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Epigenetics in migraine: the Junior Editorial Board Members' vision

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Abstract

Background Migraine represents the third leading cause of disability-adjusted life years among young females worldwide, responsible for physical and emotional distress along with reduced social functioning. The matter is further complicated by resistance and even refractoriness to the available treatments. Indeed, despite the several therapeutic strategies, remarkably improved by the development of the novel, specific drugs directed towards calcitonin-gene related peptide (CGRP) signalling, 40% patients, also undergoing anti-CGRP therapy, are still difficult-to-treat. The potential role of environmental factors and epigenetic modifications in the pathogenesis of migraine and in the responsiveness to treatments still remains poorly investigated. Moreover, the expression of a wide panel of serum microRNAs was recently related to frequency and features of migraine attacks. Thus, the aim of the present study is to analyze the possible epigenetic mechanisms at the root of differences in migraine features and response to treatments.

Methods Eligibility criteria, search strategy and information sources are established *a priori.* PubMed, Scopus and Web of Science were inspected for studies published from database inception to the date of last search on October 2nd, 2025.

Results A few studies so far support the role of DNA methylation in migraine chronification, indicating that these stable but reversible epigenetic modifications may influence the process of progression and transformation from episodic to chronic migraine. Altered DNA methylation sites were linked to genes involved in synaptic plasticity and estrogen receptor signaling. Up-regulation of circulating miRNAs was reduced following treatment with gepants. Within this complex figure, the role of the transient receptor potential (TRP) vanilloid 1 (TRPV1) in the trigeminal ganglia deserves deep investigation, including the prediction of response to first-line therapies such as triptans. Likewise, TRP ankyrin 1 (TRPA1) expression is subjected to pain-induced epigenetic modifications. DNA methylation and the modulation of histone deacetylase activity are implicated in the mechanisms of action of currently used preventative drugs, such as valproic acid and topiramate, and could serve as biomarkers of drug response. Finally, the role of miRNAs as potential biomarker for predicting the response to novel monoclonal antibodies, such as erenumab, has emerged in recent studies.

Conclusions The role of epigenetic modifications of genes involved in the CGRP pathway, synaptic plasticity and TRPV1, TRPA1 and estrogen receptor signaling in migraine is emerging. Therefore, a deeper understanding of the impact of epigenetics in migraine pathophysiology and neuropharmacology is needed to revert chronification

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and personalize medicine in the field of migraine, improving efficacy and safety of treatments and widening the therapeutic armamentarium.

Keywords Migraine, Pediatric migraine, Epigenetics, DNA methylation, Histone acetylation/deacetylation, Noncoding RNAs, Therapy refractory/resistance, Migraine comorbidities, Migraine therapy, Tailored medicine, CGRP in migraine

Background: epigenetic mechanisms and migraine

Migraine is a complex neurovascular disorder characterized by recurrent headache attacks and associated symptoms such as photophobia, phonophobia, osmophobia, nausea, and vomiting that vary in severity and frequency. Recent research has highlighted the potential role of epigenetics in migraine pathogenesis, offering new insights into how genetic and environmental factors interact to influence disease susceptibility and progression. Epigenetics refers to all molecular mechanisms that influence how a genotype is expressed as a particular phenotype. The term 'epigenetics', proposed by Conrad Hal Waddington in 1942, now refers to heritable and stable changes in the expression of genes [1]. Epigenetic mechanisms modulate gene expression patterns without altering the underlying DNA sequence, through DNA methylation, regulation of noncoding RNA, and post-translational histone modification [2]. DNA methyltransferases add a methyl group to the 5th carbon position of cytosine residues after DNA replication, forming 5-methylcytosine. This epigenetic mark occurs primarily in CpG dinucleotides, particularly within CpG islands, frequently located in gene promoter regions. DNA methylation in these regions silences gene expression via inhibition of transcription factor binding to promoter regions [3]. Non-coding RNAs (ncRNAs) are functional RNA molecules that are transcribed but not translated into proteins [4]. ncRNAs include microRNAs (miRNAs) and small interfering RNAs (siRNAs), which are typically fewer than 30 nucleotides long, as well as long non-coding RNAs (lncRNAs), which exceed 200 nucleotides. miRNAs function as critical regulators of gene expression by either inhibiting translation or promoting the degradation of specific messenger RNAs (mRNAs), primarily through binding to the 3′-untranslated region (3′-UTR) of their target mRNAs [5]. Circular RNAs (circRNAs) represent a type of ncRNA without a 5′ cap or 3′ poly (A) tail implicated in synaptic function [6]. Another epigenetic mechanism is post-translational histone modifications, which activate or repress gene expression via modulating transcriptional activity of encoded proteins. Key histone modifications are acetylation, DNA methylation, phosphorylation, and ubiquitination [7]. The impact of a given modification either activates or represses gene expression, depending on the modification and the specific histone involved [8].

