Review

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Sex hormone-related polymorphisms in endometriosis and migraine: A narrative review

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Abstract

Some evidence indicates endometriosis and migraine have a common genetic predisposition in sex-hormone genes, which could have important implications for the treatment of these two heterogenous conditions. To date, the genes responsibility remains unknown. Based on the biological hypothesis that polymorphisms of genes involved in sex-hormone pathways may influence estrogen levels and phenotypes of both disorders, we did a literature search for candidate sex-hormone genes and genes involved in the metabolism of estradiol. The aim was to review the evidence for shared sex-hormone-related polymorphisms between endometriosis and migraine and provide an exhaustive overview of the current literature. We included case-control studies investigating associations between candidate sex-hormone-related genes and the disorders endometriosis and migraine, respectively. Results showed three overlapping sex-hormone-associated polymorphisms in estrogen receptor genes that are associated with both conditions. To confirm possible associations with other sex-hormone genes, larger studies are needed.

Keywords

endometriosis, migraine, polymorphism, sex hormone genes, sex hormone receptor

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Introduction

Endometriosis and migraine are two distinctive disorders associated with chronic pain, inflammation and a high grade of disability. Endometriosis is a common gynecological disease where endometrium-like tissue is manifested outside the uterine cavity.[1] Migraine, on the other hand, is a neurological disorder distinguished by recurrent headache attacks.[2] Based on the high prevalence in women during their reproductive life phase, it is assumed that estrogens or other female sex hormones might play a crucial role in the pathophysiology of both conditions. There is also some evidence that both conditions might share a common genetic background.[3,4] The lifetime prevalence of endometriosis is at least 10% and the global prevalence of migraine in women is 18.9%, which corresponds to over a billion women suffering worldwide.[5,6] Both conditions generate a huge social and economic burden and exert a significant negative impact on women's quality of life.[7–9] Migraine is the number one cause of disability in women during their reproductive years (aged 15 - 49 years).[10,11] Large twin studies indicate that both disorders have a heritable trait, with heritability estimated to be between 30–60% for migraine and circa 50% for endometriosis, indicating that genes are of importance in the etiology of both conditions.[12–16] Therefore, it has been suggested that endometriosis and migraine might be comorbidities, at least in a subset of women.[3] Menstruation is a major trigger for endometriosis-associated pain and menstrual-related migraine.[17,18] In women, migraine typically starts during puberty and resolves during menopause. More than

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50% of women report an association between migraine and their menstrual bleeding.[19] Both disorders are estrogen-dependent and may lead to exceptionally strong symptoms during menstruation.[18,20]

The role of female sex hormones in the pathogenesis of migraine is well established.[21] The drop of estrogen levels at the end of the menstrual cycle and at the beginning of the hormone-free interval in users of exogenous estrogens plays a crucial role in the pathophysiology of migraines in women.[22–24] In addition, it has been shown that the use of combined oral contraceptives in the standard regimen may initiate and worsen migraine in predisposed women.[25–28] Interestingly, a positive impact on the frequency of migraine episodes and the intensity of pain was observed in a continuous regimen with Desogestrel, a progestin-only contraceptive.[29,30] Likewise, endometriosis symptoms can be successfully treated with hormones, in particular progestins.[31,32]

In line with the biological hypothesis that polymorphisms of genes involved in sex-hormone pathways may influence estrogen levels, we aimed to study the main sex-hormone genes (ESR1, ESR2, PGR, FSHR, AR, SHBG) and selected the most regularly studied genes affecting the metabolism of estradiol (COMT, NRIP1, CYP1A1, CYP17A1, CYP19A1).[33] There are two types of estrogen receptor (ESR) genes; estrogen receptor 1 (ESR1 or ER-alpha) and estrogen receptor 2 (ESR2 or ER-beta). Estrogen levels rise in the early phase of the cycle as a result of increasing levels of follicle stimulating hormone (FSH). During the menstrual cycle, not only estrogen levels but also levels of FSH, progesterone, and androgens fluctuate. Therefore, FSH receptor (FSHR), progesterone receptor (PGR), and androgen receptor (AR) genes must also be investigated as a potential source for a genetic predisposition. The PGR gene has two protein isoforms that modulate the biological action of progesterone: isoform A (PRA), which is capable of inhibiting the activation of the estrogen receptors, and isoform B (PRB), which has the capacity to activate the estrogen receptors.[34] Similar to the ESR, the PGR can undergo ligand-independent activation and is involved in various intracellular signaling pathways. A specific polymorphism in the PGR gene called PROGINS seems to impact the ligand-binding and the entire signaling pathway.[35] Moreover, the sex hormone-binding globulin (SHBG) gene, which codes for a glycoprotein that binds to androgens and estrogens, is of interest. For the final step of estrogen biosynthesis, aromatase enzymes such as Cytochrome P450, family 19, subfamily A, polypeptide 1 (CYP19A1), which is involved in the conversion of androgen to estrogen, are essential. Another enzyme of this family, Cytochrome P450, Family 17, subfamily A, polypeptide 1 (CYP17A1), mediates both 17-alpha-hydroxylase and 17,20-lyase, which play a key role in androgen biosynthesis.[36] Finally, Cytochrome P450, family 1, subfamily A, polypeptide 1 (CYP1A1) participates in this process by catalyzing estrogen hydroxylation in extrahepatic tissues.[37] Other genes involved in estrogen metabolism, like catechol-estrogen or its products, including catechol-O-methyl-transferase (COMT) and nuclear receptor interacting protein 1 (NRIP1), could also have an impact. NRIP1 negatively regulates the transcription of estrogen receptors, particularly ESR1.[38] Catechol-O-methyltransferase (COMT) is an omnipresent enzyme of the estrogen metabolizing pathway that catalyzes O-methylation and subsequently inactivates estradiol metabolites.[39]

The association between most of these sex hormone gene variants (ESR1, ESR2, PGR, FSHR, AR, SBHG) and estradiol-metabolizing enzymes (NRIP1, COMT, and CYP family members) has been studied in women with migraine or endometriosis, however mostly for each disorder separately.[40–42] One large Australian family study with 815 monozygotic and 457 dizygotic twin-pair sisters with surgically confirmed endometriosis investigated whether the combination of the two conditions is the result of chance, selection bias, or common environmental and genetic factors. The findings suggest that endometriosis and migraine have common genetic predispositions with a bivariate heritability of 17%.[3]

To our knowledge, no previous study has specifically assessed the shared polymorphism between endometriosis and migraine. A possible genetic link could lead to better therapeutic care of these patients who suffer from chronic pain.

The aim of this narrative review is to obtain evidence for shared sex-hormone related polymorphisms in migraine and endometriosis. We aspire to present a comprehensive review of the existing literature and rationale for new research. We included studies focusing on sex-hormone receptor polymorphisms as well as those investigating enzymes affecting the metabolism of estradiol.

Materials and methods

Search strategy

We searched the PubMed database for publications from between January 2000 and July 2021 on sex hormone polymorphisms in endometriosis and migraine, respectively. To search and include as many related studies as possible, we used the MeSH terms "endometriosis" and "migraine disorders" with different combinations of the keywords for each sex hormone receptor. For Estrogen Receptor 1, for example, we used: ESR1, ESR1 gene, ESR alpha, ESR alpha gene, ESR1 polymorphism, ESR alpha polymorphism, estrogen receptor alpha polymorphism, estrogen receptor 1 polymorphism. We did the same for ESR2, FSHR, PGR, AR, SHBG and the estrogen-metabolizing association genes NRIP1, CYP1A1, CYP17A1, CYP19A1

