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Integrative Systems Biology Approach to Identify Metastatic Biomarkers in PCOS-associated Reproductive Cancers

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Abstract

Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder with significant implications for women's health. In addition to enlarged ovaries with numerous tiny cysts and hormonal disturbances; it raises the risk of reproductive malignancies. There are only a few studies linking the association of PCOS to breast, ovarian, and uterine cancer, but no study highlights the comprehensive analysis of their association. To gain insights into the molecular mechanisms, we conducted a literature mining analysis focused on genes associated with PCOS, uterine, ovarian, cervical, and breast cancers. Genes were retrieved from the DisGeNET database, and a gene interaction network was constructed using the STRING database. Clustering analysis and hub gene identification were performed using Cytoscape and the CytoHubba plugin. The biological functions and pathways associated with the identified hub genes were analyzed using the ClueGO plug-in. Three important hub genes were found by our study namely PTEN, BRCA1, and BRCA2 whose cellular locations were provided by cluePedia. These genes might be promising as potential biomarkers for PCOS, uterine, ovarian, cervical, and breast cancers. This study identified hub genes that highlight the molecular complexity underlying PCOS-associated reproductive cancers. Understanding the roles of PTEN, BRCA1, and BRCA2 can aid in early detection, personalized treatment approaches, and the development of targeted therapies for those with PCOS-related reproductive cancers.

Keywords: Pcos; Metastasis; Breast Cancer; Ovarian Cancer; Uterine

Introduction

A significant proportion of women worldwide are affected by the complex endocrine condition known as polycystic ovary syndrome (PCOS). It is a metabolic and hormonal problem that affects women's long-term health in addition to being a reproductive disorder. PCOS is characterized by hormonal abnormalities, enlarged ovaries with numerous tiny cysts, and a variety of clinical symptoms [1]. It is one of the most common hormonal conditions in women of reproductive age, with a prevalence rate of between 4–20% globally [2]. However, the actual prevalence may change based on the diagnostic criteria and the demographic category under study. Despite its high occurrence, PCOS frequently goes untreated or is misdiagnosed due to its numerous clinical presentations and symptoms that coincide with those of other disorders. Although the exact cause of PCOS is unknown, it is thought to be a result of an association of genetic, hormonal, and environmental factors [1,3,4]. These factors interfere with normal ovarian function, which results in PCOS-specific symptoms. PCOS is linked to a higher risk of particular kinds of reproductive malignancies in women, in addition to reproductive and metabolic issues. Several investigations have emphasized the connection between PCOS and the emergence of breast, ovarian, and endometrial cancers [5,6] with little information on the association with cervical cancer. PCOS is closely related to endometrial cancer, which damages the lining of the uterus. Chronic anovulation in PCOS-afflicted women causes unopposed estrogen exposure, which raises the risk of endometrial cancer and endometrial hyperplasia. Endometrial abnormalities are a result of hormonal imbalances, such as increased estrogen levels and decreased progesterone levels [7] which are observed as common symptoms in PCOS patients. Ovarian cancer risk has also been associated with PCOS. In women with PCOS, prolonged exposure to high androgen levels and elevated insulin levels may contribute to the development of ovarian cancer. Multiple ovarian cysts are a common finding in PCOS, which may further raise the risk of ovarian cancer [8,9]. Compared to endometrial and ovarian malignancies, the relationship between PCOS and breast cancer is less obvious; however, some research has revealed a possible connection. According to Ge et al. (2013), there may be a link between PCOS and breast cancer, with women with PCOS having a twofold increased risk of developing breast cancer and a tenfold increased chance of developing uterine cancer. As for ovarian cancer, Chittenden et al., (2009) conducted a systematic study and concluded that PCOS is related with an increased risk of endometrial and ovarian cancer. The development of breast cancer may be influenced by hormonal abnormalities in women with PCOS, such as high estrogen levels and impaired estrogen metabolism, which may affect breast tissue [9]. Improving patient outcomes and advancing our understanding of these complicated diseases depend on our ability to fully understand the molecular pathways of metastasis in PCOS-associated reproductive malignancies. Several significant improvements in the field can be accomplished by understanding the complex systems involved in these reproductive cancer growths. The establishment of more sensitive and focused diagnostic tools that enable rapid diagnosis and individualized treatment approaches can be facilitated by the identification of specific biomarkers linked to metastasis of cancers related to PCOS. The link between PCOS and cancer in women offers us with a unique chance to investigate the relationship between PCOS and the likelihood of women having cancer later in life. Therefore, the entitled study "Integrative Systems Biology Approach to Identify Metastatic Biomarkers in PCOS-associated Reproductive Cancers" is essential to comprehend the underlying mechanisms that promote the development of reproductive cancers in women suffering from PCOS. It may be possible to develop targeted medicines and interventions to stop or treat metastasis in these patients by figuring out the molecular pathways involved, thereby improving their prognosis and quality of life. This study has the potential to close a significant information gap and promote personalized treatment for reproductive malignancies linked to PCOS.