Migraine is characterized by its dynamic nature with fluctuations in attack duration, severity, frequency, and symptomatology over time. It is crucial to understand the molecular and biological mechanisms regulating these variations. Epigenetic mechanisms can alter gene expression in response to environmental stimuli and may play a critical role in the development and chronification of migraine. Studies have identified differential DNA methylation patterns in migraine patients, particularly in genes related to inflammation, pain pathways, and synaptic plasticity [9], suggesting that epigenetic changes may contribute to the sensitization and modulation of migraine pain. Furthermore, epigenetic regulation of specific genes, such as CALCA, was associated with migraine characteristics and symptoms [10]. These findings support the potential for epigenetic markers to serve as therapeutic targets or predictors for migraine treatment response.

Several studies have investigated miRNA expression profiles in migraine patients as potential peripheral migraine biomarkers. Altered miRNA expression profiles associated with neurotransmitter and immune regulation, neuroinflammation, oxidative stress, circadian rhythm, and endothelial functions were detected in migraine patients, implicating a complex network where miRNAs influence immune, inflammatory, vascular, and circadian pathways critical to migraine development and symptoms [11–16].

Neuronal plasticity relies heavily on cytoskeletal flexibility, which can be reduced by histone deacetylase 6 (HDAC6) through alpha-tubulin deacetylation. HDAC6 inhibition has been shown to not only reverse migraine-like pain and reduce neurite outgrowth in brain regions involved in headache processing in the NTG-induced chronic migraine model, but also to reduce the occurrence of cortical spreading depression (CSD) [17]. In an eletriptan-induced medication overuse headache (MOH) model, HDAC inhibitors were shown to reduce the overexpression of calcitonin gene-related peptide (CGRP) and its receptor subunit RAMP1, alleviating MOH symptoms, capsaicin-induced vasodilation, photophobia, and cephalic allodynia [18]. These findings suggest that HDACs and epigenetic regulation have a role in the development of chronic migraine and MOH, and HDAC inhibition targeting the restoration of microtubule integrity and neuronal plasticity could be a promising strategy to prevent migraine chronification.

The influence of environmental factors and epigenetic modifications on migraine pathogenesis and treatment response has yet to be fully elucidated. This review

aims to investigate the potential epigenetic mechanisms underlying the variability in migraine characteristics and therapeutic outcomes. A deeper understanding of epigenetic factors is crucial for advancing knowledge on migraine development and improving treatment strategies.

Methods

The inclusion criteria, search strategy and information sources were established a priori to the search. PubMed and Scopus were inspected for studies published from database inception to the date of last search October 2nd, 2025. The following keywords were used to perform the search: "migraine", "chronic migraine", "epigenetics", "DNA", "methylation", "deacetylation", "HDAC", "non-coding RNAs", "miRNA(s)", "miR-34", "chronification", "refractoriness/resistance", "therapy", "tailored medicine", "valproate", "propranolol", "botox" and "CGRP pathway migraine", "paediatric migraine", "adolescent migraine", "HPA axis", "adverse childhood experiences", "psychological comorbidities", "stress response", "circadian genes", "biopsychosocial model", "CALCA", "CLR", "RAMP1", "CALCRL", "PACAP", "ADCYAP1", "ADCYAPR1", "5-HT", "serotonin", "HT1R", "HT2R", "HT3R", "HT4R", "HT5R", "HT6R", "HT7R" The search term "botox" refers to onabotulinumtoxinA. The reference lists of retrieved articles were inspected for missing records. According to the set a priori eligibility criteria, original articles (both preclinical and clinical), systematic reviews and meta-analyses, published in English language and available in full text were included in the results. Systematic reviews and meta-analyses could still be cited in the background section if useful, but not included as core evidence. Reviews editorials, commentaries, abstracts and book chapters were deemed not eligible for inclusion in the analysis, also using exclusion filters ("not review") at the search stage.

