Current Pain and Headache Reports (2024) 28:169–180
https://doi.org/10.1007/s11916-024-01228-4

CHRONIC DAILY HEADACHE (S-J WANG AND S-P CHEN, SECTION EDITORS)

Influences of Genetic and Environmental Factors on Chronic Migraine: A Narrative Review

Po-Kuan Yeh[1,2] · Yu-Chin An[3] · Kuo-Sheng Hung[4] · Fu-Chi Yang[1,4]

Accepted: 7 February 2024 / Published online: 16 February 2024

Abstract

Purpose of Review In this narrative review, we aim to summarize recent insights into the complex interplay between environmental and genetic factors affecting the etiology, development, and progression of chronic migraine (CM).

Recent Findings Environmental factors such as stress, sleep dysfunction, fasting, hormonal changes, weather patterns, dietary compounds, and sensory stimuli are critical triggers that can contribute to the evolution of episodic migraine into CM. These triggers are particularly influential in genetically predisposed individuals. Concurrently, genome-wide association studies (GWAS) have revealed over 100 genetic loci linked to migraine, emphasizing a significant genetic basis for migraine susceptibility.

Summary In CM, environmental and genetic factors are of equal importance and contribute to the pathophysiology of the condition. Understanding the bidirectional interactions between these elements is crucial for advancing therapeutic approaches and preventive strategies. This balanced perspective encourages continued research into the complex gene-environment nexus to improve our understanding and management of CM.

Keywords Chronic migraine · Genetic factors · Environmental factors · Genetic loci

Introduction

Migraine, which affects an estimated one billion individuals worldwide, is a complex disorder characterized by intense recurring headaches. These episodes are often accompanied by multiple symptoms such as nausea, vomiting, and extreme sensitivity to light and sound. Chronic migraine (CM), a particularly debilitating subtype of migraine, is defined as the presence of headaches for 15 days or more per month, with at least 8 days meeting the specific criteria for migraine. Depending on their severity and frequency, the headaches can substantially impair the quality of life and productivity of patients, making CM a major public health concern [1].

The etiology of CM involves a complex interplay between genetic and environmental factors. The genetic influences are substantial with heritability estimates ranging from 50 to 80%. Recent studies have identified more than 100 genetic loci associated with migraine that affect nerve transmission, inflammation, and pain perception [2]. Furthermore, the advent of genome-wide association studies (GWAS) has been instrumental in elucidating the polygenic nature of migraine [3••]. Environmental factors also play critical roles, particularly in genetically predisposed populations. These factors not only precipitate migraine episodes but also contribute to migraine chronification [4].

In this review, we aim to provide an up-to-date summary of the genetic variants and environmental exposures with potential roles in CM pathogenesis. Elucidating the genetic and environmental underpinnings of CM may provide biological insights into the development of targeted therapeutics and personalized prevention strategies for this disabling disorder.

Po-Kuan Yeh and Yu-Chin An contributed equally to this work.

✉ Fu-Chi Yang
fuji-yang@yahoo.com.tw; fujiyang88@gmail.com

1 Department of Neurology, Tri-Service General Hospital, National Defense Medical Center, Section 2, Cheng-Kung Road, Neihu 114, No. 325, Taipei, Taiwan

2 Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, Beitou Branch, Taipei, Taiwan

3 Department of Emergency Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

4 Center for Precision Medicine and Genomics, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

Environmental Factors in CM

A myriad of environmental exposures have been implicated as triggers capable of precipitating acute migraine episodes, especially among genetically vulnerable individuals, based on their polymorphic risk profile. Common triggers include but are not limited to stress, sleep dysfunction, fasting, hormonal changes, weather patterns, odors, dietary compounds, and sensory stimuli [4]. Exposure to a combination of these triggers may also contribute to migraine chronification in patients prone to progressive sensitization. In this section, we review external and lifestyle-related factors (Table 1) linked to either provoking individual migraine attacks or gradually lowering the migraine activation threshold.

Stress

Migraine can activate the autonomic nervous system, particularly the hypothalamic–pituitary–adrenal (HPA) axis, when stress experienced exceeds an individual's coping capacity. This stress response includes the release of cortisol and other stress hormones, potentially triggering or exacerbating migraine [5]. Furthermore, emotional disorders such as anxiety and depression are closely linked to the occurrence of migraine. These emotional states may enhance pain perception by affecting the pain-processing mechanisms in the brain. Conversely, migraine can also lead to changes in a patient's emotional state, especially in those with CM. These emotional responses, potentially stemming from the pain itself or the effect of headaches on daily life, form a vicious cycle that further intensifies the pain [6].

Patients with CM often face higher stress due to frequent, prolonged headaches, potentially overactivating their HPA axis and leading to abnormal cortisol levels. In contrast, patients with episodic migraine (EM) have fewer headache episodes and less HPA axis disturbance. Fluctuations in the levels of neurotransmitters, particularly serotonin and norepinephrine, which are key to pain and emotion regulation, are more pronounced in CM, possibly because of frequent headache episodes and a high risk of depression or anxiety [7]. Specific brain regions such as the amygdala and prefrontal cortex also play major roles. The amygdala, which is involved in emotion processing, also functions in the emotionalization of pain [8]. The enhanced connectivity between the amygdala and visual processing areas in patients with CM, which has been implicated in pain and emotional response, may account for their increased pain sensitivity and emotional distress. This alteration in brain connectivity could be either a developing trait of CM, potentially acting as a risk factor, or an adaptive response mechanism of the brain to extended pain and stress, indicative of neural plasticity in response to continuous pain stimuli in CM [9•]. Some regions of the prefrontal cortex are also crucial for directing attention to pain and emotional responses [10].

Considering these factors, the current review emphasizes the importance of psychotherapy in migraine treatment strategies, particularly cognitive behavioral therapy (CBT) and stress management techniques, which have proven effective in reducing migraine attacks [11].

Sleep Disturbances

Individuals with migraine are more prone to sleep problems, such as insomnia and poor sleep quality, than the general population. Insufficient sleep can trigger migraine attacks, and prolonged poor sleep quality may lower the pain threshold, thereby exacerbating the migraine symptoms [12]. Further studies have revealed that sleep disturbances associated with migraine may be linked to the hypothalamus [13]. The posterior hypothalamus, pivotal in managing various physiological functions such as pain perception and sleep regulation, plays a key role in migraine pathophysiology, and its activity is regulated by pituitary adenylate cyclase-activating peptide (PACAP). PACAP, existing in forms such as PACAP-38 and PACAP-27, influences migraine development through its action on PAC1 receptors, which are closely linked to migraine attacks. It has been observed that PACAP can sensitize trigeminal neurons, an effect that can be inhibited by PAC1 antagonists. During migraine attacks, the concentration of PACAP-38 reportedly increases. The posterior hypothalamus, integral to the circadian rhythm entrainment, is associated with intrinsically photosensitive retinal ganglion cells (ipRGCs) via the retinohypothalamic tract (RHT). In this pathway, PACAP is crucial to modulating the transmission of light signals from the retina to the hypothalamus, thereby playing a vital role in the regulation of the sleep–wake cycle [14••].

Specific sleep stages are also associated with migraine. The maximum episodes of migraine attacks often occur early in the morning or late at night, which may be related to the rapid eye movement (REM) sleep stage. Serotonin levels also decrease throughout the body during REM sleep, which potentially explains the relationship between REM sleep and migraine [15]. Lack of sleep can sensitize the trigeminal pain pathway, thereby triggering migraine attacks. Untreated sleep disorders, such as obstructive sleep apnea (OSA), may also contribute to the progression of migraine by affecting hypoxia and oxidative stress pathways, further sensitizing the trigeminal nociceptors [16]. However, additional research is essential to better understand and define the association of sleep stages with CM.

