

Genetic determination in endometriosis

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ABSTRACT

Endometriosis represents a debilitating disease affecting women at fertile age which is associated with severe symptoms such as chronic pelvic pain, dysmenorrhea, dyspareunia and infertility. The pathogenesis of this disease is not fully understood so far, multiple theories being proposed. However, more recently, attention was focused on identifying the role of genetic factors in endometriosis development. In the current paper we aimed to review the most important theories regarding pathogenesis. Furthermore we discuss the genetic factors regarding this illness as well as other genes that are suspected to be culprits in leading to this pathology.

Keywords: endometriosis, genetic factors, genes, pathology

INTRODUCTION

Endometriosis is a chronic disease defined by ectopic growth of the endometrial glands and stroma [1-4].

Chronic pelvic pain, dyspareunia, dysmenorrhea and infertility are the basic symptoms, but laparoscopy and biopsy remain the gold standard for accurate diagnosis [1,2]. Endometriosis-induced infertility occurs predominantly because of ovarian dysfunction, following certain processes that interfere with folliculogenesis and endometrial receptivity, and is the main reason why women of reproductive age use assisted reproductive methods, such as IVF (in vitro fertilization) and ICSI (intracytoplasmic sperm injection) [4].

ASSESSMENT

The real incidence of endometriosis has not been accurately determined, but remains a topic of particular interest to clinicians and researchers, as reported estimates range between 10-15% for all women of reproductive age and 25-35% for women diagnosed with infertility [1, 2, 5-8]

The etiology of endometriosis remains an enigma, although previous studies have shown genetic involvement and family predisposition to the development of this disease. The genetics of the disease refer to the inherited characteristics of patients, which increase their susceptibility to this condition and explain the family component of the disease. The hereditary model of endometriosis was first proposed by Goodall in 1943, referring to 5 cases with a family history, since then several families have been studied [1,4,9-12].

The established information has shown a family aggregation of endometriosis, yet the inheritance pattern doesn't appear to be a mendelian one. Endometriosis is clearly hereditary, but the genetics of endometriosis are complex and still unexplained, however, most researchers believe it is a polygenic/multifactorial condition [1,2,12].

The phenotype is determined by the effect of the combination of several genes and the interaction of environmental factors. There are several factors that make the process of determining the genetic transmission of endometriosis difficult, primarily the fact that endometriosis can only be diagnosed invasively by laparoscopy or laparotomy. As a result, there are

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many undiagnosed cases, which leads to underreporting of the disease. Transmission is polygenic, although mendelian mode of transmission cannot be ruled out if endometriosis is thought to be a single condition. The increased severity in family cases is also consistent with predictions based on a polygenic model, rather than a monogenic one. The model predicts that as the severity increases, so does the underlying genetic responsibility, and therefore the higher ratio of affected relatives [1,2,4,5,13].

Another explanation, perhaps the most likely, is genetic heterogeneity (not all cases of endometriosis have the same genetic defects). Some may be with mendelian transmission, despite the fact that, however, studies have shown that the higher proportion is polygenic/multifactorial.

Genetic tests are underway, trying to locate various mutations in genes essential for the etiology of endometriosis. The identification of several unrelated genes would be expected, assuming either polygenic inheritance or genetic heterogeneity [5].

Several genes were taken into consideration as candidates for their association with endometriosis, including genes involved in apoptosis, inflammation, hormone receptors, estrogen metabolism, steroid synthesis, oncogenes, growth factors, cell cycle regulation, and other enzymes. Single nucleotide polymorphisms (SNPs) have been found in genes, such as: TBL2, ZNF366, HLA-G, MPDZ, SNX16, FOXP2, VEZT, PAPP, KCTD12, FSTL5, WTN4, FSHB [4,6].

An association between estrogen receptor polymorphism (PGR) and endometriosis has been demonstrated.

The VEZT vesatin gene is located on the 12q22 locus of chromosome 12, it encodes vesatin, an element of the cadherin-catenin complex, which plays an essential part in the formation and maintenance of intercellular junctions. Vesatin is a component of the membrane plasma with a short extracellular domain, a transmembrane domain and an extended intracellular domain. The intracellular domain connects to myosin as part of the junction complex of epithelial cells [4,5].

It is well known that the VEZT gene is extensively expressed in the endometrium and myometrium. In the secretory phase of the menstrual cycle, VEZT expression increases in the glandular epithelium significantly. Also, the activity of VEZT is crucial for facilitating the implantation, being that in the case of the sensed gene, intercellular adhesion is lost. Given the physiological role of VEZT, it may potentially be involved, functionally, in endometriosis. As VEZT has been shown to be overregulated in the ectopic endometrium relative to the eutopic endometrium in patients with endometriosis [4-7].

The WNT4 gene positioned on the cytogenetic location 1p36.23-p35, encoding a protein is essential

in the formation of the female reproductive system. It critically regulates the proper postnatal uterine maturation as well as the growth of the ovarian antral follicle. The WTN family of genes is a large group of 19 secreted glycoprotein-encoding genes involved in the signaling pathway responsible for the management of several cellular responses, such as: cell growth, cell survival, differentiation, migration, movement, polarity, and immune response. Studies have shown that WNT4 is the first signaling molecule that causes the chain of events that ends with the determination of sex, by local secretion of growth factors. WTN4 activity is a key component in the development of the renal and gonadic systems, as well as the adrenal glands. WNT4 expression has been detected at elevated levels in the peritoneum, which can "help" the transformation of peritoneal cells into endometrial cells [5,6,8,14].

The FSHB gene encoding the follicle-stimulating hormone beta subunit, located on chromosome 11, cytogenetic region 11p14.1, has been associated with endometriosis. FSH and LH are related hormones that have the same alpha subunit. These two hormones have a common regulatory mechanism, both of which are key elements in managing the development of follicles in the ovary, influencing the release of estradiol during the proliferative phase, so mutations in the FSHB gene help increase the risk of endometriosis [4,5,6,9,10,15].

Using in situ fluorescent hybridization (FISH) with chromosome-specific probes, endometrial biopsy cells with monosomy 16 and 17, trisomy 11, and tetrasomy 17 were found. Comparative genome hybridization was used to identify 1q+, 4q-, 11p-, 13q-, loss of 9, 12 and 18 and 6p.32 amplification. These findings suggest that various acquired chromosomal abnormalities, could be important in the development of endometriosis, potentially caused by clonal expansion of abnormal chromosomal cells [1,2,11,16].

Whole exome (WES) sequencing, performed to detect somatic mutations in eutopic and ectopic endometrial tissue, has shown in 16 cases that most genes involved in regulation of cellular adhesions, intercellular junctions, and chromatin remodeling complexes have undergone mutations. The multifactorial nature of the disease implicates it in angiogenic processes, immune mechanisms and biochemical alterations, so genetic factors and epigenetic changes act together [4,6].

Subsequent studies will shed light on these associations and determine the genes with a more significant role that play a part in the pathogenesis of endometriosis.

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