Introduction

Movement disorders often arise from the basal ganglia nuclei or when their connections malfunction, resulting in hypokinetic, hypokinetic, or dystonic disorders [1]. A seizure is the result of abnormally excessive or synchronous neuronal activity in the brain, defined as "momentary arising of signs and/or symptoms," whereas epilepsy is characterized by one or more seizures with a relatively high recurrence risk [2]. Although they are caused by a number of different conditions, both movement disorders and seizures present abnormal movements with coinciding phenomenology [3]. Both movement disorders and epilepsy occur in many genetic disorders ranging from inborn errors of metabolism to developmental and epileptic encephalopathies, epilepsy syndrome with stereotypies, and paroxysmal dyskinesias [3,4].

Paroxysmal dyskinesias are an important disease paradigm associated with overlapping movement disorders and seizures [5]. In many paroxysmal dyskinesias, movement disorders and seizures occur simultaneously at the time of, before, or even a long time after diagnosis. The most well-known is paroxysmal kinesigenic dyskinesia (PKD) in which PRRT2 mutations have been identified. In this case, infantile convulsions often occur in advance [6]. With the development of exome sequencing in recent years, many genetic abnormalities identified in epilepsy that occur in conjunction with paroxysmal dyskinesias have been identified [3,7-9]. This review aims to gather the most updated literature regarding paroxysmal movement disorders, and seizures and we will discuss the genetic abnormalities that come with seizures for each paroxysmal
movement disorders. Table 1 summarizes the clinical manifestations of each epilepsy-paroxysmal movement disorders.

**Clinical overview**

Paroxysmal dyskinesias have distinct features with episodic occurrences of involuntary extrapyramidal movements [3]. It is a heterogeneous disorder group characterized by episodes of abnormal involuntary movements, such as chorea, dystonia, and ballism [3]. Most of these movements do not cause loss of consciousness but sometimes a sensory aura precedes them [3]. Some clinicians may mistake these movements for focal seizures, either focal awareness seizure or focal impaired awareness seizure [3]. In such cases, the absence of ictal discharges in a scalp electroencephalography may be helpful in the diagnosis of paroxysmal dyskinesias [2].

Paroxysmal dyskinesias are divided into three clinical syndromes (Fig. 1): PKD, paroxysmal non-kinesigenic dyskinesia (PNKD), and paroxysmal exercise-induced dyskinesia (PED) [6,8]. PKD is the most common type and is caused by voluntary movements, such as standing from a seated position or transitioning from walking to running. PKD attacks usually develop during childhood and are well controlled by carbamazepine [5,10]. Infantile convulsions, often with choreoathetosis, frequently precede PKD [6]. PNKD attacks are usually triggered by alcohol, coffee, or strong emotions [6], and can often last longer than PKD attacks ranging from 10 minutes to an hour and even up to 12 hours [6]. However, their frequency is low, typically occurring only a few times a year [6]. Of the three paroxysmal movement disorders, PED is the rarest. PED attacks are induced by physical exertion after long periods of exercise with migraines, hemiplegia, ataxia, and epilepsy being associated with PED [6,11].

In terms of co-occurrence with epilepsy, patients with mutations in PRRT2 [9,12], SCN8A [13,14], SLC16A2 [15,16], and CHRNA4 [17] have been reported in PKD (Fig. 1). In PNKD, CACNA1A [18] and KCNMA1 [19]-related diseases have been reported, while SLC2A1-related glucose transporter-1 (GLUT1) protein deficiency [6] and recently, TBC1D24 mutations, have been reported in PED [20]. Other paroxysmal movement disorders associated with epilepsy include hemiplegic migraine and episodic ataxias. A combination of familial hemiplegic migraine and epilepsy have been found in PRRT2, CACNA1A, SCN1A, and ATP1A2 mutation-positive patients [8,21]. In addition, PRRT2 [8], CACNA1A [18], and KCNMA1 [8,22,23] mutations are mainly responsible for the co-occurrence of episodic ataxias and epileptic seizures.

