Genetic polymorphisms and endometriosis: contribution of genes that regulate vascular function and tissue remodeling

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Summary

Endometriosis is a benign gynecological disease characterized by the presence and growth of endometrial cells outside the uterus. Genetic, endocrine, immunological, and environmental factors have been suggested in its pathogenesis. A great number of studies have related genetic polymorphisms as a factor that contributes to the development of endometriosis. This review presents a detailed description of the contribution of genetic polymorphisms in genes that regulate vascular function and tissue remodeling in endometriosis (alpha 2-HS glycoprotein [AHSG], epidermal growth factor receptor [EGFR], vascular endothelial growth factor [VEGF], endostatin, plasminogen activator inhibitor 1 [PAI-1], angiotensin I-converting enzyme [ACE], and matrix metalloproteinases [MMPs]). Some polymorphisms of the VEGF (-460 C/T, +405 G/C, +936 C/T), PAI, MMP-1, 2, and 3 genes were widely studied, while polymorphisms of the AHSG, EGF, endostatin, and VEGF (-1154 G/A, -2578 A/C) genes were not. In this latter case, additional studies are required to confirm the findings of the few studies that have analyzed these single nucleotide polymorphisms (SNPs). Additionally, studies that found a positive or negative association of SNP with endometriosis emphasize the relevance of studies with a large number of control cases to confirm their findings. The haplotype analysis was performed only for the VEGF (-460, +405, -1154 and -2578), ACE (-240/2350) and MMP-1, 2, 3, and 9 genes, and in most of them, there was no association with endometriosis. Of the eight works that analyzed haplotypes of the VEGF gene, five did not associate them with endometriosis. Haplotypes of ACE and MMP-2 genes were not associated with endometriosis, while those of MMP-1, 3, and 9 genes were related to a high risk for the disease.

Keywords: Endometriosis; genetic polymorphisms; vascular endothelial growth factor; matrix metalloproteinases; plasminogen activator inhibitors; peptidyl dipeptidase A.

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Introduction

Endometriosis is a complex gynecological condition characterized by endometrial tissue outside the uterus. Main clinical symptoms include dysmenorrhea, chronic pelvic pain, deep dyspareunia, infertility, and cyclic bowel and urinary symptoms, such as pain or bleeding when defecating/urinating during the menstrual period[1,2]. A study performed by Bellelis et al.[3] showed that the main complaint reported by patients with endometriosis was dysmenorrhea, with a prevalence of 62.2%. Nonetheless, when all symptoms reported were considered, chronic pelvic pain was the most prevalent symptom, followed by deep dyspareunia, reported by 56.8% and 54.7% of the patients, respectively. Infertility was reported by 39.8% of the 892 patients. A study aiming at understanding the Brazilian gynecological practices regarding the diagnosis of endometriosis showed early detection of endometriosis when the patient complained of infertility or chronic pelvic pain[4]. An interesting finding of this study was that the time elapsed until indication of a diagnostic procedure was lower in case of doctors that had participated in congresses and lectures on gynecological endoscopy and endometriosis, thus evidencing that better-informed gynecologists detect the disease earlier[4].

Endometriosis is similar to cancer, as the implantation of endometrial cells requires neovascularization in order to establish, grow, and invade tissues. Additionally, theories on the etiopathogenesis of endometriosis involve growth factors and cytokines associated with the regulation of cell multiplication and neoangiogenesis that may act in carcinogenesis. It is estimated that 1% of endometriosis cases are related to cancer and, for some types of endometriosis, its benign nature has been questioned[5,6].

Although the final diagnosis of endometriosis requires needs a surgical intervention, videolaparoscopy, several findings in the physical, image, and laboratory examinations can already predict, with a high degree of reliability, that the patient has this disease. During this surgical procedure, it is possible to view lesions suggestive of the disease and to obtain a tissue sample for anatomopathological analysis and confirmation of the endometriosis diagnosis[7]. The classification used for endometriosis is that of the American Society of Reproductive Medicine/ASRM, revised in 1996, which classifies this disease into four stages: minimal (stage I), mild (stage II), moderate (stage III), or severe (stage IV)[8]. Currently, the most widespread treatments are surgery, ovarian suppression therapy, or the combination of both[5,7].

The cause of endometriosis remains unknown. Nonetheless, there are evidences of immunological[9,10], environmental[11], and genetic[12-14] factors involved in its pathogenesis.

Regarding the immune response, the role of cytokines in the development of endometriosis[15] is emphasized; high levels of many cytokines were found in patients with endometriosis[16-18]. The same group of researchers, in independent works, assessed the levels of cytokines involved in immune response patterns Th1 [interleukin (IL)-2, tumor necrosis factor (TNF)-alpha, and interferon (IFN)-gamma] and Th2 (IL-4 and IL-10) in patients with endometriosis (n = 65) and in those without the disease (n = 33)[16-18]. Podgaec et al. noted an increase in the levels of IFN-gamma and IL-10 in patients with endometriosis, evidencing the co-existence of both responses[16]. However, when considering the ratio between cytokine levels and these responses, there was a predominance of IL-4 and IL-10, thus reflecting a potential change of the Th2 immune response component. In the subsequent study, cytokine levels were associated with the clinical symptoms of endometriosis[18]. Patients with endometriosis that presented deep dyspareunia and infertility showed high levels of TNF-alpha and IL-2, respectively. These cytokines are related to the Th1 immune response, and almost 70% of the patients that presented these results had severe endometriosis. The authors concluded that, when specific clinical data are associated with a high production of certain cytokines, there is a Th1 response pattern that may be related to severe endometriosis. The induction of the Th1 immune response was also reported by Fairbanks et al., who demonstrated high levels of IL-12 in patients with severe endometriosis[17].

