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Genetics and Genomics of Endometriosis

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Abstract

Endometriosis is a common cause of morbidity in women with an unknown etiology. Studies have demonstrated the familial nature of endometriosis and suggest that inheritance occurs in a polygenic/multifactorial fashion. Studies have attempted to define the gene or genes responsible for endometriosis through association or linkage studies with candidate genes or DNA mapping technology. A number of genomics studies have demonstrated significant alterations in gene expression in endometriosis. A more thorough understanding of the genetics and genomics of endometriosis will facilitate understanding the basic biology of the disease and open new inroads to diagnosis and treatment of this enigmatic condition.

Keywords

endometriosis; genetics; familial; genomics; candidate genes; gene mapping

Introduction

Endometriosis is defined as the extrauterine growth of endometrial glands and stroma. The etiology of endometriosis remains an enigma, however, previous studies have demonstrated a familial predisposition to development of this disease. Genetics refers to characteristics that are heritable through genes and helps to explain familial clustering of disease. In regard to complex diseases such as endometriosis, genetics refers to inherited genes that cause or increase the susceptibility of an individual to a disease or condition.

The genetics of endometriosis is complex and remains unexplained, however, most investigators feel that it is inherited in a polygenic/multifactorial mode. The polygenic/multifactorial type of inheritance occurs when phenotype is determined by a combination of multiple genes and environmental effects. There are a number of factors which specifically make it difficult to determine the mode of inheritance of endometriosis. First and foremost is the fact that endometriosis can only be diagnosed invasively with laparoscopy or laparotomy. This can result in under-reporting of patients afflicted with the disease since

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diagnosis relies on an invasive test. Another contributing factor is that endometriosis may actually be a number of different disease processes as evidenced by the differences in peritoneal, ovarian endometriomas and deeply infiltrating endometriosis. Other potential complicating factors are environmental exposures, such as dioxin.

Familial Clustering

Studies have demonstrated familial clustering of endometriosis, but the disease does not appear to be inherited in a simple Mendelian mode. Studies in the rhesus monkey have provided unique insight into the inheritance of endometriosis. The rhesus monkey is an excellent model for endometriosis since it spontaneously develops the disease and the ectopically implanted tissue is indistinguishable from endometrial implants. The Wisconsin Regional Primate Research Center is an excellent site for genetic studies because they have a large population of rhesus monkeys as well as well-documented pedigrees for these monkeys. They discovered 142 animals with endometriosis and were able to construct a detailed multigenerational pedigree. This study demonstrated the familial nature of endometriosis with a significantly higher kinship coefficient for affected animals and a higher occurrence risk in full sibs. Future studies in this unique animal model should help understand the genetic contribution to this enigmatic disease.[1]

Ranney[2] was one of the first to suggest the familial nature of endometriosis in humans using a survey. In this study a questionnaire asking about close relatives with endometriosis was sent to 350 subjects with surgically confirmed endometriosis. The results suggested a familial nature of endometriosis.

A number of studies have demonstrated the familial clustering of endometriosis and that first-degree relatives of affected women are 5 to 7 times more likely to have surgically confirmed disease. Simpson et al in 1980[3] evaluated 123 subjects with surgically proven endometriosis and discovered that 5.9% of their mothers and 8.1% of their sisters had endometriosis, compared with only 0.9% of controls. Following studies have reinforced Simpson et al's findings. Kennedy et al[4] in a study where endometriosis was diagnosed with magnetic resonance imaging demonstrated an increased relative risk of 15 for an affected sister in a proband with severe disease.

Other findings support polygenic/multifactorial inheritance of endometriosis. First endometriosis that occurs in families tends to be more severe compared to sporadic cases. This suggests that there is more genetic propensity or liability in individuals with severe disease, and hence there is more likelihood to have affected sibs or offspring. Other factors which suggest a genetic predisposition to endometriosis include the similar and earlier age of onset of symptoms in affected families.[5]

Twin studies have demonstrated a higher concordance for endometriosis in monozygotic versus dizygotic twins, which suggested increased heritability. Treloar et al[6] sent questionnaires to 3298 monozygotic and dizygotic twin pairs identified within an Australian twin registry. 3096 (94%) of the twins returned the questionnaires, and 215 (7%) reported a diagnosis of endometriosis, with 2% of monozygotic and 0.6% of dizygotic twins

concordant for the disease. These authors established that genetic influence accounts for 51% of the latent liability of this disease.

