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Epilepsy genes

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Abstract

The identification of epilepsy genes has been complicated by phenotypic heterogeneity of individual epilepsy syndromes and clinical overlap between different epilepsy syndromes. Benign familial neonatal convulsions has been mapped to chromosome 20q and 8q, but other genetic loci may be involved in certain families. Benign familial infantile epilepsy has been mapped to 19q. Nocturnal frontal lobe epilepsy has been mapped to 20q where a mutation has been found in the neuronal nicotinic acetylcholine receptor alpha4 subunit in one of several families studied. A family with partial epilepsy with auditory hallucinations has been mapped to 10q. Progressive myoclonic epilepsy of the Unverricht-Lundborg type has been localised to 21q and associated with abnormality in the cystatin B gene. Bilateral periventricular nodular heterotopia is closely linked to markers in distal Xq28. Mitochondrial DNA mutations are often associated with epilepsy syndromes. The best studied are mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), and myoclonus, epilepsy, ragged-red fibers (MERRF). Both disorders are caused by point mutations on mitochondrial transfer RNAs. Studies on inheritance of three common epilepsy syndromes: idiopathic generalised epilepsy, benign Rolandic epilepsy and febrile seizures have produced controversial results.

Key words: epilepsy syndromes, genetic, heterogeneity, Mendelian, mitochondrial DNA, polygenic.

INTRODUCTION

The identification of epilepsy genes has been complicated by phenotypic heterogeneity of individual epilepsy syndromes and clinical overlap between different epilepsy syndromes. Genetic heterogeneity in terms of chromosome region involved (linkage heterogeneity) and types of mutation within a gene (allelic heterogeneity) also complicate matters.

The number of Mendelian traits associated with epilepsy was 103 in 1983, and 180 in 1994. Although these account for only 1-2% of epilepsy cases, the number and variety of such traits indicates a wide variety of pathogenetic mechanisms. The vast majority of epileptic syndromes are complex, polygenic and multifactorial in their mode of inheritance.[1] Rare epilepsy syndromes are caused by mitochondrial deoxyribonucleic acid (mtDNA) mutations.

I will discuss in turn the epileptic syndromes with Mendelian, polygenic and mitochondrial inheritance.

EPILEPSIES WITH AUTOSOMAL DOMINANT INHERITANCE

Benign familial neonatal convulsions

This epilepsy syndrome has an autosomal dominant mode of inheritance, with onset of seizure within the first week, usually in the first 3 days of life, and spontaneous remission by the sixth month. It is now realised that this epilepsy syndrome may be more heterogeneous than initially thought. Affected individuals may have neonatal convulsions, febrile seizures and later afebrile seizures.

In genetic studies to date, most of the families map to chromosome 20q13[2], but two families with essentially the same phenotype map to 8q24[3] and another family does not map to either 20q or 8q. In this apparently simple autosomal dominant disorder, the identification of the responsible genes has been complicated by both phenotypic as well as linkage heterogeneity.

Benign familial infantile epilepsy

This epilepsy syndrome is probably more common than is recognised. Patients present with afebrile seizures between the ages of 3 and 19 months, normal neuro-developmental status, normal interictal EEG and a family history of

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similar seizures. Patients invariably outgrow their seizures and remain intellectually and neurologically normal. Inheritance is probably autosomal dominant with incomplete penetrance. It has been mapped to chromosome 19q in five Italian families.[4]

Familial partial epilepsies

Until recently, most epilepsy syndromes with partial seizures were thought to be acquired, but over the last few years, several epilepsy syndromes with partial seizures have been shown clearly to be inherited in a Mendelian manner.

