Reproductive Sciences
2014, Vol. 21(8) 966-972

DOI: 10.1177/1933719114526473
rs.sagepub.com
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Genes Downregulated in Endometriosis Are Located Near the Known Imprinting Genes

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Abstract

There is now accumulating evidence that endometriosis is a disease associated with an epigenetic disorder. Genomic imprinting is an epigenetic phenomenon known to regulate DNA methylation of either maternal or paternal alleles. We hypothesize that hypermethylated endometriosis-associated genes may be enriched at imprinted gene loci. We sought to determine whether downregulated genes associated with endometriosis susceptibility are associated with chromosomal location of the known paternally and maternally expressed imprinting genes. Gene information has been gathered from National Center for Biotechnology Information database geneimprint.com. Several researchers have identified specific loci with strong DNA methylation in eutopic endometrium and ectopic lesion with endometriosis. Of the 29 hypermethylated genes in endometriosis, 19 genes were located near 45 known imprinted foci. There may be an association of the genomic location between genes specifically downregulated in endometriosis and epigenetically imprinted genes.

Keywords

endometriosis, imprinting genes, chromosomal location, hypermethylation

Introduction

Endometriosis represents a common gynecological disease, but the mechanisms contributing to the establishment of this disorder lesions still remain controversial.[1] Retrograde transplantation of endometrial tissue into the pelvic cavity at the time of menstruation is believed to account for peritoneal endometriosis. Nobody explains why most women of reproductive age experience retrograde menstruation but do not develop endometriosis.[2]

One possibility is that eutopic endometrium in women who will develop endometriosis in later life has increased proliferative potential, which promotes establishment of endometriotic lesions, possibly through aberrant expression of specific genes in the eutopic endometrium. Epigenetic alterations have been explored in pathological conditions such as endometriosis. The previous report showed that many decidualization-related genes were downregulated in eutopic endometrium of endometriosis.[3-10] The promoter region of these genes has been hypermethylated in endometriosis when compared with controls. Twenty-nine endometriosis susceptibility genes were silenced by epigenetic aberration (Table 1, left column). These genes are considered to be upregulated during the decidualization process for successful implantation and pregnancy, suggesting that dysfunctional expression of decidualization-related genes in endometrium appears critical to endometriosis.[56]

The decidualization process is characterized by terminal differentiation of endometrial stromal cells.[57] Synchronization of embryonic development with the stromal decidualization is a key step for the establishment of successful implantation and pregnancy. A defective decidualization response might be associated with a reduced differentiation and a relatively increased proliferative potential. Targeted deletion of decidualization-related genes such as HOXA10 and cyclooxygenase 2 has demonstrated marked infertility.[58,59] A decrease in these gene expressions in eutopic endometrium has been found in women with endometriosis-associated infertility.[60] Promoter hypermethylation of eutopic endometrium is considered to be the leading mechanism for epigenetic gene regulation in women who will develop endometriosis in later life.[61]

Genomic imprinting, DNA methylation, and chromatin remodeling are known to regulate transcription of target genes. Genomic imprinting is an epigenetic process by which the male and

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Table 1. Endometriosis-Susceptibility Genes Silenced By Epigenetic Aberration (Left Column) Located on Chromosomes Where Human Imprinting Genes Are Located (Right Column).[a]

