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Identification Target Genes for Potential Biomarkers in Endometriosis from Transcriptomics Database

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ABSTRACT

Endometriosis is a common benign gynecological disease characterized by the ectopic growth of endometrial tissue. Its pathogenesis is influenced by complex genetic and epigenetic factors, making diagnosis and treatment challenging. This study aimed to identify molecular pathways and candidate genes associated with endometriosis using transcriptomic data. Three datasets (GSE7307, GSE23339, and GSE25628) were retrieved from the Gene Expression Omnibus (GEO) database and analyzed to identify differentially expressed genes (DEGs). A total of 339 intersecting DEGs were obtained and subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses. The results indicated enrichment in biological processes related to epithelial cell proliferation and angiogenesis, cellular components associated with the lysosomal lumen and extracellular matrix, and molecular functions involving Wnt-activated receptor activity and low-density lipoprotein particle binding. Ten genes (TAGLN, C7, TCF21, GATA6, GPC3, FZD7, TCEAL2, KLF2, FMO1, and HOXC6) were identified as potential candidate biomarkers. These findings provide preliminary molecular insights into endometriosis and may support future experimental and clinical studies for biomarker development.

INTRODUCTION

Endometriosis is a chronic gynecological disorder characterized by the presence of endometrial glands and stroma outside the uterine cavity [1]. It affects approximately 10–15% of women of reproductive age, with prevalence rising to nearly 70% among women suffering from chronic pelvic pain [2]. Clinically, endometriosis is associated with dysmenorrhea, chronic pelvic pain, and infertility, and its persistent symptoms significantly impair quality of life, mental health, social relationships, and work productivity [3],

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[4]. The pathogenesis of endometriosis remains complex and multifactorial. The most widely accepted theory is retrograde menstruation, in which viable endometrial cells reflux through the fallopian tubes into the peritoneal cavity. However, this mechanism alone cannot fully explain disease development, as retrograde menstruation also occurs in women without endometriosis. Other proposed mechanisms include oxidative stress and inflammation within the peritoneal environment, altered steroid hormone signaling, impaired immune surveillance, and enhanced angiogenesis [5]. Increasing evidence suggests that genetic and epigenetic factors play a substantial role in disease susceptibility and progression. Early observations by Goodall in 1943 first proposed a hereditary component based on familial clustering of cases [6]. More recently, whole-exome sequencing studies have identified somatic mutations in genes related to chromatin remodeling, cell adhesion, and junctional complexes in both eutopic and ectopic endometrial tissues, further supporting a molecular basis for the disease [3]. Despite advances in understanding its biology, endometriosis remains challenging to diagnose and manage. Laparoscopy with histopathological confirmation is still considered the gold standard for diagnosis [6], making early detection invasive and often delayed. Current treatment options include hormonal therapy, surgery, or a combination of both, while nonsteroidal anti-inflammatory drugs are commonly used for pain management. However, these therapies are largely symptomatic, show variable efficacy, and do not provide a definitive cure [7]. Consequently, there is a critical need for improved diagnostic tools and more effective, targeted therapeutic strategies.

In this context, the identification of reliable molecular biomarkers is essential for early diagnosis, prognosis assessment, and the development of personalized treatments. Recent advances in genomics and bioinformatics have generated vast amounts of transcriptomic data, offering unprecedented opportunities to uncover disease-associated genes and pathways. Genomic-based and computational approaches also enable drug repurposing strategies, allowing existing drugs to be evaluated for new therapeutic indications with greater precision and efficiency [8], [9] . Therefore, this study aims to analyze transcriptomic data to identify potential gene biomarkers associated with endometriosis that may contribute to improved diagnostic accuracy and the development of novel therapeutic targets.

METHOD

Data we used provided in website NCBI-GEO (https://www.ncbi.nlm.nih.gov/geo/), the aim of this study was to gather information about potential genes could be used as potential endometriosis biomarker in human so we investigated using keywords “endometriosis” then choose “homo sapiens” as the organism and subsequently RNA sequencing investigation such as RNA expression and “tissue” as the sample, through data analysis we found 33 datasets.

