Review Article

Migraine is a Multifaceted Condition That is More Than Just a Headache: A Review

Amrit Sudershan[1,2], Meenakshi Bhagat[3], Shikha Bharti[4], Sheetal Bhagat[5], Pallavi Sachdeva[6], Hardeep Kumar[7], and Parvinder Kumar[1,3]*

[1]*Institute of Human Genetics, University of Jammu, India*
[2]*Department of Human Genetics, Cluster University Srinagar, India*
[3]*Department of Zoology, University of Jammu, India*
[4]*Department of Zoology, Lovely Professional University, India*
[5]*Department of Psychology, University of Jammu, India*
[6]*Department of Lifelong Learning, University of Jammu, India*
[7]*Department of Neurology, Super Specialty Hospital, India*

Abstract

Background: Migraine is a complex and common neuro-vascular disorder with a distinctive periodicity and is described by a reduced level of neuronal hyper-excitability. It is imperative to comprehend the complexity of the disorder from the standpoint of pathological mechanisms, genetic variable associations that contribute to disease severity, and a debatable phenotype i.e., inflammation which might contribute to the chronification of the condition, migraine as a channelopathy, and constellations network of co-morbidities.

Aim: In the present review, we aim to better understand the complexity of migraine by consolidating the provided data.

Material & method: Online repositories including PubMed, Web of Science, and Google Scholar were used for the literature survey and relevant articles were utilized to comprehend the complexity of migraines for better understanding.

Result: Migraine is a complex neurological disorder featuring a heap of candidate gene alterations that predispose by altering the function of channels in the brain, hindering the process of inflammatory homeostasis, microglial activation, and complex interaction with different diseases.

Conclusion: In conclusion, featured with a wide abnormal pattern of phenotype enlightened the complicated nature of migraine, and it can't be said that migraine is not just a headache but more than it.

INTRODUCTION

Chronic pain has a negative impact on one's quality of life but it is undeniable that pain perception (acute pain) is important as it is the "survival mechanism". Therefore, defined as an adaptive response that helps to protect the body from injury and stimulates the repair system of the injured tissues [1]. But the pain (chronic pain) at any time is still a serious medical challenge, affecting approximately 30% of the population [2,3]. One such example is migraine, which is defined as a complex, polygenic/ multifactorial, dysautonomic, common, and chronic neurovascular disorder featuring unilateral head pain [4]. It is responsible for high disability-adjusted life years (DALYs), an overall high prevalence (15.75%) (Healthdata.org) with varied prevalence rates between sexes i.e., the female occurrence is more (12-17%) than male prevalence [5,6]. Migraine patients have significantly higher visits to healthcare providers, and

diagnose the condition according to the ICHD-3 are unilateral headache, vomiting, phono-phobia, photophobia, and some patient also experiences stomach and abdominal pain, dizziness, pale skin color, and tiredness. For decades, various physiological and pathological pathways have been established, including Cortical Spreading Depression (CSD), the trigeminovascular system, inflammation, and brain structural alteration[13-16], but the precise underlying processes responsible for the different characteristics of the condition, such as reduced neural threshold and chronification, remains elusive.

Finding the cause of this complex condition is a tremendous challenge as it's the result of various influences, such as genetic defects, epigenetics, environmental factors, and their interactions. The motivation for writing this review primarily stems from its complexity, and integrating the various risk attributes that have been identified over the last few decades into a single draft

will probably benefit in a better understanding of this complex disorder. Also, the fact that cannot be neglected is that migraine is a significant cause of disability but many continue to neglect it and seek medical attention only when they have a severe attack or a chronic progression. This lack of understanding among individuals is also a matter of concern.

Therefore, in this culminating convection, we tried to grasp the various aspects of this neurological condition and tried to provide the information to the reader who says that "migraine is just a headache" and not to be worried about.

MATERIAL AND METHOD

A structured survey of research articles and review of the literature was done in the electronic databases of Google Scholar, PubMed, Springer, and Elsevier of the last two decades using the keywords "migraine as a neurological disorder, migraine, and inflammation, role of immune cells in migraine, pro-inflammatory molecules activation, migraine, and neuro-inflammation, a risk factor associated with migraine, migraine as a disease of the channel, migraine, and channelopathy, channels abruption in migraine, epigenetic, and migraine, epigenomic association and migraine, genetic polymorphism and migraine, genetic architecture, and migraine. Only articles published in the English language were evaluated using the linguistic filters as a factor for publication selection primary and secondary research sources included scientific work, meta-analysis, systematic reviews, and peer reviews. The study excluded data that was unpublished, incomplete, or only partially available, as well as publications in several languages. Because partial and missing data are not included in the study, there is no such detrimental effect and we did our utmost to eliminate any undesirable characteristics. This narration includes a significant quantity of current material. The relevant writers independently verified the data's validity.

Background

Because of migraine's complicated nature, researchers still try to figure out the various aspects of the disease, including lower neuronal threshold, chronic progression, genetic susceptibility/ genetic predisposition, and phenotypic variability. For decades, various physiological and pathological pathways, such as cortical spreading depression, the trigeminovascular system, inflammation, and brain structural changes, have been established, but the fundamental underlying cause of the complexity has remained unknown. Discussing the various aspects of the disease here in this piece of the review may aid in gaining a thorough understanding of the complexity of the disorder.

Genetics of migraine

It is well known and recognized that a phenotype is encoded by the genes and alteration in the same leads to the abrupt phenotype i.e., disorder and migraine is an astonishing example of polygenic inheritance i.e., caused due to a plethora of changes in many genes (www.genecards.org/).In human disease genes,

there is a wide range of allelic variations, and one such prevalent type of variation is single nucleotide polymorphism (SNP), a fascinating genomic "marker" that acts as a causative variation by altering the susceptibility [17]. Numerous candidate gene association studies (CGAS) have been performed for migraine which aimed to find risk variations associated with the disease [147,148,150]. This inexpensive, quick-to-conduct approach i.e., a candidate gene association study has provided numerous candidate variants [Table 1]. Using the String-Cytoscape tool (String-Database.Org) interaction between the different candidate genes has revealed that the BDNF and TNF-α protein shows the highest interaction with the highest node degree i.e., 14 undirected edges. (Figure 1).

On the other side of the basic candidate gene association approach, a statistical high throughput association study i.e., Genome-Wide Association Studies (GWAS) is now the most frequent method for discovering highly significant common variations, and in migraine, various GWAS have been conducted from last few years[18,19]. Conducting GWAS for migraine, enlightened various aspects including the polygenic risk score (PRS), heritability, genetic predisposition, phenotypic variability, etc. Hautakangas and colleagues conducted a large meta-GWAS with a sample size of 102,084 cases and 771,257 controls, identifying 123 migraine risk loci, 86 of which are novel compared to the previous migraine meta-analysis, which yielded 38 loci [19].

The findings of the GWAS significantly improved migraine genetic data and revealed that migraine susceptibility is conferred by a combination of many genetic variations with
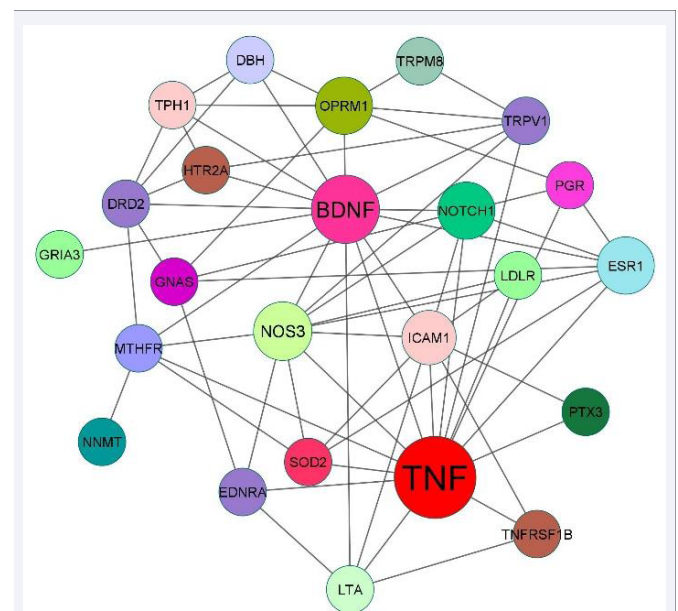
Figure 1 Candidate gene-gene interaction: Using string database, the interaction between candidate gene product was created. This complex protein-protein interaction revels that the BDNF and TNF-α shows the highest node degree of about 14 undirected edges. This intricate network revealed the disease's complexity as well as the strong genetic component in determining susceptibility.