Role of genetics and epigenetics in migraine progression and transformation

The progression from episodic to chronic migraine, often referred to as migraine chronification, involves maladaptive neural plasticity and persistent central sensitization, characterized by heightened responsiveness of the trigeminovascular system and central pain pathways [19–21]. Epigenetic modifications are now thought to play a key role in consolidating these pathological states, by lowering the threshold for migraine initiation and perpetuating a cycle of hyperexcitability and recurrent pain [22, 23]. In fact, HDAC6 inhibition has been shown to reduce the occurrence of CSD in animal models [17]. Through these mechanisms, environmental exposures, lifestyle factors, and repeated migraine headache attacks can progressively remodel neuronal networks, driving the transition toward chronicity. Two studies so far support the role of DNA methylation in migraine chronification, indicating that these stable but reversible epigenetic modifications may influence the transition from episodic to chronic migraine. In a population-based retrospective study, Winsvold et al. (2017) found that individuals with chronic headache exhibited distinct DNA methylation patterns compared to episodic headache controls, suggesting that DNA methylation changes are not merely secondary effects, in spite of the small sample [9].Remarkably, the altered DNA methylation sites were linked to genes involved in synaptic plasticity and estrogen receptor signaling, both of which are closely associated with migraine pathophysiology [24]. In a longitudinal epigenome-wide association study, Mehta et al. (2024) reported that patients with chronic migraine undergoing withdrawal from simple analgesics or triptans showed clinical improvement that paralleled dynamic DNA methylation changes in genes related to chromatin organization and synaptic plasticity [25]. In contrast, an earlier longitudinal study by Carsen et al. (2013) found no DNA methylation changes associated with reduction in headache frequency in a mixed cohort of patients with medication-overuse headache (including both migraine and tension-type headache) undergoing withdrawal from a variety of treatments [26]. These contrasting findings suggest that DNA methylation changes may be specific to chronic migraine or dependent on the type of medication withdrawn. Collectively, the evidence indicates that DNA methylation may not only mirror disease states but also represents a mechanism through which environmental exposures, such as medication overuse, contribute to migraine chronification. From a translational standpoint, this positions DNA methylation as a potential biomarker for identifying individuals at risk of chronification and for monitoring therapeutic response over time. In addition to DNA methylation, histone modifications have been increasingly recognized as important mediators of the maladaptive plasticity underlying migraine chronification. As previously mentioned, histone acetylation regulates chromatin accessibility and gene transcription, and alterations in this balance can produce long-lasting changes in neuronal function [27]. In a seminal preclinical study, Batti et al. (2021) demonstrated that HDAC-6 inhibition restored dendritic complexity and reduced pain hypersensitivity in a nitroglycerine mouse model of chronic migraine [17].This suggests that aberrant histone deacetylation may contribute to the structural and functional changes (reviewed in [28]). Incidentally, the epigenetic modification of the reactive oxygen and nitrogen species (RONS)-TRPA1 channels axis may be at the root of pathophysiology of migraine since TRPA1-expressing neurons are grouped near trigeminal primary afferent neurons that innervate the dura and cerebral vessels [5].

Complementary evidence from Urru et al. (2022) demonstrated that two non-selective HDAC inhibitors were able to counteract CGRP signaling and prevent the development of pronociceptive sensitization in a rat model of medication overuse headache (MOH) [18]. Given that CGRP is a key mediator of migraine pathophysiology and the therapeutic target of several approved monoclonal antibodies and small-molecule receptor antagonists [29], the observed link between histone modification and CGRP signaling provides a direct mechanistic connection between epigenetic regulation and clinically-relevant migraine pathways. These preclinical results underscore the therapeutic potential of epigenetic modulation, suggesting that selective HDAC inhibitors might one day complement existing CGRP-targeted therapies, particularly in patients vulnerable to medication overuse, where HDAC-3 activity appears to contribute to excessive drug consumption in MOH patients [30]. miRNAs represent another layer of epigenetic regulation that may contribute to migraine chronification. Dysregulated expression of specific inflammatory-associated miRNAs has been reported in both experimental and clinical settings. For example, miR-34a-5p, miR-155-5p and miR-382-5p have been linked to altered trigeminal nociceptive signaling, and have been reported to be elevated in patients with chronic migraine [31–33]. In a recent clinical study, Ornello et al. (2024) showed that women with chronic migraine not only displayed distinct miRNA expression profiles compared to those with episodic migraine, but their profiles shifted in response to erenumab, though profiling was in small, pooled groups of ≤ 8 women [34]. Parallel evidence from preclinical models further support a mechanistic role: in two rodent models of chronic migraine, the up-regulation of circulating miRNAs was reduced following treatment with gepants or a selective miR-155-5p antagomir [32, 35]. Other preventatives therapies such as onabotulinumtoxinA, propranolol and valproate have been also shown to influence miRNA expression [36–38], however, whether their clinical effectiveness is mediated through epigenetic mechanisms remains uncertain. Taken together, these findings suggest miRNA dysregulation as attractive therapeutic target and practical biomarker to diagnose migraine stages. Notably, the first composite miRNA-genetic risk score model has already been developed and was able to identify disease-state miRNA signatures that differentiated migraine patients from controls with high accuracy [39]. These advances highlight the translational potential of miRNA research, suggesting that integrating miRNA profiling into clinical practice could both refine patient stratification and open new venues for personalized treatments. In conclusion, epigenetic mechanisms including DNA methylation, histone modifications, and miRNA regulation appear to play a key role in the dynamic (and reversible) nature of migraine chronification. Emerging evidence supports their utility as biomarkers for risk stratification and treatment response, while preclinical findings suggest they could be targeted to reverse maladaptive plasticity and persistent central sensitization. Such approaches could complement existing therapies that primarily target receptor activity or neuropeptide ligands, broadening the therapeutic arsenal for patients with chronic migraine. However, further large-scale longitudinal, mechanistic and validations studies are clearly needed to fully map the relationship between epigenetic mechanisms and migraine chronification.

Epigenetic modifications of migraine signaling pathways

Accumulating evidence supports a role for epigenetic alterations in pain conditions. Accordingly, recent findings point to a substantial contribution of epigenetic mechanisms in regulating the CGRP pathway in migraine pathophysiology.