The thirty three datasets that we got from GEO we do excluded several datasets that unrelated to endometriosis, the inclusion of this datasets were specified RNA, high-throughput sequencing, could be analyzed by GEO2R, endometrium tissue, and datasets with normal endometrium as control and

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endometriosis. Resulting of the retension we get three relevan datasets, the chosen datasets that used for analysis were GSE7307, GSE23339, and GSE25628. GEO explain that GSE7307 refers to the data from earlier research with title human body index-transcriptional profilling, the GSE23339 is gene expression profiles of endometriosis, then GSE25628 is endometriosis transcription profiling. The GSE7307 dataset consists of normal endometrial tissue samples and was used as the control group. The GSE23339 dataset contains endometrial samples from patients with endometriosis, including eutopic endometrium. The GSE25628 dataset includes both eutopic and ectopic endometrial tissue samples derived from endometriosis lesions. These datasets were chosen because they provided comparable gene expression profiles between control and endometriosis groups and were suitable for differential expression analysis using GEO2R. Statistical significance was estabilised when padj.value <0.05.

We used venn diagram (accessible : https://bioinformatics.psb.ugent.be) to assess the overlap between three datasets, and we found that 339 intersection genes. Then we analyze the pathway using Kyoto Encyclopedia of Genes and Genomes (KEGG) via ShinyGO 0.77 (accessible at http://bioinformatics.sdstate.edu/go/). We also analyzed the Genes Ontology (GO) to examine and identified gene pathway that related to endometriosis. Then in 339 genes we searched top ten most high expression genes in endometriosis.

RESULTS AND DISCUSSION

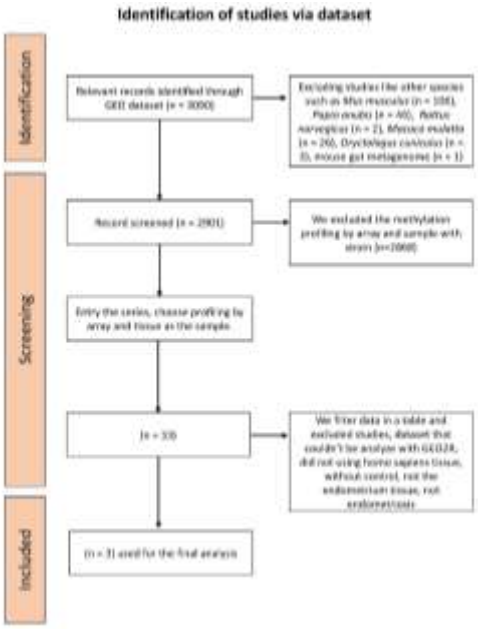

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Figure 1. Flow diagram illustrating the method to identified and analyzed all the datasets related to endometriosis, focusing in human tissue. Out of the 3090 datasets, only 3 datasets remain ; GSE7307, GSE23339, GSE25628.

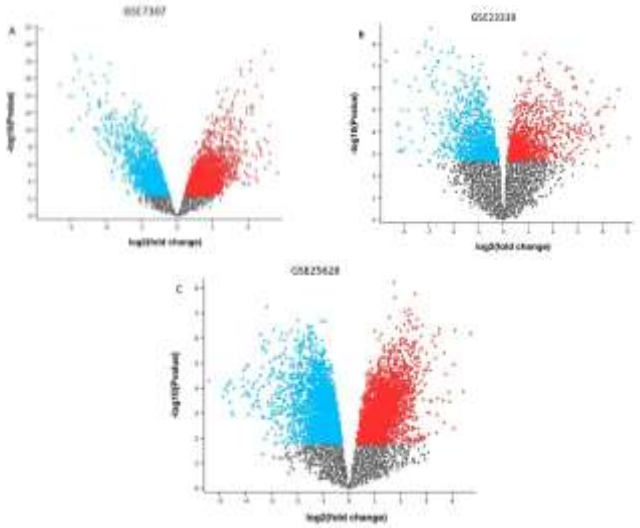

Figure 2. Differential gene expression in the GSE7307 (A), GSE23339 (B) and GSE25628 (C) datasets.

