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REVIEW

The genetic relationship between epilepsy and hemiplegic migraine

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Abstract: Epilepsy and migraine are common diseases of the nervous system and share genetic and pathophysiological mechanisms. Familial hemiplegic migraine is an autosomal dominant disease. It is often used as a model of migraine. Four genes often contain one or more mutations in both epilepsy and hemiplegic migraine patients (ie, *CACNA1A*, *ATP1A2*, *SCN1A*, and *PRRT2*). A better understanding of the shared genetics of epilepsy and hemiplegic migraine may reveal new strategic directions for research and treatment of both the disorders.

Keywords: epilepsy, migraine, *CACNA1A*, *ATP1A2*, *SCN1A*

Introduction

Epilepsy and migraine are common diseases of the nervous system. The overall prevalence of epilepsy in populations of the USA is 0.025%–0.05%, and the prevalence of migraine in the adult population is approximately 5%. Of the patients with epilepsy, 8%–24% also experience migraines.[1] The risk of migraine in these patients is onefold greater compared with healthy controls.[2] The risk of epileptic seizure in children who experience migraines is 3.2 times higher than that of children with tension headaches.[1] It is possible that a headache similar to a migraine is caused by the seizure. However, there is clearly a strong association between epilepsy and migraine.

The relationship between migraine and epilepsy is not a cause-and-effect relationship. Migraine and epilepsy share the same physiological pathway. It is possible that both are caused by cortical neuron over-excitation. Epilepsy results from the synchronized discharge of neurons. Migraine is associated with cortical spreading depression (CSD),[3] which is the strong depolarization of a large group of nerve cells or neuroglia that spreads to adjacent areas and inhibits neural activity.[4,5] Epilepsy and migraine can spontaneously induce CSD.[6] The results of animal studies have suggested that many changes that occur during CSD (eg, the increased release of glutamate, the increased concentrations of extracellular potassium ions, and the inhibition of the Na^+/K^+ ATPase) are also associated with the sense of foreboding experienced by some migraine patients.[7] Taken together, these results indicate that CSD may be the basis for migraine aura.

Some shared mutations have been identified in the cases of epilepsy and migraine, which suggests that there is a common genetic basis for these conditions. The two categories of migraine are migraine without aura and migraine with aura; hemiplegic migraine is a rare form of migraine with aura. Hemiplegic migraine can be subdivided into familial hemiplegic migraine (FHM) and sporadic hemiplegic migraine (SHM). FHM is a monogenic (Mendel's Laws determine the inheritance pattern) autosomal dominant disease. It is often used as a model during studies of mechanisms associated

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with migraine. This article discusses the possible common genetic basis for epilepsy and migraine.

CACNA1A gene

The *CACNA1A* gene is located at the gene map locus 19p13, between microsatellite markers D19S216 and D19S215. The *CACNA1A* gene encodes for the Ca2.1α1 subunit. Voltage-gated P/Q-type calcium channels are composed of α1 subunits. The subunits contain four homologous regions (I–IV); each region contains six transmembrane segments.[8] The S4 segment connects to a positively charged amino acid to form the S4 transmembrane α-helix, which acts as a "voltage sensor". The S5–S6 connecting section forms a channel hole, which selectively allows the passage of ions.[9] The P/Q-type calcium channel mediates neurotransmitter release by promoting the flow of calcium to stimulate the presynaptic membrane. The specific mutations that occur in individuals with FHM type 1 are missense mutations of the *CACNA1A* gene. The mutations are often near the ion channel or in the voltage sensor. The most common mutation is T666M, which can change the current densities and gating properties. A genetic analysis of a 14-year-old girl who experienced epileptic activity during an FHM attack revealed an I170T mutation in the *CACNA1A* gene (district IV of the S5 segment).[10] S218L knock-out mice develop severe FHM symptoms,[11] and the S218L mutation (a type of *CACNA1A* mutation) has been identified in patients with epilepsy.[12,13] Conversely, the C5733T mutation (a *CACNA1A* mutation) is associated with non-FHM childhood absence epilepsy.[14] Genetic mutations can damage Cav2.1 channel function, which may lead to generalized seizures.[15,16] Mutations in the *CACNA1A* gene occur in patients with epilepsy,[17,18] in patients with FHM, and in patients with epilepsy and FHM as comorbid conditions.[19]