Research Method

Retrieval of Genes

Genes that have been reported to be involved in PCOS, breast, uterine and cervical, and ovarian cancer were retrieved from DisGeNet database (http://www.disgenet.org) and downloaded in Excel file format [10]. The genes common amongst these diseases were obtained with the help of Intravein tool available online.

Construction of Gene Interaction Network

STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) database (https://string-db.org/) was used to construct protein-protein interaction network of the genes found common amongst PCOS and breast, uterine and cervical and ovarian cancer followed by analysis of the network using various plug-ins of Cytoscape v:3.7.2 software [11].

ClusterONE: (http://apps.cytoscape.org/apps/clusterone) ClusterONE (Clustering with Overlapping Neighborhood Expansion) plugin analyzes protein-protein interaction data to identify overlapping protein complexes. It was used to find highly connected regions in the form of clusters [12].

Cytohubba (http://apps.cytoscape.org/apps/cytohubba) CytoHubba plug-in of cytoscape was used to rank hub genes using scoring method of maximal clique centrality present in the interaction network of genes common amongst PCOS and breast, uterine and cervical and ovarian cancer [13].

ClueGO (http://apps.cytoscape.org/apps/cluego) ClueGO plug-in of Cytoscapewas used to create a functionally organized GO/pathway term network using databases such as Gene Ontology, KEGG, WikiPathways and Reactome [14].

CluePedia (http://apps.cytoscape.org/apps/cluepedia) The CluePediaCytoscape plug-in was used to identify biomarkers associated with genes and pathways common amongst PCOS and breast, uterine and cervical and ovarian cancer [15].

Results and Discussion

Retrieval of Genes

Genes involved in PCOS, uterine, ovarian and cervical and breast cancers were retrieved from DisGeNET database in which 6776, 54 and 1881, 2841 and 988 gene entries were present respectively. Out of all these genes, 35 genes were common in all the three diseases. The common genes were retrieved with the help of interactive Venn tool available online.

Construction of Gene Interaction Network

Network construction was done using STRING database. All of the 35 genes common amongst PCOS, uterine, ovarian and cervical and breast cancers were specific to Homo sapiens. The interaction network was constructed using STRING database from these 35 nodes (representing the genes) and 199 edges (representing the interaction between genes). The PPI enrichment P.value of the string network was <1.0e-16, which signifies that these genes have more interactions amongst themselves than expected. The number of nodes represents the number of entities connected within the network and indicates about the size of the network. The edges along with the nodes provide us with useful information of networks topology and density of the network generated.

Clustering of Genes the network obtained from STRING (Figure1) was imported in Cytoscape. This network was then analyzed using Cytoscape plug-in ClusterONE and a main network was obtained in which red nodes represent highly significant genes, while yellow and grey nodes represent least significant nodes and outliers respectively (Figure 2). From the exported network only one cluster was obtained, which had significant P-value (<0.05) and was further used in hub gene analysis.