Volcano plot used to visualizing significant differents in gene expressions between GSE7307, GSE23339, and GSE25628 datasets that presented in **Figure 2**, the plots provides to an overview of gene expression that are common in three datasets, the blue colour presented to the genes that significant in normal endometrium (control), while the red colour presented to the genes in endometriosis, then the grey colour presented to the genes with no significant change of expression. Positive log2 (fold change) values upregulated gene expression in endometriosis, while negative values indicate downregulated gene expression in endometriosis and the significant in statistically to observed changes in gene expressions present in y-axis.

Deleted: Negative

Deleted: positive

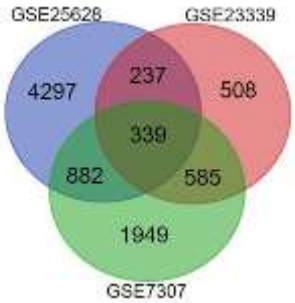

Figure 3. Venn diagram illustrating the overlap between genes in the GSE7307, GSE23339, and GSE25628 datasets, revealing 339 intersecting genes, we used ShinyGo for additional analysis to the function of this common genes.

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Figure 4. The genecology analysis in biological process (A), cellular component (B), and Molecular function (C).

Analysis Gene Ontology (GO) in **Figure 4**, shows that in biological process (A) epithelial cell proliferation plays a most significant in normal endometrium and endometriosis, then in cellular component (B) shows that lysosomal lument play a important role as part of cell, also in molecular function (C) shows that Wnt-activated receptor activity could affected in normal endometrium and endometriosis. The top ten genes we analyzed from 339 intersecting genes in three datasets were in list in **Table 1.**

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Table 1. Significant genes expression in endometriosis

Gene	Log2 (fold change)	-Log10(Pvalue)
TAGLN	-4.635	4.188
C7	-4.538	3.05
TCF21	-4.451	4.014
GATA6	-3.892	2.967
GPC3	-3.713	3.224
FZD7	-3.598	4.1555
TCEAL2	-3.532	3.747
KLF2	-3.445	4.497
FMO1	-3.425	6.145
HOXC6	-3.296	2.826

Endothelial cell proliferative was significantly high in endometriosis compared with controls [10], its relate with the results from molecular function in Figure 4C that Wnt-receptor activity is higher in endometriosis because Wnt/β-catenin signaling is a pathway that plays a key role in the development and progression of endometriosis with signaling promotes cell proliferation, invasion and inhibits apoptosis [11], Wnt also a critical event in stimulating endometriosis fibrosis [12].

The TAGLN is genes code for transgelin [13]**,** several studies have reported that endometriosis is associated with elevated levels of TAGLN proteins and transcripts[14], [15], [16]. endometriotic lesions were shown to have higher levels of the TAGLN expression gene than eutopic endometrium in both the proliferative and secretory phases of the menstrual cycle, [17]. the TAGLN levels rise directly in ectopic tissue rather than in nearby peritoneal tissue[18],Transforming Growth Factor (TGF β), a cytokine involved in multiple cell functions, including immunologic response, proliferation, apoptosis, motility, differentiation, and carcinogenesis, is crucial in controlling the expression of the TAGLN gene in smooth muscle[19]**.** Jones et al. have also identified elevated TGF β expression in the endometrium and peritoneal fluid of women with endometriosis[20], TGF β is located in cytoplasm of glandular epithelial cells and in endometriotic cyst, this observed by immunohistology and immunoassay[21]**.** In the data that we analyzed, we also found that TAGLN has the most higher expression in endometriosis, that is why TAGLN could be one of potential genes biomarker in endometriosis.

The second genes with high expression in endometriosis in Table 1 is The complements factor 7 (C7) genes it is related to research by swati et al (2014) that the C7 genes is highly expressed in endometriosis and ovarian cancer while normal endometrium has no mRNA expression of that's complements factor [22], C7 involved in inflammation and tumor growth which is the key part of the complement system [23]. Transcription factor 21 (TCF21) gene expressions is undetected in normal endometrium, in eutopic endometriosis it is had weakly detected, moderated detected in ovarian endometriosis and highly detected in deep infiltrating endometriosis, TCF21 are involved in the regulation of the fibrosis in endometriosis [24], TCF 21 may be a potential target and biomarker in endometriosis.

