Genetics of Menstrual Migraine and Their Association with Female Hormonal Factors

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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,[1] mental,[4] and gastrointestinal[9] 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 classified 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.
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.[30-35] 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.
and irritable bowel illness.\cite{41,42} The gene has been connected with nerve injury and distress in reaction to diverse cellular circumstances, such as hypoxia and hyperthermia, consequently connected to metabolic pathways that affect MMg onset and Mg initiation.\cite{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.\cite{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.\cite{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.\cite{26}

### Catechol-O-Methyltransferase (COMT) gene

The catechol-O-methyltransferase (COMT) gene, located on chromosome 22q11.21, encodes the primary enzyme
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. 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. 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 is hereditarily distinct from other Mg subtypes and find risk genes. 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.

**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 menstrual cycle [Figure 2]. The beginning of menstruation is the luteal 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.

**Progestosterone 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. used progesterone pills to heal six women who experienced Mg problems during the late luteal phase, indicating that progesterone “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. Progesterone 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 women are deficient in estrogen after menopause which may mean that their standard doses of estrogen replacement may be excessively high.

**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.

**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...
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. *NRPI, TNF, SYNE1*, and *COMT* are the candidate genes explained in this review. Among these, *NRPI* 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.

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