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Original Research

Genome-wide association study of recurrent endometriosis related with ovarian cancer

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Summary

Purpose: Endometriosis is a painful and chronic gynecological disease affecting approximately 10% of reproductive-age women and has an increasing rate of recurrence. However, studies of recurrent endometriosis are lacking. Ovarian cancer is related to recurrent endometriosis. In this study, the authors' objectives were to determine whether DNA mutations or variants observed in endometriosis are involved in recurrence and whether genome-wide sequences in recurrent endometriosis tissues are related to DNA mutation patterns of known ovarian cancer cluster genes. *Materials and Methods:* The authors collected two recurrent endometriosis tissue samples in which the patients had severe endometriosis with greater than revised American Society for Reproductive Medicine (rASRM) classification stage 3. They then conducted target next-generation sequencing (NGS). A library was constructed, and the data were compared to those from a comprehensive cancer panel (CCP). *Results:* The bioinformatics analysis revealed 39 gene mutations with significant frequency in the two recurrent endometriosis samples. However, the DNA mutations associated with recurrent endometriosis differed from the CCP variants. *Discussion:* The genes identified herein are associated with DNA repair, transcription, fibrosis, and proliferation in the endometrium and ovary-induced endometriosis or ovarian carcinoma.

Key words: Endometriosis; Recurrence; Ovarian neoplasm; Next-generation sequencing.

Introduction

Endometriosis is a painful and chronic gynecological disease affecting approximately 10% of reproductive-age women, causing infertility and the development of adhesions due to extra-uterine growth of endometrium-like tissue [1]. Endometriosis has mixed traits of benign disease and malignancy. Although endometriosis cannot be termed a premalignant condition, epidemiologic, histopathologic, and molecular data suggest that endometriosis does have malignant potential [2]. Additionally, the medical literature, supported by our meta-analysis, provides sufficient evidence to conclude that women with endometriosis are at an increased risk of developing epithelial ovarian cancer (EOC), predominantly of the clear cell and endometrioid subtypes [3].

Epidemiological evidence of relationships between endometriosis and EOC has been obtained from many studies. In total, 36% of clear cell carcinomas (11–70%) and 10% of endometrioid carcinomas (5–43%) have been associated with endometriosis [4]. Although many studies support a positive association between endometriosis and EOC, many uncertainties remain [5]. Endometriosis is associated with an increased risk of ovarian clear cell, serous low-grade endometrioid cancer, but its role in the development of other histopathological subtypes of ovarian cancer, such as high-grade serous borderline tumor subtypes or borderline tumors, remains unclear [6].

The molecular switch that transforms benign endometriosis into EOC is not well understood. It is highly likely that the inflammatory microenvironment of endometriotic cysts, which are rich in iron-induced oxygen free radicals, trigger DNA damage. Previous studies have recommended following patients with benign ovarian endometriotic cysts and ARID1A mutations [7]. Additionally, several genes have been identified as common risk factors of ovarian cancer.

Recent progress in next-generation sequencing (NGS) technologies and an exponential decrease in the cost of sequencing may help provide more comprehensive genomic information to improve treatment decisions. It will be important to investigate the clinical relevance of NGS for determining the mutational status of disease samples.

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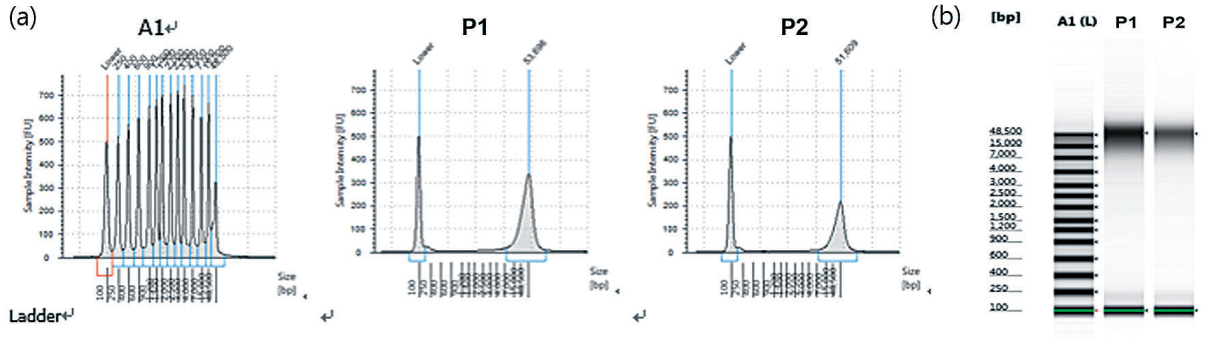

