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Gazerani, Parisa

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Review

Current Evidence on the Role of Epigenetic Mechanisms in Migraine: The Way Forward to Precision Medicine

Parisa Gazerani *

Biomedicine, Department of Health Science and Technology, Aalborg University, Frederik Bajers Vej 3 B, Aalborg East, Denmark; E-Mail: gazerani@hst.aau.dk

* **Correspondence:** Parisa Gazerani; E-Mail: gazerani@hst.aau.dk

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Abstract:

Interactions between genetic and environmental factors in migraine are well known and can potentially determine an individual's susceptibility to disease and responsiveness to treatment. Consequently, several epigenetic studies have been conducted to determine if and how genes are activated or inactivated in response to a diverse range of environmental migraine triggers. The results, in turn, have helped elucidate how these factors can promote or inhibit migraine progression or therapeutic response and can guide development of precision medicines for migraine treatment. This review summarizes the current evidence and latest findings (accessible mainly through Medline-PubMed) that reveal epigenetic processes contributing to migraine pathogenesis acting via various distinct mechanisms. One of the most studied mechanisms, DNA methylation within the human methylome, may provide a potential epigenetic signature for migraine. Recent basic experimental data and clinical findings will be presented here to highlight that epigenetic studies hold great potential to explain risk factors, migraine chronification, and therapeutic responses. Current challenges and unmet needs are also addressed to promote further investigation of the role of migraine epigenetics in disease pathophysiology and to discover useful biomarkers to guide development of more effective therapeutics.

Keywords
Epigenetics; pain; headache; migraine; DNA methylation; migraine with aura; migraine without aura; epigenetic therapies; EWAS, epigenome-wide association studies

1. Migraine

Migraine is a recurrent neurological disorder characterized by moderate to severe headache attacks that are often accompanied by neurological and systemic symptoms [1, 2]. Hypersensitivity to light and sound, cutaneous allodynia, nausea and vomiting, and various degrees of cognitive impairment often occur during one or several migraine phases [2]. These symptoms highlight a complex pathophysiology that reflects the involvement of multiple neural networks and brain regions in triggering the disorder [3, 4]. Current understanding of migraine pathophysiology collectively suggests that migraine is a disorder of the nervous system characterized by structural and functional changes in the trigeminovascular system. More specifically, alterations observed in brain connectivity, as well as in activation of brain stem, hypothalamic, and thalamocortical circuits are suspected to play key roles in the disorder [4]. Advances in understanding of migraine pathogenesis have led to identification of new migraine-associated genes and brain regions that are activated at the earliest stages of a migraine attack; these results highlight the potential roles of cervical nerves and neuropeptides in migraine initiation [4].

Migraine is ranked as one of the most prevalent and disabling medical disorders around the globe [5]. Lifetime prevalence of migraine is 33% in women and 13% in men [1]. The mean prevalence of current migraine in adults is 14.7% (8% in men and 17.6% in women) [6]. Migraine poses a significant personal and economic burden [7, 8], with an annual cost burden estimated at $20 billion in the US and €27 billion in Europe [9]. Continuous absenteeism from the workplace due to debilitating migraine attacks has been shown to impose a higher cost burden than actually generated by treatment costs [10]. Indeed, 19% of total lost work productivity is a result of the collective impact of all chronic diseases, with migraine alone responsible for 89% of disease-related burden [11].

Current strategies to manage migraine are largely inadequate [12] and are largely based on the use of triptans [13] for acute management of migraine and of botulinum neurotoxin for prevention of chronic migraine [14]. However, recent progress in mechanistically informed drug development has resulted in the creation of a new class of drugs [15] with promising disease-specific therapeutic effects for migraine management. These drugs include monoclonal antibodies developed against calcitonin gene-related peptide (CGRP) (eptinezumab, galcanezumab, fremanezumab) and the CGRP receptor (erenumab). These drugs have shown promising efficacy and acceptable safety profiles in clinical trials [16]. In May 2018, the FDA (Food and Drug Administration) and EMA (European Medicines Agency) approved erenumab (Aimovig), a first-in-class drug for the prevention of migraine in adults.

Genes and environment encompass numerous known risk factors for migraine pathogenesis [4, 17]. Changes in barometric pressure, stress, altered metabolism, diet, hormones, and sleep disturbances have all been demonstrated to influence migraine susceptibility and treatment response. Meanwhile, several factors known to increase the risk of transition from episodic to

chronic migraine include recurrent attacks, abortive medication overuse, inadequate migraine attack management, and obesity [1, 18]. Female gender, depression, anxiety, and comorbid pain, as well as other disorders, are also risk factors for chronic migraine [18], a phenotype likely determined by both genetic and environmental factors [17].

Migraine has been long considered to be a heritable disorder [19]. While genome-wide association studies have yet to demonstrate large effects of genetic alterations on migraine risk [20], single gene mutations have been identified for rare migraine, including familial hemiplegic migraine (FHM) [21]. FHM is a rare autosomal dominant type of migraine with aura characterized by reversible motor weakness that typically resolves within minutes to hours [22, 23]. Classically, three genes are known to be associated with the three known types of FHM [1]. FHM type 1 is characterized by gain-of-function mutations in the gene for CACNA1A, a protein which encodes the α1 subunit of neuronal Cav2.1 calcium channels on excitatory glutamatergic neurons. FHM type 2 is known for gain-of-function mutations in ATP1A2, which encodes the α2 subunit of Na^+/K^+-ATPase pumps located on astrocytes. In these two types of FHM, net excitatory neurotransmission is evident, due to unregulated release or reduced uptake of synaptic glutamate. FHM type 3 is characterized by loss-of-function mutations in SCNA1, which encodes the pore-forming α1 subunit of neuronal Nav1.1 sodium channels that span membranes of inhibitory interneurons. This mutation results in unregulated firing of excitatory neurons [1, 22, 23].