Table 1: Candidate genes significantly associated with migraine from different demography

Gene	Function	rs' ID/Loci	Study	Case	Control	Pop./Ethnic
ETA	Vasoconstrictor	-231 A/G	Cohort	1048	140	France
5-HT2A	Serotonin transporter	T102C	CC	61	44	Turkey
LDLR	Receptor-mediated endocytosis	G142A	CC	140	200	Italy
eNOS	Vascular smooth muscle relaxation	Glu298Asp	CC	56	125	Italy
TPH	Catalyzes the biosynthesis of serotonin	A218C	CC	55	62	Turkey
GNAS1	inhibit the adenylyl cyclase-stimulating activity of guanine nucleotide-binding protein G(s)	T393C	CC	365	347	Spain
MTHFR	Folate biosynthetic pathway	677C>T	MA	6446	24578	n. CP
Notch	Development of cell	rs1043994	CC	258	247	Australian
HRH3	Histamine signaling	A280V	CC	147	186	Mexico
OPRM1	Receptor for endogenous opioids	A118G	Cohort	153	-	Australia
TNFRSF1B	TNF-α Receptor	rs5745946	CC	416	415	China
PRNP	Neuronal development and synaptic plasticity	V129M	CC	384	185	Italy
GRIA3	Glu. Receptor excitatory synaptic transmission	rs3761555	CC	472	472	CP
ICAM1	Cell proliferation, differentiation, motility	rs5498	CC	114	125	AP
TNF-β	Inflammatory and antiviral responses,	252 A>G	MA	5557	20543	Asian
uPAR	Receptor for urokinase plasminogen activator	rs344781	CC	103	100	Iran
ESR1	ER- ligand-activated transcription factor	594G>A	MA	2293	2026	CP
ESR1	ER- ligand-activated transcription factor	325C>G	MA	2027	1919	CP
ESR1	ER- ligand-activated transcription factor	XbaI	CC	102	115	Indian
PGR	TF activity & signaling receptor binding.	rs1042838	CC	380	185	Italy
SOD2	Protein binds to the superoxide byproducts	rs4880	Cohort	490	246	Italy
PTX3	Fibrocyte differentiation & Inflammation	rs3816527	CC	103	148	Iran
TNF-α	Proinflammatory reaction	rs1800629	MA			nCP
NNMT	Regulating cellular methylation potential	rs694539	CC	433	229	Turkey
DBH	Expressed in neurosecretory vesicles	+1603C>T	CC	200	267	Turkish
BDNF	Catalyzes the conversion of dopamine to NE	rs6265	MA	1598	1585	CP
BDNF	Differentiation of neuronal cells and growth	rs2049046	MA	1598	1585	CP
GABA	Inhibitory neurotransmitter IN CNS	rs1186902	CC	197	298	CP
eNOS	Vascular smooth muscle relaxation	-786T>C	MA			CP
GABA	Inhibitory neurotransmitter IN CNS	rs3810651	CC	197	394	Spain
DRD2	A GPCR that inhibits adenylyl cyclase activity	rs1800497	CC	250	250	China
TRPM8	Receptor-activated non-selective cation channel	rs10166942	Cohort	1904		Taiwan
5-HTR6	Regulate cholinergic neuronal transmission	rs770963777	CC	92	100	AP
TRPV1	Convey inf. about noxious stimuli to CNS	rs8065080	CC	46	50	Russian

CC: Case- control, **MA**: Meta-analysis, **CP**: Caucasian Population, **n. CP**: non-Caucasian Population, **AP**: Asian population, **ETA**: Endothelin type A, **5-HT2A**: 5-Hydroxytryptamine (Serotonin) Receptor 2A, **LDLR**: Low-Density Lipoprotein Receptor, **eNOS**: Nitric Oxide Synthase 3 (Endothelial Cell), **TPH**: Tryptophan Hydroxylase 1 , **GNAS1**: Guanine Nucleotide Binding Protein (G Protein), Alpha Stimulating, **MTHFR**: Methylenetetrahydrofolate Reductase, **Notch**: Neurogenic Locus Notch Homolog Protein 1, **HRH3**: Histamine H3 Receptor, **OPRM1**: Opioid Receptor Mu 1, **TNFRSF1B**: TNF Receptor Superfamily Member 1B, **PRNP**: Prion Protein · **GRIA3**: Glutamate Ionotropic Receptor AMPA Type Subunit 3, **ICAM1**: Intercellular Adhesion Molecule 1 , **TNF-β**: Tumor Necrosis Factor , **uPAR**: urokinase plasminogen activator surface receptor, **ESR1**: Estrogen Receptor 1, **PGR**: Progesterone Receptor , **SOD2**: Superoxide Dismutase 2 , **PTX3**: Pentraxin 3, **NNMT**: Nicotinamide N-Methyltransferase, **DBH**: Dopamine Beta-Hydroxylase, **BDNF**: Brain-Derived Neurotrophic Factor, **GABA**: gamma-aminobutyric acid, **DRD2**: Dopamine Receptor D2, **TRPM8**: Transient Receptor Potential Cation Channel Subfamily M, **5-HTR6**: 5-Hydroxytryptamine Receptor 6 , **TRPV1**: Transient Receptor Potential Cation Channel Subfamily V.

small effect sizes, as well as environmental factors. However, it is unavoidable that highly significant GWAS-SNPs with low penetrance do not aid in the identification or classification of a common and complex disorder; rather, they provide information about a specific observable intermediate trait [20]. Another astonishing feature related to genetics is the PRS, which has been enlightened by the large study including 1,589 families from Finland and the calculation of PRS for all 8,319 family members and 14, 470 individuals from the FINRISK population cohort. They found a significantly higher common variant burden in familial cases and also found a significant polygenic burden for different features of migraine [21].

Now the second issue is "What is the heritability of the condition?" which provides a glimpse of the relative significance of genes and environment to the variance of characteristics within and across populations [22]. Heritability appears to be due to a large number of weak associations with many genetic variants, rather than a few common risk variants [23]. Noble-Topham and colleagues provided the evidence that the "MA population" is heterogeneous i.e., arises due to the interaction of genetic and environmental factors with a crude recurrence risk to siblings of probands were 2.7-fold higher in three-generation compared with two-generation MA families and 4.8-fold higher compared with one generation MA families [24]. These results showed the numerous features of migraine-related hypotheses such as the first-degree relatives of individuals with MA show a considerably higher risk.

Enclosing the section, migraine susceptibility is influenced

by several common variations, implying that genetics plays a substantial role in defining susceptibility and making a person vulnerable to migraine. But still, there is a diverse important issue that is still unanswered such as "how likely is it that a person who has been diagnosed with the condition would have had possible variations found in the last 20 years"? Another question that remains unresolved after the larger meta-analysis is "how much genetic variation exists between MWA and MA?" [18,19]. Aside from sequence variations, there is also evidence that epigenetic factors may play a major role in determining migraine susceptibility and development thus increasing the complexity of the risk of the disorder [25].

Epigenetic and migraine

The introduction of a new notion of "heritable change in the genome that cannot be explained by mutation" has significantly changed the way things are about the subject [26] and is now referred to as "epigenetic". The word "epigenetic" has expanded over time [27], and has made a significant achievement over the last two decades in understanding different genetic disorders. Epigenetics plays a pivotal role in a wide range of diseases including neurodegenerative disorder [28], and has advanced at a breakneck rate. Epigenetics in migraine is an emerging field and various research groups have started exploring epigenetics in migraine [29].

Histone modification which is the addition of acetyl groups from acetyl-CoA to lysine residues of histone-by-histone acetyl-transferase (HATs) [30] and removal of acetyl group by Histone acetyltransferase (HDACs) [31] is another exciting phenomenon which found to be signification associated with migraine. Different research groups [32-36] found that abrupt DNA methylation of the different genes and found significantly associated with migraine.

Another element of gene regulation is a small (~22 nucleotide) non-coding RNA called miRNAs that are associated with migraine [37]. Shreds of evidence from the serum miRNAs level studies, where it was found the level of miRNAs level in the serum of migraineurs during attacks and pain-free periods have altered values. Notably, the miR-34a-5p shows a 9-fold increase in expression [38], along with the elevated level of miR-155, miR-126, and Let-7g [39], hsa-miR-34a-5p and hsa-miR-375 in aura untreated patients as compared to control participants and aura treated patients [40]. Whereas miR-29c-5p and miR-382-5p showed modest 4.2 or 4.1 increases, respectively [38]. In order to establish a connection between inflammation and epigenetics, it has been evidenced that the proinflammatory cytokine *TNF-α* (Tumor Necrosis Factor-alpha) activates the miR-342, which is well known for its crucial role as an activator of NF-kB/p65 factor by destroying BAG-1, a negative regulator of NF-kB [41]. Recent meta-analyses of *TNF-α* have also shown a significant increase in the risk of migraine [42].

Discovering the association between miRNAs and migraine opens the doors for a new treatment strategy and this could be a game-changer in migraine miRNA pharmaco-epigenomics.

The 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 [43], and neurodegenerative disorders [44]. 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 [45].

Migraine as an inflammatory disease

Inflammation is a defensive mechanism with molecular and cellular activities responsible for limiting immediate harm to the system. This ensures the restoration of tissue homeostasis and the resolution of acute infection [46]. Uncontrolled inflammation on the other hand can develop chronic reactions leading to a range of chronic inflammatory disorders [47]. Neurogenic neuroinflammation migraine is characterized by inflammatory reactions in the trigeminovascular system's central and peripheral components in response to abnormal neuronal hyperactivity or hyperexcitability [48]. Microglia cells (the immune member of the CNS immune system family) continuously check for infection and physiological changes in their environment thus helping in the maintenance of CNS homeostasis [49]. Activation of microglial has been investigated in migraine for decades [50,52]. Excessive and persistent microglial activation may be the trigger for the progression and transition of the migraine. The key ligand required for the activation of the microglial cell is CGRP (calcitonin gene-related peptide), which is released by the CSD from the trigeminal neurons. The increased CGRP levels rise during a migraine attack, most likely responsible for the release of inflammatory cytokines importantly TNF-α which is released in or near trigeminal ganglion neuronal cell bodies and may act as a neuronal signal enhancer, resulting in sensitization [48].

Activation of microglial is an important variable for the migraine progression, transition, and linking of the various candidate signaling pathways molecules which are reviewed in detail [51]. The likelihood that migraine will be classified as a neurogenic neuroinflammation condition is increased by the fact that these molecules are essential for the activation of microglial cells. This is further supported by the GWAS study, which identified several inflammatory genes, including TSPAN2, MEF2D, NLRP1, JAM3, and NOTCH4 [21].