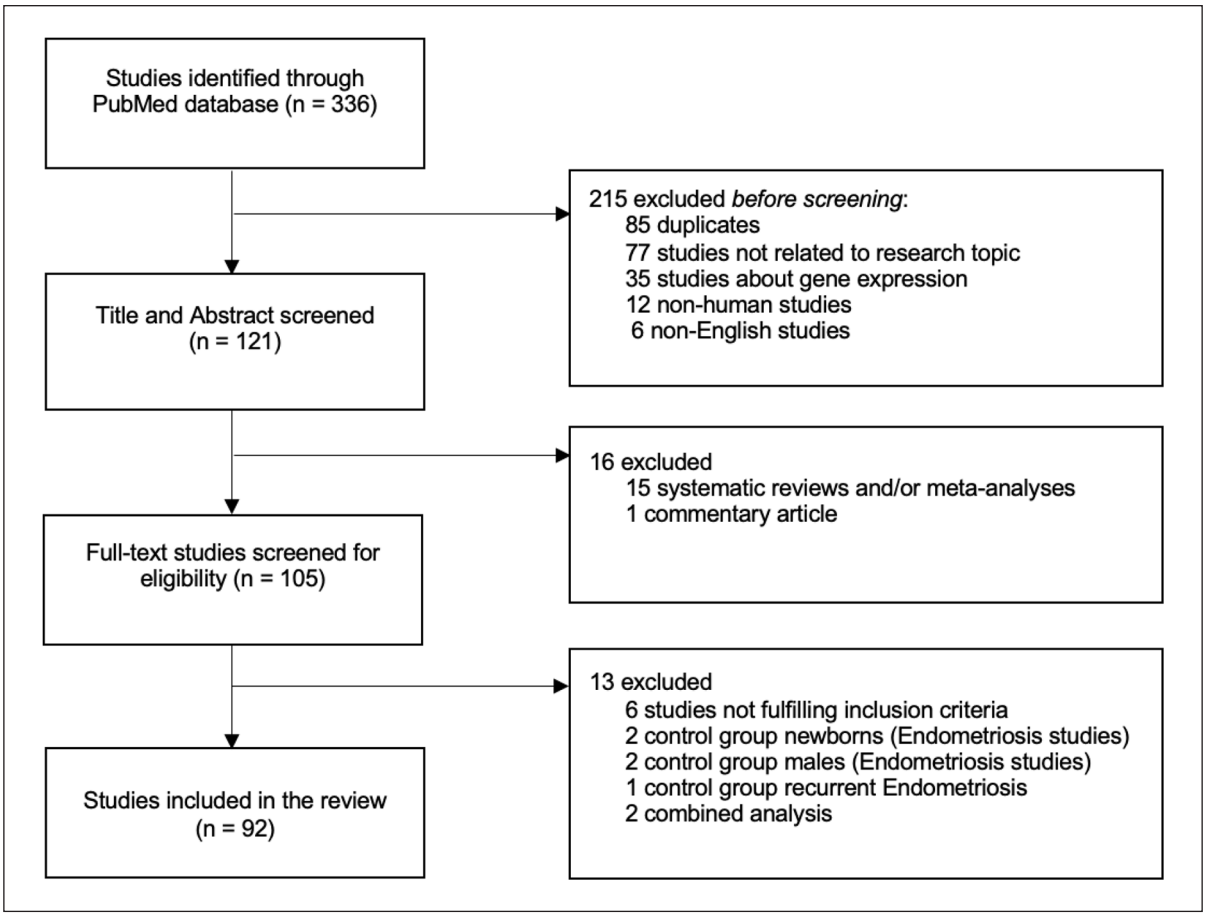

Figure 1. Flow diagram of the literature search and study selection process.

and COMT. For each sex hormone-related gene included in the present study, a literature search was performed to find case-control studies and potential previous reviews and/or meta-analyses in order to identify potential additional records through other sources.

Study selection

The eligibility of each publication was assessed independently by two reviewers (JFV and GM). After the titles and abstracts were screened, the full text of articles eligible for our review was examined. Studies had to meet the following inclusion criteria: 1) published between January 2000—July 2021, 2) original case-control study investigating associations between polymorphisms in the candidate sex hormone genes (ESR1, ESR2, FSHR, PGR, AR, SHBG) and the estradiol metabolizing association genes (NRIP1, CYP1A1, CYP17A1, CYP19A1, COMT) and 3) diagnosis of endometriosis confirmed by surgery and/or histology and diagnosis of migraine according to the criteria of the International Headache Society (IHS).[2] While reviewing publications, a novel gene, the FSH beta-subunit (FSHB) gene, consisting of a FSH beta-subunit (FSHβ), was added to our gene selection.[43] A new literature search for this FSHB gene was carried out. We excluded systematic reviews and/or meta-analyses, commentary articles, and duplicated studies. In the endometriosis studies, control groups with unrelated males or neonates were excluded, considering endometriosis is a disease occurring in women of reproductive age. However, we included one study with a very large sample size that included both parents of the women with endometriosis, due to their comparable hereditary genetic makeup. Studies with self-reported or self-diagnosed endometriosis or migraine were excluded. We excluded two case-control studies that investigated the combination of two sex hormone polymorphisms[44,45] (Supplemental Table S1). Figure 1 summarizes the study selection process for identifying eligible studies.

Data extraction

For each eligible study, data were extracted by one investigator (JFV) using a standardized Microsoft Excel spreadsheet and checked by a second investigator (GM). Discrepancies were resolved through discussion. The following data were listed for each study: Author, year of publication, country in which the research was conducted, ethnicity of the women,

sample size, sex hormone gene, dbSNP (RefSNP or rs),[46] associated alleles if available, and the type of genetic analysis. For the endometriosis studies, we also extracted the type of control population and the endometriosis stage according to the American Society for Reproductive Medicine (ASRM) classification or the American Fertility Society score (AFS) respectively, if available.[47]

Results

In total, 92 studies fulfilled the inclusion criteria for this review (Figure 1). The characteristics of the included studies are listed in Table 1. For some of the candidate genes, a broad variety of SNPs were investigated. SNPs that were mentioned more than once in our literature search are grouped, see Table 1. Other SNPs that have been mentioned only once in our search are listed at the end. In the CYP17A1 gene, SHBG gene, and FSHB gene, the SNPs have only been assessed in one of both conditions. Since we are looking for overlapping SNPs between both conditions, these SNPs will not be described in our results but can be found in Table 1.

ESR1 gene

We found two overlapping polymorphisms in the ESR1 gene that could possibly play a role in the common genetic cause (Table 2).

rs2234693, Pvull. Four studies in endometriosis patients found an association of this polymorphism in Caucasian and Asian women,[51,48–50] while three studies did not.[52–54] This, in spite the sample sizes of the seven studies were comparable. Only two of four studies investigating the base-pair change T > C in different ethnicities found an association.[48,49,52,53] Three out of four studies found an association with migraine, all conducted in Asian populations, while no association with migraine was found in the study with a Caucasian population.[55–58] Only one study specified the affected base-pair change T > C.[57] Two large studies with Caucasian migraineurs did not find a significant association.[58,67]

rs9340799, Xbal. Two of four studies found an association with endometriosis, and one of two studies found a significant association with migraine (Table 1). The associations with endometriosis were found in trials with Asian women.[48,54] The association was not confirmed in Caucasian women in studies with similar sample sizes.[50,53] All four endometriosis studies investigated the same base-pair change, A > G. For migraine, the studies for this SNP showed contradictory results[55,56] (Table 1).

rs2228480. In an Asian study, no association with endometriosis was found.[61] For migraine, an association was significant in two of eight studies with the same alleles G > A[55,62] (Table 1).

rs1801132. No association with endometriosis was found and a significant association with migraine was reported in three studies including large sample sizes of Caucasian women, two of them investigating the base-pair change G > C. The largest study investigated a C > G change.[64] Seven studies did not find an association for this SNP with migraine, two also studying the C > G change.[57,58] The majority of these seven studies included Asian populations.[55–57,121]

ESR2 gene

One overlapping polymorphism that could possibly play a role in the common genetic cause of the two diseases was found in the ESR2 gene (Table 2).

rs4986938. Endometriosis and migraine were both associated with this polymorphism in four of eight studies. Two studies with Caucasian endometriosis patients found a significant association with the base-pair change G > A,[73,74] while such an association was not confirmed in women of Asian descent.[61,75] Moreover, two studies in Caucasian migraineurs, but not those including Asian populations, reported an association with this SNP.[55,67,68,121]

rs1256049. One of two studies found an association with endometriosis.[76] A total of three Asian studies investigated this polymorphism, but none found an association with endometriosis or migraine.[55,56,61]

PGR gene

PROGINS. Four studies showed an association with endometriosis. All four studies included Caucasian participants.[78,79,81,93] The sample sizes of these four studies were relatively small compared with the studies without an association.[49,82,84,85]One association was found in a migraine trial with Caucasian women.[86] Two other migraine trials with Caucasian women and slightly smaller sample sizes did not find an association.[66,67]

rs1042838. No associations were found, for neither endometriosis nor migraine.[40,57,61,83,87,89]

AR gene

CAG repeat. Three studies showed an association with endometriosis. All three studies consisted of participants of Asian ethnicity.[90–92] Three other studies did not find an association, one of which was a study investigating an association with migraine.[80,86,94]

Table 1. Summary table of the included studies according to sex-hormone genes.