Genome-wide association studies (GWAS) [24, 25] examining migraine susceptibility genes have identified one DNA variant within the MTDH gene that is associated with migraine with aura, as well as six gene loci (MEF2D, TGFBR2, PHACTR1, ASTN1, TRPM8, and LRP1) for migraine without aura. Notably, these genes are involved in glutamatergic neurotransmission or neuronal and synapse development and could influence enhanced cortical excitability in migraine. Meanwhile, a meta-analysis of GWAS [25] revealed 44 independent single-nucleotide polymorphisms significantly associated with migraine risk. These single-nucleotide polymorphisms mapped to 38 distinct genomic loci. Of these loci, 28 had not been previously reported and included the first X-linked migraine-associated gene ever identified. Notably, five of the loci are involved with or linked to ion channels that influence neuronal excitability. In other studies, genes expressed in vascular and smooth muscle tissues have also been identified, indicating that vascular homoeostasis could be integral to migraine pathogenesis for at least some patients [1, 24, 25].

Despite great efforts, until now GWAS have only explained a fraction of the total heritability of migraine. Therefore, non-genetic factors such as known environmental triggers of migraine should also be included in the analysis [26]. In fact, twin studies have provided information on genetic-environment interaction in migraine, showing that heritability ranges from 40 to 60%, with a contribution of nonshared environmental factors of 35-55% [27-29]. These results thus suggest that genetic factors and environment play almost equally important roles in migraine. Various environmental factors, such as alcohol consumption, smoking, nutrition, stress, environmental changes, exercise, and menstrual cycles in women, have been frequently reported to be associated with migraine [30]. Such modifiable risk factors could be controlled to enhance patient quality of life and reduce the burden of disease.

To investigate the role of environmental factors in migraine, studies have recently demonstrated that epigenetics may play an important role [31]. For instance, a direct correlation has been observed between cortical spreading depression (CSD) and changes in epigenetic markers within neuronal plasticity genes [32]. Meanwhile, other studies have revealed a

suggestive link between mitochondrial dysfunction and a decrease in migraine attack threshold, highlighting the potential participation of dysfunctional mitochondrial DNA methylation as a new avenue of migraine research [33]. Unfortunately, current symptomatic and prophylactic treatments for migraine are effective in less than half of patients [34]. Moreover, the effects of some analgesics and triptans change over time and are dependent upon frequency of use. Because these observations are not solely explained by genetic alterations, the possibility that epigenetic changes might play a role should be investigated further. Recent techniques including array-based analysis or next-generation sequencing enable genome-wide and high-throughput analysis of epigenetic markers [31, 35]. These techniques permit analysis of histone modifications (by chromatin immunoprecipitation), DNA methylation (by bisulfite conversion of unmethylated cytosines or by immunoprecipitation of methylated DNA using antibodies), and methyl-CpG-binding domains [36].

A recent study proposed for the first time that the pattern of DNA methylation in genetic regulatory elements involved in migraine pathogenesis might be altered, increasing susceptibility to migraine attacks. Consequently, Gerring et al. [37] investigated genome-wide patterns of DNA methylation in whole blood from migraine patients compared with sex- and age-matched controls. Association analyses between migraine and DNA methylation detected using probes demonstrated 62 independent regions that were differentially methylated. Further analysis by this group [37] found that these regions were enriched within genomic regulatory elements residing in close proximity to genes involved in solute transport and hemostasis [37].

Recently, epigenome-wide association studies have proposed that associations of epigenetic markers to a trait could be used in conjunction with genetic variations discovered using GWAS [38] to advance our understanding of gene-environment interactions in migraine, although at present the role of epigenetics in migraine is an emerging but underexplored field. A 2017 review [39] included 15 English-language publications based on a Medline-PubMed literature search focusing on the involvement of various epigenetic mechanisms in headache. Although migraine was included in their search terms, the review [39] that included other primary headaches is the most recent review in the field of epigenetics and headache. Collectively, the reviewers concluded that limited but consistent evidence points to a relationship between epigenetics and headaches, particularly for migraine headaches [39]. A summary of the findings revealed potential participation of hypomethylation, hypermethylation, hyperacetylation of H3 histones, and alterations in certain miRNAs. These findings are reviewed below. After epigenetics is first briefly defined, primary epigenetic-based mechanisms are discussed, followed by presentation of detailed evidence on the role of epigenetic mechanisms in migraine.

Epigenetics was first defined by Conrad Waddington in 1942 [40] and is used to describe modifications to the function of a gene that do not alter the DNA sequence of the gene itself. Epigenetic processes encompass a range of chemical modifications to diverse types of chromosomal sites, including RNA- and protein-coding sequences, transcription factor-binding sites, and DNA methylation sites, that mediate effects of genetic, environmental, and stochastic factors on gene expression [41]. Epigenetics encompasses molecular mechanisms that include DNA methylation, histone posttranslational modifications (PTMs), nucleosome repositioning, chromatin remodeling, effects of noncoding RNAs, and RNA editing [42, 43]. Ultimately, epigenetics represents partially heritable alterations that can influence gene expression through higher structural modifications of chromatin, not through DNA sequence alterations [44].