Migraine as a channelopathies

Migraine is described as an episodic condition of abnormal brain excitability [53] and despite recent progress in migraine research, the pathogenic mechanism of migraine is related to the lower neuronal hyperexcitability, which remains a controversial subject among scientists. It is still under-recognized and inadequately treated and this is only due to the complexity that is involved in migraine pathogenesis, chronification, etc. It is well understood that ion channels are essential for the generation, representation, and modulation of the brain's response to external

SciMedCentral

stimuli and that when these channels work or behave abnormally, the risk of an abrupt phenotype increases. One such example is "abnormal brain excitability" which has been widely linked to the abnormal behavior of brain channels. The malfunctioning of channels leads to chronic neurological conditions and is broadly categorized under channelopathies.

Therefore, channelopathies are defined as the reason for the diverse category of neurological conditions caused by ion channel malfunction in biological membranes and organelles. Defects in many ion channels or transporters can frequently underlay a single neurological presentation. Various neurological conditions are already categorized under the class channelopathy [54-57], and there has also been an attempt to categorize migraine under channelopathy. Over the past two decades, various channels and their mutations have been recognized by different research groups and linked with migraine pathology [Table 2]. This channel dysregulation leads to episodic disturbances of the excitation–inhibition balance and cortical network hyperactivity in response to particular migraine triggers serving as the ground for CSD ignition susceptibility [53]. Decreased neuronal hyperexcitability is a major consequence of abnormal behavior and cross-talk of mutated channels and opens the gate and provides a solid base for migraine is not just a headache but a complex channelopathy [58]. Several disorders are associated with migraine, and the mechanism that connects them is the abrupt channels [59-62]. Enclosing the paragraph, ion channel mutations can damage the entire nervous system if they are inherited [62] and these channelopathies are one of the diverse categories of neurological conditions and migraine i.e., "lower neuronal hyperexcitability disorder" fall under channelopathies.

Migraine Co-morbidity

Another major issue to consider is co-morbidity, which is defined as the presence of two or more chronic conditions at the same time [63]. More than one-third of patients with migraines observed by primary care doctors found four or more chronic health conditions associated with migraine (Co-morbidity) (Morbinet). There are several causes for such disease comorbidity with migraine, some of which include having similar pathophysiological mechanisms [64], common risk factors including common genetic variants, and common environmental risk factors.

The most widely used and validated recipe notably, a "literature survey" was first used to search for "migraine's comorbidity", which revealed that migraine is comorbid with various common and detrimental conditions which include temporomandibular disorders (TMD) [65], mood and anxiety disorders [66,67], restless legs syndrome (RLS) [68], alexithymia and post-traumatic stress disorder [69], depression [70], ischemic strokes [71], hypertension [72], asthma [73], dementia [74,75], cardiovascular disorders [76], sleep disorders [77], PFO (Patent Foramen Ovule) [78], gastroesophageal reflux, tooth wear, systemic inflammation of Behçet's disease (BD) [79], irritable bowel syndrome [153], Chronic Fatigue Syndrome (CFS) where that mechanisms of migraine pathogenesis such as central sensitization may contribute to CFS pathophysiology [80]. It has been also shown that sleep fragmentation and oxygen desaturation may worsen migraine but migraine may help in reducing apneas by a more superficial sleep [152]. Patients with Sydenham's chorea (SC), rheumatic fever (RF), and other basal

Table 2: List of Genes that are activate during migraine in microglial cells

| Gene	Protein	Ligand/ Activator	Function	Brain Expression	Activators
CGRPR	Calcitonin receptor like receptor	CGRP	The calcitonin-gene-related peptide (CGRP) receptor works with RAMP1 and the adrenomedullin receptor works with RAMP3 (By similarity). Together with RAMP2, this receptor binds to adrenomedullin CGRP. This receptor's action is mediated by G proteins that activate adenylyl cyclase.	Hypothalamus, Spinal Cord & White Matter	P38 phosphorylation & NF-kβ activation
TNFR1	Tumor necrosis factor Alpha	TNF-α	It can induce cell death of certain tumor cell lines. It has the ability to increase cell proliferation and differentiation under certain conditions	Hypothalamus, White Matter & Medulla Oblongata	NF-kβ activation
mGluR	Glutamate metabotropic receptor	Glutamate	Ligand binding produces a conformational shift in G proteins, which stimulates signaling and affects the activity of downstream effectors such adenylate cyclase	Pons, Medulla Oblongata & White Matter	Hyperexcitability (enhance CSD)
P2Y12Rs	Purinergic receptor P2Y12	ATP	Receptor for ADP and ATP coupled to G-proteins that inhibit the adenylyl cyclase second messenger system	White Matter, Spinal Cord &Pons	P38 phosphorylation
NOTCH1	Notch receptor 1	Jagged-1	To regulate cell fate determination, it acts as a receptor for membrane-bound ligands Jagged-1 (JAG1), Jagged-2 (JAG2), and Delta-1 (DLL1). It forms a transcriptional activator complex with RBPJ/RBPSUH and activates genes of the enhancer of split locus after ligand activation through the released notch intracellular domain (NICD).	Medulla Oblongata, Pons, & Basal Ganglia	NF-kB translocation and enhance signaling
P2X4Rs	Purinergic receptor P2X 4	ATP	This gene's product belongs to the ATP purinoceptor family. This receptor works as a calcium-permeable ligand-gated ion channel	Cerebellum, White Matter & hypothalamus	P38 phosphorylation & BDNF secretion
CNR2	Cannabinoid receptor 2	2-AG	Adenylate cyclase inhibition is mediated via a heterotrimeric G protein-coupled receptor for the endocannabinoid 2-arachidonoylglycerol. It's possible that it's involved in the inflammatory response, nociceptive transmission, and bone homeostasis	Cerebellum	MMPs (Matrix metalloproteinases)

Table 3: Different channels that behaves abnormally and are responsible for the condition.

| Gene	Chr. Loc	Protein	Expression in brain	Function
CACNA1A	19p13.13	Voltage-dependent P/Q-type calcium channel subunit alpha-1A	Cerebellum, Pons & White Matter	VSCCs mediate calcium ion entrance into excitable cells and are also engaged in a number of calcium-dependent activities such as muscle contraction, hormone or neurotransmitter release, gene expression, cell motility, cell division, and cell death.
ATP1A2	1q23.2	Sodium/potassium-transporting ATPase subunit alpha-2	Thalamus, Pons & Medulla Oblongata	This is the active enzyme's catalytic component, which catalysis the hydrolysis of ATP as well as the exchange of sodium and potassium ions across the plasma membrane. This activity generates an electrochemical gradient of sodium and potassium, which provides energy for active nutrient transport.
SCN1A	2q24.3	Sodium channel protein type 1 subunit alpha	Cerebral Cortex, Pons & White Matter	Excitable membranes' voltage-dependent sodium ion permeability is mediated by Sodium channel protein type 1 subunit alpha
TRPA1	8q21.11	Transient receptor potential cation channel subfamily A member 1	Hippocampal Formation & Cerebral Cortex	Receptor-activated non-selective cation channel involved in pain detection and possibly also in cold perception, oxygen concentration perception
TRPM8	2q37.1	Transient receptor potential cation channel subfamily M member 8	Mid brain	It allows the entry of Na^+ and Ca^{2+} ions to the cell, Depolarization
KCNMA1 / BKCa	10q22.3	Calcium-activated potassium channel subunit alpha-1	Cerebral Cortex, Basal Ganglia& Amygdala	Potassium channel that is triggered by both membrane depolarization and a rise in cytosolic Ca^{++} and mediates K (+) export. The concentration of cytosolic Mg^{++} also activates it. Its activation diminishes the excitatory processes that raise cytosolic Ca^{++} levels and/or depolarize the cell membrane.
KCNJ8	12p12.1	ATP-sensitive inward rectifier potassium channel 8	Hypothalamus, Thalamus & Cerebral Cortex	Allow potassium to flow into a cell rather than out of a cell
KCNK18	10q25.3	Potassium channel subfamily K member 18	Hypothalamus	It is possible that this channel acts as a background potassium channel, determining the resting membrane potential and Calcium signals directly activate channel activity.
PRRT2	16p11.2	Proline-rich transmembrane protein 2	Cerebellum, Cerebral Cortex &Hippocampal Formation	It is engaged in synaptic transmission in the central nervous system, particularly hippocampal neurons, in presynaptic terminals, and plays a critical role in the last steps of neurotransmitter release, potentially through regulating Ca(2+)-sensing. In the cerebellum, may prevent the development of SNARE complexes and reduce short-term facilitation.
Panx1	11q21	Pannexin-1	Hypothalamus, Basal Ganglia & Cerebral Cortex	It is a structural component of gap junctions and hemichannels that are involved in ATP release and nucleotide permeation. It may also act as a Ca(2+)-leak channel to regulate ER Ca(2+) homeostasis.
NMDA R/ GRIN2A	16p13.2	Glutamate receptor ionotropic, NMDA 1 /Glutamate receptor ionotropic, NMDA 2A	Cerebral Cortex, Hippocampal Formation & Hypothalamus	NMDA receptor complex component that functions as a heterotetrametric, ligand-gated ion channel with high calcium permeability and voltage-dependent magnesium sensitivity.
AMPA R/ GRIA1	5q33.2	Glutamate receptor 2	Cerebral Cortex, Hippocampal Formation & Cerebellum	The glutamate ionotropic receptor is a type of glutamate receptor that is found in the brain Many synapses in the central nervous system use L-glutamate as an excitatory neurotransmitter. The excitatory neurotransmitter L-glutamate binds to the receptor, causing a conformational shift that opens the cation channel, converting the chemical signal to an electrical impulse.
SLC6A4	17q11.2	Sodium-dependent serotonin transporter	Midbrain ,Pons& Thalamus	The major function of the serotonin transporter in the central nervous system is to regulate serotonergic signaling by transporting serotonin molecules from the synaptic cleft to the pre-synaptic terminal for re-use. Plays an important role in regulating the availability of serotonin to other serotonergic receptors.

ganglia disorders like essential tremor and Tourette's syndrome experience migraines more frequently [81]. Furthermore, compared to controls, migraine patients had higher diastolic blood pressure, lower systolic blood pressure, and lower pulse pressure, according to the population-based study [82]. Ito and colleagues suggest that migraine-like PIH epileptic seizure (Post Ictal Headache: PIH) is related to particular regions of epileptogenic focus and that susceptibility to migraine headache predisposes to migraine-like PIH [83]. Additionally, studies have found that individuals who have a history of migraines without aura may also have probable analgesic-use headache (PAH) or probable analgesic-abuse headache (PAAH) which is defined as the transformation of episodic to chronic headache due to medication overuse, and probable chronic migraine (PCM) (>8 migraine attack for at least 3 months) [84].

