

Migraine in the era of precision medicine

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Abstract: Migraine is a common neurovascular disorder in the neurologic clinics whose mechanisms have been explored for several years. The aura has been considered to be attributed to cortical spreading depression (CSD) and dysfunction of the trigeminovascular system is the key factor that has been considered in the pathogenesis of migraine pain. Moreover, three genes (*CACNA1A*, *ATPLA2*, and *SCN1A*) have come from studies performed in individuals with familial hemiplegic migraine (FHM), a monogenic form of migraine with aura. Therapies targeting on the neuropeptides and genes may be helpful in the precision medicine of migraineurs. 5-hydroxytryptamine (5-HT) receptor agonists and calcitonin gene-related peptide (CGRP) receptor antagonists have demonstrated efficacy in the acute specific treatment of migraine attacks. Therefore, ongoing and future efforts to find new vulnerabilities of migraine, unravel the complexity of drug therapy, and perform biomarker-driven clinical trials are necessary to improve outcomes for patients with migraine.

Keywords: Migraine; precision medicine; neuropeptides; genes

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Introduction

Migraine is a common neurovascular disorder which is characterized by attacks of moderate to severe headaches lasting from 4 to 72 hours, often unilateral and pulsating, and associated with nausea, vomiting, photophobia and phonophobia (1). Migraine has been ranked as the 6th disabling condition by World Health Organization (WHO) (2), with a domestic prevalence of 9.3% (3) and the global prevalence of around 10% (4). Patients with migraine are generally aged from 25 to 50, and the risk of migraine in females is three times higher than that in males (5,6). Migraine has become a significant impact on the quality of people's lives, as well as a major economic and societal burden (3,7,8).

The mechanisms of migraine have been explored for

several years and the most accepted opinion is that a combination of both vascular and neural mechanisms is involved in the initiation and perpetuation of migraine (9,10). Primarily the generation of migraine pain is attributed to activation of the trigeminovascular system. The aura has been considered to be attributed to cortical spreading depression (CSD) (11). However, the pathogenesis of migraine is not clear enough. Therefore, recent studies have devoted the genetic susceptibility research which may also be a neurobiological factor in the etiology of this disorder (12-14). Familial hemiplegic migraine (FHM), an autosomal dominant migraine with special aura, has been identified mutations in three causal genes (15). Functional studies in cellular and animal models of mutant alleles provide direct evidence for neuronal hyperexcitability as one cellular mechanism underlying headache or aura in

FHM (16). While genome wide association studies (GWAS) have also shed new light on the types of genes involved in common migraine susceptibility, many candidate gene association studies have focused on neurotransmitter related pathways. Therefore, genes affecting synthesis and activity of neurotransmitters are potential candidates for involvement in migraine susceptibility. With the rapid development of genetics, the treatment of diseases has entered the era of precision medicine.

Precision medicine

As early as in 2004, the discovery of epidermal growth factor receptor (EGFR) provided a theoretical basis for targeted therapy of lung cancer (17). However, it did not get a further description until a paper occurrence in 2012 in *The New England Journal of Medicine*—coupling established clinical-pathological indexes with state-of-the-art molecular profiling to create diagnostic, prognostic, and therapeutic strategies precisely tailored to each patient's requirements (18). From then on, the term precision medicine was used to describe accurate medical treatments according to each patient's molecular data, genomics, and systems biology. When we talk about the precision medicine, we have to mention the term “Personalized Medicine”. Precision medicine is similar to but always much more than personalized medicine. Personalized medicine refers to determining specific information about a patient and then prescribing a treatment that is specific for that patient. Personalized medicine involves defining disease subtypes and defining biomarkers that can identify which patients who are most likely to benefit from a specific treatment (19). It is just the addition of data mining to improved genomic analyses leading to the new term “precision medicine” (20).

Therefore, a greater understanding of the pathogenesis of migraine will be helpful to leading to identification of clinically relevant biomarkers, possibly actionable genetic mutations, and then getting an ideal treatment.

The pathogenesis of migraine

Migraine is viewed as a neurovascular disease caused by a primary brain dysfunction, leading to activation of the trigeminovascular system and the release of vasoactive neuropeptides. CSD originating in the occipital region is thought to represent the neurobiological underpinning of visual aura (21).

Cortical spreading depression (CSD)

CSD is a self-propagating wave of neuronal and glial depolarization (22), which is identified as the reason of the neurological aura symptoms (23). CSD is initiated by massive increases in extracellular potassium ion concentration and excitatory glutamate. The biochemical changes can trigger the activations of meningeal trigeminal endings and trigeminovascular system, causing the headache phase. CSD can also cause regional cerebral blood flow decreased in the cortex (24).