Genes Specifically Downregulated in Endometriosis (Endometriosis Susceptibility Genes)			The Known Imprinted Genes Near Endometriosis-Susceptibility Genes			
Location	Gene Symbol	Reference	Location	Gene Symbol	Paternal/Maternal	Reference
1p31.2	PGE2R	11,12	1p31 AS	DIRAS3	Paternal	13-15
2q14.2	IL1RN					
2q33-q35	IHH	16	2q33.3 AS	GPR1	Paternal	17
			2q33.3	ZDBF2	Paternal	
4q13-q21	IL8					
5q23	HBEGF					
6p21.2	CDKN1A		6q21	AIM1, LIN28B	Paternal	18,19
			6p21 AS	BTNL2	Maternal	
6p22.3	PRL					
6q25.1	ESR1					
7p13-p12	IGFBP1	20	7p13 AS	GLI3	Maternal	21
7p15.2	HOXA10	22,23	7p15-p14 AS	HOXA5, HOXA4, HOXA2, HOXA11, HOXA3	Maternal	24-26
			7p15-p14	EVX1	Paternal	
7p21	IL6					
7p21.2	TWIST					
9p21	CDKN2A		9q21.13	C9orf85	Paternal	
9p21	CDKN2B		9q21.32	FLJ46321	Maternal	
9q34	PAEP		9q34.3	PHPT1	Maternal	27-30
			9q34.3	EGFL7	Paternal	
11q22-q23	PR-B	6	11q22.3	ZC3H12C	Paternal	31-34
			11q22.3 AS	KBTBD3	Paternal	
12p13.1-p12	CDKN1B	35	12p12.1 AS	ABCC9	Maternal	36-38
			12p13.31 AS	RBP5	Maternal	
12p13.33	FKBP4	38	12p13.31 AS	RBP5	Maternal	37
13q14.1	FOXO1	39	13q14-q21 AS	HTR2A	Maternal	
			13q14.2	RB1	Maternal	
16q22.1	CDH1	5,40	16q22.1 AS	ACD	Maternal	41,42
17q11.2	CCL8		17q11	PYY2	Paternal	43
19q13.1	TGFbeta	44	19q13.1	CHST8	Maternal	
19q13.3-q13.4	IL11	45	19q13.4 AS	PEG3, ZIM2	Paternal	46-49
			19q13.4 AS	MZF1	Maternal	
			19q13.4	MIMT1, ZNF264	Paternal	
			19q13.4	LILRB4	Maternal	
20p12	BMP2	50	20p12.1	C20orf82, ISM1	Paternal	51
20q12-q13	SRC1		20q13.3	COL9A3, GNAS	Maternal	52-55
			20q13.32 AS	GNASAS, MIR296, MIR298	Paternal	
			20q13.32	SANG	Paternal	
			20q13.33	C20orf20	Maternal	
22q12.2	LIF		22q12.2	FLJ20464	Paternal	
22q12.3	TIMP3					
20q13.1	C/EBPbeta					
Xp11.22-p11.21	TRO					

[a] The imprinted gene information has been gathered from NCBI database geneimprint.com (http://www.geneimprint.com/site/genes-by-species). Left column, 29 hypermethylated genes were included as our working data set. Right column, 45 known imprinted genes that are located within or in close proximity to endometriosis susceptibility genes.

female germ lines guide the allele-specific DNA methylation marking and histone modification onto specific gene regions of parental alleles.[62] The majority of imprinted genes tend to be nonrandomly grouped in clusters.[13] The unique chromatin packaging at certain gene promoters provides these genomic loci how and when a gene becomes accessible or inaccessible to the transcription machinery. Since, in mammals, imprinted genes are critical for normal development, growth, behavior, and numerous physiological processes, endometriosis susceptibility genes affected by the loss or duplication of the active allele can cause disease. Misregulation of the clusters of imprinted genes is implicated in several diseases including Beckwith-Wiedemann syndrome, Silver-Russell syndrome, Prader-Willi syndrome, Angelman syndrome, pseudohypoparathyroidism, transient neonatal diabetes, metabolic syndrome, and cancer.[13] This phenomenon may expand the significance of the epigenome in

endometriosis development. Simultaneous hypermethylation in targeted decidualization-related genes via the unique chromatin packaging may be an important mechanism producing rapid epigenetic variation in endometriosis development. Although downregulation of decidualization-related genes has been implicated in endometriosis, genomic interactions between endometriosis-associated hypermethylated genes and epigenetically imprinted genes are poorly understood.

Therefore, we hypothesize that hypermethylated endometriosis genes may be enriched at imprinted gene loci. The objective of this study was to determine an association of the genomic location between hypermethylated gene sites in endometriosis and known imprinted gene regions.

Materials and Methods

A computerized literature search was performed to identify relevant studies reported in English language. We searched MEDLINE electronic databases (http://www.ncbi.nlm.nih.gov/sites/entrez) published up to October 2013, combining the key words "endometriosis," "maternal," "paternal," "imprinting," and "programming." Various combinations of the terms were used, depending on the database searched. The imprinted gene information has been gathered from National Center for Biotechnology Information (NCBI) database geneimprint.com (http://www.geneimprint.com/site/genes-by-species). Each gene was also linked to NCBI Entrez Gene pages (http://www.ncbi.nlm.nih.gov/sites/entrez). In addition, references in each article were searched to identify potentially missed studies.

Results

The analysis of parent-of-origin patterns of expression resulted in the identification of 83 imprinted genes in human, including 55 paternally expressed genes (PEGs) and 28 maternally expressed genes (MEGs) (http://www.geneimprint.com/site/genes-by-species). Among a total of 83 genes identified as parentally imprinted genes, 16 genes were associated with human reproduction and embryogenesis. They include 10 PEGs (DIRAS3,[14-16] BMP8B,[63-65] CYP1B1,[66,67] ZFAT,[68-70] ZFAT-AS1,[68-70] IGF2,[70-74] IGF2AS,[75] MIMT1,[76] MIR296,[77,78] and MIR298[77,78]) and 6 MEGs (DVL1,[72,79-82] FGFRL1,[83] CDKN1C,[84] PEG10,[85] KCNQ1DN,[86] and KCNQ1[87]; Supplementary data 1). Supplementary data 1 shows the known paternally and maternally expressed imprinting genes associated with human reproduction and embryogenesis.