In addition to the literature review, comorbidity data of migraine were retrieved from the large Spanish data repository which collected the data from the Information System for Research Development in Primary Care (SIDIAP), with a sample size of about 5.5 million people, or 74% of Catalonia's population which was studied retrospectively in a population-based study (Morbinet.org). In this electronic record, diseases were coded using the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) system. With a sample size of around 167905 (4.1%), this Spanish registry represents migraine (ICPC2 code: N101) and formed an interesting multimorbidity network based on the disease's co-occurrence rate, which is higher than expected based on its prevalence.

The Multimorbidity network has enlightened here on
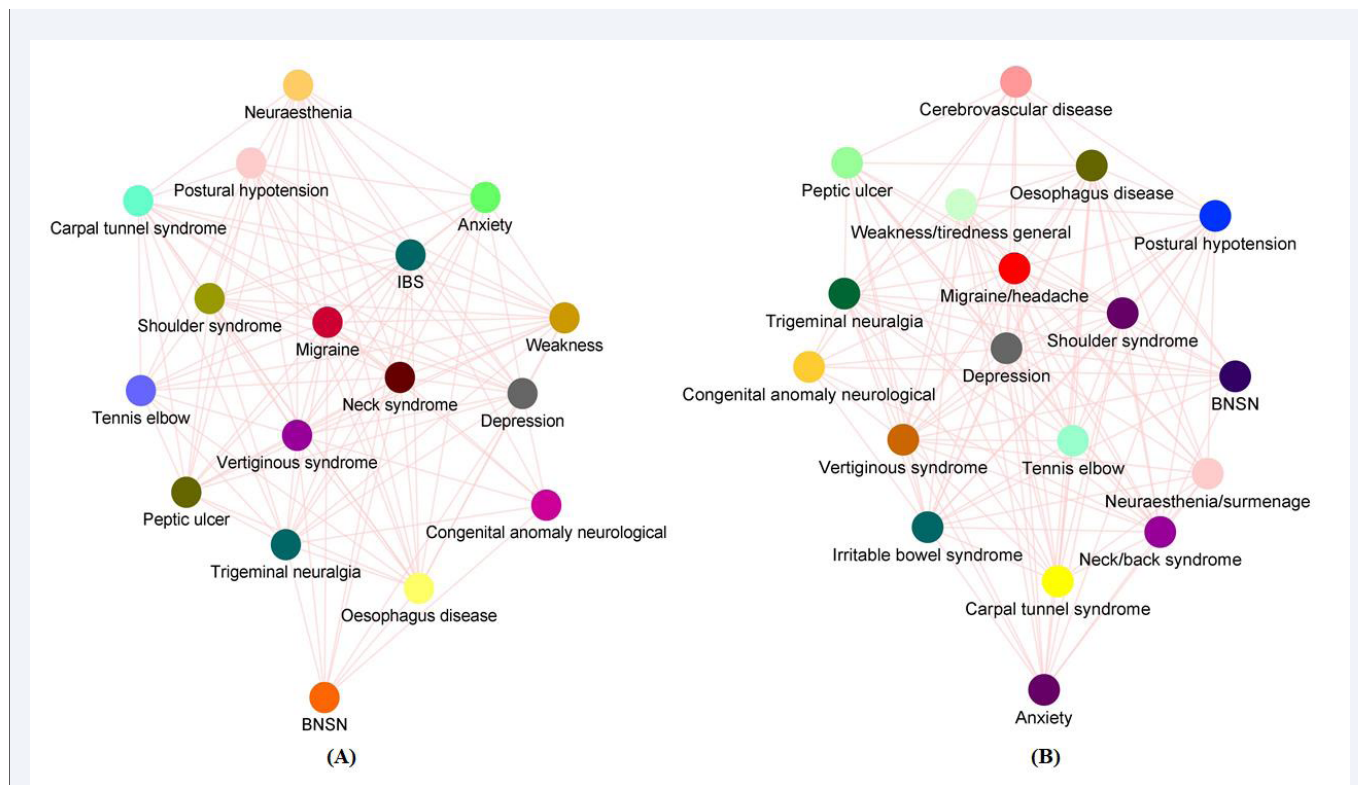
Figure 2 (Morbinet): Network graph shows a complex interaction of different diseases with the migraine disorder. (A): Multimorbidity network adjusted for both sex female and all age group which shows 17 interconnected nodes with 112 edges and an average shortest path of 1.176. (B): Multimorbidity network adjusted for female sex found 18 nodes with 118 edges with an average shortest distance of 1.229.
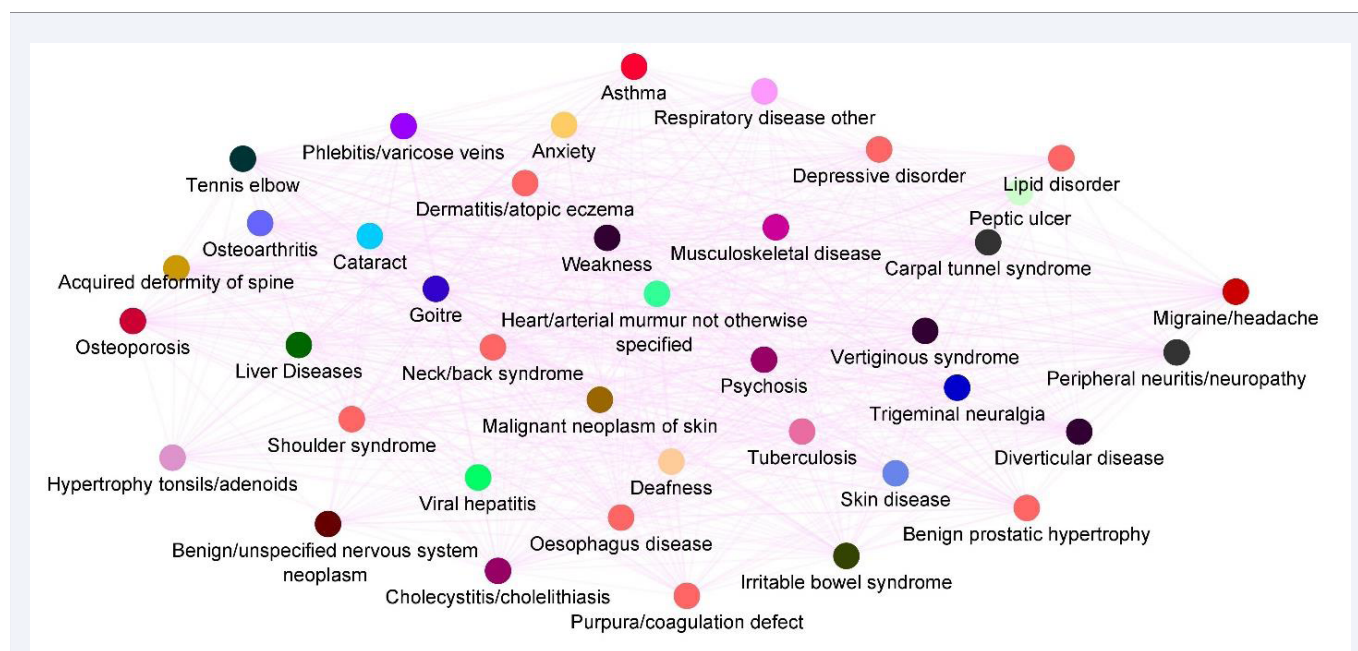
Figure 3 Multimorbidity network of migraine in age group of >72 years adjusted for both sexes showing the complex interaction among different diseases. This seem to as the age is progressed the comorbidity network of migraine expand exponentially (**Morbinet**).

the numerous aspects of migraine features, including the fact that women have a more complicated multimorbidity network than men (Figure 2B) and that as age progresses, the multimorbidity network of migraine becomes more complex (Figure 3). Females with complex multimorbidity networks have several female dominance risk factors, one of which is the existence of female dominance estrogen hormone, and it has also been well established that ESR1 and its polymorphisms have a significant influence on illness risk by increasing disease likelihood.

FUTURE PERSPECTIVE

After discussing various aspects of the condition, the interesting and necessary question is what the condition's future is, and what are the current possibilities for understanding the condition?

Machine Learning in the diagnosis of headache

Identifying a disease is an important stage in the treatment process and takes a lot of time and effort to identify a disease (i.e., disease diagnosis). Humans are prone to making mistakes that go unnoticed, making it difficult to assess the type and severity of the condition. As a result, different techniques have been developed to assess this human aid diagnostic error and one such astonishing method is artificial intelligence" (AI). With little human interaction, computer intelligence is used to replace a doctor's diagnostic skills in a variety of healthcare applications [85]. Machine learning (ML), is a branch of artificial intelligence focused on the creation and development of algorithms that enable computers to evolve behaviors based on empirical data. It has become increasingly popular in recent years and has had an impact on many fields [86] with a recognizable success for improving medical diagnostics by increasing accuracy, reproducibility, and speed, as well as reducing clinician burdens [87].