Epigenetic functions can be divided into three main systems that include methylation, histone modification, and RNA-associated silencing [42]. These alterations often involve chemical addition or removal of methyl or acetyl groups, resulting in altered chromatin conformation that subsequently induces altered gene expression. Alterations are triggered by either environmental factors or aging processes [45], the latter of which have been recently reviewed with emphasis on the role of DNA methylation in age-related disease [46]. For common diseases of aging, an epigenetic framework can help provide an explanation of three important characteristics: age-dependence that is not well explained by accumulated mutations, the quantitative nature of a trait, and the mechanism by which the environment may modulate genetic predisposition [46, 47]. Epigenetic alterations may influence disease phenotypes by affecting the target gene directly, regardless of sequence variation within the gene. Alternatively, the influence of epigenetic markers on disease phenotypes can occur via interactions with specific DNA sequence variants [47].

2.1. DNA Methylation

DNA methylation (5-methylcytosine) involves the addition of methyl groups via the covalent modification of CpG (5'-cytosine-phosphate-guanine-3') sites distributed throughout the genome. These modifications exhibit transcriptional regulatory properties, with high levels of DNA (or CpG) methylation observed particularly near transcription start sites. Although such methylation has been traditionally associated with decreased gene expression, recent studies have shown CpG methylation to be actually associated with increased expression as well [48]. Thus, regulatory properties of CpG methylation are far more complex than previously envisaged. Notably, DNA methylation changes in response to genetic, environmental, and stochastic factors can be preserved between cell divisions, as well as across generations in some instances [49]. DNA methylation therefore represents a critical cellular phenotype that can be mapped on a genome-wide scale to DNA sequence variation and gene expression, providing an integrated model of disease susceptibility. Indeed, methylation [43] is the primary form of epigenetic modification, with numerous diseases associated with differentially methylated regions. Consequently, demethylating agents or methyl donors are being intensively evaluated as epigenetic therapies [50].

The mechanistic action whereby methylation of DNA sites blocks binding of transcription factors to other regulatory sequences (e.g., enhancers) occurs through the recruitment of MECP2 proteins, which bind to methylated cytosines and attract histone deacetylases (HDACs). HDACs, in turn, promote formation of a closed chromatin conformation that also prevents the transcriptome, a critical complex involved in DNA polymerase binding, from associating with promoter sites. In this way, methylation further downregulates transcription and, by acting in conjunction with other pathways, partly controls gene expression [51-54]. Therefore, DNA methylation patterns can be inherited but can also be altered, ultimately influencing DNA expression without modifying the DNA sequence. Preferential sites of DNA methylation include DNA strands with a high concentration of cytosine and guanine repeats (CpG islands) [55]. Indeed, alterations in the levels of DNA methylation are a known mechanism for the fine-tuning of gene expression [56] in response to changing environmental conditions, with an increasing number of studies correlating epigenetic modifications with disease phenotypes [57, 143]. These studies have focused almost

exclusively on DNA methylation, since the associated quantitative assays permit detection of small methylation changes associated with a phenotype in heterogeneous tissue samples [37, 58].

2.2. Histone Modification

Histones [59] are the principal nuclear proteins responsible for DNA condensation and decondensation. DNA is wrapped around protein octamers containing four pairs of core histone proteins associated with linker and specialized variant histones. This complex of multiple histones and interlaced DNA comprises a nucleosome, which mediates the structure and function of individual transcriptional units. Histones contain basic N-terminal tails that preferentially undergo multiple posttranslational modification events, such as acetylation, methylation, phosphorylation, ubiquitylation, sumoylation, ADP ribosylation, deamination, or proline isomerization. These events determine nucleosomal conformational properties, environmental responsiveness, and transcriptional activity that can subsequently and influence additional epigenetic DNA modifications [60]. Through reactions catalyzed by histone acetyltransferase enzymes, histones are acetylated by activators, promoting chromatin structural shifts from closed to open configurations; the opposite effect is induced by inhibitors that direct deacetylation of histones. Meanwhile, ubiquitination is another type of chemical modification that can alter histone structure through the formation of internal chains attached to lysine residues within histone 2A. Ubiquitination ultimately reduces the positive charge of the histone, promoting a more open conformation that is permissive to transcription. Phosphorylation is yet another modification that creates an open chromatin structure to allow transcription; introduction of negative charges of phosphate groups make histones less positively charged, resulting in greater repulsion between histones and negatively charged DNA [61]. Finally, various combinations of the aforementioned chemical changes can also act to affect chromatin structure. For example, phosphorylation of histone residue H3 on serine 10 promotes acetylation on the adjacent lysine 14 residue [62].

2.3. Noncoding RNAs

Noncoding RNAs (ncRNAs) are RNA molecules of various sizes with diverse functions that are abundantly found across many cell types and play an essential role in gene regulation [63]. ncRNAs are divided into several subclasses, one of which includes long noncoding RNAs (lncRNAs) associated with important functions, most of which are regulatory in nature [64-66]. Within the epigenetics field, ncRNAs are defined as either long or short, with an arbitrary length demarcation between types set to 200 nucleotides [67]. This size distinction is useful for distinguishing among the current characterized classes of small functional RNAs, including miRNAs, piRNAs (PIWI-interacting RNAs), siRNAs (small interfering RNAs), snoRNAs (small nucleolar RNAs), and tRNAs (transfer RNAs) from long noncoding RNAs (lncRNAs) [68]. Functions that have been associated with ncRNAs include transcriptional activation, gene silencing, imprinting, dosage compensation, translational silencing, and modulation of protein function [69]. Short and lncRNAs play important roles in neuronal epigenetic mechanisms [70], where the roles of ncRNAs in neuronal and cognitive functions are just beginning to be explored. Emerging studies have recently introduced the concept that ncRNAs are involved in the epigenetic process underlying cognition, as well as in cognitive disorders such as schizophrenia and Alzheimer's disease [71]. Meanwhile, although assessment of lncRNA in pain and headache disorders is still in its infancy, lncRNAs may serve

crucial roles in cell development, proliferation, differentiation, migration, and invasion [72]. It is important to note that epigenetic changes are not independent of one another and crosstalk does exist [73]. It is therefore important to examine additional layers of epigenetic regulation. Understanding epigenetic regulation at both genome-wide and gene-specific levels will provide insights into how changes occur and how they can be reversed.

