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Review article:

IMPRINTING GENES ASSOCIATED WITH ENDOMETRIOSIS

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ABSTRACT

Purpose: Much work has been carried out to investigate the genetic and epigenetic basis of endometriosis and proposed that endometriosis has been described as an epigenetic disease. The purpose of this study was to extract the imprinting genes that are associated with endometriosis development.
Methods: The information on the imprinting genes can be accessed publicly from a web-based interface at http://www.geneimprint.com/site/genes-by-species.
Results: In the current version, the database contains 150 human imprinted genes derived from the literature. We searched gene functions and their roles in particular biological processes or events, such as development and pathogenesis of endometriosis. From the genomic imprinting database, we picked 10 genes that were highly associated with female reproduction; prominent among them were paternally expressed genes (DIRAS3, BMP8B, CYP1B1, ZFAT, IGF2, MIMT1, or MIR296) and maternally expressed genes (DVL1, FGFRL1, or CDKN1C). These imprinted genes may be associated with reproductive biology such as endometriosis, pregnancy loss, decidualization process and preeclampsia.
Discussion: This study supports the possibility that aberrant epigenetic dysregulation of specific imprinting genes may contribute to endometriosis predisposition.

Keywords: endometriosis, imprinting gene, pathogenesis

INTRODUCTION

Although endometriosis occurs in ~10 % of women of reproductive age and in ~50 % of women with infertility, the etiology is poorly understood. There is accumulating evidence supporting a concept that endometriosis is a disease associated with a genetic (Albertsen et al., 2013; Xiao et al., 2010) and also an epigenetic disorder (Izawa et al., 2013; Nasu et al., 2011; Guo, 2009; Colón-Díaz et al., 2012). Genetic mechanisms have been ascribed important roles in endometriosis (Albertsen et al., 2013; Xiao et al., 2010). Genetic and network-based pathway analysis of endometrial and endometriotic tissues revealed that the unique endometriosis susceptibility genes include genes encoding cell cycle, growth factors, signal transduction, transcription factors, hormones, cytokines, chemokines and (pro)inflammation, proteases, cell adhesion and motility, stress response and detoxification, immune response and metabolism (Khan et al., 2012; Kobayashi et al., 2013). Kobayashi et al. (2013) recently showed the overlapping genetic signatures between endometriosis development and decidualization process, suggesting that insufficient decidualization

may underline this disorder. Epigenetic alterations reported to date in endometriosis include the genomic DNA methylation of progesterone receptor (PGR)-B, E-cadherin (CDH1), homeobox A10 (HOXA10) (Cakmak and Taylor, 2011), estrogen receptor-beta (ESR2), steroidogenic factor-1 (NR5A1), aromatase (CYP19A1) (Nasu et al., 2011), histone deacetylase inhibition (HDACi) (Colón-Díaz et al., 2012), CDKN2A/B (Kawano et al., 2011), IGFBP-1 (Cakmak and Taylor, 2011), leukemia inhibitory factor (LIF) (Cakmak and Taylor, 2011) and DNA-methyltransferase (DNMTs) (Wu et al., 2007).

There are no data, however, when and how the disruption of such epigenetic changes occurs. DNA methylation lies at the basis of genomic imprinting by epigenetic processes. The parentally imprinting-related epigenetic basis of endometriosis is poorly understood. Imprinted genes are expressed mainly from one parental allele due to an epigenetic mechanism while the other allele is inactivated. The paternally expressed / maternally imprinted genes such as insulin-like growth factor (IGF)-2 were related to promoting cell proliferation, differentiation and metabolism, and are involved in regulating placental size and birth weight (Haggarty et al., 2013). Maternally expressed / paternally imprinted genes reduce the flow of resources to the fetus and are associated with fetal growth restriction, supporting the "parental conflict hypothesis".The previous studies have not yet provided convincing evidence for any susceptibility genomic imprinting genes of endometriosis.

In the present study, from the genomic imprinting database, we search for the first time the parentally imprinted genes that are reported to be involved in the reproductive process including endometriosis.

MATERIALS AND METHODS

The genomic imprinting database is now freely accessible at http://www.geneimprint.com/site/what-is-imprinting.

