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Review

Progress in unraveling the genetic etiology of rolandic epilepsy

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ABSTRACT

Rolandic epilepsy (RE), or benign epilepsy of childhood with centrotemporal spikes (BECT), is the most frequent idiopathic partial epilepsy syndrome of childhood, where the "idiopathic" implies a genetic predisposition. Although RE has long been presumed to have a genetic component, clinical and genetic studies have shown a complex inheritance pattern. Furthermore, the underlying major genetic influence in RE has been challenged by recent reports of twin studies. Meanwhile, many genes or loci have been shown to be associated the RE/atypical RE (ARE) spectrum, with a higher frequency of causative variants in ARE. However, a full understanding of the genetic basis in the more common forms of the RE spectrum remains elusive.

1. Introduction

Rolandic epilepsy (RE), also known as benign epilepsy with centrotemporal spikes (BECT), accounts for about 10–20% of childhood epilepsy [1–3]. The age of onset of RE is typically 3–13 years, with a peak incidence between 7–9 years old, and invariably shows remission by 14 years [4]. The core clinical characteristics include a focal seizure with sensorimotor symptoms, involving the face and laryngeal muscle, or secondary generalized tonic–clonic seizures, mainly during sleep. Characteristic centrotemporal spikes (CTS) and typical seizures are sufficient for diagnosis. The prognosis of RE is relatively benign, as the name indicates; however, moderate behavior and learning problems may exist in some patients. Compared to typical RE, atypical RE (ARE) includes atypical benign partial epilepsy (ABPE), Landau–Kleffner syndrome (LKS), and epileptic encephalopathy with continuous spike-and-waves during sleep (CSWS), which are at the severe end of the clinical spectrum of epileptic disorders with speech and language dysfunction. Most RE patients do not show a simple Mendelian inheritance pattern; therefore, the genetic origin of RE has been the subject of much speculation but remains but remains largely unknown. Given their overlapping clinical characteristics, RE and ARE are presumed to have a shared genetic etiology. In this review, we will concentrate on RE, the most common disease in the spectrum, and the recent research progress on its genetic basis, as well as some promising new genes or loci that might act as scientific resources to guide future research.

1.1. Confusing clinical genetic studies

1.1.1. Family aggregation

Family aggregation, the phenomenon of a high percentage of epilepsy in close relatives, has long been found in RE, suggesting a case for pathogenic genes in RE. The first article reporting family aggregation was published in 1964, with a family history of more than 10% convulsions or epilepsy in RE [5]. The concept of a major genetic basis for RE received support from studies in the 1960s–1990s that showed a positive family history of patients with RE ranging from 3.5% to 59% [4,6–11]. Later, one study reported that families of patients with RE showed no aggregation of Rolandic epilepsy, but did show variable seizure types, such as febrile convulsion and generalized tonic-clonic seizures instead [12], leading to the hypothesis that RE was controlled by a single autosomal dominant gene with age-dependent penetrance and multifactorial inheritance. It is critical to verify the spectrum of clinical manifestations and electroencephalogram (EEG) traits in the family members of patients with RE or CTS without epileptic seizure respectively, to generate hypotheses for further research.

1.1.2. Twin studies

In the pre-genetic era, twin studies were a powerful tool to study the genetic influence on diseases. Although RE was thought to be a genetically influenced disease, twin studies revealed another side to the story. The small number of cases of RE twins meant that the few case reports demonstrated that the concordance rate in RE (4/8) was lower than that in the presence of CTS (6/6), which made the hereditary nature of CTS and RE, or the linkage between them, more complicated [13–18]. An RE study of eight twins based on a twin database later demonstrated, for the first

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time, that there was no concordance for CTS or RE (0/6 in homozygous twins and 0/2 in dizygous twins), which was a striking finding arguing for the auto-dominant trait of RE [19]. Two years later, the same team provided more evidence from a study of another 10 twins with RE from other twin registries, which also showed zero concordance [20]. The gap between the twin studies and molecular testing was so large that could not be easily explained by environmental factors, somatic mutations, or epigenetic influences. Comprehensive genetic sequencing of twin patients might permit significant progress in understanding the underlying pathophysiological mechanisms.

1.1.3. Loci linkage on CTS

Focal sharp waves in the centrotemporal area, called centrotemporal spikes or CTS, are the primary EEG characteristics of RE or ARE; however, they are also found in healthy children [21] or children with autism spectrum disorder (ASD) without clinical seizures [22]. When comparing investigations of the prevalence of clinical seizures, some family studies, which included the EEG traits in symptom-free relatives, indicated that CTS were was transmitted as an autosomal dominant trait with age-dependent penetrance, with or without male preponderance [5,23,24]. However, another study argued for a more complex mode of inheritance [25], because the detection of CTS was influenced significantly by the age of the subject when the EEG was performed. In addition to the complex clinical genetic studies, genome-wide linkage scans demonstrated linkage of CTS to 16p12–11.2 (logarithm of odds (LOD) 3.68 [26]), 15q14 (LOD 3.56; [27]) and 11p13 (LOD 4.30; [28]) respectively, with the last locus being pleiotropic for speech dyspraxia and CTS in RE [29].

The inheritance of CTS is clearly not identical to the inheritance of RE. CTS is necessary, but not sufficient, for RE, because only around 10% of children fulfilling the EEG criteria of CTS actually have seizures [23]. The mechanisms that underlie the seizure expression in subjects with CTS and the inheritance of CTS have been mutually exclusive until now.