Gene	Polymorphism	Allele	Association	Disease	Ref. citation	Cases/Controls	Ethnicity	Country	Analysis	Cases Surgery Yes/No	Control Surgery Yes/No	ASRM	IHS
ESR1	rs2234693, PvuII	T>C	Yes	Endometriosis	Hsieh et al.[48]	112/110	Asian	Taiwan	PCR-RFLP	Yes	No	Yes	
ESR1	rs2234693, PvuII	T>C	Yes	Endometriosis	Lamp et al.[49]	150/199	Caucasian	Estonia	PCR-RFLP	Yes	No	Yes	
ESR1	rs2234693, PvuII	C>T	Yes	Endometriosis	Paskulin et al.[50]	98/115	Caucasian	Brazil	Taqman assay	Yes	Yes	Yes	
ESR1	rs2234693, PvuII	*	Yes	Endometriosis	Kitawaki et al.[51]	109/179	Asian	Japan	PCR-RFLP	Yes	No	Yes	
ESR1	rs2234693, PvuII	T>C	No	Endometriosis	Govindan et al.[52]	110/115	Asian	India	PCR-RFLP	Yes	No	Yes	
ESR1	rs2234693, PvuII	T>C	No	Endometriosis	Renner et al.[53]	98/98	Caucasian	Germany	PCR-RFLP	Yes	No	Yes	
ESR1	rs2234693, PvuII	*	No	Endometriosis	Xie et al.[54]	214/160	Asian	China	PCR-RFLP	Yes	No	No	
ESR1	rs2234693, PvuII	*	Yes	Migraine	An et al.[55]	494/533	Asian	China	MALDI-TOF MS				Yes
ESR1	rs2234693, PvuII	C>T	Yes	Migraine	Ghosh et al.[56]	334/200	Asian	India	PCR-SSCP				Yes
ESR1	rs2234693, PvuII	T>C	Yes	Migraine	Joshi et al.[57]	217/217	Asian	India	PCR-RFLP				Yes
ESR1	rs2234693, PvuII	C>T	No	Migraine	Colson et al.[58]	240/240	Caucasian	Australia	PCR-RFLP				Yes
ESR1	rs9340799, XbaI	A>G	Yes	Endometriosis	Hsieh et al.[48]	112/110	Asian	Taiwan	PCR-RFLP	Yes	No	Yes	
ESR1	rs9340799, XbaI	A>G	Yes	Endometriosis	Xie et al.[54]	214/160	Asian	China	PCR-RFLP	Yes	No	No	
ESR1	rs9340799, XbaI	A>G	No	Endometriosis	Renner et al.[53]	98/98	Caucasian	Germany	PCR-RFLP	Yes	No	Yes	
ESR1	rs9340799, XbaI	A>G	No	Endometriosis	Paskulin et al.[50]	98/115	Caucasian	Brazil	Taqman assay	Yes	Yes	Yes	
ESR1	rs9340799, XbaI	*	Yes	Migraine	An et al.[55]	494/533	Asian	China	MALDI-TOF MS				Yes
ESR1	rs9340799, XbaI	*	No	Migraine	Ghosh et al.[56]	334/200	Asian	India	PCR-SSCP				Yes
ESR1	TA repeat	(TA)n	Yes	Endometriosis	Kim et al.[59]	180/165	Asian	Korea	PCR-RFLP	Yes	Yes	Yes	
ESR1	TA repeat	(TA)n	Yes	Endometriosis	Hsieh et al.[60]	119/108	Asian	Taiwan	PCR-RFLP	Yes	Yes	Yes	
ESR1	TA repeat	(TA)n	Yes	Endometriosis	Lamp et al.[49]	150/199	Caucasian	Estonia	PCR-RFLP	Yes	No	Yes	
ESR1	rs2228480	*	No	Endometriosis	Wu et al.[61]	121/171	Asian	Taiwan	Taqman assay	Yes	No	Yes	
ESR1	rs2228480	G>A	Yes	Migraine	Colson et al.[62]	224/224	Caucasian	Australia	PCR				Yes
ESR1	rs2228480	G>A	Yes	Migraine	An et al.[55]	494/533	Asian	China	MALDI-TOF MS				Yes
ESR1	rs2228480	G>A	No	Migraine	Coşkun et al.[63]	142/141	Asian	Turkey	PCR				Yes
ESR1	rs2228480	G>A	No	Migraine	Kaunisto et al.[64]	898/900	Caucasian	Finland	Multiplex-PCR				Yes
ESR1	rs2228480	G>A	No	Migraine	Oterino et al.[65]	599/232	Caucasian	Spain	Real-Time PCR assay				Yes
ESR1	rs2228480	G>A	No	Migraine	Corominas et al.[66]	210/210	Caucasian	Spain	PCR-RFLP				Yes
ESR1	rs2228480	G>A	No	Migraine	Ghosh et al.[56]	334/200	Asian	India	PCR-SSCP				Yes
ESR1	rs2228480	G>A	No	Migraine	Rodriguez-Acevedo et al.[67]	282/155	Caucasian	Australia	PCR-RFLP				Yes
ESR1	rs1801132	*	No	Endometriosis	Wu et al.[61]	121/171	Asian	Taiwan	Taqman assay	Yes	No	Yes	
ESR1	rs1801132	C>G	Yes	Migraine	Kaunisto et al.[64]	898/900	Caucasian	Finland	Multiplex-PCR				Yes
ESR1	rs1801132	G>C	Yes	Migraine	Oterino et al.[65]	599/232	Caucasian	Spain	Real-Time PCR assay				Yes
ESR1	rs1801132	G>C	Yes	Migraine	Oterino et al.[68]	356/374	Caucasian	Spain	Real-Time PCR assay				Yes
ESR1	rs1801132	*	No	Migraine	Coşkun et al.[63]	142/141	Asian	Turkey	PCR				Yes
ESR1	rs1801132	C>G	No	Migraine	Colson et al.[58]	240/240	Caucasian	Australia	PCR-RFLP				Yes
ESR1	rs1801132	*	No	Migraine	Corominas et al.[66]	210/210	Caucasian	Spain	PCR-RFLP				Yes
ESR1	rs1801132	*	No	Migraine	Ghosh et al.[56]	334/200	Asian	India	PCR-SSCP				Yes
ESR1	rs1801132	C>G	No	Migraine	Joshi et al.[57]	217/217	Asian	India	PCR-RFLP				Yes
ESR1	rs1801132	*	No	Migraine	Rodriguez-Acevedo et al.[67]	282/155	Caucasian	Australia	PCR-RFLP				Yes
ESR1	rs1801132	*	No	Migraine	An et al.[55]	494/533	Asian	China	MALDI-TOF MS				Yes
ESR1	rs3798573	A>G	Yes	Endometriosis	Wang W et al.[69]	312/357	Asian	China	PCR-RFLP	Yes	Yes	Yes	
ESR1	rs2077647	*	No	Endometriosis	Wu et al.[61]	121/171	Asian	Taiwan	Taqman assay	Yes	No	Yes	
ESR1	rs3853250	*	No	Endometriosis	Trabert et al.[40]	256/567	Caucasian	USA	PCR-RFLP	Yes	No	Yes	
ESR1	rs3853251	*	No	Endometriosis	Trabert et al.[40]	256/567	Caucasian	USA	PCR-RFLP	Yes	No	Yes	
ESR1	rs1159327	A>G	No	Endometriosis	Wang W et al.[69]	312/357	Asian	China	PCR-RFLP	Yes	Yes	Yes	
ESR1	rs3020348	A>C	No	Endometriosis	Wang W et al.[69]	312/357	Asian	China	PCR-RFLP	Yes	Yes	Yes	
ESR1	rs1884049	*	No	Endometriosis	Matsuzaka et al.[70]	100/143	Asian	Japan	PCR	Yes	Yes	Yes	
ESR1	rs1884053	*	No	Endometriosis	Matsuzaka et al.[70]	100/143	Asian	Japan	PCR	Yes	Yes	Yes	
ESR1	rs1884054	*	No	Endometriosis	Matsuzaka et al.[70]	100/143	Asian	Japan	PCR	Yes	Yes	Yes	
ESR1	Intron 1 HaeIII	GGCC>GGCT	No	Endometriosis	Sato et al.[71]	105/125	Caucasian	Brazil	PCR-RFLP	Yes	No	Yes	
ESR1	Exon 1 MspI	CCGG>CTGG	No	Endometriosis	Sato et al.[71]	105/125	Caucasian	Brazil	PCR-RFLP	Yes	No	Yes	