Concerning headaches, ML appears to be a promising platform for creating intelligent solutions because it expands the range of analytical operations required to boost diagnostic proficiency for primary headache diagnosis [88,89] . It may also have the potential to help identify the best predictor responsible for the progression of the disease [90].To diagnose, ML requires a dataset that is readily available online (act as a secondary source) or directly from patients (primary source), giving a doctor the advantage, they need to make a precise diagnosis. However, it is well known that the headache dataset contains a significant number of features such as somatosensory evoked potential, pain, analgesics, score MDQ-H (Medication-dependence questionnaire in headache), total pain month and examine patient-reported surveys, etc. [91]which showed high dimensionality, therefore necessitating the use of a different machine learning algorithm. A few examples of algorithm includes Random Forest (RF), Extreme Gradient-Boosting Trees (EGBT), K-nearest neighbors, multilayer perceptron, linear discriminant analysis, logistic regression [92],

Convolutional Neural Network (CNN) [93], Naive Bayes classifier, Support Vector Machine classifier (SVM) [94] that have been used for Computer-Aided Classification (CAC).

Using such discriminative features, these classification algorithms helped in classifying the migraine as migraine or not migraine, chronic or not chronic, and so on, increasing the chance of getting a high probability of correctly classifying the subject. Using a classification algorithm that makes extensive use of data from a variety of functional and structural MRI patterns, patients with primary headaches can be precisely separated from a group of controls [95].

Enclosing the section, ML has been a promising tool for computer-based diagnosis, finding the best predictor for disease occurrence, etc. But many things have yet to be used, one of which is the use of machine learning on the classification of migraine subtypes using genetics/gene variants as a feature, and the second is the future prediction for the outcome of comorbid conditions. Also, by combining the applications of machine learning techniques, neuronal network models, imaging technology, and clinical data, researchers anticipate being able to develop trustworthy biomarkers that will enable them to choose the best treatment for each headache patient [96].

Drugs and migraine

Different medicines have been available for treatment but all medicines are symptomatic medicines therefore, no cures are available [97]. Migraine treatment is divided into three categories: preventative, abortive, and biofeedback. Existing therapies are frequently ineffective in relieving pain, causing side effects, and increasing the risk of medication-related headaches. However, recent research has revealed a promising and potential treatment option that includes atogepant [98,99], erenumab [100, 101], rimegepant [102] and galcanezumab, and fremanezumab. Eletriptan may be the best treatment for migraines overall, according to a network meta-analysis. In the meantime, ibuprofen's high level of tolerance makes it a viable alternative [103]. Another recent network meta-analysis confirmed that CGRP mAbs, particularly galcanezumab 240 mg, monthly fremanezumab, and eptinezumab 300 mg, are the most effective treatment for patients with migraines who have not responded to prior therapies [104]. Prescription of these CGRP inhibitor medications may enhance the quality of life for migraine sufferers. Pathology and altered vulnerability to disease arise from alterations in certain proteins and the signaling pathways they regulate. Therefore, relying on existing medications may not deliver a complete cure, so this opens the possibility for the discovery of novel therapeutics.

Here are a few examples of newly-emerging potential migraine therapies that go beyond anti-CGRP [105] and include acid-sensing ion channels [106], Short-Chain Fatty Acids (SCFAs) [107], PAC1 receptor [108], KATP channel blockers [109], use of nanoparticle for the drug delivery [110], prevention of chronic

migraine by blocking microglia P2X4R-BDNF signaling pathway [111]**,** BKCa channel [112]**,** G-protein coupled receptors, glutamate, ion channels, and neuro-modulatory devices *see review* [113]**.** These new potential candidate drugs may prove to be a wonderful, safe anti-migraine medication and, hopefully, will have a good impact on the lives of migraine sufferers.

Strengths and limitations of the study

Regarding the strength of the present review, different aspect of migraine which includes migraine as an inflammatory disorder, migraine as a channelopathy, and such abrupt phenotypes are due to the alteration in the genes, epigenetics dysregulation of different hemostatic pathways which leads to the decreased pain threshold susceptibility and interestingly the environmental risk factors hinder the with the susceptibility. Also, we have discussed the role of machine learning in computer aid diagnoses and how it will revolutionize the face of diagnosis of migraine. In addition to some limitations, there is also the substantial contribution of vascular change in the genesis of the migraine [153], which we have not explored in this review due to space constraints. Therefore, this concluding conviction, with specific limitations, is incapable of capturing all of the parts of migraine causation due to their multifaceted nature and interplay, and so only represents the "tip of the iceberg," leaving the remainder undiscovered.

CONCLUSION

Migraine is a complicated neurological disorder characterized by unusually low neuronal hyper excitability, referred to as "migrainous brain," which is caused by mutations in genes involved in cellular hemostatic maintenance. Environmental influences, on the other hand, and their intricate interplay with the migrainous brain, obstruct the normal cellular system and induce pain (the cardinal character). The repeated disruption damages the normal brain structure and leads to numerous brain lesions that may become candidate structures for late-onset neurological diseases. To this end, it can't be said that migraine is not just a headache but more than it, As migraine is an intricate and complicated condition, its complexity cannot be fully characterized in a single article, which is why it is beyond the scope of this piece of article, and this merely represents only the "tip of the iceberg"

Availability of data and material

All the data related to the review are present in the manuscript.

AUTHOR'S CONTRIBUTION

Detail of the author's contribution, according to the CRediT (Contributor Roles Taxonomy) System**:** Parvinder Kumar & Amrit Sudershan contributed to the stud design, Amrit Sudershan, Meenakshi Bhagat, & Shikha Bharti downloaded & filter the literature, Amrit Sudershan drafted the manuscript, picture drawing and table editing, Parvinder Kumar, Sheetal Bhagat & Pallavi Sachdeva edited the manuscript, Parvinder Kumar finalize the manuscript.

REFERENCES

1. Raouf R, Quick K, Wood JN. Pain as a channelopathy. J Clin Invest. 2010; 120: 3745-3752.

2. Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ Open. 2016; 6: e010364.

3. Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth. 2019; 123: e273-e283.

4. Steiner TJ, Birbeck GL, Jensen RH, Katsarava Z, Stovner LJ, Martelletti P, et al. Headache disorders are third cause of disability worldwide. J Headache Pain. 2015; 16: 58.

5. Andreou AP, Edvinsson L. Mechanisms of migraine as a chronic evolutive condition. J Headache Pain. 2019; 20: 117.

6. Sudershan A, Pushap AC, Younis M, Sudershan S, Bhagat S, Kumar H, et al. Neuroepidemiology study of headache in the region of Jammu of north Indian population: A cross-sectional study. Front Neurol. 2023; 13: 1030940.

7. Hjalte F, Olofsson S, Persson U, Linde M. Burden and costs of migraine in a Swedish defined patient population - a questionnaire-based study. J Headache Pain. 2019; 20: 65.

8. Buse DC, Yugrakh MS, Lee LK, Bell J, Cohen JM, Lipton RB, et al. Burden of Illness Among People with Migraine and ≥ 4 Monthly Headache Days While Using Acute and/or Preventive Prescription Medications for Migraine. J Manag Care Spec Pharm. 2020; 26: 1334-1343.

9. Kogelman LJA, Falkenberg K, Buil A, Erola P, Courraud J, Laursen SS, et al. Changes in the gene expression profile during spontaneous migraine attacks. Sci Rep. 2021; 11: 8294.

10. Baksa D, Gonda X, Eszlari N, Petschner P, Acs V, Kalmar L, et al. Financial Stress Interacts With CLOCK Gene to Affect Migraine. Front Behav Neurosci. 2020; 13: 284.

11. Katsarava Z, Buse DC, Manack AN, Lipton RB. Defining the differences between episodic migraine and chronic migraine. Curr Pain Headache Rep. 2012; 16: 86-92.

12. [Sudershan A, Mahajan K, Singh K, Dhar MK, Kumar P. The complexities of migraine: A debate among migraine researchers: A review. Clin Neurol Neurosurg. 2022; 214: 107136.

13. Leao AAP. SPREADING DEPRESSION OF ACTIVITY IN THE CEREBRAL CORTEX. J Neurophysiol. 1944; 7: 359-390.

14. Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. Nat Med. 2002; 8: 136-142.

15. Ramachandran R. Neurogenic inflammation and its role in migraine. Semin Immunopathol. 2018; 40: 301-314.

16. Spekker E, Laborc KF, Bohár Z, Nagy-Grócz G, Fejes-Szabó A, Szűcs M, et al. Effect of dural inflammatory soup application on activation and sensitization markers in the caudal trigeminal nucleus of the rat and the modulatory effects of sumatriptan and kynurenic acid. J Headache Pain. 2021; 22: 17.

17. Patnala R, Clements J, Batra J. Candidate gene association studies: a comprehensive guide to useful in silico tools. BMC Genet. 2013; 14: 39.

18. Gormley P, Anttila V, Winsvold BS, Palta P, Esko T, Pers TH, et al. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. Nat Genet. 2016; 48: 856-866.

19. Hautakangas H, Winsvold BS, Ruotsalainen SE, Bjornsdottir G, Harder AVE, Kogelman LJA, et al. Genome-wide analysis of 102,084 migraine cases identifies 123 risk loci and subtype-specific risk alleles. Nat Genet. 2022; 54: 152-160.

20. Bush WS, Moore JH. Chapter 11: Genome-wide association studies. PLoS Computes Biol. 2012; 8: e1002822.

21. Gormley P, Kurki MI, Hiekkala ME, Veerapen K, Häppölä P, Mitchell AA, et al. Common Variant Burden Contributes to the Familial Aggregation of Migraine in 1,589 Families. Neuron. 2018; 98: 743-753.

