RESEARCH PROGRESS OF EPILEPSY GENE AND ITS THERAPEUTIC SIGNIFICANCE

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ABSTRACT

Objective: *Epilepsy is the general name of a kind of disease with the characteristics of recurrent seizures. Due to its different syndromes, different phenotypes and individual differences, it brings challenges to clinical treatment.*

Methods: *At present, clinical treatment is limited to the combined application of a variety of antiepileptic drugs with different action mechanisms, which can only control some symptoms, and more than one third of patients may even aggravate the disease. However, great progress has been made not only in the research of gene mutations leading to epilepsy, but also in the molecular level of clarifying the pathogenesis of epilepsy.*

Results: *This paper summarizes the research progress of three proteins closely related to the pathogenesis of epilepsy and discusses the possibility of their treatment.*

Conclusion: *In the next few years, the treatment of epilepsy may be different from the empirical treatment at this stage, but adopt the "precision medical" method for individualized targeted treatment.*

Keywords: *Epilepsy, gene mutation, protein, precision medicine.*

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Introduction

Epilepsy is one of the common diseases of the nervous system, affecting about 10% of the global population, of which about 1% suffer from epilepsy. Clinical seizures are short-lived clinical symptoms caused by abnormal discharge activities of neurons in the brain.

The attack needs to have the following elements:

- Mode of onset and termination;
- Clinical manifestation;
- Abnormal enhanced neuronal discharge characteristics.

The etiology of epilepsy is not very clear. Children's epilepsy is mostly related to heredity, perinatal injury and abnormal development of neonatal cerebral cortex[(1)]. In adults without epilepsy susceptibility factors, it is mostly caused by sequelae of encephalitis and meningitis, craniocerebral injury and intracranial tumor[(2)]. In the elderly, the incidence of epilepsy is also related to primary neurodegeneration[(3)]. Epilepsy genetics can be roughly divided into two categories: one is single gene epilepsy, that is, genetic diseases caused by a specific gene abnormality on the chromosome; The other is polygenic epilepsy, which is a genetic disease caused by multiple gene mutations on the chromosome. Epilepsy genetics is changing from gene level to molecular level. This paper mainly discusses the correlation between synaptic fusion protein binding protein, sodium channel protein, potassium channel protein and epilepsy genetics.

Synaptic fusion protein binding protein

Stxbp1, which encodes synaptic membrane fusion protein-1 (stxbp1), is located on chromosome 9 and is related to synaptic vesicle transport and neurotransmitter release. It mainly promotes vesicle initiation by regulating syntaxin-1a,Participate in the formation of soluble N-methyl maleamide sensitive factor attachment protein receptor (SNARE) complex and the fusion of synaptic vesicles and presynaptic membrane, and regulate the release of neurotransmitters[4, 5].

Mutations in stxbp1 are associated with severe early-onset epileptic encephalopathy.Stxbp1 gene mutation was first discovered by Japanese scholar saisu in children with Ohtahara syndrome (OS) in 2008[6]. The types of OS seizures include epileptic spasm, focal seizures, tonic seizures, etc. the electroencephalogram (EEG) shows that there are outbreak inhibition patterns in the EEG whether in awake or sleep.Accompanied by severe mental retardation, the mortality rate is very high.

The related clinical phenotypes of stxbp1 gene mutation are epilepsy and psychomotor retardation. Epilepsy symptoms are mostly concentrated from 13 hours to 13 years old after birth, and most of them occur in infancy. Clinically, epilepsy is mostly intractable epilepsy, and spastic and focal seizures are the most common[7, 8]. Currently reported stxbp1 encephalopathy carries heterozygous mutations, ranging from whole gene deletion to single point mutation of the whole gene length[9]. Another important clinical phenotype is psychomotor retardation. All children with stxbp1 deficiency show different degrees of mental retardation and are not parallel to epileptic symptoms[10]. Heterozygous mutations of stxbp1 gene include frameshift, missense, splice site and nonsense mutation, and whole gene and intragene deletion. Most of them are stxbp1 gene point mutation, deletion and insertion. Missense mutation will destroy the stability of stxbp1 protein, resulting in protein aggregation and degradation. These misfolded proteins may affect the stability of their binding proteins and produce CO aggregation[11, 12].