While there is still debate over whether improving sleep quality can reduce the frequency of migraine, some clinical studies have confirmed the positive effect of managing sleep disorders on headache outcomes, including the use of suvorexant, an orexin antagonist [17], and implementation of behavioral sleep intervention programs [18].

Table 1 Summary of the environmental factors, mechanisms, and features associated with migraine

Environmental factors	Mechanisms	Migraine features	References
Stress	Activates the hypothalamic–pituitary–adrenal (HPA) axis and releases cortisol and other hormones. Affects neurotransmitters involved in emotion regulation, such as serotonin and norepinephrine. Activates emotion-processing brain regions such as the amygdala and prefrontal cortex	Stress activates the autonomic nervous system, leading to functional dysregulation and pain. The causal relationship between stress and migraine is under investigation, with implications for management	Grangeon et al. [2] Pistoia et al. [7] Torres-Ferrus et al. [10]
Sleep disturbances	Sleep deprivation sensitizes trigeminal nociceptive pathways. Sleep disorders such as obstructive sleep apnea can enhance trigeminal input via hypoxia and oxidative stress pathways	Sleep dysfunction is a common trigger for migraine episodes, particularly in genetically vulnerable individuals	Sacmaci et al. [12] Martinelli [4]
Fasting	Enhances cortical excitability and activates trigeminal pain fibers. Induces cerebral vasodilation, cortisol release, and hypoglycemia	Regular eating schedules can reduce the frequency of headache episodes by stabilizing serum glucose levels. Fasting is linked to migraine onset, potentially due to hypoglycemic states affecting cortical spreading depression susceptibility	Yadav et al. [19] Alstadhaug [20] Friedman and Lipton [21]
Weather changes	Atmospheric pressure changes affect intracranial pressure. Stormy weather releases inflammatory mediators and causes vasodilation. High temperatures increase emergency hospital visits for migraine attacks	Weather patterns are possible triggers for migraine episodes, especially in genetically susceptible individuals	Kimoto et al. [23] Kelman [22] Ordás et al. [26] Martinelli et al. [4]
Hormones	Estrogen level fluctuations can trigger migraine attacks involving the regulation of CSD-related signaling molecules such as CGRP and 5-HT	Hormonal changes are a trigger for migraine; they manifest differently in female individuals, often with specific symptoms such as photosensitivity, and may require sex-specific treatment approaches	Chauvel et al. [36] Allais et al. [28] Vetvik and MacGregor [32]
Dietary compounds	Compounds, such as tyramine, nitrites, and MSG, and alcohol can trigger migraine. Dietary inflammation positively correlates with migraine risk	Dietary compounds are listed as common triggers, although specific details are not provided	Hindiyeh et al. [42] Liu et al. [44••] Martinelli et al. [4]
Sensory stimuli	Abnormal amplification of olfactory, visual, and auditory inputs activates trigemino-thalamo-cortical pathways	Sensory stimuli such as loud noises and flickering screens can trigger migraine due to sensory processing dysregulation	Rocha-Filho et al. [46] Yadav et al. [19] Hauge et al. [50]

Fasting and Meal Skipping

Delaying or missing meals are among the most frequently cited but underrecognized dietary contributors to migraine attacks. Nearly 40% of individuals with CM identify fasting or hunger as an attack trigger in surveys [19]. The mechanisms by which fasting promotes migraine episodes likely involve cerebral vasodilation, cortisol release, and hypoglycemia, all of which can enhance cortical excitability and sensitize meningeal trigeminal pain fibers [20]. Maintaining regular eating schedules has demonstrated some efficacy in reducing headache frequency, plausibly by stabilizing the serum glucose levels and preventing hypoglycemic states linked to cortical spreading depression (CSD) susceptibility [21]. However, additional research is essential to better understand and define its association with CM.

Weather Changes

Studies have indicated that the effect of weather on migraine remains contentious. Numerous patients with migraine have reported that specific weather conditions can trigger headaches. Over half of the patients suffering from migraine consider weather to be a trigger factor [22], especially when the atmospheric pressure drops by more than 5 hectopascals (hPa) [23]. The proposed mechanism involves changes in the intracranial pressure or the release of inflammatory mediators during storm fronts, which may promote vasodilation and activate meningeal nociceptors. Migraine attacks and the associated disabilities often peak during the transitional periods of spring and autumn [23].

Humidity and rainfall are also thought to affect migraine occurrence, but the association remains unclear. Some small-scale studies have suggested that cloudy and thundery weather conditions may trigger migraine, although these conclusions require cautious interpretation [24]. Large-scale studies, such as those conducted by Zebenholzer et al. did not confirm a significant correlation between weather conditions and migraine episodes [25]. High temperature has been identified as a major trigger of migraine and is possibly related to increased body temperature [26]. Some small-scale studies indicate that the preventative adjustment of behavioral habits based on predicted weather changes can alleviate weather-induced attacks in specific patients [27]. However, additional research is essential to better understand and define the association of high temperature with CM.

Hormones

Migraine presents with significant sex disparities in incidence rates, pathogenic mechanisms, and clinical manifestations. Female individuals exhibit a higher lifetime prevalence, especially during their reproductive years [28]. Estrogen has been linked to CM occurrence; it enhances pain sensitivity by increasing CSD sensitivity and disrupting neuronal vascular function, particularly in the central trigeminovascular system. It acts through estrogen receptor β (ERβ), affecting the central nervous system and leading to neurogenic inflammation and central sensitization. The binding of estrogen to the receptor increases calcium concentration in neurons, lowering the nociceptive neurotransmission threshold and contributing to central sensitization and cortical hyperexcitability [29]. This process is further amplified by enhanced N-methyl-D-aspartate (NMDA) receptor activity on glutamatergic neurons. Changes in the estrogen level also affect the levels of neurotransmitters such as CGRP and serotonin, potentially contributing to the progression of CM [30]. Prolonged-cycle oral contraceptive use can stabilize hormone levels and reduce symptomatic migraine episodes [31]. Overall, sex-dependent differences are likely the result of an interplay between genetics and hormones.

Clinically, migraine manifests differently in female individuals, often as unilateral headaches with photosensitivity and without nausea or vomiting [32]. They also frequently report nonspecific symptoms, such as neck stiffness, leading to potential misdiagnosis. Owing to physiological differences, the male and female individuals may respond differently to certain medications, with women being more sensitive to 5-HT1B/1D receptor agonists [28]. The transgender population experiences unique migraine patterns owing to hormonal changes and shifts in gender identity [33]. Sex-related differences also influence migraine treatment strategies, which is possibly related to the hormonal regulation of neurotransmitter signaling pathways. Oral contraceptives alleviate menstruation-related migraine attacks [34].

The biological basis of the increased susceptibility of females to migraine includes the distribution of estrogen receptors in the central structures related to pain processing, which affects pain management [35]. Nitric oxide synthase plays a role in migraine pathology, with a more concentrated distribution in the spinal neurons of female rats, and estrogen promotes increased nitric oxide synthesis in migraine models [36]. Variations in osteopontin gene polymorphisms related to calcium metabolism have been linked to an increased susceptibility to migraine in females. The neuropeptide PACAP plays a major role in migraine onset, and genetic polymorphisms in females are notably related to higher susceptibility [36].

Sex-related differences are also evident in the peak incidence of migraine. Before puberty, male and female individuals exhibited similar incidence rates. However, postmenstrual women are more prone to migraine, related to hormonal secretions and endometrial shedding. Pregnancy and menopause are high-risk periods due to drastic hormonal fluctuations, whereas males achieve a delayed peak, which is associated with increased androgen levels and decreased estrogen levels at puberty [28].

