Defining the genetic profile of endometriosis (Review)

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Abstract. Endometriosis is a pathological condition which has been extensively studied, since its pathophysiology stems from a broad spectrum of environmental influences and genetic factors. Familial studies aim at defining inheritance trends, while linkage analysis studies focus on the identification of genetic sites related to endometriosis susceptibility. Genetic association studies take into account candidate genes and single nucleotide polymorphisms, and hence target at unraveling the association between disease severity and genetic variation. The common goal of various types of studies is, through genetic mapping methods, the timely identification of therapeutic strategies for disease symptoms, including pelvic pain and infertility, as well as efficient counselling. While genome-wide association studies (GWAS) play a primary role in depicting genetic contributions to disease development, they entail a certain bias as regards the case-control nature of their design and the reproducibility of the results. Nevertheless, genetic-oriented studies and the implementation of the results through clinical tests, hold a considerable advantage in proper disease management. In this review article, we present information about gene-gene and gene-environment interactions involved in endometriosis and discuss the effectiveness of GWAS in identifying novel potential therapeutic targets in an attempt to develop novel therapeutic strategies for a better management and treatment of patients with endometriosis.

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1. Introduction

Endometriosis is an estrogen-dependent disease, defined by the development of endometrial tissue in ectopic sites (1). Chronic pelvic pain, dysmenorrhea and impaired fertility represent the main symptoms, with laparoscopy and biopsy still being the gold-standard for diagnosis (2). Endometriosis-induced infertility predominantly occurs due to ovarian dysfunction, as a result of mechanisms interfering with folicullogenesis and endometrial receptivity, and represents the main reason women of reproductive age resort to methods of assisted reproduction, such as *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) (3). Thus, endometriosis has been an issue of particular interest for clinical doctors and researchers, since it hinders fecundity in approximately one tenth of women elapsing their reproductive years.

Multiple theories have been put forward regarding the operative events provoking the disease, with the hypothesis of retrograde menstruation dispelling functional endometrial cells into the peritoneal cavity along the salpinges, being the oldest and most prevalent (4). Previously, whole-exome sequencing, in search of somatic mutations in the endometrial tissues of 16 cases, demonstrated that the majority of genes involved in cell adhesions, junctions and chromatin-remodeling complexes were mutated in both eutopic and ectopic tissues (5). Additional suggestions regarding disease pathophysiology pertain to steroid function, an altered peritoneal biochemical and cellular environment (6), oxidative stress and induced inflammation, as well as defective immune surveillance and augmented angiogenesis (7).

Indeed, its etiology and pathogenesis exhibit complexity, as both genetic influences and environmental contributors seem to formulate the disease phenotype (8). Since the multifactorial nature of endometriosis involves the participation of immune mechanisms, angiogenetic processes and biochemical alterations, it can be deduced that genetic factors, as well as epigenetic modifications act together for disease manifestation. The heritability pattern of endometriosis was first proposed by Goodall in 1943, through his references on 5 family history cases (9). Ever since, further familial studies have been performed.

2. Family aggregates and twin studies

Familial aggregation studies generally pertain to the amassing of specific traits encountered in a given family, which cannot be attributed to coincidental events. These studies are utilized for the detection of genetic factors that contribute to the manifestation of a studied disease (10), designed by gathering representative subjects, named as probands, and recording an extensive family history.

In previous a case-control study, including a British population sample of 64 women with a visual diagnosis of endometriosis, 9.4% of patients had a first-degree relative with endometriosis (11), while in another retrospective cohort study of 80 patients, endometriosis was detected in 5.9% of the patients' first-degree relatives, underlining the familial tendency of the disease (12). In accordance with this, another study reported that patients' sisters presented with an 8.8% percentage of endometriosis, with the relative risk being equal to 5.7, in a total of 339 women with the disorder (13). Upon further expanding this to further degrees of kinship, disease prevalence was previously examined in relatives of a group of 101 patients with diagnosed endometriosis; 7 first-, 3 second- and 2 third-degree relatives were affected, further verifying the hereditary character of the disorder (14). Moreover, the heritability of endometriosis has been put under investigation in multitudinous Utah families. For this purpose, three-generation family histories were retrieved from 117 probands; not only first-degree relatives, but also second-degree relatives were reportedly diagnosed with the disease (15). In a previous population-based study, the risk ratio for female siblings equaled to 5.20, as opposed to 1.56 for cousins, while the average kinship coefficient for female patients was notably elevated in comparison to the one estimated for 1,000 sets of 750 matched controls (16). In another study, the assessment of 800 medical reports, including 400 surgical patients, suggested that the total risk for endometriosis of first-degree patients' relatives increased up to 10.2%, with the same percentage being only 0.7% for the controls (17). Complementary to the above-mentioned results, an investigation of 526 medical records at the Yale Haven Hospital for the sexennial period between 1996-2002, revealed an association of familial risk for ovarian, colon and prostate cancer in women with endometriosis, both for patients and for their first- and second- degree relatives (18). Endometriosis can, in fact, manifest in species, whose reproductive function involves menstruation. Familial aggregation has been studied in a species belonging to the primates order, where it has been displayed to be elevated, as well as the risk of recurrence among members of the same family, indicating the inheritance pattern of endometriosis in other species, apart from humans (19).

Twin studies are utilized for the evaluation of genetics participation in contrast to the environmental influences regarding a given feature. Limitations and assumptions are an intrinsic trait of these types of studies; their results, however, have been shown to be ascertained by molecular genetic studies (20). A previous monozygotic and dizygotic twin pair study entailed 215 twins with self-reported endometriosis, with the data varying in relevance to medical reports, indicating that this deviation may be attributed to further genetic impingement. The ratio between monozygotic and dizygotic twins was 2:1, with the overall available information suggesting that genetic contribution bears an important association with disease manifestation (21). In another study, in 16 monozygotic pairs, 9 were in congruence with an advanced endometriosis stage, while in 5 pairs out of the 7 discordant pairs, one twin had mild disease, while the other had either advanced or deep infiltrating disease. Furthermore, women in the two discordant monozygotic twins presented with infertility (22). In a cohort study comprised of 3,595 monozygotic and 3,601 dizygotic female twin pairs, concordance among probands was 0.21 and 0.1 for monozygotic and dizygotic twins, respectively, while in monozugotes the tetrachoric correlation was elevated as well (23). It can thus be deduced that genetic influences in this sample accounted for almost half of the total contribution to the disease phenotype, with environmental factors seemingly playing an equal role.