Nocturnal Frontal Lobe Epilepsy

Patients with this syndrome are intellectually and neurologically normal. They have clusters of brief nocturnal motor seizures, with hyperkinetic or tonic manifestations. These rarely evolve into generalised tonic-clonic seizures. Subjects often have an aura and remain aware throughout the attacks. Seizures occur in clusters (mean 8 seizures/night) typically as the subject dozes or shortly before awakening. Age of onset ranges from 2 months to 53 years (median 8 years) and seizures persist through out life. The inter-ictal EEG is usually normal but ictal recordings show that these events are epileptic and appear to arise from the frontal lobes. Neuro-imaging is normal. Carbamazepine monotherapy is usually effective. The condition is autosomal dominant with a penetrance of 75% and marked intra-familial variation in severity.[5]

In a large Australian pedigree with nocturnal frontal lobe epilepsy, linkage was found to 20q13.2, and a presumptive causal mutation has been identified in the gene for the neuronal nicotinic acetylcholine receptor alpha4 subunit.[6] The missense mutation replaces serine with phenylalanine at codon 248 in the second transmembrane domain, coincident with the position where other site-directed substitutions have impaired pore function. Four other families and sporadic cases of idiopathic frontal lobe epilepsy thus far studied do not show this mutation.

This gene is in the same candidate region (20q13.2-20q13.3) as that found in some patients with benign familial neonatal convulsions. The two epilepsy syndromes are clinically distinct disorders, frontal lobe seizures have never been observed in patients or families with benign familial neonatal convulsions and vice versa.

Autosomal dominant familial temporal lobe epilepsy

Epilepsy begins in adolescence or early adult life (median 19 years). Patients have simple partial seizures with psychic or autonomic features, infrequent complex partial seizures and rare secondarily generalised seizures. Inter-ictal EEG abnormalities are uncommon and MRI scans are normal. Usually seizures are very mild and therapy responsive and not infrequently unrecognised by patients or physicians.[7]

The condition appears to be autosomal dominant with a penetrance of approximately 60%. There is moderate variation in intra-familial severity.

Ottman et al recently described a family where auditory hallucinations were common and linkage to chromosome 10q was found.[8] The 10q locus is not responsible for the disorder in the larger Australian families studied to date.

Autosomal dominant partial epilepsy with variable foci[9] and Autosomal dominant rolandic epilepsy with speech dyspraxia[10]are recently recognised epilepsy syndromes whose genetic loci have not yet been identified.

Dentatorubral-pallidoluysian atrophy (DRPLA)

DRPLA is a rare autosomal dominant neurodegenerative disease with a variable clinical phenotype. Progressive ataxia, choreoathetosis, and dementia are the main clinical features of adult-onset cases, whereas the main features in juvenile-onset (before age 20) DRPLA is progressive myoclonus epilepsy. Earlier onset is apparent in successive generations (anticipation). The molecular abnormality underlying DRPLA is an expanded, unstable CAG trinucleotide repeat in chromosome 12p. Patients with juvenile onset had significantly larger repeats than those with adult onset, and there was a significant correlation between CAG repeat length and younger age at onset.[11]

EPILEPSIES WITH AUTOSOMAL RECESSIVE INHERITANCE

Progressive myoclonic epilepsy

Progressive myoclonic epilepsy refers to a heterogeneous group of several inherited epilepsies characterised by myoclonic seizures, generalised epilepsy, and progressive neurological deterioration, including dementia

and ataxia.

One of the five recognised members of this group is progressive myoclonic epilepsy of the Unverricht-Lundborg type (EPM1). This form of epilepsy is inherited as an autosomal recessive disease with severe stimulus-sensitive myoclonus and tonic-clonic seizures beginning between ages 6 and 15 and a variable rate of progression. Seizures tend to diminish at 25 to 30 years of age, although mild dementia generally develops late in the course of the disease. The phenotype is relatively homogeneous both within families and between families, even in different racial groups, as is characteristic of autosomal recessive conditions. All families with this condition (including both the Baltic and Mediterranean types) consistently map to 21q. Recently two mutations, a 3' splice site mutation in one family and a stop codon mutation in two families, were identified in the gene encoding cystatin B. No sequence difference was detected in several other EPM1 families, but Northern blot experiments showed that gene expression is defective in all families tested.[12] This suggests linkage homogeneity combined with allelic heterogeneity.