The trigeminovascular system

The activation of trigeminovascular system is the widely accepted theory of migraine headache. This system consists of pseudo-unipolar neurons in the trigeminal ganglion with primary afferents innervating the pial and dural meningeal vessels surrounding the brain and efferent projections synapsing with second order neurons in the trigeminal nucleus caudalis (TNC) (25) which is also called trigeminocervical complex (TCC) that extends from the dorsal medulla to the dorsal spinal horn of the first two cervical segments. The second-order neurons of the TCC project to the posterior thalamus (26).

The pain during a migraine attack is associated with the release of the CGRP which has a key role in migraine pathophysiology. CGRP is a 37 amino acid neuropeptide belongs in the calcitonin gene peptide super family. Activation of trigeminal nociceptive terminals will stimulate the release of CGRP, which can increase the sensitivity of perivascular nociceptors and dilate cranial vessels. Clinical studies have fully established the importance of CGRP in migraine pathogenesis (27-29). CGRP levels have been reported to be elevated during spontaneous and nitroglycerine-induced migraine and reduced coincident with pain relief. Intravenous injection of CGRP caused delayed headaches, which for some subjects met the criteria for induced migraine (30,31). Notably, the delayed onset of migraine-like headaches was seen only in migraineurs. Nonmigraineurs experienced only an initial mild headache or fullness-of-head sensation. This suggests that migraineurs are unusually sensitive to CGRP actions.

Another neuronal messenger molecule that has been suggested to have an important role in migraine pathophysiology is pituitary adenylate cyclase-activating polypeptide (PACAP). PACAP is encoded by *ADCYAP1* gene,

which expresses two forms containing either 27 or 38 amino acids with PACAP-38 representing 90% of PACAP forms in mammalian tissues (32). In the trigeminovascular system, PACAP is expressed in the spinal cord, trigeminal ganglia, and TNC (33). Intravenous injection of PACAP induces migraine-like symptoms and dilation of the middle meningeal artery (MMA) in both healthy and migraine patients. Migraineurs had elevated levels of PACAP peptide during the ictal phase relative to the interictal phase (34).

Genomic analyses for migraine

Identifying genes for multifactorial disorders like migraine is difficult because multiple genes are always with low penetrance, contributing to susceptibility of the disorder (35). Moreover, the resulting phenotype is influenced by both endogenous and exogenous non-genetic factors. Specifically, FHM is a rare monogenic migraine. Besides the FHM, genetics work also has been done to explore the mechanism of other migraine generation including exploring the fields of neuropeptides, hormonal related genes and so on. Although much effort has been done to explore the genetics of migraine, there are only few outcomes.

FHM related genes

There are three causative genes have been described in FHM: *CACNA1A* on chromosome 19p13 (FHM1) (36), *ATP1A2* at 1q23 (FHM2) (37), and *SCN1A* at 2q24 (FHM3) (38). The *CACNA1A* gene encodes the α 1A subunit of the P/Q type neuronal calcium channel (39) presenting with FHM1 (40). FHM1 mutations produce gain-of-function of the Ca (V) 2.1 channel and as a consequence, increased Ca (V) 2.1-dependent neurotransmitter release from cortical neurons and facilitation of *in vivo* induction and propagation of CSD (41). *ATP1A2*, encodes the α 2 subunit of the Na⁺/K⁺ ATPase, is expressed in astrocytes and involved in the clearance of extracellular K⁺ and production of a Na⁺ gradient used in the reuptake of glutamate. *SCN1A* encodes the α 1 subunit of the neuronal voltage gated sodium channel Nav1.1. This channel is critical in the generation and propagation of action potentials (42). *SCN1A* gene mutation leads to accelerated channel recovery from fast inactivation which increases dendrite excitability and neuronal firing. Mutations in ion channels could have led towards the vasogenic path but the consequent elevated extracellular glutamate and K⁺ levels support neurogenic theory leading to reduced CSD threshold in migraine (43).

In 2012, mutations in the proline-rich transmembrane protein 2 gene (*PRRT2*) have been shown to be associated with hemiplegic migraine (44). *PRRT2* codes for a transmembrane protein, which has an unknown function that is capable to bind to synaptosomal-associated protein 25 (SNAP25), suggesting a role in synaptic exocytosis (45). Mutations in the *SLC4A4* gene (46) and *SLC1A4* gene (47) have also been reported in the FHM, although these four mutations are relatively rare or even “private”.

Hormonal related genes

Clinical and epidemiological observations indicate a strong correlation between female gender, sex female hormones, and migraine susceptibility. For these years, some genes have been verified participate the menstrual migraine (MM) generation.

