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REVIEW ARTICLE

The genetics of epilepsies

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Abstract

Objectives: To discuss some of the clinical and molecular genetic aspects of new discoveries in the field of the genetics of the epilepsies and relate these with relevant clues for a better understanding of the mechanisms underlying some of the monogenic epilepsy syndromes.

Sources: Many study designs have been performed over the years and these include family-based studies, genetic-epidemiology surveys. More recently, molecular genetics studies and gene discovery strategies have been used to unravel the molecular and cell mechanisms involved in several Mendelian epilepsy syndromes.

Summary of the findings: The importance of genetic factors in the epilepsies has been recognized since the time of Hippocrates.

Conclusions: In the modern era, many studies have demonstrated the existence of an inherited component in the generalized and focal epilepsies and in the last 2 decades a number of families segregating different types of monogenic epilepsy have been described leading to progresses in the characterization of the molecular defects in these families.

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Introduction

Epilepsies are one of the most common neurological conditions with a prevalence of approximately 1-1.5% in the general population and, therefore, are considered a public health problem. The molecular genetics revolution provided new insights into the human idiopathic epilepsies and, more recently, a major role has been suggested for the ligand-gated and voltage-gated ion channels in the etiology of many epilepsy syndromes.[1] To date, genes encoding for sodium and potassium channel subunits as well as nicotinic cholinergic receptor subunits have been identified for Mendelian idiopathic epilepsies.[2] *In vitro* and *in vivo* studies of mutations demonstrate functional changes, allowing new insights into mechanisms underlying hyperexcitability.[3] Progress in this area has been so intense that researchers are now trying to identify genes for the more common forms of epilepsy following complex inheritance.[4] We believe that once such genes are discovered, the more complex interactions between genes and environment will be better understood making it easier to assess the mechanisms producing specific epilepsy syndromes, as well as determining clinical variability among different patients.

In the 1950's the pioneer studies by Lennox[5] and Metrakos[6] were the first to propose scientific evidence for the genetic predisposition to idiopathic generalized epilepsies (IGE). These initial studies reported that the risk of developing epilepsy was 1.5 to 5 times higher in the relatives of patients with epilepsy than that observed in the general population.[5,6] In addition, the risk for relatives of patients with IGE was twice that observed for patients with focal epilepsy.[7,8] These results were confirmed by twin studies in which the concordance rates for monozygotic (MZ) twins were higher as compared to dizygotic (DZ) twins.[9] By contrast, until recently focal epilepsies were widely believed to be nongenetic. This view probably resulted from the recognition that epilepsy following environmental insults is usually partial; and that a greater proportion of partial than generalized epilepsies are environmental in origin. However, the importance of the genetic contributions to the focal epilepsies is now well established. Evidence for this genetic contribution has come from different study designs, such as a) familial aggregation studies; b) twin studies; c) clinical description of families; and d) the identification of specific genes.[10]

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Table 1 - Main loci described for idiopathic generalized epilepsies (excluding regions on chromosome 5q and 6p which are presented in Table 2)

Loci	Syndrome	Study	Result	Gene	References
2q11.1	AME	Linkage	+		21
2q23-24.3	JME	Mutation	-	*KCNJ3*	22
	IGE	Mutation	-	*SCN2A*	23
	IGE	Association	+	*KCNJ3*	24
2q36	IGE	Linkage	+		25
	IGE	Association	+	*SLC4A3*	26
3p14-12	IGE	Linkage	+		27
3q26	IGE	Linkage	+		25
	IGE	Association	-	*mGluR7*	28
	IGE	Mutation	+	*CLCN2*	29
6q24	IAE and JAE	Association	+	*OPRM1*	25
	IGE	Association	+	*OPRM1*	30
8p11-12	IGE no JME	Linkage	+		31
	IGE	Linkage	-		32
8q24-	IAE	Linkage	+		33
	IGE	Linkage	-		34
	AME	Linkage	+		35
	IAE	Linkage	+		36
	IGE	Mutation	-	*ARC*	37
	IAE	Mutation	-	*T-STAR*	38
	AME	Mutation	-	*KCNV1*	39
	AME	Linkage	-		21
	IAE	Mutation	-	*KCNK9*	40
14q23	IGE	Linkage	+		25
15q11-14	JME	Linkage	+		41
	IGE	Linkage	-		42
	JME	Association	-	*GABRA5, GABRB3*	43
	IGE	Mutation	-	*KCC3*	44
	JME	Mutation	-	*CHRNA7*	45
15q	IGE	Linkage	-		46
	JME	Linkage	-		47
16p13	FIME	Linkage	+		48
18q21.1	IGE	Linkage	+		47
	IGE	Linkage	-		49
21q22	JME	Linkage	-		50
	JAE	Association	+	*GRIK1*	42
	JME	Mutation	-	*KCNJ6*	22
	JAE	Mutation	-	*GRIK1*	51

AME = adult myoclonic epilepsy; FIME = familial infantile myoclonic epilepsy; IAE = infantile absence epilepsy; IGE = idiopathic generalized epilepsy; JAE = juvenile absence epilepsy; JME = juvenile myoclonic epilepsy.