(Continued)

Table 1. (Continued)

Gene	Polymorphism	Allele	Association	Disease	Ref. citation	Cases/Controls	Ethnicity	Country	Analysis	Cases Surgery Yes/No	Control Surgery Yes/No	ASRM	IHS
ESR1	IVS1 –401 > C	*	No	Endometriosis	Huber et al.[72]	32/790	Caucasian	Austria	Multiplex-PCR	Yes	No	Yes	
ESR1	rs6557170	G > A	Yes	Migraine	Kaunisto et al.[64]	898/900	Caucasian	Finland	Multiplex-PCR				Yes
ESR1	rs6557171	C > T	Yes	Migraine	Kaunisto et al.[64]	898/900	Caucasian	Finland	Multiplex-PCR				Yes
ESR1	rs2347867	A > G	Yes	Migraine	Kaunisto et al.[64]	898/900	Caucasian	Finland	Multiplex-PCR				Yes
ESR1	rs4870062	T > G	Yes	Migraine	Kaunisto et al.[64]	898/900	Caucasian	Finland	Multiplex-PCR				Yes
ESR1	rs726281	*	Yes	Migraine	Coşkun et al.[63]	142/141	Asian	Turkey	PCR				Yes
ESR1	rs2295193	*	No	Migraine	Coşkun et al.[63]	142/141	Asian	Turkey	PCR				Yes
ESR1	rs3798577	*	No	Migraine	Coşkun et al.[63]	142/141	Asian	Turkey	PCR				Yes
ESR1	rs2077647	*	No	Migraine	Corominas et al.[66]	210/210	Caucasian	Spain	PCR-RFLP				Yes
ESR2	rs4986938, AluI	G > A	Yes	Endometriosis	Bianco et al.[73]	108/210	Caucasian	Brazil	PCR-RFLP	Yes	Yes	Yes	
ESR2	rs4986938, AluI	G > A	Yes	Endometriosis	Szaflik et al.[74]	100/100	Caucasian	Poland	Sanger sequencing	Yes	No	Yes	
ESR2	rs4986938, AluI	*	No	Endometriosis	Wu et al.[61]	121/171	Asian	Taiwan	Taqman assay	Yes	No	Yes	
ESR2	rs4986938, AluI	G > A	No	Endometriosis	Lee et al.[75]	239/287	Asian	Korea	PCR-RFLP	Yes	Yes	Yes	
ESR2	rs4986938, AluI	*	Yes	Migraine	Rodriguez-Acevedo et al.[67]	282/155	Caucasian	Australia	Taqman assay				Yes
ESR2	rs4986938, AluI	*	Yes	Migraine	Oterino et al.[68]	356/374	Caucasian	Spain	Real-Time PCR assay				Yes
ESR2	rs4986938, AluI	*	No	Migraine	Coşkun et al.[63]	142/141	Asian	Turkey	PCR				Yes
ESR2	rs4986938, AluI	*	No	Migraine	An et al.[55]	494/533	Asian	China	MALDI-TOF MS				Yes
ESR2	rs1256049	*	Yes	Endometriosis	Silva et al.[76]	54/46	Caucasian	Brazil	PCR	Yes	No	Yes	
ESR2	rs1256049	*	No	Endometriosis	Wu et al.[61]	121/171	Asian	Taiwan	Taqman assay	Yes	No	Yes	
ESR2	rs1256049	*	No	Migraine	An et al.[55]	494/533	Asian	China	MALDI-TOF MS			Yes	
ESR2	rs1256049	*	No	Migraine	Ghosh et al.[56]	334/200	Asian	India	PCR-SSCP				Yes
ESR2	rs17179740	*	Yes	Endometriosis	Smolarz et al.[77]	200/200	Caucasian	Poland	HRM	Yes	No	Yes	
ESR2	rs17179740	A > G	No	Endometriosis	Wang W et al.[69]	312/357	Asian	China	PCR-RFLP	Yes	Yes	Yes	
ESR2	rs928554, A > G	A > G	Yes	Endometriosis	Szaflik et al.[74]	100/100	Caucasian	Poland	Sanger sequencing	Yes	No	Yes	
ESR2	rs944052	*	Yes	Endometriosis	Trabert et al.[40]	256/567	Caucasian	USA	PCR-RFLP	Yes	No	Yes	
ESR2	CA repeat	(CA)n	Yes	Endometriosis	Lamp et al.[49]	150/199	Caucasian	Estonia	PCR-RFLP	Yes	No	Yes	
ESR2	rs1255998	*	No	Migraine	Coşkun et al.[63]	142/141	Asian	Turkey	PCR				Yes
ESR2	rs1271572	*	No	Migraine	Ghosh et al.[56]	334/200	Asian	India	PCR-SSCP				Yes
PGR	PROGINS Alu ins	*	Yes	Endometriosis	Costa et al.[78]	54/45	Caucasian	Brazil	PCR-RFLP	Yes	No	No	
PGR	PROGINS Alu ins	*	Yes	Endometriosis	De Carvalho et al.[79]	121/281	Caucasian	Brazil	PCR-RFLP	Yes	No	Yes	
PGR	PROGINS Alu ins	*	Yes	Endometriosis	Lattuada et al.[80]	131/127	Caucasian	Italy	PCR-RFLP	Yes	Yes	Yes	
PGR	PROGINS Alu ins	*	Yes	Endometriosis	Wieser et al.[39,81]	95/107	Caucasian	Austria	PCR-RFLP	Yes	Yes	Yes	
PGR	PROGINS Alu ins	*	No	Endometriosis	Lamp et al.[49]	150/199	Caucasian	Estonia	PCR-RFLP	Yes	No	Yes	
PGR	PROGINS Alu ins	*	No	Endometriosis	Treloar et al.[82,83]	980/2940	Caucasian	Australia	PCR-RFLP	Yes	No	Yes	
PGR	PROGINS Alu ins	*	No	Endometriosis	Gimenes et al.[84]	148/179	Caucasian	Brazil	PCR-RFLP	Yes	Yes	Yes	
PGR	PROGINS Alu ins	*	No	Endometriosis	Govindan et al.[85]	100/108	Asian	India	PCR	Yes	No	No	
PGR	PROGINS Alu ins	*	Yes	Migraine	Colson et al.[86]	300/300	Caucasian	Australia	PCR				Yes
PGR	PROGINS Alu ins	*	No	Migraine	Corominas et al.[66]	210/210	Caucasian	Spain	PCR				Yes
PGR	PROGINS Alu ins	*	No	Migraine	Rodriguez-Acevedo et al.[67]	282/155	Caucasian	Australia	PCR				Yes
PGR	rs1042838	*	No	Endometriosis	Trabert et al.[40]	256/567	Caucasian	USA	PCR-RFLP	Yes	No	Yes	
PGR	rs1042838	*	No	Endometriosis	Wu et al.[61]	121/171	Asian	Taiwan	Taqman assay	Yes	No	Yes	
PGR	rs1042838	G > T	No	Endometriosis	Treloar et al.[82,83]	980/2940	Caucasian	Australia	PCR-RFLP	Yes	No	Yes	
PGR	rs1042838	*	No	Endometriosis	Van Kaam et al.[87]	72/102	Caucasian	Netherlands	PCR-RFLP	Yes	Yes	Yes	
PGR	rs1042838	*	No	Migraine	Joshi et al.[57]	217/217	Asian	India	PCR				Yes
PGR	rs1042838	G > T	No	Migraine	Palmirotta et al.[88]	380/185	Caucasian	Italy	Sanger sequencing				Yes
PGR	rs10895068	G > A	No	Endometriosis	Van Kaam et al.[87]	72/102	Caucasian	Netherlands	PCR-RFLP	Yes	Yes	Yes	
PGR	rs10895068	G > A	No	Endometriosis	Gentilini et al.[89]	199/300	Caucasian	Italy	PCR-RFLP	Yes	Yes	Yes	
PGR	rs10895068	G > A	No	Endometriosis	Treloar et al.[82,83]	980/2940	Caucasian	Australia	PCR-RFLP	Yes	No	Yes	
PGR	rs10895068	G > A	No	Endometriosis	Lamp et al.[49]	150/199	Caucasian	Estonia	PCR-RFLP	Yes	No	Yes	
PGR	rs500760	A > G	Yes	Endometriosis	Treloar et al.[82,83]	980/2940	Caucasian	Australia	PCR-RFLP	Yes	No	Yes	
PGR	rs1042839	C > T	No	Endometriosis	Treloar et al.[82,83]	980/2940	Caucasian	Australia	PCR-RFLP	Yes	No	Yes	