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Causative genes are listed in order of the main type of movement disorders. MD, movement disorder; AD, autosomal dominant; PKD, paroxysmal kinesigenic dyskinesia; BFIS, benign familial infantile seizures; ICCA, infantile convulsion with choreoathetosis; GTCS, generalized tonic-clonic seizures; DEE, developmental epileptic encephalopathy; GEFS+, genetic epilepsy with febrile seizures plus; HM, hemiplegic migraine; EA, episodic ataxia; IS, infantile spasms; PNKD, paroxysmal non-kinesigenic dyskinesia; LGS, Lennox-Gastaut syndrome; PED, paroxysmal exercise-induced dyskinesia; GLUT1, glucose transporter-1; AR, autosomal recessive; EIMFS, epilepsy of infancy with migrating focal seizures; MAE, myoclonic-ataxic epilepsy.

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Historically, paroxysmal dyskinesias and other episodic neurological disorders have been considered an ion channel dysfunction [5]. Accordingly, it has been suggested that the relationship between paroxysmal dyskinesias and epilepsy is in the form of “basal ganglia epilepsy,” meaning that paroxysmal dyskinesias attacks are due to the altered functions of ion channels in both the cortex and subcortex [26]. However, with the discovery of the major paroxysmal dyskinesias genes PRRT2 and SLC2A1, the hypothesis of channelopathy lost its strength because neither encoded ion channels [5]. While novel mutations in genes related to ion channel function, such as KCNA1, KCNMA1, SCN8A, and CACNA1A, have recently been described, genes encoding synaptic proteins/receptors, such as PRRT2, CHRNA4 and transporters including, SLC2A1, SLC16A2, and ATP1A2, have also been identified (Fig. 1) [5]. As the understanding of the genetic basis of epilepsy syndrome and paroxysmal dyskinesias increase, it provides insights into the shared mechanisms behind the two conditions and reveals the role of ion channels and the proteins associated with vesical synapse or energy metabolism [5,6,14,27].

PKD and epilepsy

1. PRRT2

PRRT2, which represents proline-rich transmembrane protein 2, encodes a transmembrane protein involved in synaptic transmission, although its function is relatively unknown [12]. Genetic mutations of PRRT2 not only occur in PKD patients, but also in most cases of benign infantile familial seizure, infantile convulsions with paroxysmal choreoathetosis (infantile convulsion with choreoathetosis, frequent cases of hemiplegic migraine, and a minority of cases of episodic ataxias, childhood absence epilepsy, paroxysmal torticollis, and febrile seizure [5,8,12].

PKD affects about 1:150,000 in the general population [12]. As is well known, the major gene responsible for PKD is PRRT2, and according to the case ascertainment, the frequency ranges from about 40% to 90% or more [5,6,12,28]. A majority of PRRT2 cases have an obvious kinesigenic trigger with anxiety or prolonged exercise triggering PKD attacks in up to 40% of cases [5]. PKD attacks are typically very short (i.e., less than 1 minute), but with a high frequency (i.e., occurs more than once daily). They usually consist of chorea and dystonia but also rarely athetosis, ballism, hemiballism, tongue movements, perioral dyskinesias, and clawing of the hands or a frozen gaze [5,12]. The attacks are bilateral or some-

Fig. 1. Phenotypic overlap for genes associated with both paroxysmal movement disorders and epilepsy. This figure summarizes how the genes associated with paroxysmal dyskinesias, hemiplegic migraine, episodic ataxia, and epilepsy. Genes are categorized by their underlying pathomechanisms in the right column. PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal non-kinesigenic dyskinesia; PED, paroxysmal exercise-induced dyskinesias.
times unilateral and tend to generalize [5,12]. Symptoms most commonly manifest shortly before or during puberty in PRRT2 mutation carriers with less than 5% of PRRT2-associated cases experiencing an onset after 18 years of age [12]. Patients often experience several attacks a day but regardless of treatment, the frequency decreases with advancing age after puberty [5].