The polymorphic estrogen receptor 1 (*ESR1*) gene at human chromosome 6q25.1 has eight exons and seven introns and spans about 300 kb in length (48). A meta-analysis in 2015 get a conclusion that exon 4 325C>G and exon 8 594G>A polymorphisms of the *ESR1* gene conferred increased susceptibility to migraine, basing on data from molecular and epidemiological studies (49). At the same time *ESR1* is expressed in many areas of the brain regulating many functions including regulating gene expression through cell signaling affecting glutamate and serotonin synthesis and CGRP and can regulate vascular tone by stimulating release of nitric oxide (NO) (50,51). Progesterone receptor gene (*PGR*), located on chromosome 11q22 (OMIM# 607311), encodes a steroid receptor that principally mediates the effect of progesterone on the establishment and maintenance of reproductive events (UniProt# P06401). *PROGINS* *PGR* polymorphism does not directly predispose to migraine but significantly delays migraine onset probably via a reduction in brain neuronal excitability (52).

Migraine related neurologic syndrome

Migraine has been reported as clinical manifestations in several genetic vasculopathies. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a monogenic-inherited form systemic vasculopathy linked to mutations in the *Notch3* gene (located on chromosome 19p13.2-p13.1), which encodes a cell surface receptor (53). The incidence of migraine with aura in CADASIL is five times greater

compared with the general population (54,55).

The other one is retinal vasculopathy with cerebral leukodystrophy (RVCL) which is a neurovascular syndrome characterized by vascular retinopathy, cognitive impairment, depression, migraine (mainly without aura), focal neurologic symptoms and intracerebral mass lesions. The *TREX1* gene has just been reported independently, and it is still unclear how the carboxyl truncating mutations in *TREX1* lead to the phenotype or pathogenesis of RVCL (56).

COL4A1 related-syndromes is caused by *COL4A1* mutations which will cause neurological symptoms including hemiparesis, seizures, visual loss, dystonia, stroke, mental retardation, cognitive impairment and dementia. The association of *COL4A1* mutations with migraine is not entirely certain. To date, migraine with aura has been described only in one family with *COL4A1* mutation (57).

Two families with migraine with aura and familial anticipated sleep phase syndrome (FASPS) have been screened with a mutation in the circadian Period2 (*PER2*) gene, within the casein kinase 1 (CK1)-binding domain of the Per2 protein. Mice carrying the CK1δ T44 mutation have a reduced threshold for CSD after exposure of the cortical surface to 1 μM potassium chloride and increased spontaneous and evoked calcium activity in astrocytes (58).

Neuropeptides related genes

Receptor activity modifying protein 1 (RAMP1) is known to be a key receptor subunit of CGRP, which functions as an important neural transmitter in migraine (59). The changes in the expression of *RAMP1* can affect the sensitivity of cell to CGRP (60). The over-expressed human *RAMP1*Nestin/*RAMP1* transgenic mice, can mimic photophobia and allodynia just like migraine, when intracerebral ventricular administration of CGRP (61,62). However, genetic polymorphism studies failed to link migraine with variations in *RAMP1* gene (63,64). A few attempts are to investigate the relationship between deoxyribonucleic acid (DNA) methylation of *RAMP1* gene and migraine. Recently a study provides that DNA methylation at *RAMP1* promoter might play a role in migraine. A lower methylation level at (+89, +94, +96) CpG unit may be a risk of migraine in females (65).

As a potent vasodilator implicated in migraine, NO has a strong correlation with CGRP. NO synthase 3 (*NOS3*) by expressing enzyme NOS regulates endothelial derived NO. The *NOS3* gene is located on chromosome 7 and consists of 26 exons. The *NOS3* gene has numerous poly-morphisms which among them the Glu298Asp at exon 7 is the only

single nucleotide polymorphism (SNP) (guanine to thymine at position 894) which leads to amino acid substitution (from glutamic acid to aspartic acid at position 298). Study has verified that migraine attacks after use of tricyclic antidepressants (TCAs) was significantly decreased in all genotypes of *NOS3*. Use of TCAs had no significant effect in intensity of headache in migraine patients, but by decreasing frequency of migraine attacks had an inhibitory role in migraine generation, particularly in patients with TT genotype (66).

Others

Recent studies have highlighted the role that the potassium channel, subfamily K, TWIK-related spinal cord K⁺ channel (*TRESK*) gene may play in migraine with aura. A main physiological function of *TRESK* is the modulation of nociception. Down-regulation of *TRESK* expression by siRNA increased the sensitivity to painful stimuli (67). Overexpression of *TRESK* in DRG neurons attenuates nerve injury-induced mechanical allodynia (68). The *TRESK* channel presents perhaps the best opportunity for development of antimigraine therapeutics, given its predicted role in controlling neuronal excitability (69).