A landmark study by Park et al. [40] investigated how CALCA gene expression was influenced by epigenetic modifications, using rat and human cell lines, as well as primary cultures of glia from rat trigeminal ganglia. They measured DNA methylation and histone acetylation at CpG islands located in the promoter region. The authors found that DNA methylation negatively correlated with CALCA gene expression, as the CpG islands analyzed were hypermethylated in cells not expressing the gene and hypomethylated in cells that did. Treatment with the DNA methyltransferase inhibitor 5-aza-2′-deoxycytidine and a HDAC inhibitor synergistically reactivated gene expression, indicating that chromatin remodeling plays a critical role in maintaining cell-type specificity in CGRP expression. In a preclinical study, intrathecal administration of CGRP was shown to increase the number of astrocytes displaying Histone H3 lysine 9 acetylation (H3K9ac), an important regulator of cytokine and chemokine gene expression, in the spinal dorsal horn of rats [41]. Moreover, mouse microglial cells treated with CGRP showed altered HDAC2 enrichment patterns in 1271 promoters, with most of them linked to immune and inflammation-related pathways [42]. These results suggest that downregulation of CGRP could be achieved through epigenetic modulation. Interestingly, valproate, an antiepileptic medication commonly used for the prophylactic treatment of migraine [43, 44], has been shown to act as an HDAC inhibitor. More studies are needed to evaluate the therapeutic potential of epigenetic modulations in migraine therapy.

More recently, a study compared the DNA methylation at two CpG-rich islands located in the distal (-2762 to -2362 bp) and proximal (-1662 to -1028 bp) promoter regions of the CALCA gene in 22 patients (15 females) with episodic migraine without aura and 20 healthy

controls (12 females) [10]. The study found hypomethylation of two CpG sites (-1461 and – 1415 bp) in patients with migraine. Additionally, when exploring the association between DNA methylation and clinical characteristics, methylation at CpG site – 1461 positively correlated with the age of migraine onset; while methylation at CpG site – 1393 inversely correlated with the presence of nausea and vomiting. Anxiety and mood scores also significantly correlated with the degree of DNA methylation in the CALCA promoter. This is the first study to show differences in methylation patterns in patients with migraine, as well as an association between DNA methylation and specific disease characteristics.

Studies have further shown that the expression of RAMP1, a component of the canonical CGRP receptor [45], can be modulated by epigenetic mechanisms. Wan et al. [46] evaluated the *RAMP1* promoter in blood samples from 26 migraine patients (17 females) and compared them to 25 healthy volunteers (14 females). The authors did not find significant differences in overall DNA methylation levels, but reported a trend toward lower DNA methylation in patients. When stratifying the data, they observed that the methylation level at (+ 25, + 27, +31) CpG units was higher in patients with a family history of migraine compared to those without. Furthermore, methylation level at (+ 89, + 94, +96) CpG units was lower in female patients than in female healthy controls, with levels below 3.50%, associated with a higher risk of being diagnosed with migraine. In contrast, a more recent study with 54 female patients and 50 female controls described a novel CpG unit at position – 284 in the RAMP1 promoter that was significantly hypermethylated in patients compared to controls [47]. The contrasting data highlight the complexity of epigenetic regulation and the need for more studies in larger cohorts with harmonized protocols that allow for comparison and sequence matching.

Using in vivo and in vitro models, another study investigated whether estrogen-dependent changes in RAMP1 expression are mediated by DNA methylation. In human neuronal cells, estradiol increased *RAMP1* expression, while administration of 5-aza-2'-deoxycytidine reduced it. Notably, the combination of estradiol and 5-aza-2'-deoxycytidine restored RAMP1 levels. Similar trends were observed in rat trigeminal ganglion cultures. These findings suggest that DNA methylation plays an important role in the modulatory effects of estrogen on the CGRP pathway [48]. These results are particularly relevant given the higher prevalence of migraine in females, and the impact of hormonal fluctuations on migraine headache attack frequency, severity and chronification [49, 50].

In a preclinical model of medication overuse headache (MOH), chronic administration of eletriptan, a 5-$HT_{1B/1D/1F}$ agonist [51] induced an overexpression of CGRP and RAMP1 in the trigeminal ganglion. This was prevented by the administration of the HDAC inhibitors Panobinostat and Givinostat. Moreover, treatment with these inhibitors reduced the capsaicin-induced trigeminal vasodilatory responses, photophobic behavior and cephalic allodynia. These results not only provide evidence for a key role of HDACs in the pathophysiology of MOH, but also highlight the therapeutic potential of HDAC inhibition in the prevention of migraine chronification. In line with this, a previous study using preclinical models of migraine with aura and chronic migraine suggested that HDAC inhibitors could be a potential therapeutic strategy for migraine [17].

