsy and dyskinesia,^{45,46,54} migraine and dyskinesia,⁶³ episodic ataxia and dyskinesia,⁶⁴ episodic ataxia and epilepsy, have been described. In this latter case, a mutation in the potassium channel gene KCNA1 is associated with the phenotype.⁶⁵ Ion channel diseases share several features in common, including paroxysmal symptoms and high level of clinical variability. Mutations in ion channel genes obviously could account for the variable association and co-segregation of different paroxysmal cerebral disorders.

Conclusion

Four genes encoding ion channels (CHRNA4, KCNQ2, KCNQ3, SCN1B) are responsible for rare epileptic disorders inherited as Mendelian traits. In addition, another

potassium channel gene (KCNA1) is mutated in patients displaying episodic ataxia and epileptic seizures in one family. These epilepsies can thus be considered as channelopathies. Linkages have been found in many other epileptic syndromes, and there is no doubt that the causing genes will be identified in the near future. An important challenge will then be to identify the genes participating in the more frequent epilepsies that are polygenic or multifactorial. To achieve this goal, sib-pair studies as well as association studies on the numerous candidate genes (ion channels, neurotransmitter receptors, etc.) that are present in the human genome could be very powerful. Those studies will take advantage of the identification of polymorphic markers (SNPs) specific to each putative epilepsy gene, coupled with the use of DNA microarrays.

To date, only a few genes are known. Nevertheless, the products of these genes represent obvious targets for the design of new pharmaceutical drugs that could act not only on the given syndrome where the gene is mutated, but also on the more frequent idiopathic epilepsies that are inherited as complex traits.

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