Genetics of Menstrual Migraine and Their Association with Female Hormonal Factors

Iyshwarya B. Kalarani, Vajagathali Mohammed, Ramakrishnan Veerabathiran

Faculty of Allied Health Sciences, Human Cytogenetics and Genomics Laboratory, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam, Tamil Nadu, India

Abstract

Perimenopause is linked to increased migraine (Mg), especially menstrual Mg (MMg), influenced by hormonal changes. Compared to nonmenstrual attacks, menstrual attacks are more disabling and less responsive to treatment. Women with perimenstrual estrogen withdrawal have been linked to Mg during menstruation, whereas Mg during perimenopause has been linked to unpredictable fluctuations in estrogen levels. It has been widely established that female sex hormones play a role in Mg, but how it occurs remains unclear. This narrative review was identified using Medline and PubMed searches between 1946 and 2021. Search terms included "headache," "migraine," "menstrual migraine," "menstruation," "menopause," "perimenopause," "estrogen," and "progesterone." This article focuses on the candidate genes and female hormones that play a role in MMg. More study is necessary to understand better the environmental components that play a critical role in disease development. Currently, there is insufficient clinical evidence to support the function of menstrual Mg. The specific research facts examined MMg unique candidate genes and female hormonal factors that support their association and found MMg etiologic processes for generating an early diagnostic marker.

Keywords: Genetics, menstrual migraine, perimenopause, polymorphism

Introduction

Migraine is a type of headache that affects 14 percent of the worldwide population.[1] This sickness may express itself in many ways, with various degrees of severity and frequency. The most severe Mg is chronic Mg, which happens 15 times a month.[2] It is commonly accompanied by vascular,[3] mental,[4] and gastrointestinal[5] comorbidities all of which may delay headache onset. Due to high estrogen levels and their frequent oscillations, Mg prevalence and related impairment are incredibly considerable in young women.[6] It is relatively frequent, with a global frequency of 18.9 percent for women and 9.8 percent for males. The most prevalent variety of Mg is Mg without aura, which affects 70–80 percent of Mg patients, described by acute episodic Mg attacks enduring up to 72 h. Mg is more likely in infertile women in the days leading up to menstruation[7,8] due to an abrupt decline in estrogen levels known as "estrogen withdrawal."[9] Menstrual Mg (MMg) episodes are more intense, continue longer, and resist acute therapies than nonmenstrual Mg attacks. The monthly pattern of Mg is so prevalent that it is recognized in the International Classification of Headache Disorders (ICHD) as "pure menstrual Mg" and "menstrual-related Mg."[10] Photophobia, incapacity, and nausea are the three most crucial criteria for detecting Mg without aura: Patients who report two of these symptoms have an 81 percent likelihood of getting Mg, with three symptoms raising the risk to 93 percent.[11] "Menstrual Mg" is a word used to describe two forms of Mg connected to menstruation and is classed as such by the ICHD. Non-menstrual Mg is prevalent in MMg patients. Women with pure MMg experience frequent Mg episodes with or without aura only 2 days before menstruation and during the first 3 days of menstruation.[12]

A significant cause of menstrual Mg is estrogen, which affects glutamate and serotonergic systems in the CNS. There is an intricate relationship between serotonin and estrogen levels, which explains its connection to Mg. At least in part because estrogen levels are low during the latter part of the menstrual cycle, serotonin production declines, and calcitonin gene-related peptide (CGRP) levels rise. The vascular dilatation and mechanical sensitivity of the trigeminal nerve caused by these substances play a role in the pathophysiology of general Mg. The blood-brain barrier becomes more permeable, releasing pro-inflammatory chemicals into the pain-sensitive meninges.[13] Around menstruation, cranial nociception is more acute due to a reduction in endogenous opioid activity

Address for correspondence: Dr. Ramakrishnan Veerabathiran, Faculty of Allied Health Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam - 603 103, Tamil Nadu, India.
E-mail: rkgenes@gmail.com

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that aggravates the pain pathway. Genetic variations include higher expression of membrane protein channels and receptors implicated in the pathogenesis of Mg.[14]