The methylenetetrahydrofolate reductase (*MTHFR*) gene has been verified to increase the risk of ischemic stroke in migraine with aura (70). The gene encodes MTHFR enzyme that converts 5, 10-methylenetetrahydrofolate into 5-methylenetetrahydrofolate, which is the circulating form of folate in plasma. Folate is needed for conversion of homocysteine to methionine (71). In the presence of either homozygous or heterozygous C677T or A1298C variants of the *MTHFR* gene, the activity of the enzyme is downregulated, therefore homocysteine level in blood plasma increases (72). The decreased activity of the MTHFR enzyme is considered an important risk factor for migraine.

Transient receptor potential (TRP) channels are expressed in dural afferents including those containing CGRP. Activation of TRP channels promotes excitation of nociceptive afferent fibers and potentially leads to pain. In addition to pain, allodynia to mechanical and cold stimuli can result from sensitization of both peripheral afferents and of central pain pathways. In the TRP family, TRPV1 is highly expressed on peripheral nociceptors (73).

The relation of angiotensin-converting enzyme (ACE) and migraine is not clear. Recent studies showed the ACE D/D genotype have a synergistic effect with the *MTHFR* T/T genotype toward developing migraine (74).

The dopaminergic system and glutamate also play major roles in migraine. Skorobogatykh *et al.* did a research about dopamine beta hydroxylase (DBH) polymorphisms rs1611115 and showed that the T-allele carriers (46.9%) as compared to the CC genotype patients (53.1%) have more severe migraine (75). TT genotype of rs2049046 in brain-derived neurotrophic factor (*BDNF*) gene appears to influence susceptibility to migraine chronification. This polymorphism could also be a link for comorbidity of chronic migraine and mood disorders (76).

Precision treatment for migraine

Lots of studies have been done to explore the initiation, propagation, pathogenesis, and genetics of migraine. However, the ultimate aim is to get an excellent option to deal with migraine. We have reviewed the different pathogenesis of migraine including 5-HT, NO, CGRP, PACAP and other related neuropeptides. Hence, one strategy to abort migraine is to block the release of neuropeptides or their receptor activation. Abortive agents in acute migraine management exert a modulatory effect on the levels of circulating neuropeptides. Some of the material's receptors, agonist have been researched even used in the treatment.

5-HT receptor agonist

5-HT_{1B/1D} receptor agonists have a long history in the treatment of migraine. Ergot is the oldest medicine used as the antimigraine drug. Methysergide, a 5-HT_{2B} receptor antagonist, and ergotamine, a 5-HT_{1A/1B/1D/1F/2A/2B} agonist, in migraine treatment spurred the early research at a pharmacological level (77). However, the side effects such as gangrene of the limbs due to a potent and long lasting vasoconstriction limited its popularization. After that, the triptans were demonstrated can induce downregulation in TNC activity (78) and decreased the enhanced neuronal firing in the brain stem in animal models (79). Sumatriptan, the first triptan as an agonist at 5-HT_{1B/1D} receptor (80), is verified effective and well-tolerated in patients (81). However, the agonist also has a peripheral vasoconstriction because of the presence of some 5-HT_{1B} receptors on coronary arteries, so sumatriptan is contraindicated in patients with cardiovascular disease (82). But it still has been proven to be effective and well-tolerated when used properly. In addition, sumatriptan stimulates 5-HT_{1D} receptors located in trigeminal fiber endings, which inhibits the release of neuropeptides (83). As the first generation

of triptans, sumatriptan has a low oral bioavailability (14%), and a short half-life period of about 2 hours (84). The second generation triptans including zolmitriptan, naratriptan, rizatriptan, frovatriptan, almotriptan and eletriptan have a greater bioavailability, longer plasma half-life, and higher lipophilicity (85). Evidence-based medicine has indicated that the triptans are of level A for the acute treatment of migraine headache (85). The use of pure 5-HT_{1F} agonists is hypothesized could be effective as antimigraine abortive treatment due to higher receptor selectivity (26). However, recently clinical studies about 5-HT_{1F} receptor agonist, lasmiditan, revealed a high rate of central nervous system side effects in clinical trials included dizziness (often classified as severe), paresthesia, fatigue and vertigo (86,87). Novel antimigraine drugs without peripheral vasoconstrictor side effects are still needed; compounds binding specifically to 5-HT_{1D}, 5-HT_{1F} and 5-HT₇ receptors have been or are currently being investigated.