Table 2 - Summary of the results of genetics studies in idiopathic generalized epilepsies conducted on candidate regions on chromosomes 5q and 6p

Loci	Syndrome	Study	Result	Gene	References
5q32-34	IGE	Linkage	-		52
	JME	Mutation	+	*GABRA1*	53
	IAE with FC	Mutation	+	*GABRG2*	54
	JME	Mutation	-	*GABRA1*	55
5q	IGE	Linkage	-		
6p21	JME	Linkage	+		57
	JME	Linkage	+		58
	JME	Linkage	+		59
	JME	Association	+	*HLA*	60
	JME	Linkage	-		61
	JME	Association	+	*HLA*	62
	JME	Linkage	-		63
	JME	Linkage	-		64
	JME	Linkage/Association	+/-	*HLA*	65
	JME	Association	-	*HLA*	66
	JME	Linkage/Association	+/+	*DQB1 and RING3*	67
	JME	Linkage	-		68
	JME	Association	+	*BRD2*	69
	JME	Association	-	*GRM4*	70
6p12	JME	Linkage	+		61
	JME	Linkage	+		64
	JME	Linkage	+		63
	JME	Linkage	+		68
		Mutation	-	*CLIC5, KIAA0057, GCLC*	71
6p	JME	Linkage	-		41

FC = febrile convulsions; IAE = idiopathic absence epilepsy; IGE = idiopathic generalized epilepsy; JME = juvenile myoclonic epilepsy.

Familial aggregation studies, which use an epidemiological approach to assess the degree of increased risk in relatives of individuals with partial epilepsy, as compared to other groups (generalized epilepsy or normal controls), are consistent in showing an increased risk of epilepsy in the relatives of patients with partial epilepsies.[11,12] However, this contribution is in a lower magnitude than that of the generalized epilepsies.[12,13] Early studies also provided evidence for a genetic contribution to epilepsy with complex partial seizures (most of which was probably temporal lobe epilepsy).[12] Two recent studies further elucidated the familial aggregation of partial epilepsies. Standardized morbidity ratios (SMR) for unprovoked seizures, a measure of the risk of unprovoked seizures, were determined for a large North American population.[13] The SMR were very similar for offspring of patients with generalized (SMR = 3.3) and partial epilepsy (SMR = 3.2). However, risk was increased in the offspring of parents with absence seizures (SMR = 9.2), suggesting that the greater genetic contribution to generalized epilepsy may be restricted to specific syndromes.[8] Another study examined the risk, calculating the relative risk (RR) of epilepsy in first degree relatives of 1,498 patients with cryptogenic epilepsy.[8] Risk was significantly elevated in both groups, focal and generalized epilepsy, when compared to the controls. In parents and siblings, the RR was lower if the probands epilepsy was focal (RR =2.4 for focal epilepsy and RR = 4.7 for generalized epilepsy). By contrast, in offspring, the risk was actually greater if the probands epilepsy was focal (RR = 4.2 for focal epilepsy and RR = 1.6).[10]

However, clustering of disease within families can sometimes result from shared exposure to environmental factors

Table 3 - Idiopathic focal epileptic syndromes with identified loci

Syndrome	Mode of inheritance	Loci/Reference
Benign familial infantile seizures	AD	19q[72]16p12-q12[21]2q24[22]
Benign familial infantile convulsions and choreoathetosis	AD	16p12-q12[51]
Benign epilepsy of childhood with centrotemporal spikes	Complex	15q14[23], no linkage to chr15[23]
Autosomal recessive rolandic epilepsy with paroxysmal exercise induced dystonia	AR	16p12-11.2[24]
Partial epilepsy with pericentral spikes	AD	4p15[25]
Familial temporal lobe epilepsy with febrile seizures with digenic inheritance	AD	1q and 18q[28]
Familial partial epilepsy with variable foci	AD	22q11-q12[26]

AD = autosomal dominant; AR = autosomal recessive.