3. Linkage analysis studies

The aim of linkage analysis studies is the mathematical interpretation of pedigree data for the investigation of allelic cosegregation at a suspect genetic locus (24). This correlation does not imply a random event, rather their adjacent location on chromosomes, which enables their co-inheritance (25). Linkage analysis studies were widely used over the past 50 years of the previous century, conceding their place to genome-wide association studies (GWAS) (26). Linkage studies contribute to the investigation of genomic regions that are likely to include genetic polymorphisms related to disease risk (27). However, an intrinsic drawback is that the exact accountable gene or polymorphism cannot be singled out, since elongated genomic regions are given prominence to. In an attempt to mitigate this problem, single nucleotide polymorphism (SNP) association studies have been put into implementation.

The Oxford Endometriosis Gene (OXEGENE) study, an international undertaking, aimed, via the technique of linkage analysis, at the identification of genetic loci associated with susceptibility to endometriosis (28). For this purpose, the International Endogene Study, a conflation of the OXEGENE and the Genes Behind Endometriosis Australian study, recruited >1,000 families, whose participants belonged mainly to affected sibling-pair groups, for a positional cloning strategy (29). Three years later, in a similar linkage study of 1,176 families, segments of important linkage were detected on chromosome 10q26 and suggestively 20p13, along with several minor potential loci (30). Aiming at positional cloning approach, this combined study included at least 2 affected members with surgical diagnosis of the disease. The sibling recurrence ratio was calculated as ≥1.3 ($\lambda s = 1.3$) in comparison to the general population. In an effort to determine whether this particular accumulation of cases among families with numerous members affected

can be justified according to (near-) the Mendelian autosomal inheritance principle, Zondervan *et al* in 2007 (31) came across the conclusion that one or more high-penetrance susceptibility loci on chromosome 7p13-15 exist for endometriosis, following the afore-mentioned pattern of inheritance. Genes included in regions highlighted by linkage analysis, should subsequently be examined as potential candidates bearing mutations responsible for disease development. Since no single gene is solely linked with a disease, localizing respective genes proves to be a rather demanding task. In another study investigating 3,223 cases of endometriosis for 11,948 SNPs located on chromosome 10 (on chromosome 10q26 in a study of 1,176 families), it was revealed that through linkage analysis method, a relation existed between endometriosis on chromosome 10 (32).

4. Genetic association studies

Genetic association studies are widely used for the detection of candidate genes and genomic regions that contribute to formation of disease phenotype, by examining the relation between disease status and genetic variation. Given the suggested pathophysiology mechanisms of endometriosis, study subjects revolve around cellular proliferation/differentiation/migration, tumor suppression/growth, apoptosis, angiogenesis and inflammation-related genes (Table I), particularly aiming at tracing SNPs, microsatellite markers, insertion/deletion variable tandem repeats and copy-number variants (33).

Cellular cycle-, proliferation- and apoptosis-related loci

i) DNA mismatch repair. The Arg399Gln polymorphism in the X-ray repair cross-complementing group 1 (*XRCC1*) gene, one of the DNA repair pathway genes, has been suggested to be associated with the risk of developing endometriosis, particularly in Asian populations. Specifically, the A allele has been shown to consist of a preventive factor for the disease (34), with the AA genotype exhibits a significant association with a reduced risk of endometriosis if compared to GG. The *XRCC1* Arg399Gln polymorphism is not only associated with an increased disease susceptibility (as regards the '*GG*' genotype), but may also potentially serve as a biomarker (35). As regards *XRCC4*, codon 247*A- and promoter 1394*T-related genotypes and alleles might as well be associated with endometriosis (36). *hMLH1* is another component of the DNA mismatch repair system genes that corrects errors in DNA replication for the achievement of genomic integrity. The suppressed expression of *hMLH1* can possibly lead to the deterioration of the endometriosis progression stage (37).

ii) Proliferation/differentiation. Modifications have been identified in endometriotic lesions in the homeobox (HOX) genes cluster, which encode for fetal development. The *HOXA10* gene participates in the embryogenesis of the uterus and embryo implantation through the regulation of downstream genes. *HOX-A* and *HOX-B* incur downregulation, while *HOX-C* upregulation (38). *HOXA10* and *HOXA11*, known to be upregulated during implantation, reportedly exhibit reduced product levels during the same period in women with endometriosis (39). It seems that patients do not display the expected mid-luteal rise of *HOXA10* expression, hence endometriosis-induced infertility can be partially explained (40). Empty spiracles homeobox 2 (*EMX2*) is a transcription factor necessary for female Müllerian duct differentiation and development, also being a known direct target of *HOXA10* in the reproductive tract. *EMX2* regulates human teneurin transmembrane protein 1 (*TENM1*) in a direct manner, the expression of the latter being associated with embryonic pattern formation and morphogenesis. Thus, it has been proposed that alterations in *HOXA10*, *EMX2* and *TENM1* expression levels may act in infertile women with a Müllerian duct anomaly to cause a partially septate uterus (41). In a study of 45 affected women, HOXA11-AS1 lncRNA was shown to participate in the development of peritoneal endometriosis. In detail, the HOXA11-AS1 lncRNA and HOXA9, HOXA10, HOXA11 and HOXA13 mRNAs were expressed at notably decreased levels in the eutopic than in the ectopic endometrium in women with peritoneal endometriosis. Indeed, patients with peritoneal endometriosis, compared to the healthy control samples, demonstrated a noticeably reduced expression of HOXA10 and HOXA11 in the eutopic endometrium, while the lncRNA (HOXA11-AS1), HOXA9 and HOXA13 levels did not present a considerable difference between the two patient groups (42). The expression of not only *HOXA11*, but also of leukemia inhibitory factor (*LIF*) and basic transcriptional element binding protein1 (*BTEB1*) in the endometrium during the mid-luteal phase, was shown to be suppressed in women with endometriosis compared to healthy women (43).

The *p27* gene is responsible for maintaining cellular cycle and differentiation; the single nucleotide polymorphism in codon 109 (V109G) has been shown to be related to an increased risk of developing endometriosis (44). The secretory phospholipase A2 group IIa (*PLA2G2A*) gene induces cell proliferation; its polymorphism 763C>G has been linked with endometriosis in an Iranian women population (45). Moreover, an association has been observed between polymorphisms in the laminin subunit alpha 1 (*LAMA*) and kazrin, periplakin interacting protein (*KAZN*) genes and endometriosis. The *KAZN* is a gene encoding a protein for cell adhesion; the G variant of the rs10928050 SNP of this gene seems to be encountered more frequently in patients with endometriosis than in healthy controls. The *LAMA5* is a gene involved in various cellular processes, including differentiation, adhesion, migration and angiogenesis. An important association has been accentuated among the *LAMA5* rs2427284 SNP and endometriosis stages III and IV (46).

iii) Apoptosis. The eutopic endometrium of patients seems to hold a unique molecular signature, since in 91 out of 579 genes involved in cell apoptosis modulation and decidualization, a significant aberration has been noted between cases and controls (47). A notable aberration seems to exist in the Fas cell surface death receptor (*FAS*) gene rs13416436 and rs2037815 SNPs, among patients and controls of Brazilian origin; the haplotype containing the rs3740286 A and rs4064 G alleles in the *FAS* gene hold statistical significance (48). Calpains are also involved in the regulation of apoptosis; indeed, calpain5 acts as a target of *HOXA10* transcriptional regulation in endometrial cells, indicating that a low *HOXA10* expression affects calpain5 expression accordingly (49). The KRAS proto-oncogene, GTPase (*KRAS*), sirtuin 1 (*SIRT1*) and B-cell lymphoma 6 (*BCL6*) genes, involved in multiple physiological progresses regarding differentiation, proliferation and apoptosis, seem to be overexpressed in a coordinated manner in the eutopic endometrium of patients and contribute to the pathogenesis of endometriosis (50).