CGRP receptor and monoclonal antibodies

CGRP receptor antagonists have been developed as novel antimigraine drugs and found to be effective in the treatment of acute migraine attacks. Olcegepant (BIBN4096BS) is the first discovered selective CGRP-RAs (88). A multicenter, double blind, randomized (126 patients with migraine), clinical proof-of-concept study revealed the effectiveness of olcegepant for the treatment of acute migraine attacks (89). However, the intravenously administration limited its wide clinical use. Telcegepant was developed as an orally available medicine instead. It proved effective as a migraine abortive agent, with efficacy for 2-hour pain and 2-hour pain freedom, sustained pain freedom for 2–24 hours and 2–48 hours (90–92) and toward the migraine accompanying symptoms (nausea, photo and phono-phobia). However, the study was abandoned (93–95) because of asymptomatic liver toxicity in some patients. Another orally CGRP receptor antagonist MK-3207, also showed hepatotoxicity in some cases and its development was thus discontinued (96). Monoclonal antibodies targeting CGRP (CGRP-mAbs) or its receptor appear more promising with no liver toxicity. Whereas the small-molecule CGRP-RAs were developed only for the acute treatment of episodic migraine, the anti-CGRP mAbs were designed for the prophylaxis of frequent episodic and chronic migraine in severe cases. Because of the large size of the mAbs, they cannot be administered orally, but only subcutaneously or intravenously. The humanized mAbs LY2951742 (developed by Arteus Therapeutics),

ALD403 (developed by Alder Biopharmaceuticals) and LBR-101 (developed by Labrys Biologics—TEVA) have been investigated against episodic migraine. The studies are still in clinical trials. Currently, the only anti-CGRP-R mAb AMG 334 (a compound developed by Amgen) has been undergoing the Phase II clinical studies of episodic and chronic migraine. The results are still not yet available (97).

Further, PACAP-induced MMA dilation was abolished by the ATP-Sensitive Potassium (KATP) channel blocker glibenclamide. These observations that PACAP dilates MMA via activation of vascular KATP channels may provide a potential therapeutic target of migraine (98).

Genes targeting

Specifically, genetic analysis could contribute to better treatment choices. Collectively these data indicate that SNP analysis of candidate genes can assist in the diagnosis of migraine, as well as opening up the possibility of gene therapy for this disorder (99).

Though we have known *CACNA1A*, *ATP1A2*, *SCN1A* and *PRRT2* genes play important roles in migraine, the gene targeting therapies related studies are very few. Loredana Leo et al had generated the first FHM2 knock-in mouse model carrying the human W887R mutation in the *Atp1a2* orthologous gene (100). However, there is still no FHM related knock-out models or other genetic therapies reported.

Parthenolide, a bioactive compound contained in the antimigraine preparations from *Tanacetum parthenium* (also known as feverfew), has been very recently shown to act as a partial agonist at TRPA1 channels (101). Although TRP channels appear a promising target for migraine treatment, there are no other products of this class in current development in clinical trials.

The *MTHFR* gene mutation has been verified if the *MTHFR* enzyme activity is down-regulated, homocysteine level in blood plasma will increase. Therefore, supplementation with folic acid, vitamin B₆, and vitamin B₁₂ for the people with *MTHFR* gene variant will be helpful. The T/T individuals should receive higher doses (102). However, the efficiency of ACE inhibitor lisinopril (103) and angiotensin 1 receptor blocker olmesartanin migraine prophylaxis suggests a potential relation between the renin-angiotensin system (RAS) and migraine.

Conclusions

Migraine is a common, disabling, and undertreated

worldwide problem. The activation of the trigeminovascular system and the genomic anomaly has been verified playing important roles in the migraine. The antimigraine drugs such as 5-HT receptors agonists, CGRP receptor and monoclonal antibodies even have been used in the clinical treatment. Though research efforts have been done but there are still not enough specific therapies to treat migraine. So more complete understanding of the molecular pathways involved and the relevant genomic profile of migraine will aid in the development of new anti-migraine drugs and treatments, and or enable those currently available to be better targeted to suit individuals. In the era of precision, the integration of genomic data, functional studies, and data from biomarker-driven clinical trials will shape molecular profiling of migraine in the near future. Ongoing and future efforts to find new vulnerabilities of migraine, unravel the complexity of drug therapy, and perform biomarker-driven clinical trials are necessary to improve outcomes for patients with migraine. The best way to move forward is with a multidisciplinary approach incorporating results from emerging biochemical, pharmacologic, genetic studies and imaging techniques in order to better understand and treat this debilitating disease.

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Footnote

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