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EDITORIAL OPEN ACCESS

Are all types of migraine channelopathies?

Wenjing Tang, Shengyuan Yu

Migraine is a typical episodic brain disorder. Based on migraine attacks with or without transient aura symptoms, migraine can be divided into migraine with aura (MA, including visual, sensory, motor, or speech difficulties) and migraine without aura (MO). Cortical spreading depression (CSD) is believed as the pathophysiological mechanism of aura. Familial hemiplegic migraine (FHM) is an autosomal dominant migraine with hemiplegic aura, which is extensively researched as a migraine model for pathophysiology because of the definite mutations of three disease-causing genes coding ion channels. Numerous studies on CSD and FHM tried to elucidate the role of ion channels in the migraine development. Studies on ion channel antagonists also showed efficiency in migraine prophylactic treatment. All above bring a false appearance that migraine is a channelopathy. However, with the discovery of PRRT2 gene related brain disorders, it is challenging whether migraine, even FHM, is a channelopathy. Over 5000 SNPs of 155 ion channel coding genes were all denied the connection between themselves and migraine susceptibility by a candidate gene linkage study. And genome-wide association studies not only denied the connection between common migraine and the three FHM causing genes, but also found 12 non-ion channel coding genes highly related to common migraine. More and more contrary evidences indicate that migraine is a kind of ion channel related disorder, which needs further studies on multiple levels from one single gene function to several genes and their encoding ion channels interactions.

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Migraine is a primary brain disorder, causing episodic headache attacks with photophobia, phonophobia, nausea and vomiting [1]. It has been confirmed that migraine is highly impacted by genetic factors [2], and most of basic understanding of neurobiological mechanisms are contributed to genetic studies on aura and pain pathways in migraine [3].

Channelopathy has three features:

1) symptoms often present as paroxysmal attacks with normal function interictally;
2) most channelopathies are inherited as autosomal dominant traits;
3) most channelopathies cause single-organ involvement [4].

Familial hemiplegic migraine (FHM) is characterized by migraine attacks, which is with transient, unilateral motor weakness as its episodic aura. FHM is an autosomal dominant migraine, three encoding protein genes have been identified: CACNA1A encodes α1 subunit of calcium channel Cav2.1 [5], ATP1A2 encodes α2 subunit of Na^+/K^+-ATPase pump [6], and SCN1A encodes α subunit of sodium channel Nav1.1 [7]. All these proteins are specially expressed on nervous system, and all the mutations mainly cause brain dysfunction [5–7]. Series studies on FHM indicated that mutations on Cav2.1 and ATP1A2 increased the concentration of glutamate in synapses and disturbed the excitatory and inhibitory balance, which induced the brain dysfunction [8]. Although the same result has not yet been concluded firmly enough from the functional studies on sodium channels (Nav1.1) owe to the more perplexed expression and structure of Nav1.1 and its encoding gene SCN1A [9–11], it firmly concluded that all the mutations of the three genes cause brain dysfunction [5–7]. All above indicate that FHM is a definitely channelopathy. Are other types of migraine channelopathies?

It is believed that cortical spreading depression (CSD) contributes to aura [12–14], which is a slowly propagating wave, causing depolarization of neural cells and silencing brain electrical activity for several minutes [12–14]. Studies focusing on CSD described a scenario

of collapsing of ion homeostasis, which included a rapid outward current of K^+, a rapid inward current of Na^+, Ca^{2+} and Cl^-, and a transient inward current of H^+ [13, 15, 16]. This scenario causes Ca^{2+} intracellular increasing while K^+ and glutamate releasing to the interstitium, which changes the excitability of local brain cells then turns on a positive-feedback cycle and finally induces brain dysfunction resulting in migraine [8, 12, 17]. Multiple ion channels involve in different stages of the initiation and propagation of CSD, which implies that CSD is a presentation of channelopathies or ion channel related disorders and migraine with aura may be channelopathic disorder.

Many other studies focused on the activation and sensitization of trigeminovascular system (TGVS), which mainly involved in the releasing vasoactive proinflammatory factors from trigeminal ganglion cells, meningeal neurogenic inflammation surrounding the perivascular afferents, and the formation of a positive feedback triggering the next endogenous neurogenic inflammatory process [18–21]. Most receptors of proinflammatory factors are ion channels, including voltage-gated ion channels and ligand-gated ion channels: sodium channels (Nav1.7, Nav1.8, Nav1.9) [22], potassium channels (K2P, K_V1, etc.) [23–25], ATP receptors (P_2X) [26, 27], acid-sensing ion channels (ASICs) [28, 29], transient receptor potential (TRP) ion channel family (TRPV1, TRPA1, TRPM8, etc.) [30, 31], etc. All of them can be found around the sensitized trigeminal nuclei, trigeminal ganglia and related blood vessels [18, 32–34]. However, these ion channels can also be found in dorsal root ganglia, dorsal horn of the spinal cord and different levels along the pain pathway in neuropathic pain [35, 36], which means that these ion channels are not specific to the migraine pathophysiology and it seems that these ion channels need exogenic triggers to be activated, but triggers of migraine originate from nervous system itself. Thus, ion channels involved in the activation and sensitization of TGVS just proved that migraine is an ion-channel related disorder.