3. Epigenetics of Pain

Although epigenetics of pain [73-78] is beyond the main scope of this review, environmental and behavioral factors that influence pain through epigenetic processes [79, 80] may also be relevant to the epigenetics of migraine. Indeed, evidence exists for epigenetic modulation, both in the acute pain response and in chronic pain [76, 81]. For example, in both animal models and humans, continuous DNA methylation induced by low back pain has been linked to increased and faster degeneration of vertebral disks [75, 82]. In animal nerve injury models, sustained histone deacetylation has been reported to generate permanent C-fiber dysfunction [83], decreased responsiveness to morphine analgesia, and upregulation of pronociceptive metabotropic glutamine receptors [75, 83]. Epigenetic processes have also been linked to variations in the production of stress-induced glucocorticoids, differential responsiveness to steroidal anti-inflammatory drugs, and glucocorticoid resistance that have all been proposed to contribute to pathological chronic pain conditions [75]. The role of the nonneuronal glial cell [84] is also becoming apparent in chronic pain [85], since these cells are highly responsive to environmental insult. It has been suggested that defects in mRNA editing or in DNA regulation within glial cells promotes deregulated pain. Thus, chronic pain may be due to pathological RNA editing and DNA rewriting that persistently affects glial cell activity [86]. Because DNA methylation associated with chronic pain appears to be widespread, it is possible that general modulators of DNA methylation acting system-wide may also participate [73]. Although DNA methylation modifiers are still only tools for research, a novel genome-editing technology may offer clinical value moving forward. For example, TET-TALE fusion proteins have been shown to effectively target and demethylate individual genes in vitro [87], while Cas9 DNA-editing systems offer novel and flexible approaches to individual gene targeting [88].

Interestingly, several readily available nutritional compounds have been identified that can modify DNA methylation, such as folate, a B-vitamin administered to pregnant women to reduce the risk of infant neural tube defects. Meanwhile, for treatment of neuropathy, folate has been shown to facilitate neural regeneration in a dose-dependent manner via DNA methylation machinery-dependent processes [89]. For another disorder, idiopathic juvenile arthritis, the oral HDAC inhibitor Givinostat relieved arthritic symptoms after 12 weeks of treatment but did not reduce the pain component of the disease [90]. Another nutritional compound, glucosamine, is produced by the body for biosynthesis of cartilage-repairing glycoproteins and glycosaminoglycans and is available as a nutritional supplement for joint and pain management in osteoarthritis [91]. Evidence suggests that glucosamine also alters the methylation status of chromatin [92]. Therefore, a role for epigenetic modifications in pain is likely [75] and the therapeutic potential already exists to alter epigenetic processes to improve analgesic outcome.

Numerous diverse studies are exploring roles of lncRNAs in different types of pain, including neuropathic pain. Recent evidence indicates that lncRNAs are upregulated or downregulated in

some neuropathic pain models. For example, the expression of lncRNA colon cancer-associated transcript-1 (CCAT1) in a neuropathic pain model of bilateral sciatic nerve chronic constriction injuries (bCCI) has been found to be decreased [93]. In this study, lncRNA CCAT1 overexpression was demonstrated to increase pain threshold and reverse cold allodynia in rats. Collectively, findings from these studies highlight a potential role of lncRNAs as a novel group of targets for the treatment of neuropathic pain [94]. Consequently, RNA-associated silencing and the role it plays in disease is becoming an important research area [95, 96].

4. Migraine Epigenetics

Accumulating evidence is implicating epigenetic mechanisms as important in migraine pathogenesis. These results may eventually guide development of tests to determine disease susceptibility and predict disease course for a given individual. Eventually this information should inform the development of precision medicines, including epigenetic-based therapies for efficient pharmacotherapy of migraine [31]. In a 2008 review [97], a detailed outline of genetic studies of patients with primary headaches (mainly migraine) and a comprehensive hypothesis incorporating advances in epigenetics were presented [98]. After considering epigenetic factors, environmental factors likely to act via epigenetic changes were later highlighted by Schürks [98], suggesting that medication responses could be rooted in epigenetics. His pharmaco-epigenetic model of migraine was based on his argument that only half of migraine patients respond to abortive and preventive drugs [34]. In addition, the observation that patient responses to triptans change over time and depend on administration frequency might also be explained by epigenetic factors [98].

4.1. Environmental Factors and Migraine

Environmental factors originate from nutritional, psychological, hormonal, or behavioral factors that may trigger migraine either directly or indirectly by lowering the migraine attack threshold of the brain, making the brain more susceptible to triggering factors [31]. Female sex hormones have long been associated with migraine [99] and migraine affects up to three times more females than males [100, 101]. Hormonal events in females are known to be key contributors and include the menstrual cycle, pregnancy, or contraceptive use [102]. Menopause is, however, associated with a decline in migraine risk, most likely as a result of reduced estrogen and progesterone production [103]. Meanwhile, animal studies have demonstrated that female hormones directly affect migraine-associated processes. For example, in a transgenic mouse model of FHM using mice carrying the pathogenic gene mutation [19], increased susceptibility for CSD induction was observed, but only in female mice [104]. When female mice underwent ovariectomy, susceptibility for CSD induction was reduced but could be subsequently restored by exogenous administration of estrogen [104]. A number of other studies in rats have also demonstrated that menstrual cycle, ovariectomy, or exogenous administration of estrogen altered activity of the trigeminal nociceptive pathway [99]. These results could be attributed to female hormonal signals transmitted predominantly via nuclear receptors that subsequently adjust epigenetic programming of their target genes [105]. One such target, the estrogen receptor beta gene, regulates expression of the glucose transporter Glut4 through low-level DNA methylation [106]. Exogenous administration of an estrogen receptor beta agonist has been reported to increase gamma-aminobutyric acid (GABA) synthesis [107], while estrogen receptor alpha activation is

associated with enhanced expression of the astrocytic glutamate transporter GLAST [108]. Considering these findings, a change in the balance between inhibitory and excitatory neurotransmission may contribute to increased neuronal excitability during migraine attacks, ultimately leading to hyperexcitable brain [109]. Indeed, this has been demonstrated in a transgenic mouse model of FHM1, where glutamatergic signaling and cortical neuronal activity are increased [110].

