Annals of Genetics and Genomics

Review Article

Genetic Variations of GABA Metabolism Pathway and Epilepsy

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Abstract

Epilepsy is a kind of paroxysmal brain dysfunction disease, which is the result of the imbalance between excitation and inhibition of brain neurons. Gamma-Aminobutyric acid is the most important inhibitory neurotransmitter in the brain and plays an important role in the occurrence and development of epilepsy. Abnormalities in all aspects of the metabolic pathway of GABA in the body, including GABA synthesis, transport, receptor gene variation, and GABA inactivation, will lead to epilepsy. Among them, the mutation of GAD1 gene leads to the loss of catalytic activity, which is more likely to have seizures. PNPO gene mutation leads to PLP deficiency. In the process of GABA transport, SLC6A1 gene mutation may lead to the decrease or loss of GABA transport activity, leading to seizures. Receptors such as GABRA1, GABRA2, GABRA5, GABRB1, GABRB2, GABRB3, GABRG2 and GABBR2 are common epileptic genes that encode GABA receptor genes. These gene mutations lead to a variety of epileptic syndromes with different clinical phenotypes mainly by reducing the level of receptor expression and the amplitude of GABA-evoked current. Finally, in terms of metabolism, GABA is metabolized by GABA transaminase and succinate semialdehyde dehydrogenase, which are encoded by ABAT gene and ALDH5A1 gene respectively. ABAT and ALDH5A1 mutations will show symptoms related to GABA transaminase deficiency and succinate semialdehyde dehydrogenase deficiency, such as epilepsy and cognitive impairment. This article will focus on the research progress of the relationship between the gene variation of GABA metabolic pathway and epilepsy, to provide a basis for accurate diagnosis and treatment of patients with epilepsy.

Keywords: GABA; Epilepsy; GABA receptor; GAT-1; GABA transaminase; Succinate semialdehyde dehydrogenase

Abbreviations & Acronyms

GABA: Gamma-Aminobutyric Acid; GAD: Glutamate Decarboxylase; GABA-T: GABA Transaminase; EEG: Electroencephalogram; MRI: Magnetic Resonance Imaging; SSADH: Succinate Semialdehyde Dehydrogenase; PNPOD: Pyridoxamine 5'-Phosphate Oxidase Deficiency; GABA-TD: GABA-Transaminase Deficiency; SSADHD: Succinic Semialdehyde Dehydrogenase Deficiency; DDE: Developmental and Epileptic Encephalopathy; MAE: Myoclonic-Atonic Epilepsy; CAE: Childhood Absence Epilepsy; JME: Juvenile Myoclonic Epilepsy; EE: Epileptic Encephalopathy; ID: Mild Mental Retardation; FS: Febrile Seizure; GEE: Hereditary Generalized Epilepsy; FS+: Febrile Seizure Addition Syndrome; EMAS: Epilepsy with Myoclonus-Atonic Seizure; GEFS+: Generalized Epilepsy with Febrile Seizures Plus; AD: Autosomal Dominant; AR: Autosomal Recessive; XD: X Chromosome Dominant; ASM: Antiseizure Medications; VPA: Valproic Acid; VGB: Vigabatrin; KD: Ketogenic Diet; PLP: Pyridoxal Phosphate; TGB: Tiagabine; OXC: Oxcarbazepin; LTG: Lamotrigine; CBZ: Carbamazepine; VNS: Vagus Nerve Stimulation; PB: Phenobarbital; ESX: Ethosuximide; RAPA: Rapamycin; DRE: Medically Refractory Epilepsy; DD: Developmental Retardation

Citation: Feng Y, Wei Z-H, Qiao X-Z, Deng Y-C. Genetic Variations of GABA Metabolism Pathway and Epilepsy. Ann Genet Genom. 2021; 2(1): 1006.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Nov 10th, 2021

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Introduction

Epilepsy is a common chronic neurological disease. In China, the incidence of epilepsy is 7/1000. Finding its pathogenic factors can provide a basis of individual accurate diagnosis and treatment [1]. In 1950, Eugene Roberts first reported that Gamma-Aminobutyric Acid (GABA) is a non-protein amino acid in the brain. Its physiological function is related to regulating synaptic transmission, promoting neuronal development, preventing insomnia and depression [2]. GABA is the most important inhibitory neurotransmitter in the brain, which is widely distributed in the brain [3]. With the continuous progress and update of research methods and techniques, the role of gene variation in GABA metabolic pathway in the mechanism of epilepsy has been paid more and more attention. In presynaptic cytoplasm, glutamate produces GABA under the action of Glutamate Decarboxylase (GAD) and coenzyme Pyridoxal Phosphate (PLP), which is stored in vesicles and released into the synaptic space through exocytosis to bind to the receptor on the postsynaptic membrane. GABA transporter absorbs GABA into surrounding glial cells and degrades to succinate under the action of GABA Transaminase (GABA-T) and Succinate Semialdehyde Dehydrogenase (SSADH). Succinic acid reproduces glutamate through tricarboxylic acid cycle, which completes glutamate-GABA- glutamate cycle. Epilepsy may be due to extensive changes in the function of GABA, resulting in reduced neuronal inhibition and destruction of brain neuronal excitation-inhibition balance [4,5]. Abnormalities in all aspects of the metabolic pathway of GABA in the body, including GABA synthesis, transport, receptor, inactivated gene variation, and abnormal function of regulatory interneurons, will lead to epilepsy genesis. In this paper, the research progress on the relationship between gene variation in GABA metabolic pathway and epilepsy is reviewed.