Table I. An overview of genetic polymorphisms related to the development of endometriosis, as they have been confirmed by gene association studies and GWAS.

SNPs	Endometriosis-associated gene	Function	(Refs.)
rs1042522	*TP53*	Tumor suppressor protein	(53)
rs2234693 rs9340799	*ESR1*	Nuclear receptor activated by the sex hormone estrogen	(153)
rs743572	*CYP17A1*	Hydroxylase-type enzyme, ubiquitously expressed in many tissues and cell types	(61,62)
rs700519 rs1048943	*CYP1A*	Enzyme involved in phase I xenobiotic and drug metabolism	(58,87)
rs10046 rs700518	CYP19	Drug metabolism and synthesis	(67)
rs1056836	*CYP1B1*	Member of cytochrome P450 superfamily	(87)
rs244285 rs12248560	CYP2C19	Member of the cytochrome P450 mixed-function oxidase system	(68)
rs4072111 rs1131445 rs11556218	*IL-16*	Pleiotropic cytokine that functions as a chemoattractant, a modulator of T cell activation and an inhibitor of HIV replication	(88,89)
rs6542095	*IL-1A*	Pleiotropic cytokine involved in inflammatory processes and hematopoiesis	(172)
rs1800871	*IL-10*	Anti-inflammatory cytokine	(107)
rs17860508	*IL12B*	Cytokine acting on T and natural killer cells	(109)
rs20417	*COX-2*	Enzyme responsible for inflammation and pain	(97)
rs1632947 rs1233334	HLA-G	Histocompatibility antigen playing a role in immune tolerance in pregnancy	(114)
rs41308748	*LILRB1*	Leukocyte immunoglobulin-like receptor	(114)
rs383369	*LILRB2*	Leukocyte immunoglobulin-like receptor	(114)
rs10794288 rs10902088	*MUC2*	Glycoprotein produced by many epithelial tissues	(115)
rs882605 rs1104760 rs2688513 rs2258447	*MUC4*	Transmembrane glycoprotein that functions in cell growth signaling pathways and tumor progression	(115,116)
rs699947 rs1570360 rs9582036	*VEGF*	Signaling protein involved in both vasculogenesis and angiogenesis	(130,136)
rs1341643 rs2037815 rs3740286 rs4064	*FAS*	Member of the TNF-receptor superfamily, playing a central role in the physiological regulation of programmed cell death	(48)
rs34536443	*TYK2*	Tyrosine kinase	(118)
rs2268613	*PLGF*	Vascular endothelial growth factor associated with angiogenesis	(136)
rs11549465	*HIF-1α*	Transcriptional regulator of cellular and developmental response to hypoxia	(136)
rs144240142	*MAP3K4*	Component of a protein kinase signal transduction cascade	(174)
rs10928050	*KAZN*	Protein that plays a role in desmosome assembly and cell adhesion	(46)
rs2427284	*LAMA5*	Extracellular matrix glycoprotein	(46)
rs2235529	*LINC00339-WNT4*	RNA gene affiliated with the non-coding RNA class - protein implicated in oncogenesis and in several developmental processes	(163)
rs1519761 rs6757804	*RND3-RBM43*	Negative regulator of cytoskeletal organization - nucleic acid binding and nucleotide binding	(163)

Table I. Continued.

SNPs	Endometriosis-associated gene	Function	(Refs.)
rs4703908	*ZNF366*	Transcription co-repressor and estrogen receptor binding	(164)
rs12700667	*NFE2L3-HOXA10*	Membrane bound glycoprotein - DNA-binding transcription factor	(134)
rs7521902 rs1333049	WNT4	Promotes female sex development, represses male sex development	(166,167)
rs13394619	*GREB*	Regulator of estrogen-induced breast cancer	(166)
rs10859871	*VEZT*	Plays a pivotal role in the establishment of adherens junctions	(166)
rs2475335	*PTPRD*	Induction of pre- and post-synaptic differentiation of neurons	(169)
rs17773813	*KDR*	Regulation of angiogenesis and vascular development and permeability	(173)
rs1250248	*FN1*	Cell adhesion, cell motility, opsonization, wound healing	(167)
rs2479037	*VTI1A*	Intracellular trafficking	(164)

Tumor growth/suppression loci. Chromosome 17 aneuploidy appears to be significantly higher in patients with endometriosis in contrast to healthy individuals. This augmented heterogeneity of chromosome 17 supports the scheme of a versatile pathway involving somatic genetic alterations in disease progression (51). Molecular studies of cancer explain that genomic instability, involving chromosome 17, plays a role in the development and progression of various tumor types. *TP53* is a tumor suppressor gene essential for cell growth development modulation and protection form carcinogenesis, located at 17p13.1 and encoding nuclear phosphoprotein p53, which partakes in apoptosis, as well as DNA repair processes. The C allele of p53 codon 72 may be associated with the development of endometriosis, and can also be utilized as a potential predictive biomarker (52). One of its polymorphisms, TP53 Arg72Pro has been associated with various diseases, including endometriosis; in particular, the rs1042522 polymorphism has been linked with the risk of endometriosis in an Asian populations (53). In a prospective study of 118 patients, the results revealed that p53 arginine homozygotes had a decreased risk of the disease, while heterozygotes and proline homozygotes demonstrated an increased risk (54). Indeed, in a relevant study, p53 codon 72 Pro/Pro + Arg/Pro genotypes were found to be associated with an augmented disease risk in Asian women (55). Furthermore, the decreased expression of phosphatase and tensin homolog (*PTEN*), another tumor suppressor gene, has been shown to possibly contribute to the malignant progression of endometriosis (37).