Studies also evaluated the heritability of endometriosis using large population-based genealogy databases. The first study conducted in Iceland by Stefansson et al[7] identified 750 women with surgically-defined disease and these subjects had a statistically significant higher kinship coefficient than unaffected subjects. They also identified a significantly higher relative risk that sisters (5.20) and cousins (1.56) would be affected. In Utah, Farrington et al[8] confirmed the Icelandic studies in that subjects with endometriosis were more likely to be closely related than controls, that the relative risk for endometriosis was higher in close family members and there was a higher kinship coefficient.

These studies demonstrated the familial clustering of endometriosis. A recent report reminds us that familial clustering does not always reflect a genetic etiology. In fact familial clustering could represent other risk factors for the disease in question which cluster in the family, like life-style and diet or an intermediary factor associated with development of endometriosis that is inherited, like age of menarche. Another potential mechanism which can mimic familial clustering is reporting and ascertainment biases.[9]

Endometriosis is a neoplastic process that shares some similarities with malignancy, that is, local invasion and angiogenesis. Studies have also demonstrated an increased frequency of endometroid carcinoma of the ovary in patients with endometriosis. These two findings have prompted investigations into applying areas of basic cancer research especially genetic changes into the study of endometriosis.

Loss of Heterozygosity (LOH) is a well defined predisposing factor for the development of cancer. One of the first genes investigated as a cause of cancer was tumor suppressor gene *RB1* (*retinoblastoma tumor suppressor gene*) in which mutations have been associated with the development of retinoblastoma. In the familial forms of retinoblastoma the individual inherits a normal allele from one parent but the other allele is mutated and not producing the tumor suppressor (LOH). The normal allele continues to make active tumor suppressor product so this individual does not develop the tumor. However, if the normal allele later is inactivated by a somatic mutation then a retinoblastoma will develop. [10]

A number of studies have evaluated endometriotic tissue with both cytogenetic and molecular techniques for the presence of loss of heterozygosity. If mutations in tumor suppressor genes play a role in the etiology of endometriosis one would expect to find evidence of loss of heterozygosity at such alleles, especially in familial cases. Jiang et al[11] demonstrated a loss of heterozygosity at 9p, 11q and 22q. Further studies demonstrated loss of heterozygosity at 5q, 6q, 9p, 11q and 22q in one third of cases of ovarian cancer associated with endometriosis. [12, 13]

Kosugi et al[14] found evidence of increased frequency of monosomy 17 and specifically the loss of the *TP53 tumor suppressor* gene locus in endometriotic samples as compared to controls. They discovered that in 16 endometriotic samples 12/16 had monosomy 17 and the remaining 4 had loss of heterozygosity for the TP53 allele.Mutations in the *PTEN tumor*

suppressor gene located on 10q23 has also been discovered in endometroid and clear cell carcinomas of the ovary as well as in endometriotic samples. [15]

These data led Bischoff and Simpson to propose a multi-hit strategy with the accumulation of mutations as a mechanism to explain the development of endometriosis, similar to the sequential multi-step process that occurs in the development of colorectal carcinoma. [16] In this model the first hit (either inherited in familial disease or a somatic mutation in sporadic disease) occurs in genes involved in cellular attachment or persistence within the cells of the menstrual effluvium. These mutated endometrial cells which reflux through the fallopian tubes then have the ability to attach to the peritoneum and survive. Following this initial attachment of cells further mutations can occur which alter the metabolism and basic biology of the cell, resulting in endometriosis. Those who inherit a mutated gene are more likely to experience a second hit that then results in the development of endometriosis, than those who require two sporadic mutations. In certain situations, mutations will accumulate and if they involve tumor suppressor genes or oncogenes then the endometriotic cells could develop into malignant cells. [13]

Gene Mapping

Another method used to investigate for gene mutations or polymorphisms associated with endometriosis involves gene mapping. These methods of evaluating for informative genes include candidate gene studies, linkage mapping and genome wide association studies. In all of these type of studies it is important that the proposed affected gene makes biological sense and that the study is large enough to detect a relatively small gene effect, since in complex diseases each gene probably has a small effect on the phenotype. In addition it is vital to demonstrate consistent affect in replication studies.