Benign infantile familial seizure is inherited in an autosomal dominant pattern with up to 80% of cases exhibiting mutations in PRRT2 [3,12]. It is characterized by seizures that occur between 3 and 12 months of age [10] and involve brief, focal motor manifestations accompanied by cyanosis, hypertonia, and limb jerks [3,12]. They can occur in clusters of multiple seizures, up to eight to ten seizures per day, which occur every 2 to 3 hours on average [10]. However, patients have an excellent response to antiepileptic drugs and seizures generally resolve by the age of 2 years [12,29]. That aside, patients demonstrate normal developmental outcomes, neurological examinations, brain imaging patterns, and electroencephalography background signals [10].

Similarly, nearly 90% of infantile convulsion with choreoathetosis syndrome patients have PRRT2 mutations [5]. Overall, the clinical findings and genetic features overlap with cases of PKD and benign infantile familial seizure. This syndrome is characterized by the development of PKD after infantile convulsions (PKD usually develops by the age of 5 years) as some epileptic seizures may exhibit at a much later age than typical benign infantile familial seizure [5]. Remission rate for treated infantile convulsion with choreoathetosis cases is up to 89%, which means that only a small number of patients maintain partial response to therapy [12].

The PRRT2 gene has recently been implicated in the shared pathophysiology of epilepsy and hemiplegic migraine [30]. Although PRRT2 mutations are rare, they have also been identified in hemiplegic migraine with PKD, and/or benign infantile familial seizure [31]. Interestingly, CACNA1A, ATP1A2, or SCN1A genes, or in certain combinations, have been found in approximately 75% of familial hemiplegic migraine patients and also in a smaller number of sporadic hemiplegic migraine patients [32].

Historically, PKD, infantile convulsion with choreoathetosis, and benign infantile familial seizure have been considered to be allelic disorders because they occurred together in some families and were linked to the same region on chromosome 16p11.2-q12.1 [33,34]. In 2011, Chen et al. [9] first identified mutations of PRRT2 located on chromosome 16p11.2 in eight Chinese PKD families by whole exome sequencing. A significant number of PRRT2 mutations associated with loss-of-function and missense amino-acid change mutations have since been identified [6]. To date, a total of 97 different PRRT2 mutations have been reported [35], of which c.649dupC is a hotspot. It is found in 60% to 80% of PRRT2-associated PKD, benign infantile familial seizure, and infantile convulsion with choreoathetosis patients [12]. In addition, deletion mutation at the same location (c.649delC; approximately 4%) and at the more proximal part (c.291delC; approximately 2%) have also been identified [12]. However, a c.579dupA mutation of the PRRT2 gene presents more commonly in infantile convulsion with choreoathetosis [12].

The PRRT2 gene comprises of four exons that encodes the 340-amino acid, proline-rich transmembrane protein 2 [12]. PRRT2 is found throughout the central nervous system, especially at high expression levels in the cortical layers of the cerebral cortex, basal ganglia, and cerebellum [9]. The contribution of alteration of the basal ganglia-thalamocortical circuit to the pathogenesis of PRRT2-associated PKD has been proposed [36,37]. It is mainly recognized in the axons but not in the dendrites of neurons at the subcellular level [12]. A yeast two-hybrid assay found that PRRT2 interacts with the synaptic t-SNARE protein synaptosomal-Associated Protein, 25kDa (SNAP25) [38,39]. SNAP25 alters neurotransmitter release and calcium channel dynamics, which affects vesicle synapse accordingly [40]. It has been suggested that PRRT2 mutations impair SNAP25 function by altering Cav2.1 activity, which lead to neuronal hyperexcitability and subsequently cause epilepsy, PKD, or other paroxysmal movement disorders [41]. In addition to the relation between PRRT2 and SNAP25, many studies proposed that PRRT2 has postsynaptic roles in alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor signaling [42,43].