Stress is another well-known trigger of migraine [111] and is heavily influenced by environmental programming through epigenetic mechanisms. A rat model of early life stress imposed by deficient maternal care demonstrated effects on the epigenome [112, 113] that resulted in behavioral and stress responsiveness effects that persisted for life. The mechanism underlying this phenomenon was attributed to increased DNA methylation observed within the brain-specific promoter of the glucocorticoid receptor gene Nr4a3, the main receptor for glucocorticoid stress hormones [112]. Other studies have also shown that early life stress may lead to increased risk for migraine [114], with evidence demonstrating a link between posttraumatic-stress disorder (PTSD) and migraine [115]. Although the odds of PTSD are increased in both female and male migraine patients, this association is stronger in men [115].

There are a number of other environmental factors [116] known to trigger migraine attacks, but whether epigenetic mechanisms are involved has yet to be demonstrated. Odors and air pollution are reported as migraine triggers, as several reports have demonstrated strong links between airborne chemicals and headaches [117]. Recently, it was suggested that TRPA1 agonists are critically involved in air pollution-induced human headache [118]. TRPA1 agonists acrolein and formaldehyde are environmental irritants found in indoor and outdoor pollution. Although few studies [119, 120] have examined whether environmental irritant exposures induce migraine behavioral phenotypes, the results from these studies suggest that inhalation exposure to environmental irritants induces trigeminovascular and central nervous system sensitization, reproducing some features of chronic migraine models [119, 120]. These studies highlight that TRPA1 receptors have important roles in migraine and that they could be targeted for therapeutic purposes [119, 121]. Lipid signaling may be another potential mechanism by which repeated exposure to acrolein may drive trigeminovascular sensitization [120].

Wu et al. [122] evaluated the role of the JNK/c-Jun cascade in regulation of histone H3 acetylation within rat trigeminal neurons in vitro following neurotoxic stimulation with mustard gas. This study [122] was the first to provide solid evidence for JNK kinase involvement in the epigenetic modulation of histones within peripheral trigeminal neurons in response to chemical environmental stimulation. More recently, c-Jun has also been shown to be an inducible transcription factor whose phosphorylation occurs in response to nerve injuries, infections, and nervous system inflammation [123-125].

The importance of CGRP in migraine pathophysiology has been demonstrated in migraine patients by induction of migraine headaches through injection of CGRP receptor agonists [126] and conversely through the alleviation of migraine pain using a CGRP receptor antagonist [127]. Meanwhile the indirect involvement of regulation of CALCA and RAMP1 genes in migraine susceptibility has been suggested in several studies. Wan et al. examined whether the methylation pattern in the promoter region of the RAMP1 gene in peripheral leukocytes is associated with migraine [128] by studying 51 subjects (26 patients with migraine and 25 healthy age- and gender-matched controls) who were treated with bisulfite followed by measurement of DNA methylation

levels within the RAMP1 promoter region. Overall, no significant difference between migraine patients and controls was observed in the methylation of 13 CpG sites within the promoter region of the gene, specifically at base positions between -300 and 205 bases with respect to the start of transcription. However, a slight tendency for globally increased methylation was found in migraine patients. A later stratified analysis showed that methylation levels of CpG dinucleotides at base positions +25, +27, and +31 bases from the transcription start site were significantly associated with a family history of migraine. In addition, methylation of CpG at positions +89, +94, and +96 was related to migraine in women. Interestingly, when methylation levels in the latter region decreased below 3.50%, the risk of migraine increased significantly in women but not in men. Therefore, the authors suggest that methylation of this region in peripheral leukocytes could be considered an "epigenetic biomarker" to predict migraine risk in the female population [128]. Despite its limitations in terms of the limited number of samples and testing only in leukocytes, this study provides the first evidence that DNA methylation in the promoter region of the RAMP1 gene may play a role in migraine.

Considering growing evidence of the involvement of glia in pain, Park et al. [129] investigated whether epigenetic mechanisms influence specific cellular expression of the CALCA gene. This group used rat and human commercially available cell lines and primary glial cell cultures of rat trigeminal ganglia to measure DNA methylation and histone acetylation within a CpG island close to an enhancer region that is active in neurons but inactive in glia. They found that DNA methylation and acetylation of H3 histones of the CpG island correlated with expression of the CALCA gene, with hypomethylation observed in cells that express the gene and hypermethylation or hypoacetylation observed in cells that do not express it (e.g., glial cells). This indicates that the specific cellular pattern of histone methylation and acetylation could explain silencing of both rat and human CALCA genes in different cell types. In addition, this study examined the functional consequence of altered chromatin status using quantitative measurements of calcitonin mRNA and CGRP after addition of the methylation inhibitor 5-aza-2'-deoxycytidine and an inhibitor of histone deacetylase, trichostatin A. Treatment of cells with 5-aza-2'-deoxycytidine induced expression of the CALCA gene in both human and rat glia cultures, while treatment with trichostatin A had no effect. Surprisingly, combined treatment of trichostatin A and 5-aza-2'-deoxycytidine showed a very powerful synergistic effect on the induction of CALCA gene expression in glia, suggesting that DNA demethylation must occur prior to histone acetylation. Nevertheless, methylation of this region is a key determinant for specific cellular expression of this gene and epigenetic modulation is sufficient for the induction of CALCA gene expression in glia.