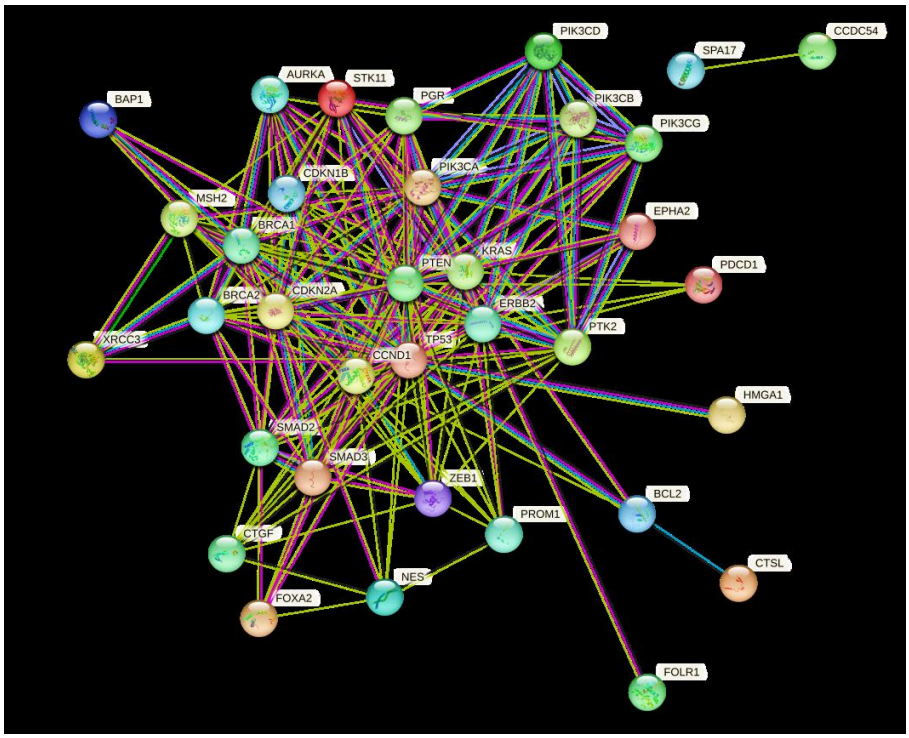

Figure 1: Protein-Protein interaction (PPI) network using string for 35 common genes amongst PCOS, uterine, ovarian and cervical, and breast cancers

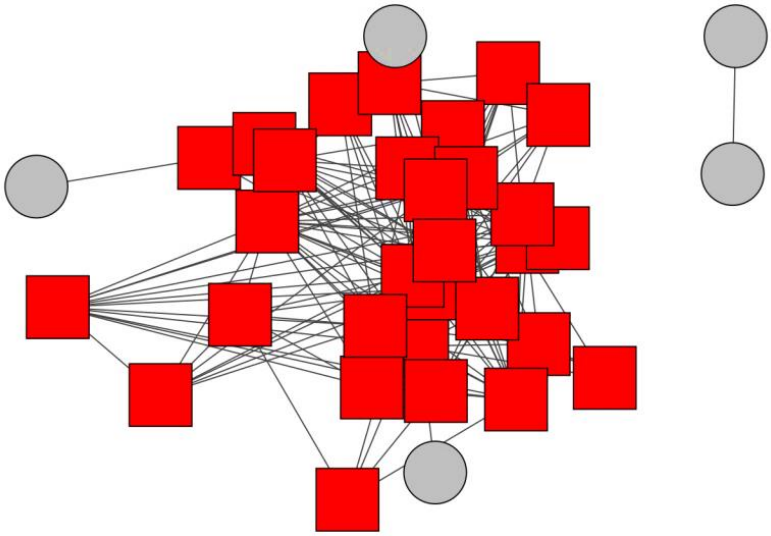

Figure 2: ClusterONE results obtained by analyzing the Network

Identifying Hub Genes

Hub genes were identified using CytoHubba plug-in of Cytoscape that uses Maximum Clique Centrality (MCC) method. The network obtained from ClusterONE (Figure 2) was analyzed with CytoHubba and top 10 ranked genes were obtained that are colour coded as highly significant genes in red, followed by orange and least significant in yellow (Figure 3). Ten genes were found to be significant amongst the common genes of PCOS, uterine, ovarian and cervical cancers namely PTEN, PIK3CA, BRCA1, KRAS, BRCA2, ERBB2, CDKN1B, CDKN2A, TP53, and CCND1

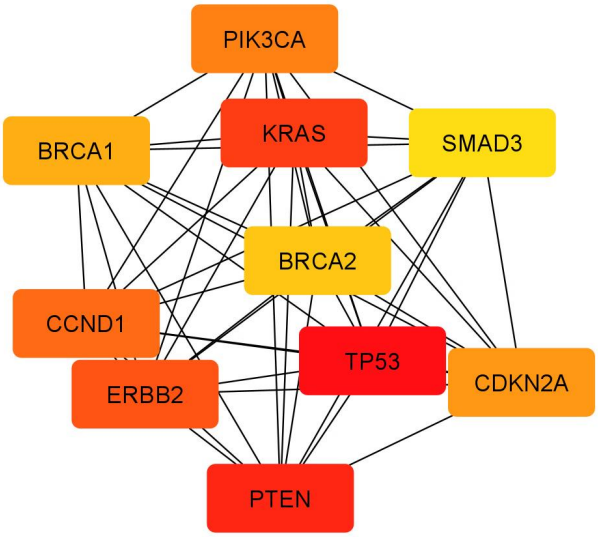

Figure 3: Graphical view of ranked hub nodes obtained from Cytoscape plug-in Cytohubba