Dietary Compounds

Recent studies have identified a significant correlation between specific foods and beverages and the occurrence of migraine. Tyramine, a biogenic amine present in foods such as aged cheese, red wine, and fermented products, has been implicated in the onset of migraine. It is metabolized to dopamine, which promotes vasodilation and contributes to migraine pathogenesis; dopamine may also affect serotonin release [37]. Research indicates that abnormalities in tyrosine metabolism may play a role in the transformation of migraine without an aura into CM [38].

Nitrates and nitrites found in processed meat are also considered potential triggers of migraine. These compounds can be converted to nitric oxide (NO) in the body, causing vasodilation, which may lead to changes in cerebral blood flow and trigger headaches. Furthermore, nitrates and nitrites may induce migraine by stimulating the neural system in the brain [39].

Caffeine has a paradoxical relationship with migraine, serving as both a common treatment and, in cases of excess intake or withdrawal, a reported trigger. Adenosine levels in the blood increase during migraine attacks, and caffeine, which blocks adenosine receptors, inhibits the effects of adenosine. However, the specific mechanisms by which caffeine controls pain and induces headaches remain unclear [40].

Monosodium glutamate (MSG) intake has been linked to migraine induction in sensitive individuals and plays a major role in its pathophysiology [41]. Alcohol can stimulate meningeal nociceptors in the trigeminal ganglion and cause vasodilation and dehydration, potentially contributing to alcohol-induced migraine [42]. Foods rich in flavonoids, such as chocolate, wine, and tea, are also recognized triggers in some patients. This may be because of flavonoid-enhancing vanilloid receptors in the neurogenic inflammatory pathways associated with migraine [43].

Studies using the dietary inflammatory index (DII) as an assessment tool have found that higher DII scores are significantly correlated with an increased risk of severe headaches or migraine [44••]. Research shows that diets with a low glycemic index; low fat, ketogenic diets; and Dietary Approaches to Stop Hypertension (DASH) can help reduce the frequency and severity of CM [42].

Sensory Stimuli

External sensory stimuli, especially bright or flickering light, loud noise, and strong odor, can immediately trigger acute migraines in the majority of patients with CM [45], causing inconvenience in their daily lives. Odor sensitivity (olfactory hypersensitivity) is also common among patients with migraine. Odors such as those of perfumes, vehicle exhaust, cigarette smoke, cleaning agents, and other volatile chemicals can quickly induce headaches in patients with CM [46]. Studies have suggested that patients with severe migraine are more prone to odor-induced attacks and are more likely to experience insomnia, depression, fatigue, and sensory hypersensitivity [47]. Flickering light sources can also easily trigger migraine attacks in patients with CM, and specific patterns and colors may evoke discomfort, especially black-and-white stripes and high color contrasts [48]. Noise in the environment is one of the risk factors for migraine onset. Intense sounds or specific auditory stimuli (such as ambulance sirens or railway-level crossing bells) can easily trigger migraine attacks in patients with CM. Exposure to such sounds during an attack exacerbates the pain level. To avoid sound-induced pain, patients often adopt avoidance strategies, attempting to stay away from specific sources of sound that may trigger headaches. These strategies limit their daily activity range [49].

Overall, photosensitivity, odor sensitivity, and sound sensitivity reflect interictal dysregulation in sensory processing, lowering the migraine activation threshold, and potentially restricting daily activities [50]. Treatments targeting the regulation of trigeminal excitability and central amplification have been shown to reduce the sensitivity of patients with migraine to odor, light, and sound [45]. However, optimizing the sensory environment to avoid strong triggers has also been proven effective in reducing the frequency and severity of migraine attacks [50]. Additional research is essential to better understand and define the association of sensory stimuli with CM.

Genetic Factors in CM

Extensive research has explored the association between genes and migraine, with large-scale GWAS uncovering numerous genetic variants [3••, 51•]. Genetic research has also underscored the shared genetic factors between migraine and major comorbidities such as depression and high blood pressure [2]. Although genetic predisposition is believed to play a role, specific genetic markers associated with migraine chronification have not been fully identified. The transition from episodic migraine to CM typically occurs gradually and involves multiple risk factors.

An early comprehensive study [52•] on single-nucleotide polymorphisms in patients with CM and the subsequent whole-genome sequencing in another large cohort [53] revealed no distinct genetic differences between chronic and episodic migraine cases. The lack of specific rare variants or higher polygenic risk scores suggests that environmental factors, rather than genetic factors, play a more pronounced role in the progression of migraine from an episodic to chronic form.

Recent studies comparing chronic and episodic migraines have identified some genetic variants that may contribute to

migraine chronification (Table 2). Additionally, several influential genes have been widely discussed in the literature as being involved in CM therapy. In this section, we summarize recent research on how genetic factors may contribute to CM.

Transient Receptor Potential Family

In CM research, transient receptor potential (TRP) ion channels, especially TRPV1 and TRPM8, are recognized as pivotal in transforming episodic migraine to CM [54–56]. These channels are integral in converting noxious stimuli into pain signals and are associated with CGRP, a key mediator of migraine development. Genetic variations in TRPV1, such as the 1911A > G variant, have been linked to CM and implicated in the sensitization of pain receptors [57]. TRPV1 activation results in increased CGRP release, which exacerbates migraine symptoms and prolongs meningeal nerve activation [58]. TRPM8, which is responsive to cold stimuli, also plays a role in migraine pain perception, with individuals carrying the rs10166942 T allele showing an increased risk of CM [56]. Moreover, TRPA1's interaction with NMDARs and mu-opioid receptors underscores its significance in the modulation of pain signals [59]. Variants such as TRPV1 rs222741 and TRPM8 rs7577262 are associated with increased anxiety in certain migraine populations, indicating the role of TRP channels in migraine-related comorbidities [60].

Human Leukocyte Antigen Class I

Human leukocyte antigen (HLA) class I molecules are crucial components of the immune system and are primarily involved in the presentation of peptides to T cells [61]. Previous studies have suggested that migraines have genetic similarities with inflammatory diseases [62]. In a case–control study, Huang et al. found that genetic variations in HLA class I molecules positively correlated with the incidence of clinic-based migraine. In addition, the HLA-B*58:01 and HLA-C*03:02 alleles were significantly associated with CM. Drug molecules may affect the immune responses related to migraine, which could lead to the aggravation or chronification of headaches, particularly when painkillers or medications are overused [63].

Dopamine Beta-Hydroxylase

Dopamine beta-hydroxylase (DBH) converts dopamine to norepinephrine, which is important for neurotransmitter synthesis and plays a pivotal role in the pathophysiology of migraine [64]. Previous studies have indicated that the DBH rs7239728 and rs6271 polymorphisms increase the risk of migraine, and DBH rs2097629 increases the risk of migraine with aura [65–67]. According to a recent validation study, the DBH 19-bp insertion/deletion polymorphism may not be associated with migraine susceptibility but is linked to medication overuse in patients with CM. Prefrontal cortex hypofunction may be counteracted by lower dopaminergic activity in patients with CM carrying the I allele (increased DBH activity and reduced dopamine levels), thus shielding them from the risk of medication overuse [68].

Catechol-O-Methyltransferase

Catechol-O-methyltransferase (COMT) has been studied for its potential contribution to migraine. A study focused on assessing the significance of COMT polymorphisms in migraine suggested that the L allele of COMT is overrepresented in patients with migraine, particularly those with a family history of migraine, indicating the potential pharmacological importance of COMT polymorphisms in migraine [69]. In contrast, a study on the association of five single nucleotide polymorphisms (SNPs) in *COMT* with migraine in Western Japan found no significant differences between the patients with migraine and controls [70]. Thus, COMT's specific link to CM remains uncertain and requires further research.