Pathophysiology

The specific etiology of menstrual Mg is uncertain. According to Somerville's research, intramuscular estradiol valerate injections during the luteal phase of the menses might postpone the MMg beginning, which was the earliest connection between sex hormones and menstrual Mg. This may occur if serum estrogen levels fall below 45 to 50 pg/mL.[15] Female sex hormones alter Mg formation and pain transmission by many neurotransmitter systems. The activity of these systems fluctuates in response to variations in hormone concentrations. The μ-opioid system, for example, is controlled by estrogen. The level of progesterone and estrogen decreases in the late luteal phase is linked to a reduced ability to activate the μ-opioid system, which leads to pain vulnerability.[16,17]

Furthermore, estrogen increases glutamate excitatory neurotransmission while reducing gamma amino butyric acid (GABA) ergic activity, explaining why Mg aura is more prevalent in high-estrogen circumstances like pregnancy.[18] Allopregnanolone, a precursor of progesterone, may resist the impacts of estrogen by reducing cortical activity and increasing GABA receptor expression.[19] The pathophysiology of MMg is prostaglandin release and withdrawal in estrogen that has been recognized to date. Other methods are predicted to be known in the future. The level of estrogen and progesterone in the blood is reduced in the premenstrual time of menstruation.[20] Estrogen levels fall postovulation and before menstruation. However, only the premenstrual drop has been connected to Mg. It is uncertain whether this is because of a prolonged course of luteal phase liability to elevated estrogen levels; consequently, genetic impacts on nuclear estradiol receptors occur, e.g., the interaction of progesterone-estrogen.[21] Estrogens can trigger the endogenous opioid process that improves pain and emphasizes oxytocin decay, a neurohormone secreted by the hypothalamus, that may have an anti-Mg impact. In Mg sufferers, estrogens and oxytocin influence the release of calcitonin gene-related peptide (CGRP), the chemical responsible for Mg pain. [Figure 1].[22]

Genetics of Menstrual Mg

Genetic factors play an essential role in Mg physiological processes by reducing the trigger threshold for Mg episodes. While studies have demonstrated that genetic determinants have a role in Mg, gene discovery has proven problematic, in part owing to the disorder's significant prevalence in the population and genetic and clinical variability. Candidate genes are found which demonstrate a substantial relationship with Mg, and menstruation-associated Mg has been explained below [Table 1].[23]

Many factors may cause migraine, but it also has a vital hereditary factor. In genome-wide association studies (GWAS) of common Mg, single nucleotide polymorphisms (SNPs) in thirteen loci were discovered to have GWAS significance in connection to migraine.[28,29] Although the genes are implicated in various pathways, some have been connected to synapse or neural function. Hormone-related inheritable factor has yet to be revealed among migraine GWAS sites with genome-wide significance. Due to the increased occurrence of migraine in women, several candidate gene studies have looked at the consequence of female hormone–related genes, such as estrogen and progesterone receptors.[30-33] MMg genetic analyses have predominantly concentrated on hormone genes, specifically, those associated with estrogen, with conflicting results. Spectrin Repeat Containing, Nuclear Envelope 1 (*SYNE1*) was revealed to be positively associated by Rodriguez-Acevedo *et al*.[34-36]

Neuropilin-1 (*NRP1*) gene

A transmembrane protein encoded by neuropilin 1 is located on chromosome 10 (10p11.22), and it acts as a receptor for class 3 semaphorins, which regulate neuronal development through repulsive axonal transport in the neurological and vascular systems.[37] The activity of *NRP1* facilitates menstruation. Estrogen and progesterone act on the endometrium when produced by the ovary during the menstrual cycle by developing, altering, and shedding vasculature. Increased levels of estrogen and progesterone during the proliferative and secretory phase, when the vascular tissue develops and remodels.[38,39] Neuropilin-1 (*NRP1*)'s involvement in neurovascular tissue and menstruation pathways implies transmembrane protein function in the pathophysiology of MMg. The increase in activity of *NRP1* during menstruation might be that this marker is more predictive of MMg occurring during menstruation in association with endometrial prostaglandin release rather than estrogen "withdrawal."[37] Despite the lack of data on *NRP1* expression during menstruation, during the proliferative phase of endometrial remodeling, there is an increase in activity,[40] which decline in estrogen is considered to initiate MMg. Studies have found Mg-related SNPs in a particular menstrual Mg for a putative involvement of rs2506142 in this gene (OMIM: 602069). The recent GWAS studies have added to our understanding of migraine genetics. However, some migraine subtypes, such as MMg, remain unsolved, and further research is needed. In MMg, *NRP1* might play a particular role, though a replication in a large cohort is necessary to confirm this.[24]