GABA Synthesis

GABA is synthesized by the action of GAD and coenzyme PLP on glutamate. GAD is widely distributed and located in the axon terminals of inhibitory neurons, as well as in cell bodies and dendrites. GAD is located in the GABA neurons of the central nervous system or outside the β cells of the pancreas [6]. The two subtypes of GADS, GAD67, and GAD65, are expressed by different genes and have different regulatory processes and molecular characteristics. The molecular weights of GAD67 and GAD65 are 67 and 65 kDa, respectively. The GABA level of GAD65/GAD67 double gene knockout mice was very low. However, these mice had no general brain histological changes. No obvious developmental abnormalities were found in GAD65 knockout mice, and the basic level of GABA was normal, but these mice were more prone to seizures and anxiety. More than 90% of the GABA in the brain is produced by GAD67, which is necessary for the cerebral cortex to suppress the production of electrical signals [7]. GAD1 gene is located in 2q31.1. It has 21 exons and encodes GAD67. NicolasChatron et al reported 11 patients with developmental and epileptic encephalopathy from 6 independent consanguineous families in 2020 [8]. All patients carried a homozygous variation of GAD1 gene, and a total of 5 different variation sites were detected, including 1 missense variation, 1 nonsense variation, 2 insertion-deletion variations, and 1 splice site variation. At present, 23 pathogenic variants of GAD have been found, which are early-onset seizures (2 to 6 months), GTCS or myoclonic seizures, focal motor seizures, Electroencephalogram (EEG) shows common burst-inhibition or explosive attenuation in neonatal period, and MRI shows dysplasia of the corpus callosum, progressive cerebellar and cerebral atrophy, and joint contracture or equinovarus, cleft palate, omphalocele and facial deformities in the peripheral system. For epilepsy with GAD1 gene mutation, vigabatrin is effective or combined therapy in the early stage, but the problem of brain development cannot be solved. GAD1 mutation leads to loss of catalytic activity and is more likely to have seizures. As a coenzyme of GAD, PLP participates in the synthesis of GABA. Pyridoxamine 5-phosphate produces PLP under the catalysis of pyridoxine phosphate oxidase [9]. PLP is the active form of vitamin B6, which plays an auxiliary role in more than 140 enzymes in the human body, many of which are involved in the synthesis and degradation of neurotransmitters. PLP deficiency can be manifested as seizures, growth retardation, and so on. PNPO gene encodes pyridoxine 5-phosphate oxidase, which is located in 17q21.32 and has 7 exons, the size of which is 7.7kb [10]. PNPO deficiency is an autosomal recessive PLP vitamin responsive epileptic encephalopathy. Alghamdi M reported 87 patients with PNPO deficiency in 2020 [11], showing neonatal epileptic encephalopathy. Seizures can occur on the first day after birth, and the most common are long-term seizures and recurrent status epilepticus. It can also be characterized by clonic seizures (focal and multifocal), tonic-clonic seizures, generalized seizures, and abnormal motility. The most common feature of EGG is the burst-inhibition mode, followed by multifocal spike and spike waves, as well as generalized spike discharges. The most common brain imaging abnormalities in MRI are brain dysplasia, diffuse atrophy delaying myelin formation and atrophy because PLP is the coenzyme of multiple enzymes in the body. Therefore, PNPO mutations can also affect multiple systems, such as prenatal and perinatal complications, including preterm delivery, fetal distress and intrauterine growth restriction with oligohydramnios, hematology with normal red blood cell anemia or pancytopenia, eye changes in pigmented retinopathy, gastrointestinal manifestations, including abdominal distension, constipation, biochemical features including increased urinary vanillic acid, decreased PLP in cerebrospinal fluid, and increased glycine in cerebrospinal fluid. For epilepsy with PNPO gene mutation, it is ineffective to conventional anticonvulsant drugs. Early administration of pyridoxal phosphate can effectively improve seizures.