Neurogenic inflammation has also been implicated in migraine. Because CALCA gene expression is systematically induced only during inflammation in tissues lacking normal expression of this gene, procalcitonin, a calcitonin precursor produced upon CALCA induction, is a biomarker worth exploring in migraine [129]. A limitation is that due to the inaccessibility of human neurological tissue, most studies have been performed using human leukocytes, cell lines, or rat neurological tissues. It is therefore unclear whether patterns of DNA methylation in blood leukocytes correlate with patterns in neurological tissue. To address this concern, Labruijere et al. [130] studied DNA methylation patterns in rat leukocytes and tissues including dura mater, trigeminal ganglia, and caudal trigeminal nucleus. DNA methylation patterns of genes associated with migraine pathophysiology that are likely epigenetically regulated, including genes for CALCA, RAMP1, CRCP, and CALCRL, were compared in various tissues. For previously studied genes coding for CALCA and

RAMP1, methylation pattern concordance was observed among all tissues, thus demonstrating that CALCA and RAMP1 gene results could be extrapolated to neurological tissue [130]; however, this result was not observed for the other two genes. Meanwhile, the authors observed high agreement between DNA methylation in rat and human leukocytes [130], indicating that it is possible to study DNA methylation in rat tissues for tissues or samples that would be difficult to obtain from humans. In contrast, several genes encoding proteins involved in the methylation cycle, such as the methylene tetrahydrofolate reductase gene (MTHFR), have not been associated with migraine using GWAS. Nevertheless, methylation of some genes associated with migraine might be epigenetically regulated [130].

Inflammation has long been suggested to play a role in migraine. For example, proinflammatory cytokines are released during CSD in rat hippocampus [131]. Interestingly, inflammatory mediators may induce gene expression changes by altering epigenetic processes [132], while their expression may be reduced by treatment with HDAC inhibitors [133]. Immune mediators have also been shown to be involved in sensitization of nerve endings in the meninges that promote pain sensation [134]. This sensitization is the result of vasodilation and the release of proinflammatory cytokines. Notably, prolonged inflammatory pain was shown to promote pain sensitivity by causing histone hypoacetylation of the Gad2 gene, which is involved in GABAergic signaling [135]. Therefore, migraine-related pain may induce the sensitization of certain pain pathways via inflammation-induced changes in epigenetic gene regulation.

4.2. Chronification of Migraine

Attack frequency may change over the lifetime of a migraine patient and, in some patients may progress to chronic migraine. Because migraine patients with a high baseline attack frequency are at increased risk for chronic migraine [136], migraine attacks themselves might promote development of chronic migraine. Additionally, recent studies have shown that synchronous neuronal activity, such as that occurring during CSD, results in changes in epigenetic markers within genes involved in neuronal plasticity and neuroprotection [32, 137]. These results align with evidence that epigenetic mechanisms involved in the regulation of basal synaptic activity can also induce long-term changes in synaptic activity levels [138]. CSD is a wave of neuronal and glial depolarization that propagates slowly throughout the cerebral cortex, followed by sustained suppression of spontaneous neuronal activity. During CSD, cortical changes and activation of metalloproteinases break down the blood-brain barrier, allowing chemical mediators to activate trigeminal terminals surrounding meningeal vessels [139]. Evidence exists that suggests that CSD also may be involved in the epigenetic control of gene expression through induction of histone modifications. It has been established that trimethylation of lysine 4 in histone H3 (H3K4) occurs in all active genes, while trimethylation of H3K9 occurs in compact heterochromatin that is transcriptionally inert. Based on these facts, Passaro et al. [32] assessed whether CSD causes epigenetic modifications in rat chromatin levels of H3K4 and H3K9 methylation by comparing results for a cerebral hemisphere with CSD induction to results for the contralateral hemisphere without CSD induction. Subsequently, epigenetic modifications of chromatin were evident in rats 24 hours after CSD induction, with a significant decrease in dimethylation and monomethylation of H3K4 and an increase in dimethylation of H3K9 [32]. In another study, Rana et al. [140] examined H3K4 and H3K9 dimethylation levels at specific loci in rat brains 24 h after CSD induction.

The neuroprotective genes iNOS and HIF-1α showed marked increases in lysine 4 dimethylation and decreased lysine 9 dimethylation of H3 histones. These results confirm the hypothesis that epigenetic regulation of gene expression is influenced by CSD.Taken together, it is conceivable that increased neuronal activity in migraine alters the brain epigenome, thereby promoting subsequent migraine attacks and creating a feed-forward loop. In this paradigm, epigenetic programming of genes and pathways underlying excitability may be altered towards a more sensitive baseline state as a mechanism underlying migraine chronification.

A study conducted by Winsvold et al. [141] supports the association between changes in the methylation of genes that regulate synaptic plasticity and chronification of headache. This study was conducted using 36 female patients who progressed from episodic to chronic headache between initial assessment and follow-up 11 years later, with 35 age- and gender-matched controls experiencing episodic headache. DNA methylation was subsequently quantified at 485,000 CpG sites and changes in methylation in cases and controls were compared in two steps using linear regression analysis [141]. After combining the results from both stages of analysis, 20 CpG sites were identified that were associated with the chronification of headaches, although none reached the threshold of statistical significance in a fixed-effect meta-analysis. CpG sites with greatest association with chronification were located within genes for SH2D5 and NPTX2, both regulators of synaptic plasticity. Ultimately, the complete list of CpG sites with the greatest association exhibited enrichment of genes related to calcium ion-binding function. Nevertheless, given that this was a cross-sectional study, it is not possible to conclude whether changes in methylation of these genes were a cause or consequence of frequent headaches [141].

