

Co-occurrence of endometriosis with psoriasis and psoriatic arthritis: Genetic insights (Review)

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Abstract. Immunological factors appear to play an important role in the development of endometriosis, as evidenced by the aberrant functioning of immune cells often observed in affected women. Although endometriosis is not classified as an autoimmune disease, individuals with the condition show a higher tendency to develop various autoimmune disorders as comorbidities. There appears to be a bidirectional association between laparoscopically confirmed endometriosis and diagnosed psoriasis (PS) and psoriatic arthritis (PsA). Endometriosis is a chronic, complex, estrogen-dependent and progressive gynecological disorder, characterized by the growth of endometrial tissue outside the uterine cavity. PS is an autoimmune, T-cell-mediated chronic inflammatory and proliferative skin disease, characterized by focal formation of inflamed, erythematous, raised plaques that shed scales derived from excessive growth of skin epithelial cells. PsA is a seronegative chronic inflammatory joint disease that is associated with PS, characterized by inflammatory changes in attachments of articular capsules, tendons, and ligaments to bone surface. The co-occurrence of endometriosis with PS and PsA raises some intriguing points regarding their possible shared genetic background. In the context of the present study, an extensive review of the current literature was conducted

to identify shared genetics factors and shed light into the underlying pathogenetic mechanisms.

Contents

1. Introduction
2. Genetics of endometriosis, PS and PsA
3. Shared genetic loci associated with endometriosis, PS and PsA
4. Biological mechanisms relative to the co-occurrence of endometriosis with PS and/or PsA
5. Conclusions and future perspectives

1. Introduction

Numerous studies have shown that women with endometriosis are at a higher risk for developing various diseases as comorbidities, including asthma (1), various types of cancer (2), cardiovascular and psychiatric diseases (3,4), hypothyroidism and fibromyalgia (1). Notably, over the past decade, it was found that women with endometriosis have increased prevalence of several autoimmune diseases such as autoimmune thyroid disorder, ankylosing spondylitis (AS), coeliac disease, multiple sclerosis, rheumatoid arthritis (RA), scleroderma, Sjogren's syndrome (SS), systemic lupus erythematosus (SLE) and inflammatory bowel diseases. A recent study highlighted an association between endometriosis and both psoriasis (PS) and psoriatic arthritis (PsA) (5). The comorbidity of autoimmune diseases with endometriosis supports the current understanding of dysregulation of the immune system observed in women with endometriosis (6). However, it remains under investigation whether the disrupted immunological response and chronic inflammation characteristic of endometriosis contribute to a long-term risk of developing autoimmune diseases.

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Endometriosis is a common, inflammatory, estrogen-dependent, benign gynecologic disease, affecting 8-10% of women of reproductive age (7), which results in a vast array of gynecological problems, such as deep dyspareunia, dysmenorrhea, chronic pelvic pain, heavy or irregular menstrual bleeding, pain during intercourse, urinary tract symptoms, diarrhea, subfertility and infertility, in 30% of patients (8,9). This disorder is defined by the growth of endometrial tissue outside the uterine cavity on other organs, due to the ectopic localization of endometrial cells. Endometriosis is a multifactorial disease and its susceptibility depends on the complex interaction of genetic, epigenetic, immunologic, proinflammatory, pro-angiogenic, hormonal and environmental factors (10,11). In addition to earlier theories such as metaplasia (12) and the widely accepted retrograde tubal endometrial reflux theory of Sampson (13), other immune-mediated pathways including chronic inflammation, apoptosis, angiogenesis and endothelial dysfunction have also been implicated (14,15). At present, substantial evidence indicates the significant role of the aberrant function of immune-related cells in the peritoneal environment and the consequent development of endometriosis (16,17). Accordingly, the dysregulation of the immune system leads to a chronic inflammatory response in the ectopic endometrium and influences endometriosis through the production of antibodies against various ovarian and nuclear antigens (18,19). It is worth noting that endometriosis fulfills most of the classification criteria for an autoimmune disease, such as abnormal T- and B-lymphocyte activation and function, tissue damage and multi-organ involvement (20). Consequently, endometriosis is often considered an autoimmune disease, due to the presence of autoantibodies, increased levels of cytokines and its co-occurrence and association with other autoimmune diseases (21,22).

PS is a complex, chronic, debilitating, T-cell mediated autoimmune, proliferative skin condition, related to a combination of genetic and immunological factors that interact with each other, which can be triggered by environmental factors (23). Environmental factors include chronic infections, stress, low humidity, streptococcal infections, medications, alcohol consumption, smoking, psychosocial factors and obesity (23-25). The estimated global prevalence is 2-3% (26), with peak occurrences in both males and females between the ages of 20-30 and 60-70 (23), although approximately one-third of PS cases are manifested in childhood (27). PS is characterized by well-demarcated, erythematous oval plaques, with adherent silvery scales and hyperplasia of the epidermis, due to increased proliferation of keratinocytes, and is categorized in multiple subtypes that manifest as various phenotypes (28). The commonest form of PS is generalized plaque-type PS. In addition to the influence of PS in the appearance of the skin of the patients, due to its chronic course and recurrent attacks, it has been reported to greatly affect their psychological health as well (29). Although the exact pathogenetic mechanisms leading to the development of PS remain unclear, research has demonstrated the importance of the immunogenetic component in pathogenesis of this disorder (30). In this context, the key role of T-helper (Th)17 as well as Th1 lymphocytes and the abnormal regulation of their activity by regulatory T cells (Tregs), which are known as suppressors of lymphocytes, have been highlighted (31). In