The contribution of environmental factors to the development of endometriosis was reviewed by Bellelis et al., who related the influence of these factors, together with the diet, on the genesis of this disease[11]. The authors concluded that the mechanism by which dioxin and dioxin-like compounds (2,3,7,8-tetrachlorodibenzo-p-dioxin[TCDD] and polychlorinated biphenyls [PCBs]) act and change the endometrial physiology is uncertain and speculative. They also affirm that there is insufficient evidence as to the use of specific diets as preventive or even adjuvant factors in the treatment of endometriosis.

The genetic and hereditary basis for endometriosis was evidenced in the study by Bellelis et al.[3], in which approximately 5.3% of the patients reported first-degree family history of endometriosis. Familial aggregation, a high concordance rate among monozygotic twins, and a risk of 4% to 7% for first-degree relatives support the contribution of genetic factors to the pathogenesis of this disease[14]. In this context, the identification of genetic variants or single nucleotide polymorphisms (SNPs) responsible for susceptibility to endometriosis has been researched in recent years[19-21]. Different classifications have been proposed for the genes responsible for susceptibility to endometriosis (Box 1).

Box 1 – Classification of endometriosis susceptibility genes according to (a) Falconer et al.[19] and (b) Tempfer et al.[21]

a) Group of genes and frequency of positive correlation with endometriosis	b) Group of genes
1) Cytokines/inflammation, 42.9%	1) Inflammatory mediators
2) Steroid-synthesizing enzymes and detoxification enzymes and receptors, 46.2%	2) Involved in sexual hormone activity
3) Hormone receptors, 60%	3) Metabolic enzymes
4) Estradiol metabolism, *NI	4) Regulators of vascular function and tissue remodeling
5) Other enzymes and metabolic systems, 42.9%	5) Other genes linked to endometriosis
6) Growth factor systems, 66.7%	
7) Adhesion molecules and enzymes from the matrix, 40%	
8) Apoptosis, cell-cycle regulation and oncogenes, 22.2%	
9) Human leukocyte antigen system and immune components, NI*	

*NI, not informed

This bibliographic review presents a detailed description of the contribution of genetic polymorphisms in genes regulating vascular function and tissue remodeling into the pathogenesis of endometriosis. Genes belonging to this category include: alpha 2-HS glycoprotein (AHSG), epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), endostatin, plasminogen activator inhibitor 1 (PAI-1), angiotensin I-converting enzyme (ACE), and matrix metalloproteinases (MMPs).

For this purpose, a bibliographic research was performed in PubMed, with no time limitation, using the following terms (n = number of articles retrieved):

1 – endometriosis and AHSG polymorphisms (n = 1);
2 – endometriosis and EGFR polymorphisms (n = 2);
3 – endometriosis and VEGF polymorphisms (n = 19, 14 articles were selected for reading);
4 – endometriosis and endostatin polymorphisms (n = 1);
5 – endometriosis and PAI-1 polymorphisms (n = 6, 4 articles were selected for reading);
6 – endometriosis and ACE polymorphisms (n = 4);
7 – endometriosis and MMPs polymorphisms (n = 11, 9 articles were selected for reading).

Articles were selected based on titles and summaries, and the full texts or summaries of those related to the topic were analyzed. An aggregate of 35 publications on polymorphisms in these genes were included in this review. Table 1 summarizes the main results of these studies.

Excluded articles associated polymorphisms in these genes to other types of disease/sample (adenomyosis, pterygium, and placenta, n = 4), or endometriosis to polymorphism in another gene (IL-10, n = 1), or were included in the review category (n = 3), or were published in Chinese and the abstract was not available (n = 1).

Articles addressing general information on endometriosis or mentioned in the references of the studies retrieved from PubMed were also researched due to their relevance to this review.

AHSG and endometriosis

The alpha-2 Heremans Schmid glycoprotein (AHSG) is a protein present in human plasma secreted by the liver. The AHSG gene appears in the endometrium of women with endometriosis, and these women showed high levels of AHSG in serum and peritoneal fluid, in addition to anti-AHSG antibodies[22-24].

The AHSG gene is located at 3q27-29[25] and consists of seven exons and six introns[26]. Two polymorphisms, termed AHSG1 and AHSG2, have been described and occur in exons 6 and 7, respectively. Allele 1 is characterized by a replacement of cytokine for thymine, i.e., the triplet ACG (threonine) at position 230 was modified to ATG (methionine), resulting in the missense mutation p.T230M (rs4917). Allele 2 corresponds to a change from cytokine to guanine, with the respective missense mutation at position 238 of the protein, from threonine (ACC) to serine (AGC), i.e., p.T238S (rs4918)[27].