Figure 1. — Results of quality control data from each endometriosis sample. (a) In the DNA profile generated by Agilent TapeStation, P1 and P2 are interpreted as high-quality DNA because of a clearly defined single band. (b) Gel image of the same DNA in P1 and P2 generated by Agilent TapeStation. Ladder (A1), patient 1 (P1), and patient 2 (P2).

In this study, the authors' objectives were to determine whether DNA mutations or variants observed in endometriosis samples are involved in recurrence and whether genome-wide sequences of recurrent endometriosis are related with DNA mutation patterns of known ovarian cancer cluster genes.

Materials and Methods

Endometriosis patients were recruited from the Department of Obstetrics and Gynecology, Tertiary University Hospital, Korea. All samples were obtained after receiving written informed consent, and patient genetic testing for this study was approved by the Institutional Review Board (SCHBC 2013-01-027). The authors recruited two patients from their endometriosis disease clinics with at least two episodes of endometriosis. Endometrial biopsies were isolated during surgical treatment of endometriosis. The samples were collected at the time of primary surgery and snap-frozen within 60 minutes of collection.

Genomic DNA was isolated from the ectopic endometrial tissues using a blood and tissue kit according to the manufacturer's instructions. Genomic DNA was employed as a quality control (Figure 1).

Targeted gene sequencing was performed as previously described [7]. DNA (10 ng) from a comprehensive cancer panel (CCP) covering hotspot mutations in the following ovarian cancer-related genes was used for multiplex polymerase chain reaction (PCR) [8]. Fragment libraries were constructed by DNA fragmentation, barcode and adaptor ligation, and library amplification using an ion DNA barcoding kit according to the manufacturer's instructions. The size distribution of the DNA fragments was analyzed on a Agilent bioanalyzer using a high sensitivity kit. Template preparation, emulsion PCR, and ion sphere particle (ISP) enrichment were performed using an ion template kit according to the manufacturer's instructions. The ISPs were loaded onto a P1 chip and sequenced using an ion P1 sequencing 200 kit. Ion Torrent platform-specific pipeline software (Torrent Suite v2.0) was used to separate the barcoded reads, generate sequence alignment with the hg19 human genome reference, perform target-region coverage analysis, and filter and remove poor signal reads. The alignment file from Torrent Suite was transferred to Ion Reporter (Ion Reporter v4.0) for variant file generation using default parameters.

Bioinformatics analysis was performed as previously described with slight modifications [8]. After a successful sequencing reaction, the raw signal data were analyzed using Torrent Suite v3.4.2. The pipeline includes signal processing, base calling, quality score assignment, adapter trimming, read alignment with the human genome 19 reference, mapping quality control, coverage analysis, and variant calling. After completion of the primary data analysis, the detected sequence variants (single nucleotide variants and insertions and deletions) were compiled in a variant call file (VCF) format. For downstream analysis, variants with a minimum coverage of 500 reads containing at least 10% of the altered allele per total allele were selected. Variant calls were further analyzed using internally developed software that allows variant filtering and annotation using refGene in the University of California, Santa Cruz, COSMIC v.67, single nucleotide polymorphism database (dbSNP) build 138. To minimize the number of false-positives, variants were filtered with a normal population variant database, the Korean Personal Genome Project (KPGP; http://opengenome.net/) [9]. Reported loci in dbSNP were included in the analysis, since filtering out dbSNP loci may cause a loss of true reliable genomic alterations [10]. After filtering, the comparison of significantly altered target genes was performed by searching the cBioportal mutations between our results and ovarian serous cystadenocarcinoma (TCGA, Nature 2011, 316 samples).