Tumor necrosis factor (*TNF*) gene

The Tumor necrosis factor gene is situated on chromosome 6 (6p21.33), containing four exons. It is a pro-inflammatory cytokine that plays a role in several biological methods, such as the multiplication of cells, cell death, and cell movement. It is linked to pain and damage in neurons in response to certain conditions, including hypoxia and hypothermia, which strongly relate to practical ways that may impact MMg onset. This is primarily due to progesterone and estrogens' impact on inflammation, and this relationship might point to a straightforward process by which MMg originated. It has also been connected to migraine comorbidities, such as depression

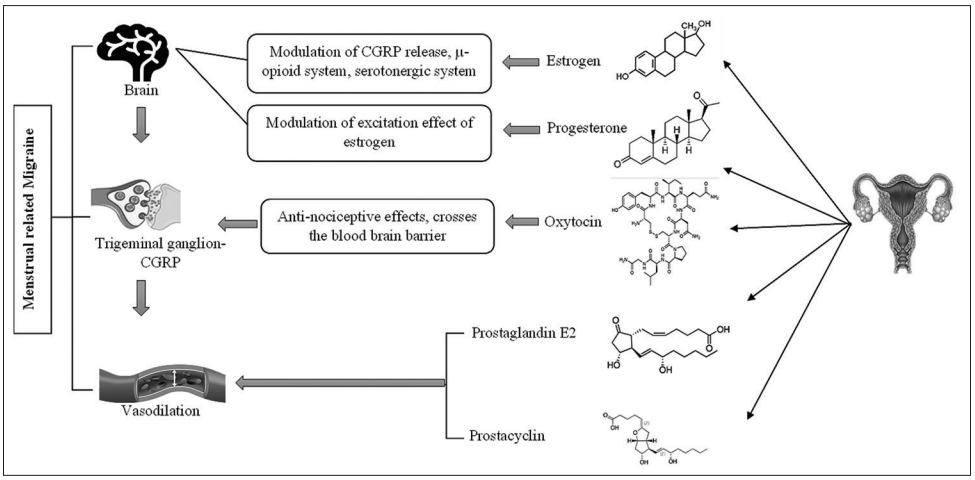

Figure 1: Pathophysiology of menstrual migraine

Table 1: Candidate genes associated with menstrual migraine

Gene symbol	Gene Name	Chromosome Location	Exon	Function	rs ID	Reference
NRP1	Neuropilin 1	10p11.22	18	Cell-surface receptor involved in the development of the cardiovascular system, in angiogenesis, in the formation of certain neuronal circuits and in organogenesis outside the nervous system. Mediates the chemorepulsant activity of semaphorins	rs2506142	[24]
TNF	Tumor necrosis factor	6p21.33	4	The primary role of TNF is in the regulation of immune cells. TNF, as an endogenous pyrogen, is able to induce fever, apoptotic cell death, cachexia, and inflammation, inhibit tumorigenesis and viral replication, and respond to sepsis	rs3093664	[25]
SYNE1	Spectrin repeat containing protein 1	6q25.2	154	This gene provides instructions for making a protein called Syne-1 that is found in many tissues, but it seems to be especially critical in the brain. The Syne-1 protein plays a role in the maintenance of the part of the brain that coordinates movement	rs9371601	[26]
COMT	Catechol-O-Methyltransferase	22q11.21	8	This gene provides instructions for making an enzyme called catechol-O-methyltransferase. Two versions of this enzyme are made from the gene. The longer form, called membrane-bound catechol-O-methyltransferase (MB-COMT), is chiefly produced by nerve cells in the brain.	rs4680	[27]

and irritable bowel illness.[41,42] The gene has been connected with nerve injury and distress in reaction to diverse cellular circumstances, such as hypoxia and hypothermia, consequently connected to metabolic pathways that affect MMg onset and Mg initiation.[43] The rs3093664 in *TNF* is an intronic SNP situated among exons 3 and 4, far from the intron intertwining sites. It was found to be linked with MMg.[25]

