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Review Article

Epigenetics in migraine: A review

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ABSTRACT

Background: Genetic diseases are not only caused by direct mutations in "genes," but also consequences of heritable change other than mutation referred to as epigenetics and the science called epigenomics.
Aim: In the present study, we aimed to review epigenetics, where we covered a quick overview of epigenetics, diseases that are caused by epigenetic modification, epigenetic as risk factors linked with migraine a cause leads to the neurodegenerative condition, and most accepted mechanisms of epigenetics.
Materials and Methods: A structured research article and review of the literature was searched in the electronic databases of Google Scholar, PubMed, Springer, and Elsevier until Nov 2022 using multiple keywords.
Results: Aberrant DNA methylation pattern including hypermethylation in genes such as SLC6A5, SLC2A9, and SLC38A4, *DGKG*, DOCK6, COMT, GIT2, ZNF234, SOCS1. EZH2, a DNMTs enzyme is generally associated with the downregulation of gene expression but in the case of microglial, it is responsible for the upregulation of various genes including TRAF3IP2, BCL2L11, ITGAM, DAB2, NLRP12, WNT3, ADAM10. Increased expression of miRNAs such as miR-34a-5p, miR-29c-5p, miR-382-5p, miR-155, miR-126, Let-7g, hsa-miR-34a-5p, hsa-miR-375.
Discussion & Conclusion: Migraine is not only caused by non-genetic factors/ environmental factors or by brain structural alterations or genetic variations but also by alteration in epigenetics and their interaction too with other elements.

1. Introduction

Genetic diseases are caused by direct mutations in "genes," which are known to be a critical component of the human genome (~1.1%) and are responsible for providing the first comprehensive glimpse of our genetic ancestry.[1] But, the introduction of a new notion i.e., "heritable change in the genome that cannot be explained by mutation " has significantly changed the way things about the subject[2] which is now referred as “epigenetics”**.** The word "epigenetics" has expanded over time to encompass chromatin modification such as methylation, acetylation, phosphorylation, ubiquitylation, and sumoylation,[3] chromatin structure sensitivity (DNase hypersensitivity), and control of gene expression (post-transcriptionally through non-coding regulatory RNA)

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collectively referred as “epigenome”. These epigenetic modifications are retained during numerous cycles and differentiation, allowing cells to have diverse identities while holding the same genetic material. But, improper maintenance or failure of heritable epigenetic marks leads to various disorders such as inflammatory disorder, cancer[4–9] where epigenetics has advanced at a breakneck rate and these alterations have now become one of the disease hallmarks.

In the case of migraine, epigenetics represents a unique step towards determining the causative hidden dots, which will, in turn, help in the process of determining the appropriate treatment for migraine. Migraine is a complex neuro-inflammatory disorder characterized by a "reduced threshold of neuronal hyper-excitability" termed "the migrainous brain" which leads to vascular dysfunction and has a particular periodicity.[10,11] Migraine is known to be the 7^{th} most disabling disorder,[12] with the highest disability-adjusted life years (Figure 1), and repeatedly a migraine attack can harm neurons and may contribute to dementia.[13,14] In India, the disability-adjusted life years (DALYs) per 100,000 is 552.79 (Figure 2) with high prevalence high prevalence.[15–17] It affects 2.7 percent to 10.0 percent of younger children (both sexes are affected equally), but as children get older, the female sex hormone affects more females (12 percent -17 percent) (Estrogen) and males with 4% -7%.[18,19] Migraine has multifactorial involvements including environment, genetic,[10,20] brain structure abnormalities, and their interaction[21] (Figure 3). The various pathological mechanism has been already established[20,22,23] but there are still matters of contention that what is the seed etiology of the condition. Finding a causal agent for complex diseases is a monumental task because it is the consequence of environmental influences, genetic aberrations, and their interactions[24] and thus needs a differential approach.

The inheritable epigenetic marks, which can be assessed as a novel type of risk attribution in addition to genetic differences, have already been the focus of an investigation by a wide variety of research organizations that have just started doing so. As a result, we attempted to analyze and combine all of the previously published studies associated with the topic of "epigenetics in migraine" to provide some ideas that may also be used in migraine research and to motivate additional exploration.

2. Materials and Methods

A structured research article and review of the literature were searched in the electronic databases of Google Scholar, PubMed, Springer, and Elsevier until Nov 2022 using keywords “epigenetics”, “epigenetics and complex disorder”, “epigenetics and cancer”, “inflammatory diseases caused by epigenetics mechanism”, “neurodegenerative disorders”, “epigenomics”, and “epigenetics and neurodegenerative” “methylation pattern and neurodegenerative disorders”. The relevant writers independently verified the data’s validity.