Results

Patients 1 and 2 were had recurrent endometriosis. Only two samples were analyzed by NGS, both of which were collected more than once (Table 1). The two patients were also diagnosed with serous cystadenoma, and this was accompanied by stomach cancer, adenomyosis, and adhesion endometriosis in patient 2. Neither subject had gone through menopause or delivery (Table 2). A gonadotropin-releasing hormone agonist was used for the treatment of endometriosis before the operation.

The variant type of recurrent endometriosis is indicated in Table 3. The variant types of synonymous coding and the intron region occupied a higher percentage compared with the others in patient 1 and 2 (66.7 and 68.2%) (Table 3). Variants acquired from the CCP platform and those

Table 1. – *Summary of next-generation sequencing results from each clinical sample as recurrent endometriosis.*

	P1	P2
Number of mapped reads	21715719	21562866
Percent reads on target	98.46%	98.45%
Total aligned base reads	2351141301	2357180213
Total base reads on target	2248386775	2254205882
Bases in target regions	1688650	1688650
Percent base reads on target	95.63%	95.63%
Average base coverage depth	1331	1335
Uniformity of base coverage	90.42%	91.43%
Target base coverage at 1x	99.61%	99.60%
Target base coverage at 20x	98.16%	98.25%
Target base coverage at 100x	95.66%	96.07%
Target base coverage at 500x	81.53%	83.38%

Table 2. – *Clinical data of each patient in this study. Patient 1 (P1) and patient 2 (P2) were diagnosed as recurrent endometriosis with one or more episodes of endometriosis.*

Variable	P1	P2
Age (years)	21	43
BMI (kg/m^2)	22.9	32.0
rASRM	4	3
Recurrence	3	2
Menopause	None	None
CA125†	30.1	20.0
Drug treatment	GnRH agonist	GnRH agonist
Myoma	None	< 4 cm
Anamnesis	NA	Stomach cancer III
Clinical history	Serous cystadenoma	Serous cystadenoma

BMI, body mass index. †CA125 (normal range: 0 < 35 U/ml).

identified following comparison of the gene platform in ovarian cancer and endometriosis were filtered with the KPGP data and synonymous coding (Figure 2). In-house data were not selected. The filtered conditions required that the frequency was less than 0.5. The authors identified 49 filtered mutation genes associated with recurrent endometriosis. The mutations identified in all patients are listed in Table 4. All patients had mutations in 39 common genes (Figure 3): *ADAMTS20*, *ARNT*, *BIRC3*, *CARD11*, *CDH1*, *DCC*, *DICER1*, *DST*, *EPHA3*, *FANC*, *FANCD2*, *FBXO11*, *FGFR3*, *FGFR4*, *GATA2*, *IGF1R*, *ITGA9*, *KIT*, *KMT2C*, *LIFR*, *MBD1*, *MN1*, *MYH11*, *NTRK3*, *NUP214*, *NUP98*, *PDE4DIP*, *PHOX2B*, *PKHD1*, *RAF1*, *ROS1*, *SGK1*, *TAF1*, *TAF1L*, *THBS1*, *TIMP3*, *TRIP11*, *TSHR*, and *ZNF521*. To compact the filtered condition, 18 mutated genes with a frequency less than 0.1 were selected and included the following: *ADAMTS20*, *DCC*, *DST*, *EPHA3*, *FANCA*, *FGFR4*, *IGF1R*, *KMT2C*, *LIFR*, *MYH11*, *NUP214*, *NUP98*, *PDE4DIP*, *RAF1*, *ROS1*, *TAF1L*, *TRIP11*, and *TSHR*.

The comparison of 49 gene mutations detected by NGS and variant information is summarized in Table 4 [11-31]. The 49 mutations compared between the present data and ovarian carcinoma were processed from cBioportal (www.cbioportal.org) using cancer gene mutational information. The variant information of recurrent endometriosis and ovarian carcinoma did not coincide in the selected genes.