Enrichment of Genes and their Pathway

All the 10 hub genes obtained from CytoHubba were analyzed using Cytoscape plug-in ClueGO that allows analysis of interrelations of terms and functional groups in the biological networks. In Figure 4, each node represents a significant pathway and edge represents a pathway crosstalk, i.e., a significant overlap of the component genes between two linked pathways. A total of 109 pathways were obtained which were divided into five GO groups that represent the pathways with GO terms with colours in the nodes being based on their respective GO groups and shared genes between them respectively (Figure 5). ClueGo also provides pie-chart which shows the summarized output of all GO groups represented by different colours along with their occurrence in the group with their respective percentages (Figure 6). The biological role of the genes visualized with ClueGo are associated with GO and KEGG terms-Pathways in cancer, cellular response to organic substances, cell population proliferation, circulatory system development and negative regulation of metabolic process.

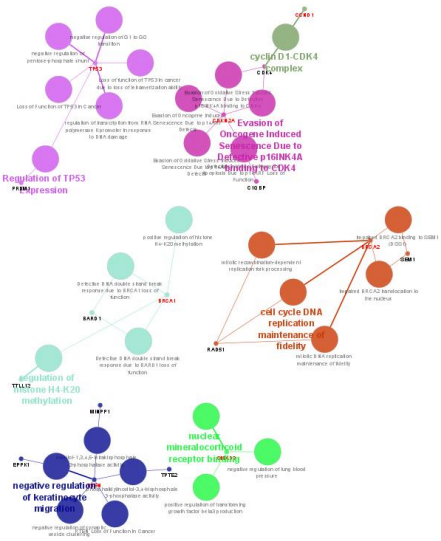

Figure 4: Pathways crosstalk and functional map obtained using Cytoscape plug-in ClueGo

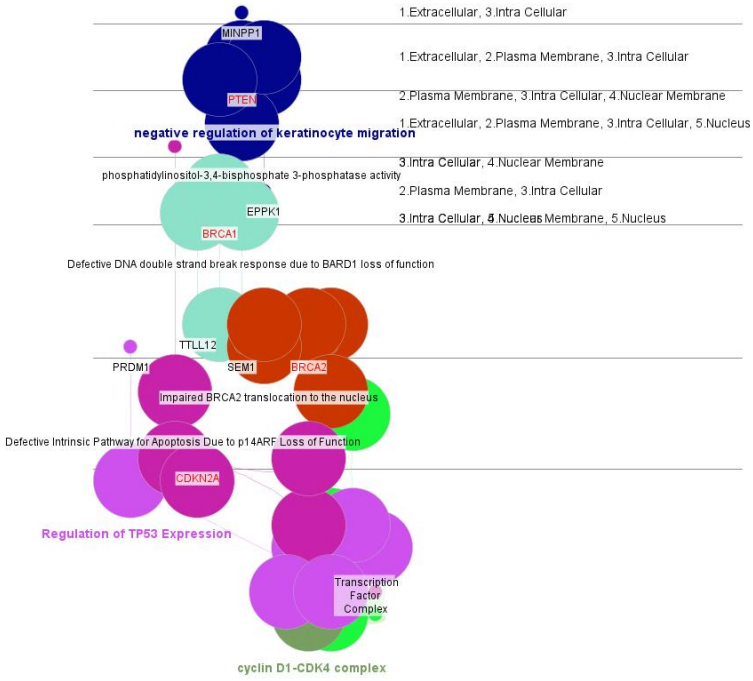

Figure 5: Potential markers and their cellular location obtained from cluepedia plug-in of cytoscape