(Continued)

Table 1. (Continued)

Gene	Polymorphism	Allele	Association	Disease	Ref. citation	Cases/Controls	Ethnicity	Country	Analysis	Cases Surgery Yes/No	Control Surgery Yes/No	ASRM	IHS
PGR	rs2008112	G>A	No	Endometriosis	Treloar et al.[82,83]	980/2940	Caucasian	Australia	PCR-RFLP	Yes	No	Yes	
PGR	rs2020880	C>T	No	Endometriosis	Treloar et al.[82,83]	980/2940	Caucasian	Australia	PCR-RFLP	Yes	No	Yes	
PGR	rs3740754	G>C	No	Endometriosis	Treloar et al.[82,83]	980/2940	Caucasian	Australia	PCR-RFLP	Yes	No	Yes	
PGR	rs518162	G>A	No	Endometriosis	Treloar et al.[82,83]	980/2940	Caucasian	Australia	PCR-RFLP	Yes	No	Yes	
AR	CAG repeat	(CAG)n	Yes	Endometriosis	Hsieh et al.[90]	110/99	Asian	Taiwan	PCR	Yes	No	No	
AR	CAG repeat	(CAG)n	Yes	Endometriosis	Shaik et al.[91]	90/101	Asian	India	PCR	Yes	No	No	
AR	CAG repeat	(CAG)n	Yes	Endometriosis	Shin et al.[92]	421/349	Asian	Korea	PCR	Yes	Yes	Yes	
AR	CAG repeat	(CAG)n	No	Endometriosis	Lattuada et al.[93]	105/92	Caucasian	Italy	PCR	Yes	Yes	Yes	
AR	CAG repeat	(CAG)n	No	Endometriosis	Tong et al.[94]	24/114	Asian	China	PCR	Yes	No	Yes	
AR	CAG repeat	(CAG)n	No	Migraine	Colson et al.[86]	275/275	Caucasian	Australia	PCR				Yes
FSHR	rs6165	*	Yes	Endometriosis	Kerimoglu et al.[95]	100/100	Asian	Turkey	PCR-RFLP	Yes	Yes	Yes	
FSHR	rs6165	*	Yes	Endometriosis	Liaqat et al.[96]	156/208	Asian	Pakistan	PCR	Yes	No	No	
FSHR	rs6165	G>A	No	Endometriosis	Andre et al.[97]	352/510	Caucasian	Brazil	Taqman assay	Yes	Yes	Yes	
FSHR	rs6165	A>G	No	Endometriosis	Wang HS et al.[98]	300/337	Asian	Taiwan	MALDI-TOF MS	Yes	No	Yes	
FSHR	rs6166	*	Yes	Endometriosis	Kerimoglu et al.[95]	100/100	Asian	Turkey	PCR-RFLP	Yes	Yes	Yes	
FSHR	rs6166	*	No	Endometriosis	Liaqat et al.[96]	156/208	Asian	Pakistan	PCR	Yes	No	No	
FSHR	rs6166	A>G	No	Endometriosis	Andre et al.[97]	352/510	Caucasian	Brazil	Taqman assay	Yes	Yes	Yes	
FSHR	rs6166	A>G	No	Endometriosis	Wang HS et al.[98]	300/337	Asian	Taiwan	MALDI-TOF MS	Yes	No	Yes	
FSHR	rs6166	A>G	No	Endometriosis	Schmitz et al.[99]	67/65	Caucasian	Brazil	PCR-RFLP	Yes	Yes	Yes	
FSHR	rs6166	*	Yes	Migraine	Oterino et al.[68]	356/374	Caucasian	Spain	Real-Time PCR assay				Yes
FSHR	rs6166	*	No	Migraine	Rodriguez-Acevedo et al.[67]	282/155	Caucasian	Australia	MALDI-TOF MS				Yes
FSHR	rs6166	*	No	Migraine	Coşkun et al.[63]	142/141	Asian	Turkey	PCR				Yes
FSHB	rs11031006	*	Yes	Endometriosis	Angioni et al.[100]	72/41	Caucasian	Italy	Sanger sequencing	Yes	Yes	Yes	
FSHB	rs11031006	*	Yes	Endometriosis	Matalliotakis et al.[101]	166/150	Caucasian	Greece	Taqman assay	Yes	No	Yes	
SHBG	rs6259	*	No	Migraine	Coşkun et al.[63]	142/141	Asian	Turkey	PCR				Yes
NRIP1	rs2229741	G>A	No	Endometriosis	Caballero et al.[102]	59/141	Caucasian	Spain	Real-Time PCR assay	Yes	No	Yes	
NRIP1	rs2229741	*	Yes	Migraine	Rodriguez-Acevedo et al.[67]	282/155	Caucasian	Australia	MALDI-TOF MS				Yes
NRIP1	rs2229741	*	No	Migraine	Coşkun et al.[63]	142/141	Asian	Turkey	PCR				Yes
NRIP1	rs2229741	*	No	Migraine	Oterino et al.[68]	356/374	Caucasian	Spain	Real-Time PCR assay				Yes
NRIP1	rs2229742	C>G	Yes	Endometriosis	Caballero et al.[102]	59/141	Caucasian	Spain	Real-Time PCR assay	Yes	No	Yes	
NRIP1	rs2506142	*	Yes	Migraine	Pollock et al.[103]	235/140	Caucasian	Australia	PCR-RFLP				Yes
COMT	rs4680	*	No	Endometriosis	Christofolini et al.[44,104]	198/168	Caucasian	Brazil	Taqman assay	Yes	Yes	Yes	
COMT	rs4680	*	No	Endometriosis	Trabert et al.[40]	255/567	Caucasian	USA	PCR-RFLP	Yes	No	Yes	
COMT	rs4680	G>A	No	Endometriosis	Wang HS et al.[98]	300/337	Asian	Taiwan	MALDI-TOF MS	Yes	No	Yes	
COMT	rs4680	G>A	No	Endometriosis	Wieser et al.[39,81]	91/92	Caucasian	Australia	PCR-RFLP	Yes	Yes	Yes	
COMT	rs4680	G>A	No	Endometriosis	Juo et al.[105]	105/312	Asian	China	PCR-RFLP	Yes	No	No	
COMT	rs4680	G>A	No	Endometriosis	Huber et al.[72]	32/790	Caucasian	Austria	Multiplex-PCR	Yes	No	Yes	
COMT	rs4680	G>A	Yes	Migraine	Emin Erdal et al.[106]	62/64	Asian	Turkey	PCR-RFLP				Yes
COMT	rs4680	*	Yes	Migraine	Sullivan et al.[107]	1740/1132	Caucasian	USA	Illumina sequencing				Yes
COMT	rs4680	*	No	Migraine	De Marchis et al.[108]	380/132	Caucasian	Italy	Sanger sequencing				Yes
COMT	rs4680	*	No	Migraine	Todt et al.[109]	270/272	Caucasian	Germany	Taqman assay				Yes
COMT	rs4680	G>A	No	Migraine	Sutherland et al.[110]	268/140	Caucasian	Australia	PCR-RFLP				Yes
COMT	rs4680	G>A	No	Migraine	Takigawa et al.[111]	223/191	Asian	Japan	PCR-RFLP				Yes
COMT	rs4680	G>A	No	Migraine	Hagen et al.[112]	982/1468	Caucasian	Norway	PCR				Yes
COMT	rs4680	G>A	No	Migraine	Park et al.[113]	97/94	Asian	Korea	PCR				Yes
COMT	rs1544325	*	No	Migraine	Corominas et al.[66]	259/287	Caucasian	Spain	SNPlex assay				Yes
COMT	rs165774	*	No	Migraine	Corominas et al.[66]	259/287	Caucasian	Spain	SNPlex assay				Yes
COMT	rs4633	C>T	No	Migraine	Takigawa et al.[111]	223/191	Asian	Japan	PCR-RFLP				Yes
COMT	rs4646316	*	No	Migraine	Corominas et al.[66]	259/287	Caucasian	Spain	SNPlex assay				Yes
COMT	rs4818	*	No	Migraine	De Marchis et al.[108]	380/132	Caucasian	Italy	Sanger sequencing				Yes
COMT	rs6267	G>T	No	Migraine	Takigawa et al.[111]	223/191	Asian	Japan	PCR-RFLP				Yes