Discussion

Although molecular data suggest that endometriosis has potential for malignancy, this is the first report in which a sequence variant within a gene observed in recurrent endometriosis was associated with ovarian carcinoma. Several studies have reported various risk factors related to disease recurrence. High revised American Fertility Society scores and younger age are both risk factors of recurrence [32]. The samples examined herein possess the following risk factors of recurrent endometriosis: high level of pain, absence of pregnancy, and high rARSM stage. Other studies on women with endometriosis with an increased risk of EOC have been performed using a meta-analysis [3]. Luisi *et al*. reported that the estrogen receptor alpha gene poly-

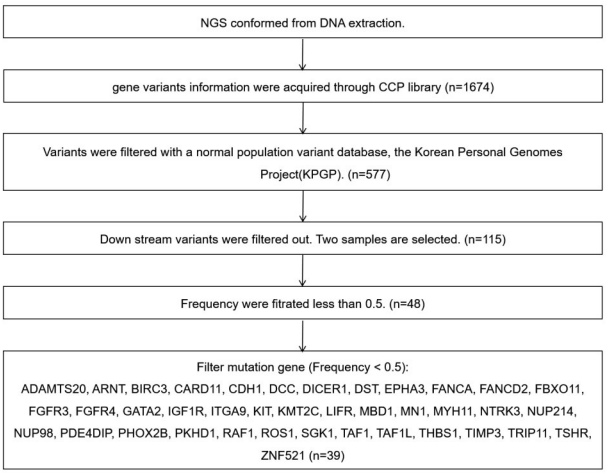

Figure 2. — Flow chart of target gene selection from NGS results. To minimize false-positives, variants were filtered with a normal population variant database, the Korean Personal Genome Project. Downstream region variants were filtered out. Common variant genes were selected.

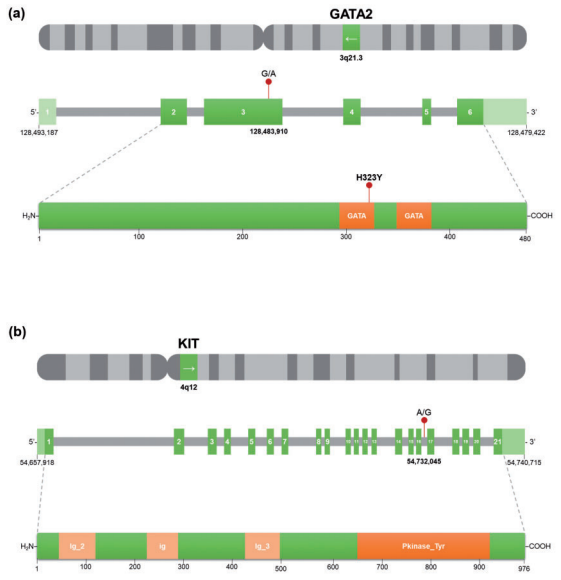

Figure 3. — Schematic illustration of gene information of two representative target genes from 39 candidate genes which might be highly associated between endometriosis and ovarian cancer. (a) GATA2 and (b) KIT. The filtered gene variants were compared with those from ovarian serous cystadenocarcinoma.

* GATA2: GATA-binding protein 2, GATA: Zinc finger GATA DNA-binding domain.

* KIT: KIT proto-oncogene receptor tyrosine kinase, Ig_2: Immunoglobulin-like, ig: Immunoglobulin domain, Ig_3: Immunoglobulin domain, Pkinase_Tyr: Protein tyrosine kinase.