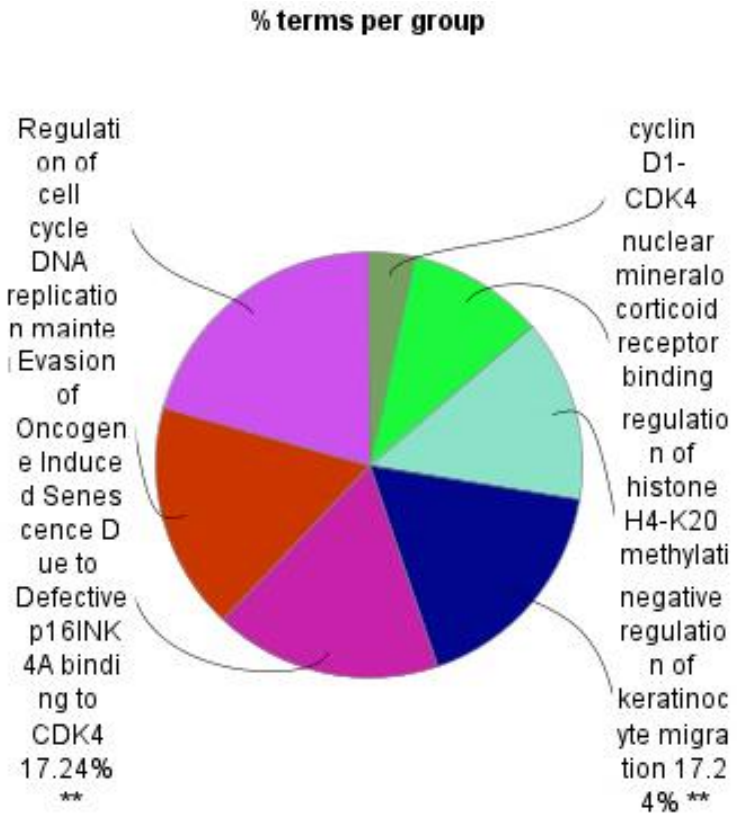

Figure 6: Pie-Chart showing the output of all the GO groups obtained from Cytoscape plugin ClueGO

Identification of potential biomarkers

The CluePedia plugin in Cytoscape was employed in this study to map the localization of biomarkers on specific cellular compartments using Gene Ontology (GO) terms. Out of the initial set of 10 genes, CluePedia provided cellular location information for only three genes, namely PTEN, BRCA1, and BRCA2. These genes are considered potential biomarkers for PCOS, uterine, ovarian, cervical, and breast cancers. Three hub genes that are frequently linked to these kinds of malignancies were effectively discovered by the study, and these conclusions were confirmed by existing literature.

Through the PI3K/AKT pathway, PTEN prevents cell proliferation and functions as a tumour suppressor. It is regarded as a passable risk factor for PCOS as well [16]. It is one of the most common mutation associated with endometrial cancers [17]. CCND1 is frequently reported to be overexpressed in breast, ovarian, and uterine malignancies and is implicated in encouraging cell cycle progression [18]. The BRCA1 and BRCA2 genes are frequently altered in hereditary breast and ovarian malignancies and play significant roles in DNA repair [7,19,20]. The discovery of these genes offers an important new understanding of the molecular processes driving PCOS-related reproductive malignancies.

Validating Study

The gene expression analysis using dataset GSE138518 having 6 control and 6 PCOS samples was done using R-Bioconductor package *limma*. The criterion used was: FDR adjusted p-value less than 0.05 and absolute log2 (fold-change) greater than 1.0. Total of 225 differentially expressed genes between Control and PCOS samples were shortlisted. Further the network construction was done using string to visualize the interactions between the genes. The string network was then exported to Cytoscape where cluster analysis followed by hub genes analysis using clusterOne and cytoHubba plug-ins respectively was done. 10 hub genes were identified and their interaction visualization with the identified PTEN, BRCA1 and BRCA2 was done to understand the linking pattern of the identified hub genes with them.Top of Form

Results and Discussion

In our current study, we have specifically identified three genes, PTEN, BRCA1, and BRCA2, which show promise as potential biomarkers for PCOS associated uterine, ovarian, cervical, and breast cancers. The validating study provided us with 10 hub genes and when their interactions with these three genes were visualized using STRING. The network showed us the mitigating factor PTPRC gene which connects the cancer progression genes and the genes involved in PCOS. The PCOS is not considered as a major risk factor for causing cancer, but substantial studies have shown its linkage with cancers in women. The association of PTEN, BRCA1 and BRCA2 with PTPRC, highlights the significance of considering PCOS and one of the risk factors in women to cause cancer.

This study is unique in that it is the first of its type to provide insight into the molecular processes behind the association of PCOS, uterine, ovarian, cervical, and breast malignancies. We aim to offer important insights into the complex biological connections between these diseases by identifying and examining these three genes. Our findings may help us learn more about the same pathways and procedures that these diseasesonset and progression require.

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Competing Interest

The authors have no relevant financial or non-financial interests to disclose.

Author's Contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Ritika Patial. The first draft of the

manuscript was written by Ritika Patial and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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