Spectrin repeat–containing protein 1 (*SYNE1*) gene

Spectrin repeat–containing protein 1 (*SYNE1*) originates in the nucleus membrane, localized on chromosome 6 (6q25.2), and is intricate in specific protein synergies, where it helps as a chaperone and structure for distinct necessary partners. The gene has been related to various head illnesses, including depression, cerebellar, and ataxias in spinocerebellar, which have overlapped with the ancestral headache, caused by variations and may directly impact MMg onset via these processes.[44] Fascinatingly, *SYNE1* is still situated nearby to the receptor of estrogen, and it has associated substantial variations within *SYNE1* to estrogen facilitated actions, including ovarian malignancy. Therefore, it is persuasive that the interaction found with MMg may signify connectivity to estrogen-associated implements. Furthermore, this concept is better supported because rs9371601 is similarly an intronic SNP among exons 13 and 14 of the gene, strongly associated with the menstrual migraine.[26] Previously, *SYNE1* polymorphisms were linked to estrogen-related events; hence, an expression link between *TNF* and *SYNE1* might explain why both genes are linked to MMg. In MMg, this pathway could represent differences between the effects of polymorphisms examined, linked to nearby SNPs of interest, on pathway signal transduction.[45]

Catechol-O-Methyltransferase (*COMT*) gene

The catechol-O-methyltransferase (*COMT*) gene, located on chromosome 22q11.21, encodes the primary enzyme

responsible for the breakdown of catecholamines. It is generated by tyrosine metabolism through a hydroxylase-related pathway. Two transcript isoforms are produced, creating a soluble protein and membrane-bound protein.[46] Reduced mitochondrial energy promotes a metabolic remodeling that pushes tyrosine metabolism towards the decarboxylation route rather than the hydroxylation pathway, resulting in decreased catecholamine synthesis and increased trace amine levels in the pain matrix as activation of the trigeminovascular system, which commences the attack.[35] It is the enzyme that is responsible for breaking down estrogen and catecholamines. At amino acid position 158 (Val158Met), the *COMT* rs4680 SNP produces a valine (Val) to methionine (Met) substitution, affecting the enzyme's thermal stability and activity. Human pain perception, cognitive traits, mental diseases, brain activity, and structural changes have been linked to the rs4680 gene.[27]

It has been suggested that a functional polymorphism of *COMT* may be associated with Parkinson's disease and other neuropsychiatric illnesses, including schizophrenia and bipolar affective disorders. A limited number of studies have looked at the link between *COMT* polymorphisms and MMg.[47] In a menstrual migraine cohort, Sutherland *et al*. looked at four SNPs in three genes involved in estrogen metabolism that were shown to affect levels of the enzyme. [29] Using Chi-square analysis, no significant differences in frequencies (allele/genotype) for the *COMT* and *CYP* SNPs genotyped were detected between menstrual migraineurs and controls ($P > 0.05$). As a result, no link between polymorphisms in the estrogen metabolism genes *COMT*, *CYP1A1*, or *CYP19A1* and MMg was discovered. More research is needed to determine if MMg ishereditarily distinct from other Mg subtypes and find risk genes.[47] *COMT* plays an important role in detoxifying a wide range of compounds in estrogen. Several environmental chemicals are taken into the body via food, tea, coffee, cigarettes, and drugs, which may alter enzyme activities. A decrease in serum magnesium levels or the release of prostaglandins can also cause MMg.[48]