Table 2 Genetic variants associated with chronic migraine

Polymorphism	Gene	Cases of episodic migraine	Cases of chronic migraine	Variant change	Function and implication in pathophysiology	Reference
rs8065080	*TRPV1*	27	19	A > G	Non-selective cation channel, primarily involved in pain perception	Yakubova et al. [55]
rs10166942	*TRPM8*	1320	584	T > C	Ligand-gated calcium channel, implicated in cold-induced thermogenesis and pain perception	Ling et al. [56]
HLA-B*58:01 HLA-C*03:02	*HLA*	104	52	-	Integral to the immune system function, presenting endogenous peptides to T cells	Huang et al. [63]
19-bp I/D	*DBH*	270	130	Deleted allele	Influences dopamine to norepinephrine conversion, related to neurotransmitter synthesis	Barbanti et al. [68]

Calcitonin Gene-Related Peptide

Calcitonin gene-related peptide (CGRP) exists as αCGRP (CALCA) and βCGRP (CALCB) in the human body and plays a crucial role in pain transmission in the trigeminovascular system, making it a significant factor in migraine pathophysiology [71]. CGRP receptor antagonists are effective as a therapeutic strategy for migraine treatment [72–74]. Although GWAS have identified new loci in CALCA/CALCB, the relationship between CGRP gene variants and migraine chronification has not been fully established [71]. Epigenetic modifications of CALCA are associated with various migraine clinical features and can be potential targets for migraine therapy [75]. Moreover, inhibition of HDAC6 expression, which affects CGRP pathways, represents another promising treatment avenue [76].

Histone Deacetylase Inhibitors

Histone deacetylases (HDACs) have emerged as potential targets for the treatment of chronic pain syndromes such as CM [77]. HDACs play a crucial role in modulating neuroinflammatory responses. Studies have shown that HDAC inhibitors can effectively reduce neuroinflammation [78], and they have been implicated in modifying epigenetic changes in genes associated with chronic pain conditions [79]. Research using rat models has highlighted the effectiveness of HDAC inhibitors in treating medication overuse headache (MOH), a common complication of migraine management. These inhibitors have been found to counteract the overexpression of genes encoding CGRP and its receptor subunit RAMP1 in the trigeminal ganglion [80]. Additionally, HDAC6 inhibitors have shown promise in reversing structural neural disruptions and mitigating the symptoms of CM, including CSD [81]. A recent GWAS also identified a genetic variant of HDAC9 (rs1178326) associated with insomnia in patients with migraine, although its relevance to CM remains to be established [82].

Efficacy of Therapy

Although the association between genetic polymorphisms and CM remains debatable, numerous studies have discussed the effects of genetic variability on drug efficacy in patients with CM. In particular, the MAOA uVNTR polymorphism showed a strong correlation with triptan response. In addition, the CYP1A2*1F variant is associated with triptan overuse and response in certain patient groups [83, 84]. Further research on the efficacy of onabotulinumtoxinA highlights the role of genetic variations in the treatment response. Polymorphisms in the CALCA rs3781719 and TRPV1 rs222749 genes have been identified as potential markers for predicting the response to onabotulinumtoxinA in female patients with CM [85]. These genetic insights pave the way for personalized treatment approaches for CM.

Comorbidities

Numerous comorbidities have been identified as risk factors for the development of CM [86], and researchers have explored whether there is a correlation between genetic polymorphisms in migraine and these comorbidities. In a study, 14 SNPs were found to be associated with insomnia and CM [82]. Among the candidate genes, SLC38A10, which acts as a glutamate transporter, has been studied for its potential relationship with migraine onset. This gene can affect neuronal viability by protecting against glutamate toxicity and oxidative stress, which are assumed to contribute to migraine and insomnia onset [87, 88].

GWAS conducted in European populations have shown a genetic correlation between migraine and depression. The genetic profiles of patients who suffer from both depression and migraine are more closely aligned with those of patients with depression alone [89]. Ashina et al. utilized a validated questionnaire (PHQ-9 score ≥ 15) to analyze patients transitioning from episodic migraine to CM. They suggested that depression is associated with an increased risk of progression to CM and that this risk escalates with the severity of depression [90]. In a study involving Chinese population, the intergenic SNP rs9356570 was associated with CM and depression [91]. However, the underlying pathophysiological mechanisms require further investigation.

Cognitive dysfunction is a major issue in patients with migraine, with many reports of subjective cognitive decline (SCD). Clinical and neuroscientific studies have found that migraine episodes often coincide with reduced cognitive performance [92]. Depression and limited sleep during workdays have been linked to SCD in adult individuals with migraine [93]. Genetic research has identified two specific SNPs, rs17111293 in LOC107984361 and rs17111293 in ARHGAP29, which are associated with SCD and CM [94]. The dysregulation of the ARHGAP29 gene is implicated in a range of cognitive and neurological disorders, including migraine without aura [95]. The potentially shared genetic underpinnings between CM and SCD, particularly the genes influencing neuronal development, present a compelling area for future exploration.

Suicide, migraine, and mental illnesses have been linked by a strong bidirectional association, most likely due to shared neuropathic mechanisms. To understand the potential genetic links to suicidal risk in patients with CM with affective temperamental dysregulation, a focused study explored the association between specific gene variants (MAO-A3, CYP1A2*1F, and GNB3) and suicidal tendencies. This study found a correlation