Considering the possibility of associating these SNPs to endometriosis, Kim et al.[28] investigated these polymorphisms in 79 Korean women with endometriosis and 105 women without the disease. They observed that those not carrying the AHSG2 allele had twice the risk of developing endometriosis than those with at least one copy of this allele, thus evidencing a positive association between endometriosis and polymorphisms in the AHSG gene in this population.

Table 1 – Summary of the articles that assessed polymorphisms in genes that regulate vascular function and tissue remodeling in endometriosis. In the sample size, women with endometriosis belonging to the study group followed the stage classification of the American Society for Reproductive Medicine – ASRM, 1996[8]

Gene	Exchange of nucleotide/ haplotypes	Sample size	Origin	Main findings	Reference
AHSG	p.T230M (allele 1) p.T238S (allele 2)	79 women with endometriosis (I = 14, II = 32, III = 8, IV = 25) 105 women without endometriosis	Korea	Women who did not carry the AHSG2 allele had twice the risk for endometriosis than those carrying at least one copy of this allele.	Kim et al. 2004[28]
EGFR	+ 2073 A/T	122 women with endometriosis 159 women with leiomyoma 139 control women	Taiwan/China	Association with increased risk for endometriosis and leiomyoma: genotypes and alleles related to EGFR + 2073T	Hsieh et al. 2005[34]
EGFR EGF	+ 2073 A/T + 61 G/A	146 women with endometriosis 181 controls	Japan	These SNPs were not associated with endometriosis	Inagaki et al. 2007[35]
VEGF	- 460 C>T	122 women with endometriosis 131 women without the disease	Taiwan/ China	Association with increased risk for endometriosis: VEGF -460TT genotype and VEGF -460T allele	Hsieh et al. 2004[45]
VEGF	- 460 C>T + 936 C>T - 2578 A>C - 1154 G>A -460T/-1154G/-2578C -460C/-1154A/-2578A -460C/-1154A/-2578C -460C/-1154G/-2578A -460C/-1154G/-2578C -460T/-1154A/-2578A -460T/-1154A/-2578C -460T/-1154G/-2578A	344 women with endometriosis (III/IV) 360 women without the disease	Northern China	No association with endometriosis: VEGF -460 C>T and VEGF + 936 C>T SNPs Association with reduced risk for endometriosis: VEGF -2578AA and VEGF -1154AA genotypes (VEGF -1154A and -2578A alleles protective against the development of endometriosis) Haplotypes that reduced the risk for endometriosis: -460C/-1154A/-2578A -460T/-1154A/-2578A -460T/-1154A/-2578C Haplotypes that increased the risk for endometriosis: -460C/-1154A/-2578C	Liu et al. 2009[46]
VEGF	- 460 C>T - 1154 G>A	344 women with endometriosis (III/IV) 360 controls with endometriosis 174 women with adenomyosis 199 controls with adenomyosis	Northern China	No association with endometriosis and adenomyosis: VEGF -460 C>T SNP Association with increased risk for endometriosis and adenomyosis: VEGF -1154GG genotype	Liu et al. 2009[47]
VEGF	- 460 C>T + 405 G>C -460C/+405G -460C/+405C -460T/+405G -460T/+405C	215 women with advanced stage endometriosis (III = 65 and IV = 150) 219 control women 70 fertile women	Korea	No association with endometriosis: VEGF -460C>T SNP and -460/+405 haplotypes Association with increased risk for endometriosis: VEGF + 405CC genotype	Kim et al. 2005[48]
VEGF endostatin	+ 936 C>T 4349 G>A	105 women with endometriosis (I = 20, II = 41, III = 11, IV = 33) 101 control women	Korea	Tested polymorphisms were not associated with endometriosis	Kim et al. 2008[49]

(cont.)