Detoxification genes. *CYP* genes are responsible for the production of enzymes useful for the metabolism of xenobiotics. Thus, genetic variations in the afore-mentioned regions incite false cellular signals impacting metabolic pathways. AhR is a ligand-dependent transcription factor that modulates cellular differentiation and induces the activation of phase I and II drug-metabolizing enzymes. Since the AhR signaling pathway modulates the induction of CYP1A1 and CYP1B1 (partaking in phase I), potential modifications herein can evidently affect disease risk. AhRR codon 185 variation has been reported to be associated with the susceptibility to and severity of endometriosis in a Japanese population (56). This pronounced inclination in an Asian population has also been recorded elsewhere; in a meta-analysis examining the effects of *CYP1A1A* polymorphisms in disease risk, Ile462Val polymorphism was found to be associated with an increased risk (57). Moreover, in patients of Asian origin, polymorphism rs700519 has been shown to be related to the riskt of developing endometriosis, while among Caucasians, the same meta-analysis revealed that the putative endometriosis-associated genetic variation was rs10046 in *CYP19* (58). The dioxin-induced increased expression levels of *CYP1A1* and *γ-SYNUCLEIN* in the ectopic endometrium have also been observed in patients with endometriosis (59).

CYP17 (cytochrome P450c17a1) is a gene responsible for encoding the enzyme for estrogen biosynthesis. In a case control study of Iraqi women from 23 to 46 years of age, a significant association was noted between endometriosis and specific SNPs of the *CYP17* gene, with homozygous genotypes being associated with a diminished disease risk (60). In a case-control study, patients homozygous for the *CYP17A1* C allele of the rs743572 SNP were associated with a markedly increased risk of leiomyoma (61); in particular, the *CYP17A1* rs743572 genetic variation can also act as a potential risk factor for endometriosis, according to published data (62). In a case-control study of 143 patients, the presence of the rs743572 TT genotype of *CYP17A1* appeared to constitute a risk factor for endometriosis, although it did not affect disease progression. While *COMT* polymorphisms have been presented to affect the risk of adenomyosis, *CYP17* and *CYP1A1* were not recorded to be relevant to affecting endometriosis manifestation in another study (63). Furthermore, in a study of 100 women that previously underwent laparotomy/laparoscopy, the analysis of genomic DNA by real-time PCR revealed that the CYP2C19*2 heterozygote genotype was associated with an increased disease risk (64).

The decreased expression of CYP19A1 in cumulous cells of infertile women with endometriosis may also be linked to endometriosis-induced infertility (65). The AA and CC genotypes were importantly represented in the Val80 and C1558T polymorphisms of *CYP19* (66) in women with the disease. In Chinese women, it has been proposed that *CYP19* gene polymorphisms are not related to endometriosis susceptibility, although the *CYP19* rs700518 AA genotype pertains to

endometriosis-related infertility (67). The sequencing of the *CYP2C9* gene region has revealed a wide number of known and novel SNPs. The genotyping of 80 SNPs in 901 patients has revealed an association for SNPs in moderate or complete linkage disequilibrium with rs244285, a functional SNP in exon 5 that abolishes *CYP2C19* function via an alternative splice site formation, and association in an SNP in the *CYP2C19* promoter, rs12248560. Thus, it can be deduced that polymorphisms in *CYP2C19* can trigger susceptibility to endometriosis (68).

It is well known that individual polymorphisms are, to a varying degree, associated with endometriosis; it is, however, worth noting that genetic variations acting cooperatively can augur novel relations regarding disease risk. In a retrospective case-control study of a 340-women sample, the combined analysis of polymorphisms in *PGR-CYP17A1-CYP19A1* seemingly suggested a gene-gene interaction in disease susceptibility (69). The glutathione family (*GST*) genes appear to play a role in endometriosis. In a previous study, when comparing the frequencies of *GSTM1* and *GSTT1* polymorphisms between cases and controls, the GSTM1 null genotype frequency was found to be similar in both groups, while the GSTT1 null genotype was encountered in a higher frequency in the control group (70).

The human arylamine N-acetyltransferase 2 (*NAT2*) gene, on chromosomal region 8p22 11, plays a key role in the conjugation of xenobiotic substances. The *NAT2* G590A SNP may be associated with the susceptibility to endometriosis, and the 590A allele may play a protective role in the development of endometriosis. The *NAT2* 481C, 803A, 590A, 587A haplotypes have also been associated with a higher risk of endometriosis in an Iranian population (71).

It has been suggested that the *GSTM1*, *GSTT1* and combined *GSTM1*/*GSTT1* null genotypes increase susceptibility to endometriosis (72). Indeed, another meta-analysis that included 25 case-control studies investigated the association of null *GSTM1* and *GSTT1* genotypes with the disease risk, which was found to be positive (73). According to a systematic review, *GSTT1* null deletion carriers present with a medium disease risk, at approximately 29% (74). The association between glutathione S-transferases genes variants in an Iranian population consisted of 151 cases and 156 controls was found to be positive, since the *GSTM1* null genotype presented a rate of 7.3% in comparison to 1.3% in the control group, while the *GSTP1* 313 AG genotype was notably lower in the cases than the controls (75). The *CYP1A1* m1 polymorphism, the *GSTM1* null deletion and the *CYP19* VNTR $(TTTA)_{10}$ allele seem to be directly associated with the penetration of the endometriosis phenotype (76,77), as it occurred in a case-control study, with a larger sample size of 275 patients (77). The *CYP1A1* T6235C polymorphism and *GSTM1* null mutations and genetic association to endometriosis has been examined in a sample of 131 patients belonging to a North Indian population, where the *GSTM1* null genotype was positively linked to endometriosis, while the homozygous mutant and allele frequency of *CYP1A1* T6235C presented an important difference between the cases and controls (78). Contrarily, no profound difference has been noted between frequencies of the *GSTM1* null genotype in case and control groups in the study by Seifati *et al* in 2012; therefore, no association has been depicted at this point regarding disease severity (79).

As regards exposure to endocrine disruptors, genetic association studies are concerned, apart from candidate genes, with the investigation of impact and outcomes stemming from exposure to endocrine disruptors. It is widely known that exposure to numerous environmental chemicals can affect physiological processes and induce adverse effects. Endocrine disruptors possess the ability to interfere with hormonal functions. Organochlorines are endocrine disruptors acting as xenoestrogens and inducing steroid hydroxylation, thus hindering reproductive capacity and potentially neoplasia (80). The endometrium is vulnerable to endocrine disruptors, since it undergoes endocrine and immune signaling in a circular mode. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) has lipophilic traits and presents the ability to accumulate in adipose tissue (81), and can affect the levels of steroid receptors and their respective gene expression (82). TCDD can intercept cannabinoid signaling important for the anti-inflammatory effects of progesterone, while several types of TCDD can disrupt the procedures of the AhR pathway, as well as immune activity (83). TCDD also possesses the ability to permeate the placenta, and has been described to cause homeobox-Tbox remodeling in the prenatal period (84).