principle, the function of Tregs is related to the prevention of autoimmune diseases by suppressing the excessive immune response (32), considering that they suppress pathogenic Th1 and Th17 cells and maintain immunological homeostasis (33). However, in PS, elevated levels of Th1 and Th17 cytokines and decreased levels of Th2 and Tregs have been observed (34). As a consequence, Tregs are unable to produce sufficient amounts of suppressive cytokines such as IL-10, IL-35 and transforming growth factor (TGF- β), and cannot properly regulate the immune response (35,36). Notably, it has been suggested that inflammatory processes induce the migration of the interferon (IFN)- γ -producing Th1 lymphocytes into the skin with these cells being involved in keratinocyte and small vessel proliferation as well as inflammatory infiltration (37).

PsA is a multifactorial, seronegative for rheumatoid factor, chronic inflammatory joint disease with prevalence rates ranging between 0.3 and 1% worldwide that is associated with PS, characterized by cutaneous PS, nail changes (onycholysis, subungual hyperkeratosis) and inflammatory changes in attachments of articular capsules, tendons and ligaments to bone surface (38). PsA occurs in 10-30% of patients with PS, often developing concurrently with PS, and it manifests all the typical features of arthritis, including enthesitis (39). Although the precise etiology of PsA remains unclear, both genetic and environmental factors have been implicated. The importance of the genetic component underlying the pathogenesis of PsA has been highlighted by previous research focusing on twins or family members, which showed the strong heritability of PsA (40).

Given the long-standing interest of our research group in the investigation of the genetics of autoimmune diseases and endometriosis, efforts in recent years have been focused on the delineation of the genetic components that are involved in the co-occurrence of endometriosis with various autoimmune diseases, including RA (41), AS (18), SS (18,41), as well as SLE (unpublished data). Thus, within this framework, the genetic basis of the recently reported association between endometriosis and the risk of PS and/or PsA (5) was analyzed in the present review, aiming to detect the relevant genetic polymorphisms that are known to date and provide insights regarding their functional significance and involvement in the underlying pathogenetic pathways, as well as the perspectives of putative immunomodulatory therapies.

2. Genetics of endometriosis, PS and PsA

Genetics of endometriosis. Strong evidence has highlighted the contribution of both genetic and epigenetic factors, which interact with environmental ones, in the pathogenesis of endometriosis and the formulation of the complex phenotype of the disease. This topic has been extensively analyzed and reviewed in various studies conducted by our group and others (11,18,41-44). Briefly, twin studies demonstrated that the sibling genetic relative risk is 2.3 and the estimated overall heritability has a rate of 51% (7,45). Despite the endometriosis-associated loci detected by independent gene association studies, the hypothesis-free approach of Genome Wide Association Studies (GWAS) as well as the high-throughput next generation sequencing (NGS) techniques offer valuable assistance in the efforts concentrated

on identifying numerous novel disease susceptibility loci, although the exact functional relevance to endometriosis of most of these single nucleotide polymorphisms (SNPs) remains elusive. Notably, the largest trans-racial GWAS and replication meta-analysis of endometriosis performed to date, managed to identify 31 novel loci, in addition to the 11 previously known, which are involved in progesterone resistance, inflammatory processes, cell cycle regulation and angiogenesis (44). It has been reported that common genetic variation accounts for ~26% of the risk of the disease (46). Notably, the majority of these disease-associated SNPs, revealed by an increasing rate over the last years, confer a moderate effect in endometriosis and, according to the function of the respective proteins, were found to be involved in the immune system and autoimmunity, estrogen-induced cell growth, cell adhesion, differentiation, proliferation, apoptosis, matrix remodeling and oxidative stress (43,47-50). The importance of the epigenetic modifications, which play a pivotal role in pathogenesis of endometriosis, has been described in detail in recent studies from our group (5,51,52).

Genetics of PS. PS is a multifaceted, complex genetic disease, resulting from an interplay between genetic and environmental factors, as aforementioned. This has been demonstrated by studies involving monozygotic and dizygotic twins, where it was shown that monozygotic twins appear to have a 3-fold increased risk for the disease when compared to the dizygotic twins, while the concordance rate among monozygotic twins was never 100%, thus suggesting a role for environmental factors (53,54). Notably, the overall genetic variation accounts for 50-70% of PS susceptibility (55). Furthermore, a familial recurrence has been well established as well, considering that the incidence of the disease is greater among first- and second-degree relatives of patients than among the general population (56). Currently, advances in large-scale analysis of the human genome provide valuable insights into the genetic dissection of PS, with over 40 genomic regions of the genome and >400 SNPs associated with the disease identified through GWAS and/or NGS approaches (57-60). Most of the identified PS susceptibility genes are skin-specific, mediate epidermal differentiation, are involved in neo-vascularization or are related with adaptive immunity (61). Moreover, many of these genes are involved in antigen presentation, type 1 IFN pathways, T-cell polarization axis, negative regulation of immune response, inflammatory processes and innate immunity (57,62,63). Recently, Patel *et al* (64) classified the PS-associated genes into categories reflecting the pathway that they participate in and influence. These categories include interleukins, interleukin receptors, human leukocyte antigen (HLA) genes, nuclear factor- κ B (NF- κ B)-pathway related genes, IFNs, genes participating in the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. Additional categories include genes linked to hypercholesterolemia and hypertriglyceridemia, negative regulators of T-cell activation, inflammatory markers, and nuclear hormone receptors (64).