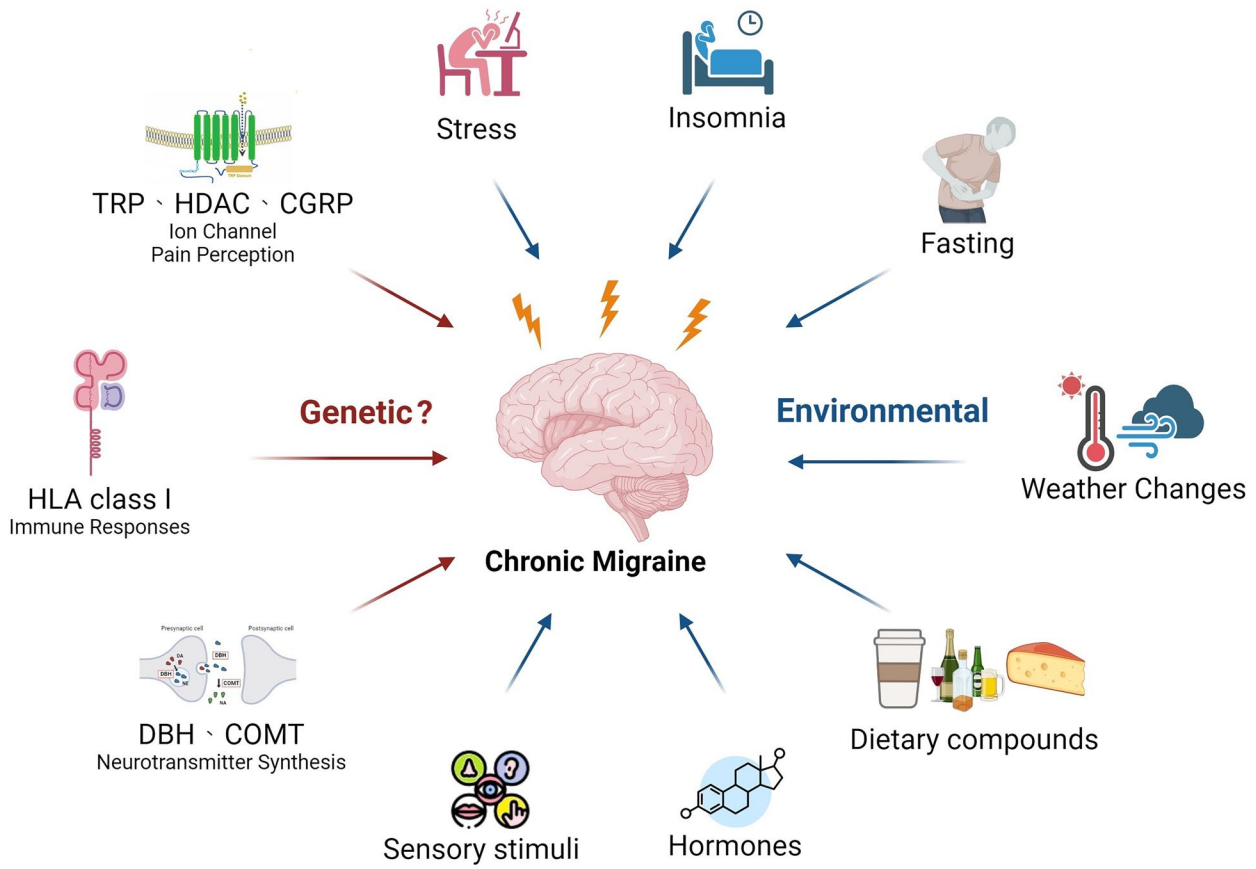

Fig. 1 Environmental and genetic factors contributing to chronic migraine. This diagram illustrates the association between environmental and genetic factors influencing the development of chronic migraine. A question mark has been placed next to genetic factors with a low level of evidence or a degree of uncertainty regarding their direct association with chronic migraine

among high levels of affective dysregulation, increased hopelessness, and suicide risk. However, there was no direct association between the studied genetic variants and an increased risk of suicide. This outcome indicates that the risk of suicide in patients with CM is likely due to a multifaceted combination of genetic and environmental factors [96].

Epigenetics of Migraine Chronification

Recent research has focused on the role of epigenetic mechanisms in the chronification of migraine by exploring how changes in DNA methylation and gene expression can influence migraine susceptibility and its evolution from an episodic to chronic form [97, 98•, 99]. Studies have identified specific genes, such as SH2D5 and NPTX2, that are involved in regulating synaptic plasticity and may play a role in migraine chronification, although the findings have been inconclusive [98•, 99]. The exact biological mechanisms and effects of environmental factors, inflammation, and brain plasticity on these epigenetic changes are not yet fully understood [100].

This gene-environment interaction indicates the complexity of migraine as a chronic condition. The exact biological mechanisms underlying these epigenetic influences remain as areas of active investigation. However, considering epigenetics as a bridge between genetic and environmental factors is important for understanding the pathophysiology of migraine and developing effective treatment strategies.

Conclusions

In conclusion, both genetic predisposition and environmental influences contribute significantly to the pathogenesis of CM (Fig. 1). GWAS have identified numerous genetic variants associated with migraine; however, the specific factors driving the transition from an episodic to chronic form extend beyond genetics alone. Environmental triggers such as stress, sleep disturbances, and dietary factors are crucial in this process. Moreover, key genetic variants and the involvement of genes emphasize the genetic complexity of CM. Additionally, epigenetic mechanisms reveal how environmental factors affect gene expression, thereby

influencing migraine susceptibility and chronification. This review highlights the need for a holistic approach to understand and manage CM. Advancements in this field promise more personalized and effective treatments, potentially easing the burden of CM in patients globally.

Author Contribution Po-Kuan Yeh, Yu-Chin An, and Fu-Chi Yang wrote the main manuscript text and Yu-Chin An and Kuo-Sheng Hung prepared Fig. 1. All authors reviewed the manuscript.

Funding This work was partially supported by the Ministry of Science and Technology of Taiwan (grant number MOST 110–2314-B-016–036-MY2) and the Tri-Service General Hospital, Taiwan (grant numbers TSGH-D-113108 and TSGH-D112097).

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Eigenbrodt AK, Ashina H, Khan S, Diener HC, Mitsikostas DD, Sinclair AJ, Pozo-Rosich P, Martelletti P, Ducros A, Lantéri-Minet M, Braschinsky M, Del Rio MS, Daniel O, Özge A, Mammadbayli A, Arons M, Skorobogatykh K, Romanenko V, Terwindt GM, Paemeleire K, Sacco S, Reuter U, Lampl C, Schytz HW, Katsarava Z, Steiner TJ, Ashina M. Diagnosis and management of migraine in ten steps. Nat Rev Neurol. 2021;17:501–14.
2. Grangeon L, Lange KS, Waliszewska-Prosół M, Onan D, Marschollek K, Wiels W, Mikulenka P, Farham F, Gollion C, Ducros A, European Headache Federation School of Advanced Studies (EHF-SAS). Genetics of migraine: where are we now? J Headache Pain. 2023;24:12.