This database search identified all the existing publications on the imprinting events. In the current version, the database contains 150 human imprinted genes, including information such as gene name, aliases, gene location and expressed allele. Particular emphasis was given on the imprinting genes associated with female reproduction, including endometriosis. Additional information was manually collected by keyword searches of the biomedical literature database PubMed (http://www.ncbi.nlm.nih.gov/pubmed).

RESULTS

The genomic imprinting database contains 90 paternally expressed genes (Figure 1) and 60 maternally expressed genes (Figure 2). Supplementary data show biological functions of a total of 150 imprinted genes, with preferential expression from the paternal or maternal allele. Biological functions of each imprinting gene were manually searched by PubMed. By analyzing the cellular functions of these 150 imprinted genes, they play an essential role in

1. multiple metabolism pathways including
   - diabetes (Mackay and Temple, 2010; El Hajj et al., 2013; Santin and Eirizik, 2013; Travers et al., 2013; Hamed et al., 2012),
   - hyperphagia (Zhang et al., 2012),
   - adipogenesis (Hudak and Sul, 2013),
   - obesity (Zhang et al., 2012; Liu et al., 2013a; Do et al., 2013),
   - atherosclerosis, cardiovascular disease, myocardial ischemia and reperfusion, hypertension (Karagiannis et al., 2013; Small et al., 2011; Zhu et al., 2009),
   - Prader-Willi syndrome (Zhang et al., 2012; Rodriguez-Jato et al., 2013; Gallagher et al., 2002; Rieusset et al., 2013),
   - Angelman syndrome (Rodriguez-Jato et al., 2013; Mabb et al., 2011),

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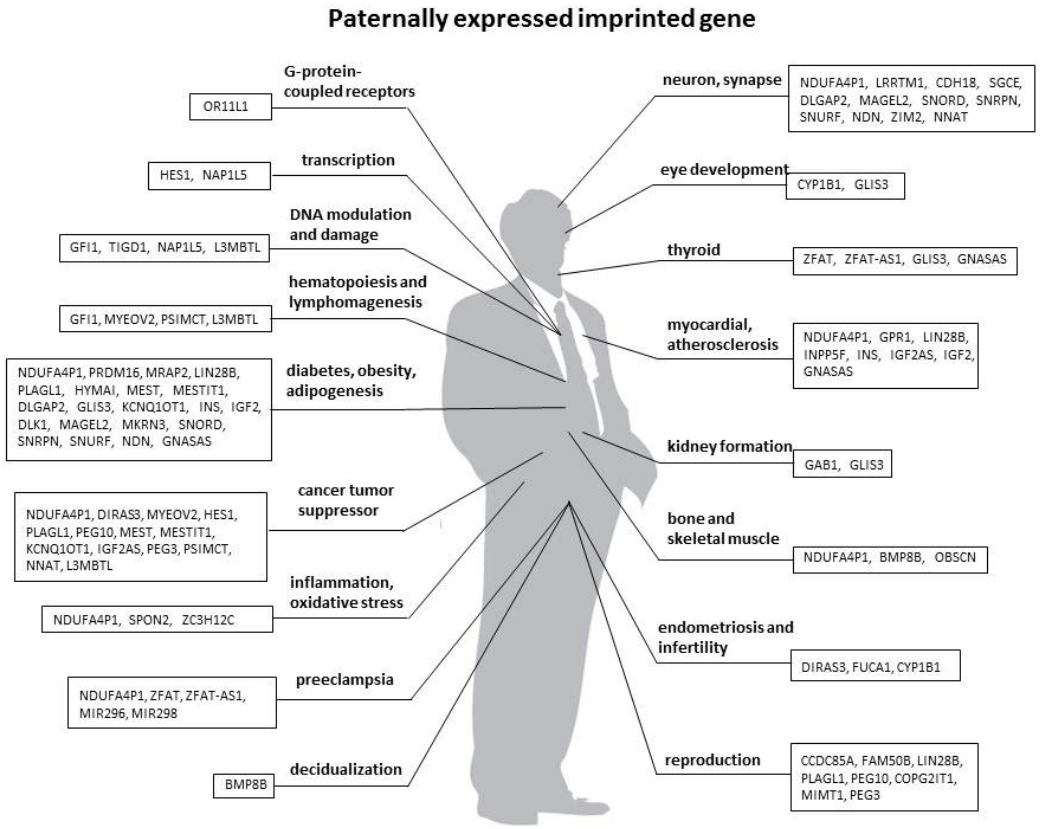