Some researchers have performed an integrative pathway analysis of a microarray gene expression and proteomics data sets in endometriosis.[88-92] We obtained a comprehensive pathway annotation set of the endometriosis susceptibility genes specifically defined based on insufficient decidualization from knowledge-based public resources.[88] Table 1 shows endometriosis susceptibility genes silenced by epigenetic aberration located on chromosomes where human imprinting genes are located. Supplementary data 2 shows the endometriosis-susceptibility genes that are located in close proximity to the known imprinting genes. In all, 29 hypermethylated genes were previously analyzed[89-91] and included as our working data set. We have examined the relation between these genes and their location in the human genome that is available in the imprinting gene database (http://www.geneimprint.com/site/genes-by-species).

Of the 29 hypermethylated genes, we emphasized 19 pairs of interactions between endometriosis-susceptibility genes and parentally imprinted genes with potential implication. A total of 19 genes were located near 45 known imprinted foci (Figure 1).

Discussion

This study revealed that among 29 decidualization-related genes specifically downregulated in endometriosis, 19 genes were located within, or in close proximity to, the 45 known imprinting gene loci. However, there has been so far virtually no data that 19 genes are located directly adjacent to these imprinted genes in a "head-to-head" orientation that regulates adjacent genes organized in a divergent fashion. This study also does not confirm functional interactions between endometriosis genes and imprinted genes.

The following 2 or 3 examples may exemplify functional interactions between genes associated with disease susceptibility and imprinted genes. First, Greig cephalopolysyndactyly syndrome (GCPS) is a rare autosomal dominant disorder, caused by genetic alterations in the GLI3 imprinting gene. Greig cephalopolysyndactyly syndrome is mainly characterized by craniofacial abnormalities and limb malformations. Wagner et al showed hemizygosity for the genes of IGFBP1 and GLI3, located on 7q13, in patients with GCPS.[93] Second, a monoallelic loss of FOXO1 gene and RB1 imprinting gene, located on 13q14, was identified in some cases of cellular angiofibroma, a rare benign stromal tumor of the female genital region.[94] Loss of heterozygosity or epigenetic alterations in targeted genes colocalized or near localized within certain imprinted loci have been explored in these disorders, which may appear to result from altered activity of one or more genes near the imprinted gene cluster. In future, genome-wide analysis of the location of histones and histone modifications will be analyzed by isolation and purification of DNA bound to histones and protamines for evaluating DNA methylation status of candidate genes in endometriosis.

Allele-specific DNA methylation is well studied in imprinted domains by parent-of-origin mechanism, with the maintenance of genomic imprinting memory.[13] On the other hand, differential epigenetic marking or epigenetic asymmetry is found more commonly at nonimprinted loci, where the DNA methylation is dictated by the local haplotype. Epigenetic alterations in targeted genes colocalized or near localized within certain imprinted loci have been explored in pathological conditions such as male infertility. Hammoud et al reported that, unlike fertile men, infertile men had changes in the amount of H3 lysine 4 or H3 lysine 27 methylation retained at developmental transcription factors and certain imprinted genes.[95] The genome-wide analysis of epigenetic markings in the sperm of infertile men demonstrates differences in composition and epigenetic markings compared