Genetics of PsA. PS and PsA are interrelated disorders given that most patients with PsA also have PS. However, PsA represents a distinct entity having its own clinical, genetic and epidemiological features. Notably, PsA exhibits a greater

heritability among first-degree relatives in comparison with PS (40), thus suggesting a marked difference regarding the genetic architecture of the two disorders and indicating a larger genetic component for PsA (65). A stronger association with PsA than PS has been observed for various loci, including *HLA-B*27* (66), *CSF2* (67), *PTPN22* (68), *KIR* (69), *IL-13* (70), *IL-12B* (71), *ZNF816A* (71), *IL23R* (57), *TNFAIP3* (57), *IFNLRI* (57), *IFIH1* (57), *NFKBIA* (57), *MIF* (72), *IL-1A* (40) and some variants in *LCE3A* (39).

3. Shared susceptibility loci between endometriosis, PS and PsA

Recent findings have suggested a bidirectional association between endometriosis and PS as well as PsA (5), raising intriguing questions about the possible role of a partially shared genetic background in the co-occurrence of endometriosis with PS, with or without PsA. This role appears to be strengthened considering the link of these conditions with systemic inflammation (73) and, therefore, further exploration of the functional role of all shared gene loci may shed light on the mechanisms underlying these diseases. Aiming to provide a comprehensive update on the current understanding of the potential shared genetic component of the disorders under investigation, extensive research of the current literature was performed to identify gene polymorphisms associated with these diseases.

In this context, it was found that tumor necrosis factor- α (*TNF- α*) rs1800629 SNP is associated with the development of the three diseases (74,75). Furthermore, in the recent study by Harris *et al* (5) it was stated that no association was observed between PS without PsA and the risk of endometriosis. However, various gene polymorphisms were identified, including the forkhead box protein 3 (*FOXP3*) rs3761549 (-2383 C/T) (76,77), major histocompatibility complex (MHC), class II, DR β 1 (*HLA-DRB1*) rs 660895 (64,78), *IL-10* rs1800871 (79,80), 5,10 methylenetetrahydrofolate reductase (*MTHFR*) rs1801133 (Ala222Val) (81-83), *STAT4* rs7574865 (84,85) and vascular endothelial growth factor (*VEGF*) rs1570360 (86-91) SNPs, all of which are associated with increased susceptibility to endometriosis and PS only. This observation by Harris *et al* (5) is indicative of the fact that other factors apart from the genetic ones are involved in the co-occurrence of endometriosis and PS without PsA.

Furthermore, the findings also showed that *IL-1A* rs17561 (40,92,93) and rs3783553 (40,92), macrophage migration inhibitory factor (*MIF*) rs755622 (72,94) and protein tyrosine phosphatase, non-receptor type 2 (*PTPN22*) rs2476601 (68,95,96) SNPs are associated with both endometriosis and PsA. A detailed overview of the shared gene polymorphisms is provided in Table I, while a Venn diagram illustrating the number of these shared gene polymorphisms based on the referenced studies, is presented in Fig 1.

4. Biological mechanisms related to the shared risk loci for endometriosis, PS and PsA

Polymorphisms in genes associated with endometriosis, PS and PsA. The *TNF- α* gene, consisting of four exons and mapped to 6p21, is a member of the class III MHC genes (97). It

Table I. An overview of the genetic polymorphisms associated with the development of endometriosis, PS and PsA, as they have been confirmed by gene association and/or genome-wide association studies.

dbSNP ID SNP	Gene	Function	Endometriosis	PS	PsA	(Refs.)
rs1800629	<i>TNF-α</i>	A multifunctional pro-inflammatory cytokine	✓	✓	✓	(74,101)
rs3761549	<i>FOXP3</i>	A regulator of T-cell activation and cytokine production	✓	✓	-	(76,77)
rs660895	<i>HLA-DRB1</i>	An HLA member; presents peptides derived from extracellular proteins	✓	✓	-	(78,64)
rs1800871	<i>IL-10</i>	An anti-inflammatory cytokine; inhibitor of Th1 differentiation	✓	✓	-	(79,80)
rs1801133	<i>MTHFR</i>	A key regulatory enzyme in folate and homocysteine metabolism	✓	✓	-	(81,134)
rs7574865	<i>STAT4</i>	A transcription factor involved in Th17 differentiation and IFN- γ production	✓	✓	-	(84,85)
rs1570360	<i>VEGF</i>	A signaling protein involved in vasculogenesis and angiogenesis	✓	✓	-	(88,89)
rs17561	<i>IL-1A</i>	A pleiotropic cytokine involved in inflammatory processes and hematopoiesis	✓	-	✓	(92,93)
rs3783553	<i>IL-1A</i>	A pleiotropic cytokine involved in inflammatory processes and hematopoiesis	✓	-	✓	(40,92)
rs755622	<i>MIF</i>	A pro-inflammatory cytokine	✓	-	✓	(72,94)
rs2476601	<i>PTPN22</i>	A lymphoid-specific phosphatase; downregulator of T-cell activation	✓	-	✓	(68,95)

PS, psoriasis; PsA, psoriatic arthritis.