Figure 1: Paternally expressed/maternally imprinted genes
List of paternally expressed and maternally imprinted genes in humans. Imprinting gene information has been gathered from NCBI database (http://www.geneimprint.com/site/genes-by-species)

- Wilms tumor (Jacobi et al., 2013; Hubertus et al., 2013; Xin et al., 2000) and
- Beckwith-Wiedemann syndrome (Zhang et al., 2012; Rodriguez-Jato et al., 2013; Gallagher et al., 2002; Rieusset et al., 2013; Mabb et al., 2011; Hubertus et al., 2013; Xin et al., 2000),

2. the emotional, social and neurological behavior and the appearance of certain neurodegenerative diseases such as schizophrenia, parkinsonism, Huntington disease, auitism, and mature synaptic function (Becanovic et al., 2010; Gos, 2013),
3. malignancies such as Wilms tumor, rhabdomyosarcoma, adrenocortical carcinoma, and lung, ovarian, and breast cancer (Jacobi et al., 2013; Hubertus et al., 2013; Xin et al., 2000; Ozdemir, 2012; Fernández Massó et al., 2013; Zhong et al., 2012; Kim et al., 2012; Britschgi et al., 2013; Ho et al., 2007; Peltomäki and Bützow, 2011),
4. female reproductive system including placental development, fetal growth, infertile, decidualization and endometrial function, menarche, puberty, pregnancy loss such as spontaneous miscarriages or fetal deaths, preeclampsia, endometriosis, sexual behaviors, and spermatogenesis (Albertsen et al., 2013; Izawa et al. 2013; Nasu et al., 2011; Guo, 2009; Colón-Díaz et al., 2012; Khan et al., 2012; Kobayashi et al., 2013; Cakmak and Taylor, 2011; Kawano et al., 2011; Wu et al., 2007; Peltomäki and Bützow, 2011; He et al., 2004; Li et al., 2011; Brandelli and Passos, 1998; Wetendorf and DeMayo, 2012; Sonderegger et al., 2010; Monteiro et al., 2014; Tiberi et al., 2010; Li and Wang, 2009; Kang et al., 2010; Choi et al., 2013; Vinatier et al., 2000; Nyholt et al., 2012), and

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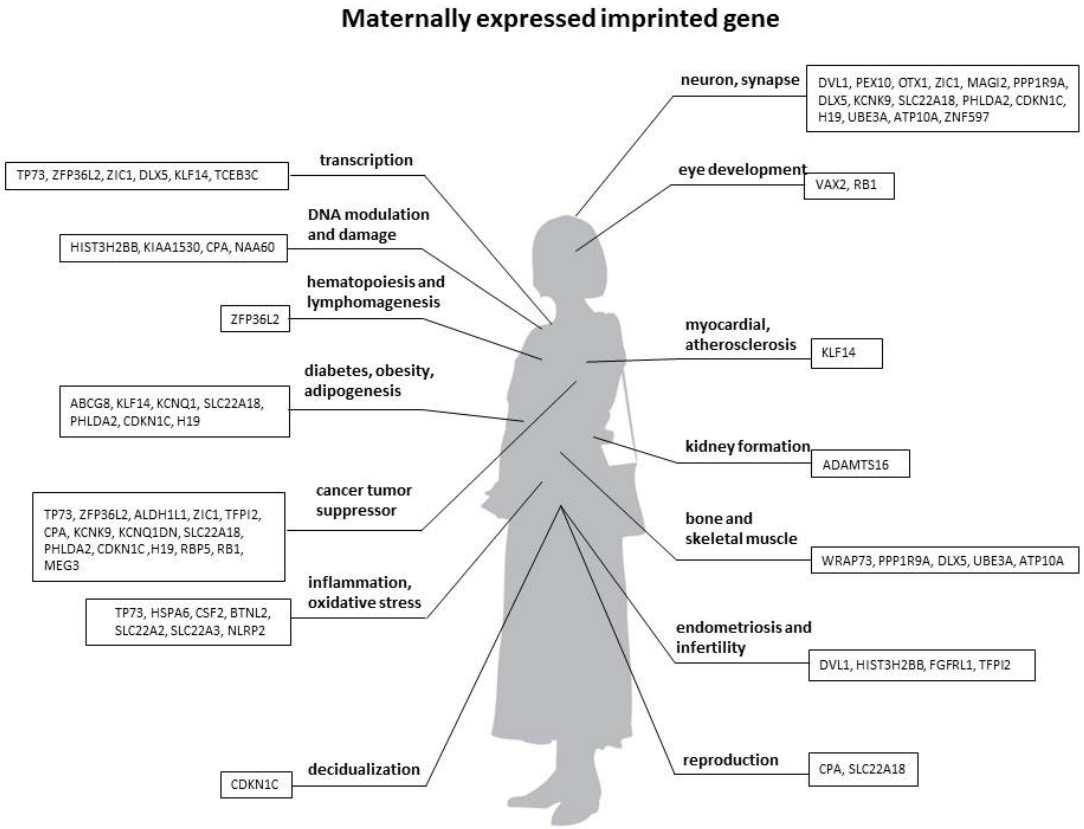

