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Topical Review

Novel Genes of Early-Onset Epileptic Encephalopathies: From Genotype to Phenotypes

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ABSTRACT

BACKGROUND: Early-onset epileptic encephalopathies are severe disorders in which seizure recurrence impairs motor, cognitive, and sensory development. In recent years, next-generation sequencing technologies have led to the detection of several pathogenic new genes. **METHODS AND RESULTS:** A PubMed search was carried out using the entries "early onset epileptic encephalopathies," "early infantile epileptic encephalopathies," and "next generation sequencing." The most relevant articles written on this subject between 2000 and 2015 were selected. Here we summarize the related contents concerning the pathogenic role and the phenotypic features of 20 novel gene-related syndromes involved in the pathogenesis of early-onset epileptic encephalopathy variants. **CONCLUSIONS:** Despite the increasing number of single early-onset epileptic encephalopathy genes, the clinical presentations of these disorders frequently overlap, making it difficult to picture a systematic diagnostic evaluation. In any case, a progressive approach should guide the choice of molecular genetic investigations. It is suggested that clinicians pay particular attention to mutated genes causing potentially treatable conditions in order to take advantage of expert counseling.

Keywords: early-onset epileptic encephalopathies, next-generation sequencing, epilepsy, children

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Introduction

Next-generation sequencing technologies, which enable the high-throughput sequencing of a large number of DNA regions in a single reaction, have emphasized the role of several new genes in the pathogenesis of early-onset epileptic encephalopathies in the past few years.[1-4] The present review aims to report on the pathogenic and the clinical implications of these newly recognized genes and to update the analyses that were published in articles by Mastrangelo and Leuzzi in this journal in 2012[5] and by Sharma and Prasad in 2013.[6]

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Search Criteria

A PubMed search was carried out using several entries, for instance "early-onset epileptic encephalopathies," "early infantile epileptic encephalopathies," and "next-generation sequencing and epileptic encephalopathies." In total, 113 articles were selected that concerned this field of interest and published between 2000 and 2015. To ensure the validity of the search strategy, articles were excluded based on the following.

- Articles that were not written in English
- Studies not including data taken from human beings
- Articles concerning group of structural genes that were already discussed in the previously mentioned article (including ARX, CDKL5, STXBP1, SLC25A22, SPTAN1, PLCβ1, membrane-associated guanylate kinase inverted-2, PNKP, SCN1A, PCDH19, and PNPO)[5]
- Articles on metabolic epileptic encephalopathies that have been discussed elsewhere.[7]

Finally, 43 articles, both original articles and case reports, were included, allowing the in-depth analysis of 20 new early-onset epileptic encephalopathy genes.

Classification

Table summarizes genes involved in the pathogenesis of early-onset epileptic encephalopathies comprising:

- Genes encoding ion channels
- Genes encoding regulators of synaptic vesicles release
- Genes encoding regulators of intracellular/intercellular signal transduction
- Genes encoding neurotransmitters membrane receptors
- Genes encoding intracellular transporters or enzymes

In the same table, the main clinical, electroencephalographic and neuroradiologic features are listed. Here in the text, these genetic disorders will largely be discussed in clusters concerning both protein function/impairment and regarding clinical phenotypes.

Genes Encoding Ionic Channels

Sodium channel neuronal type 2α subunit (SCN2A, OMIM number 182390)

Gene and protein function

SCN2A gene encodes the NaV1.2 subunit of the voltage-gated sodium channel type 2α. This transmembrane glycoprotein is highly expressed in neurons and is involved in the generation and the propagation of the action potentials.[7]

Clinical presentations and genotype–phenotype relationships

SCN2A mutations have been classically related to autosomal dominant benign familial neonatal-infantile seizures.[7,8] More recently, several *de novo* heterozygous SCN2A mutations have been associated with more severe phenotypes presenting with early-onset epileptic encephalopathy, intractable childhood epilepsy, movement disorders, and severe intellectual disability or autism without epilepsy.[9-17]

Kamiya et al. ascribed the wide variety of the clinical phenotypes to the different impact of nonsense truncating mutations compared with missense mutations on SCN2A protein function and tridimensional structure.[10] The authors presented the clinical and molecular genetic characteristics of a 29-year-old woman affected by early-onset versive and atonic drug-resistant seizures, hyperkinetic movements, autistic spectrum symptoms, and brain atrophy shown with magnetic resonance imaging (MRI).[10] However, even in the case of point mutations, clinical severity of the disease seems to relate to the involvement of highly preserved critical protein domains. Nakamura et al., as an example, reported on nine patients with Ohtahara syndrome that displayed missense mutations in several SCN2A regions, all encoding for linkers between transmembrane domains.[11] These regions are believed to be critical for fast inactivation of sodium channel and so greatly affect the ion channel function.[11] In another article, Zerem et al. described a paternal germline mosaicism for a mutation located in a similar transmembrane region (c.4007C>A; p.) as a possible inheritance pattern of Ohtahara syndrome in two half-siblings.[12] A more severe phenotype, including intractable seizures, developmental delay, optic atrophy, callosal hypoplasia, and brain atrophy, has been described by Bach et al. in a 5-year-old female carrying the c.5645G>T (p.R1882 L) missense mutation.[13] Finally, Hackenberg et al. detected a *de novo* missense mutation (c.4025T>C; p.L1342P) in a girl presenting with epileptic encephalopathy together with transient choreoathetosis and hypersomnia.[14]

Moreover, missense mutations in the SCN2A gene are also associated with Dravet syndrome, both as a pathogenic factor and as a genetic modifier of SCN1A gene function.[5,15,16]

Another possible mechanism for the disease is the one described by Touma et al., who identified the gain of function effect of c.788C>T (p.A263 V) mutation in a pair of twins presenting with tonic seizures and suppression burst pattern at the electroencephalograph.[17] The autopsy evidenced a dentate olivary dysplasia in one of the two patients, with a controversial significance.[17]

Sodium channel neuronal type 8α subunit (SCN8A, OMIM number 600702)

Gene and protein function

SCN8A gene encodes a 1980-amino acid protein belonging to the sodium channel family (Nav1.6 subunit) and involved in membrane depolarization during the generation of action potentials both in neurons and in muscles.[18]

Clinical presentations and genotype-phenotype relationships

Pathogenic heterozygous mutations in SCN8A gene can be responsible for both early-onset epileptic encephalopathies and intellectual disability without epilepsy, with or without cerebellar ataxia.[18]

Veramah et al. identified, through whole genome sequencing, a de novo heterozygous missense gain of function mutation (c.5302A>G; p.N1768D) on the SCN8A gene in a 15-year-old female presenting with severe early-onset epileptic encephalopathy with epileptic spasms, evolving into a sudden unexplained death in epilepsy.[18] The authors stated that this mutation causes structural alterations of Nav1.6 subunit leading to an incomplete channel inactivation and, subsequently, to persistent excitatory impulses.[18] Similarly, a different gain of function mutation (c.667 A>G; p.R223G) resulted in a temperature-sensitive reduction of Nav1.6 expression and activity, as reported by de Kovel et al. in a 6 month-old-female presenting with eye rolling, mouthing movements and flexor spasms, developmental impairment, and diffuse brain atrophy on MRI.[19]

Moreover, Carvill et al. reported on a heterozygous c.3868C-G transversion that was inherited through a paternal mosaicism in a 18-month-old boy with an undefined epileptic encephalopathy.[20] Ohba et al. showed seven more SCN8A pathogenic mutations that spanned throughout the entire SCN8A gene in six patients with unclassified early-onset epileptic encephalopathies presenting