Female Hormones and Menstrual Migraine

Menstruation takes 28 days; however, this may vary considerably owing to the uneven follicular phase. The follicular, ovulation, and luteal phase are the three stages of the menarche [Figure 2]. The beginning of menstruation is the follicular phase. Chemical signal from the hypophysis generates follicle-stimulating hormone (FSH), which stimulates the ovaries signaled by estrogen generated by growing follicles to limit FSH production and release luteinizing hormone instead (LH). The eggs are released when the follicle breaks, owing to an upsurge in LH. The luteal phase occurs between ovulation and menstruation; by the influence of this phase, the corpus luteum produces progesterone and estrogen, which develops into a follicle. High hormone concentrations affect FSH and LH levels. After ovulation, progesterone and estrogen levels quickly fall in the absence of pregnancy. Progesterone levels drop at this point of the cycle, increasing Mgs.[19]

Progesterone and Migraine

A progesterone deficiency initially causes menstrual Mg during the luteal phase. However, no research has been done to back up this claim. Somerville *et al*.[49] used progesterone pills to heal six women who experienced Mg problems during the late luteal phase, indicating that progestogen "withdrawal" was a plausible reason. Even though four of these women's menstruation was delayed, five got Mg episodes during their regular periods, which had nothing to do with progesterone levels in their blood. In subsequent research, women with ovulatory failure had Mg episodes after receiving depot estradiol, associated with declining estrogen concentrations. Progestogen therapy was shown to prevent menstrual Mgs; the menstrual cycle was suppressed.

Estrogen and Migraine

The existence of elevated estrogen levels in women with Mg with aura during the usual menstrual cycle has been proven. However, it is unknown whether women who experience Mgs with aura have episodes not associated with an aura. Estrogen levels vary during the menstrual cycle, with substantial changes, exposing Mg sufferers to this specific Mg trigger. Furthermore, due to hormonal changes, some women continue to make multiple levels of oestrone and oestradiol in different ovarian areas, including adipose tissue. Consequently, not all womens are deficient in estrogen after menopause which may mean that their standard doses of estrogen replacement may be excessively high.[50]

Oral contraceptives (OCPs)

Estrogen-containing OCPs are often linked to increased headache, particularly during the placebo week. It is similar to an average menstrual week, decreasing plasma estrogen levels. The elevated estrogen levels with OCPs showed a more fantastic estrogen transition during the OCP placebo week than throughout the untreated menstrual cycle. Mg attacks are ten times more likely to occur in women who take OCPs than women who do not. When OCPs are used by women who already have an Mg pattern, 18% to 50% of them see an increase in headaches. Mgs are less likely to worsen while using progestogen contraception.[51]

Ovarian hormones and neurotransmitters

Ovarian hormones impact neurotransmitter systems, which govern a wide range of brain functions. On the other hand, the impact of hormones is influenced by several factors. The specificity of the location and neurons where hormones exert their effects is one of the most critical variables in controlling neurotransmitters by hormones. In this respect, estrogen or progesterone may increase the gene expression coding certain enzymes in a particular part of the brain, whereas it lowers the release or activity of specific neurotransmitters in another part of the brain. The activation or inhibition of various systems is a second variable. For example, greater estrogen levels trigger the Gonadotropin hormone-releasing hormone (GnRH) production during the menstrual cycle, whereas lower levels