(Continued)

Table 1. (Continued)

Gene	Polymorphism	Allele	Association	Disease	Ref. citation	Cases/Controls	Ethnicity	Country	Analysis	Cases Surgery Yes/No	Control Surgery Yes/No	ASRM	IHS
COMT	rs740601	*	No	Migraine	Corominas et al.[66]	259/287	Caucasian	Spain	SNPlex assay				Yes
COMT	rs740603	*	No	Migraine	Corominas et al.[66]	259/287	Caucasian	Spain	SNPlex assay				Yes
COMT	rs9332377	*	No	Migraine	Corominas et al.[66]	259/287	Caucasian	Spain	SNPlex assay				Yes
COMT	rs933271	*	No	Migraine	Corominas et al.[66]	259/287	Caucasian	Spain	SNPlex assay				Yes
COMT	rs2020917	*	No	Migraine	Corominas et al.[66]	259/287	Caucasian	Spain	SNPlex assay				Yes
CYP1A1	rs4646903	*	Yes	Endometriosis	Arvanitis et al.[114]	275/346	Caucasian	Greece	PCR	Yes	No	Yes	
CYP1A1	rs4646903	T>C	Yes	Endometriosis	Barbosa et al.[115]	52/42	Caucasian	Brazil	PCR-RFLP	Yes	Yes	Yes	
CYP1A1	rs4646903	T>C	No	Endometriosis	Babu et al.[116]	310/215	Asian	India	PCR-RFLP	Yes	Yes	Yes	
CYP1A1	rs4646903	T>C	No	Endometriosis	Rozati et al.[117]	97/102	Asian	India	PCR-RFLP	Yes	Yes	Yes	
CYP1A1	rs4646903	T>C	No	Endometriosis	Juo et al.[105]	105/312	Asian	China	PCR-RFLP	Yes	No	No	
CYP1A1	rs4646903	T>C	No	Endometriosis	Babaki et al.[118]	93/139	Asian	Iran	PCR-RFLP	Yes	Yes	Yes	
CYP1A1	rs4646903	T>C	No	Endometriosis	Huber et al.[72]	32/790	Caucasian	Austria	Multiplex-PCR	Yes	No	Yes	
CYP1A1	rs4646903	*	No	Endometriosis	Wu et al.[119]	121/171	Asian	Taiwan	Taqman assay	Yes	No	Yes	
CYP1A1	rs4646903	T>C	No	Migraine	Sutherland et al.[110]	268/140	Caucasian	Australia	PCR-RFLP				Yes
CYP1A1	rs1048943	A>G	No	Endometriosis	Huber et al.[72]	32/790	Caucasian	Austria	Multiplex-PCR	Yes	No	Yes	
CYP1A1	rs1048943	A>G	No	Migraine	Sutherland et al.[110]	268/140	Caucasian	Australia	PCR-RFLP				Yes
CYP1A1	rs4646422	G>A	No	Endometriosis	Wang HS et al.[98]	300/337	Asian	Taiwan	MALDI-TOF MS	Yes	No	Yes	
CYP17A1	rs743572	T>C	Yes	Endometriosis	Bozdag et al.[120]	46/39	Asian	Turkey	PCR	Yes	Yes	Yes	
CYP17A1	rs743572	*	Yes	Endometriosis	Hsieh et al.[60]	119/108	Asian	Taiwan	PCR	Yes	Yes	No	
CYP17A1	rs743572	A>G	Yes	Endometriosis	Szczepańska et al.[121]	115/197	Caucasian	Poland	HRM	Yes	Yes	Yes	
CYP17A1	rs743572	T>C	No	Endometriosis	Vietri et al.[122]	104/86	Caucasian	Italy	PCR	Yes	Yes	Yes	
CYP17A1	rs743572	T>C	No	Endometriosis	De Carvalho et al.[79]	121/281	Caucasian	Brazil	PCR-RFLP	Yes	No	No	
CYP17A1	rs743572	T>C	No	Endometriosis	Huber et al.[72]	32/790	Caucasian	Austria	Multiplex-PCR	Yes	No	Yes	
CYP17A1	rs743572	T>C	No	Endometriosis	Vietri et al.[122]	104/86	Caucasian	Italy	PCR	Yes	Yes	Yes	
CYP17A1	rs743572	T>C	No	Endometriosis	Juo et al.[105]	105/312	Asian	China	PCR-RFLP	Yes	No	No	
CYP17A1	rs743572	*	No	Endometriosis	Kado et al.[36]	140/177	Asian	Japan	PCR-RFLP	Yes	No	Yes	
CYP17A1	rs743572	*	No	Endometriosis	Trabert et al.[40]	256/567	Caucasian	USA	PCR-RFLP	Yes	No	Yes	
CYP17A1	rs743572	*	No	Endometriosis	Wu et al.[61]	121/171	Asian	Taiwan	Taqman assay	Yes	Yes	Yes	
CYP17A1	rs619824	G>T	No	Endometriosis	Zhao et al.[123]	768/768	Caucasian	Australia	MALDI-TOF MS	Yes	Yes	Yes	
CYP17A1	rs3740397	C>G	No	Endometriosis	Zhao et al.[123]	768/768	Caucasian	Australia	MALDI-TOF MS	Yes	Yes	Yes	
CYP17A1	rs4919687	G>A	No	Endometriosis	Zhao et al.[123]	768/768	Caucasian	Australia	MALDI-TOF MS	Yes	Yes	Yes	
CYP17A1	rs6163	C>A	No	Endometriosis	Zhao et al.[123]	768/768	Caucasian	Australia	MALDI-TOF MS	Yes	Yes	Yes	
CYP17A1	rs6162	G>A	No	Endometriosis	Zhao et al.[123]	768/768	Caucasian	Australia	MALDI-TOF MS	Yes	Yes	Yes	
CYP17A1	rs743572	T>C	No	Endometriosis	Zhao et al.[123]	768/768	Caucasian	Australia	MALDI-TOF MS	Yes	Yes	Yes	
CYP17A1	rs2486758	T>C	No	Endometriosis	Zhao et al.[123]	768/768	Caucasian	Australia	MALDI-TOF MS	Yes	Yes	Yes	
CYP17A1	rs10786712	*	No	Endometriosis	Wu et al.[61]	121/171	Asian	Taiwan	Taqman assay	Yes	No	Yes	
CYP19A1	rs10046	*	No	Endometriosis	Wu et al.[61]	121/171	Asian	Taiwan	Taqman assay	Yes	No	Yes	
CYP19A1	rs10046	C>T	No	Endometriosis	Lamp et al.[49]	150/199	Caucasian	Estonia	PCR-RFLP	Yes	No	Yes	
CYP19A1	rs10046	C>T	No	Endometriosis	Szaflik et al.[74]	100/100	Caucasian	Poland	Sanger sequencing	Yes	No	Yes	
CYP19A1	rs10046	*	No	Endometriosis	Szczepańska et al.[122]	115/197	Caucasian	Poland	HRM	Yes	Yes	Yes	
CYP19A1	rs10046	T>C	No	Endometriosis	Wang L et al.[124]	146/225	Asian	China	PCR	Yes	No	No	
CYP19A1	rs10046	*	Yes	Migraine	Coşkun et al.[63]	142/141	Asian	Turkey	PCR				Yes
CYP19A1	rs10046	*	Yes	Migraine	Ghosh et al.[56]	334/200	Asian	India	PCR-SSCP				Yes
CYP19A1	rs10046	*	No	Migraine	Rodriguez-Acevedo et al.[67]	282/155	Caucasian	Australia	MALDI-TOF MS				Yes
CYP19A1	rs10046	*	No	Migraine	An et al.[55]	494/533	Asian	China	MALDI-TOF MS				Yes
CYP19A1	rs10046	*	No	Migraine	Oterino et al.[68]	356/374	Caucasian	Spain	Real-Time PCR assay				Yes
CYP19A1	rs4646	C>A	No	Endometriosis	Szaflik et al.[74]	100/100	Caucasian	Poland	Sanger sequencing	Yes	No	Yes	
CYP19A1	rs4646	*	Yes	Migraine	Ghosh et al.[56]	334/200	Asian	India	PCR-SSCP				Yes
CYP19A1	rs4646	*	No	Migraine	An et al.[55]	494/533	Asian	China	MALDI-TOF MS				Yes
CYP19A1	rs4646	*	No	Migraine	Rodriguez-Acevedo et al.[67]	282/155	Caucasian	Australia	MALDI-TOF MS				Yes