At present, the treatment plan for epilepsy caused by stxbp1 gene mutation only focuses on controlling the corresponding clinical symptoms, and only half of the children can control the symptom attack through epilepsy drugs. It is possible to carry out targeted treatment for the pathogenesis in the future[13]. The action site of levetiracetam (Lev) is synaptic vesicle protein SV2A, which is a specific membrane glycoprotein of neuronal secretory vesicles. Lev is considered to be the first choice for the treatment of epilepsy caused by stxbp1 gene mutation by inhibiting the release of calcium channel and intracellular calcium[14, 15]. Stxbp1 related epilepsy is complex and changeable.

Patients with early-onset epilepsy combined with psychomotor retardation should actively look for its potential cause. For those with unknown etiology, genetic testing should be carried out as soon as possible and targeted individualized treatment should be taken (Figure 1).

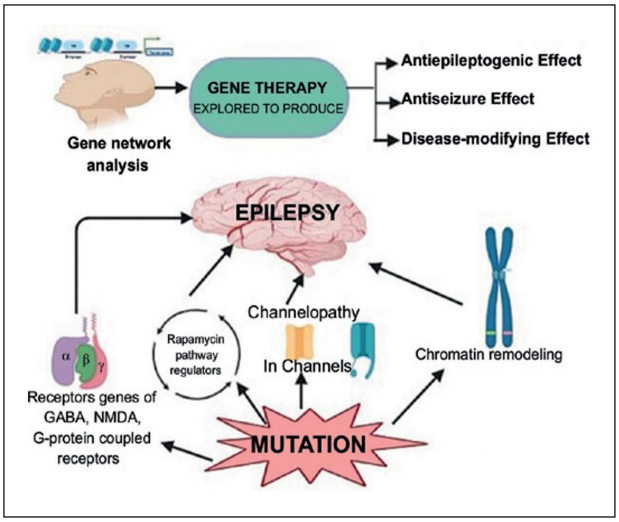

Figure 1: Schematic of EPILEPSY GENE and mechanisms.

Sodium channel protein

Scn2a gene is located on chromosome 2, which contains 26 exons and encodes neuron voltage-gated type II sodium channel protein (NaV1.2), which is an autosomal dominant inheritance[16]. Mutations in scna2 gene not only lead to seizures, but also to developmental retardation, schizophrenia and ataxia[17-20]. Nav12 is abundantly expressed in the axon initial segment (AIS), so it plays an important role in the excitation of neurons and plays an important role in the initiation and conduction of action potentials[21]. Scn2a gene mutation is one of the most common causes of neurodevelopmental disorders. Its phenotypes include OS, eimfs, infantile spasm and darvet syndrome.

Scn2a is divided into three phenotypes: benign familial neonatal seizures (bfnis), developmental epileptic encephalopathy (DEE), and delayed encephalopathy (id/asd) with intellectual disability and / or autism. Bfnis accounts for about 20% of the phenotypic spectrum[17,20,24-26], and is related to Scn2a missense mutation[27]. Its seizure types include focal

clonic, tonic and generalized tonic clonic seizures. The focal seizures are characterized by eye and head deviation, followed by tonic clonic movement. The seizure frequency varies from person to person[28]. The possible cause of the initial seizure is the drug resistance to standard antiepileptic drugs (AED)[17]. The EEG in the interictal period shows the normal background activity of focal or multi focal peaks, which may be completely normal in some cases.Bfnis pedigree related epilepsy is easy to be controlled by AEDs or stop without treatment, but paroxysmal ataxia is difficult to be corrected by drugs[20, 29].

Dee is the most common clinical manifestation in Scn2a[17, 30]. Most newborns with Dee have seizures three months after birth. At present, there are two types of epilepsy syndromes that can be determined: OS and eimfs. OS is the most common phenotype of dee. The egg of eimfs shows that seizures migrate from one cerebral hemisphere to the other. EEG shows a sudden inhibition mode at the initial stage of eimfs; Both are related to Scn2a gene mutation[22]. The study found that phenytoin sodium (PHT) has the best effect on Dee phenotype at this stage. About half of epilepsy can reduce the seizure frequency by 40% - 80%, and about 30% of patients can completely control their symptoms[31].Studies have shown that the loss of function (LOF) mutation of perfect pathogenic gene leads to no epilepsy in ID, while Nav12 gating changes lead to Dee, and slight gain of function (GoF) mutation of pathogenic gene leads to bfnis[32], which reduces neuronal excitability and presents ASD phenotype. Scn2a gene mutations of ID/ASD phenotype are mostly truncation mutations, and a few have missense mutations. The symptoms of ID / ASD occur 6 months after birth[17, 33, 34], and children are mostly characterized by decreased communication ability, uncoordinated movement, gastrointestinal dysfunction and sleep problems[30]. Sodium channel blockers are ineffective for children with ID/ASD and even aggravate symptoms. Sodium valproate (VPA), benzodiazepines (BZDs) and LEV are recommended for treatment. Ketogenic food (KD) can protect brain neurons, inhibit abnormal discharge and achieve anticonvulsant effect. It can replace glucose to supply energy for the body. It has been used in the treatment of refractory epilepsy and epileptic encephalopathy, but the safety and exact efficacy of KD treatment are still unknown.