A number of candidate genes have been evaluated for their association with endometriosis and include genes involved in inflammation, steroid-synthesis, detoxification, hormone receptors, estrogen metabolism, growth factors, adhesion molecules, apoptosis, cell-cycle regulation, oncogenes, other enzymes and metabolic systems. These studies have *a priori* defined the gene of interest which is then tested for association in a case-control or in a linkage study in individuals from an affected family. Most of these studies have failed to support or confirm an association between the candidate gene and endometriosis with a few interesting exceptions.

In terms of genes from detoxification pathways the *glutathione S-transferase* (*GST*) and the *cytochrome P450* (*CYP*) gene families have been investigated for association with endometriosis. The *GSTM1* gene located on 1p13.3 and the *GSTT-1* gene located on 22q11.23 have been studied in over 20 studies with pooled odds ratios of 1.96 (95% CI: 1.29-2.98) and 1.77 (95% CI: 1.19-2.63), respectively, for association with endometriosis. [17] For the *CYP1A1* gene overall there was no association, but for the Msp1 polymorphism of *CYP1A1* there was an OR of 1.44 (95% 1.00-2.06), suggesting an association with endometriosis. [18]

Endometriosis is an estrogen dependent disease which has stimulated interest in investigating a number of genes involved in steroid hormone synthesis and their signaling

pathways. A recent meta-analysis demonstrated an association between endometriosis and the progesterone receptor (PGR)-PROGINS polymorphism with a pooled OR: 1.94 (95% CI, 1.31-2.88) and estrogen receptor 1-PvuII polymorphism with a pooled OR: 2.1 (95% CI, 1.20-3.68). [19, 20]

There has recently been concern that these and other less well documented associations may be spurious. This concern relates to the heterogeneity between studies, potential for bias including selection and publication bias as well as a lack of replication. Less than half of the studies which demonstrated a significant association have been investigated in a repeat independent sample, and of those that have been investigated, many have not been replicated. This lack of association is thought to be due to a number of factors including failure to type the same gene variant, differences in data analysis, population differences and a lack of sufficient power to detect a small gene effect in many of these studies. This has led Di and Guo[9] to question the genetic contribution to endometriosis and suggest more well designed genetic studies.

Linkage Studies

Investigators in the United Kingdom and Australia have recruited individuals with surgically confirmed endometriosis and their families for sib-pair analysis. These investigators have used linkage mapping, where they analyze the genome for excess sharing of informative polymorphic microsatellite markers in affected sibs. These authors, as part of the International Endogene Consortium, investigated DNA extracted from 1176 affected sister pairs for evidence of linkage. In this analysis the authors described a peak of linkage on chromosome 10 (p=0.047) and another suggestive peak on chromosome 20. Further fine mapping on chromosome 10 confirmed linkage. [21]

The authors then performed an analysis on a subset of the families where there were at least three or more affected individuals, assuming that there would be more genetic liability in these families and possibly even a Mendelian type of inheritance in this group. The Oxford group had 52 and the Australian group 196 families with three or more affected individuals and linkage analysis demonstrated another peak of linkage on chromosome 7p. This area may represent a susceptibility allele with high penetrance for endometriosis and deserves further investigation. [22]