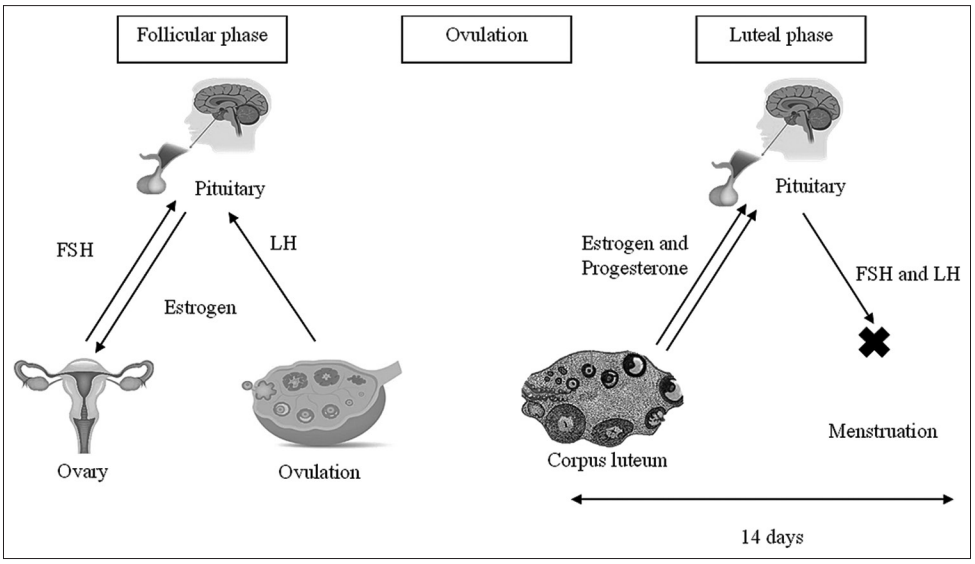

Figure 2: Phases of menstrual cycle

suppress it. Furthermore, when estrogen and progesterone operate together, they have distinct effects than when they act independently.[48]

Conclusion

Mg is the third most prevalent cause of ailment in sexually active women, with considerable effect on their quality of life. Although our knowledge of the genetic basis of recent GWAS increased Mg, the etiologies of MMg are not known, demanding an additional targeted investigation. This study's conclusions contained evidence for the relevance of genetics in the pathophysiology of MMg. More study in these areas is needed to understand MMg better. *NRP1*, *TNF*, *SYNE1*, and *COMT* are the candidate genes explained in this review. Among these, *NRP1* genes may contribute specifically to the development of MMg. However, more studies are required to verify this theory.

Furthermore, a greater awareness of these systems and their function in MMg is necessary to develop effective therapeutics and prevention strategies. Various genetic variations are directly or indirectly responsible for the development of MMg and may be utilized as biomarkers to identify MMg in its early stages. Other Mg research, including biochemical and neuroimaging studies, will benefit from this by providing data and critical insights for directing future genetic investigations.

Author's contributions

IBK has written the contents of this manuscript.

VM edited the figures.

RV designed the study, corrected and approved the manuscript for submission.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

All authors have read and approved the manuscript.

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Conflicts of interest

There are no conflicts of interest.

References

1. Stovner LJ, Nichols E, Steiner TJ, Abd-Allah F, Abdelalim A, Al-Raddadi RM, *et al*. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: A systematic analysis for the Global burden of disease study 2016. Lancet Neurol 2018;17:954-76.
2. Headache classification committee of the International headache society (IHS) the International classification of headache disorders, 3rd edition. Cephalalgia 2018;38:1-211.
3. Sacco S, Olivieri L, Bastianello S, Carolei A. Comorbid neuropathologies in migraine. J Headache Pain 2006;7:222-30.
4. Minen MT, De Dhaem OB, Van Diest AK, Powers S, Schwedt TJ, Lipton R, *et al*. Migraine and its psychiatric comorbidities. J Neurol Neurosurg Psychiatry 2016;87:741-9.
5. Arzani M, Jahromi SR, Ghorbani Z, Vahabizad F, Martelletti P, Ghaemi A, *et al*. Gut-brain axis and migraine headache: A comprehensive review. J Headache Pain 2020;21:15.
6. Delaruelle Z, Ivanova TA, Khan S, Negro A, Ornello R, Raffaelli B, *et al*. Male and female sex hormones in primary headaches. J Headache Pain 2018;19:117.
7. Stewart WF, Lipton RB, Chee E, Sawyer J, Silberstein SD. Menstrual cycle and headache in a population sample of migraineurs. Neurology 2000;55:1517-23.
8. MacGregor EA, Hackshaw A. Prevalence of migraine on each day of the natural menstrual cycle. Neurology 2004;63:351-3.
9. MacGregor EA, Frith A, Ellis J, Aspinall L, Hackshaw A. Incidence of migraine relative to menstrual cycle phases of rising and falling