Potassium channel protein

Sporadic ataxia (EAS) belongs to paroxysmal dyskinesia (PMDS). EAS is divided into 8 subtypes. The gene of EA1 is KCNA1, which is an autosomal dominant disease located on chromosome 12p13. KCNA1 gene encodes 495 amino acids, voltage-gated potassium channel Kv1oneαSubunit[35]. KCNA1 is 40 human kVαOne of the subunit genes, distributed in 12 different gene subfamilies[36].Kv1.1 it plays a role in regulating neuronal excitability by controlling action potential properties, repolarization and discharge characteristics [37], because it has a lower activation threshold and plays a role in balancing depolarization and preventing neuronal overexcitation. Kv1.1, Kv1.2, Kv1.The expression of subunit 4 in the brain depends on brain region, cell type and subcellular localization[38], but Kv1The level of Kv1 is low in cerebellum and hippocampus[39], which is particularly vulnerable to Kv11 injury caused by loss.The disease most associated with KCNA1 mutation is EA1. At the cellular level, basket cells form inhibitory synapses on Purkinje cells, and KCNA1 is expressed in interneurons including cerebellar basket cells[40].

The general age of onset of EA1 is under 20 years old. The inducements are mostly related to the stimulation of stress sources such as exercise, emotional stress and temperature[41]. The clinical manifestations are ataxia, myasthenia and dysarthria[35, 42]. Epileptic symptoms are more common in EA1 patients, which seem to be related to kv11. The function of hole area is affected. Kv11 is widely expressed in brain neurons, including hippocampus, peripheral neurons and cerebellum. It is located in axons in cells, including unmyelinated axons, axon initiation segments and myelinated axons near the paranodal region, affecting action potential propagation, repetitive discharge characteristics and neurotransmitter release[37, 43]. When kv1When the neuron function of subunit 1 is defective, it shows increased excitability at the level of axon and multicellular network, and then presents epileptic symptoms[44].

Most of the KCNA1 gene mutations in EA1 patients with epilepsy are located in kv1S1, S2 and other specific areas of 1[45], with high concealment, are not easy to be found. In the case of infantile epilepsy with generalized tonic clonic seizures or focal seizures, followed by transient ataxia, myotonic, motor retardation, cognitive dysfunction, decreased language expression, etc., and without obvious abnormalities in cranial imaging and various examinations, it is necessary to consider the possibility of EA1. Full exon gene sequencing should be carried out in time to find out whether there are

other phenotypes of EA1, So as to carry out targeted treatment. Unfortunately, there is no targeted drug for epilepsy caused by KCNA1 gene mutation at this stage. KD with high fat, low carbohydrate and low protein is a treatment that can reduce the frequency of seizures[45, 46]. Amanda Rogers[47] et al.

Found that the combined use of acetazolamide, lamotrigine and sodium valproate improved the seizures of patients with the P405L variant site of KCNA1 gene, but had resistance to the patients with the p405s variant site. Two children with the p403s variant site of KCNA1 gene had different clinical manifestations after taking lamotrigine (LTG), It is considered to be related to newborn site mutation.

Conclusion

Gene sequencing increasingly reveals the role of non-coding genetic materials in the human genome[48, 49]. It is recommended that all forms of epileptic encephalopathy should be tested as soon as possible, which is helpful to judge the type of disease and provide a reference basis for disease prognosis and genetic counseling. At present, AEDs are mostly used in clinical treatment, which can only control some symptoms. More than one-third of patients may be ineffective or even aggravate the disease. With the in-depth study of the molecular pathogenesis of epilepsy, our understanding of epilepsy has been improved, and more individualized treatment schemes will be adopted for patients. In the future, we will focus on the clinical phenotype brought by mutant genes, Looking for appropriate treatment to control symptoms, rather than relying on the empirical application of genes to specific drugs.

There is still a long way to go to fully integrate precision medicine into clinical practice. In the future, we should improve our knowledge of pharmacogenomics, including but not limited to efficacy, pharmacokinetics, pharmacodynamics and susceptibility to adverse reactions, so as to obtain the results of precision medicine and improve patients' health.

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