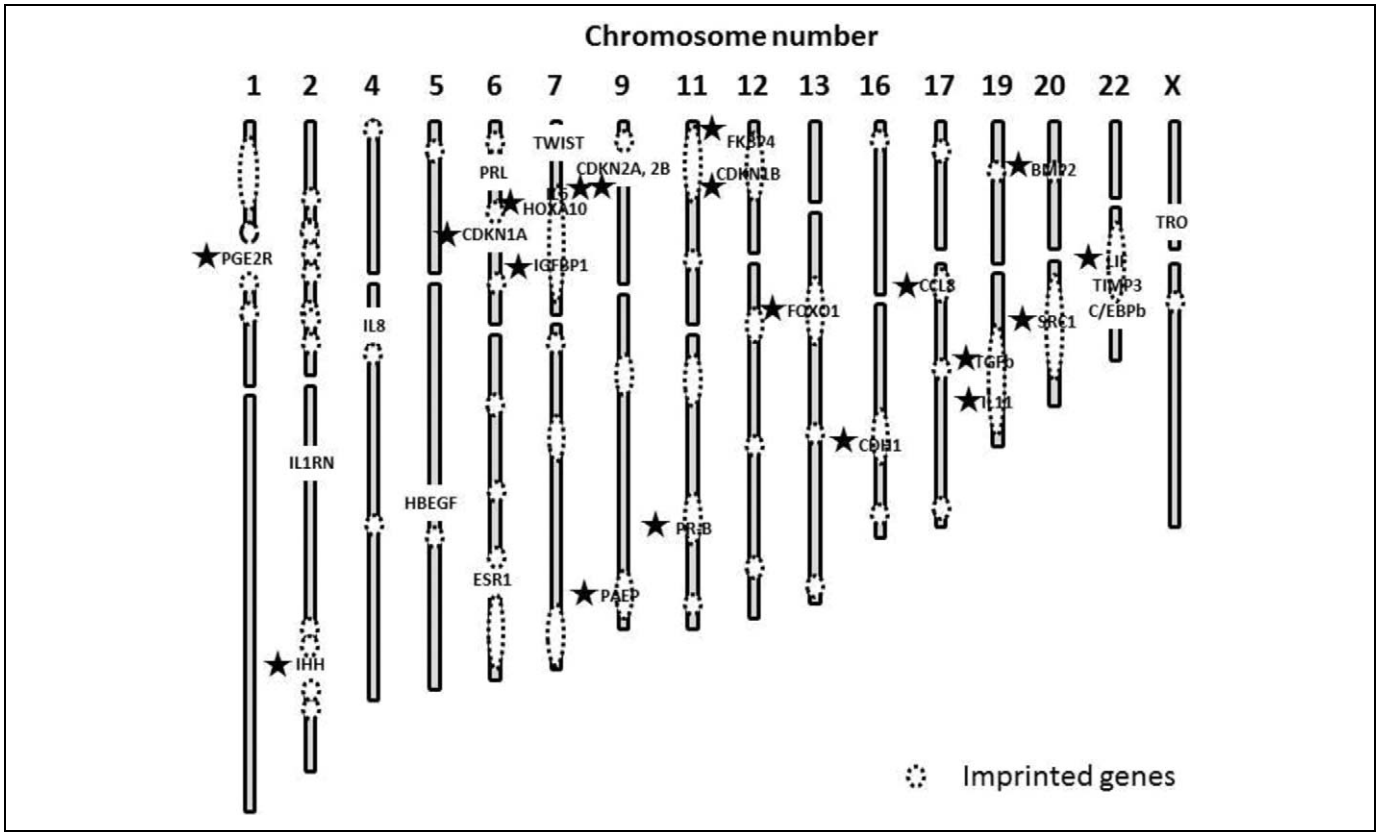

Figure 1. Geographical interactions between endometriosis-susceptibility genes and parentally imprinted genes of the 29 hypermethylated genes, 19 genes (⋆) were located within, or in close proximity to, 45 known imprinted foci (dot circle).

with fertile men, especially at certain imprinted and developmental loci.

The gametic differentially methylated regions (DMRs) are directly inherited from the mature gametes during spermatogenesis or oogenesis at fertilization. The somatic DMRs are only acquired in postimplantation embryos during embryogenesis. The analysis of endometriosis-specific genes enriched in a set of DMRs using the mature gametes or somatic cells in patients with endometriosis may offer the opportunity to elucidate the dynamics of genomic methylation of gametic or somatic imprinting.

The fetal origin hypothesis of a wide range of adverse outcomes in later life, including adult obesity, type 2 diabetes, hypertension, and cardiovascular diseases, in persons born with fetal malnutrition has been well established.[96] Maternal nutrition seems to play a key role in fetal programming of metabolic and cardiovascular risks.[97] Similar to developmental origins of health and disease theory, maternal conditions, lifestyle factors, and intrauterine adverse environment during pregnancy may increase endometriosis risk in adulthood.[11] Decidualization resistance resulting from the restriction of intrauterine development of fetal uterus is considered as an important cause of endometriosis in adults.[12,17] Decline in decidualization-related genes in the fetus may contribute to endometriosis and infertility in her later life. Shared genetics between endometriosis and infertility could account for this association. Epigenetic imprinting can underlie the described pathomechanisms.

In conclusion, the present study found that there is an association of the genomic location between genes specifically downregulated in endometriosis and epigenetically imprinted genes. Future studies are needed to explore the functional interactions and actual distances/differences in localization between the imprinted genes and hypermethylated endometriotic genes.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This work was supported by Grant-in-aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan to the Department of Obstetrics and Gynecology, Nara Medical University (H. Kobayashi).

Supplemental Material

The online supplemental data are available at http://rs.sagepub.com/supplemental

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