Transport of GABA

The transport of GABA is mediated by transporters. Since the advent of cloning technology, many GABA transporters have been found. Four subtypes of GAT-1, GAT-2, GAT-3, and BGT-1 [12], GAT-1 is a voltage-dependent GABA transporter responsible for re-uptake of GABA from synapses. GAT-2 locates at presynaptic nerve endings to maintain plasma levels of taurine and GABA [13]. GAT-3 is located on extra synaptic astrocytes and neurons responsible for GABA uptake. BGT-1 is mainly located in renal cells transporting betaine and maintaining the osmotic pressure of renal epithelial cells, transporting betaine and acting as an osmotic regulator, also known as betaine transporter. GABA is released from the vesicles of the axonal terminals of presynaptic inhibitory intermediate neurons, affecting the cell bodies and dendrites adjacent to postsynaptic targets. In this neural circuit, the outgoing GABA activates the GABA receptor located on the postsynaptic membrane. Once GABA is released, it spreads through the synaptic space and is cleared by plasma membrane transporters [14]. GABA uptake by astrocytes cannot be used immediately for synaptic transmission. In contrast, the GABA absorbed by the axon terminals either undergoes the same transformation as astrocytes (significantly different from the fact that the nerve endings contain GAD and can re-synthesize GABA) or circulate directly into synaptic vesicles. Therefore, GABA uptake by neuron transporters is more likely to be further released. Transporters play an important role in maintaining GABA-Ergic neurotransmission [15]. The SLC6A1 gene is responsible for coding GAT-1, which is located in 3p25.3 and has 18 exons [16]. Katrine M Johannesen reported 34 patients with SLC6A1 mutations in 2017 [17], of which 18 missense variants, 2 splice site variants, 1frameshift mutation, 3 nonsense variants, and 1 frame deletion mutation were found. So far, a total of 72 pathogenic variants have been found. It is characterized by agitation, myoclonic atonic seizures, mild to moderate mental retardation, speech disorders, behavioral problems (such as hyperactivity, inattention, aggressive and autistic characteristics), ataxia, and so on. EEG is common in diffuse irregular spikes, multi-spikes, and slow waves. Most people have normal MRI, and a few abnormalities are mild dysplasia or enlarged frontal lobe space. Valproic acid is the most effective drug for SLC6A1 mutation epilepsy, which enhances the effect of GABA by inhibiting the degradation of GABA and increasing its production. GAT1 selective inhibitor Tiagabine (TGB) can also be used for treatment. SLC6A1 mutations may lead to the decrease or loss of GABA transport activity, and the decrease of GABA transport may lead to a decrease in intracellular GABA levels, leading to seizures and highly synchronous epileptic neuronal activity.

GABA Receptor

GABA receptors can be divided into GABAA type ($GABA_A$) and GABAB type ($GABA_B$) receptors. $GABA_A$ receptors are ligand-gated chloride ion channels and $GABA_B$ receptors are G protein-coupled receptors. $GABA_A$ receptors are hetero polymers composed of different subunits (α1-α6, β1-β3, γ1-γ3, δ, ε, π, θ, ρ1-ρ3). Most $GABA_A$ receptors contain two α subunits, two β subunits, and the other is usually γ subunit. Each subunit has four transmembrane domains

(four α-helix M1-M4), and the second transmembrane domain (M2) of five subunits is combined to form the central ion channel [18,19]. $GABA_A$ receptors are ligand-gated chloride ion channels that mediate fast synaptic inhibition. Once GABA binds to $GABA_A$ receptors, ion channels open, and chloride influx or outflow [20]. The direction of chloride ion depends on its concentration gradient and is regulated by KCC2 and NKCCl co transporters. In the immature neurons of the embryonic nervous system, NKCCl is dominant, resulting in an increase in intracellular cl^- concentration, resulting in GABA-mediated cl^- outflow and cell membrane depolarization, which makes neurons excited. It is of great significance for the excitability, differentiation, migration, and proliferation of neurons. In mature neurons, high expression of KCC2 leads to low intracellular chlorine concentration, and then GABA mediates cl^- influx, resulting in hyperpolarization of cell membrane and inhibition of neurons. The correct expression of each subunit gene is of great significance to the function of $GABA_A$ receptor. The mutation will cause epilepsy and other nervous system diseases. $GABA_B$ receptor is a heterodimer composed of GB1 subunit and GB2 subunit. GB1 subunit includes GB1a and GB1b, which are two products of gene GABBR1 transcribed by different promoters. GB2 subunit is encoded by gene GABBR2 [21]. Axons mainly express GB1a/2 receptors. Dendrites express both GB1b/2 receptors and GB1a/2 receptors. $GABA_B$ receptor is a G protein coupled receptor, which mediates slow synaptic inhibition. When GABA is released into the synaptic gap, it binds to the VFT domain of GB1 and activates the receptor. The transmembrane domain of GB2 binds to GDP-Gi protein and catalyzes the conversion of GDT to GTP, Gi protein dissociation to Gαi and Gβγ. Gαi inhibited Adenylate Cyclase (CA) and decreased intracellular cAMP level, while Gβγ activated G protein coupled inward rectifier potassium channel (GIRK) to induce K+ efflux. Potassium Channel Tetramerization Domain Protein (KCTD) was assembled into the C-terminal of GB2, and $GABA_B$ signal pathway was regulated by separating Gβγ from GIRK. It can self-inhibit the release of GABA or inhibit the release of other presynaptic transmitters (glutamic acid, norepinephrine, 5-hydroxytryptamine or dopamine, etc.), and regulate the excitability of neurons. GABRA, GABRB, GABRG, and other genes encode GABRA receptor, and GABBR encodes receptor protein GABRB receptor. The mutation of each receptor gene can cause epilepsy (Figure 1).