Increasing evidence indicates that a number of adult diseases occur due to environmental exposure during the fetal period and early-life. It has been observed through experimental tests that exposure to endocrine disruptors affects fertility in male and female mice and may lead to spontaneous pre-term birth (85). The impairment of endometrial progesterone sensitivity in a murine model has been supported, and has been linked to an inflammatory pathway affecting not only the reproductive success, but also contributing to the manifestation of adenomyosis and adhesions (86). In a sample of 138 patients diagnosed with endometriosis-induced infertility, the assessment of plasma polychlorinated biphenyl (PCB) levels revealed that patients carrying the *CYP1A1* rs1048943 genetic variation, demonstrated an decreased risk of developing advanced endometriosis, in the cases where dioxin plasma levels were elevated. Circulating PCB levels are also associated with advanced endometriosis, in carriers of the *CYP1B1* rs1056836 polymorphism (87).

Inflammation and autoimmunity-related genes. Diverse associations have been observed between interleukin genetic alterations and endometriosis pathophysiology. Interleukin (IL)-16 is a pro-inflammatory cytokine, chemotactic for $CD4^+$ T lymphocytes, monocytes and eosinophils, known to be associated with various ailments. Genotype distribution in two exon variations have been identified as notably different between diseased patients and healthy women. Moreover, a correlation has been underlined between the rs4072111 and rs1131445 SNPs with disease progression, implying a potential role of *IL-16* polymorphisms as a susceptibility factor for endometriosis (88). The role of *IL-16* genetic variations has also been studied in a total sample of 159 patients of Greek origin. A positive correlation was apparent between the GG and GT genotype, as well as the 'G' allele of rs11556218 in patients with endometriosis, while the rs4072111 SNP of the *IL-16* gene was not associated with an increased disease susceptibility, regardless of disease stage (89).

The intracellular adhesion molecule-1 (*ICAM-1*) gene is located on chromosome 19 (19p13) and its expression ensures immunocompetence. The additive effect of several

polymorphisms of the immune system can reportedly lead to alterations in immune balance, thus contributing to the establishment of endometrial cells in ectopic sites (90). A synergistic action has been described in the *IL-6* -634C/G and *ICAM-1* 469 K/E polymorphism acting together to influence endometriosis in a Japanese female sample (n=202) (91). In contrast to the findings of previous studies discussed above, variations in K469E and G241R of *ICAM-1*, as well as G634C of *IL-6* have been previously described to not be associated with a greater disease vulnerability, in a sample of 200 Brazilian women (92). No significant association either has been observed in the variation of IL-6 promoter -174G/C in a South Indian population (93). However, the *ICAM-1* polymorphisms, G241R and K469E, have been suggested to be independently associated with the risk of endometriosis in a Japanese population (94).

The excessive expression of cyclooxygenase (COX)-2 has been associated with the pathogenesis of endometriosis. In a study where tissue samples of 28 premenopausal women were examined, a denser COX-2 stain was observed in the ectopic endometrial tissue, with the *COX-2* mRNA levels presented a 5-fold elevation in the patients' ectopic tissue, compared to the eutopic endometrium. These findings suggested that aberrant COX-2 activation with abnormal prostaglandin production may contribute not only to the pathophysiology, but also to disease progression (95). Furthermore, the medial expression of the *COX-2* gene (mRNA PTGGS2) in females with endometriosis has been shown to be elevated in comparison to the controls, while the distribution of alleles in fertile women with endometriosis of stages II/III has demonstrated an association of statistical significance of the ancestral allele -765G, with an elevated risk (96). Similarly, the G-765C (rs20417) polymorphism of the *COX-2* gene pertains to an elevated hazard of endometriosis of stages III and IV, with the eutopic endometrial tissue of patients presenting an elevated expression of COX-2 in comparison to the controls (97).

The *BsrBI* restriction enzyme creates a C to A transition at position 52 in exon 1C of the IL-1 receptor type I (*IL-1RI*) gene. Protective action against disease development demonstrated a *BsrBI* created C/A heterozygote genotype according to a previous study (98). The chromosomal 2q13 locus belongs to a broader region with intense presence of inflammatory gene transcripts, since it includes the IL-1 gene cluster. Therefore, modifications in IL-1 family expression can lead to significant disease susceptibility (99). The sequencing of *IL1A* exons in 377 Japanese female patients has, in fact, revealed 4 SNPs strongly associated with endometriosis (100).

There is a scientific debate regarding the association of *IL-1β* and its role in endometriosis. Non-relation has been underlined between endometriosis and the *IL-1β* -511 promoter, *IL-1β* exon 5 and *IL-1* receptor antagonist genetic variations, since proportions of various polymorphisms did not seem to differ significantly between a group of patients (n=120) and healthy controls (n=103) in a previous study (101). Notably, the association between *IL-1β* (+3953) polymorphism endometriosis in a Turkish population was assessed as negative, since statistically insignificant proved to be the increased frequency of the respective genotypes (102). On the other hand, additional evidence exists for a positive correlation between the *IL1A* locus and endometriosis (103). *IL-2Rβ* -627*C homozygotes are linked with a higher predisposition to endometriosis (104). By contrast, the *IL-2β* receptor gene C624T variation in Korean women with the disease has been shown to be independent of the disease risk (105).

A functional promoter variant in the *IL-10* gene has been suggested to contribute in the development of endometriosis. The *IL-10* ACC/ACC homozygous genotype seems to be associated with endometriosis (106). Subjects carrying the minor allele C of rs1800871 SNP located on a functional promoter of *IL-10* appear to have an approximately 2-fold decreased risk of endometriosis compared to those with the TT genotype, with the T allele presenting reduced gene expression levels compared to the C allele, insinuating a deficient suppression of inflammation that fosters the development of endometriosis (107).

It has been suggested that women with advanced endometriosis present higher IL-4 plasma levels, although this event is not influenced by the *IL-4* -590C/T genetic polymorphism (108). In addition, the rs17860508 polymorphism in the *IL12B* promoter region may influence the risk of developing ovarian endometriosis, through the modification of the endometrial expression of *IL12B* in the Northern Chinese women, in a sample of 815 cases (109).

Genetic polymorphisms of matrix metalloproteinase (*MMP*)*-12* and *-13* have been suggested to trigger superficial, although not deep infiltrating endometriosis, an event that can possibly be interpreted as the provocation of a protective mechanism that these polymorphisms offer, which can possibly act preventively against a more in-depth penetration in tissues (110). The upregulation of survivin and *MMP-2*, *-9* and *MT1-MMP* may act in combination as regards the invasive behavior of endometriosis (111). While the reticulocyte-type 15-lipooxygenase-1 (*ALOX15*) gene is involved in implantation, ALOX15 -292 C/T does not appear to be associated with disease or infertility risk; other *ALOX15* gene polymorphisms may possibly exhibit a different pattern, thus, should not be excluded from future research prospects (112).