codes for the TNF- α cytokine, a key regulator of both autoimmunity and inflammation (98), and it has been correlated with the pathogenesis of various autoimmune, inflammatory and infectious diseases (99). The *TNF- α* -308 G/A rs1800629 SNP, located in the promoter region of the *TNF- α* gene, has been associated with an increased susceptibility to severe-stage endometriosis (74) as well as PS with PsA (100,101). It is a well-studied polymorphism from the functional viewpoint, and the presence of minor allele 'A' was reported to enhance the transcription levels of TNF- α , compared with allele 'G', thus leading to the production of higher protein levels in serum (102,103). Notably, this SNP has also been shown to modify the consensus sequence of the AP-2 transcription factor-binding site (104). The role of this polymorphism in endometriosis has been highlighted by the increased levels of TNF- α detected in peritoneal fluid as well as the upregulation of *TNF- α* gene in peritoneal macrophages and peripheral blood

monocytes (105,106). Moreover, high levels of TNF- α have been correlated with the severity of endometriosis (107), while the implantation of ectopic endometrial tissue is facilitated by elevated levels of TNF- α (108). All these findings underscore the important role of this SNP in the development of endometriosis. With regard to PS, the presence of 'A' at position-308 in the *TNF- α* gene has been associated with elevated cytokine production in both psoriatic lesional skin (109,110) and the serum of patients with PS (111). Notably, the GA genotype has been associated with a later age of onset for PsA (101), while an increased frequency of the 'A' allele has been observed in female patients with PS (100).

Polymorphisms in genes associated with endometriosis and PS without PsA. The *FOXP3* gene is positioned at the Xp11.23 locus of chromosome X (112). It encodes the FOXP3 transcription factor, a major regulatory factor involved in the

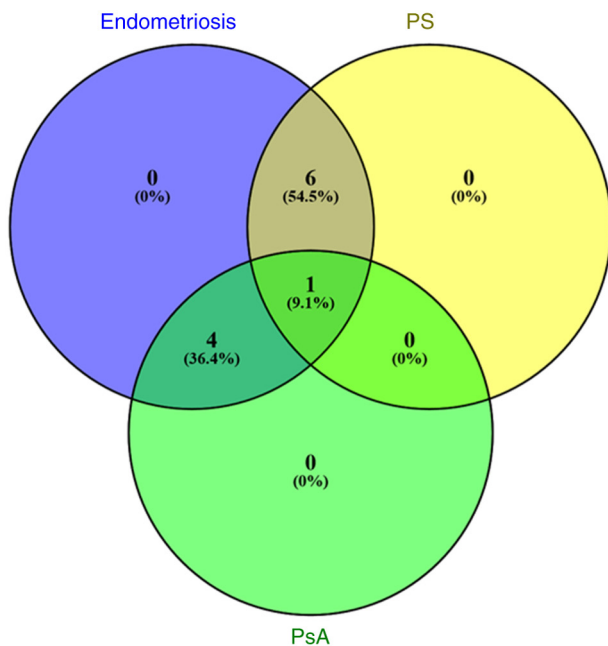


Figure 1. Venn diagram of endometriosis, PS and PsA shared susceptibility genes. (Core Graphic Module by Vijayaraj Nagarajan, and Web implementation by Mehdi Pirooznia. October 2006, usm.edu; <https://www.bioinformatics.org/gvenn/>). PS, psoriasis; PsA, psoriatic arthritis.

T-cell activation and the development and function of Treg cells in the peripheral blood, which are considered to be inhibitors of autoimmune responses (113,114). The *FOXP3* rs3761549 (-2383 C/T) SNP, located in an intronic region, has been reported to be associated with endometriosis and PS (76,77). Particularly, it was found that increased risk of PS was associated with the CC genotype and the 'C' allele of this SNP (77). This SNP was found to alter the *FOXP3* expression pathway and affect Treg regulation in PS (115,116). Notably, an association of the rs3761549 SNP with an increased risk for endometriosis, but not with the severity or stage of the disease has been previously reported (76).

HLA molecules, which play an important role by restricting the antigenic peptides by T cells, are encoded by genes of the MHCs on chromosome 6 and help the body to discriminate between self and non-self proteins (117). These antigens exhibit the highest level of variability within the human genome and function by presenting identifying proteins to cytotoxic T cells, thereby triggering subsequent immune responses (118). The *HLA-DRB1* gene belongs to the group of MHC class II genes, which are expressed on the surface of antigen-presenting cells and display peptides to Th CD4⁺ cells, thus inducing their activation (119). The *HLA-DRB1* (A/G) rs660895 SNP, has been associated with an increased risk for moderate to severe endometriosis (78). The functional significance of this SNP in endometriosis remains unclear. Patients with endometriosis exhibit reduced levels of circulating HLA class II molecules, while the proportion of HLA-DR-positive stromal and glandular epithelial cells is higher in ectopic endometrium compared with eutopic tissue (120). Therefore, it has been hypothesized that the HLA-DR antigen may play an important role in the immunological dysregulation observed in endometriosis (78). Notably, the rs660895 SNP of the *HLA-DRB1* gene

has been shown to be associated with increased susceptibility to PS, particularly in early-onset cases (64,121,122). Additionally, hypomethylation of *HLA-DRB1* was also found to play a role in PS pathogenesis by affecting the mRNA expression of *HLA-DRB1* (123).