Progressive myoclonic epilepsy of the Lafora type is an autosomal recessive disease characterised by epilepsy, myoclonus, dementia, and periodic acid-Schiff-positive intracellular inclusion bodies (Lafora bodies). Onset is during late childhood or adolescence and the disease leads to a fatal outcome within a decade of first symptoms. Lafora bodies contain branched polysaccharide (polyglucosans) and have been described in brain, spinal cord, liver, skin, skeletal muscle, heart and retina.

A study of nine families with progressive myoclonic epilepsy of the Lafora type, revealed linkage to chromosome 6q.[13] Three families were not informative, however, and most of the evidence came from two families.

The neuronal ceroid lipofuscinosis (NCL) are a group of inherited neurodegenerative disorders characterised by the accumulation of autofluorescent lipopigment in neurons and other cell types. Inheritance is autosomal recessive for the childhood onset forms which include infantile (CLN1; Haltia-Santavuori disease), late-infantile classical (CLN2; Jansky-Bielschowsky disease), Finnish-variant late-infantile (CLN5) and juvenile (CLN3, Batten or Spielmeyer-Vogt-Sjogren disease).

Three childhood onset NCL genes have been localised by linkage analysis - CLN1 to chromosome 1p[14], which encodes palmitoyl protein thioesterase; CLN3 to chromosome 16p[15] and CLN5 to chromosome 13q.[16]

Progressive myoclonic epilepsy can also be caused by the juvenile type of Gaucher's disease, which maps to chromosome 1q, and by the "cherry-red-spot-myoclonus" syndrome of Guazzi or sialidosis type 1, which has been localised to chromosome 10.

EPILEPSIES WITH X-LINKED DOMINANT INHERITANCE

Bilateral periventricular nodular heterotopias

Subependymal nodular heterotopias are clinically heterogenous. Focal and unilateral subependymal heterotopias have not been observed in multiple members of the same family. In contrast, bilateral and symmetric subependymal (periventricular) heterotopia are often familial.

Most probands with typical bilateral periventricular nodular heterotopia have normal intelligence and epilepsy with multiple seizure types which may or may not prove difficult to control.[17] Some affected individuals may be asymptomatic. In males, the clinical manifestation is more severe. Whilst some males have normal intelligence and epilepsy, others have severe mental retardation, and many affected male fetuses are aborted spontaneously.

Bilateral periventricular heterotopia is closely linked to markers in distal Xq28. Affected females are obligatory mosaics for the mutation. The periventricular heterotopia malformations consist of well-differentiated cortical neurons filling the adult subependymal zone.[18] On CT scan, the periventricular heterotopias appear as multiple uncalcified nodules on the lateral ventricular walls. On MRI, the intensity of the nodules are the same as that of the cerebral gray matter, and no other cerebral abnormalities are observed. Despite extensive examinations, these patients do not show evidence of tuberous sclerosis.

EPILEPSIES WITH POLYGENIC INHERITANCE

Idiopathic generalised epilepsy

Idiopathic generalised epilepsy (IGE) is characterised by recurring unprovoked generalised seizures in the absence of interictal neurological abnormalities, detectable brain lesion and/or metabolic abnormalities. It is a very common condition, accounting for about 40% of epilepsy up to age 40. Generalised

spike-wave activity is the electroencephalographic (EEG) hallmark of IGE, and it may be present in seizure-free family members of probands with IGE. IGE has been classified into several syndromes: juvenile myoclonic epilepsy (JME), childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), generalised tonic-clonic seizures (GTCS). However, the boundaries between the various syndromes are indistinct.