Figure 2: Maternally expressed/paternally imprinted genes
List of maternally expressed and mpaternally imprinted genes in humans. Imprinting gene information has been gathered from NCBI database (http://www.geneimprint.com/site/genes-by-species)

5. other important spheres including
   - developmental (Jacobi et al., 2013; Wetendorf and DeMayo, 2012; Kajimura et al., 2010; Matsumoto et al., 2006; Yuen et al., 2011; Bergman et al., 2013; Lambertini et al., 2012; Godfrey et al., 2011),
   - transport (Balsa et al., 2012; Burger et al., 2010),
   - regulatory (Hubertus et al., 2013; Sturrock et al., 2013),
   - transcriptional, G-protein signaling processes, inflammatory responses (Santin and Eirizik, 2013; Arnett et al., 2007; Liu et al., 2013b),
   - oxidative stress (Srinivasan and Avadhani, 2012),
   - DNA replication and transcription (Nasu et al., 2011; Haggarty et al., 2013; El Hajj et al., 2013; Gos, 2013; Yuen et al., 2011; Du et al., 2013; Schwertman et al., 2013; Tobi et al., 2011; Calicchio et al., 2013),
   - chromatin remodeling (Du et al., 2013),
   - bone and skeletal diseases (Nakabayashi et al., 2004),
   - muscle function (Karagiannis et al., 2013; Nakabayashi et al., 2004; Devaney et al., 2007),
   - energy expenditure (Zhou et al., 2012),
   - eye development and hypothyroidism (Figure 1 and Figure 2).

Aberrant genomic imprinting is an important epigenetic process involved in regulating metabolic disease, the emotional and social behavior, malignancies, placental and fetal growth, reproductive disorders and other important biological processes in later life.

Among 150 differentially expressed parentally imprinted genes, we extracted ten genes that showed a reproductive biology in the set of imprinted genes in human. They include paternally expressed genes

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(DIRAS3 [DIRAS family, GTP-binding RAS-like 3], BMP8B [bone morphogenetic protein 8b], CYP1B1 [cytochrome P450, family 1, subfamily B, polypeptide 1], ZFAT [zinc finger and AT hook domain containing], IGF2 [insulin-like growth factor-2], MIMT1 [MER1 repeat containing imprinted transcript 1], or MIR296 [microRNA 296]) and maternally expressed genes (DVL1 [dishevelled segment polarity protein 1], FGFRL1 [fibroblast growth factor receptor-like 1], or CDKN1C [cyclin-dependent kinase inhibitor 1C (p57, Kip2)]) (Table 1).Biological functions of seven paternally expressed genes associated with female reproduction (Table 1):

DIRAS3, DIRAS family, GTP-binding RAS-like 3

DIRAS3 is a member of the Ras superfamily, and appears to be a putative tumor suppressor gene (http://www.ncbi.nlm.nih.gov/gene/9077). Up-regulation of DIRAS3 expression is associated with infertility and endometriosis (Li et al., 2011).

BMP8B, bone morphogenetic protein 8b

BMP is a part of the transforming growth factor-beta (TGFB) superfamily that induces ectopic bone growth (http://www.ncbi.nlm.nih.gov/gene/656). Progesterone-dependent Ihh, Wnt, and BMP signaling pathways within the endometrium play a role in decidualization, implantation and embryo attachment (Wetendorf and DeMayo, 2012).