Another indirect evidence to prove that migraine is highly associated with ion channel is that some effective prophylactic drugs for migraine such as amitriptyline, valproate and topiramate could inactivate sodium channels and other ion channels [22, 37, 38].

All above suggest that ion channel is an essential part of migraine pathophysiology, but not all types of migraine are channelopathies.

First, not all genes linked to monogenic migraine syndromes encode ion channels. One third of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) patients suffer from migraine with aura in the third decade of life [39]. Mutations in NOTCH3 have been identified as the responsible cause, which encodes Notch3 on cell membrane and interacts with its ligands, provoking intracellular GPCR and ERK signaling pathways, mediating the neurogenesis and angiogenesis [40–42]. So far, it remains unknown how the NOTCH3 mutations in CADASIL triggers aura and headache, and whether these mutations lead to CSD and ionic chaos [43]. The similar condition has also been found in RVCL (retinal vasculopathy with cerebral leukodystrophy) with TREX1 mutations [44], and FASPS (familial advanced sleep phase syndrome) with CSNK1D mutations [45]. TREX1 is the coding gene of a nuclear protein, three prime repair exonuclease 1 [44]; while CSNK1D is a member of the casein kinase I gene family and its corresponding protein may regulate DNA replication and repairing [46]. Both of them seem irrelevant to ion channels. The mutations of PRRT2 cause a series brain disorders which had been usually regarded as channelopathies: hemiplegic migraine, infantile convulsions, paroxysmal dyskinesia [47]. However, PRRT2 encodes a transmembrane protein with a proline-rich domain in N-terminal half and is predominantly expressed in central nervous system during fetal and postnatal stages [47, 48]. Yeast 2-hybrid experiment elucidates that PRRT2 modulates the neurotransmitters releasing indirectly by interacting with synaptosomal-associated protein 25 kDA (SNAP25), which means PRRT2 mutations can interfere the excitatory - inhibitory homeostasis indirectly though it is not an ion channel protein [49]. Considered as the fourth FHM gene by more neurologists, the emergence of PRRT2 implies that migraine is far more than a channelopathy.

Second, both candidate gene association study and genome-wide associated study (GWAS) failed to confirm the involvement of ion channel genes in common migraineurs. Nyholt et al. screened 5257 SNPs covering 155 ion channel genes in over 3 thousand migraineurs, but none of them has a positive association [50]. Bouje et al. from the international headache genetics consortium re-evaluated genes from candidate gene association studies in migraine systematically using a large GWA data set. And the result was also negative, even the three well-known FHM genes all showed negative evidence for the involvement in common polygenic migraine [51]. A possible theory to explain the results above is that common migraine has multiple susceptibility genes which modulate ion and neurotransmitter homeostasis in a more subtle and multiplex manner, compared with monogenic migraine [3].

Third, three large GWASs and a subsequent meta-analysis identified 13 susceptibility genes underlying common migraine based on large population [3]. Except TRPM8, other 12 genes all encode non-ion channel proteins. Screened those 12 genes on NCBI Gene database, we found that most of them are highly-related to cell migration and differentiation. MEF2D, ASTN2 have been found in nervous system exerting a role in neural cell differentiation and development [52, 53]; PHACTR1 exerts a regulating function of angiogenesis and vascular endothelial cells [54]; PRDM16 and FHL5 are transcription factors of cellular differentiation

or maturation, while TGFBR2 belongs to the TGFR superfamily which modulates the transcription of proliferation relevant proteins, especially in the vascular endothelial cell proliferation process [55–57]; TSPAN2 expresses on cellular membrane, while MMP16 in extracellular matrix, both exert a broad function in cell development, activation, modeling and motion [58, 59]. So far, a few experiments have showed that AJAP1 is a tumor suppressor while others indicated that MTDH is an oncogenesis factor, especially for astrocytoma [60, 61]. And LRP1 is the only protein to hinder cell apoptosis and acts as a scavenger of toxic protein deposit [62, 63]. Tolner et al. speculated the possible roles of these genes in the migraine pathophysiology [3], but the results of GWASs still need to be confirmed in functional and ethnological studies [3]. The results from GWASs further imply that as a complicated neurological condition, migraine involving in multifactorial mechanisms disturbing the brain homeostasis from single causal gene to multiple genes interact with each other [64], from molecules to the whole nervous system, from genotype to phenotype, not only limited in ion channels.

Migraine pathophysiology has been studied over 30 decades, but the mist on it is still uncovered. To the channelopathies, migraine may be one part of its wide range of clinical spectrum; to the genetic vasculopathies, migraine may be one symptom of its wide range of clinical manifestations; to the migraine itself, it is an unstable condition of different levels in nervous system including brain tissue, trigeminovascular system and nociceptors on meninges, and each level may have several factors finally make headache happen. As a multifactorial disorder, ion channel is a pivotal part involving in migraine development, the relationship between ion channel and migraine needs to be studied further.

Keywords: Channelopathy, Ion channel, Ion-channel related disorder, Migraine

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Conflict of Interest
Authors declare no conflict of interest.

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