Genome Wide Assocation

Another gene mapping technique which holds promise in investigating the inheritance of endometriosis is Genome-wide Association scans. This is a very powerful, hypothesis free technique using single nucleotide polymorphisms (SNPs) to evaluate the genome for risk-associated variations. Two recent advances in technology allow for Genome-Wide Association studies: 1. The International Haplotype Mapping (Hap Map) project which has catalogued millions of SNPs and haplotypes and identified informative areas of the Hap Map. 2. High-Throughput platforms which allow for the investigation of hundreds of thousands up to a million SNPs in thousands of individuals in a single experiment. These Genome-wide Association studies are very powerful methods of searching for informative SNPs in common diseases in a large number of individuals. This information should allow

for the identification of areas of the genome which are associated with endometriosis, even those areas with a minimal, but important effect on the final phenotype. Genome-wide Association studies hold promise of determining areas of interest within the genome which can than be further investigated. [23]

Albertsen et al[24] performed genotyping of 588 endometriosis patients and 1534 controls with the Affymetrix 6.0 GeneChip which contains 906,000 SNPs. After their initial evaluation for ethnicity using the Eigenstrat package the data was analyzed using the Armitage trend test using the PLINK package. They identified 20 SNPs with p-Trend values less than 10^{-4} and 12 autosomal SNPs with p-values between 9.4×10^{-6} and 1.56×10^{-8}. There are a number of genes located near these informative SNPs including FSTL5, ZNF366, HLA-G, TBL2, FOXP2, SNX16, MPDZ, PAPPA and KCTD12. Further studies will help define these associations and determine the significant genes involved in the pathogenesis of endometriosis.

Genomics of Endometriosis

Whereas genetics refers to the heritability of a trait, genomics refers to how genes are expressed. At the most fundamental level, the genome is a list of the DNA sequences of all of the chromosomes with annotation of genes, introns and exons, promoters, and regulatory sequences. Genomics can be defined as any study that takes a global approach to examination of a genome; we will define it here as studies of global gene expression. The DNA microarray is one of the most important tools of genomics.

DNA microarray technology

All of the cells in our bodies contain the same set of chromosomes with the same set of genes, the genome, but each differentiated cell type expresses only a fraction of the total available genes. DNA microarray technology allows a determination of which genes are expressed in a given cell type under basal conditions. Perhaps more importantly, the technology can measure changes in gene expression in response to disease, inflammation, pharmaceutical agents, hormones, growth factors, developmental changes, or other deviations from homeostasis. In regard to endometriosis, DNA microarrays allow a determination of gene expression under basal conditions and in the presence of the disease. Examples of medical advances that can be made based on insights into gene expression include the development of better treatments of disease and new diagnostic tests, as well as a better understanding of the pathology of disease; these concepts are relevant to endometriosis as well as other diseases.

Methods for obtaining RNA for analysis of gene expression in endometriosis have been described for intact eutopic and ectopic endometrial tissue.[25] DNA microarray technology takes advantage of the fundamental nature of DNA and RNA to bind to complementary strands of nucleic acids.[26] On a DNA microarray, single-stranded sequences of DNA, corresponding to specific genes, are arrayed on a matrix such as a glass microscope slide or a cassette. RNA is extracted from the tissue or cells of interest and incubated with the microarray. The complementary base pairing sequence structure of DNA and RNA allows the RNA in the sample to bind to the DNA sequence on the microarray. The gene sequences

on the microarray to which RNA from the tissue sample bound are identified to develop gene expression profiles for that tissue.

Gene expression profiles in endometriosis

Two experimental paradigms have been used to examine the genomics of endometriosis: (1) Comparison of gene expression of eutopic endometrium to ectopic endometrium of the same patient [25, 27] or the same animal in animal models[28], and (2) Comparison of eutopic endometrium from women with endometriosis to eutopic endometrium from women without endometriosis. [29-31] The goals of the two approaches are different. When eutopic and ectopic endometrium are compared from women with endometriosis, the goals include identification of unique features of the ectopic endometrium that could lead to better treatments for endometriosis through identification of new therapeutic targets or to noninvasive diagnostic tests for endometriosis. This type of data will also lead to a better understanding of the pathology of the disease. The goals of comparing eutopic endometrium from women with endometriosis to that from women without endometriosis include a search for factors that may prevent implantation in women with endometriosis (i.e., the causative factors of endometriosis-associated infertility), identification of factors in endometrium that could trigger development of endometriosis when the endometrium escapes from the uterus (in support of the hypothesis that the endometrium of women who develop endometriosis is different from that of women who do not develop the disease), and a predictive measure to determine which women might develop endometriosis.