CYP1B1, cytochrome P450, family 1, subfamily B, polypeptide 1

The cytochrome P450 metabolizes procarcinogens and synthesizes cholesterol, steroids and other lipids (http://www.ncbi.nlm.nih.gov/gene/1545). This enzyme is involved in eye development. The gene polymorphisms of CYP1B1 in exon 2 codon 119 are also an associated risk factor for endometriosis (Li and Wang, 2009).

Table 1: The imprinted gene candidates associated with the pathogenesis of endometriosis

Paternally expressed genes

Gene Official Symbol	*Official Full Name*	*Location*	*Major biological functions*	*Refs.*
DIRAS3	DIRAS family, GTP-binding RAS-like 3	1p31 AS	tumor suppressor, infertility, endometriosis	42
BMP8B	bone morphogenetic protein 8b	1p35-p32 AS	decidualization	44
CYP1B1	cytochrome P450, family 1, subfamily B, polypeptide 1	2p21 AS	endometriosis, eye development	48
ZFAT	zinc finger and AT hook domain containing	8q24.22 AS	preeclampsia, thyroid disease	72
IGF2	insulin-like growth factor-2	11p15.5 AS	metabolic syndrome, type 2 diabetes, coronary heart disease	56,70, 110
MIMT1	MER1 repeat containing imprinted transcript 1	19q13.4	abortion, stillbirth	73
MIR296	microRNA 296	20q13.32 AS	preeclampsia	50,74

Maternally expressed genes

Gene Official Symbol	*Official Full Name*	*Location*	*Major biological functions*	*Refs.*
DVL1	dishevelled segment polarity protein 1	1p36 AS	infertility, endometriosis	45,75, 76,77
FGFRL1	fibroblast growth factor receptor-like 1	4p16	endometriosis	49
CDKN1C	cyclin-dependent kinase inhibitor 1C (p57, Kip2)	11p15.5 AS	diabetes, endometriosis, cancer	16,31, 78

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ZFAT, zinc finger and AT hook domain containing

ZFAT-AS1, ZFAT antisense RNA 1

The encoded protein, ZFAT, is a DNA binding protein and functions as a transcriptional regulator involved in cell survival and apoptosis (http://www.ncbi.nlm.nih.gov/gene/57623). SNPs of the ZFAT gene are associated with an increased risk of autoimmune thyroid disease. ZFAT expressed in syncytiotrophoblasts is downregulated in placentas from preeclampsia (Barbaux et al., 2012). The ZFAT-AS1 gene encodes a small antisense RNA that regulates the sense strand locus, ZFAT (http://www.ncbi.nlm.nih.gov/gene/594840)

IGF2, insulin-like growth factor 2 (somatomedin A)

The IGF2 gene is involved in cell proliferation, growth, migration, differentiation and survival. Epigenetic changes at this locus are associated with Wilms tumor, Beckwith-Wiedemann syndrome, rhabdomyosarcoma, Silver-Russell syndrome and cardiovascular disease (Bergman et al., 2013) (http://www.ncbi.nlm.nih.gov/gene/3481). IGF2 gene was among the most regulated genes in endometriosis.

MIMT1, MER1 repeat containing imprinted transcript 1

MIMT1 is a non-protein coding gene that forms part of the imprinted PEG3 (paternally expressed gene 3) domain. Loss of paternal MIMT1 expression results in the phenotype of late term abortion and stillbirth in cattle (Flisikowski et al., 2010).

MIR296, microRNA 296

Several miRNAs including MIR296 are found to be dysregulated in placenta of preeclampsia patients (Choi et al., 2013). MIR296 is important for the pathogenesis of preeclampsia (Choi et al., 2013;. MIR296 lies within the GNASAS transcription units (Robson et al., 2012). DNA methylation of GNASAS gene might be associated with small for gestational age and myocardial infarction among women (Tobi et al., 2011).