The *IL-10* gene is located on 1q31-32, spanning a genomic region of 4.7 kb and containing 5 exons (124). It encodes IL-10, a potent anti-inflammatory cytokine that is mainly produced by T-cell subsets, including Th2 and Treg cells, but it is also produced by macrophages, monocytes, natural killer (NK) cells and B cells (125,126). The IL-10 protein modulates Th2-mediated inflammatory processes and functions as an inhibitor of the synthesis of pro-inflammatory mediators, including, cytokines and chemokines as well as adhesion and accessory molecules, thus suppressing T-cell stimulation (127,128). *IL-10* rs1800871 (-819C/T), a functional promoter SNP located in a regulatory region of the promoter, has been reported to be associated with an increased risk for endometriosis and PS (79,80). It has been reported that women with the TT genotype or carrying the 'T' allele of rs1800871 appear to have a 2-fold increased risk for endometriosis compared with the carriers of the 'C' allele (79,129). Notably, the 'C' allele has been associated with higher levels of both IL-10 mRNA and protein compared with the 'T' allele in patients (130,131), suggesting that this allele may contribute to the downregulation of cell inflammation in the peritoneal cavity (79). Considering that the aforementioned SNP is located in the promoter area of *IL-10* gene, it has been suggested that rs1800871 may change the binding site of a transcription factor, thus decreasing the production of IL-10, altering the immunological homeostasis and resulting in development of PS (80).

The human *MTHFR* gene is located on chromosome 1p36.3, a region with numerous identifiable SNPs (132) and encodes the MTHFR protein. MTHFR represents a key regulatory enzyme in the folate metabolic pathway, with its main function being the conversion of 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate (133). The *MTHFR* rs1801133 (Ala222Val) SNP, located in exon 4 and substituting nucleotide C with T, has been found to be significantly associated with endometriosis (81,83) and PS (134). This SNP results in the reduced activity of the enzyme in TT homozygotes, thus resulting in a decreased production of the antioxidant glutathione, due to alterations of both gene expression levels and protein function, and increased homocysteine levels (135-138). Notably, the 677T variant, which is suggested to be unstable, may influence the thermostability and activity of the MTHFR protein (139). In endometriosis, individuals homozygous for the TT genotype have been associated with a higher susceptibility to endometriosis (81). Furthermore, the TT genotype and 'T' allele were found to increase the risk of PS compared with controls (82,134,140,141). Of note, it was found that rs1801133 also affects the severity of PS according to a cross-sectional study conducted by Karabacak *et al* (142) and a meta-analysis performed by Wu *et al* (143).

The *STAT4* gene, which is located at 2q32.2-q32.3 and consists of 24 exons (144), codes for the STAT4 protein that is a key transcriptional factor expressed in various immune-related cells, such as macrophages, peripheral blood monocytes and dendritic cells (145). This protein, which is a

member of the JAK/STAT pathway, is involved in transmission of signals from IL-12, IL-23 and type 1 IFN (146) and is necessary for the induction of IFN- γ production (147). As a consequence, STAT4 has a crucial role in the establishment of chronic inflammation (148). The intronic *STAT4* rs7574865 G/T SNP has been associated with an increased risk of both endometriosis and PS (84,85). Thus, the TT genotype rs7574865 SNP was shown to be associated primarily to cases of endometriosis at minimal or mild stages of endometriosis compared with controls (84). However, the functional role of this SNP in the development of endometriosis remains unclear. A previous bioinformatics analysis was unsuccessful in identifying any activator or transcription factor whose binding sites are disrupted by the presence of the risk allele 'T' (149). Thus, considering the role of the STAT4 protein in IFN signaling, it can be inferred that rs7574865 SNP contributes to disease development, especially given the strong association between the Th1 response pattern and deep infiltrating endometriosis (150). Furthermore, the 'T' allele was previously found to be associated with the development of PS (85). Notably, STAT4 affects the optimal differentiation of Th17 cells, which are involved in the pathogenesis of both PS and RA (151,152).

The *VEGF* gene is located on chromosome 6p21.3, consists of 8 exons and gives rise to a family of proteins through alternative splicing events (153). It encodes the VEGF protein, which plays an important role in the regulation of angiogenesis (154) as well as endothelial cell dysfunction (155). Several transcription-factor binding sites have been detected in the 5'-UTR of this gene. Moreover, polymorphisms within this region result in an increase of the transcriptional activity of the gene (156) and may be significant in the etiology of the associated pathological conditions (157). The rs1570360 (-1154G/A) SNP, located within a transcription factor binding site in the *VEGF* promoter, has been associated with both endometriosis (90,158) and PS (88,89,91). Particularly, the 'G' allele and GG genotype have been associated with an increased risk of developing endometriosis in comparison with controls, while it has also been associated with deep infiltrating endometriosis as well as moderate to severe forms of the disease (stages III and IV) (63,90). Notably, four potential transcriptional factor binding sites were found to be created by the 'G' allele for EGR1, KLF4, MZF1 and SP2 factors (159). In previous studies, elevated levels of VEGF mRNA and protein have been observed in serum and peritoneal fluid of women with endometriosis (90,160,161). Angiogenic activity has been found to be dysregulated in the eutopic endometrium of patients with endometriosis (162,163). Considering that VEGF is a regulator of various processes contributing to the ectopic implantation and growth of the endometrial tissue (164), including neoangiogenesis and tissue remodeling (153), it has been suggested that any alteration in the levels of VEGF may promote the initiation of endometriosis (63,90). Of note, rs1570360 has been associated with the development of PS and the 'G' allele was observed significantly more frequently among patients with PS (88). Furthermore, significantly increased VEGF serum levels were found in patients with PS compared with healthy controls, while a positive correlation between the serum levels of VEGF and the severity of the disease was also detected (88). Collectively, this SNP may alter the function of the immune system and increase the susceptibility to PS.