3. •• Hautakangas H, Winsvold BS, Ruotsalainen SE, Bjornsdottir G, Harder AVE, Kogelman LJA, Thomas LF, Noordam R, Benner C, Gormley P, Artto V, Banasik K, Bjornsdottir A, Boomsma DI, Brumpton BM, Burgdorf KS, Buring JE, Chalmer MA, de Boer I, Dichgans M, Erikstrup C, Färkkilä M, Garbrielsen ME, Ghanbari M, Hagen K, Häppölä P, Hottenga JJ, Hrafnsdottir MG, Hveem K, Johnsen MB, Kähönen M, Kristoffersen ES, Kurth T, Lehtimäki T, Lighart L, Magnusson SH, Malik R, Pedersen OB, Pelzer N, Penninx BWJH, Ran C, Ridker PM, Rosendaal FR, Sigurdardottir GR, Skogholt AH, Sveinsson OA, Thorgeirsson TE, Ullum H, Vijfhuizen LS, Widén E, van Dijk KW, International Headache Genetics Consortium, HUNT All-in Headache, Danish Blood Donor Study Genomic Cohort, Aromaa A, Belin AC, Freilinger T, Ikram MA, Järvelin MR, Raitakari OT, Terwindt GM, Kallela M, Wessman M, Olesen J, Chasman DI, Nyholt DR, Stefánsson H, Stefansson K, van den Maagdenberg AMJM, Hansen TF, Ripatti S, Zwart JA, Palotie A, Pirinen M. Genome-wide analysis of 102,084 migraine cases identifies 123 risk loci and subtype-specific risk alleles. Nat Genet. 2022;54:152–60. **The research identified 123 risk loci using a genome-wide association study, including 86 previously unidentified loci. It offers valuable insights into the genetic components specific to different subtypes and further supports the significance of neurovascular mechanisms in the pathophysiology of migraines.**
4. Martinelli D, Pocora MM, De Icco R, Putortì A, Tassorelli C. Triggers of migraine: where do we stand? Curr Opin Neurol. 2022;35:360–6.
5. Stubberud A, Buse DC, Kristoffersen ES, Linde M, Tronvik E. Is there a causal relationship between stress and migraine? Current evidence and implications for management. J Headache Pain. 2021;22:155.
6. Radat F. What is the link between migraine and psychiatric disorders? From epidemiology to therapeutics. Rev Neurol (Paris). 2021;177:821–6.
7. Pistoia F, Salfi F, Saporito G, Ornello R, Frattale I, D'Aurizio G, Tempesta D, Ferrara M, Sacco S. Behavioral and psychological factors in individuals with migraine without psychiatric comorbidities. J Headache Pain. 2022;23:110.
8. Stankewitz A, May A. Increased limbic and brainstem activity during migraine attacks following olfactory stimulation. Neurology. 2011;77:476–82.
9. • Hadjikhani N, Ward N, Boshyan J, Napadow V, Maeda Y, Truini A, Caramia F, Tinelli E, Mainero C. The missing link: enhanced functional connectivity between amygdala and visceroceptive cortex in migraine. Cephalalgia. 2013;33:1264–8. **This study proposes that increased connectivity between the amygdala and visceroceptive cortex in individuals with chronic migraine may exacerbate migraine symptoms and increase the likelihood of developing chronic migraines. This finding holds potential implications for disease prognosis and genetic factor identification.**
10. Torres-Ferrus M, Pareto D, Gallardo VJ, Cuberas-Borrós G, Alpuente A, Caronna E, Vila-Balló A, Lorenzo-Bosquet C, Castell-Conesa J, Rovira A, Pozo-Rosich P. Cortical metabolic and structural differences in patients with chronic migraine. An exploratory (18)FDG-PET and MRI study. J Headache Pain. 2021;22:75.
11. Bae JY, Sung HK, Kwon NY, Go HY, Kim TJ, Shin SM, Lee S. Cognitive behavioral therapy for migraine headache: a systematic review and meta-analysis. Medicina (Kaunas). 2021;58.
12. Sacmaci H, Tanik N, Inan LE. Current perspectives on the impact of chronic migraine on sleep quality: a literature review. Nat Sci Sleep. 2022;14:1783–800.
13. Vgontzas A, Pavlovic JM. Sleep disorders and migraine: review of literature and potential pathophysiology mechanisms. Headache. 2018;58:1030–9.
14. •• Kuburas A, Russo AF. Shared and independent roles of CGRP and PACAP in migraine pathophysiology. J Headache Pain. 2023;24:34. **This study investigated the functions of neuropeptides CGRP and PACAP in the pathophysiology of migraines. It highlights the effect of PACAP-38 and PACAP-27 on migraines, providing insights into potential treatment approaches. These findings could pave the way for the development of innovative therapies targeting CGRP and PACAP.**
15. Messina A, Bitetti I, Precenzano F, Iacono D, Messina G, Roccella M, Parisi L, Salerno M, Valenzano A, Maltese A, Salerno M, Sessa F, Albano GD, Marotta R, Villano I, Marsala G, Zammit C, Lavano F, Monda M, Cibelli G, Lavano SM, Gallai B, Toraldo R, Monda V, Carotenuto M. Non-rapid eye