In addition to the roles at the synapse, recent studies have suggested that PRRT2 interacts with ion channels, such as Nav1.2/Nav1.6 channels, major regulators of the excitability of excitatory neurons, but not with Nav1.1 channels, which is essential for the excitability of inhibitory neurons [44]. Thus, the disturbance in cellular excitability by lack of negative modulation of Na+ channel was assumed to be the main pathogenetic mechanism of paroxysmal character [44].

Currently, there is no clear evidence to propose genotype-phenotype correlations [12,35]. Variable phenotypes are found within and between families with the same PRRT2 mutations [10]. Patients with a 16p11.2 deletion not only have PRRT2-PKD but also additional clinical features, including developmental delay, intellectual disability, and/or autism spectrum disorder [45,46]. Analogously, patients with biallelic PRRT2 mutations often show more severe phenotypes, including intellectual disability, episodic ataxia, and different seizure types [47,48].

2. SCN8A
Pathogenic variants of SCN8A, which encode the sodium channel
电压门控α8-亚单位（Nav1.6），在患者中与发育性及癫痫性脑病有关 [13,49]。然而，最近的研究表明SCN8A致病性变异具有广泛表型谱，从发育性及癫痫性脑病到行为障碍或运动障碍 [50]。一种变异类型的发病类型与频繁的运动障碍有关，有时类似于PKD，可能由SCN8A基因突变引起 [5,14]。

临床综合征的PRRT2变异（PKD，婴儿型家族性癫痫，和婴儿型痉挛与舞蹈病样痉挛）已被报告在SCN8A基因突变患者中 [14]。一些个体在出现运动障碍时（如，伸展运动）或/或情绪刺激时 [14]。舞蹈病样及痉挛性舞蹈病样痉挛在一些SCN8A相关的癫痫性脑病中被发现 [13]，这表明发作性运动障碍也与SCN8A变异相关。

患有PRRT2和SCN8A变异的患者有相似的临床表现，但有大量显著的发现有助于鉴别诊断 [13]。SCN8A变异的患者有典型发作类型与局灶性、运动性、肌阵挛性及姿势性发作，和运动障碍及面部/颈部无力，以及面部及肌肉的丧失。这些变异通常是选择性的抗癫痫药物不敏感 [14]。此外，无论早期发育是否正常，患者与SCN8A变异变异发展程度与智力障碍及肌张力障碍 [13]，并且可能与非-癫痫性运动障碍综合征，包括舞蹈症及肌张力障碍有关 [13]。此外，大多数SCN8A变异为de novo突变但仅有一种单系谱运动障碍的无症状父母被报道 [13]。所有这些特征使SCN8A相关运动障碍与PRRT2不同。

3. SLC16A2

SLC16A2基因位于X染色体Xq13.2位置，编码单羧酸载体8（MCT8），是一种活性运输蛋白在人类中 [16]。MCT8运输多种碘代酪氨酸，包括三碘甲腺原氨酸（T3）和四碘甲腺原氨酸（T4） [16]。MCT8缺乏，也被称为Allan-Herndon-Dudley综合征，可能由T3水平增加引起，正常人T3水平低，T4低，T4水平正常，和高甲状腺刺激激素水平没有显著或与先天性甲低有关 [15]。临床特征包括可变的智力低下，肌张力障碍，张力障碍及面部/颈部无力，舞蹈症，及运动无目的运动，与静态或缓慢进行性过程 [15,16]。

癫痫性发作，包括热性发作，肌阵挛性发作，和普遍性肌阵挛发作，及广泛性癫痫发作，是约半数Allan-Herndon-Dudley综合征患者 [16,51,52]。不自主运动，包括运动性及/或肌张力障碍，和姿势性或肌张力障碍痉挛，是常染色体隐性患者的典型症状 [15,53]。发作性活动通过伸展身体，打开嘴巴，或肢体伸展或屈曲1到2分钟 [53]。运动性刺激，包括衣服或尿布的改变，或提升受影响的儿童可以触发攻击 [53]。

