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Genetic models of focal epilepsies

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HIGHLIGHTS

- Several focal epilepsy syndromes are proven to be monogenic disorders.
- Mutations in *CHRNA4*, *CHRNB2*, *CHRNA2* and *KCNT1* cause autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).
- Mutations in *LGI1* cause autosomal dominant epilepsy with auditory features (ADEAF).
- This review provides an update of the mutational spectrum in these genes.
- We review cellular and genetic animal models generated for autosomal dominant focal epilepsies.

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ABSTRACT

Focal epilepsies were for a long time thought to be acquired disorders secondary to cerebral lesions. However, the important role of genetic factors in focal epilepsies is now well established. Several focal epilepsy syndromes are now proven to be monogenic disorders. While earlier genetic studies suggested a strong contribution of ion channel and neurotransmitter receptor genes, later work has revealed alternative pathways, among which the mammalian target of rapamycin (mTOR) signal transduction pathway with *DEPDC5*. In this article, we provide an update on the mutational spectrum of neuronal nicotinic acetylcholine receptor genes (*CHRNA4*, *CHRNB2*, *CHRNA2*) and *KCNT1* causing autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), and of *LGI1* in autosomal dominant epilepsy with auditory features (ADEAF). We also emphasize, through a review of the current literature, the contribution of *in vitro* and *in vivo* models developed to unveil the pathogenic mechanisms underlying these two epileptic syndromes.

Contents

Abbreviations: ACh, acetylcholine; ADEAF, autosomal dominant epilepsy with auditory features; ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; CHRNA4, CHRNB2, CHRNA2, α4, β2 and α2 subunits of nicotinic acetylcholine receptors; KCNT1, potassium channel, subfamily T, member 1; LGI1, leucine-rich, glioma inactivated 1; nAChR, nicotinic acetylcholine receptor.

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1. Introduction

Twenty years have now passed since the first identification of a mutated gene in inherited focal epilepsies. In 1995, a mutation in *CHRNA4*, encoding the α4 subunit of the nicotinic acetylcholine receptor (nAChR), was identified in autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) (Steinlein et al., 1995). Subsequently, mutations in *CHRNB2* and *CHRNA2*, encoding, respectively, the β2 and α2 subunits of nAChRs, were reported in a subset of ADNFLE families (Aridon et al., 2006; De Fusco et al., 2000), reinforcing the commonly held view that monogenic focal epilepsies belonged to the channelopathies. Since then, great advances have been made in gene discovery, revealing a genetic heterogeneity that extended pathophysiological mechanisms to non-ion channel biological pathways in focal epilepsies. The first mutations in a non-ion channel gene, leucine-rich glioma inactivated 1 (*LGI1*), were identified in families with autosomal dominant epilepsy with auditory features (ADEAF) (Kalachikov et al., 2002; Morante-Redolat et al., 2002). More recently, whole-exome sequencing identified mutations in the potassium channel *KCNT1* gene in families with severe forms of ADNFLE with intellectual disability and psychiatric features (Heron et al., 2012). Lately, mutations in the *DEPDC5* (dishevelled, Egl-10 and pleckstrin domain-containing protein 5) gene have been linked to diverse focal epileptic phenotypes, ranging from apparently nonlesional focal epilepsies to malformation-associated focal epileptic syndromes (for review Baulac, 2014). *DEPDC5* is the major cause for familial focal epilepsy with variable foci (FFEVF), an autosomal dominant syndrome characterized by focal epileptic seizures arising from different cortical regions in different family members (Dibbens et al., 2013; Ishida et al., 2013). *DEPDC5* mutations were also reported in ∼13% of a cohort of ADNFLE families (Picard et al., 2014) as well as families with focal epilepsies and focal cortical dysplasia (Baulac et al., 2015). Finally, a causative role for the corticotrophin-releasing hormone (*CRH*) gene has also been suggested in ADNFLE (Sansoni et al., 2013).

We will review the respective contribution of *in vitro* and *in vivo* models to the understanding of the pathogenic mechanisms of genetic focal epilepsies. Due to the current lack of functional studies concerning mutations in *DEPDC5*, we will focus on *CHRNA4*, *CHRNB2*, *CHRNA2*, *KCNT1* and *LGI1*. This choice will allow us to exemplify both gain- and loss-of-function pathogenic mechanisms in focal epilepsies caused by mutations in ion channel and non-ion channel genes.

2. Investigation methods and models of genetic focal epilepsies

While numerous models of acquired epilepsy (induced chemically or by electroshocks) exist, we will focus on investigation methods of genetic focal epilepsies, which follow a logical progression from cellular to animal models, offering specific and complementary advantages. Basically, *in vitro* models are needed to assess if a given genetic variant is responsible for the phenotype, while intact living organisms allow us to integrate pathomechanisms in neuronal networks and to recapitulate the clinical features observed in the patients. In addition, *ex vivo* techniques, including acute brain slices and organotypic cultures, are also used in epilepsy research paired with electrophysiology, but these will not be covered in this review. We provide a brief overview of the methods and models that are used step-by-step to link a mutation to its pathological consequences, together with their advantages and limitations.

2.1. Types of disease-causing mutations

Mutations are typically classified in different types, including most commonly missense, nonsense, splice-site and frameshift mutations. Missense mutations (a non-synonymous substitution) lead to an amino acid exchange in the protein sequence, which may modify the functional properties of the protein. Mutations found in ion channel genes are typically missense. In this case, the pathomechanism is defined as a gain-of-function. Additional dominant-positive or dominant-negative effects can act on associated proteins. The positional clustering of mutations along the gene can also provide useful clues regarding functional domains of the protein playing a key role in the pathology. In contrast, nonsense, splice-site and frameshift mutations lead to the introduction of a premature stop codon that may result in the truncation of the protein or its absence due to nonsense-mediated decay (NMD) degradation, the pathogenic mechanism being most likely a loss-of-function. Thus, the type of mutations constitutes a first piece of information to select the appropriate model and assess their functional consequences on the function of the protein of interest.

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