Killer immunoglobulin-like receptors (KIR) are inhibitory receptors on the surface of HLA molecules. It has been demonstrated that patients who are KIR2DS5-positive present a 13-fold lower risk of peritoneal disease invasion than their KIR2DS5-negative counterparts, while KIR2DSdel-positive ones have similarly an 11-fold lower risk of peritoneal disease. On the whole, it has been suggested that KIR2DS5 may act protectively against endometriosis, while KIR2DSdel may be associated with advanced disease, possibly through the omission of KIR2DS5 (113). Placental trophoblasts express, in particular, human leukocyte antigen-G (HLA-G), essential for pregnancy upkeep. This can also be expressed by the ectopic endometrium in the peritoneal cavity, thus being recognized by cells of the immune system, through the receptors LILRB1 and LILRB2. By performing genotype assays in a total of 590 individuals, researchers have deduced that genotypes *LILRB1* rs41308748 AA and *LILRB2* rs383369 AG, as well as the *HLA-G* rs1632947 GG and *HLA-G* rs1233334 CT are regulators of disease progression and susceptibility (114).

Mucins constitute a category of highly glycosylated proteins, responsible for the protection and lubrication of epithelial surfaces of respiratory, gastrointestinal and reproductive tracts, and it has been suggested that several mucins are involved in endometriosis-induced infertility. In a case-control study of 195 patients, the assay of the mucin 2 (*MUC2*) gene revealed

an association of polymorphisms rs10794288 and rs10902088 with endometriosis and a low fertility (115). As regards mucin 4 (*MUC4*), a case-control study involving 140 patients of Taiwanese origin, suggested that the T/G genotype of the rs882605 SNP and the frequency of the haplotype TT of rs882605 and rs1104760 were elevated in women with endometriosis to a statistically significant degree, while the C allele at the SNP rs1104760, the C allele at rs2688513, the G allele of rs882605 and the A allele of rs2258447 were associated with advanced endometriosis. Furthermore, particularly the G allele of rs882605 was described as an important risk factor for infertility in women with endometriosis (116).

In the promoter tumor necrosis factor-α gene (*TNF-α*), genetic variations have been suggested to be associated with an advanced stage of endometriosis in a Korean female sample (117). Tyrosine kinase 2 (*TYK2*) is a part of Janus kinase (JAK) that binds to the type I interferon -α receptor (IFNAR) and plays a critical role in autoimmunity and inflammation. It has been suggested that the polymorphism rs34536443 is associated with protection against endometriosis-induced infertility, particularly in advanced disease stages. In addition, the 'CTATG' haplotype has been linked to a reduced susceptibility to endometriosis in a Brazilian female population (118). Acid phosphatase locus 1 (*ACP1*) is involved in allergy manifestation; in a study including 113 participants, the *ACP1*C* allele was more frequently encountered in women with endometriosis than in healthy individuals (119).

The protein tyrosine phosphatase non-receptor 22 (*PTPN22*) gene, located on chromosome 1p13.3-13.1, encodes a lymphoid-specific phosphatase known as Lyp, a potent downregulator of T-cell activation. In a case control study of 140 patients and 180 controls from Brazil, the investigation of a *PTPN22* (C1858T) polymorphism brought out the importance of this polymorphism as a predisposing factor, particularly for the advanced disease stages of the disease (120). Despite the fact that *PTPN22* variations do not, at present, provide a lucid picture of their direct involvement in endometriosis (121), nevertheless *PTPN22* may act cooperatively with other genetic factors, thus resulting in the regulation of disease course and immune interposition, due to an important elevation of *PTPN22* *T allele observed in patients (122).

FCRL3_3 is a polymorphism of Fc-receptor like-3 gene (*FCRL3*), a gene that incites activation of NF-κβ/MAPK pathways. This variation has been associated with an increased disease risk of endometriosis-induced infertility, regardless of the symptoms and disease stage (123). Caspase recruitment domain family member (*CARD*)*10* and *CARD11* mutations have been suggested to be linked with endometriosis. CARD11 belongs to the CARD protein family, since it binds with B-cell CLL/lymphoma 10, and activates the inflammation-associated NF-κβ signaling pathway as well. Four novel somatic mutations in *CARD10* and *CARD11* genes detected among 101 patients with ovarian endometriosis, suggesting their role in the development of ovarian endometriosis (124).

Angiogenesis-related genes. A positive association has been observed between genetic polymorphisms in fibroblast growth factor (FGF)2 and the risk of endometriosis and adenomyosis in a North Chinese women population. The *FGF2* 754C/G polymorphism has been shown to be associated with the risk of developing endometriosis and adenomyosis (125). Fibroblast growth factor receptor 2 (*FGFR2*) variations, although being associated with endometrial and breast cancer, have not been proven to be associated with disease susceptibility, according to a case-control study of 958 cases and 959 controls (126).

Vascular endothelial growth factor (VEGF) is considered one of the most prominent contributors to the development of endometriosis. The *VEGF* +405 C/G polymorphism is reportedly associated with the risk of endometriosis atan advanced stage in a Korean population (127). By contrast, according to a meta-analysis including 2,947 cases, the *VEGF* +405 G>C genetic polymorphism was not profoundly associated with disease risk, since no important interrelation was extrapolated, neither in terms of genetic models nor ethnicities (128). However, the *VEGF* -2578 A/C SNP has been reported to be a potential factor for disease susceptibility among an Estonian women population consisting of 150 subjects (129). In a systematic review and meta-analysis, where 14 case-control published articles were studied, the rs699947 (A>C) and rs1570360 (G>A) polymorphisms of the *VEGF* gene were linked with a reduced disease risk, while rs3025039 (C>T) as enhancing contributors to disease risk. The rs833061 (T>C) and rs2010963 (G>C) polymorphisms do not appear to affect disease susceptibility (130). The association between VEGF gene variations and endometriosis was found in a meta-analysis that processed the results retrieved from 11 studies, with the *VEGF* +936TC gene polymorphism proving to be a risk factor of endometriosis (131). Similarly, the VEGF 2460/21154/22578 TGC, CAA, TAA and TAC haplotypes were associated with endometriosis. In addition, the 21154A and 22578A alleles were shown to act protectively against the development of endometriosis in North Chinese women (132). A positive association between *VEGF* -1154G>A and disease risk has also been noted in a Brazilian population, with the CCGG haplotype probably acting protectively against disease development (133). An independent association was found between *VEGF* C/T, +405 G/C and +936 C/T SNPs and endometriosis-related infertility (134), while, contradictory results emerged according to a meta-analysis, where the *VEGF* +936T/C genetic polymorphism induced susceptibility to endometriosis, particularly as regards advanced disease stages (135).

A noteworthy correlation has also been shown to occur between the rs2268613 variation of the placental growth factor (*PLGF*) gene and PLGF serum levels (136). Women with the AA variant of the rs2268613 *PLGF* gene exhibit considerably decreased PLGF serum levels, compared to those with the AG variant. Circulating levels of VGF are described as increased in patients with endometriosis. In the same study, a correlation, albeit weak, occurred between endometriosis and variations of *PLGF* (rs2268614), *HIF-1α* (rs11549465) and *VEGFR1* (rs9582036).