3. Background

Migraine is a polygenic, dysautonomic, complex neurological condition[10] that is classified into two main types such as spontaneous migraine which include MA (Migraine with Aura), and MWA (Migraine without Aura) and secondly the chronic migraine (more than 14 migraine attacks/ month) by International Criteria for Headache Disorder -3^{rd} edition (ICHD-3). Cardinal symptoms include unilateral headache, vomiting, phonophobia, and photophobia in addition to these some patients experience stomach and abdominal pain, dizziness, pale skin color, tiredness, etc. (ICHD-3). Many medicines have been produced but no cures are yet available, since all medicines are symptomatic medicines.[25] Migraine co-morbidity problems include depression, metabolism, and diabetes-mellitus, ischemic strokes, hypertension, asthma, dementia, cardiovascular glaucoma, open-angle glaucoma, chronic renal disorders, sleep disorders, epilepsy.[26,27]

Concerning risk attribution, different factors are found such as environmental influences that include everything that isn’t inherited such as weather conditions: cold, hot, wind, sunlight, diet: caffeine, vegetarian, non-vegetarian, dairy products, alcohol consumption, smoking, insufficient water intake, stress, which further can be physiological (loneliness, social disruption, work environment, and social integration) oxidative stress (imbalance between the generation of reactive oxygen species (ROS) and antioxidant defense systems) which may be responsible for the disruption of various structural proteins,[28,29] so-called non-genetic factors. Other than environmental variables, genetic variations such as missense variation cause changes in protein sequence and other nonsynonymous substitutions (silent mutation)[30] are also responsible for increasing the risk susceptibility**.** Genome-wide association study (GWAS) has revolutionized the theme of genomics in finding the novel disease susceptibility genes associated with migraine[31] from the population which is an advantage over candidate gene association study[32] but have some disadvantage too.[33] The total phenotypic variance “heritability” is 0.374,[34] and using polygenic risk score (PRS), there is about 5.5% of phenotypic variance in families with MA, 3.5% with MO, and 8.2% with FHM.[35]

But other than genetic variations, epigenetics have been expanded over time to encompass chromatin modification such as methylation, acetylation, phosphorylation, ubiquitylation, sumoylation, chromatin structure (DNase hypersensitivity), and control of non-coding regulatory RNA collectively referred to as “epigenome” and any dysregulation have a critical role in the pathogenesis of several complex disorders.[36,37]

3.1. DNA methylation

Methylation is an essential process in gene silencing,[38] and the site is the cis-regulatory sequences comprised mostly of promoters having typical CpG dinucleotide (~70% of gene promoters connected to it) known as the CpG island (CGIs). These CGIs are short (~1000 bp long), dynamic, and preserved spreading DNA sequences with heavily methylated cytosine strongly correlate to the stable shutdown of the corresponding promoter.[39] These methyl groups are added by DNA methyltransferases (*DNMTs*) which are donated by S-adenosylmethionine (SAM).[40] Various approaches, including methylation-specific microarrays and sequencing tools, have been developed during the last decade to examine these methylation patterns, which are referred to as epigenome-wide association studies (EWAS).

Many research groups have explored such methylation patterns in many genes which are important for migraine expressions, such as Labruijere *and group* performed animal experiments (Female Sprague Dawley rats) to investigate whether DNA methylation in rats may be representative of that in humans. They found a high degree of concordance between human and rat DNA methylation, suggesting that it is possible to study effects on DNA methylation in rat tissues that are difficult to obtain from humans, they also found the variation of DNA methylation in the*CRCP, CALCRL, ESR1,* and*NOS3* genes suggests that these genes are prone to changes in DNA methylation.[41]

Wan and group have founded lower methylation levels at different CpG units such as +89, +94, +96 in the RAMP1 gene where they found that decreasing the methylation will significantly increase the migraine thus showing an inverse relationship, they also found +25, +27, +31 CpG island association with migraine having a family history.[42]

Winsvold and group conducted a retrospective case-control study to discover DNA methylation associated with the transformation of episodic migraine to chronic headaches, during an 11-year follow-up period. They found the significant CpG site at the SH2D5 gene, NPTX2 (76 kb downstream), and GRID2 (glutamate receptor d2, an ionotropic glutamate receptor) (brain, blood, and cerebellum). These proteins coding genes have putative roles in synaptic plasticity regulation.[36] They supported the notion of "epigenetics in migraine" by providing pieces of evidence of epigenetics regulation of synaptic plasticity in headache Chronification.[37]