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Gene	Exchange of nucleotide/ haplotypes	Sample size	Origin	Main findings	Reference
VEGF	- 460 C>T + 405 G>C -460C/+405G -460C/+405C -460T/+405G -460T/+405C	215 women with endometriosis and (III = 80 and IV = 135) 210 women without the disease	Southern India	No association with endometriosis: VEGF -460C>T SNP VEGF +405GG genotype was more frequent in patients with endometrioma > 3 cm, compared to controls. The frequency of -460T/+405C haplotype was significantly lower in women with endometriosis, compared to controls.	Bhanoori et al. 2005[50]
VEGF	- 460 C>T + 405 G>C + 936 C>T -460C/+405G -460C/+405C -460T/+405G -460T/+405C	147 cases of endometriosis (I = 9, II = 15, III = 27, and IV = 96) 181 controls	Japan	No association with endometriosis: VEGF -460C>T SNP, VEGF + 405G>C SNP and -460/+405 haplotypes Association with increased risk for stage III-IV endometriosis: VEGF +936T allele	Ikuhashi et al. 2007[51]
VEGF	+ 405 G>C	203 women with endometriosis (I/II = 78, III/IV = 125) 140 women without the disease	Italy	Association with increased risk for endometriosis: VEGF + 405C allele	Gentilini et al. 2008[52]
VEGF	- 460 C>T + 405 G>C + 936 C>T -460C/+405G -460C/+405C -460T/+405G -460T/+405C	186 women with endometriosis (I/II = 19, III/IV = 167) 180 controls	Spain	No association with endometriosis: VEGF -460C>T SNP, VEGF + 405G>C SNP and -460/+405 haplotypes Association with increased risk for endometriosis: VEGF + 936T allele	Cosin et al. 2009[53]
VEGF	- 460 C>T + 405 G>C	98 women with endometriosis (I = 4, II = 18, III = 41, IV = 35) 94 women without the disease	Turkey	No association with endometriosis: VEGF – 460 C>T SNP Association with increased risk for endometriosis: VEGF + 405GC genotype and VEGF +405G allele	Altinkaya et al. 2009[54]
VEGF	- 460 C>T + 405 G>C -460C/+405G -460C/+405C -460T/+405G -460T/+405C	52 women with endometriosis (I/II = 11 and III/IV = 41) 60 women without endometriosis	Turkey	No association with endometriosis: VEGF -460 C>T SNPs Association with increased risk for endometriosis: VEGF + 405CC genotype (2.3 times higher risk for the development of endometriosis) and -460T/+405C haplotype Protective factor against endometriosis: VEGF +405G allele (higher frequency in the control group)	Attar et al. 2010[55]
VEGF	- 460 C>T + 405 G>C + 936 C>T - 2578 A>C -2578A/-460C/+405G -2578C/-460T/+405C -2578C/-460T/+405G	958 family cases of endometriosis (I/II = 559, III/IV = 394) 959 controls	Australia	The analysis by individual SNP or haplotype demonstrated no association with endometriosis	Zhao et al. 2008[56]

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Gene	Exchange of nucleotide/ haplotypes	Sample size	Origin	Main findings	Reference
VEGF	+ 405 G>C + 936 C>T - 2578 A>C - 1154 G>A -2578A/-1154G/+405G -2578A/-1154A/+405C -2578C/-1154G/+405G -2578C/-1154A/+405C	150 women with endometriosis (I = 53, II = 39, III = 36, IV = 22) 199 control women	Estonia	Association with reduced risk for endometriosis: VEGF -2578CC genotype. Other SNPs and haplotypes of the VEGF and ACE genes were not associated with the disease.	Lamp et al. 2010[57]
ACE	-240 A>T 2350 A>G -240A/2350A -240A/2350G -240T/2350A -240T/2350G				
VEGF	- 460 C>T + 405 G>C	480 women with endometriosis 600 controls	Northern Iran	Association with increased risk for endometriosis: VEGF + 405CC genotype and VEGF +405C allele. VEGF -460C/T SNP was not associated with the disease.	Emamifar et al. 2011[58]
PAI-1	4G/5G	75 women with endometriosis 43 control women	Canada	4G/4G genotype was observed in 52 (69%) of the 75 women with endometriosis and in only five (12%) of the 43 women without the disease. Thus, the 4G allele was associated with endometriosis. 5G/5G genotype was found in two (3%) of the 75 women with endometriosis, compared to 24 (56%) of the 43 controls. Association with endometriosis: PAI-1 4G/4G, 4G/5G genotype and PAI-1 4G allele	Bedaiwy et al. 2006[67]
PAI-1	4G/5G	170 women with endometriosis (I/II = 17, III/IV = 153) 219 control women	Spain	This polymorphism was not associated with endometriosis	Ramon et al. 2008[68]
PAI-1	4G/5G	204 women with endometriosis (I = 34, II = 25, III = 66, IV = 79) 164 gynecological control group 329 general population control group	Italy	This polymorphism was not associated with endometriosis	Gentilini et al. 2009[69]
PAI-1	4G/5G	140 women with endometriosis (I/II = 79, III/IV = 61) 148 controls	Brazil	This SNP was associated with increased risk for endometriosis related to infertility	Gonçalves-Filho et al. 2011[70]
ACE	2350 A>G -240 A>T	150 women with endometriosis (III/IV) 159 women without endometriosis	Taiwan/China	Association with increased risk for endometriosis: genotypes and alleles related to ACE 2350G and ACE -240T	Hsieh et al. 2005[73]