R192Q mutant mice can undergo a shift in the balance of excitation and inhibition in cortical neurons,[20] which reduces the threshold for CSD and accelerates its propagation rate. Susceptibility to CSD is also increased in S218L mutant mice.[11,21,22] A *CACNA1A* gene knock-in mouse model (6J-Tg) is a typical absence seizure animal model;[23] we found that patients with absence seizures have a *CACNA1A* mutation.[16,24] In 6J-Tg mice, the amino acid sequences of the S4–S5 connecting area, the S5, and part of the S5–S6 connecting region also have a high number of mutations.[25] Mutations in FHM knock-in mice also occur in the S4–S5, S5, and S5–S6 connecting region,[26] which suggests that *CACNA1A* gene mutations may be shared between patients with absence seizures and patients with FHM. Studies of tg/tg mice, which have genetically linked epilepsy and may have *CACNA1A* gene mutations, revealed that loss of the CaV2.1 channel function can induce synaptic dysfunction of cortical interneurons and specifically reduce or impair the function of cortical GABA neurotransmitter.[27]

ATP1A2 gene

In 2003, *ATP1A2* mutations were identified in families with FHM (FHM type 2, FHM2).[28,29] The *ATP1A2* gene is in chromosome 1q23; it codes for the α2 subunit of Na^+/K^+ ATPase, which consists of an α and a β subunit. ATP hydrolysis releases energy and reversibly transmits three Na^+ into the extracellular, and two K^+ into the intracellular, regions. The α subunit includes subtypes 1–4 and has a catalytic function. Neurons and astrocytes highly express α2 subunits, and in astrocytes, Na^+/K^+ ATPase can regulate the extracellular K^+ concentration. This regulation increases neuron excitability and induces a threshold value that can lead to CSD.

A genetic study of an Italian family with members with both hemiplegic migraine and epilepsy found that they also had the *ATP1A2* mutation.[30] The epilepsy incidence is increased in families with FHM2; approximately 20% experience seizures[29] such as partial seizures, benign familial infantile convulsions, and high fever convulsions. In a family with FHM2, one member had partial epilepsy as a child, and electroencephalography revealed a focal migratory epilepsy-like discharge waveform. The M721T and R689Q mutations of the *ATP1A2* gene were found in two families with FHM2 in Holland. While patients with the R689Q mutation experienced benign familial infantile convulsions, those with the M721T mutation did not have epilepsy.[31] Other studies found that the D718N and P979L mutations increase the risk for epilepsy and mental retardation.[32] Similarly, the R1007W mutation may be a factor that increases susceptibility for epileptic seizures.[33]

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. EAAT1 also has an important role in glutamate clearance.[34] The distribution of EAAT1 is consistent with that of Na^+/K^+ ATPase. EAAT1 must be driven by the influx of three Na^+ ions and the efflux of one K^+ ion for glutamic acid uptake. Taken together, this evidence indicates that EAAT1 and Na^+/K^+ ATPase have a close relationship in structure and physiology.[35] When Na^+/K^+ ATPase function is impaired, transport of K^+ into the cell by astrocytes is reduced. This change results in an accumulation of K^+ in the extracellular fluid, which increases cell discharge frequency and excitability, and induces CSD.[19] In summary, abnormal Na^+/K^+ ATPase system function disrupts the K^+

gradient and impairs glutamate clearance, which likely contributes to CSD, FHM, and epilepsy.

SCN1A gene

Dozens of mutations are associated with epilepsy.[36] However, only some mutation sites are associated with FHM type 3 (FHM3). Mutation of the *SCN1A* gene can result in seizures and FHM3.[37–39] The *SCN1A* gene encodes for Nav1.1 – a voltage-gated sodium channel that is abundant in the central nervous system. Nav1.1 protein is mainly located in the cerebral cortex and spinal cord and is highly expressed in cell bodies and dendrites in these locations. *SCN1A* gene mutations are found in Dravet syndrome (DS) and infant idiopathic comprehensive epilepsy patients.[40–42]