Table 4 - Idiopathic focal epileptic syndromes with identified genes

Syndrome	Mode of inheritance	Loci	Genes	Channels
Benign familial neonatal convulsions	AD	20q13	*KCNQ2*	Voltage-gated potassium channel[27]
		8q24	*KCNQ3*	Voltage-gated potassium channel[46]
Benign familial neonatal – infantile seizures	AD		*SCN2A*	Voltage-gated sodium channel[43]
Infantile convulsions and choreoathetosis	AD	16p12-q12	*KST1*[32]	
Familial temporal lobe epilepsy with auditory symptoms	AD	10q24	*LGI1*[18]	
Autosomal dominant nocturnal frontal lobe epilepsy	AD	20q13	*CHRNA4*	Nicotinic acetylcholine receptor α4 subunit[42]
		1q	*CHRNB2*	Nicotinic acetylcholine receptor β2 subunit[30]

AD = autosomal dominant.

or shared behavioral patterns, rather than from genetic susceptibility.[14] One of the best strategies to confirm that familial aggregation is indeed caused by shared genetic predisposition is twin studies. These have consistently found higher concordance rates of epilepsy in MZ than DZ twins, providing strong evidence for genetic contributions to epilepsy.[15-17] However, very few of these studies have examined focal epilepsies specifically, or compared focal and generalized epilepsies. Berkovic et al.[8] studied the concordance rates for specific epilepsy syndromes in 253 twin pairs in which one or both twins had epilepsy or febrile convulsions. Concordance rates were significantly higher in MZ than in DZ pairs in both generalized (MZ = 82% vs. DZ = 26%) and focal epilepsies (MZ = 36% vs. DZ = 5%). Interestingly, all of the evidence for a genetic effect in the focal epilepsies came from 30 pairs with cryptogenic epilepsy, in whom the concordance in MZ and DZ pairs was 55% and 0. In the 10 pairs with idiopathic partial epilepsies, most of whom had benign rolandic epilepsy; concordance rates did not differ between MZ and DZ pairs. In addition, none of the 25 pairs with symptomatic focal epilepsy was concordant, excluding the possibility of a major genetic determinant for these types of focal epilepsy.[15]

Several studies have described the clinical manifestations of epilepsy in single families, or sets of families. These

studies are interesting because they show the full spectrum of symptoms different patients within single families can have, giving a very accurate idea of the clinical variability of specific syndromes. However, prove of the genetic contribution to epileptogenesis is only achieved when the causative genes are localized. To date, familial aggregation has been documented in many epilepsy syndromes. A partial list of these types of epilepsy is presented in Tables 1 to 4. It is important to note that any listing of this type becomes out of date in a short period of time, since new syndromes, loci or genes are identified continuously. In many cases in which the genes have been identified they are voltage-gated or receptor genes, except in familial temporal epilepsy with auditory symptoms, in which the leucine-rich, glioma-inactivated 1 gene (LGI1) has been implicated.[18] The exact functional properties of the LGI1 gene remain unknown.[18] This gene was cloned from the breakpoints of a glioblastoma cell line and its expression is reduced or absent in many high-grade gliomas. This evidence indicates a possible function related to cellular proliferation and tumor suppression.[18] Furthermore, this gene is characterized by a central leucine-rich repeat region, which is involved in regulation of cell growth, adhesion, and migration.[18,19] The exact relationship of the LGI1 gene mutation with epilepsy is still unclear. Gu et al.[17] demonstrated the presence of *h*lgi1 protein in the human brain, particularly in neurons from the frontal and temporal lobes, but no definite pathogenic mechanism was found which could correlate mutations in this gene and epileptogenesis.

As discussed above, in only a small proportion of epilepsy syndromes a causative gene has been identified. This comprises a very small proportion of all partial epilepsies described.[72] However, they hold great promise for elucidating the basic mechanisms of epileptogenesis, and in particular the genetic basis for pathology expression in localized brain regions. It is very interesting to note that despite the widespread assumption of a greater genetic effect on generalized epilepsies, more progress has been made to date in localizing genes for focal epilepsies than for generalized epilepsies.[8]

In summary, significant progress has been made in recent years in understanding the genetics of the epilepsies. Research in this area is moving rapidly, and genes that raise risk for new syndromes will undoubtedly be discovered soon. This information will be crucial for elucidating pathogenesis, and also for clarifying definition of syndromes with a major genetic contribution.

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