# Genetics of Menstrual Migraine: The Molecular Evidence

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**Abstract**

Migraine is considered to be a multifactorial disorder in which genetic, environmental and in the case of menstrual and menstrually related migraine, hormonal events influence the phenotype. Certainly the role of female sex hormones in migraine has been well established yet the mechanism behind this well known relationship remains unclear. This review focuses on the potential role of hormonally related genes in migraine, summarises results of candidate gene studies to date and discusses challenges and issues involved in interpreting hormone related gene results. In light of the molecular evidence presented, we discuss future approaches for analysis with the view to elucidate the complex genetic architecture that underlies the disorder.

## Introduction

Female sex hormones have long been considered to play a role in migraine [1, 2]. There is little gender difference in migraine prevalence prior to puberty, yet after puberty, prevalence in women increases and exceeds that in men by approximately three-fold [3]. Furthermore, the different stages in a woman's life where changes in female hormone levels occur (such as puberty, pregnancy, and menopause) are commonly coupled with concurrent changes in migraine frequency and severity [4, 5]. Studies report that more than half of female migraineurs suffer migraine associated with the menstrual cycle [1, 4, 6]. The International Headache Society (IHS) has addressed this by including 'menstrual' and 'menstrually related' migraine in their revised classification of headache disorders [7]. Menstrual migraine (MM) is defined as migraine without aura starting on or between day 1 +/- 2 days of the menstrual cycle whereas menstrually related migraine (MRM) includes additional attacks outside of the menstrual period. Several studies have assessed the hypothesis that the fall in hormone levels prior to menstruation may trigger an attack. Treatment involving stabilisation of hormone levels has been effective in some women [8, 9] but certainly not in all women with MM or MRM [10]. Undoubtedly the correlation between sex steroid hormone levels and migraine is complex and not merely a positive or negative one. In an early paper, Epstein et al. (1975) suggested a role for hormonal variation in all women with migraine, but also a role for factors additional to the hormonal environment [11]. With continuing advances into the understanding of migraine as a multifactorial disorder with a significant genetic component, it is highly likely that genetic susceptibility is a most important additional factor in migraine development.

## Migraine Genetics

Family and twin studies have indicated a significant genetic component to migraine [12-14]. The degree to which migraine is genetically determined has been estimated in a 2003 study that looked at genetic variance across six countries and reported heritability estimates ranging from 34% - 57% [15]. While studies have reported an important role for genetic factors in migraine, gene identification has proven difficult, in part because of the high prevalence in the population and the genetic and clinical heterogeneous nature of the disorder. Unlike Familial Hemiplegic Migraine (FHM), a rare subtype of migraine with aura where defects in neuronal ion channel genes have been identified, in the more common forms of migraine both with and without aura (MA & MO), no causative mutations have been positively identified. All implicated variants to date are also present in the general population, and it is their increased frequency in migraineurs that has linked them to the disorder. Thus, in the case of MA and MO it appears likely that common variants in many susceptibility genes, each with weak to moderate individual effects, may account for much of the burden of the disorder.

## Steroid Hormones and Migraine

Various hypotheses may be proposed whereby genetic factors could interact with steroid hormones to impact on migraine susceptibility. Steroid hormones regulate a wide range of biological functions either through genomic (transcription dependent) or non-genomic (non-transcription dependent) mechanisms. Most importantly they can modulate the central nervous system and vascular tone [4]. Sex steroids are produced in the ovaries and adrenal glands. They are able to passively diffuse through the blood brain barrier with studies showing similar levels in the brain to circulating

levels [16]. The human brain produces several enzymes necessary for the production of steroids such as cytochrome $P450_{SCC}$, aromatase, 5alpha-reductase, 3alpha-hydoxysteroid dehydrogenase, 17 beta-hydroxysteriod dehydrogenase, and various other steroidogenic enzymes necessary for the production of estrogens, progesterone and androgens from cholesterol [17]. The brain also contains additional steroid metabolizing enzymes, including sulfotransferases and sulfohydrolases, which convert classic steroid hormones to a variety of neuroactive compounds. Thus it is understood that the brain can synthesize neurosteroids, which may act via their cognate receptor or other receptor systems [18] and have significant effects on neurotransmission within the brain.