虽然MCT8缺陷的病因已被报道在有甲状腺异常的患者，导致运动障碍的异常运动障碍的表型仍然不完全清楚 [15]。

4. CHRNA4

CHRNA4，编码α亚单位的乙酰胆碱受体（nAChR），常与β2亚单位（由CHRNB2）组成异源五聚体α4β2-nAChR [56]。致病性变体为CHRNA4已被发现是主要的基因携带者的原发性额叶癫痫，它导致频繁的运动障碍在非快速眼运动睡眠 [57]。

最近，Jiang et al. [17] 发现，热性发作及PKD患者在非PKRRT2家族中存在CHRNA4突变。不同类型的运动障碍被观察到，包括反复热性发作，这些发作发生在3和7岁之间，热性发作，包括肌阵挛性发作，发生在6和11岁之间，及广泛性肌阵挛发作，发生在14岁之后 [17]。症状包括舞蹈症和运动障碍，可能由突然的运动和仅在白天发生 [17]。攻击通常持续不超过30秒，且不会导致意识丧失或用奥卡西平治疗，它们被得到很好的控制 [17]。

PNKD和癫痫

1. KCNMA1

KCNMA1基因编码大 conduc-ANCE，电压及钙敏感的钾通道，它也由细胞内镁离子激活 [15]。它在小脑、大脑皮层、腹侧苍白球、脊髓和皮质细胞中表达的细胞 [58,59]。KCNMA1基因的基因性变异在PNKD和癫痫中首次被报道在大型家族中，有广泛性发作 [27]。最近，KCNMA1基因的变异在患有小脑萎缩、发育性延迟，及发作中被描述 [60]。

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Mutations in the KCNMA1 gene produces a syndrome of PNKD and epilepsy, either in the form of absence seizures or generalized tonic-clonic seizures [5,19]. In 2005, Du et al. [27] reported a family with an autosomal dominant form of generalized epilepsy and paroxysmal dyskinesia carrying a mutation in the KCNMA1 gene. Clinically, paroxysmal dyskinesias attacks that involve KCNMA1 mutations were described to resemble the non-kinesigenic variant with alcohol being a possible trigger [27]. Recent studies established a correlation of the homozygous KCNMA1 mutation with cerebellar ataxia, corticocerebellar tract atrophy, developmental delay, paroxysmal dyskinesia, and variable epilepsies, including absence, myoclonic, atonic, tonic, and generalized tonic-clonic seizures [19,60]. In addition, both gain- and loss-of-function have been proposed as the underlying molecular mechanism behind the channelopathy, which causes an increase in excitability [60].

PED and epilepsy

1. SLC2A1

GLUT1 deficiency syndrome is caused by mutations in SLC2A1, which presents early-onset refractory seizures, PED, and movement disorders [6]. SLC stands for solute carrier, while 2A1 represents the family number 2 and member number 1 in the family. As GLUT1 is one of the proteins located on the blood-brain barrier, GLUT1 deficiency syndrome was previously described in association with infantile epilepsy with low cerebrospinal fluid glucose [61]. Both epilepsies, particularly early-onset absence, and PED co-occur in families and individuals [5].

This disorder is usually classified into two groups: classical and nonclassical. Classical or typical GLUT1 deficiency involves infantile-onset, pharmaco-resistant epilepsy, intellectual disability, microcephaly, and complex movement disorders; while nonclassical or atypical GLUT1 deficiency involves paroxysmal movement disorders, atypical childhood absence epilepsy, and myoclonic atonic epilepsy [61]. Infantile-onset epilepsy can be alleviated during childhood but movement disorders tend to emerge later, which may be due to changes in brain metabolism over time [62].