Polymorphisms in genes associated with endometriosis and PsA. The *IL-1* gene cluster, located on the chromosomal 2q12-13 locus (165), consists of nine inflammation-related genes. The encoded protein, IL-1A, is a pro-inflammatory cytokine that is primarily produced by activated macrophages, and it promotes the activation of macrophages as well as T- and B-lymphocytes (166). Both *IL-1A* rs17561 (p.A114S) and rs3783553 SNPs, located in exon 5 and the 3'-UTR of the gene, respectively, have been shown to be associated with susceptibility to endometriosis and PsA (40,92,93,167). With respect to endometriosis, it has been suggested that the impairment of the IL-1 family network may result in a disrupted activation of the immune system in the peritoneal cavity of patients with endometriosis compared with the serum of affected women, thus leading to the establishment of chronic inflammation (168). Moreover, the increased expression levels of IL-1A in the peritoneal fluid and serum of women with endometriosis (169,170) may be involved in the implantation of menstrual endometrium on peritoneal surfaces (9). Thus, functional alterations of IL-1A probably play a role in the pathogenesis of endometriosis. In this context, it has been suggested that rs3783553, located in the 3'-UTR, may impair mRNA stability and lead to an alteration of the expression levels of IL-1A (171). A strong association of rs17561, which results in an A114S substitution, and endometriosis has been reported, especially among women with moderate to severe forms of the disease (92). Although, a three-dimensional model of the mature IL-1A protein has been constructed (172), the biological significance of the p.114S variant remains unclear given that no functional analyses have been performed in endometriotic cells thus far. However, by using the bioinformatics tool, PolyPhen-2 (<http://genetics.bwh.harvard.edu/pph2/>) (173), it was suggested that the risk variant might affect processing efficiency at the protein level (92). An increased expression of IL-1A has been detected in the serum synovial fluid and skin of patients with PsA, but no extensive studies have been performed to date, clarifying the protein function in patients with PsA (174,175). Genetic variants of *IL-1A* may induce inflammation in PsA through intracellular effects, thus contributing to the development of the disease.

The *MIF* gene, located on chromosome 22q11.2 region and consisting of three exons (176), encodes the MIF protein, a key pro-inflammatory cytokine produced by T lymphocytes and activated macrophages (177). Furthermore, MIF is involved in the upregulation of *IL-6*, *IFN- γ* and *TNF- α* genes (178). Notably, MIF has been implicated in the pathogenesis of various autoimmune diseases, such as RA, multiple sclerosis, inflammatory bowel disease, PsA and juvenile rheumatoid arthritis (94,179). This protein has also been found to activate several molecular pathways in ectopic endometrial tissue, including immune-inflammatory processes, angiogenesis, and the growth, development and implantation of endometriotic tissue (180). It has been reported that the rs755622-173 G>C SNP, located in the promoter region of the *MIF* gene, has been associated with an increased risk of endometriosis and PsA (72,94). The increased transcriptional activity of the *MIF* gene in women with endometriosis, due to the presence of 'C' allele, leads to an increased synthesis of local estrogen in ectopic tissues, which has been suggested to be involved in both maintenance and progression of endometriosis (181). A significant increase of MIF levels was found in patients with

ENDOMETRIOSIS- ASSOCIATED GENE FACTORS

Involved in:

Cell-cycle regulation
Cell adhesion
Differentiation
Proliferation
Apoptosis
Sex steroid receptors
Matrix remodeling
Oxidative stress



+

- Inflammation
- Autoimmunity
- IFN pathways
- Intracellular signaling
- Angiogenesis
- Vascular function
- Cell migration
- Metabolism

+

PS- and PsA- ASSOCIATED GENE FACTORS

Involved in:

Epidermal differentiation
Adaptive immunity
T cell polarization axis
Innate immunity
Nuclear hormones receptors
Signal transduction



ENDOMETRIOSIS AND PS/PSA CO-OCCURRENCE

Figure 2. Proposed pathogenetic mechanisms for endometriosis, PS and/or PsA co-occurrence. Genetic risk loci associated with these diseases are classified into major distinct mechanistic pathways. Shared genetic risk loci are associated with inflammation, autoimmunity, IFN pathways, intracellular signaling, angiogenesis, vascular function, cell migration and metabolism. PS, psoriasis; PsA, psoriatic arthritis.

PsA, while the-173C allele and the CG genotype were revealed to be associated with both an increased susceptibility to PsA and elevated levels of MIF in circulation, in several populations (72). It is worth noting that the increase in serum levels of MIF was observed in early stages of PsA, thus suggesting a crucial role of MIF in PsA onset by elevating its levels at the beginning of the inflammatory process (72). Moreover, a previous study by Donn *et al* (176) demonstrated that the presence of 'C' allele of rs755622 SNP creates a binding site for the activating enhancer binding protein 4 (AP-4) transcription factor, and as a consequence, this allele significantly increases the affinity of the *MIF* promoter for AP-4 binding.

The protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) gene, located on the 1p13.3-13.1 region, encodes the lymphoid-specific phosphatase Lyp that prevents spontaneous T-cell activation (182). The Lyp protein physically binds to the Csk protein, thus functioning as a downregulator of T-cell activation (183). The *PTPN22* functional polymorphism rs2476601 (R620W, C1885T), leads to the production of a gain-of-function Lyp protein that is unable to bind to the Csk efficiently and, therefore, T-cell activation cannot be suppressed (182). This SNP has been reported to be associated with an increased susceptibility to both endometriosis and PsA (68,95,96). Regarding endometriosis, the minor 'T' allele has been associated with an increased risk of the disease. Moreover, this allele appears to be associated with moderate/severe (III/IV) stages of endometriosis, rather than with minimal/mild (I/II) forms (95). In the same context, the minor 'T' allele has been found at an increased frequency in patients with PsA compared with the control individuals (68,96). The finding that wild-type Lyp is among the most potent inhibitors of T-cell activation

provides a potential explanation for the association between the presence of 'T' allele and increased risk of PsA (96). Furthermore, patients with PsA carrying the 'T' allele appear to have a significantly higher number of joints with deformities, suggesting that this variant may be associated with a more aggressive disease phenotype (184).

5. Conclusions and future perspectives

Recent data have highlighted the bidirectional associations between laparoscopically confirmed endometriosis and physician-diagnosed PS and PsA (5). Although the underlying molecular mechanisms involved in the development of these diseases remain elusive, a number of shared gene polymorphisms associated with an increased risk of the diseases under examination were identified and cross-linked through common pathways (Fig. 2). To the best of our knowledge, the current study represents the first attempt in the literature to address this issue. The findings indicate that certain genes may be considered as potential risk factors for the development of these disorders, thus suggesting a partially shared genetic predisposition. Moreover, in the present review, the functional effect of some genetic factors on this co-occurrence was analyzed. Despite the endometriosis-associated loci identified to date either by independent gene association studies or the hypothesis-free approach of GWAS as well as the high-throughput NGS techniques, numerous SNPs associated with an increased risk for developing PS have been also discovered. However, only a small number of these genetic variants have had their functional significance investigated, highlighting the need for both in-depth analyses of the role

of additional gene polymorphisms and the elucidation of the underlying molecular mechanisms. Such efforts are essential for translating these genetic findings into novel therapeutic interventions.

As detailed in the Introduction, endometriosis has been shown to fulfill most of the classification criteria for an autoimmune disease (14,19-22). Moreover, it has been demonstrated that endometriosis may co-occur with a large number of different autoimmune diseases. Consistently, the current investigation revealed that many of the genetic polymorphisms that are associated with an increased risk of PS or PsA were also found to be associated with at least one other autoimmune disease previously reported to co-exist with endometriosis (18,41,139). Over the last years, researchers have attempted to use strategies for immunomodulation as a potential treatment for endometriosis, in addition to the formal surgical approach and hormone therapies that include oral contraceptives, progestins, and gonadotropin-releasing hormone agonists (185,186). Components of inflammatory or immune-cell dysfunction are challenging therapeutic targets for improved management of both endometriosis and PS (with or without PsA). In this context, the investigation of shared genetic factors underlying these diseases may substantially contribute to the generation of valuable insights with potential applications in translational medicine. Thus, the upregulation of the JAK/STAT3 pathway in endometriosis (185), provides a rationale for drug repurposing, considering that several relevant inhibitors have already been developed. In this context, inhibition of JAK/STAT signaling, specifically through the use of tofacitinib to disrupt the transduction of this pathway, may represent a promising novel therapeutic option for the treatment of endometriosis (41,185,187), since it has been shown to effectively reduce STAT3 phosphorylation in human stromal and epithelial cells derived from the eutopic endometrium of women with endometriosis (185). Notably, tofacitinib, which targets JAK1 and JAK3 and regulates the immune response, has been used for the treatment of both chronic plaques in PS (188) as well as PsA (189). Furthermore, as presented in Table I, the rs7574865 SNP of *STAT4* gene, which is associated with chronic inflammation and plays a crucial role in the JAK/STAT pathway-mediated IFN signaling (190), has been reported to be associated with both endometriosis and PS.

In addition, as shown in Table I, the rs1800629 SNP of the *TNF- α* gene is associated with an increased susceptibility to endometriosis, PS and PsA. Notably, elevated levels of TNF- α protein have been detected in both the serum and peritoneal fluid of patients with endometriosis (103,107,191), while increased cytokine production has also been observed in both psoriatic lesional skin (109) and the serum (111) of patients with PS. Thus, anti-TNF- α agents targeting TNF- α have been considered beneficial alternative therapeutics for women with endometriosis. Anti-TNF- α agents, etanercept and adalimumab, have been found to be active and effective in the treatment of both PS and PsA (192). Etanercept, a TNF- α blocker, is a soluble receptor fusion protein, that functions by directly binding to TNF molecules in both the blood and affected tissue. It represents an effective treatment for patients with moderate to severe PS, improving psoriatic skin lesions and clearance rates (193). Notably, etanercept has been reported to block the ability of the peritoneal fluid to increase