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Gene	Exchange of nucleotide/ haplotypes	Sample size	Origin	Main findings	Reference
ACE	I/D	125 women with endometriosis (III/IV) 120 women with leiomyoma 128 women without both pathologies	Taiwan/ China	Association with increased risk for endometriosis: genotypes and alleles related to ACE I Association with moderate risk for leiomyoma: genotypes and alleles related to ACE I	Hsieh et al. 2007[74]
ACE	I/D	121 women with endometriosis 122 women without endometriosis	Poland	This polymorphism was not associated with endometriosis	Kowalczynska et al. 2011[75]
MMP-1 MMP-3 	1G/2G 5A/6A 1G/5A 1G/6A 2G/5A 2G/6A	100 women with endometriosis 150 control women 80 patients with adenomyosis	China	Association with increased risk for endometriosis: MMP-1 2G/2G and 1G/2G genotype MMP-1 2G allele and 2G/6A haplotype Association with increased risk for adenomyosis: MMP-1 2G/2G genotype and MMP-1 2G allele No association with endometriosis and adenomyosis: MMP-3 5A/6A SNP	Kang et al. 2005[88]
MMP-1 MMP-3 	1G/2G 5A/6A 1G/6A 1G/5A 2G/6A 2G/5A	100 women with endometriosis (III/IV) 150 control women	Northern China	Association with increased risk for endometriosis: MMP1 2G/2G, 1G/2G genotype, MMP1 2G allele and 2G/6A haplotype No association with endometriosis: MMP3 5A/6A SNP	Shan et al. 2005[89]
MMP-1 MMP-3	1G/2G 5A/6A	56 women with endometriosis 71 control group	Italy	Polymorphisms in this gene were not associated with endometriosis.	Ferrari et al. 2006[90]
MMP-1 MMP-2 MMP-3 MMP-7 MMP-12 MMP-13	1G/2G -1575 G>A (MMP2.1) -1306 C>T (MMP2.2) 5A/6A -153C/T (MMP 7.1) -181 A/G (MMP 7.2) -82 A/G -77 A/G	227 women with endometriosis (ovarian endometriosis or endometrioma = 64, superficial endometriosis = 24 and deep endometriosis = 139) 241 controls	Paris/France	The MMP12-MMP13 A/G-A/A combined genotype was associated with superficial endometriosis	Bhorghese et al. 2008[91]
MMP-2 TIMP-2	-1306 C>T -735 C>T -1306C/-735C -1306C/-735T -1306T/-735C -1306T/-735T -418 G>C	298 women with endometriosis 324 controls 180 patients with adenomyosis	China	Association with increased risk for adenomyosis: MMP-2 -1306CC genotype Association with reduced risk for endometriosis: TIMP-2 -418CC genotype (frequency of this genotype was lower in patients with endometriosis than in control women) No association with endometriosis: MMP-2 -1306 C>T SNP No association with endometriosis: TIMP-2 -418G>C SNP No association with endometriosis: and adenomyosis: MMP-2 -1306/-735 haplotypes and MMP-2 -735 C>T SNP	Zhao et al. 2008[92]

(cont.)

Table 1 – Summary of the articles that assessed polymorphisms in genes that regulate vascular function and tissue remodeling in endometriosis. In the sample size, women with endometriosis belonging to the study group followed the stage classification of the American Society for Reproductive Medicine – ASRM, 1996[8] (cont.)

Gene	Exchange of nucleotide/ haplotypes	Sample size	Origin	Main findings	Reference
MMP-2	-1306 C/T -735 C/T -1306C/-735C -1306C/-735T -1306T/-735C -1306T/-735T	298 women with endometriosis (III/IV) 324 controls	North China	Association with reduced risk for endometriosis: TIMP-2 -418CC genotype No association with endometriosis: -1306C/T, -735C/T SNPs and -1306/-735 haplotypes	Kang et al. 2008[93]
TIMP-2	-418 G/C				
MMP-2	-735 C/T -790T/G -1575 G/A -735C/-790T/-1575G -735C/-790G/-1575A -735T/-790T/-1575G -735T/-790G/-1575A -735C/-790T/-1575A -735C/-790G/-1575G -735T/-790T/-1575A -735T/-790G/-1575G	150 women with endometriosis (I/II = 92, III/IV = 58) 199 healthy women	Estonia	Association with increased risk for endometriosis: MMP-2 -735CC genotype (stage I/II endometriosis) MMP-9 -1562 TT or TC genotype (stage III/IV endometriosis). The eight tested haplotypes were not associated with endometriosis. MMP-2 -790T/G and -1575G/A SNPs were not associated with the disease.	Saare et al. 2010[94]
MMP-9	-1562 C/T				
MMP-7 MMP-9	-181 A/G -1562 C/T	143 women with endometriosis (III/IV) 160 control women 76 women with adenomyosis	Northern China	Association with endometriosis and adenomyosis: MMP-7 -181G allele SNP of the MMP-9 gene was not associated with the occurrence of endometriosis and adenomyosis.	Shan et al. 2006[95]
MMP-9	-1562 C>T R279Q (2678G>A) P574R (4859C>G) R668Q (5546G>A) 2678G/4859C 2678A/4859G 2678G/4859G 2678A/4859C -1562C/5546G -1562C/5546A -1562T/5546G -1562T/5546A	225 women with endometriosis (III/IV) 198 control women	Korea	The risk of developing endometriosis was not associated with the individually studied SNP. The haplotype analysis showed significant association with the disease. Association with endometriosis of AC (279Q/P574), GG (R279/ 574R) and CA (-1562C/668Q) haplotypes	Han et al. 2009[96]

EGFR, VEGF, endostatin and endometriosis

Endometriosis shows characteristics similar to neoplasias, such as invasiveness and neovascularization, the latter considered an important phenomenon for the implantation of endometrial cells in ectopic sites. Thus, growth and other angiogenic factors, such as the VEGF and EGFR, could be related to the development of endometriosis[29-32].