Table 3. – *Summary of each variant type in this study.*

Variant Type	P1 (%)	P2 (%)
Non-synonymous coding	19.48	17.72
Downstream	2.22	2.37
Synonymous coding	28.35	27.58
Intron	38.41	40.64
UTR 3' prime	1.94	2.10
Upstream	1.11	1.37
Splice site region + Intron	4.71	4.66
Stop gained	0.46	0.09
Non-synonymous coding splice site region	0.46	0.55
Start gained	0.28	0.27
UTR 5' prime	0.65	1.28
Splice site region + synonymous coding	0.55	0.46
Frame shift	0.83	0.55
Codon change plus codon insertion	0.09	0.18
Codon change plus codon deletion	0.09	0.09
Codon deletion	0.18	0.00
Codon insertion	0.09	0.00
Frame shift + Stop gained	0.09	0.09

morphism is more associated with recurrence [33]; however, estrogen receptor alpha gene (ESR1) variants were excluded in this study. The present data show that recurrent endometriosis may develop into ovarian carcinoma via the mutation of genes related to DNA repair or transcription. The present authors identified 39 meaningful gene mutations in severe endometriosis. The functions of these 39 genes indicate that recurrent endometriosis is related to DNA binding, DNA repair, transcriptional regulation, reproduction, proliferation, and extracellular matrix molecule relocation (Figure 4). These genes have highly specific mutations and are related to carcinoma development because they belong to CCP genes. The P1 sample was accompanied by serous cystadenoma. The P2 sample was accompanied by stomach adenocarcinoma and adenomyosis. Both samples were accompanied by severe endometriosis and carcinoma. In this study, genome-wide sequencing analysis data were compared with the information of gene mutations in the CCP panel and in eBioportal, in order to discover the association of severe endometriosis with ovarian serous cystadenocarcinoma. As we know, this is the first attempt in genome-wide study. Unexpectedly, the present results are not consistent with the gene mutations identified in the

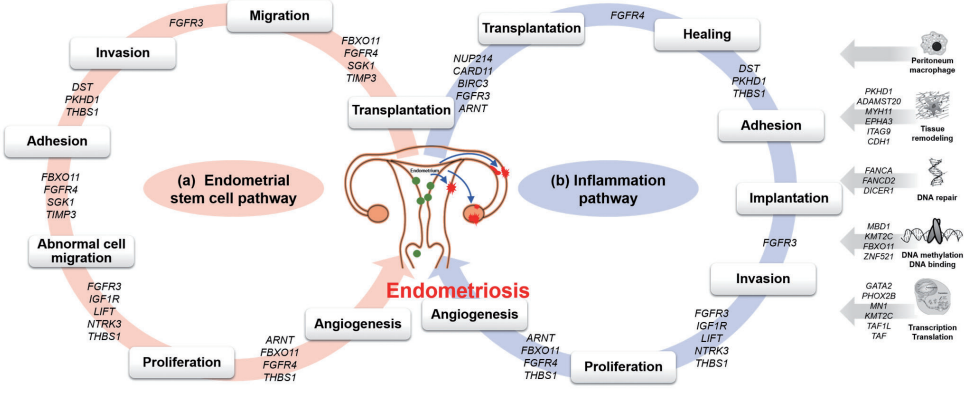

Figure 4. — Schematic illustration of expected functions of filtrated 39 genes in an endometriosis-related study. Normal endometrium influence by various environment of outer uterus. Endometriosis-associated studies report what is induced by endometrial stem cell pathway (a) and inflammation pathway (b).