movement sleep parasomnias and migraine: a role of orexinergic projections. Front Neurol. 2018;9:95.
16. Korabelnikova EA, Danilov AB, Danilov AB, Vorobyeva YD, Latysheva NV, Artemenko AR. Sleep disorders and headache: a review of correlation and mutual influence. Pain Ther. 2020;9:411–25.
17. Tiseo C, Vacca A, Felbush A, Filimonova T, Gai A, Glazyrina T, Hubalek IA, Marchenko Y, Overeem LH, Piroso S, Tkachev A, Martelletti P, Sacco S, European Headache Federation School of Advanced Studies (EHF-SAS). Migraine and sleep disorders: a systematic review. J Headache Pain. 2020;21:126.
18. Tu AY, Crawford MR, Dawson SC, Fogg LF, Turner AD, Wyatt JK, Crisostomo MI, Chhangani BS, Kushida CA, Edinger JD, Abbott SM, Malkani RG, Attarian HP, Zee PC, Ong JC. A randomized controlled trial of cognitive behavioral therapy for insomnia and PAP for obstructive sleep apnea and comorbid insomnia: effects on nocturnal sleep and daytime performance. J Clin Sleep Med. 2022;18:789–800.
19. Yadav RK, Kalita J, Misra UK. A study of triggers of migraine in India. Pain Med. 2010;11:44–7.
20. Alstadhaug KB. Migraine and the hypothalamus. Cephalalgia. 2009;29:809–17.
21. Friedman BW, Lipton RB. Headache emergencies: diagnosis and management. Neurol Clin. 2012;30(43–59):vii.
22. Kelman L. The triggers or precipitants of the acute migraine attack. Cephalalgia. 2007;27:394–402.
23. Kimoto K, Aiba S, Takashima R, Suzuki K, Takekawa H, Watanabe Y, Tatsumoto M, Hirata K. Influence of barometric pressure in patients with migraine headache. Intern Med. 2011;50:1923–8.
24. Akgün N, Acıman Demirel E, Açıkgöz M, Çelebi U, Köktürk F, Atasoy HT. The effect of weather variables on the severity, duration, and frequency of headache attacks in the cases of episodic migraine and episodic tension-type headache. Turk J Med Sci. 2021;51:1406–12.
25. Zebenholzer K, Rudel E, Frantal S, Brannath W, Schmidt K, Wöber-Bingöl C, Wöber C. Migraine and weather: a prospective diary-based analysis. Cephalalgia. 2011;31:391–400.
26. Ordás CM, Cuadrado ML, Rodríguez-Cambrón AB, Casas-Limón J, del Prado N, Porta-Etessam J. Increase in body temperature during migraine attacks. Pain Med. 2013;14:1260–4.
27. Cooke LJ, Rose MS, Becker WJ. Chinook winds and migraine headache. Neurology. 2000;54:302–7.
28. Allais G, Chiarle G, Sinigaglia S, Airola G, Schiapparelli P, Benedetto C. Gender-related differences in migraine. Neurol Sci. 2020;41:429–36.
29. Paterni I, Granchi C, Katzenellenbogen JA, Minutolo F. Estrogen receptors alpha (ERα) and beta (ERβ): subtype-selective ligands and clinical potential. Steroids. 2014;90:13–29.
30. Costa C, Tozzi A, Rainero I, Cupini LM, Calabresi P, Ayata C, Sarchielli P. Cortical spreading depression as a target for anti-migraine agents. J Headache Pain. 2013;14:62.
31. Neri I, Granella F, Nappi R, Manzoni GC, Facchinetti F, Genazzani AR. Characteristics of headache at menopause: a clinico-epidemiologic study. Maturitas. 1993;17:31–7.
32. Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. Lancet Neurol. 2017;16:76–87.
33. Hranilovich JA, Kaiser EA, Pace A, Barber M, Ziplow J. Headache in transgender and gender-diverse patients: a narrative review. Headache. 2021;61:1040–50.
34. Tonini MC. Gender differences in migraine. Neurol Sci. 2018;39:77–8.
35. Calhoun A, Ford S, Pruitt A. The impact of extended-cycle vaginal ring contraception on migraine aura: a retrospective case series. Headache. 2012;52:1246–53.
36. Chauvel V, Vamos E, Pardutz A, Vecsei L, Schoenen J, Multon S. Effect of systemic kynurenine on cortical spreading depression and its modulation by sex hormones in rat. Exp Neurol. 2012;236:207–14.
37. Akerman S, Goadsby PJ. Dopamine and migraine: biology and clinical implications. Cephalalgia. 2007;27:1308–14.
38. D'Andrea G, D'Amico D, Bussone G, Bolner A, Aguggia M, Saracco MG, Galloni E, De Riva V, Colavito D, Leon A, Rosteghin V, Perini F. The role of tyrosine metabolism in the pathogenesis of chronic migraine. Cephalalgia. 2013;33:932–7.
39. Gonzalez A, Hyde E, Sangwan N, Gilbert JA, Viirre E, Knight R. Migraines are correlated with higher levels of nitrate-, nitrite-, and nitric oxide-reducing oral microbes in the American Gut Project Cohort. mSystems. 2016;1.
40. Fried NT, Elliott MB, Oshinsky ML. The role of adenosine signaling in headache: a review. Brain Sci. 2017;7.
41. Strandwitz P, Kim KH, Terekhova D, Liu JK, Sharma A, Levering J, McDonald D, Dietrich D, Ramadhar TR, Lekbua A, Mroue N, Liston C, Stewart EJ, Dubin MJ, Zengler K, Knight R, Gilbert JA, Clardy J, Lewis K. GABA-modulating bacteria of the human gut microbiota. Nat Microbiol. 2019;4:396–403.
42. Hindiyeh NA, Zhang N, Farrar M, Banerjee P, Lombard L, Aurora SK. The role of diet and nutrition in migraine triggers and treatment: a systematic literature review. Headache. 2020;60:1300–16.
43. Nowaczewska M, Wiciński M, Kaźmierczak W, Kaźmierczak H. To eat or not to eat: a review of the relationship between chocolate and migraines. Nutrients. 2020;12.
44.•• Liu H, Wang D, Wu F, Dong Z, Yu S. Association between inflammatory potential of diet and self-reported severe headache or migraine: a cross-sectional study of the National Health and Nutrition Examination Survey. Nutrition. 2023;113: 112098. **The research involving 10,359 individuals demonstrated a correlation between elevated dietary inflammatory index (DII) scores and the occurrence of migraines. This finding highlights the potential of dietary adjustments as a non-pharmacological strategy for managing migraines.**
45. Benemei S, Fusi C, Trevisan G, Geppetti P. The TRPA1 channel in migraine mechanism and treatment. Br J Pharmacol. 2014;171:2552–67.
46. Rocha-Filho PA, Marques KS, Torres RC, Leal KN. Migraine, osmophobia, and anxiety. Pain Med. 2016;17:776–80.
47. Mese Pekdemir E, Tanik N. Clinical significance of osmophobia and its effect on quality of life in people with migraine. Acta Neurol Belg. 2023;123:1747–55.
48. Wilkins AJ, Haigh SM, Mahroo OA, Plant GT. Photophobia in migraine: a symptom cluster? Cephalalgia. 2021;41:1240–8.
49. Ishikawa T, Tatsumoto M, Maki K, Mitsui M, Hasegawa H, Hirata K. Identification of everyday sounds perceived as noise by migraine patients. Intern Med. 2019;58:1565–72.
50. Hauge AW, Asghar MS, Schytz HW, Christensen K, Olesen J. Effects of tonabersat on migraine with aura: a randomised, double-blind, placebo-controlled crossover study. Lancet Neurol. 2009;8:718–23.
51.• Harder AVE, Terwindt GM, Nyholt DR, van den Maagdenberg AMJM. Migraine genetics: status and road forward. Cephalalgia. 2023;43:3331024221145962. **This article offers a thorough overview of recent genetic findings related to migraine.**
52.• Louter MA, Fernandez-Morales J, de Vries B, Winsvold B, Anttila V, Fernandez-Cadenas I, Vila-Pueyo M, Sintas C, van Duijn CM, Cormand B, Álvarez-Sabin J, Montaner J, Ferrari MD, van den Maagdenberg A, Palotie A, Zwart JA, Macaya A, Terwindt GM, Pozo-Rosich P. Candidate-gene association study searching for genetic factors involved in migraine chronification. Cephalalgia. 2015;35:500–7. **The article represents an**