***Effect on the CNS***

Steroid hormones are believed to have a considerable effect on serotonergic, catecholaminergic, glutamatergic, GABAergic and opiatergic systems, all postulated to play a role in migraine pathogenesis. Martin and Behbehani (2006) have reviewed the potential role of steroid hormones in structures/pathways that could increase or decrease the frequency, severity or duration of migraine headache and describe how ovarian hormones could potentially affect numerous loci within the trigeminal vascular pain pathway, the brainstem, and the meningeal artery [16, 19]. All such areas have been implicated in MM [20, 21] or migraine [22, 23]. Estrogen appears to play a role in serotonin synthesis and uptake [24, 25], while evidence exists for both progesterone and estrogen effects on serotonin degradation [26]. Estrogen treatment has been shown to upregulate gene expression of tyrosine hydroxylase involved in the synthesis of dihydroxyphenylalanine (DOPA), precursors of dopamine and noradrenaline and dopamine beta hydroxylase (DBH), the enzyme responsible of the

conversion of dopamine to noradrenaline, in animal and neuronal culture studies [27, 28] and both estrogen and progesterone may affect certain sub-types of adrenoreceptors [29, 30]. Glutamic acid is the major excitatory neurotransmitter in the brain while GABA is the main inhibitory neurotransmitter. Several studies have shown the effect of estrogen alone and the addition of progesterone on the glutamatergic system [16]. GABAergic neurons are strongly modulated by ovarian hormones with studies showing an effect of estrogen and progesterone and its metabolites on GABA receptors and cortical GABA levels [31, 32]. Animal models of FHM have shown that androgen and estrogen can modulate cortical spreading depression, a wave of neurological depolarization implicated in migraine aura [33, 34]. As FHM patients also experience attacks of MA and MO, these studies may have provided an important insight into the complex interplay of hormonal and genetic factors in migraine susceptibility.

***Steroid Hormone Receptors***

The predominant biological effects of steroid hormones are mediated through their cognate receptors, which are expressed in a wide range of target tissues, notably many regions of the CNS including cerebral blood vessels, and serotonin neurons. Mutations in steroid hormone receptors have been implicated in a number of human disease states including breast cancer, endometrial and ovarian cancer, and psychiatric disease [35, 36]. Given the potential involvement of steroid hormone receptors in migraine pathways, as well as evidence indicating that steroid hormone receptors can be activated in the absence of hormones [37], it is certainly plausible that genetic variants in hormone related genes may play a role in migraine.

## Hormonally Related Candidate Gene Studies

We first investigated this hypothesis in two Australian independent study groups of 504 IHS diagnosed migraineurs and 504 matched controls in total. We chose to examine the common synonymous G594A polymorphism located in exon 8 of the estrogen receptor1 (*ESR1*) gene (SNP rs 2228480) as it had previously shown an association with breast cancer, a disease in which complex hormonal influences are considered to play a role [38]. Although this variant shows little apparent effect on receptor function, we were interested in any potential interaction of subtle molecular changes with disease mechanisms. In addition, we considered the possibility that this locus may be in close proximity to an unidentified causal variant. Results of our study indicated a positive association of the *ESR1* G594A polymorphism with migraine (MA + MO) in both cohorts [39]. There was no apparent gender effect in the first study group and although the association was only seen in women and the MA subgroups in the second study group, we believe that the small numbers in the male and MO groups resulted in loss of power. Overall our results revealed that individuals with the *ESR1* 594A allele were twice as likely to suffer from migraine as those who carried the *ESR1* 594G allele.

We followed our pilot study with an investigation of the androgen receptor gene (*AR*) exon 1 CAG repeat and the progesterone receptor gene (*PR*) PROGINS insert in the same two study groups [40]. Expansion of the *AR* CAG repeat is considered to have an inhibitory effect on receptor function. This has been demonstrated to decrease negative feedback to the hypothalamus, resulting in increased serum androgen levels [41]. The PROGINS insert is considered to have a deleterious effect on progesterone receptor expression, through recombination or mis-splicing [42]. Our results showed