22. Visscher PM, Hill WG, Wray NR. Heritability in the genomics era--concepts and misconceptions. Nat Rev Genet. 2008; 9: 255-266.

23. Silberstein SD, Dodick DW. Migraine genetics: Part II. Headache. 2013; 53: 1218-1229.

24. Noble-Topham SE, Cader MZ, Dyment DA, Rice GP, Brown JD, Ebers GC, et al. Genetic loading in familial migraine with aura. J Neurol Neurosurg Psychiatry. 2003; 74: 1128-1130.

25. Eising EA, Datson N, van den Maagdenberg AM, Ferrari MD. Epigenetic mechanisms in migraine: a promising avenue? BMC Med. 2013; 11: 26.

26. Felsenfeld G. A brief history of epigenetics. Cold Spring Harb Perspect Biol. 2014; 6: a018200.

27. Weinhold B. Epigenetics: the science of change. Environ Health Perspect. 2006; 114: A160-167.

28. Paul S, Bravo Vázquez LA, Pérez Uribe S, Roxana Reyes-Pérez P, Sharma A. Current Status of microRNA-Based Therapeutic Approaches in Neurodegenerative Disorders. Cells. 2020; 9: 1698.

29. Sudershan A, Bharti S, Sheikh JH, Wani SA, Kumar H, Kumar P, et al. Epigenetics in migraine: A review. IP Indian J Neurosci. 2023; 9: 122-131.

30. Ragsdale SW. Catalysis of methyl group transfers involving tetrahydrofolate and B(12). Vitam Horm. 2008; 79: 293-324.

31. Zakhari S. Alcohol metabolism and epigenetics changes. Alcohol Res. 2013; 35: 6-16.

32. Labruijere S, Stolk L, Verbiest M, de Vries R, Garrelds IM, Eilers PH, et al. Methylation of migraine]e-related genes in different tissues of the rat. PLoS One. 2014; 9: e87616.

33. Wan D, Hou L, Zhang X, Han X, Chen M, Tang W, et al. DNA methylation of RAMP1 gene in migraine: an exploratory analysis. J Headache Pain. 2015; 16: 90.

34. Winsvold BS, Palta P, Eising E, Page CM. International Headache Genetics Consortium; van den Maagdenberg AM, Palotie A, et al. Epigenetic DNA methylation changes associated with headache chronification: A retrospective case-control study. Cephalalgia. 2018; 38: 312-322.

35. Gerring ZF, McRae AF, Montgomery GW, Nyholt DR. Genome-wide DNA methylation profiling in whole blood reveals epigenetic signatures associated with migraine. BMC Genomics. 2018; 19: 69.

36. Terlizzi R, Bacalini MG, Pirazzini C, Giannini G, Pierangeli G, Garagnani P, et al. Epigenetic DNA methylation changes in episodic and chronic migraine. Neurol Sci. 2018; 39: 67-68.

37. Tafuri E, Santovito D, de Nardis V, Marcantonio P, Paganelli C, Affaitati G, et al. MicroRNA profiling in migraine without aura: pilot study. Ann Med. 2015; 47: 468-473.

38. Andersen HH, Duroux M, Gazerani P. Serum MicroRNA Signatures in Migraineurs During Attacks and in Pain-Free Periods. Mol Neurobiol. 2016; 53: 1494-1500.

39. Cheng CY, Chen SP, Liao YC, Fuh JL, Wang YF, Wang SJ, et al. Elevated circulating endothelial-specific microRNAs in migraine patients: A pilot study. Cephalalgia. 2018; 38: 1585-1591.

40. Gallelli L, Cione E, Peltrone F, Siviglia S, Verano A, Chirchiglia D, et al. Hsa-miR-34a-5p and hsa-miR-375 as Biomarkers for Monitoring the Effects of Drug Treatment for Migraine Pain in Children and Adolescents: A Pilot Study. J Clin Med. 2019; 8: 928.

41. Brás JP, Bravo J, Freitas J, Barbosa MA, Santos SG, Summavielle T, et al. TNF-alpha-induced microglia activation requires miR-342: impact on NF-kB signaling and neurotoxicity. Cell Death Dis. 2020; 11: 415.

42. Sudershan A, Sudershan S, Younis M, Bhagat M, Pushap AC, Kumar H, et al. Enlightening the association between TNF-α -308 G > A and migraine: a meta-analysis with meta-regression and trial sequential analysis. BMC Neurol. 2023; 23: 159.

43. Hanna J, Hossain GS, Kocerha J. The Potential for microRNA Therapeutics and Clinical Research. Front Genet. 2019; 10: 478.

44. Xu Z, Li H, Jin P. Epigenetics-Based Therapeutics for Neurodegenerative Disorders. Curr Transl Geriatr Exp Gerontol Rep. 2012; 1: 229-236.

45. Gazerani P. Current Evidence on Potential Uses of MicroRNA Biomarkers for Migraine: From Diagnosis to Treatment. Mol Diagn Ther. 2019; 23: 681-694.

46. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2017; 9: 7204-7218.

47. Muller WA. Getting leukocytes to the site of inflammation. Vet Pathol. 2013; 50: 7-22.

48. Edvinsson L, Haanes KA, Warfvinge K. Does inflammation have a role in migraine? Nat Rev Neurol. 2019; 15: 483-490.

49. Saijo K, Glass CK. Microglial cell origin and phenotypes in health and disease. Nat Rev Immunol. 2011; 11: 775-787.

50. Bartley J. Could glial activation be a factor in migraine? Med Hypotheses. 2009; 72: 255-257.

51. Sudershan A, Younis M, Sudershan S, Kumar P. Migraine as an inflammatory disorder with microglial activation as a prime candidate. Neurol Res. 2023; 45: 200-215.

52. Shibata M, Suzuki N. Exploring the role of microglia in cortical spreading depression in neurological disease. J Cereb Blood Flow Metab. 2017; 37: 1182-1191.

53. Pietrobon, D. Neuronal calcium channels and migraine. Biophysical Journal. 2009; 96: 202a–203a.

54. Graves TD, Hanna MG. Episodic ataxia: SLC1A3 and CACNB4 do not explain the apparent genetic heterogeneity. J Neurol. 2008; 255: 1097-1099.

55. Meisler MH, Hill SF, Yu W. Sodium channelopathies in neurodevelopmental disorders. Nat Rev Neurosci. 2021; 22: 152-166.

56. Kessi M, Chen B, Peng J, Yan F, Yang L, Yin F, et al. Calcium channelopathies and intellectual disability: a systematic review. Orphanet J Rare Dis. 2021; 16: 219.

57. Bartolini E, Campostrini R, Kiferle L, Pradella S, Rosati E, Chinthapalli K, et al. Epilepsy and brain channelopathies from infancy to adulthood. Neurol Sci. 2020; 41: 749-761.

58. Albury CL, Stuart S, Haupt LM, Griffiths LR. Ion channelopathies and migraine pathogenesis. Mol Genet Genomics. 2017; 292: 729-739.

59. Gordon N. Episodic ataxia and channelopathies. Brain Dev. 1998; 20: 9-13.

60. Terwindt GM, Ophoff RA, Haan J, Sandkuijl LA, Frants RR, Ferrari MD, et al. Migraine, ataxia and epilepsy: a challenging spectrum of genetically determined calcium channelopathies. Dutch Migraine Genetics Research Group. Eur J Hum Genet. 1998; 6: 297-307.

61. Zarcone D, Corbetta S. Shared mechanisms of epilepsy, migraine and affective disorders. Neurol Sci. 2017; 38: 73-76.

62. Dworakowska B, Dołowy K. Ion channels-related diseases. Acta Biochim Pol. 2000; 47: 685-703.

63. Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. Ann Fam Med. 2009; 7: 357-363.

64. Lauritzen M, Strong AJ. Evidence for CSD or CSD-Like Phenomena in Human Brain in Relation to Migraine and Stroke. Ischemic Blood Flow in the Brain. 2001; 6: 335-342.

65. Garrigós-Pedrón M, La Touche R, Navarro-Desentre P, Gracia-Naya M, Segura-Ortí E. Effects of a Physical Therapy Protocol in Patients with Chronic Migraine and Temporomandibular Disorders: A Randomized, Single-Blinded, Clinical Trial. J Oral Facial Pain Headache. 2018; 32: 137-150.

66. Seng EK, Holroyd KA. Psychiatric comorbidity and response to preventative therapy in the treatment of severe migraine trial. Cephalalgia. 2012; 32: 390-400.

67. Bougea A, Spantideas N, Galanis P, Katsika P, Boufidou F, Voskou P, et al. Salivary inflammatory markers in tension type headache and migraine: the SalHead cohort study. Neurol Sci. 2020; 41: 877-884.

68. Schürks M, Winter AC, Berger K, Buring JE, Kurth T. Migraine and restless legs syndrome in women. Cephalalgia. 2012; 32: 382-389.

69. Balaban H, Semiz M, Şentürk IA, Kavakçı Ö, Cınar Z, Dikici A, et al. Migraine prevalence, alexithymia, and post-traumatic stress disorder among medical students in Turkey. J Headache Pain. 2012; 13: 459-467.

70. Peres MFP, Mercante JPP, Tobo PR, Kamei H, Bigal ME. Anxiety and depression symptoms and migraine: a symptom-based approach research. J Headache Pain. 2017; 18: 37.

71. Spector JT, Kahn SR, Jones MR, Jayakumar M, Dalal D, Nazarian S, et al. Migraine headache and ischemic stroke risk: an updated meta-analysis. Am J Med. 2010; 123: 612-624.

72. Gardener H, Monteith T, Rundek T, Wright CB, Elkind MS, Sacco RL, et al. Hypertension and Migraine in the Northern Manhattan Study. Ethn Dis. 2016; 26: 323-330.