1.2. Genes and loci identified in RE and ARE

To date, a number of genes have been linked to the RE spectrum, with some identified in families with CTS, such as *GRIN2A*, and some that were identified by genome-wide linkage analysis (GWLS), such as *ELP4*. Other genes that were suggested to be associated with RE also play vital roles in other epileptic disorders, including *BDNF*, *KCNQ2*, *KCNQ3, DEPDC5*, *RBFOX1/3,* and *GABAA-R*. In addition to particular genes, recurrent copy number variants (CNVs) in specific loci have also been found to be related to seizures [30–32]. A large number of CNVs were found in a cohort of 47 RE patients [33]. After exclusion of non-recurrent CNVs that were not clinically necessary, the recurrent 16p11.2 microduplication was the first to be associated with RE. Furthermore, Reinthaler et al. [34]; revealed that 1.53% of patients carried the variants, which highlighted a significant association of this locus in RE/ARE patients (7/440 RE/ARE patients versus 32/65046 controls, $p = 7.53 \times 10^{-9}$). Moreover, no enrichment of the 16p11.2 microduplication was found in other common epilepsy syndromes, such as genetic generalized epilepsy (GGE) or mesial temporal lobe epilepsies (mTLEs), suggesting its selective contribution to RE/ARE. Two of the families carried other variants of known RE-related genes, *GRIN2A* and *DEPDC5* in addition to the 16p11 microduplication. However, in the case of *GRIN2A*, the specific EEG trait segregated with the *GRIN2A* mutation, and the 16p11.2 microduplication did not seem to be necessary for the phenotype. Interestingly, 16p11.2 is also a known risk factor for ASD [35]; however, its pleiotropic nature in RE/ARE and ASD has remained unclear until now. The paroxysmal kinesigenic dyskinesia (PKD)-related gene *PRRT2*, which is localized in 16p11.2, appeared to be a putative genetic factor of RE. Che et al. performed a comprehensive genetic mutation screening of the *PRRT2* gene in a cohort of 53 sporadic RE patients, and no variant was found, indicating that the *PRRT2* mutations might not be associated with RE [36].

1.2.1. Brain-derived neurotrophic factor: BDNF

BDNF is located on the short arm of chromosome 11, encoding a protein that is a member of the neutrophin family of growth factors. There is much evidence of *BDNF*'s effect on the central nervous system, and its role as a putative cellular effector of recurrent epileptic seizures in the dentate gyrus [37]. However, the most studied and promising variant of *BDNF* in the field of seizures, p.Val66Met, was not associated with temporal lobe epilepsy or febrile seizure in two different studies [38,39]. In the only case-control study of the p.Val66Met polymorphism of *BDNF* in RE, Gkampeta et al. found no p.Val66Met variant in 60 RE patients, suggesting that *BDNF* p.Val66Met does not contribute significantly to RE [40]. However, other polymorphisms in *BDNF* have not been studied and warrant further investigation.

1.2.2. DEP domain containing 5: DEPDC5

DEPDC5 is located on chromosome 22 and encodes a member of the IML1 family of proteins that play important roles in the regulation of the mechanistic target of the rapamycin complex 1 (mTORC1) pathway. Aberrant activation of the mTOR1 pathway alters cortical brain development dramatically and is associated with epilepsy [41]. Mutations in *DEPDC5* were first identified as a crucial contributor in a variety of non-lesional autosomal dominant focal epilepsies, including familial focal epilepsy with variable foci (FFEVF) [42], autosomal dominant nocturnal frontal epilepsy (ADNFLE) [43], and other rare genetic focal epilepsies [44]. Later, Lal et al. identified seven rare variants in 207 probands with RE, four of which were predicted to be severely damaging by in silico tools. However, the variants were all present in unaffected family members, indicating a rare, but potentially important role of *DEPDC5* in RE with incomplete penetrance [45]. Van Kranenburg et al. further investigated three of the reported variants, p.Val90Ile, p.Val272Leu, and p.Ser1162Gly, with regards to DEPDC5 function. Their *in vitro* effects on TORC1, GATOR-1 complex formation, and their interactions with active RAG-A–RAG-C complexes were assessed; however, none of them showed pronounced differences compared with wild-type DEPDC5 [46]. Thus, the pathogenicity of *DEPDC5* variants still requires further investigation.

1.2.3. Elongator Protein Complex 4: ELP4

ELP4 was located to 11p13 by fine mapping after the identification of linkage to CTS. ELP4 is one of the six subunit of ELP. There is little information on the mechanism of epileptogenesis for *ELP4*. One of the presumed functions of aberrant ELP4 is dysregulation of the maturation of cortical projection neurons [47,48]. Moreover, in humans, the gene locus of *ELP4* is in close proximity to *BDNF*, which enhances the possibility that *BDNF* and *ELP4* act together in RE [49]. Several polymorphic markers in the ELP4 gene showed association with the CTS phenotype; however, no causative variant was identified [28]. Later, the role of *ELP4* in RE was questioned by several reexamination analyses. A study comprising 60 RE patients and 60 controls tested two single nucleotide polymorphisms (SNPs) in *ELP4*, rs964112 and rs11031434, discovered in a previous study, but found no significant difference between the cases and controls [40]. Reinthaler et al. performed whole exome sequencing to analyze *ELP4* in 204 patients (182 RE and 22 ARE). Four missense variants were identified; however, *in silico* prediction indicated that none of them were damaging, and their frequencies were not different from those obtained for healthy controls in the public database.