GABRA1

GABRA1 gene is located in chr5q34, long 4238bps, contains 10 exons (NM_001127644.2), encodes $GABA_A$ receptor A1 subunit protein (456aa), and is widely and highly expressed in various regions of the brain [22]. Most of the GABRA1 gene mutation epilepsy is a new mutation, which is autosomal dominant inheritance, and most of them are missense variation. Its phenotypes include developmental epileptic encephalopathy-19 (DEE19), Dravet syndrome, ohtahara syndrome, infantile spasm, Lennox-Gastaut syndrome (LGS), idiopathic generalized epilepsy-13 (EIG13), childhood absence epilepsy-4 (ECA4) and adolescent myoclonic epilepsy-5 (EJM5) [18]. The first attack of DEE19 occurs before the age of one year. There are various types of seizures. Focal seizures, myoclonic seizures, and GTCS are common in DEE19. Fever and flash stimulation are easy to induce. Children are accompanied by varying degrees of mental and motor retardation and language retardation. Most of the MRI were normal. EEG showed abnormal background, global spike slow wave emission, burst-inhibitory discharge, peak irregularity (West syndrome). In terms of treatment, vigabatrin and valproic acid are GABA transaminase inhibitors, which can effectively reduce seizures. However, the mechanism of OXC exacerbation is unknown and should be carefully selected. Most epilepsy can be controlled by the use of antiepileptic drugs, but children with DEE19 are associated with varying degrees of mental and/or motor retardation. *In vitro* experiments showed that these mutations caused insufficient haploid dose, which was a dysfunctional variation. It decreased the stability of $GABA_A$ receptor protein, the expression of $GABA_A$ receptor composed of this variant subunit on the cell surface and the sensitivity to GABA, which led to the decrease of inhibitory input and increase of excitability of neurons [23,24].

GABRA2

GABRA2 gene is located in chr4p12, long 8520bps, contains 10 exons (NM_000807.4), encodes $GABA_A$ receptor a2 subunit protein (451aa), and is widely and highly expressed in various regions of the brain [25]. Most of the epilepsy with GABRA2 gene mutation is a new mutation, which is autosomal dominant inheritance. The phenotype is DEE78. At present, only 7 cases have been reported, 5 cases had their first attack within 3 months from neonatal period to birth, 1 case had its first attack at the age of 2 years, and 1 case had its first attack at the age of 17 years. Seizures take various forms and vary with the disease. The common clinical manifestations were clonic, GTCS, absence, convulsive seizures and status epilepticus, motor and language retardation, of which 3 patients could not walk (32 months, 5 years old, 11 years old), 2 patients could not speak (32 months, 11 years old), 1 patient had poor language (5 years old), and 2 patients had language retrogression (17 years old, 13 years old). All patients had moderate to severe cognitive impairment. In neurological examination, low tension was found in 5 cases, respiratory distress in 2 cases, cortical visual impairment in 2 cases, motor disturbance (spasm, dance movement) in 2 cases, and pyramidal symptoms in 1 case. EEG showed that epileptic discharge included multifocal spike wave, global spike wave, and multi-spike wave. MRI showed normal in 5 cases, myelin dysplasia in 2 cases, extensive brain atrophy, and short thin corpus callosum in 1 case. Conventional antiepileptic drugs were used, including 4 patients with refractory epilepsy, 1 patient with reduced seizures (topiramate, vigabatrin), and 2 patients without seizures after administration of single drug (oxcarbazepine, lamotrigine). Patients with poor control of epilepsy are often accompanied by severe cognitive, motor retardation and dystonia. A total of 6 mutations of GABRA2 gene were found, all of which were missense and located in the transmembrane region. *In vitro* experiments confirmed that mutations lead to loss of function, reduce the total and cell surface expression of GABRA2, reduce the current induced by GABA, and lead to seizures [26].

GABRA3

GABRA3 gene is located in chrXq28, long 3669bp, contains 10 exons (NM_000808.4), encodes $GABA_A$ receptor A3 subunit protein (492aa), and is widely and highly expressed in various regions of the brain [27]. The epilepsy with GABRA3 gene mutation is X chromosome dominant inheritance and is not completely explicit (the penetrance rate is 14 percussion 16). There were differences in phenotypes among patients with the same variation in the same pedigree (16 carriers in 5 families were reported) [28], including refractory epileptic encephalopathy, mild mental retardation, and 2 asymptomatic cases. Among them, 11 carriers had seizures, and the age of the first episode was between 1 and 21 years old. Five carriers still had no seizures from 19 to 40 years old, and 2 of them had no symptoms. The common features of seizures were GTCS, absence, and tetanic seizures.

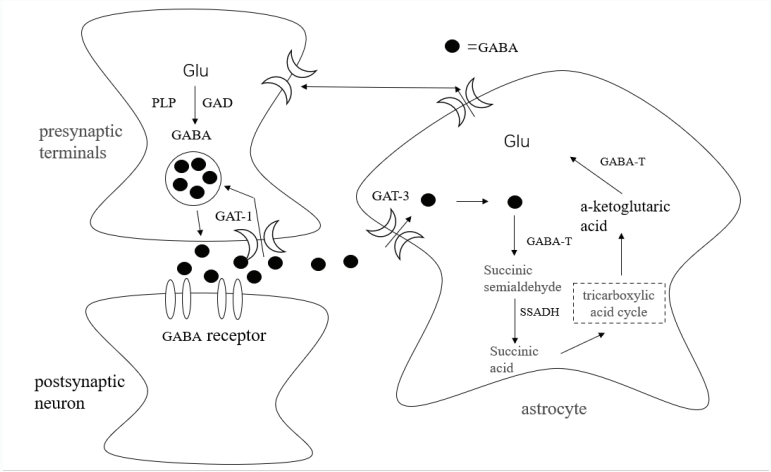

Figure 1: Shows the synthesis, transport, receptor binding and metabolism of GABA in astrocytes.