73. Kim SY, Min C, Oh DJ, Lim JS, Choi HG. Bidirectional association between asthma and migraines in adults: Two longitudinal follow-up studies. Sci Rep. 2019; 9: 18343.

74. Morton RE, St John PD, Tyas SL. Migraine and the risk of all-cause dementia, Alzheimer's disease, and vascular dementia: A prospective cohort study in community-dwelling older adults. Int J Geriatr Psychiatry. 2019; 34: 1667-1676.

75. Sharif S, Saleem A, Koumadoraki E, Jarvis S, Madouros N, Khan S, et al. Headache - A Window to Dementia: An Unexpected Twist. Cureus. 2021; 13: e13398.

76. Bigal ME, Kurth T, Santanello N, Buse D, Golden W, Robbins M, Lipton RB, et al. Migraine and cardiovascular disease: a population-based study. Neurology. 2010; 74: 628-635.

77. Tiseo C, Vacca A, Felbush A, Filimonova T, Gai A, Glazyrina T, et al. Migraine and sleep disorders: a systematic review. J Headache Pain. 2020; 21: 126.

78. Carod-Artal FJ, da Silveira Ribeiro L, Braga H, Kummer W, Mesquita HM, Vargas AP, et al. Prevalence of patent foramen ovale in migraine patients with and without aura compared with stroke patients. A transcranial Doppler study. Cephalalgia. 2006; 26: 934-939. Peşkersoy C, Peker Ş, Kaya A, Ünalp A, Gökay N. Evaluation of the relationship between migraine disorder andoral comorbidities: multicenter randomized clinical trial. Turk J Med Sci. 2016; 46: 712-718.

79. Aykutlu E, Baykan B, Akman-Demir G, Topcular B, Ertas M. Headache in Behçet's disease. Cephalalgia. 2006; 26: 180-186.

80. Ravindran MK, Zheng Y, Timbol C, Merck SJ, Baraniuk JN. Migraine headaches in chronic fatigue syndrome (CFS): comparison of two prospective cross-sectional studies. BMC Neurol. 2011; 11: 30.

81. Teixeira AL Jr, Meira FC, Maia DP, Cunningham MC, Cardoso F. Migraine headache in patients with Sydenham's chorea. Cephalalgia. 2005; 25: 542-544.

82. Gudmundsson LS, Thorgeirsson G, Sigfusson N, Sigvaldason H, Johannsson M. Migraine patients have lower systolic but higher diastolic blood pressure compared with controls in a population-based study of 21,537 subjects. The Reykjavik Study. Cephalalgia. 2006; 26: 436-444.

83. Ito M, Adachi N, Nakamura F, Koyama T, Okamura T, Kato M, et al. Characteristics of postictal headache in patients with partial epilepsy. Cephalalgia. 2004; 24: 23-28.

84. Sarchielli P, Alberti A, Candeliere A, Floridi A, Capocchi G, Calabresi P, et al. Glial cell line-derived neurotrophic factor and somatostatin levels in cerebrospinal fluid of patients affected by chronic migraine and fibromyalgia. Cephalalgia. 2006; 26: 409-415.

85. Pelaccia T, Forestier G, Wemmert C. Deconstructing the diagnostic reasoning of human versus artificial intelligence. CMAJ. 2019; 191: E1332-E1335.

86. Schmidt J, Marques MR, Botti S, Marques MA. Recent advances and applications of machine learning in solid-state materials science. npj Computational Materials. 2019; 5: 1-36.

87. Ahmed Z, Mohamed K, Zeeshan S, Dong X. Artificial intelligence with multi-functional machine learning platform development for better healthcare and precision medicine. Database: the journal of biological databases and curation. 2020.

88. Krawczyk B, Simić D, Simić S, Woźniak M. Automatic diagnosis of primary headaches by machine learning methods. Open Medicine. 2013; 8: 157-165.

89. Keight R, Aljaaf AJ, Al-Jumeily D, Hussain AJ, Özge A, Mallucci C, et al. An intelligent systems approach to primary headache diagnosis. In International conference on intelligent computing. Springer, Cham. 2017; 61-72.

90. Agrebi S, Larbi A. Use of artificial intelligence in infectious diseases. In Artificial intelligence in precision health. Academic Press. 2020; 415-438.

91. Kwon J, Lee H, Cho S, Chung CS, Lee MJ, Park H, et al. Machine learning-based automated classification of headache disorders using patient-reported questionnaires. Sci Rep. 2020; 10: 14062.

92. Zhu B, Coppola G, Shoaran M. Migraine classification using somatosensory evoked potentials. Cephalalgia. 2019; 39: 1143-1155.

93. Yang H, Zhang J, Liu Q, Wang Y. Multimodal MRI-based classification of migraine: using deep learning convolutional neural network. Biomed Eng Online. 2018; 17: 138.

94. Garcia-Chimeno Y, Garcia-Zapirain B, Gomez-Beldarrain M, Fernandez-Ruanova B, Garcia-Monco JC. Automatic migraine classification via feature selection committee and machine learning techniques over imaging and questionnaire data. BMC Med Inform Decis Mak. 2017; 17: 38.

95. Messina R, Leech R, Zelaya F, Dipasquale O, Wei D, Filippi M, et al. Migraine and Cluster Headache Classification Using a Supervised Machine Learning Approach: A Multimodal MRI Study, (P4. 10-016). 2019.

96. Messina R, Filippi M. What We Gain From Machine Learning Studies in Headache Patients. Front Neurol. 2020; 11: 221.

97. Peck J, Urits I, Zeien J, Hoebee S, Mousa M, Alattar H, et al. A Comprehensive Review of Over-the-counter Treatment for Chronic Migraine Headaches. Curr Pain Headache Rep. 2020; 24: 19.

98. Schwedt TJ, Lipton RB, Ailani J, Silberstein SD, Tassorelli C, Guo H, et al. Time course of efficacy of atogepant for the preventive treatment of migraine: Results from the randomized, double-blind ADVANCE trial. Cephalalgia. 2022; 42: 3-11.

99. Ailani J, Lipton RB, Goadsby PJ, Guo H, Miceli R, Severt L, et al. ADVANCE Study Group. Atogepant for the Preventive Treatment of Migraine. N Engl J Med. 2021; 385: 695-706.

100. Lipton RB, Tepper SJ, Silberstein SD, Kudrow D, Ashina M, Reuter U, et al. Reversion from chronic migraine to episodic migraine following treatment with erenumab: Results of a post-hoc analysis of a randomized, 12-week, double-blind study and a 52-week, open-label extension. Cephalalgia. 2021; 41: 6-16.

101. Ashina M, Goadsby PJ, Reuter U, Silberstein S, Dodick DW, Xue F, et al. Long-term efficacy and safety of erenumab in migraine prevention: Results from a 5-year, open-label treatment phase of a randomized clinical trial. Eur J Neurol. 2021; 28:1716-1725.

102. Croop R, Lipton RB, Kudrow D, Stock DA, Kamen L, Conway CM, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. Lancet. 2021; 397: 51-60.

103. Xu H, Han W, Wang J, Li M. Network meta-analysis of migraine disorder treatment by NSAIDs and triptans. J Headache Pain. 2016; 17: 113.

104. Wang X, Wen D, He Q, You C, Ma L. Efficacy and safety of monoclonal antibody against calcitonin gene-related peptide or its receptor for migraine patients with prior preventive treatment failure: a network meta-analysis. J Headache Pain. 2022; 23: 105.

105. Tepper SJ. History and Review of anti-Calcitonin Gene-Related Peptide (CGRP) Therapies: From Translational Research to Treatment. Headache. 2018; 3: 238-275.

106. Holland PR, Akerman S, Andreou AP, Karsan N, Wemmie JA, Goadsby PJ. Acid-sensing ion channel 1: a novel therapeutic target for migraine with aura. Ann Neurol. 2012; 72: 559-563.

107. Lanza M, Filippone A, Ardizzone A, Casili G, Paterniti I, Esposito E, et al. SCFA Treatment Alleviates Pathological Signs of Migraine and Related Intestinal Alterations in a Mouse Model of NTG-Induced Migraine. Cells. 2021; 10: 2756.

108. Vollesen ALH, Amin FM, Ashina M. Targeted Pituitary Adenylate Cyclase-Activating Peptide Therapies for Migraine. Neurotherapeutics. 2018; 15: 371-376.

109. Al-Karagholi MA, Ghanizada H, Waldorff Nielsen CA, Skandarioon C, Snellman J, Lopez-Lopez C, et al. Opening of BKCa channels causes migraine attacks: a new downstream target for the treatment of migraine. Pain. 2021; 162: 2512-2520.

110. Tardiolo G, Bramanti P, Mazzon E. Migraine: Experimental Models and Novel Therapeutic Approaches. Int J Mol Sci. 2019; 20: 2932.

111. Long T, He W, Pan Q, Zhang S, Zhang D, Qin G, et al. Microglia P2X4R-BDNF signalling contributes to central sensitization in a recurrent nitroglycerin-induced chronic migraine model. J Headache Pain. 2020; 21: 4.

112. Al-Karagholi MA, Hansen JM, Guo S, Olesen J, Ashina M. Opening of ATP-sensitive potassium channels causes migraine attacks: a new target for the treatment of migraine. Brain. 2019; 142: 2644-2654.

113. Do TP, Al-Saoudi A, Ashina M. Future prophylactic treatments in migraine: Beyond anti-CGRP monoclonal antibodies and gepants. Rev Neurol (Paris). 2021; 177: 827-833.

114. Tzourio C, El Amrani M, Poirier O, Nicaud V, Bousser MG, Alpérovitch A. Association between migraine and endothelin type A receptor (ETA -231 A/G) gene polymorphism. Neurology. 2001; 56: 1273-1277.