An epigenome-wide association study by Gerring and group[43] has founded novel hypomethylated loci in many genes such as SLC6A5, SLC2A9, and SLC38A4 (pre-synaptic glycine transporter, facilitative glucose transporter, and sodium-dependent neutral amino acid transporter respectively), *DGKG (*Diacylglycerol Kinase Gamma*) (responsible for transforming diacylglycerol/DAG into phosphatidic acid and controls the levels bioactive lipids,*[44]*CFD (*Complement Factor D*)* a serine peptidase catalyzes the cleavage of factor B of complement activation,[45] DOCK6 (Dedicator Of Cytokinesis 6) are components of intracellular signaling networks and act as guanine nucleotide exchange factors.[46]

Terlizzi and colleagues[47] discovered the most significant hypomethylated CpG sites in genes that are known to be associated with migraine such as COMT (catechol-O-methyltransferase), which is responsible for the catalysis of the transfer of a methyl group from S-adenosylmethionine to catecholamines (dopamine, epinephrine, and norepinephrine) and results in catecholamine transmitter degradation (GeneCards), GIT2 (GRK-Interacting Protein 2) interacts with G protein-coupled receptor kinases and has ADP-ribosylation factor (ARF) GTPase-activating protein (GAP) activity,[48] and hypomethylation of CpG site near ZNF234 gene (Zinc Finger Protein 234) a*nucleic acid binding* and *DNA-binding transcription factor activity ,* and SOCS1 (Suppressor Of Cytokine Signaling 1)[49] found in MOH (Figure 4).

Enclosing the section, these studies suggested that DNA methylation is an important epigenetic mechanism in regulating the expression of a gene associated with migraine.

3.2. Covalent histone modification

Histones proteins are positively charged molecules and are sites for post-translational modifications such as histone acetylation and methylation. Acetylation mediates the regulation of genes by the addition of acetyl groups from acetyl-CoA to lysine residues by histone acetyl-transferase (HATs) and the removal of acetyl group by Histone deacetyl-transferase (HDACs).[50] On the other side, histone methylation includes mono-, di-, and tri-methylation by an enzyme called Histone methyl-transferase (HMTs) which uses SAM as a coenzyme to transfer methyl groups to lysine or arginine residues of substrate proteins.[51] Active gene expression is mediated by the modification of histones such as H3K4, H3K36, and H3K791 whereas H3K9, H3K27, and H4K20 are generally associated with gene silencing**.** The EZH2 (enhancer-of-zest homolog 2) subunit within the PRC2 (polycomb repressive complex 2) complex, is an H3K27 methyltransferase responsible for all three states of H3K27 methylation 9.[52]

Histone modification "Epigenetics Regulation of Microglial cells in migraine**",** there is a piece of evidence that activation of the microglial cell is regulated by the epigenetics mechanisms via EZH_2 mediates $H_3K_{27}me_3$.[53] $H_3K_{27}me_3$ is traditionally a repressive mark but was found to be associated with the proliferation of cells, inflammation, and phagosome.[54] CGRP binds to its receptor complex (CGRPR, RAMP1, and RCP)[55] responsible for the activation of microglial activation and inflammation-related gene[56] expression via EZH_2 mediate $H_3K_{27}me_3$. Histone

modification ($H_3K_{27}me_3$) in the regulatory sequences of genes by EZH_2 [52] in the microglial cell is upregulated via PKA/PKC signaling pathway [57,58] (Figure 5). It is believed that under inflammatory circumstances RAMP1 (also under epigenetic regulation) (CGRP receptor subunit) is expressed on the microglial cells which indicate selectivity for CGRP. [54]

Genes that are mostly regulated by this mechanism are TRAF3IP2 and BCL2L11 (apoptotic genes), ITGAM, DAB2, NLRP12, WNT3, ADAM10 (protease) which are related to the proliferation of the cell, production of proinflammatory cytokines, and neurogenic neuroinflammation. Apoptotic genes mentioned above are repressively regulated while WNT3 overexpression stimulated BDNF (Brain-derived neurotrophic factor) responsible for neuropathic pain. [58]

