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Proceeding Paper

Potential Candidate Gene and Underlying Molecular Mechanism Involving in Tumorigenesis of Endometriosis-Associated Ovarian Cancer (EAOC) in Asian Populations †

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Abstract: Molecular aberrations in endometriosis were known to be associated with an increased risk of epithelial ovarian cancer (EOCs), especially endometrioid ovarian cancer (EnOC) and ovarian clear cell carcinoma (OCCC). Causal genetic evidence currently remains elusive. An integrated study of related prognostic markers will help to identify the tumorigenesis pathways in endometriosis-associated ovarian cancer (EAOC). The objective of this study was to gain a better understanding of the tumorigenesis mechanisms that occur in the endometriosis-associated genetic variation-progressed ovarian cancer risk. We found 104 overlapping genes from the KEGG and GO results using WGCNA analysis. To determine whether the same genes were found in one or two types of the histotypes in the EAOC, we overlapped data from the WES and WGCNA results and found three genes, *MYH11* (found in all histotypes), *KRT5* (found in endometriosis and OCCC), and *PDGFRA* (found in endometriosis and EnOC). Interestingly, the *MYH11* and *PDGFRA* are involved in the role of the actin cytoskeleton. Several proteins influence the migratory and metastatic phenotype of tumor cells, directly or indirectly, as well as myosin protein and the protein platelet-derived growth factor, suggesting an explanation for the tumorigenesis progression from endometriosis to ovarian cancer. This analysis has provided the fortification of variants for further investigation in this research. With the limitation of the computational study, it can still prove to be an asset for the identification and treatment of endometriosis-associated ovarian cancer diseases associated with the target gene.

Keywords: endometriosis; ovarian clear cell carcinoma; endometrioid ovarian carcinoma; tumorigenesis; exome; gene expression

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1. Introduction

Endometriosis is a benign condition known for affecting the gynecology system but shows many cancer-like characteristics, including the invasion of tissues, proliferation, angiogenesis, and decreased apoptosis. There is an increased risk of ovarian cancer in women with endometriosis, according to current epidemiological studies. Recent genetic studies suggest some links between endometriosis and ovarian cancer, indicating a possible association between the molecular diagnosis of endometriosis and the progression to ovarian cancer (endometriosis-associated ovarian cancer, EAOC) [1]. Likewise, certain genetic markers predisposed to endometriosis place an individual at an increased risk of epithelial ovarian cancer, most commonly endometrioid ovarian cancer (EnOC) and

clear cell carcinoma (CCC) [1,2]. Ovarian cancer accounts for about 300,000 new diagnoses and 185,000 deaths annually, being the eighth most common and deadly cancer in women worldwide [3]. The risk of ovarian cancer is estimated to be 1.9-fold higher when you have endometriosis, according to one systematic review and meta-analysis. The risk is even higher for clear-cell ovarian cancer (3.4-fold) and endometrioid ovarian cancer (2.3-fold) [4].

Of note, endometriosis still carries a higher risk of malignancy toward ovarian cancer, and its prevalence in Asian the population (15% of women) is known to be higher than in the Western population (less than 5–10%). Given this plethora of ethnic variations that exist among Asian populations [5], the epidemiological data and current trends may help update the approach to determining the risk of endometriosis in ovarian cancer in Asian populations. Therefore, it is important to focus on the EAOC phenomena in Asia. EAOC cancer genomic profiling has been performed through many sequencing technologies and yet still remains enigmatic. Some potential genetic variants might play an important role in the genetic predisposition of the endometriosis lesions, leading to carcinogenesis through common hallmark cancers such as mismatch repair deficiency, Wnt/B-catenin signaling pathways, PTEN/PIK3 activation, ARID1A inactivation, and chromatin remodeling [6]. Therefore, it is imperative that the relevant regions of the genome, with variations related to the disease pathology, need to be analyzed.

The development of ovarian cancer has been linked to variant mutations or alterations in the DNA sequence. According to several studies [7,8], some gene mutations are linked to endometriosis and are a higher risk of ovarian cancer. In endometriosis-associated ovarian cancer, it is unclear exactly how variant mutations and mRNA expression variations are related. One theory is that variant mutations may modify the mRNA expression, which would alter gene function and raise the chance of developing ovarian cancer. Alternately, alterations in the mRNA expression might be a factor in the emergence of variant mutations in ovarian cancers linked to endometriosis. The relationship between endometriosis and ovarian cancer is an important subject for research since discovering this connection can help us better understand the biology of this malignancy. More investigation is needed to completely understand the complex interactions between genetic modifications, mRNA expression variations, and the onset of endometriosis-associated ovarian cancer. In this study, we aim to uncover the tumorigenesis route in the endometriosis associated with ovarian cancer (EAOC) and reveal the genetic variant identity-based on whole exome sequencing data.