The carriers of 13 had mild to severe cognitive impairment, often accompanied with language retardation and learning disabilities. Motor retardation can also be seen in a small number of patients, including micrognathia, cleft lip and palate, horizontal nystagmus, and scoliosis. EEG showed slow background, interictal focal or comprehensive spike wave, spike-slow complex wave. MRI is normal. Routine antiepileptic drugs, ketogenic diet, and VNS were used in the treatment, of which 5 patients were refractory epilepsy and 1 patient died accidentally due to seizures. Carbamazepine and valproic acid were effective in 2 patients, lamotrigine + valproic acid was effective in 1 patient, and no intervention was found in 2 patients. At present, a total of 4 gene variants, 3 missense variants, and 1 small fragment repetitive variation have been reported. Two missense variants were located at the extracellular N-terminal and one missense mutation was located in the M4 transmembrane region. *In vitro* studies have shown that these mutations lead to loss of function, missense mutations reduce GABA-mediated currents, and micro repetitive mutations lead to reduced expression of intracellular GABRA3 [29].

GABRA5

GABRA5 gene is located in chr15q12, long 2553bp, contains 11 exons (NM_000810.4), encodes the a5 subunit of $GABA_A$ receptor, and is widely and highly expressed in various regions of the brain [30]. GABRA5 gene mutation epilepsy is a new mutation, which is autosomal dominant inheritance. Phenotype DEE79, only 4 unrelated children were reported [25], the age of onset was 2-4 months old, and the seizure patterns were different, including myoclonic, ankylotic, oropharyngeal automatism, general tonic-clonic seizures, and wandering focal seizures, all of which had severe cognitive and motor retardation, of which 3 patients had no language ability (3-7 years old). Neurological examination revealed hypodystonia and secondary microcephaly in 2 patients and limb spasm and autism in 1 patient. EEG epileptic discharge forms are various, showing extensive background slow wave, multifocal sharp wave emission, or peak irregularity. MRI showed abnormalities in all 4 patients, including thinning of corpus callosum in 3 cases, brain atrophy in 2 cases, hypomyelinization in 1 case, and reduction of white matter volume in 1 case. Given conventional antiepileptic drugs, two existing studies have proposed two different drug selection ideas: first, positive allosteric modulators of GABA receptors (e.g., phenobarbital, clonazepam, etc.) are not recommended for variants that can increase GABA desensitization; second, antiepileptic drugs with different mechanisms can be used in combination, especially drugs with GABA energy mechanisms (e.g., clopazepam, etc.). The controversy over the choice of the drug needs to be answered by more cases and studies. The prognosis of epilepsy patients with GABRA5 gene mutation was poor, and the seizures of all patients were refractory to drugs. One patient had no seizure with zonisamide + levetiracetam + oxcarbazepine, and one patient with phenobarbital + topiramate + levetiracetam + clobazone had reduced seizures. All the patients had severe mental and motor retardation, and two of them had no language development [31]. At present, three different missense variants have been found, including p.Val294Phe (two cases), p.Val294Leu and P.Ser413Phe, in which Val294 is located in the transmembrane region of the protein and Ser413 is located in the intracellular C-terminal. *In vitro* experiments showed that the three variants had different effects on the surface expression and permeability of GABA receptors, but all led to GABRA5 dysfunction and reduced its inhibition on neuronal activity [32].

GABRB1

GABRB1 gene is located in chr4p12, long 1939bp, contains 9 exons (NM_000812.4), encodes $GABA_A$ receptor β1 subunit (474aa), and is widely and highly expressed in various regions of the brain[33]. The epilepsy with GABRB1 gene mutation is autosomal dominant inheritance and the phenotype is DEE45. At present, only three unrelated children have been reported [34-36]. the age of onset is 3-12 months after birth, and the seizures are various and change with age. it can be seen that infantile spasm with high amplitude irregularity EEG, atypical absence, loss of tension and myoclonic seizures, focal seizures, tonic seizures, etc, all showed severe psychomotor retardation before or after seizures. Neurological examination showed that all of them had hypodystonia. One child had symptoms of weakness, ataxia, and cortical visual impairment, and one showed the characteristics of autism. The EEG of children is abnormal and may change with age, including high amplitude irregularity, 2Hz spike, and slow wave discharge or multifocal discharge. MRI showed thin corpus callosum in 1 case and progressive brain atrophy in 1 case, including corpus callosum and frontotemporal lobe. Among the 3 patients who were treated with routine antiepileptic drugs and ketogenic diet, 1 had no seizures at the last follow-up and 1 was refractory epilepsy, which was improved after ketogenic diet adjuvant therapy. At present, three EIEE45-related GABRB1 gene variants have been reported, all of which are missense variants and located in the transmembrane region. *In vitro* studies have found that variation causes changes in

the dynamic characteristics of GABA-induced currents, which is a dysfunctional variation, resulting in damage to the inhibitory effect of GABA energy [35].