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Zinc finger-containing transcription factor GATA6 has been demonstrated to be essential for determining cell lineage during early embryonic development and organ creation , When hypomethylated GATA binding protein 6 (GATA6) was overexpressed, normal endometrial stromal cells developed endometriotic phenotypes and lost their ability to sense hormones [24], there is also a report about that GATA 6 was shown to be significantly expressed in endometrial cells [25], [26]. According to one study, endometriotic cells active enhancer in intron II determines the expression of GATA6 mRNA(Izawa et al., 2019).

Glypican 3 (GPC3) assosiated as poor parameters in endometrial carcinoma and serous endometrial carcinoma [28] and still no studies in endometriosis. GPC3 is a heparan sulfate proteoglycan found on the cell surface that attaches to the cell membrane through glycosyl-phosphatidyl-inositol anchors[29]. GPC3 also had role in regulation during normal develepmont in cell proliferation and apoptosis[30]. according to genetic and biochemical study, numerous signaling pathways, including those induced by Wnts [31], [32], fibroblast growth factors [33], and bone morphogenetic proteins (BMPs) [34], [35], can be regulated by glypicans. There is also some reports about overexpression of glypican 3 in some types of cancers such as squamous cell carcinoma of the lung, hepatocelluler carcinoma and terticular germ cell tumors[36].

A transmembrane protein belonging to the Frizzled (FZD) family, Frizzled-7 (FZD7) is a Wnt receptor that has the ability to activate both canonical and noncanonical Wnt signaling pathways [37] and has been shown to be essential for the proliferation of immature pig Sertoli cells[38], Numerous cancer types exhibit up-regulation of FZD7, which is linked to invasiveness and cancer cell proliferation, indicating that the genes are also responsible for cancer growth[39]**.** According to bioinformatic screening studies, FDZ7 is extensively expressed in endometriotic tissues and was much more prevalent in ectopic endometrial tissues than in normal endometrial tissues[40].

In previous bioinformatic studies also found that TCEAL2 upregulated in endometriosis[41], [42], TCEAL2 (Transcription Elongation Factor A like 2) is a protein coding gene, and a nuclear phosphoprotein that modulates transcription in a promoter context-dependent manner and has been recognized as the important nuclear target for intracellular signal transduction[43]. Kruppel Like Factor 2 (KLF2) take a role in physiological and pathological prosesses, like adipohenesis, erythropoiesis in embyogenic, epithelial integrity, T-Cell motility and inflammation[44], [45]. KLF2 also promoted statis of the metabolic, blocking endothelial cell apoptosis and reducing metabolic dependence on glucose[46].

In other cases Flavin-containing monooxygenase 1 (FMO1) also found high expression in endometriosis bioinformatic research using LASSO algorithm to reduced the DEGs in order to find the factors that serve as particular endometriosis biomarkers, in the data told that FMO1 response to molecule of bacterial origin, lipopolysaccharide, and expressed in endoplasmic reticulum lumen [47]. The proteins that are essential for tumor cell development, proliferation, and metastasis, including bone morphogenic protein 7 (BMP7), fibroblast growth factor receptor 2 (FGFR2), and platelet-derived growth factor receptor α (PDGFRA), are

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regulated by Homeobox Containing 6 (HOXC6) [48], [49]. It also controls the Wnt, Notch, and PI3K/Akt signaling pathways. As evidence of its possible roles in tumor growth, overexpression of (HOXC6) promotes the creation of growing 3D colonies and stimulates the release of tumor growth factors[50].

CONCLUSION

The study highlights ten potential candidate genes identified through transcriptomic analysis that may include in the further experimental validation is essential to confirm their clinical applicability. These findings provide preliminary molecular insights into pathways associated with endometriosis and may support future experimental and clinical investigations.

Author Contributions

Dian Zahlina: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft.

Benni Iskandar: Software, Data curation, Visualization.

Wirawan Adikusuma: Software, Methodology, Validation, Writing – review & editing.

Muhammad Yusuf: Investigation, Resources, Writing – review & editing.

Rifia Tiara Fani: Formal analysis, Visualization, Writing – original draft.

Ocktariyana: Project administration, Investigation.

Darmawi: Conceptualization, Supervision, Funding acquisition, Writing – review & editing.

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