ADAM10 (A Disintegrin and Metalloproteinase Domain 10) a protease possessing both potential adhesion and protease domains and responsible for the cleavage of CX3CR1 (C-X3-C Motif Chemokine Receptor 1) MCP-1 (Monocyte Chemoattractant Protein-1) acts as a ligand for C-C chemokine receptor CCR2 and are expressed in culture microglial cells by EZH_2 mediate $H_3K_{27}me_3$ following CGRP treatment [54,59] and TNF-α (Tumor Necrosis factor-alpha). [60] CX3CR1 a microglial-specific receptor acts as a regulator of the inflammation process and plays a key role in brain microglia by regulating the inflammatory response in the central nervous system (CNS) via p38MAPK/PKC pathway. [61] Microglial-neuronal interactions, which may be linked to chemotaxis, may impact nociceptive signals via the production of pro-inflammatory cytokines and neurotrophins. [62]

Environmental factor also influences the epigenetic mechanism including stress, [37] dietary factor (Vit B6, Vit B12, and Folate), and alcohol[50] substantial results in DNA hypomethylation as a result of the significant reduction in tissue SAM. Enzymes in gene regulation including kinases, acetyltransferases, and methyltransferases consume key metabolites such as SAM for methylation, ATP for phosphorylation, and acetyl-CoA, NAD^+, NADH, and acetyl-ADP-ribose for acetylation. [63]

3.3. miRNAs

Post-transcription gene regulation is mediated by the non-coding RNA called micro-RNA (miRNAs) featured as small non-coding RNA (up to 22 nucleotides and are encoded by the miRNA gene located in the different parts of the genome. [64] MiRNAs regulate around 30% of protein-coding genes and up or down-regulation of these could be the causative one of diseases. [65]

During the last few years, various researchers have explored different miRNAs that are responsible for causing migraine. Tafuri and group conducted a pilot study where they used quantitative real-time polymerase chain reaction to validate circulating microRNA expression profiling of miR-22, miR-26a, miR-26b, miR-27b, miR-29b, let-7b, miR-181a, miR-221, miR-30b, and miR-30e. They found significantly higher expression of miR-27b and down-regulated miR-181a, let-7b, and miR-22, and levels of miR-26a, miR-29b, miR-30b, miR-30e did not reach statistical significance. [66]

The serum microRNA profiles of migraineurs in attacks and pain-free periods using the microRNA (miRNA) arrays are evaluated by Andersen and group with two cohorts, 24 migraines with age- and gender healthy controlled and found miR-34a-5p showing a 9-fold increase in expression whereas miR-29c-5p and miR-382-5p showed modest 4.2 or 4.1 increases, respective. respectively (). Upregulated miR-382-5p was also a biomarker for migraine compared with the healthy control group for migraine in pain-free periods. [67]

A pilot study with an exploratory study design adopted by Cheng and group to detect the circulating levels of miRNAs, such as miR-155, miR-126, miR-21, and Let-7g in migraine patients and found the significantly elevated miR-155, miR-126, and Let-7g in the sufferer. The results of this study include endothelial-specific miRNA levels in the blood are greater and they also consider migraine patients to be connected with syncope comorbidity. [68]

Gallelli and group conducted pilot research in which they extracted RNA from saliva and serum for expression analysis of hsa-miR-34a-5p and hsa-miR-375 using the quantitative real-time polymerase chain reaction (qRT-PCR). They discovered a significant rise in hsa-miR-34a-5p and hsa-miR-375 in aura-untreated patients as compared to control participants and aura-treated patients. They also used the Insilco tool to determine the target gene and discovered 88 and 39 anticipated target genes for hsa-miR-34a-5p and hsa-miR-375, respectively, out of which only those genes are selected which were associated with pain-migraine. At last, they concluded that hsa-miR-34a-5p and hsa-miR-375 are useful biomarkers of disease and treatment efficacy in aura patients (Figure 4). [69] Interestingly, it has been shown by Brás and group that, miR-342-driven NF-kB/p65 activation by TNF-α leads to increased secretion of TNF-α and IL-1β in an autocrine manner by promoting degradation of BAG-1 as a negative regulator of pro-inflammatory NF-kB (inducer of TNF-α) in microglia. [70] The production of pro-inflammatory cytokines and neurotrophins may influence nociceptive signals via microglial-neuronal interactions, which may be attributed to chemotaxis.