Approximately 90% of patients have clinical seizures, mainly generalized tonic-clonic seizures followed by absence, myoclonic, and focal onset seizures [61]. The PED attacks usually consist of choreoathetosis and dystonia, which mainly affect the lower limbs, and are typically triggered by sustained exercise [5]. Notably, this disturbance might be misdiagnosed as epileptic myoclonic seizures [63]. The combination of epilepsy with a possible family history and PED in the setting of an unremarkable neurological examination, along with low cerebrospinal fluid glucose concentration, represents an important clinical clue to raising the correct diagnostic suspicion [5]. An early diagnosis of GLUT1 deficiency is crucial given that the syndrome can be well managed with a ketogenic diet [5,61].

Although isolated PED caused by SLC2A1 mutations are rare, episodes of PED in those suffering from GLUT1 deficiency syndrome are common but often go unnoticed in the setting of epilepsy or more severe findings [61]. Isolated dystonia after exercise that usually only affects the lower limbs have also been observed in carriers of SLC2A1 mutations that cause early-onset Parkinsonism or dopa-responsive dystonia; however, these are rather unusual initial presentations of these conditions [8].

No clear-cut phenotype-genotype correlations have been established [64]. Patients exhibited interindividual phenotypic variability despite having the same mutations, which suggests the presence of genetic modifiers, such as secondary genes [61,64]. Therefore, the genotype does not always predict the phenotype [61].

2. TBC1D24

The gene TBC1D24 is involved in the regulation of synaptic vesicle trafficking by interacting with GTPase in brain and somatic development [65,66]. Genetic mutations in TBC1D24 have been associated with multiple phenotypes with epilepsy as the main clinical manifestation [20,66]. Epilepsy aside, TBC1D24 is also associated with deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures (DOORS syndrome), as well as nonsyndromic deafness [65].

The types of seizures and epilepsies are diverse. Seizure types include infantile spasms, febrile convulsions, myoclonic, clonic, tonic, absence, tonic-clonic seizures with or without apparent focal onset, and focal seizures with retained or impaired awareness [65]. Myoclonic or clonic seizures are the most frequent seizure types, which include infantile and progressive myoclonic epilepsies, as well as familial epilepsy of infancy with migrating focal seizures and are often unresponsive to medication [65].

TBC1D24 epilepsy syndromes occur with both compound heterozygous and homozygous recessive mutations. More than 50 missense and loss-of-function mutations have been described and associated with the exercise-induced dystonia phenotype, which persist into adulthood according to a long clinical follow-up study [20]. The additional diversity of TBC1D24 phenotypes might be due to its broader expression patterns; TBC1D24 is expressed in several human tissues with the highest expression occurring in the brain in multiple cerebral areas, including all layers of the cerebral cortex and the hippocampus [66]. In a Drosophila model, some mutations of TBC1D24 cause activity-induced locomotion and synaptic vesicle trafficking defects, which is consistent with exacer-
bated oxidative stress sensitivity, suggesting that these mutations cause dysfunctional, sustained movement disorders [20].

Other paroxysmal movement disorders and epilepsy

1. Familial hemiplegic migraine and epilepsy

CACNA1A, ATP1A2, SCN1A, and PRRT2 genes often contain one or more mutations in both epilepsy and hemiplegic migraine patients [8,21,41]. These shared mutations identified in epilepsy and migraine cases suggest that there is a common genetic basis for these conditions. There are two categories of migraine: migraine with and without aura, and hemiplegic migraine is a rare form of migraine with aura [41].

1) ATP1A2

The ATP1A2 gene is located on chromosome 1q23 and encodes for the α2 subunit of Na+/K+ ATPase, which consists of an α and a β subunit. ATP1A2 mutations were identified in families with familial hemiplegic migraine, called familial hemiplegic migraine type 2 [67,68].