Other angiogenesis-related genes have been also observed to be differentially expressed in patients. Importantly, increased levels of AKT serine/threonine kinase 1 (AKT1), thymidine phosphorylase (TYMP), Jagged 1 (JAG1), LAMA5 and TIMP metallopeptidase inhibitor 1 (TIMP1) were found in the eutopic endometrium of patients with endometriosis compared to healthy controls (137). Furthermore, the increased expression of genes responsible for cellular migration and angiogenesis, namely inhibitor of dna binding 2 (*ID2*), proline and arginine rich end leucine rich repeat protein (*PRELP*) and sparc

related modular calcium binding 2 (*SMOC2*) in women with endometriosis, suggests that this altered expression is linked to the development of the ectopic endometrium (138). Nitric oxide (NO) is known to partake in a number of physiological procedures; the endothelial subtype of this enzyme, endothelial NO synthase (eNOS), instigates VEGF-induced vascular permeability and angiogenesis, hence playing a key role in endometriosis by promoting angiogenesis (139). While a positive association has been noted between the *eNOS* Glu298Asp variation and advanced-stage disease (140), another study did not observe for the same polymorphism, any association with for disease risk in a South Indian population (141).

Hormonal function. Follicle-stimulating hormone (FSH) plays an important role in steroidogenesis and acts through a trans-membrane glycoprotein, the FSH receptor (FSHR). Since endometriosis is an estrogen-dependent disease, it can be deduced that genetic alterations in *FSHR* would affect FSH plasma concentrations and reproductive capacity. While no significant association has been noted between patients with endometriosis and controls, a positive association seems to exist among patient groups regarding fertility and disease stage in terms of *FSHR* genetic variance. Specifically, in a relevant study, the 680Ser-Ser/GG genotype and GG/307Ala680Ser haplotype were associated with an increased risk of developing endometriosis, while the presence of the GA/307Ala680Asn haplotype was associated with a reduced risk of disease development and progression (142).

Polymorphisms in LH receptor (insLQ) seem higher in patients with endometriosis and infertility, in comparison to healthy fertile controls (143). SNP in the *AMH* (anti-Müllerian hormone) gene is related to endometriosis-induced infertility, while SNPs in growth differentiation factor-9 (GDF-9) and the -482A G SNP in the *AMHR2* gene were found to not be related (144). The association between polymorphisms in progesterone receptor +331G/A and endometriosis has been presented as positive in patients with deep infiltrating endometriosis, as a considerable elevation has been highlighted as regards the risk of developing deep-infiltrating endometriosis among women bearing the +331A allele. While this particular study does not support a generic association between endometriosis and the *PR* +331G/A polymorphism, it rather proposes a possible role of this genetic variation in the invasive behavior of endometrial cells, that is dependent upon PR (145). MicroRNAs (miRNAs or miRs) are short non-coding RNAs of approximately 18-22 nt in length, firstly discovered in 1993 (146). miRNAs have been reported to regulate gene expression, while the stability and specificity that they present renders them appropriate for biomarkers (147). The downregulation of miRNA200b has been observed to occur both in endometriosis and malignancy, provoking epithelial-to-mesenchymal transition and consequently invasive growth (148). miRNA-196a has been stated to upregulate the MEK/ERK signaling pathway, inducing the downregulation of progesterone receptor in the eutopic endometrium of women with minimum/ mild endometriosis (149). As for miRNA Let-7b, it has been proposed as a novel therapeutic option for endometriosis, since it influences a number of pathways at the same time without inducing systemic hormonal adverse effects (150).

Polymorphisms in the *ER-α* gene encoding aromatase are described as disease risk factors (151). In a case-control study, patients homozygous for the *ESR1* C allele polymorphism rs2234693 were found to be associated with a significantly augmented risk of leiomyoma (61). However, in a case-control study of 100 cases, *ESR1* polymorphisms did not seem to contribute to disease susceptibility (152). In a similar study, infertile women with the *ESR1* rs9340799 GG genotype presented a 4-fold higher risk of endometriosis (153). Moreover, the *Alu*I genetic variation of the *ERβ* gene has been associated with an increased risk of severe endometriosis in a Japanese population (154). In a meta-analysis of 24 case-control studies that examined ESR1 polymorphisms, *Pvu*II proved to be associated with endometriosis regarding stage I-III only under the recessive model. The short allele and TA_{13} of $(TA)_n$ have been related to a higher risk of endometriosis, while TA_{20} repeats have been associated with a decreased disease risk. All in all, the results of this meta-analysis suggest that the $(TA)_n$ polymorphisms may participate in the susceptibility to and protection against the pathogenesis of endometriosis (155).

Forkhead Box D3 (*FOXD3*) is a protein coding gene essential for the upkeep of pluripotent cells during the implantation stages of embryogenesis. *FOXD3* has been found to be differentially expressed in the endometrium of healthy individuals and controls, as it can be deduced by the decreased levels of the protein upon the decidualization of normal human endometrial stromal cells *in vitro*, and differential endometrial expression in the stroma, in endometriosis (156). 17β hydroxysteroid dehydrogenase 1 (HSD17B1) converts estrone into 17β estradiol. In a study comprised of 290 cases and 410 controls, the *HSD17B1* 937G variant was displayed as a risk factor for infertility in disease stage I and II of a Polish Caucasian women population (157). On the other hand, no significant association was found between endometriosis stage I-II infertile women and the expression of the adhesion molecules, osteopontin and avb3 integrin (158). The expression of glycodelin-A (GdA) has been reported to be dysregulated in women with endometriosis, implying the association with hindered endometrial receptivity (159).

The expression of the p16 and pRb proteins is associated with endometriomas and adenomyosis, since these proteins may play a role in the regulation of cell growth in adenomyosis and ovarian endometriotic cysts; p16 appears to play a prominent role in proliferative-phase adenomyotic tissue, whereas pRb is more prominent in endometriomas (160).

5. Genome-wide association studies

GWAS investigate new genomic regions associated with multifactorial ailments, through the usage of computational model techniques, aiming at the comparison of genotypes between patients and healthy individuals for the identification of endometriosis-related SNPs (161).