estrogen. Neurology 2006;67:2154-8.
10. Granella F, Sances G, Allais G, Nappi RE, Tirelli A, Benedetto C, *et al*. Characteristics of menstrual and nonmenstrual attacks in women with menstrually related migraine referred to headache centres. Cephalalgia 2004;24:707-16.
11. Lipton RB, Dodick D, Sadovsky RE, Kolodner K, Endicott J, Hettiarachchi J, *et al*. A self-administered screener for migraine in primary care: The ID migraine™ validation study. Neurology 2003;61:375-82.
12. Frederiksen SD, Bekker-Nielsen Dunbar M, Snoer AH, Deen M, Edvinsson L. Serotonin and neuropeptides in blood from episodic and chronic migraine and cluster headache patients in case-control and case-crossover settings: A systematic review and meta-analysis. Headache 2020;60:1132-64.
13. Brunklaus A, Schorge S, Smith AD, Ghanty I, Stewart K, Gardiner S, *et al*. SCN1A variants from bench to bedside-improved clinical prediction from functional characterization. Hum Mutat 2020;41:363-74.
14. Calhoun AH. Understanding menstrual migraine. Headache 2018;58:626-30.
15. Smith YR, Stohler CS, Nichols TE, Bueller JA, Koeppe RA, Zubieta JK. Pronociceptive and antinociceptive effects of estradiol through endogenous opioid neurotransmission in women. J Neurosci 2006;26:5777-85.
16. Paredes S, Cantillo S, Candido KD, Knezevic NN. An association of serotonin with pain disorders and its modulation by estrogens. Int J Mol Sci 2019;20:5729.
17. Eikermann-Haerter K, Kudo C, Moskowitz MA. Cortical spreading depression and estrogen. Headache 2007;47(Suppl 2):S79-85.
18. González SL, Meyer L, Raggio MC, Taleb O, Coronel MF, Patte-Mensah C, *et al*. Allopregnanolone and progesterone in experimental neuropathic pain: Former and new insights with a translational perspective. Cell Mol Neurobiol 2019;39:523-37.
19. MacGregor EA. Oestrogen and attacks of migraine with and without aura. Lancet Neurol 2004;3:354-61.
20. Vetvik KG, MacGregor EA. Menstrual migraine: A distinct disorder needing greater recognition. Lancet Neurol 2021;20:304-15.
21. Ornello R, De Matteis E, Di Felice C, Caponnetto V, Pistoia F, Sacco S. Acute and preventive management of migraine during menstruation and menopause. J Clin Med 2021;10:2263.
22. Ferrari MD, Goadsby PJ. Migraine as a Cerebral Ionopathy with Abnormal Central Sensory Processing. New York: Elsevier; 2006.
23. Chen H, Chédotal A, He Z, Goodman CS, Tessier-Lavigne M. Neuropilin-2, a novel member of the neuropilin family, is a high affinity receptor for the semaphorins sema E and Sema IV but not Sema III. Neuron 1997;19:547-59.
24. Pollock CE, Sutherland HG, Maher BH, Lea RA, Haupt LM, Frith A, *et al*. The NRP1 migraine risk variant shows evidence of association with menstrual migraine. J Headache Pain 2018;19:31.
25. Hughes GC. Progesterone and autoimmune disease. Autoimmun Rev 2012;11:A502-14.
26. Doherty JA, Rossing MA, Cushing-Haugen KL, Chen C, Van Den Berg DJ, Wu AH, *et al*. ESR1/SYNE1 polymorphism and invasive epithelial ovarian cancer risk: An ovarian cancer association consortium study. Cancer Epidemiol Biomarkers Prev 2010;19:245-50.
27. Ira E, Zanoni M, Ruggeri M, Dazzan P, Tosato S. COMT, neuropsychological function and brain structure in schizophrenia: A systematic review and neurobiological interpretation. J Psychiatry Neurosci 2013;38:366.
28. Anttila V, Winsvold BS, Gormley P, Kurth T, Bettella F, McMahon G, *et al*. Genome-wide meta-analysis identifies new susceptibility loci for migraine. Nat Genet 2013;45:912-7.
29. Sutherland HG, Champion M, Plays A, Stuart S, Haupt LM, Frith A, *et al*. Investigation of polymorphisms in genes involved in estrogen metabolism in menstrual migraine. Gene 2017;607:36-40.