no significance for the *AR* CAG repeat, however the data showed an overall significant association of the *PR* PROGINS insert with migraine in the two large study groups. Individuals who carried the PROGINS insert were 1.8 times more likely to suffer migraine than those without. Because we found a positive association of the *PR* PROGINS insert and the *ESR1* G594A polymorphism with migraine in the same large study population, we performed interaction analysis to determine if possession of both risk genotypes conferred an increased risk of migraine. This analysis revealed that individuals who carried at least one risk allele from both genes were 3.2 times more likely to suffer migraine than those who carried no risk alleles. We further analysed additional polymorphisms in *ESR1*, the *PvuII* C/T polymorphism in intron 1 (rs2234693) and the C325G polymorphism (rs1801132) which is located in the hormone binding region in exon 4. The *PvuII* locus has been associated with variation in estradiol levels in post menopausal women [43] along with an increased risk of stroke in men [44]. Our analysis of these loci showed no significant association with migraine in 240 migraineurs matched with 240 controls although we did note a higher frequency of the exon 4 C325C genotype in male migraineurs compared to controls [45].

Several research teams have since analysed all loci described above along with other loci in these genes with results summarized in Table 1. In 2005, Oterino and colleagues examined the *ESR1* C325G and G594A polymorphisms in a Spanish study group of 367 IHS diagnosed migraineurs and 232 controls [46]. They found a positive association with the C325G but not the G594A polymorphism in female migraineurs, and observed interaction between both loci with 45.5% of female migraineurs carrying at least one C325 allele or A594 allele compared to 22.4% in

control women. As there is no linkage disequilibrium between these two loci, Oterino and colleagues hypothesized that an unknown variant located between the two may be responsible for the association. In 2006, Kaunisto and colleagues analysed 24 *ESR1* polymorphisms including C325G and G594A in 898 Finnish individuals with MA (784 fulfilled IHS criteria and 114 did not) and 900 controls. Their analyses showed significance at the C325G locus and 4 other loci in intron 3 which were in high linkage disequilibrium, however their results did not remain significant when corrected for multiple testing, which they did by multiplying p values by eighteen. Hence results were reported as negative.

Due to the association of migraine with vertigo, Lee and colleagues (2007) chose to test the *ESR1* C325G and G594A polymorphisms and the *PR* PROGINS insert in migraine-associated vertigo (MAV) [47]. They studied 150 unrelated MAV patients disgnosed at the UCLA Neurotology Clinic compared to 145 controls. Results revealed that although *ESR1* was not associated with MAV in their sample, individuals carrying the *PR* risk allele were twice as likely to suffer MAV. Due to the likelihood that MAV is a subset of migraine and the fact that all cases met IHS criteria for migraine, they reported their results as a replication of our previously reported association of *PR* PROGINS with migraine.

In 2008 Oterino and colleagues analyzed the interaction of 5 steroid hormone genes in 356 IHS diagnosed Spanish migraineurs (MA + MO) and 374 controls along with 134 pedigrees using a family based association approach [48]. They hypothesized that due to the likely polygenic nature of migraine, multi-locus analysis would better predict the migraine phenotype. Along with the *ESR1* C325G locus, they analysed the

Ser680Asn polymorphism of the follicle stimulating hormone receptor gene *FSHR*, C1672T of *CYP19A1*, which encodes the enzyme that converts androgens to estradiol, Gly75Gly of *NRIP1*, which codes for the protein that modulates transcriptional activity of ESR, and A2100G of *ESR2*. Single gene analysis implicated the *ESR1* C325G locus in migraine and *FSHR*, *ESR1* and *ESR2* in MA. Multilocus study showed genetic interaction between the *ESR2-ESR1-FSHR* loci in relation to migraine, and for the MA phenotype. Individuals with the risk *ESR2-ESR1-FSHR* haplotype were nearly twice as likely (OR =1.97) to suffer from the MA/MO phenotype. The difference was higher for the MA phenotype (OR = 2.43). These results were also corroborated using the family based approach. In 2009 Corominas and colleagues examined *ESR1* C325G and G594A as well as a synonymous polymorphism in exon 1 (rs2077647) along with *PR* PROGINS in 210 Caucasoid IHS diagnosed migraineurs and 210 controls. Results did not show a role for any of these variants in their study group. In a later study, Joshi and colleagues (2009), explored the *ESR1 PvuII* polymorphism, the *ESR1* C325G polymorphism and *PR* PROGINS for in genetic susceptibility to migraine by single gene, haplotype and interaction analysis in a North Indian population of 217 IHS diagnosed migraineurs and 217 matched controls [49]. Single gene analysis showed significant association of the *ESR1 PvuII* polymorphism with MA in females while interestingly, the PR PROGINS insert showed protection in females. No interaction was identified.