Because migraine is comorbid with other disorders, study of comorbid disorders may be helpful to understanding migraine. For example, the role of epigenetic mechanisms in depression [142], a disorder comorbid with migraine, is evident from animal models for major depressive disorder that show large changes in epigenetic programming of stress-related genes, (e.g., the gene for BDNF) that are reversed by antidepressant treatment [143, 144]. For another comorbid disorder, epilepsy, the contribution of epigenetics to epilepsy is illustrated by the high occurrence of this disorder in Rett syndrome and alpha thalassemia mental retardation, two disorders caused by mutations in epigenetic effector proteins methyl CpG binding protein 2 (MeCP2) and ATRX, respectively [145, 146]. In addition, the brain of temporal lobe epilepsy patients contains increased DNA methylation at the Reelin promoter [147], a gene involved in brain plasticity, with reduced expression (resulting from methylation) that contributes to epilepsy pathogenesis [148]. These examples of comorbid conditions show that causal pathways shared between migraine and its comorbid disorders, including depression, epilepsy, and cardiovascular disorders [149], may be modulated by epigenetic mechanisms.

4.3. Medication Abuse

Medication abuse by headache patients may share pathogenic mechanisms and genetic factors with other types of drug through enhancement of predisposition factors [150-152]. In this sense, inhibition of histone deacetylase 3 seems to play a role in the memory processes involved in cessation of drug dependency in animal models [153]. Histone deacetylase 3 is a protein expressed in almost all tissues, including the brain, that is responsible for deacetylation of lysine residues from central histones. Pisanu et al. [154] were the first to investigate the role of histone

deacetylase 3 polymorphisms in relation to excessive medication use. Although this was only a pilot study, the results showed a significant association of the G allele polymorphism rs2530223 with higher medication consumption, although this variant was not associated with frequency or intensity of headache episodes [154].

4.4. Modification of Noncoding RNAs in Migraine

Noncoding RNAs are RNA molecules that are not translated into proteins and have a wide variety of gene regulatory functions. Among the many known types of noncoding RNA, miRNAs stand out because they have been extensively studied in recent years. MiRNAs reduce mRNA levels and play an important role in the posttranscriptional processing of genes through formation of RNA-induced silencing complexes. MiRNAs also appear to be involved in pain signaling, as shown in studies where miRNAs dysregulation was found in patients with complex regional pain syndrome, osteoarthritis pain, and fibromyalgia [155]. Based on these findings, alteration of miRNA in migraine has also been postulated, but in only a handful of preliminary studies. We examined possible changes in miRNA in the blood of patients during the course of migraine episodes versus healthy controls and assessed whether chronic differences in blood miRNA levels were observed between groups [156]. Subsequently, elevated blood levels of miRNA-34a-5p and miRNA-382-5p were observed during migraine attacks, with differences also observed during pain-free periods. It is interesting to note that miRNA-34a-5p is associated with inflammation and vascular endothelial stress response and that miRNA-382-5p is found principally in neurons and cerebrospinal fluid, appearing only in small amounts in blood. It has been suggested that the blood-brain barrier may exhibit altered integrity during migraine attacks, suggesting that increased miRNA-382-5p may originate from central nervous system structures or from cerebrospinal fluid. We propose that migraine conditions change the expression of miRNA in blood, not only during attacks but also during pain-free periods, indicating that miRNAs play an important role in the pathophysiology of migraine. Based on these results, quantification of miRNA in blood might serve as a biomarker of migraine, with potential applications for patient stratification, diagnosis, and monitoring of treatment [156].

In a pilot study, Tafuri et al. [157] evaluated expression of circulating miRNAs in female patients with history of migraine without aura during pain-free periods compared to healthy controls. A specific profile of expression of circulating miRNAs was associated with migraine that was statistically distinct from that of healthy controls, with migraine associated with overexpression of miRNA-27b and underexpression of miRNA-181a, miRNA-let-7b, and miRNA-22. In addition, in this population the specificity and sensitivity of the miRNA pattern for use in diagnosing migraine was comparable to the gold standard of clinical criteria. Therefore, concomitant evaluation of these 4 miRNAs could represent a diagnostic tool for migraine without aura [157].

New evidence indicates that endogenous pain control systems, including GABAergic and opioid systems, are regulated by miRNAs, such as miRNA-134 or miRNA-181a. In addition, specific miRNAs are associated with pathological pain and dysregulated expression of sensory neuron channels in mouse models [158-160]. Consequently, knowledge of neuronal miRNA deregulation could be applied not only to neuropathic pain but to other pain syndromes including headaches, especially migraine headaches. It is known that dopaminergic and glutaminergic signals from the amygdala, hippocampus, and prefrontal cortex that are transmitted to the nucleus accumbens

participate in impulse control circuits and in emotional aspects of pain processing. Moreover, a relationship between chronic pain and emotional dysfunction has been found, with maladaptive responses of the nucleus accumbens in neuropathic pain associated with deregulation of miRNA in that brain region [161]. Meanwhile, it has been shown that pain can alter expression of certain miRNAs influencing expression of primary nociceptive receptors in brain areas associated with emotional components of pain [161-168]. Therefore, investigation of miRNA profiles could provide potential biomarkers to predict the onset, impact, and evolution of migraine. In addition, migraine-associated miRNAs could serve as potential targets for future migraine therapies. However, since migraine miRNA research is still in the early explorative stages, further investigation and evidence to support the hypothesis are essential before any prediction can be made for application of these ideas.Currently, no study has been published yet that links alterations in lncRNAs to migraine.