Approximately 650 heterozygous *SCN1A* mutations are found in DS patients, and the mean mutation rate is approximately 85%.[43] Of these mutations, approximately 50% are nonsense mutations that result in truncated proteins and an Nav1.1 protein with only one-half of its functions (ie, one chromosome is nonfunctional). Conversely, most of the other approximately 50% of *SCN1A* mutations are missense mutations, which can either enhance or weaken Nav1.1 function.[38] Mutations of the *SCN1A* gene have been found in patients with generalized epilepsy with febrile seizures plus[44,45] and in patients with partial epilepsy with febrile seizures plus.[46,47] Different types of *SCN1A* mutations result in different effects on channel function. The Q1489K and L1649Q mutations cause FHM3, but are not associated with seizures. Conversely, a gene analysis of a Portuguese family with FHM revealed the presence of an L263V mutation; some affected family members had generalized epilepsy, and some had complex partial seizures.[48,49] The L263V mutation results in a functional enhancement that accelerates recovery, thereby prolonging current duration and increasing neuron excitability. As a result, L263V mutations can result in seizures and FHM3 in the same individual.[50] In contrast, mutations in Q1489K and L1649Q can inhibit neuronal functioning.[49,51,52] These functional mutations can cause seizures or FHM, but not both, which suggests that an additional factor is required to promote development of the excitatory loop.[19]

PRRT2 gene

The *CACNA1A*, *ATP1A2*, or *SCN1A* genes, or some combination, can be found in approximately 75% of FHM patients and in a smaller number of SHM patients.[53] The *PRRT2* gene has recently been implicated in the shared pathophysiology of epilepsy and migraine.[54] The *PRRT2* gene is located on the 16p11.2 chromosome, contains four exons, and encodes a 340-amino acid transmembrane protein. Most study results indicate that mutations occur in the second and third exons of the *PRRT2* gene. A survey of 101 patients with hemiplegic migraine (ie, 48 with FHM, 52 with SHM, and one with uncategorized hemiplegic migraine) revealed that there were no mutations of the *CACNA1A*, *ATP1A2*, or *SCN1A* genes. However, *PRRT2* mutations were identified in four of the patients. One of these patients also had paroxysmal movement disorder and generalized seizures.[55] Dale et al found that some members of an affected family experienced paroxysmal movement disorder and hemiplegic migraine. This result suggested that *PRRT2* mutation was present. No other hemiplegic migraine-related genes were detected. Studies have also found that *PRRT2* mutations are rare in patients with hemiplegic migraine or hemiplegic migraine with paroxysmal kinesigenic dyskinesia (PKD),[56] and in patients with benign familial infantile seizure (BFIS).

PRRT2 mutations are common in individuals with BFIS (ie, benign familial infantile epilepsy). BFIS is an autosomal dominant epilepsy and often occurs in infants 3–12 months of age. *PRRT2* mutations are found in 80% of BFIS families, which suggests that the gene is a major cause of BFIS.[57–59] *PRRT2* mutation is also found in individuals with benign infantile convulsions.[60] However, it is not found in infants with atypical epilepsy. This result suggests that epilepsy-associated *PRRT2* mutations are specific, self-limited, and age-dependent. These characteristics may contribute to the time-dependent differences in protein expression.[61]

c.649dupC is a hotspot for *PRRT2* mutation. c.649dupC is located at the end of a structure with eight continuous cytosine bases. This mutation causes an error in the DNA replication process that results in a truncated *PRRT2* protein with only 217 amino acids. Results of a yeast two-hybrid assay indicated that *PRRT2* and SNAP25 interact.[62,63] SNAP25 affects neurotransmitter release from the synapse and can regulate calcium channel dynamics, including for the Cav2.1 calcium channel.[64] Some investigators have hypothesized that *PRRT2* mutation impairs SNAP25 function, which then changes CaV2.1 activity, causes neuronal hyperexcitability, and results in epilepsy, hemiplegic migraine, or PKD.

Conclusion

There is a great deal of evidence suggesting that epilepsy and hemiplegic migraine have a close genetic relationship. This relationship provides a foundation for a new strategic direction for research and treatment. Epilepsy and hemiplegic migraine are disorders associated with abnormal neuronal excitability; they have overlapping regions of genetic

inheritance. However, epilepsy occurs from the synchronous discharge of excited neurons, and abnormal neuronal excitability is transformed into CSD in migraine patients. Future studies should investigate this relationship and the different phenotypes of the two disorders.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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