30. Schurks M, Rist PM, Kurth T. Sex hormone receptor gene polymorphisms and migraine: A systematic review and meta-analysis. Cephalalgia 2010;30:1306-28.
31. Rodriguez-Acevedo AJ, Maher BH, Lea RA, Benton M, Griffiths LR. Association of oestrogen-receptor gene (ESR1) polymorphisms with migraine in the large Norfolk Island pedigree. Cephalalgia 2013;33:1139-47.
32. 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.
33. Ghosh J, Pradhan S, Mittal B. Multilocus analysis of hormonal, neurotransmitter, inflammatory pathways and genome-wide associated variants in migraine susceptibility. Eur J Neurol 2014;21:1011-20.
34. Sullivan AK, Atkinson EJ, Cutrer FM. Hormonally modulated migraine is associated with single-nucleotide polymorphisms within genes involved in dopamine metabolism. Open J Genet 2013;3:38-45.
35. De Marchis ML, Barbanti P, Palmirotta R, Egeo G, Aurilia C, Fofi L, *et al*. Look beyond Catechol-O-Methyltransferase genotype for cathecolamines derangement in migraine: The BioBIM rs4818 and rs4680 polymorphisms study. J Headache Pain 2015;16:37.
36. Rodriguez-Acevedo AJ, Smith RA, Roy B, Sutherland H, Lea RA, Frith A, *et al*. Genetic association and gene expression studies suggest that genetic variants in the SYNE1 and TNF genes are related to menstrual migraine. J Headache Pain 2014;15:62.
37. Punyadeera C, Thijssen VL, Tchaikovski S, Kamps R, Delvoux B, Dunselman GA, *et al*. Expression and regulation of vascular endothelial growth factor ligands and receptors during menstruation and post-menstrual repair of human endometrium. Mol Hum Reprod 2006;12:367-75.
38. Girling JE, Rogers PA. Regulation of endometrial vascular remodelling: Role of the vascular endothelial growth factor family and the angiopoietin-TIE signalling system. Reproduction 2009;138:883-93.
39. Hess AP, Schanz A, Baston-Buest DM, Hirchenhain J, Stoff-Khalili MA, Bielfeld P, *et al*. Expression of the vascular endothelial growth factor receptor neuropilin-1 in the human endometrium. J Reprod Immunol 2009;79:129-36.
40. Oertelt-Prigione S. Immunology and the menstrual cycle. Autoimmun Rev 2012;11:A486-92.
41. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, *et al*. A meta-analysis of cytokines in major depression. Biol Psychiatry 2010;67:446-57.
42. Bashashati M, Rezaei N, Bashashati H, Shafieyoun A, Daryani NE, Sharkey KA, *et al*. Cytokine gene polymorphisms are associated with irritable bowel syndrome: A systematic review and meta-analysis. Neurogastroenterol Motil 2012;24:1102-e566.
43. Christopherson K, Hromas R. Chemokine regulation of normal and pathologic immune responses. Stem Cells 2001;19:388-96.
44. Noreau A, Bourassa CV, Szuto A, Levert A, Dobrzeniecka S, Gauthier J, *et al*. SYNE1 mutations in autosomal recessive cerebellar ataxia. JAMA Neurol 2013;70:1296-301.
45. Mathew PG, Dun EC, Luo JJ. A cyclic pain: The pathophysiology and treatment of menstrual migraine. Obstgynecsurvey 2013;68:130-40.
46. Tammimäki A, Männistö PT. Catechol-O-methyltransferase gene polymorphism and chronic human pain: A systematic review and meta-analysis. Pharmacogenet Genomics 2012;22:673-91.
47. Park JW, Lee KS, Kim JS, Kim YI, Shin HE. Genetic contribution of catechol-O-methyltransferase polymorphism in patients with migraine without aura. J Clin Neurol 2007;3:24-30.
48. Martin VT, Behbehani M. Ovarian hormones and migraine headache: Understanding mechanisms and pathogenesis--Part I. Headache 2006;46:3-23.
49. Somerville BW. The role of progesterone in menstrual migraine. Neurology 1971;21:853.
50. Chai NC, Peterlin BL, Calhoun AH. Migraine and estrogen. Curr Opin Neurol 2014;27:315-24.
51. Legato MJ, Bilezikian JP, editors. Principles of Gender-Specific Medicine. Gulf Professional Publishing; 2004.