Overall, studies analysing hormonally related genes for a role in migraine do not support the involvement of *AR*, *CYP19A1* or *NRIP1* yet despite variation in results there is support for a potential role of *ESR1* and *PR*, and possibly *ESR* and *FSHR* in migraine. To summarise, *ESR1* and *PGR* PROGINS were first identified in an

Australian study group. *ESR1* was corroborated in a Spanish study group, suggesting an unknown causal variant between exon 4 and exon 8. Five *ESR1* loci around exon 4 were also implicated in a large Finnish study group however were not reported as significant after multiple testing. *PR* but not *ESR1* was implicated in migraine associated vertigo in the USA. Notably, all patients met IHS diagnostic criteria for migraine. Multilocus analysis in a Spanish study group again corroborated *ESR1* at the exon 4 locus and also implicated *ESR2* and *FSHR*. There were significant interaction at all three loci. A role for *ESR1* and *PR* PROGINS was later reported in a North Indian study group. Only in a small Caucasoid non age-matched study group recruited from Spain was *ESR1* and *PR* reported as negative. Hence there is credible evidence that several common variants in *ESR1*, the *PR* PROGINS insert, and possibly *ESR2* and *FSHR* predispose to migraine susceptibility. Notably, these variants may play a more significant role in MM and MRM and it is important that studies are undertaken in well defined clinically characterised MM pops to clarify their potential role.

## Future Research

In the case of common complex diseases such as migraine, it has been proposed that variants of as few as 20 susceptibility genes, each of which has weak to moderate individual effects, may account for ~50% of the burden of the disease [50]. In this review we have focussed on the role of hormonally related genes in migraine susceptibility and provided evidence from candidate gene studies that variants in *ESR1*, *PR* and possibly *ESR2* and *FSHR* appear to play a role in migraine susceptibility in some populations. It is important to note that not all initial studies correlated with subsequent studies, which may be due to experimental bias, genuine

diversity in the populations or low replication power in the initial study. It has been suggested that very low initial P values are required to achieve a replication power of 80% (initial 0.005 is required at alpha 0.05) and a P value just under the nominal (alpha) results in just 50% replication power [51]. Further, because migraine susceptibility may be influenced by complex genetic architecture such as multiple epistatic and gene - environment interactions, single loci that contribute only small influences on disease susceptibility in some (but not all) individuals may be difficult to identify as well as difficult to replicate in independent studies.

In the case of MM and MRM, it is certainly plausible that the environment (the hormonal milieu) interacts with gene regulation, leading to a dysregulation of the nervous system and a subsequent migraine attack. Welch and colleagues (2006) have formulated a credible hypothesis to explain how the neuronal events modulated by steroid hormones may lead to migraine and have evaluated their hypothesis in animal studies. They have shown that ovarian steroid cycling is strongly linked to the expression of neuropeptide Y (NPY) and galanin genes in the trigeminal ganglia of cycling female mice. Therefore, the excitability of the trigeminal membrane known to be induced by estrogen, may not be correctly counterbalanced by the inhibitory effects of NPY and galanin on the trigeminal membrane during the shift of estrogen levels. This “mismatch” of modulation of the trigeminal membrane may predispose to trigger the cascade of molecular events present during migraine attacks. Based on this animal model, the hypothesis would be that an abnormal trigeminal peptide in the trigeminal ganglia will trigger migraine episodes during menstrual cycle [52, 53]. As ESR1 is localized to trigeminal ganglia, any alterations in receptor function may

enhance this effect. Clinical research in MM patients will be necessary to test this theory of modulation of estrogen on neuronal function.

