

Immunological Genetic Variants Underlying Endometriosis

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Introduction

Endometriosis is a common chronic gynaecologic disease defined as presence of endometrial tissue outside the uterine cavity, primarily on pelvic peritoneum and ovary, which affects 3-20% of women in their reproductive years and 20-50% of women with infertility [1,2]. Immune system disorders [3], genetic predisposition [4,5], altered peritoneal environment [6], and endometrial alterations [7] are believed to increase the susceptibility to the disease. The increased susceptibility varies in population based prevalence, the presence of infertility and racial disparities [8,9]. The main symptoms of endometriosis are dyspareunia, dysmenorrhea, pelvic pain, and/or sub-fertility. Endometriosis may be inherited in a polygenic manner; the incidence is seven times greater in relatives of affected individuals than in nonrelatives [10,11]. Although there is evidence regarding linkage to chromosomes 7 and 10; no relevant genes in these regions have yet been identified [12]. Endometriosis is characterized by the following alterations of peritoneal and follicular fluid cytokine concentrations: Increased levels of IL-1, IL-4, IL-5, IL-6, IL-8, IL-10, antioxidants, Bcl-2, reactive oxygen species (ROS), soluble intercellular adhesion molecule (sICAM-1), TGF- β , TNF- α , growth-related α , monocyte chemotactic protein (MCP-1), Endothelin-1, Natural killer cells, Monocytes, RANTES, increased Aromatase, and 17 β -hydroxysteroid dehydrogenase; increased B cell function; increased T-like autoantibodies against hemopexin; increased MMPs; and decreased IL-2, IL-5, IL-13, IFN- γ and TIMPs. increases in follicular fluid but VEGF decreases in the peritoneum [13].

It is believed that the effects caused by polymorphisms of the immune system may result in changes in immune homeostasis, leading or contributing to the establishment of endometrial cells in ectopic sites and also the progression of the disease.

Candidate gene	Chromosome	dbSNP ID	Function	Studies with endometriosis [Ref]
IL-2R β	22q13.1	-	It is involved in T cell-mediated immune responses	[15]
IL-10	1q32.1	rs1800871	Down-regulates the expression of Th1 cytokines, MHC class II Ags, and costimulatory molecules on macrophages. It also enhances B cell survival, proliferation, and antibody production	[16,17]
FOXP3	Xp11.23	rs3761548 rs3761549 rs2232366 rs2232368 rs2280883	Regulates the activation of T cell and functions as a transcriptional repressor and down regulates cytokine production in T cells.	[18,19]
PTPN22	1p13.3-13.1	rs2476601	Increased inhibition of T-cell-receptor signalling caused by the PTPN22C1858T polymorphism could predispose to autoimmunity, either by affecting thymic deletion of autoreactive T cells or by affecting the development or function of peripheral regulatory T cells	[20]
FCRL3	1q21-23	rs7528684 rs11264799 rs945635 rs3761959	It may play a role in the differentiation of B cells into autoreactive cells and has been presumed to function through modulating signal transduction via activation/inactivation of signalling tyrosine protein kinases.	[21,22]
CTLA4	2q33	rs231775 rs3087243	A member of the immunoglobulin superfamily that is expressed on the surface of activated T cells and downregulates T-cell function, besides being a critical mediator in peripheral tolerance.	[23]

Candidate gene	Chromosome	dbSNP ID	Function	Studies with endometriosis [Ref]
<i>NF-κB1</i>	4q24	rs28362491	It plays a key role in the immune and inflammatory response and modulates cell proliferation, apoptosis, adhesion, invasion, and angiogenesis in many cell types	[24]
<i>HLA-DRB1</i>	6p21.3	rs660895	Belongs to the HLA class II beta chain paralogs and plays a central role in the immune system by presenting peptides derived from extracellular proteins.	[25,26]
<i>BLYS</i>	13q32-q34	rs9514828	It is a member of the tumor necrosis factor super family, which is necessary for normal B cell development and induces differentiation into plasma cells	[27]
<i>TYK2</i>	19p13.2	rs34536443	This gene encodes a member of the tyrosine kinase and, more specifically, the Janus kinases (JAKs) protein families. It may decrease the endometriosis risk	[28]

A summary of case-control results from genetic association studies with endometriosis

Conclusion

Endometriosis is one of the most investigated disorders of gynaecology, but it still remains enigmatic. Immunologic theories suggest that changes in the immune system could prevent the ability of immune cells such as macrophages, NK, and cytotoxic T cells to eliminate the endometrium of the pelvic cavity. At least in some endometriosis cases, it seems to be associated with chronic local inflammation and antibody self-reactivity. SLE, hypothyroidism, rheumatoid arthritis, Sjögren syndrome and multiple sclerosis inflammatory bowel diseases are autoimmune diseases which may be associated with endometriosis. Totally, there are good evidences regarding a genetic contribution to the risk of developing endometriosis. It is believed that the combined effect of several polymorphisms of the immune system can lead to changes in immune homeostasis, contributing to the establishment of endometrial cells in ectopic sites and also the progression of the disease. Exploring the ways in which these polymorphisms act together can be a crucial step in discovering the pathophysiology of endometriosis and consequently.

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