Biological functions of three maternally expressed genes associated with female reproduction (Table 1)

DVL1, disheveled segment polarity protein 1

Wnt stimulation induces recruitment of DVL to the G-protein coupled frizzled (FZD) receptors (Kawano et al., 2011). DVL plays a key role in relaying cellular information for several developmental pathways such as cell proliferation, migration, polarity, terminal differentiation, and the self-renewal of stem cells (Dillman et al., 2013). DVL1 encodes a cytoplasmic phosphoprotein and is a substrate of NR1I2 (nuclear receptor subfamily 1, group I, member 2), which is a family of serine / threonine kinases that have been associated with differentiation of epithelial and neuronal cells (http://www.ncbi.nlm.nih.gov/gene/1855) (Elbert et al., 2006). Charcot-Marie-Tooth disease has been mapped to the same region as DVL1. This disease is the hereditary neuropathy characterized by muscular atrophy and weakness in the distal parts of the legs (Ostern et al., 2013). Failures in Wnt signalling are a cause of infertility and endometriosis (Sonderegger et al., 2010).

FGFRL1, fibroblast growth factor receptor-like 1

FGFRL1 influences mitogenesis and differentiation (http://www.ncbi.nlm.nih.gov/gene/53834). The FGF2 754C/G polymorphism may be closely associated with a risk of developing endometriosis (Kang et al., 2010). This gene stimulates cell proliferation at the ectopic endometriotic site.

CDKN1C, cyclin-dependent kinase inhibitor 1C (p57, Kip2)

The encoded protein is a strong G1 cyclin/Cdk-dependent inhibitor and a negative regulator of cell proliferation, suggesting a tumor suppressor candidate

(http://www.ncbi.nlm.nih.gov/gene/1028). Mutations in this gene are implicated in sporadic cancers and Beckwith-Wiedemann syndorome. CDKN1C plays a role in endometrial stromal cell differentiation in the process of decidualization (Qian et al., 2005).

These ten genes are mainly associated with the control of resource usage and reproductive biology such as not only endometriosis, but also abortion, stillbirth, infertility, decidualization, preeclampsia, metabolic syndrome, diabetes, coronary heart disease, eye development, autoimmune thyroid disease, tumor suppression, Wilms tumor, Beckwith-Wiedemann syndrome, rhabdomyosarcoma, Silver-Russell syndrome and Charcot-Marie-Tooth disease (supplementary data).

DISCUSSION

Using the genomic imprinting database, we identified 10 imprinted genes, of which 7 were paternally expressed, and found that these genes are associated with female reproductive functions, including decidualization (BMP8B and CDKN1C), implantation (BMP8B), embryo attachment (BMP8B), abortion (MIMT1), stillbirth (MIMT1 and MIR296), preeclampsia (ZFAT), infertility (DIRAS3 and DVL1) and endometriosis (DIRAS3, CYP1B1, IGF2, DVL1 and FGFRL1). These parentally imprinted genes are necessary for female reproductive system such as normal endometrial development, decidualization, placentation and endometriosis. As described previously, the endometriosis susceptibility genes include growth factors (DIRAS3, IGF2 and FGFRL1), Wnt signal transduction (DVL1), metabolism (CYP1B1), and stress response and detoxification (CYP1B1) (Khan et al., 2012; Kobayashi et al., 2013). Some biological aspects of endometriosis may be explained from a dysregulation of parentally imprinted gene.

Recent advances in sequencing, profiling and pathway technologies allow genome-scale approaches to endometriosis-susceptibility gene discovery, which enables us to look for evidence in support of the genetic hypothesis (Albertsen et al., 2013; Khan et al., 2012; Nyholt et al., 2012; Yuen et al., 2011). Endometriosis is also thought to be an epigenetic disease (Izawa et al., 2013; Nasu et al., 2011; Guo, 2009; Colón-Díaz et al., 2012; Kobayashi et al., 2013; Kawano et al., 2011; Wu et al., 2007; Calicchio et al., 2013). The previous study has shed new light on the overlapping genetic and epigenetic signatures between endometriosis development and insufficient decidualization process, indicating that a number of genes are essential for the decidualization and implantation processes, but up-regulation of a small number of them, including IGF, IGFBP, PRL, HOXA10, FOXO1, C/EBPbeta, IL11 and LIF, are important for this process (Kobayashi et al., 2013). Downregulation of the specific genes related to embryogenesis (the downstream targets of HOXA10) and immunoendocrine behavior (IL11, LIF, TGF-beta, FKBP4, COX2, PGs, FOXO1 and C/EBPbeta) might appear critical to the development of endometriosis (Izawa et al., 2013; Nasu et al., 2011; Guo, 2009; Colón-Díaz et al., 2012; Khan et al. 2012; Kobayashi et al., 2013; Kawano et al., 2011; Wu et al., 2007; Peltomäki and Bützow, 2011; Tiberi et al., 2010; Vinatier et al., 2000; Nyholt et al., 2012; Calicchio et al., 2013;). Kobayashi et al. (2013) reported that the upregulated genes in endometriosis may evolve for the benefit of the endometrial growth, whereas the downregulated genes evolve as a protective mechanism for the endometrial decidualization. The irreversible programming or epigenetics may cause insufficient decidualization, which in turn results in infertility and endometriosis.