EGFR is a transmembrane glycoprotein that plays important roles in controlling cell growth, differentiation, and motility. The EGFR gene is located at 7p12 and a polymorphism characterized by exchange of base A for T at position 2073 of exon 21 has been observed[33]. This modification changes the stop codon (TGA) by synthesis of the amino acid cysteine (TGT). Aiming at assessing whether the EGFR +2073A/T SNP could be used as a susceptibility flag for endometriosis, Hsieh et al. assessed 122 Taiwanese women with this pathology and 139 controls, and associated the TT and AT genotypes and the T allele to high risk

for the disease[34]. However, subsequent studies did not associate this SNP to endometriosis in Japanese people[35].

VEGF induces endothelial cell proliferation, migration, differentiation, and formation of capillaries, which contribute to the pathogenesis and progression of endometriosis. Additionally, studies have shown high levels of VEGF in the peritoneal fluid, serum, mRNA expression, and proteins of patients with endometriosis[36-42]. These data reinforce the role of VEGF in the pathogenesis of endometriosis.

The VEGF gene is located at 6p21.3[43], consists of eight exons, and shows alternative splicing, which is responsible for forming several proteins. At least 30 SNPs were described in this gene[44]. In order to determine a genetic predisposition to endometriosis, some studies were developed to investigate polymorphisms of the VEGF gene in women with endometriosis. These studies were conducted in China[45-47], Korea[48,49], India[50], Japan[51], Italy[52], Spain[53], Turkey[54,55], Australia[56], Estonia[57], and Iran[58]. Assessed SNPs were –460 C/T (rs833061), +405 G/C (also known as -634 G/C, rs2010963), +936 C/T (rs3025039), -1154 G/A (rs1570360), and -2578 A/C (rs699947).

–460 C/T polymorphism was researched in several studies[45-48,50,51,53-56,58]. Only the study of Hsieh et al.[45] associated the TT genotype and T allele to high risk for endometriosis.

With respect to +405 G/C polymorphism, no association between this SNP and endometriosis was reported by Ikuhashi et al.[51], Zhao et al.[56], Cosin et al.[53], and Lamp et al.[57], but a significant association was reported in six other studies[48,50,52,54,55,58]. However, these studies showed conflicting results regarding the relation between genotypes and alleles and endometriosis. Considering genotype and allele, Kim et al.[48], Gentilini et al.[52], Attar et al.[55], and Emamifar et al.[58] associated +405 CC and therefore the C allele, to endometriosis; Bhanoori et al.[50] and Altinkaya et al.[54] related the +405 GG and +405 GC genotypes to the disease, respectively. Thus, some works associated the C allele with endometriosis[48,52,55,58], while other works associated the G allele[50,54] with the disease. A positive association between endometriosis and SNP at position 405 became evident, suggesting an effective contribution of such polymorphism to the pathogenesis of endometriosis. The discrepancy regarding the results of analysis of +405 G/C VEGF SNP among the published works could be explained by the different populations studied, whose ethnic differences would explain the causes of these conflicting findings.

The studies by Ikushashi et al.[51] and Cosin et al.[53] investigated the same polymorphisms (-460 C/T, +405 G/C and +936 C/T) in populations with different ethnic origins. Both reported a positive association with respect to VEGF 936 T allele in women with endometriosis, while other authors[46,49,56,57] did not confirm this association.

-1154 G/A polymorphism was assessed by Liu et al.[46,47] and by Lamp et al.[57]. Studies by the same group of researchers[46,47] showed different results, as the AA genotype was associated with reduced risk for endometriosis[46], and the GG genotype was associated with high risk for the disease[47]. Different alleles of the -2578 C/A SNP were associated with reduced risk for endometriosis. The A allele of this polymorphism was reported to be protective in relation to the development of endometriosis[46]; Lamp et al.[57] associated this protection with the C allele. This polymorphism was not associated with endometriosis in a study by Zhao et al.[56].

The study by Zhao et al.[56] that assessed VEGF -460 C/T, +405 G/C, -2578 A/C, and +936 C/T SNPs (the latter also investigated by Kim et al.[49]), was the only study that did not associate these SNPs with endometriosis. Despite the conflicting results regarding some SNPs, at least one polymorphism was associated with endometriosis in the abovementioned works.

The 4349 G/A polymorphism of the endostatin gene was assessed by Kim et al.[49]. Endostatin is a specific endogenous anti-angiogenic factor derived from the proteolysis of type XVIII collagen, and it induces inhibition of endothelial cell proliferation, migration, and apoptosis. Studies have demonstrated the role of endostatin in endometriotic lesions in animal models[59,60]. This SNP was not related to endometriosis, but the endostatin level in serum was negatively correlated with the development of this disease[49].