4.5. Developing Epigenetic-Based Therapies

The idea behind epigenetic therapy originates from the rationale that DNA methylation and histone acetylation can be manipulated to reset a regulatory system to its original regulatory state [33]. Since epigenetic processes are dynamic and reversible, they are a highly attractive target for drug development. Because the association between gene silencing and histone deacetylation catalyzed by HDACs is well established, a growing number of small molecules have been designed to inhibit HDACs in order to activate gene expression in regions where aberrant silencing has taken place. For example, valproate, a potent HDAC inhibitor, facilitates chromatin remodeling [169]. This agent is one example of a prophylactic compound used to treat migraine [75].

Meanwhile, therapies targeting DNA methylation machinery are also rapidly progressing and include both pharmaceutical agents and natural compounds, such as black raspberry extracts. Such results belong to a new field of research, nutriepigenetics, which examines the influence of dietary agents including methyl donors such as L-methionine, S-adenosylmethionine (SAM), and betaine supplements, on epigenetic mechanisms [170, 171]. Indeed, the modulating effect of SAM is partly due to decreased methyltransferase activity via downregulation of the DNMT3A transcript. Methyl donor supplements reverse DNA hypomethylation that occurs in many diseases, including neurological disorders (e.g., depression), inflammatory diseases, osteoarthritis, chronic pain, chronic fatigue syndrome, and fibromyalgia [172-175]. There is, however, no direct evidence of their efficacy for treatment of migraine.

In other studies, preliminary success has been achieved using methyl donors as therapies for inflammation in vitro. In macrophages [176], SAM reduces lipopolysaccharide-induced expression of the proinflammatory cytokine TNF-α and causes increased expression of the anti-inflammatory cytokine IL-10, which are both associated with changes in specific gene promoter methylation. SAM also reduces inflammation and inhibits several pathways that include, in particular, the IL-6-dependent signaling pathway. SAM efficiency is optimized by inhibiting the polyamine recycling pathway that is possibly responsible for increased consumption of SAM in response to a diverse pathogenic mechanisms. Notably, overexpression of spermine/spermidine N1-acethyltransferase (SSAT1) increases recycling of polyamines [177] and was found to be increased in rheumatoid arthritis synovial fibroblasts. Berenil® (diminazene aceturate), an inhibitor of SSAT1 activity, increases the 5-methylcytosine content of DNA in rheumatoid arthritis synovial fibroblasts [178],

increases levels of DNMT1, decreases levels of a disease activation marker (matrix metalloproteinase-1, MMP1), and alters cell-adhesion capability. As expected, Berenil® is more efficient in cells with higher levels of SSAT1. Most interestingly, the combination of Berenil® and SAM reduces the invasiveness of rheumatoid arthritis synovial fibroblasts into cartilage by 70%, illustrating that epigenetic changes induced by increased SSAT1 levels could be of therapeutic value. Clearly, further investigations and more specific nutraceutical or pharmaceutical inhibitors are needed. In spite of cytotoxicity issues that remain to be solved, drug development that specifically targets epigenetic mechanisms may open up exciting new avenues for migraine treatment.

5. Conclusion and Future Perspectives

Migraine is a condition with important personal health and social impacts. Both environmental and genetic mechanisms are involved in migraine development. Although few studies have elucidated the roles and mechanisms of action of epigenetics in migraine, the findings discussed in this review provide evidence for the relationship between epigenetics and migraine. Specifically, three main points need to be addressed when studying epigenetics in migraine: tissue specificity and the source of cells in which epigenetic changes occur; timing of events, for example, of histone modifications and DNA methylation; and the migraine phase under study (premonitory, aura, headache attack, postdrome). Current data primarily include epigenetic changes observed under acute migraine conditions, with maintenance of migraine hypersensitivity and chronification requiring further attention.

It is still too soon to conclude that epigenetics studies will lead to identification of novel migraine-specific biomarkers and new therapeutic targets. Currently, the lack of selectivity and unwanted side effects of available epigenetic drugs, in addition to the inability to specifically target neurons and glial cells, makes it difficult to claim that this approach will be useful and readily available for managing migraine patients any time soon. In the meantime, changes in patients' diet, sleep pattern, exercise level, and stress management are more viable options for managing migraine pathology. Moreover, changes in lifestyle are highly important in preventing susceptible individuals from progressing toward chronic migraine and may be helpful in reversing the migraine phenotype.

We know more about genomics than epigenetics and even less about proteomics and metabolomics of migraine [179-181]. Meanwhile, numerous scientific studies assign an increasingly dominant role to external factors (environmental or behavioral) associated with migraine pathophysiology. Therefore, genetic, epigenetic, and "omic" approaches could potentially provide new molecular insight into migraine etiology and should provide tools for improved migraine diagnosis, patient stratification, and therapy. In addition, emerging results detailing brain epigenomes or human methylome profiles in other complex disorders should complement migraine research.

Due to the availability of so many powerful new tools, many new epigenetically based drugs are currently in development and many natural compounds are being tested. Although a combination of demethylating drugs and methyl donors appears promising for the treatment of epimutations, the majority of research on epigenetics has focused on cancer [182]. What is missing is information regarding the differences in efficacy among diverse methyl donors, e.g., SAM, L-

methionine, and betaine, in their effectiveness for treatment of various pathological states as well as their off-target effects. Notably, the discovery of a suitable specific SSAT1 inhibitor should open up a promising research area focusing on inhibition of the polyamine recycling pathway. With this and so many research avenues opening up in the epigenetics field, more effective precision medicines for migraine may be on the horizon.

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