The two most useful types of information that can be derived from DNA microarray data are lists of differentially expressed genes and groupings of differentially expressed genes into related functional groups (also called gene ontologies). Lists of individual genes that are up- or down-regulated are especially useful as a means of identifying potential targets for diagnostic tests or for new treatments. Specialty software programs such as Ariadne Pathway Studio (v6.2, Ariadne Genomics, Rockville, MD) use lists of differentially expressed genes to search for common regulatory factors in an attempt to identify the upstream ligands responsible for the aberrant gene expression in a disease state such as endometriosis. The identification of families of genes that are up- or down-regulated can shed light on pathological etiologies. Gene ontologies may identify differentially expressed gene families that overlap from different research groups using different microarray platforms when comparisons of individual genes do not show overlap. Both of these means of analyzing data are valuable to our understanding of cellular events in endometriosis.

If we examine data obtained from DNA microarray experiments that compared gene expression in eutopic endometrium to that of ectopic endometrium, only 10 genes showed differential expression in three or more experiments in human studies. The list includes caldesmon 1, CD14 antigen, cholinergic receptor muscarinic 3, complement component 1r, myosin heavy polypeptide 11 (MYH11), phorbol-12-myristate-12-acetate-induced protein 1, retinoic acid receptor responder 1, ribonuclease A family 1, thrombospondin 1 (THBS1), and tissue inhibitor of metalloproteinase 3 (TIMP3) (Table 1). There are a number of valid reasons for the lack of overlap among the different microarray studies. Many of the data sets were published before whole human genome microarrays were available. Those experiments

used arrays with only a fraction of the genes in the genome, and platforms from different manufacturers contained different subsets of the genome. Thus the overlap among reported datasets can only be as complete as the overlap of genes on the microarrays that were used. Other reasons for the shortness of the list of overlapping genes include variability among human subjects, samples that may have been obtained in the proliferative versus the secretory phase of the reproductive cycle, and the hypothesis that endometriosis samples may be different in lesions obtained from ovarian versus peritoneal versus deep pelvic lesions.[32] There are also differences in the reliability of different microarray platforms.

The ten genes identified in endometriosis microarray studies listed above show few obvious relationships to each other. Two of the genes share the gene ontology of defense, two are cytoskeleton genes, and two others share the ontology of signal transduction. Application of the bioinformatics software Ariadne Pathway Studio (v6.2, Ariadne Genomics) identified additional relationships. For example, expression of four of the genes (THBS1, TIMP3, CD14, and MYH11) is regulated by the transcription factor SP1 and by the transforming growth factor β1 signal transduction pathway. Three of those genes (THBS1, TIMP3, and CD14) appear to also share regulation by additional factors (mitogen-activated protein kinases 1 and 14, protein kinase C, interleukin 6, nuclear factor- κB, and jun). The sharing of regulatory factors by these genes implicates those factors in endometriosis. It is likely that additional genes that are regulated by these factors are also involved in endometriosis but are not on the list in because of the limitations of the microarray studies described above.

When data from DNA microarray studies of ectopic versus eutopic endometriosis in humans [25, 27] are merged with microarray data from surgically induced animal models of endometriosis[28] the number of differentially expressed genes is more extensive (data not shown). The list of differentially expressed genes is longer because most of the microarrays used for animal studies used whole genome arrays which allow more complete analysis of gene expression. Each gene ontology identified by the human studies is expanded in the merged list of genes. In descending order, the ontologies include signal transduction (50 genes), defense (including inflammatory and immune response genes, 43 genes), proteinases and their regulators (26 genes), cell cycle (25 genes), cytoskeleton (14 genes) and extracellular matrix (13 genes). Two new ontologies, transcriptional regulation (20 genes) and cell adhesion (17 genes) were added to the list of ontologies when data from animal studies were merged with the human data. Recently, Zhao and coworkers [33] took the analysis of gene ontologies a step further by performing a gene set enrichment analysis on endometriosis microarray data that had been deposited in public databases. Their results identified that pathways related to the immune system and immune disorders are highly up-regulated in endometriosis.[33]