The incidence of epilepsy is increased in families with familial hemiplegic migraine type 2, where approximately 20% experience seizures, such as focal seizures, benign infantile familial seizure, and high fever convulsions [68]. In a family with familial hemiplegic migraine type 2, one member had focal epilepsy as a child and electroencephalography revealed a focal migratory epilepsy-like discharge waveform [68].

Since maintaining the correct concentrations of Na⁺ and K⁺ via the Na⁺/K⁺ ATPase system is crucial for the ability of astrocytes to clear extracellular glutamic acid, an abnormal Na⁺/K⁺ ATPase system function disrupts the K⁺ gradient and impairs glutamate clearance, which likely contributes to the development of familial hemiplegic migraine and epilepsy [41].

2) SCN1A

SCN1A, which encodes the α1 subunit of the sodium channel, is associated with a range of human diseases [69]. The most well-recognized epilepsy phenotype associated with SCN1A is the Dravet syndrome but it also results in several other epilepsy syndromes ranging from self-limited and pharmaco-responsive epilepsies, such as genetic epilepsy with febrile seizures plus, Dravet syndrome, myoclonic-atonic epilepsy, and epilepsy of infancy with migrating focal seizures. SCN1A disorders also result in other neurological disorders such as hemiplegic migraine, intellectual disability, and autism spectrum disorder [69].

Familial hemiplegic migraine type 3 is caused by heterozygous pathogenic variants of the SCN1A [70]. In contrast to familial hemiplegic migraine due to CACNA1A and ATP1A2 mutations, in the few patients with familial hemiplegic migraine type 3 carrying SCN1A mutations and presenting with seizures [69], hemiplegic migraine attacks are always independent from seizures and the two phenotypes do not generally overlap temporally [69].

All SCN1A mutations reported in familial hemiplegic migraine type 3 are missense mutations. Most experimental results show that they cause a gain-of-function of Nav1.1 [71]. Cellular and animal data point to an increased excitability of gamma-aminobutyric acid (GABAergic) neurons in familial hemiplegic migraine type 3, which is a different mechanism from that seen in epileptogenic Nav1.1 mutations [69].

Episodic ataxia and epilepsy

Episodic ataxia is a rare neurological condition characterized by recurrent spells of truncal ataxia and incoordination. PRRT2, CACNA1A, and KCNA1 mutations are mainly responsible for co-occurrence of episodic ataxias and epileptic seizures [24,25].

1) CACNA1A

CACNA1A is located on chromosome 19p13 and encodes for the α1 subunit of the Cav2.1 P/Q-type voltage-gated calcium channel [18]. Pathogenic variants of CACNA1A are associated with three allelic autosomal dominant conditions: episodic ataxias type 2, spinocerebellar ataxia type 6, and familial hemiplegic migraine type 1 [18]. Other paroxysmal disorders, including benign paroxysmal torticollis of childhood, benign paroxysmal tonic upward gaze, and epilepsy, are also associated with CACNA1A mutations [8].

Patients with episodic ataxia type 2 usually experience intermittent episodes of ataxia and nystagmus that can last from minutes to days during childhood or early adulthood [8,72]. It usually develops with dysarthria, tinnitus, dystonia, hemiplegia, and headache with the frequency of attacks varying from once to twice a year to three or four times a week [73]. Typically, exertion, stress, heat, fever, alcohol, caffeine, or drugs, such as phenytoin, can trigger these episodes [73]. Myokymia (fine twitching or rippling of muscle) is absent on physical examination or electromyographic studies [59]. Episodic ataxia type 2 attacks can be interrupted or reduced in frequency and severity by acetazolamide or 4-aminopyridine administration [73]. Few patients have epileptic encephalopathy with generalized absence or focal seizures with or without generalized tonic-clonic seizures and/or intellectual disabilities [18,74].

About half of families with familial hemiplegic migraine have heterozygous pathogenic missense variants in CACNA1A, which are called familial hemiplegic migraine type 1 [73]. Episodic hemiplegia occurs with one or more sensory auras such as hemianopsia,
hemisensory deficit, or aphasia in familial hemiplegic migraine type 1 [73].