Interestingly, while the efficiency of estrogen therapy shows inconsistent evidence for MM prevention, serotoninergic receptor agonist treatment (triptan) has given robust and positive results in MM prophylaxis. As described in this review, sex steroids modulate neurotransmission in the brain and influence the activity of neurotransmitter systems including the serotoninergic system. However, the mechanisms underlying the benefit of triptan for MM prevention are not yet fully explored. The influence of estrogen on the serotoninergic system may also be involved in the comorbidities previously reported with MM such as depression, panic disorders and phobia. Migraine sufferers have 2 to 4 times more chance to develop one of these disorders. Further studies are necessary to characterize the mechanistic basis of the association between MM and neuropsychiatric disorders.

## Conclusion

Study results presented in this review highlight the need for further carefully designed studies, perhaps focussing on an ‘enriched’ study group of MM or MRM patients whose migraine is strongly influenced by hormonal events. The study groups should be well defined with similar inclusion criteria for follow-up studies. Identification of these common genetic factors should lead to a more targeted approach to prevention and treatment particularly in the case of MM and MRM where major environmental components (the hormonal milieu) most likely interact with genetic susceptibility. Pharmacological, dietary, or lifestyle interventions among such genetically predisposed individuals may have a positive effect on the clinical course of migraine.

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Table 1. List of published association studies analysing hormone related genes for a role in migraine

| Authors | Gene/s analysed | Locus | Sample | Results |
|---|---|---|---|---|
| **Joshi et al., 2009** | ***ESR1*** | **PvuII** | **84MA/133MO, 217C** | **Significant association (*p=0.000*)** |
| | | **C325G** | **84MA/133MO, 217C** | **No association** |
| | ***PR*** | **PROGINS** | **84MA/133MO, 217C** | **Protective affect in females (*p=0.002*)** |
| **Corominas et al., 2009** | ***ESR1*** | **T30C** | **86MA/102MO/22HM, 210C** | **No association** |
| | | **C325G** | **86MA/102MO/22HM, 210C** | **No association** |
| | | **G594A** | **86MA/102MO/22HM, 210C** | **No association** |
| | ***PR*** | **PROGINS** | **86MA/102MO/22HM, 210C** | **No association** |
| **Oterino et al., 2009** | ***ESR1**** | **C325G** | **198MA/158MO, 374C** | **Significant association MA, migraine, interaction (*p=0.005*)** |
| | ***ESR2**** | **A2100G** | **198MA/158MO, 374C** | **Significant association MA, migraine, interaction (*p=0.005*)** |
| | ***FSHR**** | **Ser680Asn** | **198MA/158MO, 374C** | **Significant association MA, migraine, interaction (*p=0.005*)** |
| | ***NRIP1*** | **Gly75Gly** | **198MA/158MO, 374C** | **No association** |
| | ***CYP19A1*** | **C1672T** | **198MA/158MO, 374C** | **No association** |
| **Lee et al., 2007** | ***ESR1*** | **C325G** | **150MAV, 145C** | **No association** |
| | ***PR*** | **PROGINS** | **150MAV, 145C** | **Significant association (*p=0.001*)** |
| **Kaunisto et al., 2006** | ***ESR1*** | **C325G** | **784MA/114Mig, 900C** | **No association after correction for multiple analyses** |

| | | | | |
|---|---|---|---|---|
| | | **G594A** | **784MA/114Mig, 900C** | **No association** |
| | | **22 other loci** | **784MA/114Mig, 900C** | **No association** |
| **Oterino et al., 2005** | ***ESR1*** | **C325G** | **197MA/170MO, 232C** | **Significant association in women (*p=0.012*)** |
| | | **G594A** | **197MA/170MO, 232C** | **No association** |
| **Colson et al., 2006** | ***ESR1*** | **PvuII** | **240MA+MO, 240C** | **No association** |
| | | **C325G** | **240MA+MO, 240C** | **No association** |
| **Colson et al., 2005** | ***AR*** | **CAG** | **575MA+MO, 575 C** | **No association** |
| | ***PR**** | **PROGINS** | **575MA+MO, 575 C** | **Significant association (*p=0.039*), *PR/ESR1* interaction** |
| **Colson et al., 2004** | ***ESR1**** | **G594A** | **575MA+MO, 575 C** | **Significant Association (*p=0.008*)** |

**MA = migraine with aura, MO = migraine without aura, Mig = unclassified migraine, HM = hemiplegic migraine, MAV = migraine associated vertigo, * denotes interaction**