In a meta-analysis based on GWAS performed in a Japanese female population, 4 prevalent SNPs were pinpointed near and within the *IL1A* region, rendering it a candidate gene (162). Another GWAS, including 2,019 diagnosed patients brought out the following results: *LINC00339-WNT4* on 1p36.12 (rs2235529), *RND3-RBM43* on 2q23.3 (rs1519761 and rs6757804), *RNF144B-ID4* on 6p22.3 and *HNRNPA3P1-LOC100130539*

on 10q11.21. A sequence of 150 kb around the *WNT4* locus was also identified, including *LINC00339* and *CDC42* (163). *ZNF366*, previously having been associated with breast cancer development, was proposed as a new contributor to the disease, since 4 SNPs were found to be significantly associated with endometrioma risk (rs227849, rs4703908, rs2479037 and rs966674). The genetic variant rs4703908 located near *ZNF366* has been linked to an increased risk of endometrioma and deep infiltrating endometriosis (164). Nakaoka *et al* (165) aimed at unlocking the molecular mechanism of 9p21 endometriosis risk genetic locus, by demonstrating allelic imbalances in the tier of transcription events, entailing from factor binding to gene expression. Through the sequencing and examination of DNAase-seq data of the 9p21 chromosomal region, rs17761446 was the predominant genetic variant in absolute linkage disequilibrium with the original GWAS SNP (rs10965235) and located on Dbase I hypersensitive site. By the usage of the chromosome conformation capture technique and high-throughput sequencing technologies, it was noted that the G allele of rs17761446 demonstrated a higher chromatin interaction with the *ANRIL* promoter; allele analysis revealed that the afore-mentioned polymorphism exerted regulating action where the G allele was linked to an elevated *ANRIL* expression. In another GWAS, including 4,604 patients, aimed to confirm previous associations and discover novel endometriosis risk loci in populations of European and Japanese descent, genetic variant rs12700667 on 7p15.2 was detected in both Japanese and Europeans, while a correlation between rs7521902 at 1p36.12 close to *WNT4* has also been confirmed. Other associations included: rs13394619 on *GREB* at site 2p25.1, rs10859871 on *VEZT* at 12q22, and some additional at 2p14, 6p22.3 and 9p21.3 (rs4141819, rs7739264 and rs1537377, respectively) (166). Risk allele frequency of the SNPs rs12700667 and rs4141819 regarding their association with infertility, that have been identified in previous GWAS, has also been confirmed in a sample of 315 Polish patients with III/IV disease stage (134).

Pagliardini *et al* (167) aimed at confirming the association of GWAS-detected susceptibility loci, previously proposed by Painter *et al* (168) and Uno *et al* (169). It emerged that the rs1333049 risk allele G frequency was higher in patients with endometriosis compared to the controls, and the exact locus was also suggested for Caucasian populations. Moreover, rs7521902 was associated with the disease at a level of significance, rs1250248 was only detected in severe stages, and an interplay was found between rs7521902 and rs1250248, particularly in ovarian disease. This meta-analysis confirmed *WNT4*, *CDKN2BAS* and *FN1* as genomic regions associated with the disease. In a GWAS among 1,364 cases involving patients with advanced-stage endometriosis, an association was found at the 7p15.2 rs12700667 locus, for every disease stage. It is noteworthy to mention that the SNP rs12700667 region is placed near the candidate genes, nuclear factor, erythroid 2 like 3 (*NFE2L3*) and *HOXA10* (168). GWAS meta-analysis revealed 13 loci associated with endometriosis, as well as endometrial cancer. Furthermore, the SNP rs2475335, located inside the protein tyrosine phosphatase, receptor type D (*PTPRD*) gene, is disease-relevant at an important genomewide extent; *PTPRD* is involved in the signal transducer and activator of transcription 3 (STAT3) pathway, which has been implicated with both endometriosis and endometrial cancer (170).

An intergenic locus on 7p15.2 has been described to be significantly associated with endometriosis, as it was observed in a GWAS. In the same study, 4 genetic polymorphisms were detected (inside or near *KIFAP3*, *CAB39L*, *WNT4* and *GRB14*), that were involved not only in endometriosis, but also in the waist-to-hip ration adjusted for BMI. In general, endometriosis has been reported to be associated with a reduced body mass index (BMI) (171). A significant reproduction of results stemming from GWAS and candidate genes studies has been observed in a meta-analysis by Sapkota *et al* in 2015 (172), where 9 identified SNPs as susceptibility loci were reported. It has also been demonstrated that the SNPs rs7521902, rs13394619, rs6542095, rs12700667, rs7739264 and rs1537377 exhibit a significant association with endometriosis. In a GWAS including 1,840 patients of Icelandic origin, a novel risk locus at 4q12 (rs17773813) was found. This genetic site is located near the *KDR* gene, which encodes one of the two *VEGFR2* receptors (173). In a study by Uimari *et al* in 2017, a novel SNP was detected, rs144240142, located inside *MAP3K4*. In particular, it was shown to be expressed in a different pattern in the eutopic endometrium among cases with minimal/mild disease and controls. In total, 14 pathways were presented to hold an association with endometriosis, including the Wnt and ERK/MAPK pathways (174).

6. Conclusions and future perspectives

It is well established that the pathogenesis of endometriosis combines both genetic and environmental influences. Familial studies, linkage analysis, genetic association studies and GWAS have shed light onto the pathophysiology of endometriosis through ample evidence associating cellular procedures with disease development. However, many aspects of the disease etiology remain obscure.

Genetic association studies, however, exhibit several limitations. While in some individuals carrying a mutation, disease may not manifest, in other cases the very same putative causal mutation may be absent. Hence, etiological mutations are not a prerequisite for disease onset and control sampling should be meticulously examined. Apart from the unequal association between etiological mutations and disease phenotype, the mutation locus plays an important role. Tight correlations being encountered among neighboring genetic polymorphisms complicate research attempts; in the meanwhile, the issue of linkage disequilibrium occurring in non-adjacent regions could augment degree of challenge. Lastly, it should not be disregarded that even subtle genetic alterations that do not ostensibly lead to expression of a different protein, can affect function and stability of the encoded product (175). GWAS, in turn, present this opportunity to reveal genetic interactions and additional candidate genes. The GWAS method offers the leverage of rapid detection of thousand SNPs for the investigation of possible correlations and provides the benefit of limited bias in comparison to candidate gene studies. By contrast, GWAS demand large samples in order to bring solid results (176).

Evidently, GWAS have trailed a notable trajectory in the detection of genetic variations that induce vulnerability to multiple diseases. GWAS utility extents from disease causality and pathogenesis elucidation, to the prominence of novel

subtypes and prediction of disease risk. Furthermore, progress in next generation sequencing provides the opportunity to search for less common variants with significant effects, through a hypothesis-neutral approach. Thus, whole exome sequencing (WES) allows the analysis of all exonic regions of a genome by next-generation sequencing (NGS) (177). However, a weakness of the new technological approaches of WES and whole genome sequencing (WGS), which have become impressively available and affordable, deals with their potential for identification of genetic factors involved mainly in monogenic diseases. Further studies encompassing genomics, cellular biology and clinical research would enhance these results and convey this knowledge in clinical practice (178).

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LV, GNG, KK, IM, DAS and MM conceived and designed the study. LV, DAS, MM, KK, MIZ, IM and CM researched the literature, performed critical analysis and review of the literature and drafted the manuscript. GNG, MIZ and DAS drafted the manuscript. GNG, DAS and IM critically revised the article for important intellectual content.

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