GABRB2

GABRB2 gene is located in chr5q34, long 7266bp, contains 10 exons (NM_001371727.1) encoding β 2 subunit (521aa) of $GABA_A$ receptor, and is widely and highly expressed in various regions of the brain [37]. Most of the GABRB2 gene variant epilepsy is a new mutation, which is autosomal dominant inheritance. Phenotypes include benign febrile seizures, febrile seizure addition syndrome (FS+), hereditary Generalized Epilepsy (GEE), and severe developmental epileptic encephalopathy, such as west syndrome, Otahara syndrome, early-onset myoclonic encephalopathy, etc. in addition, there are individual cases of growth retardation without seizures [38]. Most of the disease begins in neonatal-childhood, and a few in 13-18 years old. There are various forms of seizures, the most common tonic clonic seizures, in addition to absence seizures, clonus, myoclonus, epileptic spasm, focal motor, and non-motor seizures, fever is easy to induce seizures. Patients are often accompanied by varying degrees of motor and/or cognitive retardation and retrogression. The earlier the onset of epilepsy and the more severe the symptoms of epilepsy, the more serious the developmental retardation; the mental and behavioral manifestations such as hyperactivity disorder, irritability, obsessive-compulsive, autistic and so on; motor disorders, such as dance sign or hand and foot astragalus (appearing in infancy-early childhood), dystonia, ataxia, tremor, and other motor disorders in some patients, these symptoms are more common in patients with refractory epileptic encephalopathy [39]. Neurological examination showed that it was often accompanied by dystonia, reflex enhancement, cortical visual injury and strabismus in some patients, and microcephaly in some patients. Depending on the severity of the disease, the patient's EEG may be normal or there may be different degrees of epileptic discharge. Epileptic abnormalities include patterns of epileptic encephalopathy, such as peak irregularity, burst inhibition, and slow wave sleep epileptic wave status electroencephalogram, as well as slow background, comprehensive or/and multifocal spike waves, spike waves, multi-spike waves. Individual patients had light paroxysmal reaction. Most of the MRI were normal. Some non-specific changes were seen, including loss of brain volume, dysplasia of corpus callosum and delayed myelination. Antiepileptic drugs and ketogenic diet can be given, but the choice of drugs is still controversial. Some studies have found that antiepileptic drugs targeting GABA pathway (benzodiazepine, vigabatrin, phenobarbital) have no better efficacy or harm to the disease. In the existing cases, levetiracetam and valproic acid are most commonly used in clinic. Some scholars have found that valproic acid has a good effect on the disease. At the same time, some scholars have proposed that levetiracetam and valproic acid have no obvious advantages. Most of the patients who received a ketogenic diet or a modified Atkins diet improved. Patients with GABRB2 gene mutation epilepsy have a poor prognosis (Table 1). About 50% of the patients are drug-refractory epilepsy, and some of them die unexpectedly due to pneumonia and seizures. In addition, patients are often accompanied by varying degrees of growth retardation and mental and behavioral abnormalities, and patients with refractory epilepsy are often associated with severe growth retardation and motor disorders [40,41]. At present, almost all the pathogenic variants reported are missense variants, which are mainly distributed in extracellular N-terminal, M1, M2, M3 transmembrane regions and M2-M3 junction regions. *In vitro* experiments showed that mutation led to the loss of protein and $GABA_A$ receptor function. Previous studies have found that M1, M2, and M2-M3 junction regions are associated with more severe phenotypes, while extracellular N-terminal and M3 are associated with lighter phenotypes [42,43].

GABRB3

GABRB3 gene is located in chr15q11.2-q12, long 5767bp, contains 9 exons (NM_000814.6), encodes $GABA_A$ receptor β 3 subunit (473aa), and is widely and highly expressed in various regions of the brain [39]. Most of the epilepsy with GABRB3 gene mutation is a new mutation, which is autosomal dominant inheritance. There are many phenotypes, such as DEE43, childhood absence epilepsy-5 (ECA5), and febrile seizures [44,45]. The age of seizures is from the first day of birth to 14 years old, and the onset age of DEE43 seizures is mostly between neonatal period and one year old. The main seizures at the beginning include infantile spasm and febrile seizures. With the development of the disease, there are many kinds of seizures, such as tonic clonic seizures, myoclonic seizures, atonic seizures, absence seizures and so on. Fever is easy to induce epileptic seizures. There are often mild to severe mental retardation before or after the attack, and a small number of patients have autistic symptoms. Some of them have microcephaly, abnormal facial appearance and other developmental deformities [46]. All the patients had abnormal EEG, common background activity slowed down, multifocal spike and slow wave discharge, peak irregularity, and burst-inhibition. MRI was usually normal, and a few cases showed thinning of corpus callosum, poor myelination, cortical atrophy and so on. In the treatment of DEE43, in addition to antiepileptic drugs, often need to be combined with ACTH, ketogenic diet or VNS, the prognosis is poor, seizures need to be given a variety of antiepileptic drugs or combined with other treatments to control, patients are often accompanied by mild to severe mental retardation. Febrile seizures, childhood absence epilepsy and so on can be treated with antiepileptic drugs, the prognosis is better, most of them can achieve seizure-free. Most of the GABRB3 gene mutations are missense mutations, and they are mainly distributed in the extracellular N-terminal, TM1 and TM2 domains. *In vivo* and *in vitro* studies have found that these mutations may cause $GABA_A$ receptor dysfunction, reduce GABRB3 gene expression, destroy $GABA_A$ receptor assembly and transport, or reduce sensitivity to GABA transmitters, leading to epilepsy [47].