Previous studies identified several susceptibility genes that have highlighted the important role of endometriosis development, including IGF, IGFBP, PRL, HOXA10, FOXO1, C/EBPbeta, IL11, LIF, TGF-beta, FKBP4, COX2, and prostaglandins (Izawa et al., 2013; Nasu et al., 2011;

Guo, 2009; Colón-Díaz et al., 2012; Khan et al. 2012; Kobayashi et al., 2013; Kawano et al., 2011; Wu et al., 2007; Peltomäki and Bützow, 2011; Tiberi et al., 2010; Vinatier et al., 2000; Nyholt et al., 2012; Calicchio et al., 2013). We tried to summarize the recent literature that supports a direct or indirect relationship between the novel candidate imprinting genes and the previously reported endometriosis susceptibility genes.

Epigenetic changes induced by various environmental stress factors including nutrition or ecosystem components play a role in interactions between exposed species and chemicals. Chemicals such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and benzo(a)pyrene modulate the mRNA levels of CYP1B1, C/EBPbeta, IL11 and PRL (Cao et al., 2011; Vogel and Matsumura, 2013; Ueng et al., 2005). CYP1B1 is responsible for tumor progression in estrogen receptor-positive breast and endometrial cancers via estrogen metabolism. Allelic polymorphisms at codons 119 and 432 of CYP1B1 gene increases the risk of estrogen-dependent cancer (Sasaki et al., 2003). CYP1B1, IGF2 and HOXA10 genes are reported to be hypermethylated in breast and gastric cancer (Kang et al., 2008; Park et al., 2012). CYP1B1 is transcriptionally regulated by steroidogenic factor-1 (SF-1) (Tsuchiya et al., 2006) or PGE_2, the main product of COX-2 (Yuan et al., 2012). CYP1B1 reduces expression of CDH1 or IGFBP1 (Achary et al., 2000; Collins et al., 2009). Aromatase (CYP19A1) mRNA expression is stimulated by IGF2. ESR2 and Smads, downstream signaling cascades of TGF-beta, participates in the establishment of parent-of-origin-specific expression of IGF2 (Pathak et al., 2009; Szabó et al., 2004; Bergström et al., 2010). IGF2 induced through the transactivation of C/EBPbeta is involved in PRL signaling (Tao et al., 2013; Wang et al., 2011). LIF inhibits the glial cell-derived neurotrophic factor (GDNF)-dependent alteration of the genomic imprinting of Igf2 in mice (Jung et al., 2010). There is bidirectional regulation of insulin receptor signaling and FOXO1 (Liu et al., 2007). DVL1 is a downstream molecule of Wnt signaling (Li et al., 2013). DIRAS3 modulates estrogen and progesterone receptor expression and inhibits PRL-induced mammary gland development and lactation, which results in decreased fertility (Xu et al., 2000). DIRAS3 also induces CDH1 expression and acts as a tumor suppressor gene (Lyu et al., 2013). Taken together, ESR2 and TGF-beta downstream targets, Smads, co-localize to the IGF2 imprinting control region (Bergström et al., 2010).

No convincing evidence has been provided to suggest that these imprinting genes would control the endometriosis susceptibility genes, although some indirect indications are available. At this time, no attempt was made to ascertain whether any of these 10 genes had a “driver” role or had a role of merely a by-stander in the development of endometriosis. Since there are no known driver genes in endometriosis, complex genomic alterations may be responsible for the endometriosis phenotype. The quest for driver imprinting genes or complex genomic alterations can now open new avenues to better understand the mechanisms of endometriosis development.

In conclusion, this study supports the possibility that aberrant epigenetic dysregulation of specific imprinting genes may contribute to endometriosis predisposition. Further investigations are needed to provide biological evidence for the direct association between the novel candidate imprinting genes and the previously reported endometriosis susceptibility genes.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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