Benign paroxysmal torticollis of childhood is a rare paroxysmal disorder characterized by recurrent episodes of head tilt accompanied by general symptoms that remit spontaneously [75]. The rare association with gain-of-function and loss-of-function CACNA1A mutations has been reported [75].

Benign paroxysmal tonic upward gaze was initially described as a benign phenomenon with negative investigations and eventual complete resolution of symptoms [76]. Later publications demonstrated that a similar clinical feature may arise from structural brain lesions, channelopathies, neurotransmitter disorders, and epileptic seizures [76]. CACNA1A mutations were detected in infants and young children with benign paroxysmal tonic upward gaze especially if associated with developmental delay, cerebellar signs, and other types of paroxysmal events [76].

Patients with CACNA1A mutations experience a high rate of different seizure types, involving febrile seizures, epileptic encephalopathy, generalized absence seizure, and focal seizures with or without generalized tonic-clonic seizures [18].

Pathological manifestations are explained by the synaptic dysfunction caused by the loss of Cav2.1 channels in particular cell types [77-79]. In conditional mutant mice, selective deletions of CACNA1A in cerebellar granule cells or Purkinje cells reduce the excitatory drive and neurotransmitter release, which cause ataxia and dyskinesia [80,81]. While GABA release is impaired, generalized epilepsy in cortical and hippocampal GABAergic interneurons [77].

2) KCNA1

Episodic ataxia type 1, which is also called ataxia with myokymia, is caused by heterozygous pathogenic variants in KCNA1, which encodes a potassium channel [82]. It is characterized by brief attacks (< 15 minutes) of ataxia and dystarthis that can occur up to 15 times per day [82]. Attacks can occur spontaneously or be triggered by anxiety, exercise, startle, and/or intercurrent illness [82]. Onset typically occurs in late childhood and early adolescence, and symptoms usually remit during the second decade [83]. Between attacks, widespread myokymia of the face, hands, arms, and legs occur. Electromyographic studies reveal myokymia, so called neuromyotonia [82]. Phenytoin can control symptoms; acetazolamide is also effective [84].

Episodic ataxia type 1 may be associated with epilepsy as tonic-clonic and focal seizures, one isolated episode of photosensitive epilepsy [85], as well as symptoms, such as head-turning, eyes deviating to the same side, flickering eyelids, lip-smacking, apnea, and cyanosis, have been reported [86]. Prolonged episodes of more than 30 minutes have been reported in individuals with severe early-onset epilepsy, albeit without the typical ataxia [87].

The molecular mechanisms of episodic ataxia type 1 are described as impaired channel function and reduced outward K+ flux through the channel [85,88]. In a mouse model of episodic ataxia type 1, altered motor performance and impaired cerebellar GABAergic transmission from the basket cells to the Purkinje cells was found [89], resulting in spontaneous myokymic activity, which was exacerbated by fatigue, ischemia, and low temperature [90]. However, although a similar phenomenon to the spread of acidification in the cerebellar cortex has been described, the causes of triggering the paroxysms of ataxia remain unknown [91].

Conclusion

Several genetic disorders were identified as co-occurrences of epilepsy and paroxysmal dyskinesias. Disease and associated genes are as follows: (1) PKD: PRRT2, SCN8A, SLC16A2, CHRNA4; (2) PNKD: CACNA1A, KCNMA1; (3) PED: SLC2A1, TBC1D24; (4) hemiplegic migraine: PRRT2, CACNA1A, SCN1A, ATP1A2; and (5) episodic ataxia: PRRT2, CACNA1A, KCNA1. These conditions are divided into three pathomechanisms: (1) channelopathy: SCN8A, CACNA1A, KCNMA1, SCN1A, KCNA1; (2) synaptopathy: PRRT2, CHRNA4, TBC1D24; and (3) transportopathy: SLC16A2, SLC2A1, ATP1A2.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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