(Continued)

Table 1. (Continued)

Gene	Polymorphism	Allele	Association	Disease	Ref. citation	Cases/Controls	Ethnicity	Country	Analysis	Cases Surgery Yes/No	Control Surgery Yes/No	ASRM	IHS
CYP19A1	rs700519	C>T	No	Endometriosis	Wang HS et al.[98]	300/337	Asian	Taiwan	MALDI-TOF MS	Yes	No	Yes	
CYP19A1	rs700519	C>T	No	Endometriosis	Tsuchiya et al.[37]	75/57	Asian	Japan	PCR	Yes	Yes	Yes	
CYP19A1	rs700519	C>T	No	Endometriosis	Huber et al.[72]	32/790	Caucasian	Austria	Multiplex-PCR	Yes	No	Yes	
CYP19A1	rs700519	C>T	No	Migraine	Sutherland et al.[110]	268/140	Caucasian	Australia	PCR-RFLP				Yes
CYP19A1	rs2236722	T>C	No	Endometriosis	Wang HS et al.[98]	300/337	Asian	Taiwan	MALDI-TOF MS	Yes	No	Yes	
CYP19A1	rs2236722	T>C	No	Endometriosis	Wang L et al.[124]	146/225	Asian	China	PCR	Yes	No	No	
CYP19A1	TTTA repeat	(TTTA)n	Yes	Endometriosis	Arvanitis et al.[114]	275/346	Caucasian	Greece	PCR	Yes	No	Yes	
CYP19A1	TTTA repeat	(TTTA)n	Yes	Endometriosis	Kado et al.[36]	140/177	Asian	Japan	PCR-RFLP	Yes	No	Yes	
CYP19A1	TTTA repeat	(TTTA)n	No	Endometriosis	Lamp et al.[49]	150/199	Caucasian	Estonia	PCR-RFLP	Yes	No	Yes	
CYP19A1	TTTA repeat	(TTTA)n	No	Endometriosis	Hur et al.[125]	224/188	Asian	Korea	PCR	Yes	Yes	Yes	
CYP19A1	TTTA repeat	(TTTA)n	No	Endometriosis	Wang L et al.[124]	146/225	Asian	China	PCR	Yes	No	No	
CYP19A1	Val80	G>A	Yes	Endometriosis	Vietri et al.[122]	104/86	Caucasian	Italy	PCR	Yes	Yes	Yes	
CYP19A1	Val80	G>A	No	Endometriosis	Hur et al.[125]	224/188	Asian	Korea	PCR	Yes	Yes	Yes	
CYP19A1	C1558T	C>T	Yes	Endometriosis	Vietri et al.[122]	104/86	Caucasian	Italy	PCR	Yes	Yes	Yes	
CYP19A1	C1558T	C>T	No	Endometriosis	Huber et al.[72]	32/790	Caucasian	Austria	Multiplex-PCR	Yes	No	Yes	
CYP19A1	rs1004982	*	Yes	Endometriosis	Trabert et al.[40]	256/567	Caucasian	USA	PCR-RFLP	Yes	No	Yes	
CYP19A1	rs1870049	*	Yes	Endometriosis	Trabert et al.[40]	256/567	Caucasian	USA	PCR-RFLP	Yes	No	Yes	
CYP19A1	rs936307	*	Yes	Endometriosis	Trabert et al.[40]	256/567	Caucasian	USA	PCR-RFLP	Yes	No	Yes	
CYP19A1	rs8042086	*	Yes	Endometriosis	Wu et al.[61]	121/171	Asian	Taiwan	Taqman assay	Yes	No	Yes	
CYP19A1	TCT ins/del	*	No	Endometriosis	Lamp et al.[49]	150/199	Caucasian	Estonia	PCR-RFLP	Yes	No	Yes	
CYP19A1	115T>C	*	No	Endometriosis	Hur et al.[125]	224/188	Asian	Korea	PCR	Yes	Yes	Yes	
CYP19A1	1531C>T	*	No	Endometriosis	Hur et al.[125]	224/188	Asian	Korea	PCR	Yes	Yes	Yes	
CYP19A1	rs700518	A>G	No	Endometriosis	Wang L et al.[124]	146/225	Asian	China	PCR	Yes	No	No	
CYP19A1	rs2899470	*	Yes	Endometriosis	Smolarz et al.[77]	200/200	Caucasian	Poland	HRM	Yes	No	Yes	

ASRM: American Society for Reproductive Medicine; IHS: International Headache Society; ESR: estrogen receptor; PCR: polymerase chain reaction; PCR-SSCP: polymerase chain reaction-single-strand conformation polymorphism; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; HRM: high resolution melt; MALDI TOF MS: matrix-assisted laser desorption ionization-time-of-flight mass spectrometry; SNP: single nucleotide polymorphism; PGR: progesterone receptor; AR: androgen receptor; FSH: follicle stimulating hormone; FSHR: follicle stimulating hormone receptor; FSHB: FSH beta-subunit; SHBG: sex hormone-binding globulin; NRIP: nuclear receptor interacting protein; COMT: Catechol-O-methyl-transferase.
*Not mentioned.

Table 2. Overview of overlapping polymorphisms associated with endometriosis and migraine.

		Association Endometriosis		Association Migraine	
Gene	SNP	Caucasian	Asian	Caucasian	Asian
ESR1	rs2234693, Pvull	probable	probable	no	yes
ESR1	rs9340799, Xbal	no	yes	more studies needed	possible
ESR1	TA repeat	possible	yes	no data	no data
ESR1	rs2228480	no data	more studies needed	no	no
ESR1	rs1801132	no data	more studies needed	probable	no
ESR2	rs4986938, AluI	yes	no	yes	no
ESR2	rs1256049	no data	more studies needed	no data	no
ESR2	rs17179740	more studies needed	more studies needed	no data	no data
PGR	PROGINS Alu ins	possible	more studies needed	no	more studies needed
PGR	rs1042838	no	more studies needed	more studies needed	no data
PGR	rs10895068	no	no data	no data	no data
AR	CAG repeat	more studies needed	yes	more studies needed	more studies needed
FSHR	rs6165	more studies needed	probable	no data	no data
FSHR	rs6166	more studies needed	no	possible	no data
FSHB	rs11031006	yes	no data	no data	no data
SBHG	rs6259	no data	no data	no data	more studies needed
NRIP1	rs2229741	no data	no data	possible	more studies needed
COMT	rs4680	no	no	possible	no
CYP1A1	rs4646903, MspI	more studies needed	no	more studies needed	no data
CYP17A1	rs743572, MspA1	no	no	no data	no data
CYP19A1	rs10046	no	more studies needed	no	possible
CYP19A1	rs4646	more studies needed	no data	more studies needed	possible
CYP19A1	rs700519	no data	more studies needed	more studies needed	no data
CYP19A1	TTTA repeat	probable	possible	no data	no data

SNP: single nucleotide polymorphism; ESR: estrogen receptor; PGR: progesterone receptor; AR: androgen receptor; FSHR: follicle stimulating hormone receptor; FSHB: FSH beta-subunit; NRIP: nuclear receptor interacting protein; COMT: Catechol-O-methyl-transferase.
Yes: all studies showed an association.
Probable: ⩾ 50% with association AND largest sum of sample sizes.
Possible: ⩽ 50% with association BUT largest sum of sample sizes.
No: ⩾ 75% without association AND/OR large sample size without association.
More studies needed: ⩾ 2 studies needed for each disorder to make a statement.
No data.

FSHR gene

rs6166. One of five studies found an association with endometriosis in Turkish women, and one of three studies found an association with Caucasian migraineurs.[68,95]

NRIP1 gene

rs2229741. No association was found with endometriosis in a small study with Caucasian women.[102] One of three studies showed an association in Caucasian migraineurs.[67]

COMT gene

rs4680. In six studies investigating an association with endometriosis, none were found.[39,40,72,98,104,105] Two of eight studies found an association with migraine. One of the trials included more than 1000 participants.[107] On the contrary, another very large trial did not find an association.[112] In both groups, the ethnicity was considered Caucasian. The other association was found in a small Turkish trial focused on the G > A pair change.[106] Six studies with female migraineurs did not find an association.[107–109,111–113] Four of these six investigated the same base pair change, G > A.

