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REVIEW

NEUROIMAGING AND NEUROGENETICS OF EPILEPSY IN HUMANS

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Abstract—In the past decade, several genetic mutations have been associated with different forms of familial focal and generalized epilepsies. Most of these genes encode ion-channel subunits. Based on neurophysiological *in vitro* and *in vivo* animal studies, substantial progress has been made in understanding the functional consequences of gene defects associated with epilepsies. However, the knowledge transition from animal studies to patients carrying a mutation, or even suffering from a nonfamilial form of epilepsy, is very limited. This review will illustrate how neuroimaging studies in humans may help to bridge the gap between genotype and phenotype. We will be presenting examples of familial focal (autosomal dominant nocturnal frontal lobe epilepsy), idiopathic generalized epilepsies (severe myoclonic epilepsy of infancy). Such studies will help to better understand functional consequences of genetic alterations and may contribute to a better phenotype characterization.

Key words: epilepsy, genetics, neuroimaging, positron emission tomography, channelopathy.

Contents

GENETICS, OF EPILEPSY

With a prevalence of 0.5% and a lifetime incidence of up to 3%, epilepsy is one of the most common neurological disorders (Hauser et al., 1993). Based on their origin, epileptic seizures and syndromes can be focal or generalized, whereas their underlying cause can either be symptomatic (including cortical malformations, tumors, stroke, etc.) or idiopathic (ILAE, 1989). Idiopathic epilepsies are assumed to be mainly genetic in origin, cannot be related to structural brain abnormalities, and are estimated to represent up to 47% of all epilepsies (Freitag et al., 2001). Although symptomatic epilepsies, for example, those associated with major chromosomal defects, amino-acidopathies or storage disorders, may be caused by genetic alterations, this review will focus solely on idiopathic epilepsies and illustrate how neuroimaging studies can help to understand a possible link between genes and function in epilepsy.

Large-scale epidemiological and family aggregation studies show that epilepsies undergo a strong genetic influence (Helbig et al., 2008). About 5% of patients have a first-degree relative with epilepsy. In affected families, the recurrence risk ratios vary around 2.5 in first-degree relatives, with the concordance for monozygotic twins (40%–50%) being greater than for dizygotic twins (10%–15%). There are a number of epileptic disorders, which are characterized by a familial, in most cases, an autosomal-dominant mode of transmission, such as benign familial neonatal convulsions and infantile seizures, generalized epilepsy with febrile seizures plus (GEFS+), severe myoclonic epilepsy of infancy, autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE), familial mesial temporal lobe epilepsies, and others. These familial epilepsies constitute a basis for the search for possible candidate genes. Indeed, in 1995 the first gene for an idiopathic epilepsy syndrome, ADNFLE, was identified (Steinlein et al., 1995). Since then, mutations in at least 25 different genes have been described, although their pathogenetic role in epilepsy remains uncertain (Greenberg and Pal, 2007; Sanchez-Carpintero Abad et al., 2007; Helbig et al., 2008; Weber and Lerche, 2008). Nearly all established genes code for ion channel subunits (see Table 1) leading to the concept that idiopathic epilepsies are a family of channelopathies (Catterall et al., 2008). *In vitro* and *in vivo* studies demonstrated that dysfunction of neuronal ion channels might lead to destabilization of the membrane potential and, thus, epileptic network activity (Reid et al., 2009). Indeed, in some cases significant advances have been made in our understanding of the molecular and cellular deficits caused by mutations. However, the link between molecular deficit and clinical phenotype is still insufficiently characterized.

Physiological investigations and neuroimaging studies may contribute to better phenotype characterization resulting in increased power of genetic analysis (Tauer et al., 2005; Pinto et al., 2005) and may help to bridge the gap

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Abbreviations: ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; CAE, childhood absence epilepsy; GEFS+, generalized epilepsy with febrile seizures plus; IGE, idiopathic generalized epilepsy; MRI, magnetic resonance imaging; nACh, neuronal acetylcholine; PET, positron emission tomography; REM, rapid eye movement; SMEI, severe myoclonic epilepsy of infancy.

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Table 1. Susceptibility loci and affected genes described for various idiopathic epilepsy syndromes

Epilepsy	Chromosome	Gene	Function
ADNFLE	20q13	CHRNA4	Acetylcholine receptor
	15q24	—	
	1q21	CHRNB2	Acetylcholine receptor
	8p21	CHRNA2	Acetylcholine receptor
Lateral temporal lobe epilepsy	10q23−26	LG/1	Unknown function
Familial partial epilepsy with variable foci	22q11−12	—	
Rolandic epilepsy	15q24	—	
Rolandic epilepsy, writer's cramp, dyskinesia	16q12−p11.2	—	
GEFS+	19q13.1	SCN1B	Sodium channel
	2q24	SCN1A	Sodium channel
	5q31−33	GABRG2	GABA receptor
	2p24	—	
	1p36	GABRD	GABA receptor
SMEI	2q24	SCN1A	Sodium channel
Febrile seizures	8q13−21	—	
	19p13	—	
	2q24	—	
	5q14	MASS1	G-protein coupled receptor
	6q22−24	—	
	18p11	—	
IGE	8q24	—	
	14q23	—	
	9q32−33	—	
	10q25−26	—	
	3q26	CLCN2	Chloride channel
Childhood absence epilepsy	8q24	—	
	5q31−33	GABRG2	GABA receptor
	3q26	CLCN2	Chloride channel
	5q34−35	GABRA1	GABA receptor
Juvenile myoclonic epilepsy	6p12−11	EFHC1	Calcium channel
	15q14	—	
	6q21	—	
	5q34−35	GABRA1	GABA receptor
	2q22−23	CACNB4	Calcium channel
Benign adult familial myoclonic epilepsy	8q24	—	
	2p11−q12	—	
Benign familial neonatal seizures	20q13	KCNQ2	Potassium channel
	8q24	KCNQ3	Potassium channel
Benign familial neonatal/infantile seizures	2q23−24	SCN2A	Sodium channel
Benign familial infantile seizures (BFIS)	19q	—	
	16p12−q12	—	
BFIS with familial hemiplegic migraine	1q21−23	ATP1A2	Sodium channel
Infantile convulsions and choreoathetosis	16p12−q12	—	

The hyphens mean that the gene/mutation has not been identified yet.

between genotype and phenotype to better understand functional and structural consequences of genetic alterations (Marini et al., 2003; Fedi et al., 2008). Moreover, the observation of a putative physiological or structural change associated with gene variants may be used to validate the variant as a contributing factor to the disease (Reid et al., 2009). This is especially important for gene variants associated with complex phenotypes because these phenotypes are more difficult to characterize by conventional genetic analysis and gene variants in complex phenotypes might be expected to have a small physiological effect. Indeed, most of the idiopathic epilepsies do not follow single gene inheritance and their occurrence in large families is rare.

This review will discuss the value of neuroimaging for genetic studies in the future.

AUTOSOMAL DOMINANT NOCTURAL FRONTAL LOBE EPILEPSY (ADNFLE)

ADNFLE is an idiopathic epileptic syndrome characterized by clusters of brief motor seizures during non-rapid eye movement (REM) sleep (Scheffer et al., 1994). Ictal video-electroencephalographic studies revealed partial seizures originating in the frontal lobe, but also in parts of the insula, suggesting a defect of a broader network (Ryvlin et al., 2006). More than a hundred families with ADNFLE have been reported since the initial description of the familial