An important consideration when studying epigenetic modulation is the tissue- and species-specificity of these changes. In line with this, Labruijere et al. [52] studied DNA methylation in relevant migraine-related genes, such as CALCA, RAMP1, CGRP receptor component protein (CRCP), calcitonin receptor-like receptor (CALCRL), among others. They compared DNA methylation levels across different tissues (rat dura mater, trigeminal ganglion, trigeminal nucleus caudalis, and leukocytes) to assess whether DNA methylation in leukocytes could reflect changes in other tissues. Additionally, they compared DNA methylation patterns in rat leukocytes with those in humans. Interestingly, no correlation was observed between DNA methylation in rat leukocytes and other rat tissues. However, methylation patterns in human leukocytes correlated with those in rats. This study is fundamental, as it highlights that peripheral tissue studies may not fully reflect epigenetic changes in target tissues and that rodent models can still offer valuable insights into the role of DNA methylation in migraine.

Emerging evidence highlights the critical role of epigenetic mechanisms in the regulation of migraine-related pathways. Nonetheless, the epigenetic modulation of current and novel migraine therapeutic targets such as serotonin and PACAP remains largely unexplored. DNA methylation, histone modifications, and non-coding RNAs have been shown to modulate the expression of key genes such as CALCA and RAMP1, affecting trigeminovascular signaling and contributing to migraine pathophysiology. Altered DNA methylation patterns in CALCA and RAMP1 have been observed in migraine patients and linked to clinical characteristics including disease onset, symptom severity, and comorbidities. Studies also demonstrate that HDAC inhibitors and DNA methylation modulators can reverse gene expression changes in preclinical models, suggesting a therapeutic potential for epigenetic interventions in preventing migraine chronification and MOH medication-overuse headache. Notably, estrogen-dependent epigenetic regulation of RAMP1 may help explain sex differences in migraine prevalence and response to hormonal fluctuations. However,

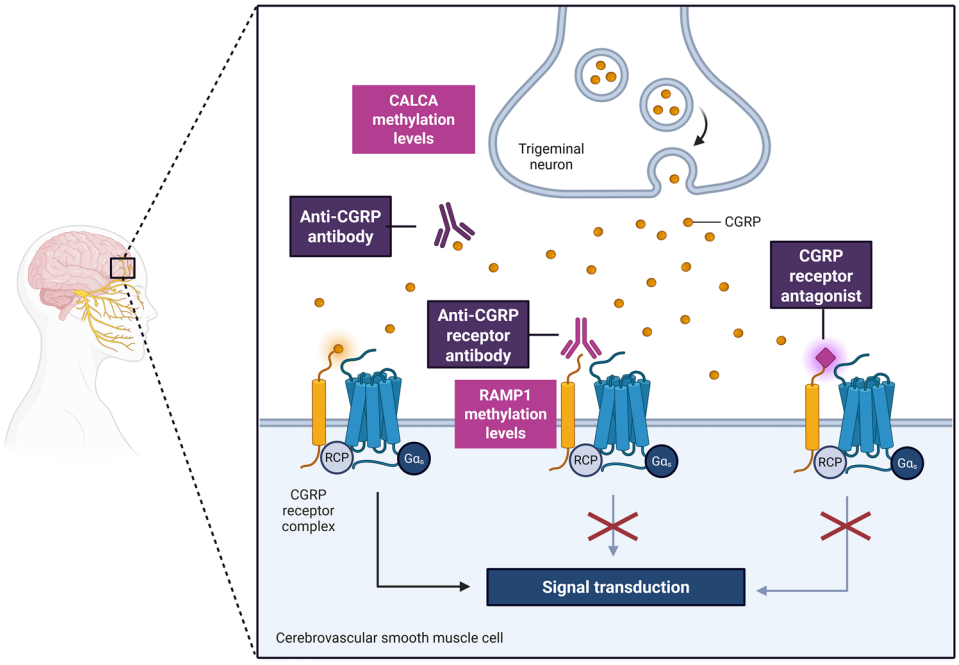

Fig. 1 Alterations of the methylation levels affecting the expression of Calcitonin gene-related peptide (CGRP) and receptor modifying protein 1 (RAMP1). CALCA and RAMP1 methylation levels might influence the response to anti-CGRP monoclonal antibodies and CGRP receptor antagonists (Created in https://www.BioRender.com and modified)

tissue- and species-specific differences in epigenetic profiles pose challenges for translation to clinical settings. Future studies using harmonized protocols and larger cohorts are needed to validate these findings and identify reliable epigenetic biomarkers or targets for treatment. The most investigated genes subjected to alterations of the methylation levels affecting the CGRP pathways are illustrated in Fig. 1.

Epigenetics of migraine and psychological comorbidities in children and adolescents