Data from genomics studies support many of the hypotheses regarding the etiology of endometriosis. For example, changes in cell adhesion factors and proteinases and their regulators that have been proposed to play a role in the adhesion and invasion of endometrial tissue in the development of endometriosis[32] are shown to be up-regulated in genomics studies.[33] Moreover, angiogenic factors, growth factors, and hormone receptor genes are also up-regulated in the genomic studies. [18] Perhaps the most interesting aspect of the gene expression studies is the highlighting of the up-regulation of inflammatory response

gene.[25, 33] The inflammatory nature of endometriosis has long been recognized[32]; the genomics studies further advance the concept that aberrant communication between ectopic endometrial cells and immune system cells participating in the inflammatory response contribute to the development and persistence of endometriosis. [25, 34] Collectively, the studies cited above support the hypothesis that endometriosis is the result of abnormal expression or regulation of certain key genes.

Eutopic endometrium of women with endometriosis versus endometrium of women without endometriosis

Three publications have addressed the genomics of endometrium of women with endometriosis compared to that of women without endometriosis. [29-31] Of the genes reported by these three groups (266 total genes reported), only one was identified as differentially expressed in more than one of the studies. Solute carrier family 1, member 1 [SLC1A1] was down-regulated in 2 of the 3 studies. The lack of overlap among these three studies is disturbing; however, the same caveats described above apply here. None of these groups used whole genome DNA microarrays. Moreover, the experiments were not designed to determine whether the differential expression of genes in eutopic endometrium was a result of the presence of endometriosis or a cause of the disease.

Genomics studies have increased the depth of our understanding of the underlying pathology of endometriosis and have highlighted the role of the immune system in endometriosis. However, genomics studies have not yet delivered on the hope of noninvasive diagnostic tests for endometriosis. Moreover, new treatments based on our increased understanding of the disease remain in the future.

Conclusions

Endometriosis remains a significant cause of morbidity and reduces quality of life in reproductive age women. The etiology of endometriosis remains enigmatic but it does appear to cluster in families. Genetic studies have demonstrated an increased frequency of the disease in close relatives with the type of inheritance most likely polygenic/multifactorial. Genomic studies continue to explore differences in gene expression and understanding the basic biology of the disease. Future genomic studies may lead to new noninvasive diagnostic strategies as well as possible new therapies. Improved understanding of the genetics and genomics of endometriosis will contribute to our understanding of the basic biology of endometriosis.

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Table 1

Differential gene expression between eutopic and ectopic endometrium: confirmed in greater than or equal to 3 human DNA microarray studies.

Accession No.		Gene Name	Gene Ontology
NM_033139	↑	caldesmon 1 (CALD1)	Cytoskeleton
NM_000591	↑	CD14 antigen (CD14)	Defense
NM_000740	↑	cholinergic receptor, muscarinic 3 (CHRM3)	Signal transduction
NM_001733	↑	complement component 1r (C1R)	Defense
NM_002474	↑	myosin, heavy polypeptide 11 (MYH11)	Cytoskeleton
NM_021127	↓	phorbol-12-myristate-13-acetate-induced protein 1 (PMAIP1)	Signal transduction
NM_206963	↑	retinoic acid receptor responder 1 (RARRES1)	Cell cycle
NM_198235	↑	ribonuclease, RNase A family, 1 (RNASE1)	Nucleic acid regulation
NM_003246	↑	thrombospondin 1 (THBS1)	Extracellular matrix
NM_000362	↑	tissue inhibitor of metalloproteinase 3 (TIMP3)	Proteinase regulation