4. Discussion

Finding a causal agent for complex diseases is a monumental task because of the consequence of environmental influences, genetic aberrations, and their interactions and thus needs a different approach.[24]

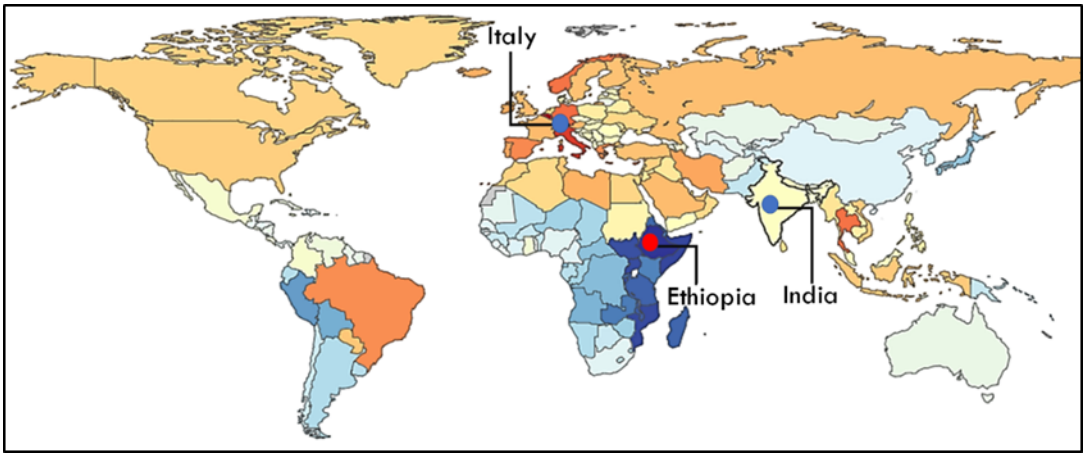

Fig. 1: Global Disability-Adjusted life Years (DALYs)rate per 100,000: Global Disability-Adjustedlife Years (DALYs) rate per 100,000 for both sexes and all age group:Italy with highest DALYs rate (775.25 per 100,000), lowest in Ethiopia (266 per100,000), and in India (552.79 per 100,000)(https://vizhub.healthdata.org/gbd-compare/).

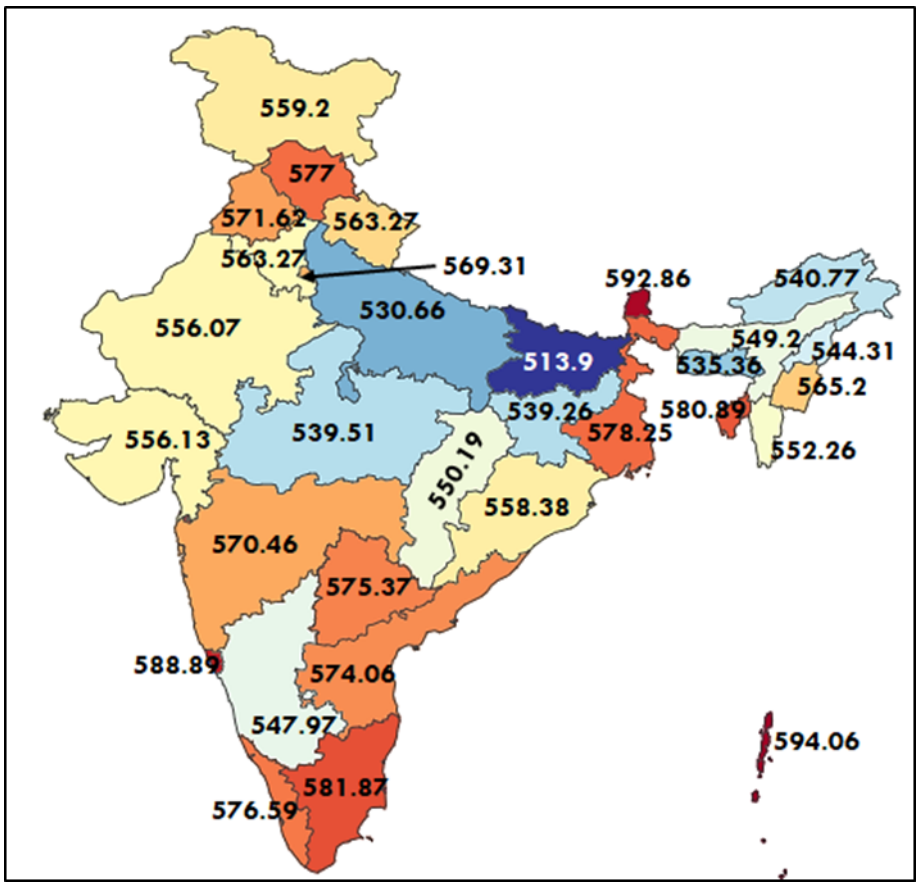

Fig. 2: India Disability-Adjusted life Years (DALYs) rate per 100,000: India Disability-Adjusted life Years (DALYs)rate per 100,000 for both sexes and all age group: Andaman-Nicobar with highestDALYs rate (594.06 per 100,000), lowest in Bihar (513 per 100,000), and in ourUT Jammu and Kashmir (559.2 per 100,000)(https://vizhub.healthdata.org/gbd-compare/).