Migraine is increasingly recognized as a disorder that extends beyond recurrent pain attacks, involving complex neurobiological pathways shaped by environmental, genetic, and psychosocial influences [53]. In children and adolescents, this condition is particularly concerning, as it emerges during critical windows of brain maturation, when vulnerability to environmental stressors is high and epigenetic programming is still dynamic. Epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNAs, act as molecular "switches" that regulate gene expression without altering DNA sequence [9]. These modifications are highly sensitive to environmental exposures such as stress, diet, infections, and psychosocial experiences, producing long-lasting changes in neuronal excitability. In migraine, such changes may enhance trigeminovascular sensitivity and alter nociceptive processing. While adult studies have demonstrated abnormal DNA methylation in genes related to synaptic plasticity and estrogen signaling [9], pediatric-specific data are lacking. This gap highlights the urgent need to clarify whether similar molecular pathways underpin early-onset migraine and its clinical trajectory. Psychological stress is one of the most consistent migraine triggers in children and adolescents. Its biological embedding likely involves epigenetic programming of the hypothalamic–pituitary–adrenal axis [54, 55]. Evidence from pediatric psychiatry shows that DNA methylation of stress-related genes, including NR3C1 and FKBP5, is associated with altered stress reactivity and anxiety. Adverse childhood experiences (ACEs), such as neglect, abuse, and bullying, have been linked to increased headache prevalence and disability. Importantly, ACEs are known to induce epigenetic changes in stress-related pathways, particularly altered DNA methylation of genes such as NR3C1 and FKBP5, which regulate hypothalamic–pituitary–adrenal axis activity [56]. These molecular imprints may amplify pain perception and increase vulnerability to psychiatric comorbidities in pediatric migraine. This bidirectional relationship may explain why recurrent migraine during development is so often accompanied by anxiety, depression, and reduced quality of life. The miRNAs regulate gene expression at the post-transcriptional level and are emerging as important mediators of migraine pathophysiology. In adults, dysregulation of inflammatory-related miRNAs such as miR-34a-5p, miR-155-5p, and miR-382-5p has been associated with chronic migraine [12]. Although pediatric

evidence is still limited, preliminary findings suggest that circulating miRNAs fluctuate with stress and emotional dysregulation in adolescents. Given the overlap between neuroinflammatory and psychiatric pathways, miRNAs may represent a shared epigenetic substrate linking migraine with psychological comorbidities. Their dynamic and reversible nature also makes them promising biomarkers for early detection and therapeutic targeting in younger populations. Sleep disturbances are highly prevalent among children with migraine and frequently co-occur with mood disorders [57]. Epigenetic modifications of circadian genes, such as CLOCK and PER1, influence sleep regulation and stress responsiveness [58]. In adolescents, irregular sleep schedules and evening chronotypes are common behavioural risk factors for migraine. Dysregulation of circadian gene networks may therefore provide a mechanistic bridge between lifestyle, migraine burden, and psychiatric vulnerability. Crucially, sleep hygiene represents a modifiable factor, and interventions such as regular sleep schedules and light exposure adjustments have proven feasible and effective in pediatric populations. Targeting circadian regulations may therefore constitute a concrete preventive strategy to reduce both migraine attacks and associated psychological symptoms. Understanding the epigenetic underpinnings of migraine and its psychological comorbidities in children and adolescents has several clinical implications. First, it underscores the need for early identification of at-risk individuals, particularly those exposed to psychosocial adversity or bullying. Second, it supports the integration of trauma-informed and psychosocial interventions into headache management, addressing not only pain but also the emotional and environmental context in which it develops. Third, the potential use of epigenetic biomarkers, such as DNA methylation signatures or circulating miRNAs, may allow for stratification of patients and monitoring of responses to pharmacological and behavioural treatments. Importantly, the reversibility of epigenetic marks offers a hopeful perspective: targeted interventions during developmental windows may not only alleviate current symptoms but also reduce the risk of chronification. Research on epigenetics in pediatric migraine is still at an early stage. Large-scale, longitudinal studies are needed to clarify how genetic predisposition, environmental exposures, and psychosocial stressors interact to shape epigenetic landscapes in young patients. Multi-omic approaches that integrate epigenomics, transcriptomics, and metabolomics could provide a more comprehensive picture of disease mechanisms. Translational studies are also required to test whether modifying epigenetic states, through pharmacological agents, dietary interventions, or stress-reduction strategies, can improve both headache outcomes and associated psychological symptoms [59]. In children and adolescents, migraine lies at the intersection of neurology and psychiatry. Epigenetic changes act as a molecular memory of early-life experiences, influencing brain development, stress regulation, and pain processing. Recognizing this role may explain why migraine so often coexists with anxiety, depression, and sleep disturbances, and also points toward innovative preventive and therapeutic strategies. Breaking the cycle of pain and psychological burden during development could ultimately foster healthier trajectories into adulthood.