In addition to the individual analysis of the VEGF gene per SNP, some studies carried out the research per haplotypes. The -460/+405 haplotype was not associated with endometriosis in the studies by Kim et al.[48], Ikushashi et al.[51], and Cosin et al.[53]. The -460T/+405C haplotype showed lower frequency in women with endometriosis[50]; in another study, it was associated with high risk for this disease[55]. Other haplotypes not related to endometriosis were -2578/-460/+405[56] and -2578/-1154/+405[57]. -460C/-1154A/-2578A, -460T/-1154A/-2578A, and -460T/-1154A/-2578C haplotypes were associated with reduced risk for endometriosis, while -460C/-1154A/-2578C was associated with high risk for the disease[46]. Therefore, only eight out of 14 studies that assessed the VEGF gene performed analyses per haplotype, with result of positive association with endometriosis in only three studies.

PAI-1 and endometriosis

The plasminogen activation system includes plasminogen activators and their inhibitors, which are involved in tissue degradation and remodeling under normal and pathological conditions. Two plasminogen activator inhibitors (PAIs), termed PAI-1 and PAI-2, regulate the plasminogen activation system[61,62]. The main PAI is PAI-1, also known as endothelial cell PAI, which also plays an important role in signal transduction, cell adherence, and cell migration[63].

The PAI-1 gene, whose official symbol is SERPINE1, is located at 7q21.3-q22 and contains 9 exons. A guanine (G) insertion/deletion polymorphism in the promoter region of the PAI-1 gene at position -675, termed 4G/5G, has been described and is involved in regulating the synthesis of this inhibitor. *In vitro* studies have showed that the 4G allele is associated with increased gene expression from its binding to an activator protein, while the 5G allele contains an additional binding site for the DNA-binding protein acting as a transcriptional repressor[64-66].

Four studies were performed in women with endometriosis from Canada[67], Spain[68], Italy[69], and Brazil[70]. A positive association for PAI-1 4G/5G SNP was reported by Bedaiwy et al.[67] and Gonçalves-Filho et al.[70]. According to Bedaiwy et al., patients with 4G/5G and 4G/4G genotypes are 38 and 441 times more likely to have endometriosis than those with a 5G/5G genotype, respectively[67]. In this study, 118 women were assessed (75 with endometriosis and 43 controls) and the 4G allele frequency was significantly higher in those with endometriosis. Nonetheless, these findings were not replicated in two studies involving a large number of patients and controls, one with 389 women (170 with endometriosis and 219 controls)[68], and the other with 204 women with endometriosis and 164 controls[69]. Therefore, according to studies of Ramon et al.[68] and Gentilini et al.[69], the predisposition to endometriosis did not involve the 4G/5G PAI-1 polymorphism.

ACE and endometriosis

The ACE catalyzes the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. Thus, ACE activity is associated with angiogenesis, which plays a key role in the pathogenesis of endometriosis. The presence of angiotensin receptors in the endometrial tissue has been demonstrated. Angiotensin II in endometrial stromal cells was mediated via angiotensin I receptors[71], and could increase the intracellular calcium concentration by interaction with the angiotensin receptor in endometrial stromal cells[72]. These findings suggest a contribution of ACE to the development of endometriosis and the endometrium.

The ACE gene is located at 17q23.3 and three SNPs were assessed to verify association with endometriosis: -240 A/T (promoter region – rs4291), 2350 A/G (alteration in exon 17, Thr776Thr – rs4343), and one insertion/deletion (I/D) of one Alu sequence (287 pb) in intron 16.

Hsieh et al.[73] and Lamp et al.[57] investigated polymorphisms at position 240 and 2350 and found conflicting results. In 2005, Hsieh et al. assessed 150 women with endometriosis and 159 controls from Taiwan/China[73]. They observed that genotypes and alleles related to ACE 2350G (heterozygous AG, homozygous GG, and G allele) and ACE-240T (heterozygous AT, homozygous TT, and T allele) were associated with high susceptibility to endometriosis in this population. However, in 2010, Lamp et al. did not identify an association between these two SNPs and endometriosis in 150 women with endometriosis and 199 controls from Estonia[57]. These same researchers investigated -240/2350 haplotypes and did not associate them with endometriosis.

Regarding polymorphism in the ACE I/D gene, the genotypes and alleles related to the ACE I were strongly associated with endometriosis in 125 patients with endometriosis and 128 controls[74]. However, Kowalczynska et al.[75] investigated this same SNP in 121 women with endometriosis and 122 without endometriosis, and did not associate it to the disease. Therefore, only studies in Taiwanese/Chinese subjects[73,74] have demonstrated positive associations of the ACE polymorphism at position 2350, 240, and ACE I/D with endometriosis. When such polymorphisms are assessed in people of other ethnic origins, the results of positive association were not confirmed[57,75].

MMPs and endometriosis

MMPs belong to a large group of 23 proteases that regulate tissue remodeling by degrading the structural components of the extracellular matrix (ECM). MMPs also control basic cellular functions (proliferation, differentiation, motility, apoptosis), as they regulate the ECM proteins that interact with cells[76].

High levels of MMPs were found in ectopic endometrium when compared to eutopic endometrium in women with endometriosis. Therefore, the overexpression of MMPs may contribute to the development of endometriosis[77-84].