CYP1A1 gene

rs4646903 (MspI). Two of eight studies showed an association with endometriosis. The case-control study with the smaller sample size investigated the T > C change.[115] Four Asian studies also investigated this base pair change, but found no association.[72,105,116–119] No association with migraine was found.[110]

rs1048943. No associations were found in endometriosis patients or migraine patients.[72,110]

CYP19A1 gene

rs10046. Within five studies, no significant associations with endometriosis were found in either Asian or Caucasian study populations.[49,61,74,124,126] Two of five studies, both of them in Asian populations, found an association with migraine. In contrast, a large Chinese case-control study did not find an association.[55]

rs4646. No association with endometriosis was found in a Caucasian study population.[74] In one Indian study, migraine was associated with this polymorphism.[56] However, two other large studies found no association.[55,67]

rs700519. None of the three studies examined found an association with endometriosis, and neither did one study with migraineurs.[37,72,98,110]

Discussion

The objectives of the present study were to provide an extensive review of sex hormone-related polymorphisms studied in endometriosis and migraine. Improved understanding of this comorbidity might facilitate early diagnosis and specific therapy. We found many probable overlapping SNPs in the candidate genes (Table 2), with mostly contradictory results, presumably due to some limitations of the included studies.

Both endometriosis and migraine are complex conditions with a variety of phenotypes. The heterogeneity of the control groups in the endometriosis studies constitutes a source of critique, as some women who have had a laparoscopy might not be representative of the normal population, and women in control groups without a laparoscopy might suffer from asymptomatic endometriosis with a probability of 2–11%.[5] Preferably, controls would be pain-free, fertile women in whom the absence of endometriosis is confirmed by surgery.[126] Such a control group will not only be difficult to establish in large study populations, but is also not acceptable for ethical reasons. A recent systematic review of polymorphisms and endometriosis confirmed the importance of being cautious regarding the criteria for selecting the control population.[33] To reduce heterogeneity, we excluded studies with self-reported endometriosis, recurrent endometriosis, female newborns, and men as controls. Arguably, including postmenopausal women in control groups is associated with the problem that these now asymptomatic women might have suffered from endometriosis in their reproductive years. Postmenopausal women could still have the genetic makeup predisposing them to endometriosis.

Another possible explanation is failed replication in subsequent studies due to the candidate-gene approach. Candidate-gene association studies have been widely used in the genetics of complex traits and diseases. This approach is based on the *a priori* selection of candidate genes with a hypothetical role in the pathogenesis of the disease and uses indirect genotyping methods.[127] Nowadays, these methods are mostly obsolete due to the rise of direct-sequencing technologies.[128] Indirect genotyping methods have a higher chance of yielding false positives compared to direct-sequencing technologies. In a simulation study, 968 of 1000 simulations (96.8%) produced at least one false positive.[129] Other drawbacks of candidate-gene studies are the small sample sizes and the lack of standardized genotyping methodologies. However, there is no universal genotyping method because choosing a suitable genotyping method for a certain variant depends on multiple factors, for example, the number of variants in the specified gene. Finally, problems with population stratification can occur in candidate-gene studies when cases and controls are poorly matched and, consequently, are responsible for significant associations.[130] We are aware that this approach has a limited ability to include all possible causative genes and polymorphisms. However, from a clinical point of view, we carefully decided to only include studies examining the candidate sex-hormone genes in question to better understand the role of these sex-hormones and to enable more targeted treatments for the comorbidity. Although subject to criticism, this approach still proves to be a robust tool for studying the genetic makeup, especially for diseases with complex traits.[131]

We found three overlapping sex hormone-associated polymorphisms in the estrogen receptor genes (ESR1 and ESR2), in particular the SNPs rs2234693 (Pvull), rs9340799 (Xbal) and rs4986938 (AluI)[48–51,54–57,67,68,73,74] (Table 2). Both Caucasian and Asian women with endometriosis showed an association between the disease and rs2234693 (Pvull), but for migraine the association was found only in Asian women.[55–58] While rs9340799 (Xbal) was associated with endometriosis and migraine in Asian women, no association was found in Caucasian women.[50,53] Both conditions were significantly associated with rs4986938 (AluI) in specifically Caucasian women. The differences between the findings in Asian and Caucasian populations demonstrate the importance of ethnicity when performing and interpreting genetic studies. The prevalence of endometriosis seems to differ among Asian and Caucasian populations. Asian women are significantly more likely to be diagnosed with endometriosis (OR 1.63, 95% CI 1.03–2.58).[132]

Some studies did not specify the allelic change in the polymorphism. However, one SNP can have several different base-pair changes and allele frequencies can vary in different ethnicities. This information was reviewed in the current dbSNP database.[46]

In the ESR1 gene, rs1801132 has been found to have an association with migraine in women, but no studies have investigated this polymorphism in women with endometriosis. Three repeat polymorphisms, TA repeat (ESR1 gene), CAG repeat (AR gene), and TTTA repeat (CYP19A1

gene) all have probable associations with endometriosis, but have not yet been investigated in migraineurs. We found overlapping polymorphisms for PROGINS (PGR gene) and rs6166 (FSHR gene), but more powered studies are required to understand if there is a significant association. Regarding the FSHB gene, rs11031006 is associated with endometriosis, but migraine studies are needed. General overlaps in the metabolizing enzymes have been assessed in our literature search for COMT, NRIP1, CYP1A1, CYP19A1, but no overlapping SNPs have been found and more data is needed (Table 2).

The strengths of this study were the strict inclusion and exclusion criteria to reduce selection bias. We included only case-control studies. To ensure the diagnosis, we only included studies with endometriosis diagnosed by laparoscopy and/or histology, and the majority was ASRM-classified. Migraineurs were diagnosed based on the criteria specified by the IHS.[2] A limitation of our study was the stratification into two ethnic groups, resulting in recruitment bias. Arguably, this could have been more specific–for example, stratifying for European, Hispanic, and Turkish populations. It is important to note that ethnicity and race have different definitions, although within medical literature these are often used interchangeably.[132] In female lifetime, the clinical pattern of migraine is linked to reproductive events with an increase around puberty, a peak during fertile age, and a decrease after menopause.[133] Age was considered, but studies for women in menopause or before menarche were not available and therefore could not be included. Other mechanisms might be involved in childhood migraine.

Migraines appear to occur more commonly in patients with endometriosis than in the general population.[134] The prevalence of migraine is significantly higher in women with endometriosis as compared to women without endometriosis.[135–137] We hypothesize that endometriosis and migraine are comorbidities in a subset of women. A recent study confirmed this comorbidity and suggested a non-causal relationship between the two traits.[4] Nevertheless, mechanistic insights for both conditions are still lacking. In addition to differences on the hormone receptor level or hormone metabolism level, this also could be a shared problem in the immune response in women with the comorbidities.

Table 2 shows an overview of overlapping genes in both conditions, which were only found in estrogen receptor genes. It seems estrogen plays a central role in the genetic link underlying the comorbidity of endometriosis and migraine. Biologically, estrogens exert their effects via the estrogen receptors localized in epithelial, stromal, and vascular cells. Progestins antagonize estrogen actions in the reproductive tissues, brain, and nerve cells by reducing estrogen receptor expression.[138] Women with overlapping estrogen receptor polymorphisms could experience a higher improvement in symptoms with estrogen-suppression by continuous treatment with progestins. The majority of women in the reproductive years use hormonal contraception. However, combined hormonal contraception frequently has a negative impact on migraine.[139] Whereas treatment with progestin-only has a positive impact on both conditions.[30,140–143] Therefore, patients with the comorbidity of migraine and endometriosis would profit if their attending physician could identify the co-occurrence to optimize hormonal treatment.

Conclusion

This literature review gives an overview of the shared sex hormone polymorphisms in women with migraine and endometriosis. Furthermore, we have identified SNPs potentially related to these conditions, which are relevant for future research. To confirm possible associations with other sex-hormone genes, larger studies are needed, in which ethnicity needs to be taken into account. We hypothesize that ESR1 and ESR2 may play a role in the genetic cause of endometriosis and migraine. For optimal treatment and patient care, we recommend actively exploring the comorbidity of migraine and endometriosis.

Author contribution(s)

Joy-Fleur van der Vaart: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing—original draft; Writing—review and editing.
Gabriele Susanne Merki-Feld: Conceptualization; Methodology; Supervision.

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According to the cantonal Swiss Ethic Committee of Zürich http://www.kek.zh.ch/ and Swiss Association of Research Ethics Committees https://swissethics.ch/en/ ethics approval is not applicable for literature reviews.

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Supplemental material

Supplemental material for this article is available online.

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