2. Materials and Method

2.1. Data Collection

To conduct this study, the literature search used the most recent 5 years of published articles. The following combinations of various search terms were used: (exome sequencing) AND (endometriosis OR endometrioma) AND (ovarian clear cell carcinoma) AND/OR (endometrioid) AND (ovary OR ovarian). Additionally, relevant references were evaluated from eligible studies. The report included all cohorts that analyze the whole exome sequencing or the sequencing in exon to detect somatic mutations among the EAOC groups within East Asian countries to identify ovarian cancer-associated genes and variant mutations.

Incomplete clinical pathology and mutation annotations from exome sequencing were also excluded, as were publications from sources other than East Asian nations, samples of lower sizes (<10), and data that could not be recovered (chromosome position, cDNA change, protein change). The 137 cases in the EAOC data were divided into four groups, non-endometriosis (six cases), endometriosis (29 cases), endometrioid ovarian cancer (EnOC) (22 cases), and ovarian clear cell carcinoma (OCCC) (80 cases). The detailed selected data is presented in Table S1 [8–12]. To reveal how SNPs encoded amino acids (nonsynonymous) can simply influence promoter activity (gene expression), mRNA stability, and protein localization in subcellular, GEO (gene expression omnibus) datasets GSE65986 and GSE7846 were used.

2.2. Data Analysis

To obtain the detailed variant annotations, we imported summary datasets from the whole exome sequencing results into web-based variant annotation tools VEP (variant effect predictor) [13]. The VEP output results can be found in VCF or TXT format. VCF is a generic format for storing DNA polymorphism data such as SNPs, insertions, deletions, and structural variants. To predict the pathogenicity impact of each variant category, a specific set of tools must be used. VEP provides a greater range of algorithms to help assess the process of the potential functions of a variant. Here we used PolyPhen-2, SIFT4D, Provean, CADD, and GERP from VEP web interface from ensemble (https://asia.ensembl.org/info/docs/tools/vep/index.html, accessed on 14 June 2022). GSE65986 and GSE7846 were analyzed using a co-expression network in iDEP web tools 1.0 web interface (http://149.165.154.220/idep11/, accessed on 6 February 2023) [14]. Co-expression networks are found and displayed by the iDEP using the weighted correlation network analysis (WGCNA) package to compare gene expression between two groups of samples (normal and EAOC). The co-expression network is divided into modules, which are colored-coded and displayed on the gene dendrogram. Each module consists of a collection of genes that are closely connected to one another. These modules are the subject of the GO and KEGG enrichment investigations.

Once the harmful effect prediction variants in the exome region had been filtered, the genes that overlapped between the exome and the mRNA datasets were screened to further investigate the gene interest. The gene must be present in at least two histotypes (EnOC or OCCC and endometriosis) of the EAOC to be identified. Afterward, we use databases, such as HPA (https://www.proteinatlas.org/, accessed on 22 February 2023) [15], cBioPortal (http://cbioportal.org, accessed on 1 February 2023) [16,17], and COSMIC (https://cancer.sanger.ac.uk/, accessed on 1 February 2023) [18], to adding information about the gene and variant information.

The Human Protein Atlas (HPA) project is a tool for identifying the subcellular location and expression of a certain protein in various tissues. The comprehension of the possible effects of the exonic variations on protein function and the identification of the probable disease-causing processes can both benefit from this knowledge, including the ovaries or endometrium. The cBioPortal is a tool for examining the cancer's genomic information, including information from sizable genomic studies similar to The Cancer Genome Atlas (TCGA). The cBioPortal can offer details on the genetic mutations and modifications that are frequently connected to endometriosis-associated ovarian cancer, as well as details on the biological networks and pathways that are affected by these changes. The COSMIC (Catalogue of Somatic Mutations in Cancer) database is a repository for details on mutations found in cancer samples. It offers details on the types, frequency, and correlation of mutations with various cancer types.

3. Result

3.1. Data Preprocessing and Normalisation

In the first step, all genes with variants in exons that meet the criteria of the study design, pertaining to the whole exome sequencing or targeted sequencing in the exon regions, were gathered from the literature. In the VEP database, we identified and annotated 17 genes in six non-endometrial tissues, 7341 genes in 29 ectopic endometrium tissues, 8206 genes in 16 eutopic endometrium tissues, 187 genes in endometrioid tissues, and 220 genes in clear cell tissues, according to their chromosome position, alternative allele, and their HGVS information collected from the summary of the whole exome sequencing processing data in five pieces of literature.