IGE is up to 95% concordant in monozygotic twins supporting an almost completely genetic etiology. Furthermore, the IGE subtype was the same in all monozygotic pairs suggesting that the specific IGE syndrome is also genetically determined.[19] Family studies have shown both a significantly increased risk of IGE in close relatives of probands and the simultaneous presence of several forms of IGE in the same pedigree.[20] The risk of IGE for relatives of probands with IGE decreases with more distant relationship. The risk for monozygotic twins is up to 95%, risk for siblings is about 7.5%, risk for nieces/nephews is about 1.5%. This very rapid decrease in risk with increasing degrees of relationship suggests that several loci interact in a multiplicative manner to produce the IGE phenotype.[21] Some of these loci are likely to act on the level of neuronal excitability, therefore determining the seizure threshold, while other loci may influence the specific seizure subtype.

Gene mapping in IGE has produced contradictory results. There is strong evidence for linkage to chromosome 6p in some families with JME[22], but a significant number of families studied do not show this linkage.[23] Zara et al used non-parametric methods to map IGE loci. The phenotypes included in their study were JME, CAE, JAE, epilepsy with generalised tonic clonic seizures, febrile convulsions as well as asymptomatic subjects wtih generalised spike-wave on EEG. No evidence for linkage to chromosome 6p was obtained. Instead, they obtained evidence for involvement of a locus at chromosome 8q24, close to the marker D8S256.[24] The same 8q24 region was previously implicated in families with benign neonatal familial convulsions. They postulated that the variety of IGE syndromes included in their studies allowed them to identify loci that may influence the epileptogenic threshold, regardless of the specific type of seizures.

There is at present much controversy about the genetic loci for IGE. This is because of the overlap of different IGE epilepsy syndromes, possible misdiagnosis, failure to identify EEG multispike wave complexes in asymptomatic family member, uncertain modes of inheritance and penetrance, and interfamilial genotypic heterogeneity.

Many IGE families show aggregation of different IGE syndromes and no clear Mendelian pattern of inheritance. In these families, IGE phenotype is probably due to multiplicative interactions of several loci. However, in some families, the IGE phenotype is remarkably homogeneous and it appears to be caused by a major, dominantly inherited gene.

Benign epilepsy of childhood with centro-temporal spikes (BECTS)

BECTS or benign Rolandic epilepsy is one of the commonest epilepsy syndrome in school-aged children. Seizures are partial with motor and/or sensory symptoms involving the one side of the face, oropharynx, or one upper limb, and may progress to generalised convulsions. The seizures usually occur in sleep. The patients are neurologically and intellectually normal and outgrow their seizures by adolescence. Typical epileptiform discharges are seen on the EEG.

Despite extensive studies, the actual mode of inheritance and the localisation of the gene(s) remain controversial. Doose et al hypothesised that the clinical manifestation of the seizures were probably multifactorial in origin with various predisposing factors influencing the expression of the clinical picture.[25] On the other hand, Heijbel et al postulated that the EEG trait of the centro-temporal foci was thought to be controlled by a single dominant gene with low penetrance and was age dependent.[26]

Linkage studies assuming autosomal dominant inheritance have excluded linkage to the fragile X region and the HLA region on chromosome 6p. A recent study has suggested multifactorial inheritance for BECTS and evidence for genetic association with other types of focal epilepsy as well as generalised epilepsy.[27]

Febrile seizures

Febrile seizures affect 2-5% of all children and is the most common epilepsy syndrome in all races. A family history of seizures occurs in up to half of all cases. Various genetic models have been proposed including autosomal dominant, autosomal recessive and polygenic or multifactorial models. Based on a complex segregation analysis of 467 families, Rich et al. found evidence of genetic heterogeneity.[28] They proposed that single febrile seizures were

associated with polygenic inheritance whilst three or more febrile seizures followed a single-major-locus model with nearly dominant seizure susceptibility.

Scheffer and Berkovic[29] have observed two clinical patterns of familial febrile seizures consistent with segregation analyses suggesting genetic heterogeneity. First, families where many individuals have infrequent febrile seizures and one or a few family members have later temporal lobe epilepsy secondary to mesial temporal sclerosis.[30,31] In this group, there is suggestive evidence for linkage to chromosome 8q13-21 in one family.[31] Secondly, there are families with febrile seizures and generalised epilepsy where linkage has not been found.[29] It is obvious that in febrile seizure, both genetic and phenotypic heterogeneity exist and complicate the identification of the genes involved.