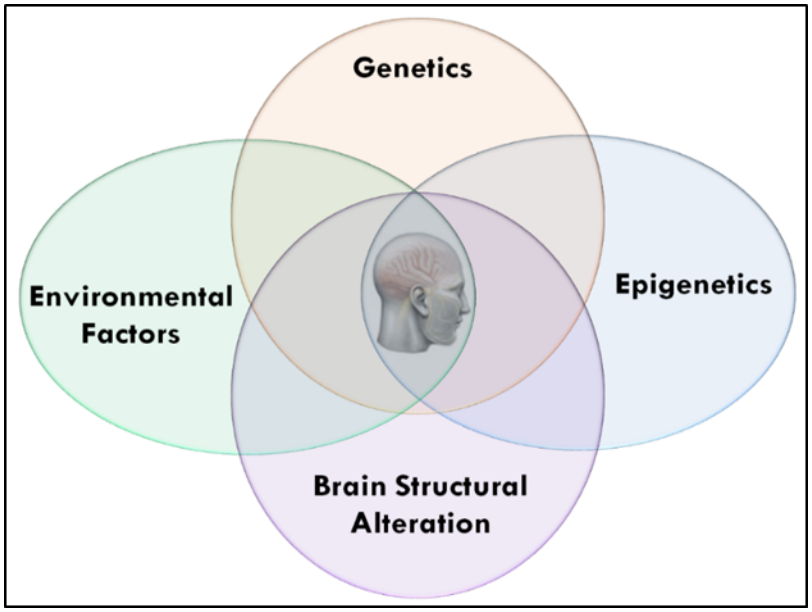

Fig. 3: Venn diagram representation: Interaction betweendifferent factors including genetics, epigenetics, environmental factors, andbrain structural abnormalities

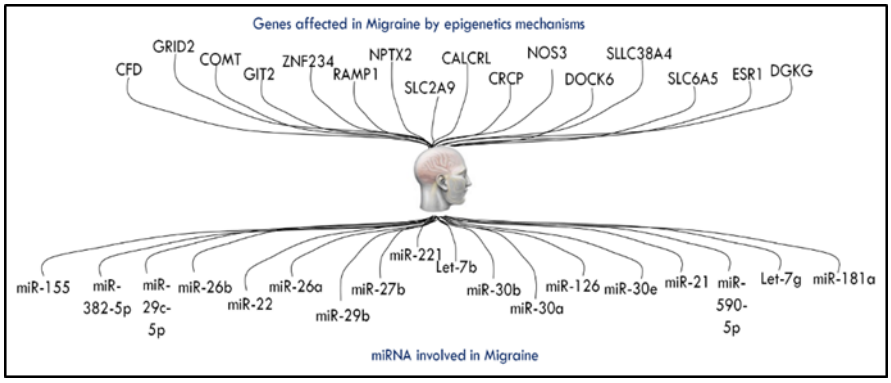

Fig. 4: Epigeneticsin migraine: Upward reflect many genes that have been linked to epigeneticregulation (DNA methylation) in migraine. MiRNAs known to be linked withmigraine are represented below.

Migraine is a complex condition and has multifactorial involvements and other than non-genetic and genetic variation, the notion of "epigenetic as a novel risk for migraine pathogenesis" has been growing exponentially.[71] Epigenetics has encompassed chromatin's wide array of gene regulation modifications such as methylation, acetylation, phosphorylation, ubiquitylation, and sumoylation chromatin structure sensitivity (DNase hypersensitivity), and control of gene expression (post-transcriptionally through non-coding regulatory RNA).[3] The interaction of multiple elements including genetics, epigenetics, environmental factors, and abnormalities enhances the condition's vulnerability and consequently raises the disease's chance.