Personalized medicine: impact on pharmacology and therapy

Resistance and non-response even to the most novel treatment options is a remarkable issue in migraine, leading to the need for a more tailored approach. This is in line with what previously reported and discussed about special populations such as children and adolescents in whom the comorbidities also deserve deep attention for treatment. The concept of personalized medicine, usually, aims at identifying possible causes of heterogeneity in the responsiveness to treatments through the use of high-throughput assays including DNA sequencing, transcriptomics, proteomics and metabolomics. Thus, detecting and targeting the epigenetic modifications occurring in difficult-to-treat patients suffering from migraine can be a fundamental therapeutic tool for personalized medicine, since the latter alterations are often reversible. This aspect is critically important in some 40% of patients who experiences failure of anti-CGRP treatment, mainly those suffering from high frequency episodic migraine or chronic migraine [60]. Within this complex emerging frame, the role of the transient receptor potential vanilloid 1 (TRPV1) in the trigeminal ganglia deserves deep investigation also for the prediction of response to first-line therapies such as triptans. In fact, the action of sumatriptan can be, at least in part, mediated by inhibition of the inward current of TRPV1 [61]. Furthermore, TRPs expressed on dural peptidergic primary sensory afferents are suggested to be involved in maladaptive neurogenic neuroinflammation, worsening pain through the release of several mediators including CGRP [62]. Among the members of this superfamily, TRPA1 expressed in trigeminal ganglia and nerve [63, 64], is subjected to pain-induced epigenetic modifications. In particular, DNA methylation, histone modifications, miRNAs, long non-coding RNAs and circRNAs may be involved in this signaling. Particularly, pain sensitivity can be affected by epigenetic modifications of TRPA1 gene at the promoter level. In fact, the promoter methylation of TRPA1 influences thermal pain threshold, as demonstrated through sequencing profiles combined with quantitative sensory testing in monozygotic twin pairs discordant for heat pain sensitivity [65].

Furthermore, the DNA methylation rate was correlated with mechanical sensitivity and threshold to pressure in healthy people [66] and with neuropathic symptoms in patients affected by neuropathic pain [67]. Also, a specific site of methylation was identified in the CpG – 628 site of TRPA1 promoter in a study comparing Crohn's diseased patients with reduced pressure thresholds to healthy individuals, highlighting sex and age-correlated differences [68]. Similar findings were highlighted for heat threshold [69]. On the other side, at a preclinical level, TRPA1 activation and inhibition were demonstrated to be involved in the epigenetic modulation of macrophage polarization to a proinflammatory profile [70]. A study investigating the expression of miRNAs in blood samples taken from several pain models including neuropathic (Spared Nerve Injury, SNI; Spinal Nerve Ligation, SNL) and inflammatory (complete Freund's adjuvant, CFA) pain showed a differential expression of several miRNAs [71]. miRNAs were reported to induce excitation of nociceptor neurons through the coupling of toll-like receptor-7 (TLR7) with TRPA1 [72]. To corroborate these findings, there is the evidence that Mus musculus miRNA-449a was reduced in SNI and it resulted able to decrease the mRNA expression levels of TRPA1 in a transfection system [73]. The expression of miR-141-5p was down-regulated and the expression of TRPA1 mRNA and protein was up-regulated in dorsal root ganglion of oxaliplatin-induced neuropathic pain rats [74]. About the influence of epigenetics on the responsiveness to therapy, a recent longitudinal study compared the DNA methylation pattern of responders and non responders on ≥ 50% reduction in monthly headache days (MHDs) in a sample of 98 chronic migraine patients with MOH [25]. The results pointed at: (1) a marker of response following the withdrawal of acute medications represented by the decrease of DNA methylation at intronic CpG site (cg14377273) within the HDAC4 gene ($p < 9.42 \times 10^{-8}$), remarkably involved in the release of neuroinflammatory mediators; (2) a marker of < 50% reduction of monthly migraine days (MMDs) after 12 weeks of treatment, consisting in decreased methylation pattern CpG probe (cg15205829) within the MARK3 gene ($p = 4.13 \times 10^{-8}$) [25], although no drug-gene association exists for the latter one. This evidence is in agreement with the role of valproate as a HDAC inhibitor: the latter drug is effective in chronic migraine and it reduces cortical spreading depression at a preclinical level, the electrophysiological correlate of migraine aura, but it is also active on depression in animal models. It was hypothesized that the antidepressant effect needs decreased HDAC activity [75]. Incidentally, inhibition of HDAC6 is involved in reduction of CSD and block of the CGRP receptor [76]. Specifically, rats subjected to CSD present epigenetic modulation operated by drugs as topiramate and valproic acid, very used in chronic migraine [77]. In fact, topiramate reduced by almost 50% and valproic acid increased by 17%, the number of differentially methylated regions [77]. Therefore, both preclinical and clinical evidence support the role of epigenetic profiling in the improvement of efficacy and safety of therapeutic options, for resistant patients mainly. An exploratory study compared miRNA levels in peripheral blood mononuclear cells from a cohort of non-menopausal women affected by migraine, proving differential expression of miR-342-3p, miR-532-3p and miR-758-5p in comparison to healthy counterparts [78]. The aim of epigenetic profiling was pursued also in the recent NCT04659226 study assessing the role of miRNAs as potential biomarkers in the prediction of the response to erenumab in women affected by episodic or chronic migraine [34]. The gathered results suggested differential expression levels of a wide set of miRNAs including the following: hsa-let-7d-3p, hsa-miR-106b-3p, hsa-miR-122-5p, hsa-miR-143-3p, hsa-miR-144-3p, hsa-miR-16-5p, hsa-miR-181a-5p, hsa-miR-221-3p, hsa-miR-25-3p, hsa-miR-29b-2-5p, hsa-miR-326, miR-363-3p, hsa-miR-424-5p, hsa-miR-485-3p, hsa-miR-532-5p, hsa-miR-543, hsa-miR-629-5p, hsa-miR-660-5p, hsa-miR-92a-3p. Among these, the levels of hsa-miR-143-3p decreased when the response to erenumab in episodic migraine increased. The cross-sectional controlled study NCT05891808 demonstrated the higher expression levels of miR-155 in patients affected by chronic migraine with MOH if compared with patients suffering from episodic migraine, but also in patients affected by episodic migraine respect to healthy controls [79]. The most novel approach relies in the integration of genome-wide association study and single-cell transcriptomics [80]. This multi-omic methodology allowed to highlight a neuroimmune-epigenetic dysregulation in migraine with aura, characterized by prenatal enrichment in neural crest-derived tissues and microglia near to hypothalamus [80]. However, all the reported results deserve further investigation in wider studies with adequate power analysis and more heterogeneous enrolment in order to be translated into clinical practice for personalized medicine in migraine treatment. Therefore, homogeneously and specifically designed epigenetic association studies with larger, more inclusive samples are essential to confirm current findings and to detect true associations with small effect sizes and extend them to the general population. This issue is of the utmost importance to shed light both on the processes of progression and transformation and on the mechanisms implicated in poor efficacy and safety of drugs in defined populations. In fact, epigenetic mechanisms including DNA methylation, histone modifications and the modulation of distinct pathways operated by ncRNAs could be exploited to revert chronic migraine to episodic attacks.