In order to analyze the mRNA expression, we gathered the GEO datasets from the GSE65986 and GSE7846, along with the microarray raw counts. Neither dataset was different from the other, and both met the tissue criteria for normal, endometriosis, and epithelial ovarian cancer (EnOC and OCCC). We used the GPL570 platform number for the

human microarray count. The GSE7846 consisted of 5 normal and 5 endometriosis tissue, while the GSE65986 used 25 clear cells and 14 endometrioid tissue (Table S2).

3.2. Overlapping Exonic Variant and mRNA Expression Data

As a result of the literature search of the whole exome sequencing, a list of the total EAOC genes after applying to filter was 9, 3892, 64, and 75 for non-endometriosis, endometriosis, EnOC, and OCCC histotypes, respectively. A total of 919 genes were found in the four modules across the entire network in the iDEP 1.0 analysis using the GSE65986 and GSE7846 datasets. After enrichment, there were 499 genes recognized in the database. Those genes were intersected with the genes from the WES data. There are 104 genes that overlap between the exonic variant and the mRNA level (Figure S1). The following genes have been found in at least one histotype of the EAOC: They were *MYH11* in all histotypes (endometriosis, EnOC, and OCCC), *KRT5* in only endometriosis-clear cell tissue, and *PDGFRA* in only the endometriosis and endometrioid. These three genes were found significantly involved in modules blue and brown. The *MYH11* and *KRT5* were found in the brown module while *PDGFRA* was found in the blue module only (Figure S1b).

Using the module in iDEP 1.0, we found that *PDGFRA* is significantly related to the biological processes and cellular components (ECM). *KRT5* and *MYH11* were also involved in the development of skeletal and tissue components of the biological processes and were found in part of the ECM (Figure S2). However, to further identify their pathway in the disease, the 104 genes that overlapped were re-analyzed in DAVID using KEGG and GO enrichment. *PDGFRA* is known to be significantly related PI3K-Akt signaling pathways, focal adhesion, regulation of actin cytoskeleton, EGFR tyrosine kinase inhibitor resistance, and pathways in cancer according to KEGG. Furthermore, *KRT5* was not found in the KEGG pathway and *MYH11* was involved in the regulation of the actin cytoskeleton, the same as the *PDGFRA* (Figure S3).

3.3. Gene of Interest for Further Investigation

MYH11, *KRT5*, and *PDGFRA* were investigated using the HPA, cBioportal, and COSMIC databases. After knowing the list of genes of interest, the public database was used for investigating the potential impact of the protein's disease-associated mechanisms. First was the *KRT5* (Keratin 5), which was found to be a highly expressed protein in the female reproduction system, especially in the vagina, cervix, and breast tissue. We also investigated the list of variants in each gene interest using the PolyPhen-2, SIFT4D, Provean, CADD, and GERP criteria from VEP web interface and found few related SNPs with each gene (Table S3). Even though their protein was not found in the endometrium or ovary tissue, their RNA expression level was 2.0 and 2.2 of normalized TPM in both tissues, respectively, according to the HPA database. They also found the samples to be highly expressed in smooth muscle cell endometrium among females above 30 years old. In the ovary tissue, they expressed in the stromal cells of females around 50 years old and later. The *MYH11* (Myosin heavy chain 11) protein was found to be highly expressed in the endometrium, breast, and ovary tissue. Their protein and RNA were equally highly expressed in the smooth muscle tissue part of the endometrium and ovary. In the *PDGFRA* (platelet-derived growth factor receptor alpha) gene, their protein, and RNA were expressed in contrast conditions. Protein in the ovary tissue was lower but higher for their RNA level, in contrast with their RNA level which showed a higher value in protein but a lower in their endometrium tissue.

Based on the literature data Using the cBioPortal database, the genetic alteration, caused by *PDGFRA* (1.6%) and *MYH11* (0.7%), was found significant, based on the GENIE cohort studies (646 samples) in the OCCC and EnOC patients. Only the *KRT5* did not show any mutation frequency in the database. Therefore, to provide complete information about somatic mutation in both genes, the COSMIC database was used. For the *MYH11* gene, the same variant (c.323G > A) was found in both the eutopic endometriosis and endometrioid samples, as well as the COSMIC database. All the *PDGFRA* variants in our data were also

found in the COSMIC database (c.2942G > A, c.2671C > T, c.2450G > A, c.2566T > G). Only the *KRT5* variants have not been found in the database.