initial thorough genetic association analysis for the process of migraine chronification. The results suggest a lack of significant findings, indicating the need for future studies to utilize larger datasets or alternative genetic methodologies in order to elucidate the genetic basis of chronic migraine.

53. Chalmer MA, Rasmussen AH, International Headache Genetics Consortium, 23andme Research Team, Kogelman LJA, Olesen J, Hansen TF. Chronic migraine: genetics or environment? Eur J Neurol. 2021;28:1726–36.
54. Shibata M, Tang C. Implications of transient receptor potential cation channels in migraine pathophysiology. Neurosci Bull. 2021;37:103–16.
55. Yakubova A, Davidyuk Y, Tohka J, Khayrutdinova O, Kudryavtsev I, Nurkhametova D, Kamshilin A, Giniatullin R, Rizvanov A. Searching for predictors of migraine chronification: a pilot study of 1911A>G polymorphism of TRPV1 gene in episodic versus chronic migraine. J Mol Neurosci. 2021;71:618–24.
56. Ling YH, Chen SP, Fann CS, Wang SJ, Wang YF. TRPM8 genetic variant is associated with chronic migraine and allodynia. J Headache Pain. 2019;20:115.
57. Okamoto N, Okumura M, Tadokoro O, Sogawa N, Tomida M, Kondo E. Effect of single-nucleotide polymorphisms in TRPV1 on burning pain and capsaicin sensitivity in Japanese adults. Mol Pain. 2018;14:1744806918804439.
58. Bernardini N, Neuhuber W, Reeh PW, Sauer SK. Morphological evidence for functional capsaicin receptor expression and calcitonin gene-related peptide exocytosis in isolated peripheral nerve axons of the mouse. Neuroscience. 2004;126:585–90.
59. Cortés-Montero E, Rodríguez-Muñoz M, Ruiz-Cantero MDC, Cobos EJ, Sánchez-Blázquez P, Garzón-Niño J. Calmodulin supports TRPA1 channel association with opioid receptors and glutamate NMDA receptors in the nervous tissue. Int J Mol Sci. 2020;22.
60. Wang M, Gu Y, Meng S, Kang L, Yang J, Sun D, Liu Y, Wan Z, Shan Y, Xue D, Su C, Li S, Yan R, Liu Y, Zhao Y, Pan Y. Association between TRP channels and glutamatergic synapse gene polymorphisms and migraine and the comorbidities anxiety and depression in a Chinese population. Front Genet. 2023;14:1158028.
61. Choo SY. The HLA system: genetics, immunology, clinical testing, and clinical implications. Yonsei Med J. 2007;48:11–23.
62. Wang K, Gaitsch H, Poon H, Cox NJ, Rzhetsky A. Classification of common human diseases derived from shared genetic and environmental determinants. Nat Genet. 2017;49:1319–25.
63. Huang C, Chen SP, Huang YH, Chen HY, Wang YF, Lee MH, Wang SJ. HLA class I alleles are associated with clinic-based migraine and increased risks of chronic migraine and medication overuse. Cephalalgia. 2020;40:493–502.
64. Peroutka SJ. Migraine: a chronic sympathetic nervous system disorder. Headache. 2004;44:53–64.
65. Ghosh J, Pradhan S, Mittal B. Identification of a novel *ANKK1* and other dopaminergic (*DRD2* and *DBH*) gene variants in migraine susceptibility. Neuromolecular Med. 2013;15:61–73.
66. Todt U, Netzer C, Toliat M, Heinze A, Goebel I, Nürnberg P, Göbel H, Freudenberg J, Kubisch C. New genetic evidence for involvement of the dopamine system in migraine with aura. Hum Genet. 2009;125:265–79.
67. Sezer S, Kurt S, Ates O. Analysis of dopamine beta hydroxylase gene polymorphisms in migraine. Clin Neurol Neurosurg. 2016;145:96–100.
68. Barbanti P, Guadagni F, De Marchis ML, Ialongo C, Egeo G, Fofi L, Aurilia C, Lovero D, Della-Morte D, Ferroni P, Palmirotta R. Dopamine-beta-hydroxylase 19-bp insertion/deletion polymorphism affects medication overuse in patients with chronic migraine. Neurol Sci. 2019;40:1717–24.
69. Emin Erdal M, Herken H, Yilmaz M, Bayazit YA. Significance of the catechol-O-methyltransferase gene polymorphism in migraine. Brain Res Mol Brain Res. 2001;94:193–6.
70. Takigawa H, Kowa H, Nakashima K. No associations between five polymorphisms in COMT gene and migraine. Acta Neurol Scand. 2017;135:225–30.
71. Russell FA, King R, Smillie SJ, Kodji X, Brain SD. Calcitonin gene-related peptide: physiology and pathophysiology. Physiol Rev. 2014;94:1099–142.
72. Russo AF. Calcitonin gene-related peptide (CGRP): a new target for migraine. Annu Rev Pharmacol Toxicol. 2015;55:533–52.
73. Wang YF, Wang SJ. CGRP Targeting therapy for chronic migraine-evidence from clinical trials and real-world studies. Curr Pain Headache Rep. 2022;26:543–54.
74. Wattiez AS, Sowers LP, Russo AF. Calcitonin gene-related peptide (CGRP): role in migraine pathophysiology and therapeutic targeting. Expert Opin Ther Targets. 2020;24:91–100.
75. Rubino E, Boschi S, Giorgio E, Pozzi E, Marcinnò A, Gallo E, Roveta F, Grassini A, Brusco A, Rainero I. Analysis of the DNA methylation pattern of the promoter region of calcitonin gene-related peptide 1 gene in patients with episodic migraine: an exploratory case-control study. Neurobiol Pain. 2022;11:100089.
76. Fila M, Sobczuk A, Pawlowska E, Blasiak J. Epigenetic connection of the calcitonin gene-related peptide and its potential in migraine. Int J Mol Sci. 2022;23.
77. Osko JD, Christianson DW. Methods for the expression, purification, and crystallization of histone deacetylase 6-inhibitor complexes. Methods Enzymol. 2019;626:447–74.
78. Dai Y, Wei T, Shen Z, Bei Y, Lin H, Dai H. Classical HDACs in the regulation of neuroinflammation. Neurochem Int. 2021;150:105182.
79. Denk F, McMahon SB. Chronic pain: emerging evidence for the involvement of epigenetics. Neuron. 2012;73:435–44.
80. Urru M, Buonvicino D, Pistolesi A, Paccosi S, Chiarugi A. Histone deacetylase inhibitors counteract CGRP signaling and pronociceptive sensitization in a rat model of medication overuse headache. J Pain. 2022;23:1874–84.
81. Bertels Z, Singh H, Dripps I, Siegersma K, Tipton AF, Witkowski WD, Sheets Z, Shah P, Conway C, Mangutov E, Ao M, Petukhova V, Karumudi B, Petukhov PA, Baca SM, Rasenick MM, Pradhan AA. Neuronal complexity is attenuated in preclinical models of migraine and restored by HDAC6 inhibition. Elife. 2021;10.
82. An YC, Tsai CL, Liang CS, Lin YK, Lin GY, Tsai CK, Liu Y, Chen SJ, Tsai SH, Hung KS, Yang FC. Identification of novel genetic variants associated with insomnia and migraine comorbidity. Nat Sci Sleep. 2022;14:1075–87.
83. Gentile G, Missori S, Borro M, Sebastianelli A, Simmaco M, Martelletti P. Frequencies of genetic polymorphisms related to triptans metabolism in chronic migraine. J Headache Pain. 2010;11:151–6.
84. Gentile G, Borro M, Lala N, Missori S, Simmaco M, Martelletti P. Genetic polymorphisms related to efficacy and overuse of triptans in chronic migraine. J Headache Pain. 2010;11:431–5.
85. Moreno-Mayordomo R, Ruiz M, Pascual J, Gallego de la Sacristana M, Vidriales I, Sobrado M, Cernuda-Morollon E, Gago-Veiga AB, Garcia-Azorin D, Telleria JJ, Guerrero AL. *CALCA* and *TRPV1* genes polymorphisms are related to a good outcome in female chronic migraine patients treated with onabotulinumtoxinA. J Headache Pain. 2019;20:39.
86. Buse DC, Greisman JD, Baigi K, Lipton RB. Migraine progression: a systematic review. Headache. 2019;59:306–38.
87. Gasparini CF, Griffiths LR. The biology of the glutamatergic system and potential role in migraine. Int J Biomed Sci. 2013;9:1–8.

88. Mormile R, Mazzei G, Vittori G, De Michele M, Squarcia U. Insomnia and shift-work sleep disorder: a crosstalk between glutamate excitotoxicity and decreased GABAergic neurotransmission? Sleep Biol Rhythms. 2012;10:340–1.
89. Ligthart L, Hottenga JJ, Lewis CM, Farmer AE, Craig IW, Breen G, Willemsen G, Vink JM, Middeldorp CM, Byrne EM, Heath AC, Madden PA, Pergadia ML, Montgomery GW, Martin NG, Penninx BW, McGuffin P, Boomsma DI, Nyholt DR. Genetic risk score analysis indicates migraine with and without comorbid depression are genetically different disorders. Hum Genet. 2014;133:173–86.
90. Ashina S, Serrano D, Lipton RB, Maizels M, Manack AN, Turkel CC, Reed ML, Buse DC. Depression and risk of transformation of episodic to chronic migraine. J Headache Pain. 2012;13:615–24.
91. Tsai MC, Tsai CL, Liang CS, Lin YK, Lin GY, Tsai CK, Yeh PK, Liu Y, Hung KS, Yang FC. Identification of genetic risk loci for depression and migraine comorbidity in Han Chinese residing in Taiwan. Front Psychiatry. 2022;13:1067503.
92. Vuralli D, Ayata C, Bolay H. Cognitive dysfunction and migraine. J Headache Pain. 2018;19:109.
93. Lee SH, Kang Y, Cho SJ. Subjective cognitive decline in patients with migraine and its relationship with depression, anxiety, and sleep quality. J Headache Pain. 2017;18:77.
94. Yeh PK, Liang CS, Tsai CL, Lin YK, Lin GY, Tsai CK, Tsai MC, Liu Y, Tai YM, Hung KS, Yang FC. Genetic variants associated with subjective cognitive decline in patients with migraine. Front Aging Neurosci. 2022;14:860604.
95. Niftullayev S, Lamarche-Vane N. Regulators of Rho GTPases in the nervous system: molecular implication in axon guidance and neurological disorders. Int J Mol Sci. 2019;20.
96. Serafini G, Pompili M, Innamorati M, Gentile G, Borro M, Lamis DA, Lala N, Negro A, Simmaco M, Girardi P, Martelletti P. Gene variants with suicidal risk in a sample of subjects with chronic migraine and affective temperamental dysregulation. Eur Rev Med Pharmacol Sci. 2012;16:1389–98.
97. Zobdeh F, Eremenko II, Akan MA, Tarasov VV, Chubarev VN, Schiöth HB, Mwinyi J. The epigenetics of migraine. Int J Mol Sci. 2023;24(11).
98. • Winsvold BS, Palta P, Eising E, Page CM, International Headache Genetics Consortium, van den Maagdenberg AM, Palotie A, Zwart JA. Epigenetic DNA methylation changes associated with headache chronification: a retrospective case-control study. Cephalalgia. 2018;38:312–22. **The study identified possible epigenetic elements in the transition from episodic to chronic headache, indicating the participation of brain-expressed genes, pathways associated with synaptic plasticity, and hormonal regulation.**
99. Camara MS, Martin Bujanda M, Mendioroz IM. Epigenetic changes in headache. Neurologia (Engl Ed). 2021;36:369–76.
100. Andreou AP, Edvinsson L. Mechanisms of migraine as a chronic evolutive condition. J Headache Pain. 2019;20:117.