Genetic polymorphisms located in the promoter region of the MMPs genes could increase the levels of gene expression, and may be associated with genetic predisposition to various diseases[85-87].

Thus, polymorphisms in the MMP-1[88-91], MMP-2[91-94], MMP-3[88-91], MMP-7[91,95], MMP-9[94-96], MMP-12[91], MMP-13[91], and TIMP-2[92,93] genes were investigated to verify whether they contribute to the development of endometriosis.

An I/D of guanine in the promoter region of the MMP1 (-1607 1G/2G) (rs112925) gene was associated with increased risk for endometriosis in Chinese women according to Kang et al.[88] and Shan et al.[89]. Both studies showed a role of the 2G allele in the pathogenesis of endometriosis in 100 women with endometriosis and 150 controls. Polymorphisms in this gene were not associated with endometriosis in Italian[90] and French[91] women.

Four SNPs in the promoter of the MMP-2 gene have been described: -735 C/T (rs2285053), -790 T/G (rs243864), -1306 C/T (rs243865), and -1575 G/A

(rs243866). -735 C/T polymorphism was investigated by Zhao et al.[92], Kang et al.[93], and Saare et al.[94]. Only in the study of Saare et al. was the -735CC genotype associated with increased risk for stage I-II endometriosis[94]. The -790 T/G SNP investigated by Saare et al.[94]; the -1306 C/T investigated by Zhao et al.[92], Kang et al.[93], and Bhorghese et al.[91]; and the -1575 G/A analyzed by Bhorghese et al.[91] and Saare et al.[94] showed no significant association with endometriosis.

No association with endometriosis was reported for the -1612 5A/6A and -1171 5A/6A SNPs of the MMP-3 gene[88-91].

1G/6A, 1G/5A, 2G/6A, and 2G/5A haplotypes related to the MMP-1 and MMP-3 genes were investigated by Kang et al.[88] and Shan et al.[89]. In both studies, the 2G/6A haplotype was associated with increased risk for endometriosis. For the -1306/-735 and -735/-790/-1575 haplotypes of the MMP-2 gene, no association with endometriosis was reported by Zhao et al[92], Kang et al.[93], and Saare et al.[94].

Two polymorphisms in the promoter region of the MMP-7 gene (-153 C/T and -181 A/G) were investigated for association with endometriosis[91,95]. Only the G allele of -the 181 A/G (rs1799750) SNP was associated with increased risk for endometriosis and adenomyosis in Chinese women[95].

R279Q (2678G>A), P574R (4859C>G), R668Q (5546G>A), and -1562 C>T (rs3918242) polymorphisms of the MMP-9 gene were investigated by Han et al.[96] and, in the analysis of individual SNP, showed no association with endometriosis. However, the AC (279Q/P574), GG (R279/574R) and CA (-1562C/668Q) haplotypes were significantly associated with endometriosis. In his research, Han et al.[96] concluded that haplotype analysis of the MMP-9 gene was more informative than individual polymorphism analysis. Regarding the -1562 C> T SNP that had been previously investigated by Shan et al.[95], the result was consistent with the study of Han et al.[82]. However, a study by Saare et al.[94] showed that the -1562 TT and TC genotypes of the MMP-9 gene were associated with advanced stage endometriosis (III-IV).

The MMP-12 – MMP-13 A/GA/A combined genotype of MMP-12 and MMP-13 genes contributed to the development of superficial endometriosis in French women[91].

Regarding the -418 G/C SNP of the TIMP-2 gene, the -418CC genotype was associated with reduced risk for endometriosis in the two studies[92,93], and the C allele was a protective factor against the development of endometriosis in Chinese women.

Regarding haplotype analysis, of nine studies on MMP genes, six assessed haplotypes, and a positive association between endometriosis and the haplotypes of MMP-1, 3, and 9[88,89,96] genes was reported, as well as a negative association for haplotypes of the MMP-2[92-94] gene.

Final considerations

In this review, a detailed description of the contribution of genetic polymorphisms in genes that regulate vascular function and tissue remodeling into the pathogenesis of endometriosis has been presented. Some polymorphisms of the VEGF (-460 C/T, +405 G/C, +936 C/T), PAI, MMP-1, 2, and 3 genes have been widely studied, while others of the AHSG, EGF, endostatin, and VEGF (-1154 G/A, -2578 A/C) genes were not. In the latter case, additional studies are required to confirm the findings by the few studies that have analyzed these SNPs. Additionally, studies that found a positive or negative association of SNP with endometriosis emphasize the relevance of studies with a large number of control cases to confirm their findings. Haplotype analysis was carried out only for the VEGF (-460, +405, -1154 and -2578), ACE (-240/2350) and MMP-1, 2, 3 and 9 genes, and in most studies, there was no association with endometriosis. Of the eight studies that analyzed haplotypes of the VEGF gene, five did not associate them with endometriosis. Haplotypes of ACE and MMP-2 genes were not associated with endometriosis, while those of MMP-1, 3, and 9 genes were related to a high risk for the disease. It is worth highlighting that studies involving polymorphisms are complex, since a genetic association, although valid for a specific ethnic population, may not be relevant to individuals of another ethnicity.

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