To this aim, a deeper knowledge also at a preclinical and neuropharmacological level of the role of epigenetics in reverting aberrant neuroplasticity and central sensitization is essential. Additional data from future studies are needed to support the identification of treatment responders and contribute to the development of reliable epigenetic biomarkers for clinical decision-making of risk and treatment response. Consequently, investigation into gene-environment interactions, but also transcriptomics, proteomics and metabolomics is warranted to identify robust biomarkers for diagnosis and prediction of treatment response, as well as to design clinical trials assessing the efficacy and safety of existing and novel pharmacological interventions.

Conclusions and future perspectives

Migraine is a chronic, paroxysmal neurovascular disorder among the leading causes of disability worldwide. Estimates of migraine incidence and prevalence demonstrate considerable variation across sex, race, ethnicity, geographic location, socioeconomic status, and educational attainment, indicating the influence of multiple intersecting determinants [81]. Epigenetic modifications are now thought to play a key role in progression and transformation to chronification of migraine states, by lowering the threshold for attack initiation and perpetuating a cycle of hyperexcitability [22, 23]. For instance, a recent study investigated the expression of a wide panel of serum miRNAs in patients affected by migraine and healthy controls, searching for differences [82]. Furthermore, individuals suffering from chronic headache display distinct DNA methylation patterns [9]. A deeper understanding of factors related to migraine pathophysiology and responsiveness to interventions, may pave the way for tailored, effective and safer treatment in a wider population [83, 84]. Personalized medicine is also needed to prevent the development of MOH, occurring in some 45–48% resistant patients [85]. A comprehensive HuGe systematic analysis identified the rs7590387 single nucleotide polymorphism (SNP) in the RAMP1 locus—implicated in the CGRP pathway—as relevant for its involvement in migraine pathophysiology and in the progression from episodic migraine to MOH [86]. However, epigenetics of the CGRP pathway is less studied than genetic variations, although it could be even more useful for its reversible features. Furthermore, specific data on the pediatric population are still very scarce in spite of the findings of a recent meta-analysis showing a robust association between elevated CGRP levels and pediatric migraine [87]. Recently, a study analyzed the levels of circulating miRNAs before and after treatment with erenumab to assess their potential as epigenetic biomarkers of response [34]. New drugs such as [88] the monoclonal antibodies (mAbs) directed towards the signaling of PACAP [89, 90] are recently emerging as novel strategies to manage the treatment of difficult-to-treat patients not responsive to available treatments. Also, the TRPV1 and TRPA1 are subjected to epigenetic modifications, such as DNA methylation, histone modifications, miRNAs, long ncRNAs and circRNAs [91]. Moreover, there is emerging evidence supporting HDAC inhibitors as future complement to the already existing specific CGRP-targeted therapies [25–76]. A role in the management of migraine might be played by a folate-rich "epigenetic diet" [92]. Finally, combination therapy, still avoiding the increase of adverse events, may aid achieving a greater therapeutic effect by targeting multiple pathways involved in the disorder. Onabotulinumtoxin A is proved useful in the reduction of the need for rescue medications implicated in MOH [93, 94]. A clinical study to evaluate how effective and safe the combination of atogepant or anti-CGRP mAbs is currently under investigation in difficult-to-treat chronic migraine [95]. The efficacy and safety of these approaches might be predicted if epigenetic association studies confirm them. Therefore, further clinical and real-world studies, also genome wide association studies (GWAS), are needed to investigate the role of epigenetic modifications of the 25 kDa synaptosomal-associated protein (SNAP-25) [96], target of the cleavage operated by onabotulinumtoxinA, to deepen the understanding of non-response to this therapetic option and to unravel other synergic and additive mechanisms involved in the combination strategies [97].

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