Epigenetics is a broad topic that goes beyond the scope of this study but we tried to establish the relationship between migraine and epigenetics and thus provide some ideas that may help in migraine research and serve as motivation for future research. Different genes have been discovered for the last decades which are under epigenetics regulation specifically by DNA methylation and also by miRNA. Aberrant DNA methylation pattern including hypermethylation and hypomethylation leads to a change in the expression of the genes (upregulation, and downregulation respectively). SLC6A5, SLC2A9, and SLC38A4, *DGKG*, DOCK6, COMT, GIT2, ZNF234, SOCS1 are some examples with their hypomethylated CpG island. EZH2, a DNMTs enzyme is generally associated with the downregulation of gene expression but in the case of microglial, it is responsible for the upregulation of various genes including TRAF3IP2, BCL2L11, ITGAM, DAB2, NLRP12, WNT3, ADAM10.[54]

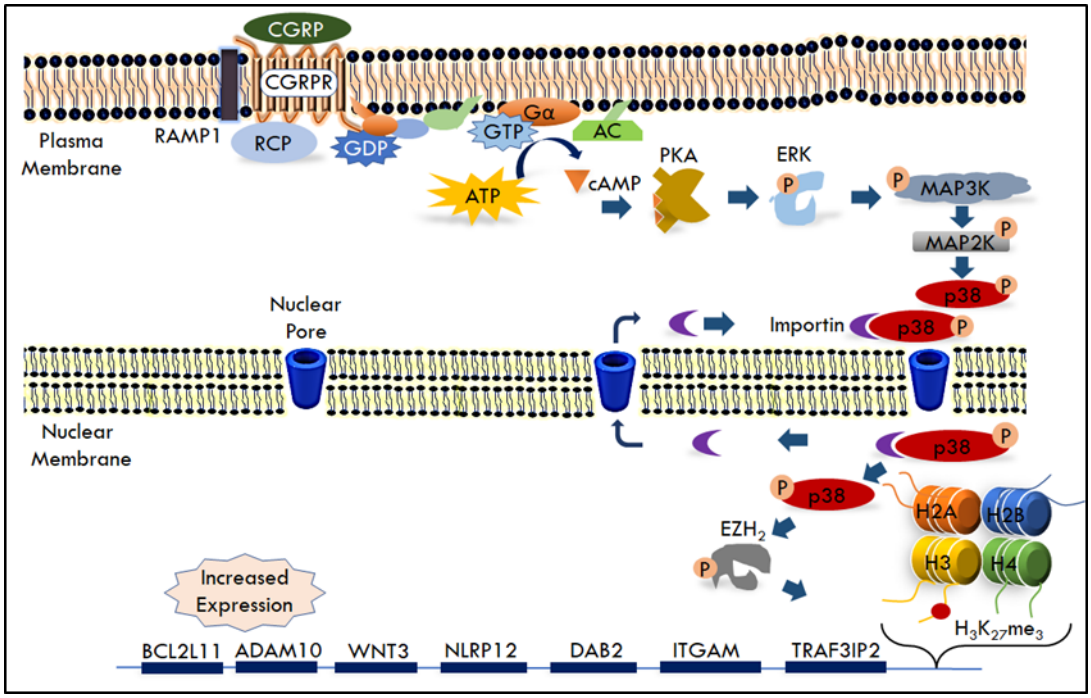

Fig. 5: Activation of EZH_2 "Histonemethyltransferase (HMT)" in microglial cells through p38 kinase: Calcitonin gene related peptide(CGRP), a potent neuropeptide binds to CGRP-receptor (CGRPR) "a GPCR" with thehelp of RAMP1 and RCP (CGRPR associated protein) and cause its activation. Uponactivation of CGRPR, trimeric G-protein (GTPase) is activated ($G\alpha_s$) anddissociates from its trimeric structure which cause activation of effectorprotein AC (adenylate cyclase) which is responsible for the forming ofcyclic-AMP (cAMP) from ATP. cAMP act as regulatory protein to regulate thefunction of PKA (protein kinase-A:*Ser/Thr protein kinase family*)by binding to the PKA regulatory subunit. PKA phosphorylate downstreamsignaling protein "ERK" which further phosphorylate MAP_3K (MitogenActivated Protein 3 Kinase) which further activate MAP_2K (Mitogen ActivatedProtein 2 Kinase). MAP_2K is responsible for the activation of p38 byphosphorylation. p38 highly versatile protein kinase which is imported into thenucleus with the help of IMPORTIN protein and where p38 phosphorylate EZH_2(Histone-Methyl-Transferase). EZH2-HMT add methyl group (recruitedfrom s-adenosyl-methionine: SAM) to $H_3K27me3$. Methylated H_3K27increases the expression of different gene which is important for cellproliferation, regulation of inflammatory responses and Chronification.