115. Erdal ME, Herken H, Yilmaz M, Bayazit YA. Association of the T102C polymorphism of 5-HT2A receptor gene with aura in migraine. J Neurol Sci. 2001; 188: 99-101.

116. Mochi M, Cevoli S, Cortelli P, Pierangeli G, Scapoli C, Soriani S, et al. Investigation of an LDLR gene polymorphism (19p13.2) in susceptibility to migraine without aura. J Neurol Sci. 2003; 213: 7-10.

117. Borroni B, Rao R, Liberini P, Venturelli E, Cossandi M, Archetti S, et al. Endothelial nitric oxide synthase (Glu298Asp) polymorphism is an independent risk factor for migraine with aura. Headache. 2006; 46: 1575-1579.

118. Erdal N, Herken H, Yilmaz M, Erdal E, Bayazit YA. The A218C polymorphism of tryptophan hydroxylase gene and migraine. J Clin Neurosci. 2007; 14: 249-251.

119. Oterino A, Ruiz-Alegría C, Castillo J, Valle N, Bravo Y, Cayón A, et al. GNAS1 T393C polymorphism is associated with migraine. Cephalalgia. 2007; 27: 429-434.

120. Schürks M, Rist PM, Kurth T. MTHFR 677C>T and ACE D/I polymorphisms in migraine: a systematic review and meta-analysis. Headache. 2010; 50: 588-599.

121. Menon S, Cox HC, Kuwahata M, Quinlan S, MacMillan JC, Haupt LM, et al. Association of a Notch 3 gene polymorphism with migraine susceptibility. Cephalalgia. 2011; 31: 264-270.

122. Menon S, Lea RA, Roy B, Hanna M, Wee S, Haupt LM, et al. The human μ-opioid receptor gene polymorphism (A118G) is associated with head pain severity in a clinical cohort of female migraine with aura patients. J Headache Pain. 2012; 13: 513-519.

123. Millán-Guerrero RO, Baltazar-Rodríguez LM, Cárdenas-Rojas MI, Ramírez-Flores M, Isais-Millán S, Delgado-Enciso I, et al. A280V polymorphism in the histamine H3 receptor as a risk factor for migraine. Arch Med Res. 2011; 42: 44-47.

124. Dong W, Jia S, Ye X, Ni J. Association analysis of TNFRSF1B polymorphism with susceptibility for migraine in the Chinese Han population. J Clin Neurosci. 2012; 19: 750-752.

125. Maher BH, Lea RA, Follett J, Cox HC, Fernandez F, Esposito T, et al. Association of a GRIA3 gene polymorphism with migraine in an Australian case-control cohort. Headache. 2013; 53: 1245-1249.

SciMedCentral

126. Palmirotta R, Ludovici G, Egeo G, Ialongo C, Aurilia C, Fofi L, et al. Prion protein gene M129V polymorphism and variability in age at migraine onset. Headache. 2013; 53: 540-545.

127. He Q, Lin X, Wang F, Xu J, Ren Z, Chen W, et al. Associations of a polymorphism in the intercellular adhesion molecule-1 (ICAM1) gene and ICAM1 serum levels with migraine in a Chinese Han population. J Neurol Sci. 2014; 345: 148-153.

128. Liu R, Ma M, Cui M, Dong Z, Wang X, Zhang W, et al. Effects of tumor necrosis factor-β (TNF-β) 252A>G polymorphism on the development of migraine: a meta-analysis. PLoS One. 2014; 9: e100189.

129. Zandifar A, Soleimani S, Iraji N, Haghdoost F, Tajaddini M, Javanmard SH. Association between promoter region of the uPAR (rs344781) gene polymorphism in genetic susceptibility to migraine without aura in three Iranian hospitals. Clin Neurol Neurosurg. 2014; 120: 45-48.

130. Li L, Liu R, Dong Z, Wang X, Yu S. Impact of ESR1 Gene Polymorphisms on Migraine Susceptibility: A Meta-Analysis. Medicine (Baltimore). 2015; 94: e0976.

131. Kumar S, Raina JK, Sudershan A, Mahajan K, Jasrotia R, Maharana C, et al. An Association Study of ESR1-XbaI and PvuII Gene Polymorphism in Migraine Susceptibility in the Jammu Region. Eur Neurol. 2023; 86: 55-62.

132. Palmirotta R, Barbanti P, Ialongo C, De Marchis ML, Alessandroni J, Egeo G, et al. Progesterone receptor gene (PROGINS) polymorphism correlates with late onset of migraine. DNA Cell Biol. 2015; 34: 208-212.

133. Palmirotta R, Barbanti P, De Marchis ML, Egeo G, Aurilia C, Fofi L, et al. Is SOD2 Ala16Val polymorphism associated with migraine with aura phenotype? Antioxid Redox Signal. 2015; 22: 275-279.

134. Zandifar A, Iraji N, Taheriun M, Tajaddini M, Javanmard SH. Association of the long pentraxin PTX3 gene polymorphism (rs3816527) with migraine in an Iranian population. J Neurol Sci. 2015; 349: 185-189.

135. Sazci A, Sazci G, Sazci B, Ergul E, Idrisoglu HA. Nicotinamide-N-Methyltransferase gene rs694539 variant and migraine risk. J Headache Pain. 2016; 17: 93.

136. Sezer S, Bozkurt N, Kurt S, Ates O. The association between migraine and +1603C→T polymorphism of the dopamine beta-hydroxylase (DBH) locus in Turkey. Curr Opini Biotechnol. 2011; 22: S104.

137. Cai X, Shi X, Zhang X, Zhang A, Zheng M, Fang Y. The association between brain-derived neurotrophic factor gene polymorphism and migraine: a meta-analysis. J Headache Pain. 2017; 18: 13.

138. García-Martín E, Martínez C, Serrador M, Alonso-Navarro H, Navacerrada F, Esguevillas G, et al. Gamma-Aminobutyric Acid (Gaba) Receptors Rho (Gabrr) Gene Polymorphisms and Risk for Migraine. Headache. 2017; 57: 1118-1135.

139. Dong H, Wang ZH, Dong B, Hu YN, Zhao HY. Endothelial nitric oxide synthase (-786T>C) polymorphism and migraine susceptibility: A meta-analysis. Medicine (Baltimore). 2018; 97: e12241.

140. García-Martín E, Esguevillas G, Serrador M, Alonso-Navarro H, Navacerrada F, Amo G, García-Albea E, et al. Gamma-aminobutyric

acid (GABA) receptors GABRA4, GABRE, and GABRQ gene polymorphisms and risk for migraine. J Neural Transm (Vienna). 2018; 125: 689-698.

141. Deng Y, Huang J, Zhang H, Zhu X, Gong Q. Association of expression of DRD2 rs1800497 polymorphism with migraine risk in Han Chinese individuals. J Pain Res. 2018; 11: 763-769.

142. Ling YH, Chen SP, Fann CS, Wang SJ, Wang YF. TRPM8 genetic variant is associated with chronic migraine and allodynia. J Headache Pain. 2019; 20: 115.

143. Wu X, Qiu F, Wang Z, Liu B, Qi X. Correlation of 5-HTR6 gene polymorphism with vestibular migraine. J Clin Lab Anal. 2020; 34: e23042.

144. Yakubova A, Davidyuk Y, Tohka J, Khayrutdinova O, Kudryavtsev I, Nurkhametova D, et al. Searching for Predictors of Migraine Chronification: a Pilot Study of 1911A>G Polymorphism of TRPV1 Gene in Episodic Versus Chronic Migraine. J Mol Neurosci. 2021; 71: 618-624.

145. Chen M, Tang W, Hou L, Liu R, Dong Z, Han X, et al. Tumor Necrosis Factor (TNF) -308G>A, Nitric Oxide Synthase 3 (NOS3) +894G>T Polymorphisms and Migraine Risk: A Meta-Analysis. PLoS One. 2015; 10: e0129372.

146. Bachiller S, Jiménez-Ferrer I, Paulus A, Yang Y, Swanberg M, Deierborg T, et al. Microglia in Neurological Diseases: A Road Map to Brain-Disease Dependent-Inflammatory Response. Front Cell Neurosci. 2018; 12: 488.

147. Sudershan A, Pushap AC, Kumar H, & Kumar P. A Comprehensive Investigation into the Association Between Mthfr C677t, A1298c, and Ace I/D Variants and Risk of Migraine: an Updated Meta-Analysis of Genetic Association Studies with Trial Sequential Analysis and Meta-Regression. J Mol Neurosci. 2023.

148. Sudershan A, Bhagat M, Singh K, Pushap AC, Kumar H, & Kumar P. A Comprehensive Investigation of Risk Association Between the -786 T > C, + 884 G > A, VNTR, rs743506, rs3918226 of eNOS and Susceptibility of Migraine: A Updated Meta-Analysis Utilizing Trial Sequential Analysis. Journal of molecular neuroscience.

149. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018; 392: 1789–1858.

150. Sudershan A, Pushap AC, Bhagat M, Sharma I, Kumar H, Digra SK, Kumar P. (2023). Comprehensive analysis of genes associated with migraine in the Indian population: a meta-analysis of genetic association studies with trial sequential analysis. Sci Rep. 2023; 13: 19070.

151. Ashina M. Vascular changes have a primary role in migraine. Cephalalgia. 2012; 32: 428–430.

152. Tiseo C, Vacca A, Felbush A, Filimonova T, Gai A, Glazyrina T, et al. Migraine and sleep disorders: a systematic review. J Headache Pain. 2020; 21: 126.

153. Lau CI, Lin CC, Chen WH, Wang HC, Kao CH. Association between migraine and irritable bowel syndrome: a population-based retrospective cohort study. Eur J Neurol. 2014; 21: 1198-1204.