Advances on the Genetics of Mendelian Idiopathic Epilepsies

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KEYWORDS

• Epilepsy • Febrile seizures • Idiopathic • Genes • Loci

More than 50 epilepsy syndromes are described and they are broadly divided into generalized and partial syndromes reflecting the evidence that some seizures are generated diffusely and bilaterally in the brain whereas others have a focal onset. Importantly, some syndromes are age specific and begin in the first year of life, whereas others have a later onset in life. It is well known that the age-specific incidence of epilepsy is high during the first year of life and childhood, and declines throughout adulthood. Classifications of epilepsies have often used the terms ''idiopathic'' and ''symptomatic''. Idiopathic epilepsies have no evidence of an underlying cause and arise in the absence of neurologic deficits or brain lesions. Most of the idiopathic epilepsies are benign or of moderate severity and are believed to have a genetic etiology. On the other hand, the term symptomatic is used when patients with epilepsy have a known or suspected cause and/or when associated with neurologic deficits. We do not discuss the numerous symptomatic genetic epilepsies (eg, progressive myoclonic epilepsies, encephalopathies, Rett syndrome) where seizure disorders are one part of a complex phenotype; epilepsy resulting from a metabolic or structural defect in the brain.

This article strictly focuses on those Mendelian idiopathic epilepsies in which the causative genes are known (or localized), although these presently account for a small proportion of all epilepsy cases. In autosomal dominant conditions, the presence of a single copy of a mutation (heterozygous state) in one *major* effect gene is sufficient to cause the disease. Penetrance is usually reduced, reflecting the fact that some patients carrying the causal mutation are asymptomatic. The genes for Mendelian diseases are localized by positional cloning in large families with multiple affected family members. Whole genome scans are usually conducted by genotyping a panel

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of several hundreds of microsatellite markers searching for co-segregation of disease with marker alleles within families. In recent times, genome-wide searches are conducted with either high-density (several thousands) SNPs (single-nucleotide polymorphisms) or DNA microarrays, which provide higher resolution and are less cost-effective. Linkage analysis determines the region of the genome shared by the affected family members. Logarithm of the odds (LOD) scores are calculated to determine the probably of the linkage. This common interval encompasses the mutated epilepsy gene. Sequencing is considered the ''gold standard'' for mutation detection because it reveals the exact location and the type of mutations. The disease-causing mutation should co-segregate with the disease among family members and should be absent from a control ethnically matched population. For missense mutations (leading to the substitution of an amino acid), it is necessary to demonstrate that the mutation has deleterious effects on the protein function. The functional consequences of each mutation are either the result of a dominant effect of the mutant protein or a loss-of-function because of haploinsufficiency (ie, a loss of 50% of the amount of protein). Notably, the presence of phenotypic heterogeneity in patients harboring the same mutation suggests that modifier genes, which are yet to be identified, also play a significant role.

Multiplex families with autosomal dominant transmission, although not representative of the general population, have been powerful for the elucidation of the molecular basis of Mendelian epilepsies. Since the identification of the first epilepsy gene, *CHRNA4*, in 1995,[1] 10 additional epilepsy genes have been identified. Most of the known genetic culprits in epilepsy are genes encoding components of neuronal ion channels (voltage-gated sodium channels and voltage-gated potassium channels) or neurotransmitter receptors (acetylcholine nicotinic receptor and $GABA_A$ receptor). The latest identified gene, *LGI1* (leucine-rich glioma inactivated 1) is a non-ion channel gene[2,3] which will probably provide new pathways for epileptogenesis.

This review provides a basic overview of idiopathic epilepsy syndromes with their corresponding causal genes. We will first describe neonatal and infancy epilepsies, then childhood and adolescence epilepsies, and last adult-onset epilepsies (**Fig. 1**).

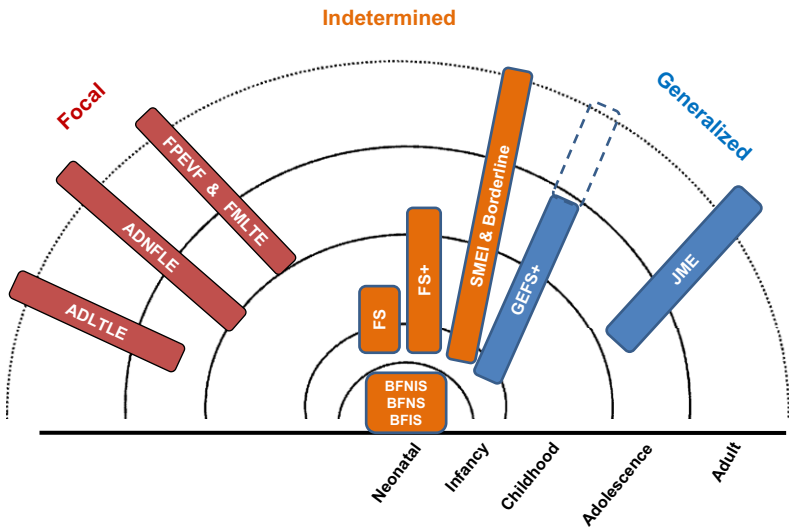

Fig. 1. Representation of the familial idiopathic epilepsies with their age at onset.