Another element of gene regulation is, a small (~22 nucleotide) non-coding RNA called miRNAs are associated with different diseases[65] and also with migraine. MicroRNA expression profiling by different research group has found increased expression of different miRNAs including miR-27b, miR-34a-5p, miR-29c-5p, miR-382-5p, miR-155, miR-126, Let-7g, hsa-miR-34a-5p, hsa-miR-375. Discovering the varied expression of miRNAs that causes functional gains and losses, leading to distinct diseases including neurodegenerative disorders[72] and has now become a useful tool in diagnosis, prognosis, and therapy. Emerging improvements in pharmaco-epigenomics are given through a precision medicine approach has recently given new hope for their use in therapy. MiRNA pharmaco-epigenomics may provide new insights into individual drug heterogeneity and response that might lead to more effective treatments. Recently, much attention was paid to the therapeutic potential of miRNAs (miRNA medicinal products) in cancer.[73] MiRNAs have been postulated as potential migraine biomarkers which are easily accessible from the saliva,[69] and based on current evidence these play a role in migraine pathogenesis via solely or may be due to complex interaction (epigenetics and environment). Information has however just begun and new studies are needed for knowledge in the field of the therapeutic role of miRNAs, the drug ability of miRNAs; and the modulation effects of current abortive and preventative drugs on miRNAs in migraine.[74]

It should be noted that epigenetics has greatly influenced by environmental factors including stress[37,75] which can be psychological[76] or maybe oxidative, and also including lifestyle factors[77] alcohol,[50] dietary factor (Vit B6, Vit B12, and Folate),[78] tobacco smoke alters DNA methylation (reversible change),[79] obesity,[80] environmental toxins, physical activity, green tea components.[78] Enzymes in gene regulation including kinases, acetyltransferases, and methyltransferases consume key metabolites such as SAM for methylation, ATP for phosphorylation, and acetyl-CoA, NAD^+, NADH, and acetyl-ADP-ribose for acetylation.[63]

To this end epigenetics play a vital role in the pathogenesis of migraine and also uplifts the transition of migraine from episodic to chronic and more research is however needed into the effectiveness of miRNAs as therapeutic goals.

4.1. Future perspective

Pharmacological treatment aims to swiftly restore function while reducing the risk of resurgence and minimizing the adverse effects. Migraine treatment is complicated, involving acute and preventive measures as well as several therapeutic approaches. There are two types of migraine treatment modalities i.e., migraine-specific and migraine nonspecific medications. Different medicines have been produced but no cures are yet available, since all medicines are symptomatic medicines.[25]

Because of recent scientific discoveries and an understanding of the relevance of epigenetics in many human illnesses, epigenetics research has a promising future. Advance in high-throughput sequencing methods and advanced algorithms is used to analyze the massive amounts of data provided by sequenced epigenomes. The epigenomic data will allow researchers to uncover novel epigenetic marks and their roles in various tissues, developmental stages, and disease states. The role of epigenetics in migraine opens a new door for curing the disease. Overall, researchers believe that epigenetics may provide novel and unique insights into a more comprehensive interpretation of migraine symptoms, therefore enhancing migraine nosology, treatment, and prevention. Shortly, epigenetic processes will undoubtedly aid the creation of improved therapeutic routes and medicines.

This review is limited since there haven't been a lot of studies done on epigenetics in migraine compared to other diseases like cancer and inflammatory disorders. However, epigenetics, with its novel, inspiring, and significant contribution to the development of diseases, opens the door for future investigations, which are required to determine the extent of the condition's cause. Information on miRNA pharmaco-epigenomics has however just begun and new studies are needed for knowledge in the field of the therapeutic role of miRNAs, the drug ability of miRNAs; and the modulation effects of current abortive and preventative drugs on miRNAs in migraine. These briefly covered ideas here to provide some ideas that may also be utilized in migraine research and to serve as motivation for future research.

5. Conclusion

Migraine is not only caused by non-genetic factors/ environmental factors or by brain structural alterations or by genetic variations but also by alteration in epigenetics and their interaction too with other elements.

6. Author Contributions

Detail of the author's contribution, according to the CRediT (Contributor Roles Taxonomy) System: Parvinder Kumar & Amrit Sudershan conceptualized the study Amrit Sudershan, Shikha Bharti, Javaid Hassan Sheikh, Showkat Ahmad Wani downloaded and filtered the literature, Amrit Sudershan, Parvinder Kumar & Javaid Hassan Sheikh drafted the manuscript, Amrit Sudershan, Parvinder Kumar, & Showkat Ahmad Wani edited the pictures and tables, Hardeep Kumar & Parvinder Kumar edited the manuscript & finalize the manuscript. All authors provided critical feedback on drafts and approved the final manuscript.

7. Conflicts of Interest

The authors declare that they have no conflict of interest.

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