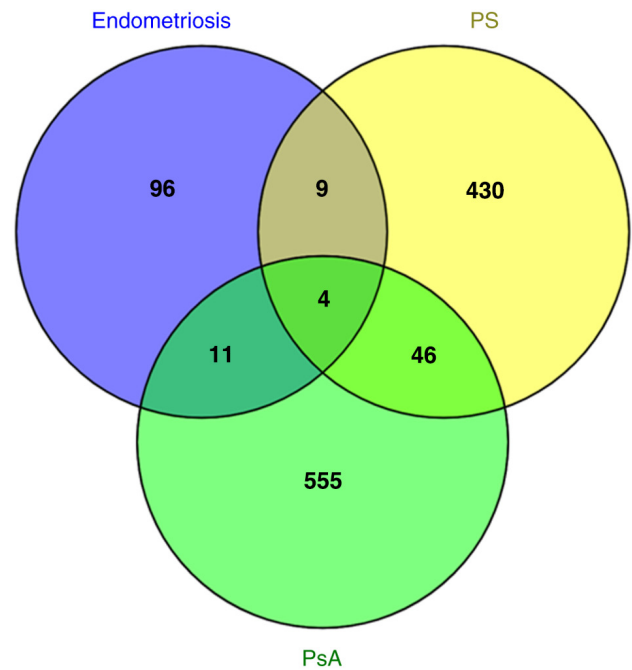


Figure 3. Venn diagram presenting the shared genes that are upregulated in endometriosis, PS and PsA (219). PS, psoriasis; PsA, psoriatic arthritis.

the proliferation levels of eutopic or ectopic endometrial cells in endometriosis (194). Adalimumab, another TNF- α blocker, is a recombinant monoclonal antibody that binds with high affinity and specificity to TNF- α , and has demonstrated significant efficacy for the treatment of patients with PsA (195) as well as those suffering from moderate to severe PS, improving both skin and joint manifestations of the disease (196,197). In the case of endometriosis, adalimumab has been suggested to play a role in the regression of endometrial implants, since it has shown antioxidant and anti-inflammatory effects on histopathological damage and fibrosis (198).

The genetic data (Table I, Figs. 1 and 2) suggest that shared pathways may underlie the co-occurrence of endometriosis, PS and/or PsA. Therefore, an attempt was made to further explore and validate this hypothesis through transcriptomic analyses, aiming to strengthen the conclusions regarding the potential therapeutic targets that have been presented above. These analyses revealed 13 genes that were found to be upregulated in both endometriosis and PS, namely *CXCL1*, *CXCL10*, *CXCL9*, *CXCR2*, *FABP4*, *IL18R1*, *IL18RAP*, *IL6R*, *S100A8*, *SCGB2A1*, *SERPINE1*, *STAT1* and *SYK* (199-208). Moreover, 15 genes were found to be expressed at elevated levels in endometriosis and PsA, namely *C1QB*, *C6*, *C7*, *CCR2*, *CD27*, *CLU*, *CXCL9*, *CXCL10*, *CXCL12*, *GREM1*, *IL-17*, *SERPINE2*, *S100A8*, *SIGIRR* and *STAT1* (209-212). Among these genes, four of them were found to be upregulated in the three diseases under study, namely *CXCL10*, *CXCL9*, *S100A8* and *STAT1*. Collectively this data is presented in Fig. 3. Of note, in addition to the aforementioned therapeutic targets identified through genetic data, transcriptomic analyses from the literature have also provided some valuable insights regarding challenging therapeutic targets. For example, tocilizumab (TCZ), a humanized antibody against the α -chain of the IL-6 receptor (IL6R)

commonly used for the treatment of inflammatory diseases, has been considered a promising option for the treatment of endometriosis (213-215). However, TCZ has the potential to induce adverse drug events including PS-like eruptions, as described when TCZ was used for the treatment of patients with RA (216,217). Notably, the *STAT1* gene was found to be upregulated in endometriosis, PS and PsA (Fig. 3). *STAT1* is a member of the JAK/STAT pathway and can enable the transcription of genes which inhibit cell division and stimulate inflammation (190). As previously reported, tofacitinib, a JAK/STAT signaling pathway inhibitor, has been used for the treatment of endometriosis (185,215), PS (188) and PsA (189). A limitation of the transcriptomic analyses across different diseases is the wide variety of tissue types investigated for each disease in the research conducted thus far, including ectopic and eutopic endometrium, fibrotic endometrium, endometriotic or peritoneal lesions, peritoneal fluid, psoriatic skin, skin fibroblasts, PS plaques, whole blood, epithelium, dermis and synovial fluid. However, transcriptome analysis has significantly contributed to the development of novel biomarkers as well as diagnostic and prognostic tools.

A limitation to be considered is the lack of replication studies in the literature to date, regarding the co-occurrence of endometriosis and PS or PsA in patients of different racial and/or ethnic backgrounds. This is a significant issue, given the differential role of the various polymorphisms involved in the development of these disorders depending on the ancestry of the populations under examination (218).

In conclusion, the genetic risk factors shared between endometriosis, PS, and/or PsA, combined with insights into the underlying cellular and biochemical pathogenetic pathways presented in this review, may significantly aid in identifying novel therapeutic targets and developing new treatment protocols. This, in turn, could offer substantial benefits for patients suffering from endometriosis and PS or PsA. Moreover, further elucidation and replication of the results presented by Harris *et al* (5) in patients of diverse ancestries, would reinforce the need for gynecologists and dermatologists to be vigilant and acknowledge the potential association between endometriosis and PS and/or PsA. This awareness would encourage collaborative efforts to coordinate the management and treatment of these co-existing conditions.

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Authors' contributions

MIZ and GNG designed the current study and drafted the manuscript. GNG, TBN, TBT, BCT, GFG, GB and MIZ searched the literature. MIZ, GNG, GB and DAS analyzed

and organized the data. DAS, TBT, BCT, GFG, GB and TBN critically revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

MIZ, BCT, GFG, GB, TBN and GNG (all authors other than DAS) declare that they have no competing interests related to this study. DAS is the Editor-in-chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article.

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