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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-I), Endothelin-1, Natural killer cells, Monocytes, RANTES, increased Aromatase, and 17β-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-2Rβ	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 *PTPN22*C1858T 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]
NF-κB1	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]
HLA-DRB1	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]
BLYS	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]
TYK2	19p13.2	rs34536443	This gene encodes a member of the tyrosine kinase and, more specifically, the Janus kinases (JAKs) protein families. It may decreases 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 areautoimmune 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 endometrialcells 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.

References

1. Vercellini P, Crosignani P, Somigliana E, Viganò P, Frattaruolo MP, et al. (2011) 'Waiting for Godot': a commonsense approach to the medical treatment of endometriosis. Hum Reprod 26: 3-13.

2. Katz VL, Lentz GM, Gershenson DM, Lobo RA (2012) Etiology, Pathology, Diagnosis, Management. Comprehensive Gyneco: Expert Consult-Online 71: 433.

3. Lessey BA (2011) Assessment of endometrial receptivity. Fertil Steril 96: 522-9.

4. Stefansson H, Geirsson RT, Steinthorsdottir V, Jonsson H, Manolescu A, et al. (2002) Genetic factors contribute to the risk of developing endometriosis. Hum Reprod 17: 555-9.

5. Bonadona V, Bonaïti B, Olschwang S, Grandjouan S, Huiart L, et al. (2011) Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. Jama 305: 2304-10.

6. Stilley JA, Birt JA, Sharpe-Timms KL (2012) Cellular and molecular basis for endometriosis-associated infertility. Cell Tissue Res 349: 849-62.

7. May K, Villar J, Kirtley S, Kennedy SH, Becker CM (2011)Endometrial alterations in endometriosis: a systematic review of putative biomarkers. Hum Reprod Update 17: 637-53.

8. Buck Louis GM, Hediger ML, Peterson CM, Croughan M, Sundaram R, et al. (2001) Incidence of endometriosis by study population and diagnostic method: the ENDO study. Fertil Steril 96: 360-5.

9. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, et al. (2004) Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. Am J Epidemiol 160: 784-96.

10. Moen MH, Magnus P (1993) The familial risk of endometriosis. Acta Obstet GynecolScand 72: 560-4.

11. Simpson JL, Elias S, Malinak LR, Buttram VC (1980) Heritable aspects of endometriosis. Am J Obstet Gynecol 137: 327-31.

12. Montgomery GW, Nyholt DR, Zhao ZZ, Treloar SA, Painter JN, et al. (2008) The search for genes contributing to endometriosis risk. Hum Reprod Update 14: 447-57.

13. Barrier BF (2010) Immunology of endometriosis. Clin Obstet Gynecol 53: 397-402.

14. Hsieh YY, Chang CC, Tsai FJ, Hsu Y, Tsai HD, et al. (2002) Polymorphisms for interleukin-4 (IL-4)–590 promoter, IL-4 intron3, and tumor necrosis factor alpha-308 promoter: Non-association with endometriosis. J Clin Lab Anal 16: 121-26.

15. Hsieh YY, Chang C, Tsai F, Hsu C, Lin C, et al. (2005) Interleukin-2 receptor β (IL-2Rβ)-627*C homozygote but not IL-12Rβ1 codon 378 or IL-18 105 polymorphism is associated with higher susceptibility to endometriosis. Fertil Steril 84: 510-2.

16. Fan W, Chen Q, Huang Z, Ma Q, Xiao Z (2013) Association between interleukin-10 promoter polymorphisms and endometriosis: a meta-analysis. Gene 515: 49-55.

17. Xie J, Wang S, He B, Pan Y, Li Y, et al. (2009) Association of estrogen receptor alpha and interleukin-10 gene polymorphisms with endometriosis in a Chinese population. Fertil Steril 92: 54-60.

18. Wu ZY, Wang WW, Wang T, Yang RF, Li Y, et al. (2013) [Association of FOXP3 gene polymorphism in Chinese women with endometriosis]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 30: 106-10.

19. André GM, Barbosa CP, Teles JS, Vilarino FL, Christofolini DM, et al. (2011) Analysis of< i> FOXP3</i> polymorphisms in infertile women with and without endometriosis. Fertil Steril 95: 2223-7.

20. Gomes FM, Bianco B, Teles JS, Christofolini DM, de Souza AM, et al. (2010) PTPN22 C1858T polymorphism in women with endometriosis. Am J Reprod Immunol 63: 227-32.

21. Teles JS, Bianco B, Vilarino FL, André GM, Christofolini DM, et al. (2011) Association of< i> FCRL3</i> C-169T promoter single-nucleotide polymorphism with idiopathic infertility and infertility-related endometriosis. J Reprod Immunol 89: 212-5.

22. Barbosa CP, Teles JS, Lerner TG, Peluso C, Mafra FA, et al. (2012) Genetic association study of polymorphisms< i> FOXP3</i> and< i> FCRL3</i> in women with endometriosis. Fertil Steril 97: 1124-8.

23. Lerner TG, Bianco B, Teles JS, Vilarino FL, Christofolini DM, et al. (2011) Analysis of CTLA4 gene variant in infertile Brazilian women with and without endometriosis. Int J Immunogent 38: 259-62.

24. Kobayashi H, Imanaka S, Nakamura H, Tsuji A (2014) Understanding the role of epigenomic, genomic and genetic alterations in the development of endometriosis (Review). Mol Med Rep 9: 1483-505.

25. Sundqvist J, Xu H, Vodolazkaia A, Fassbender A, Kyama C, et al. (2013) Replication of endometriosis-associated single-nucleotide polymorphisms from genome-wide association studies in a Caucasian population. Hum Reprod 28: 835-9.

26. Dun EC, Taylor RN, Wieser F (2010) Advances in the genetics of endometriosis. Genome Med 2: 75.

27. Christofolini DM, Cavalheiro CM, Teles JS, Lerner TG, Brandes A, et al. (2011) Promoter-817C> T Variant of B Lymphocyte Stimulator Gene (BLyS) and Susceptibility to Endometriosis-Related Infertility and Idiopathic Infertility in Brazilian Population. Scand J Immunol 74: 628-31.

28. Peluso C, Christofolini DM, Goldman CS, Mafra FA, Cavalcanti V, et al. (2013) TYK2 rs34536443 polymorphism is associated with a decreased susceptibility to endometriosis-related infertility. Hum Immunol 74: 93-7.