GABRG2

GABRG2 gene is located in chr5q34, long 3813bp, contains 10 exons (NM_198904.4), encodes R2 subunit (473aa) of $GABA_A$ receptor, and is widely and highly expressed in various regions of the brain [48]. γ2 subunit is assembled into αβγ2 receptor, which is the main subtype of $GABA_A$ receptor in the brain. Phenotypes include severeDEE74, Dravet syndrome, LGS, benign Familial Febrile Convulsion (FEB8), generalized epilepsy with febrile convulsion + 3, and MAE [49,50]. The age of onset is from the first day of birth to 1 year old, and there are various forms of seizures, including tonic-clonic seizures, tonic seizures, focal extension to bilateral tonic-clonic seizures, febrile seizures, and myoclonic seizures. Most patients have other types of seizures (atonic seizures, generalized tonic-clonic seizures, absence seizures, focal seizures). The patient has generalized developmental retardation and impaired intellectual development, especially language retardation or loss. EEG showed that a small number of patients were normal at the initial stage of the disease, with the progression of the disease, all patients could see abnormalities, and with the change of the disease, common diffuse background

slowed down, irregular generalized epileptic discharge. Most of the MRI were normal, and a few showed non-specific abnormalities, such as brain atrophy, ventricular dilatation, and delayed myelin formation. Neurological examination showed hypodystonia, dyskinesia, poor eye contact, autism, a few with abnormal eye movement, abnormal face and so on. In terms of treatment, most of the patients with epileptic encephalopathy are drug-refractory epilepsy, a few patients with levetiracetam alone, combined with valproic acid and topiramate can achieve seizure-free. In some patients, levetiracetam, lamotrigine, and phenobarbital alone can slightly improve the symptoms or be effective for a short time [41,51]. The mutation of GABRG2 gene is autosomal dominant inheritance, and most of them are missense variation. In the same family, there are significant phenotypic differences among different patients with the same mutation, including benign febrile seizures and medically refractory epilepsy. *In vitro* experiments showed that the mutant was a dysfunctional mutation, which could reduce the surface expression of $GABA_A$ receptor or decrease the inhibitory activity mediated by GABA [52]. In general, $GABA_A$ receptor gene mutations have a wide range of phenotypes, ranging from febrile seizure to severe epileptic encephalopathy, and each molecule has a more detailed review reference [18,25,26,28,34,36,38,44,50]. For epilepsy with $GABA_A$ receptor gene mutations, the function of $GABA_A$ receptor should be enhanced in the treatment as a whole.

GABBR2

GABBR2 gene is located in chr9q22.33, long 5499bp, contains 19 exons (NM_005458.8), encodes $GABA_B$ receptor subunit R2 (941aa), and is widely and highly expressed in various regions of the brain [53]. The mutation of GABBR2 gene is autosomal dominant inheritance. Three variants have been found to be new variants and one variation is mosaic inheritance. Phenotype DEE59 has been reported in 4 patients [40,54], all of whom had their first seizures before 1 year old, and there were many types of seizures, including focal cognitive seizures, ankylosis, Generalized Tonic-Clonic Seizure (GTCS), focal clonus, absence, etc., among them, 3 patients had severe generalized growth retardation, 1 patient had mild motor retardation and cognitive impairment, and neurological examination found 3 patients with dystonia. Among them, 2 patients had difficulty eating, 1 patient had mild ataxia, autism and severe sleep disorder, and 1 patient had scoliosis. EEG showed epileptic discharge in all 4 patients, with peak irregularity, comprehensive or multifocal spike slow wave discharge. In MRI, 3 cases were normal and 1 case showed widening of subarachnoid space. Treated with antiepileptic drugs, 3 patients were treated with multiple antiepileptic drugs with poor prognosis, severe mental retardation and motor retardation. One patient had no attack after administration of ethyl succinamide, and the patient received developmental treatment at the same time, and still had mild dyslexia and dyscalculia. At present, four DEE59-related pathogenic variants have been reported, all of which are missense variants, of which 3 variants are located in the extracellular N-terminal domain of TM6,1. The current cases show that when the mutation is located in TM6, the symptoms of the patients are more serious and the prognosis is worse; when the mutation is located in the N-terminal, the symptoms of the patients are mild and the prognosis is better. *In vitro* studies have shown that mutations in TM6 impair the structural integrity of $GABA_B$ receptors, thereby reducing GABA signal transduction [55-57].

Inactivation of GABA

GABA is inactivated by the uptake of presynaptic nerve endings and surrounding astrocytes by GABA. It is possible that most of the GABA released by synapses is absorbed into nerve endings and can then be re-used as neurotransmitters [58]. GABA absorbed by surrounding astrocytes is metabolized by GABA-T and SSADH, and converted to glutamate by the tricarboxylic acid cycle. Glutamate produced in this way can be transferred to GABA neurons and then converted to GABA under the action of GAD. The whole process is often referred to as the GABA-Glu-Gln loop [59]. GABA is co-metabolized by GABA-T and SSADH. GABA-T catalyzes the degradation of GABA to semialdehyde succinate [60]. The ABAT gene encodes GABA-T, which is located in 16p13.2 and has 22 exons [61]. The pathogenic variation of ABAT gene shows symptoms related to GABA transaminase deficiency, such as epilepsy, low intraocular pressure, somnolence and so on. Mary Kay Koenig reported 10 cases of GABA transaminase deficiency in 2017, including 9 cases of ABAT gene mutation and 10 patients with epilepsy [60]. The phenotype was neonatal epileptic encephalopathy, characterized by myoclonus and/

Table 1: Shows the phenotype, inheritance, treatment and prognosis of each gene mutation epilepsy.