Table 4. – *Information of filtered genes in this study.*

Gene	Loci	Alleles	Mutation type	dbSNP	Ref
ADAMTS20	chr12:43432895	A/T	Intron	-	[11]
ARNT	chr1:150831926	A/-	Intron	rs34083816	[12,13]
BIRC3	chr11:102328882	T/A	Intron	rs201836037	[14]
CARD11	chr7:2932502	A/T	Intron	rs763910845 (A/G) [15]	
CDH1	chr16:68737363	G/T	5' UTR	-	
DCC	chr18:53410607	G/A	G1031R	-	
DICER1	chr14:95099761	CACACACACAC/-	Intron	rs748368348	[16]
DST	chr6:56573104	C/T	Intron	rs2144405	[17,18]
DST	chr6:56497884	T/C	K4570R	-	[19]
EPHA3	chr3:89479522	T/C	3' UTR	-	
FANCA	chr16:89803354	A/C	Intron	-	
FANCD2	chr3:10046659	A/G	N405S	rs73126218	[20]
FANCD2	chr3:10046624	T/C	T393	rs72492998	[21]
FANCD2	chr3:10046615	C/T	S390	rs112887807	[22]
FGFR3	chr4:1805857	C/A	P587T	rs761163163 (C/T)	[23]
FGFR4	chr5:177097559	T/C	Y764	-	
GATA2	chr3:128483910	G/A	H323Y	-	
IGF1R	chr15:98913241	G/T	G596V	-	
ITAG9	chr3:37513832	G/C	V323L	rs751444216 (G/T)	
KIT	chr4:54732045	A/G	Intron	rs371533703 (A/T)	
KIT	chr4:54732044	G/T	Intron	rs367698651	[24]
KIT	chr4:54732044	GA/TG	Intron	-	
KMT2C	chr7:152185650	G/A	Intron	rs62481492	[25]
KMT2C	chr7:152265172	C/T	P350	rs62478357	[26]
KMT2C	chr7:152265180	C/T	D348N	rs201834857	[27]
KMT2C	chr7:152247987	-/T	Frame shift (Y816*)	rs150073007 (insT)	
LIFR	chr5:38504203	A/T	Intron	-	
MBD1	chr18:50273809	G/C	P401A	rs125555	[28,29]
MN1	chr22:27798939	C/T	Q535	rs570740760	
MYH11	chr16:15756347	A/G	A588	rs2272554	[30]
MYH11	chr16:15732634	A/C	V1201G	-	[31]
NTRK3	chr15:87979521	A/C	Intron	-	
NUP214	chr9:131144585	C/T	P534S	rs374644647	
NUP98	chr11:3768640	T/C	N297D	-	
PDE4DIP	chr1:149003608	T/A	Splice site region + Intron	rs71664011	
PDE4DIP	chr1:120493200	C/T	A2257	rs71246352	
PHOX2B	chr4:41745718	A/C	3' UTR	-	
PKHD1	chr6:51911737	T/C	Intron	rs12196767	
PKHD1	chr6:51753372	T/-	Intron	rs112525785	
PKHD1	chr6:51753376	A/G	Intron	rs112461846	
RAF1	chr3:12591708	C/A	R398L	rs730880382	
ROS1	chr6:117385800	C/T	W729*	-	
SGK1	chr6:134173410	C/A	Intron	rs1743965 (C/T)	
TAF1	chrX:71459608	G/A	Q1729	-	
TAF1L	chr9:32633327	G/A	G751	rs141677293	
THBS1	chr15:39592681	G/T	Q882H	-	
TIMP3	chr22:32857304	C/-	Frame shift (S87*)	-	
TRIP11	chr14:91969786	G/T	P1943T	-	
TSHR	chr14:81108496	T/C	Intron	-	

CCP panel of serous ovarian carcinomas. On the other hand, other conventional genetic studies demonstrate clear cell ovarian carcinomas are associated with severe endometriosis [34-35].

This study has a few limitations. First, the NGS data do not match the information on ovarian serous cystadenocarcinoma variants (TCGA, 2011) [36]. The present data yielded negative results because of the small sample size examined. Therefore, these results should be further analyzed using matched information on gene variants of the clear cell ovarian carcinoma type using genome-wide sequencing. Based on the present identification of genes as-

sociated with recurrent endometriosis, further studies can be performed to better understand the etiology of severe endometriosis. In the future, we will obtain additional recurrent endometriosis samples and genetic data on the clear cell ovarian carcinoma type using NGS methods.

In conclusion, recurrent endometriosis patients have mutations in 39 genes and recurrent endometriosis is not associated with serous ovarian cystadenoma. Additionally, mutations in target genes in recurrent endometriosis are not significant. Recurrent endometriosis is associated with mutations in genes involved in gene repair, transcriptional regulation, and reproduction.

Considering the target mechanisms related to recurrence, it may be possible to protect patients with endometriosis from unnecessary therapeutic strategies and to select treatments based on patient characteristics.

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