EPILEPSY SYNDROME DUE TO ABNORMALITIES IN MITOCHONDRIAL DNA

Patients with mitochondrial encephalopathies show great variability in clinical manifestations. This is due to heteroplasmy and threshold effect. Each cell contains thousands of mtDNA copies, which at cell division, distribute randomly among daughter cells. In normal tissue, all mtDNA are identical (homoplasmy). Pathogenic mutations of mtDNA usually affect some, but not all mitochondrial genomes within a cell, a tissue, and an individual (heteroplasmy). The clinical expression of a pathogenetic mtDNA mutation is largely determined by the relative abundance of mutant mtDNA in different tissues, and a minimal critical percentage of mutant mtDNA is required to cause mitochondrial dysfunction (threshold effect).

At cell division, the proportion of mutant mtDNA in daughter cells may shift and the phenotype may change accordingly. This phenomenon, called mitotic segregation, explains how certain patients with mtDNA-related disorders may shift from one clinical phenotype to another as they grow older.

At fertilisation, all mtDNA derives from the oocyte. Therefore, the mode of transmission of mtDNA point mutations differs from Mendelian inheritance. A mother carrying a mtDNA point mutation will pass it on to all her children, but only her daughters will transmit it to their progeny. A disease expressed in both sexes but with no evidence of paternal transmission is suggestive of a mtDNA point mutation.

Seizures are a common manifestation of disorders associated with mtDNA mutations.

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) presents usually in childhood with recurrent vomiting, migraine-like headaches, and stroke-like episodes causing cortical blindness, hemianopia or hemiparesis. Seizures occur in 96% of patients and often precede the stroke-like episodes.[32] The most common mutation associated with MELAS is A3243G in the $tRNA^{Leu(UUR)}$ gene.

Myoclonus, epilepsy, ragged-red fibers (MERRF) is characterised by myoclonus, generalised seizures (present in virtually 100% of patients), mitochondrial myopathy, and cerebellar ataxia. MERFF shows remarkable phenotypic variation between and within families. In most families with MERFF the molecular defect is a single base pair substitution at position 8344 of the mtDNA, resulting in a mutation in tRNA for lysine.[33] In individuals proved to have this mutation, the phenotype can vary from being clinically unaffected, to a late-onset ataxic-myoclonic syndrome, to a severe childhood-onset progressive myoclonic epilepsy with or without associated dementia and pyramidal and cerebellar signs.

The relationship between the mtDNA mutation and the clinical phenotype is not always consistent. Hammans et al. found that patients with the mitochondrial $tRNA^{Leu(UUR)}$A3243G mutation had clinical features consistent with MELAS, chronic progressive external opthalmoplegia, MERRF, myopathy alone, and diabetes and deafness.[34]

Neuropathy, ataxia, retinitis pigmentosa (NARP) usually affects young adults and causes retinitis pigmentosa, developmental delay, dementia, seizures, ataxia, proximal limb weakness and sensory neuropathy. This syndrome is associated with a mutation (T8993G) in a structural gene (ATPase subunit 6) of mtDNA.[35] When the same mutation is present in high abundance, it causes a more severe infantile encephalopathy with frequent seizures and the neuropathological features of Leigh syndrome (maternally inherited Leigh syndrome MILS).[36]

CONCLUSION

Although genetic and phenotypic heterogeneity complicate all studies on epilepsy genes, significant progress has been made in the recent years in the identification of genetic loci and in

a few cases, the gene products responsible for some of the epileptic syndromes. Careful clinical studies have delineated hitherto unrecognised epilepsy syndromes which are hereditary, and such studies will continue to be important in our attempts to identify epilepsy genes.

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