	Name	Phenotype	Inheritance	Treatment	Prognosis
GABA synthesis	GAD1	DEE	AR	ASM (VGB, KD)	Effective drug control, DD
	PNPO	PNPOD	AR	PLP	Effective drug control
	GAD2				
Transport of GABA	SLC6A1	MAE	AD	ASM (VPA, TGB)	Effective drug control
	GAT-2				
	GAT-3				
	BGT-1				
GABA receptor	GABRA1	DEE, CAE, JME	AD	ASM (VGB, VPA)	Effective drug control, DD
	GABRA2	DEE	AD	ASM (TPM, VGB, OXC, LTG)	DRE, DD
	GABRA3	EE, ID, FS	XD	ASM (CBZ, VPA, LTG), KD, VNS	DRE, DD
	GABRA5	DEE	AD	ASM (The choice of drugs is controversial)	DRE, DD
	GABRB1	DEE	AD	ASM, KD	unknown (few cases)
	GABRB2	EE, GGE, FS+, EMAS	AD	ASM (LEV, VPA), KD	DRE, DD
	GABRB3	DEE, CAE, FS	AD	ASM, KD, ACTH, VNS	DRE, DD
	GABRG2	DEE, GEFS+	AD	ASM (LEV, VPA, PB, LTG)	DRE, DD
	GABBR2	DEE	AD	ASM (ESX)	DRE, DD
Inactivation of GABA	ABAT	GABA-TD	AR	ASM (VGB)	Effective drug control
	ALDH5A1	SSADHD	AR	ASM (RAPA,LTG, CBZ)	Effective drug control

or GTCS seizures, EEG paroxysmal inhibition, multifocal spikes and generalized spikes, myelin dysfunction and brain atrophy in MRI. In addition to nervous system symptoms, there are hypotension, lethargy, dance movements and rapid growth and development [62]. For ABAT variant epilepsy, vigabatrin, as an irreversible inhibitor of ABAT, has a better therapeutic effect. Seizures occur when the concentration of the inhibitory neurotransmitter GABA in the brain falls below the threshold; increasing brain GABA levels can stop seizures. Previous studies have shown that the enzyme responsible for inhibiting the catabolism of GABA (GABA-T) can effectively inhibit excessive neural activity without affecting the discharge of basal neurons [63]. Semialdehyde succinate is metabolized by SSADH to succinic acid. SSADH is encoded by ALDH5A1 gene, which is located in 6p22.3 and has 10 exons [64]. ALDH5A1 mutation can lead to symptoms related to succinate semialdehyde dehydrogenase deficiency, such as epilepsy, cognitive impairment and dance movements succinic semialdehyde dehydrogenase deficiency, which is a rare autosomal recessive GABA degradation disease [65]. Melissa L. DiBacco reported 24 patients with ALDH5A1 mutations in 2020 [66], usually from late infancy to early childhood, characterized by seizures (myoclonus and/or GTCS), 4-hydroxybutyrate aciduria, cognitive impairment, significant language disorders, low intraocular pressure, hyperactivity, aggression, self-destructive behavior, hallucinations and sleep disorders. The signs of basal ganglia include dance movements, dystonia, common spike discharges of EEG, T2 high signal in many areas of MRI, involving globus pallidus, cerebellar dentate nucleus, subthalamic nucleus, subcortical white matter and brain stem, as well as cerebrum and sometimes cerebellar atrophy. For ALDH5A1 mutant epilepsy, lamotrigine, carbamazepine and rapamycin are effective. Valproic acid can be considered in patients with refractory epilepsy. The effects of vigabatrin on different patients are different. When succinate semialdehyde dehydrogenase is deficient, GABA and succinate semialdehyde accumulate, resulting in a significant increase in brain γ-hydroxybutyric acid and GABA concentrations, which can lead to symptoms related to succinate semialdehyde dehydrogenase deficiency, such as growth retardation, mental retardation, behavioral disorders, psychiatric symptoms, sleep disorders and many neurological symptoms. Such as ataxia and cerebral epilepsy [67,68].

Conclusion

GABA metabolic pathway exists widely in the brain and plays an important role in the occurrence and development of epilepsy. Genetic variations in all aspects of this pathway may have the phenotype of refractory epileptic encephalopathy and need to be newly discovered. Most of the genetic variations in the GABA metabolic pathway are accompanied by developmental disorders of intelligence, movement and language, and some of them are dystonia, ataxia, dance movements and so on. There are some targeted drugs for individual gene mutation epilepsy, such as GAD1 gene mutation epilepsy with Vigabatrin, PNPO gene mutation epilepsy with PLP,SLC6A1 gene mutation epilepsy with TGB, VPA,ABAT gene mutation epilepsy with vigabatrin, VPA and so on. Other drugs such as GBP, PEB, CLZ, TPM, cenobamate can also be used, looking forward to the precise treatment of GAD1, PNPO, ABAT, ALDH5A1 and receptor subunit mutant drugs.

Funding

This study was supported by the National Key R&D Program of China, Precision Medicine Program—Cohort Study on Nervous System Diseases under Grant 2017YFC0907700 (2017-2021).

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