4. Discussion

The extracellular matrix (ECM) plays a significant role in the development and progression of endometriosis-associated ovarian cancer (EAOC). It is possible that changes in the structure and composition of the ECM could contribute to the development of these disorders, which is a network of proteins and polysaccharides that provide structural support and signaling signals to cells. Endometriosis develops and maintains endometrial implants outside the uterus by regulating the ECM. The ECM participates in the construction of the cellular structures that support the growth of malignancy in ovarian cancer, as well as the control of cell survival and proliferation. Changes in the composition and organization of the ECM elements, such as laminin and tenascin which have been specifically seen in ovarian cancer, are believed to have a role in the creation of the tumor microenvironment and the progression of malignancy [19].

In both endometriosis and ovarian cancer, the ECM acts as a physical and biochemical barrier to drug delivery, and altering it may enhance delivery and efficacy. Further, since alterations in the ECM have been shown to contribute to both diseases' onset and progression, targeting the ECM has been proposed as a treatment strategy. Endometriosis-associated ovarian cancer (EAOC) may be associated with alterations of genes, including *MYH11* and *PDGFRA*, in the extracellular matrix (ECM), which plays an integral role in the tumor microenvironment.

The heavy chain of myosin IIA, a crucial part of the ECM and implicated in its organization and mechanical characteristics, is encoded by the *MYH11* gene. The expression of *MYH11* is often upregulated in cancer cells, which promotes cell migration and invasion by forming actin-myosin contractile structures. Consequently, cancer cells are able to move through the ECM and invade surrounding tissues, resulting in the spread of the disease. As a consequence of changing the mechanical properties of the ECM, changing cell behavior, and fostering malignancy, *MYH11* mutations may play a role in ECM-mediated carcinogenesis in the setting of EAOC [20].

The protein platelet-derived growth factor receptor alpha (*PDGFRA*) plays a vital role in controlling the growth and survival of cells in endometriosis and ovarian cancer. In endometriosis, a higher expression of *PDGFRA* is associated with the expansion and growth of endometrial tissues outside of the uterus, resulting in the creation of endometriotic growths. This heightened expression of *PDGFRA* triggers the release of various signaling substances which stimulate cell growth and survival, contributing to the progression of endometriosis. Similarly, *PDGFRA* is often over-expressed in ovarian cancer, and its activation has been shown to drive the growth and survival of cancer cells. *PDGFRA* signaling pathways trigger the production of various growth factors and cytokines which contribute to the advancement of ovarian cancer [21].

Based on our findings, most of the mutations were G > A type, which is known as silent mutation. Silent mutations do not alter the protein's sequence, but they can still affect how genes are expressed and cause disease even when they do not alter the protein's sequence. For instance, silent mutations can modify the secondary structure of the mRNA, which will affect how well it can be translated into protein, or they can affect the stability of the mRNA, which will vary the amount of protein generated. In some circumstances, silent mutations can also change how genes are spliced, leading to the generation of various proteins with various roles. The extracellular matrix (ECM) may change as a result of these alternative splice variants, which may also contribute to carcinogenesis in endometriosis-associated ovarian cancer (EAOC) (Figures S4 and S5).

5. Conclusions

In spite of the fact that the function variant mutations in EAOC are still poorly understood, recent studies have indicated that they can contribute to a number of illnesses,

including ovarian cancer. The effects of those mutations, including specific G > A alterations in the *MYH11* and *PDGFRA*, on the onset of EAOC require further research. Genetic variants need to be genotyped as part of further investigations. Even with the limitations of computational research, it can still be useful for locating and treating disorders linked to the target gene that is related to endometriosis-associated ovarian cancer.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/IECC2023-14214/s1, Table S1: Selected Whole Exome Sequencing (WES) data from published articles; Table S2: Microarray Data Collection Information; Table S3: Filtered exonic variants in genes of interest based on functional impact in WES data; Figure S1: Co-expression network analysis using WGCNA package in iDEP; Figure S2: Bar plot of GO enrichment analysis for 2 modules (Brown and blue) in iDEP result; Figure S3: GO analysis and Hallmark pathway enrichment of 104 genes from overlapping WES and mRNA data in EAOC; Figure S4: Summarize of cBioportal in GENIE cohort of Clear Cell Ovarian Carcinoma and Endometrioid Ovarian Carcinoma; Figure S5: An overview of tumorigenesis involving genetic predisposition and PDGFRA in extracellular matrix.

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