

Bioinformatic Analysis Identifies CAV1, KDR, and ERBB Signaling Pathways in BRCA-Associated Ovarian Cancer

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ABSTRACT

Ovarian cancer, the deadliest gynecological cancer in women, is strongly associated with mutations in the *BRCA1* and *BRCA2* genes. However, the molecular mechanisms behind this association remain incompletely understood. Using two datasets from the National Center for Biotechnology Information (NCBI), GSE135820 (primary ovarian cancer) and GSE135712 (metastatic ovarian cancer), gene expression profiling was performed using the GEO2R web tool. These datasets included ovarian tumor samples from premenopausal women carrying *BRCA1* and/or *BRCA2* mutations, which were compared with tumors from ovarian cancer patients without the mutations. The significance threshold was set at an adjusted p-value < 0.05 (Benjamini-Hochberg false discovery rate (FDR)). Differentially expressed genes were prioritized using Venn diagrams and the STRING database for protein-protein interaction (PPI) and functional enrichment analyses. Two targets were prioritized among the datasets: Caveolin 1 (CAV1) and Kinase Insert Domain Receptor (KDR). Our analysis showed that *CAV1* was downregulated in primary ovarian cancer but upregulated in metastatic tissue. In contrast, *KDR* was upregulated in both. Protein-protein interaction (PPI) network analysis revealed that the ERBB signaling pathway was the most significantly enriched for both targets, which suggests a potential link between the ERBB signaling pathway and the effect of BRCA1/2 mutations in ovarian cancer tissues. Overall, the findings identify an association between ERBB signaling and BRCA1/2-mutated ovarian cancer which can help contribute to future investigation of its potential biological and therapeutic relevance.

INTRODUCTION

Ovarian cancer is the deadliest gynecologic malignancy and remains one of the leading causes of cancer-related death among women worldwide (Caruso et al., 2025). Despite improvements in surgery and chemotherapy, survival rates remain poor because many patients are diagnosed with ovarian cancer in the later stages (Colombo et al., 2017). Because ovarian cancer can progress and metastasize rapidly, the need to better understand the molecular mechanisms that drive ovarian cancer progression and identify biomarkers is crucial in improving diagnosis and targeted treatment (Sureka & Zaheer, 2025).

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Among the strongest inherited genetic risk factors for ovarian cancer are mutations in the BRCA1 and BRCA2 genes (Petrucelli et al., 1993). BRCA1 and BRCA2 are tumor suppressor genes that play an important role in maintaining genomic integrity through homologous recombination-mediated DNA repair (Li & Greenberg, 2012). These proteins repair double-stranded DNA breaks, preventing the accumulation of deleterious genetic alterations. When either gene becomes mutated, DNA repair efficiency is reduced, leading to genomic instability and an increased susceptibility to multiple types of cancers, specifically ovarian and breast cancer (Vollebergh et al., 2011). Even though BRCA mutations are well established as major inherited risk factors for ovarian cancer, the downstream molecular mechanisms that increase disease progression are still not fully understood (Toss et al., 2015). Identifying dysregulated genes and signaling networks is essential for understanding how BRCA mutations influence tumor initiation, progression, angiogenesis, and metastasis.

By understanding how BRCA mutations influence gene expression and cellular signaling pathways, scientists can better understand cancer progression. Tumor initiation, angiogenesis, invasion, metastasis, and resistance to therapy are regulated by complex molecular networks involving hundreds of interacting genes and proteins (Lugano et al., 2019). Identifying these dysregulated pathways can improve our understanding of ovarian cancer biology while revealing potential biomarkers that can help in diagnosis, prognosis, and therapeutic decision-making (Atallah et al., 2021).

Public repositories such as the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) contain thousands of gene expression datasets that allow researchers to analyze different molecular profiles in different patient populations (*GEO - NCBI*, n.d). Through differential gene expression analysis, genes that are significantly altered can be pinpointed, while protein-protein interaction network analysis and functional enrichment analysis help explain how the genes interact within broader biological pathways (Rosati et al., 2024).

Although there have been numerous studies examining BRCA-associated ovarian cancer, not many studies have compared both primary and metastatic ovarian tumors while using differential gene expression analysis, protein-protein interaction networks, network centrality analysis, and functional enrichment analysis to identify conserved molecular targets (Paul & Paul, 2014). Comparing the disease's stages provides a chance to identify genes and signaling pathways that remain important throughout ovarian cancer progression rather than being limited to a single stage of disease. This preliminary study aims to unveil the molecular mechanism behind BRCA1/BRCA2 mutations in ovarian cancer tissue of premenopausal women. It was hypothesized that BRCA1/BRCA2-mutated ovarian tumors would show conserved alterations in gene expression and signaling pathways across primary and metastatic disease. Because of this, potential molecular targets associated with BRCA-related ovarian cancer could be identified.

METHODS

Study Design:

This study used a retrospective computational bioinformatics approach to study molecular alterations associated with BRCA1 and BRCA2 mutations in ovarian cancer. Datasets from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) were analyzed through differential gene expression analysis, protein-protein interaction (PPI) network analysis, network centrality analysis, and functional enrichment analysis (*Home - GEO - NCBI*, n.d.). These were used to identify shared and differentially regulated genes and signaling pathways associated with BRCA-mutated ovarian cancer across primary and metastatic disease.

Dataset Selection:

Publicly available microarray datasets of gene expression were used to represent ovarian cancer in premenopausal women. NCBI GEO series analyzed were GSE135820 (*GEO GSE135820*), representing primary ovarian tumors, and GSE135712 (*GEO GSE135712*), representing metastatic ovarian tumors. Samples were grouped by tumor type (primary ovarian tumor vs metastatic lesion) and by BRCA1/2 mutation vs non-mutated patients. Samples that were lacking clear clinical annotation or mutation status were not included.

Data acquisition and preprocessing:

Gene expression data were analyzed using GEO2R (*GEO2R - GEO - NCBI*, n.d.), an online differential gene expression analysis platform provided by the NCBI that utilizes the Bioconductor limma package (*Limma*, n.d.). Probe summarization and normalization were performed using the default GEO2R pipeline, and log2 transformation was applied to stabilize expression values across samples. All normalized expression values were used for analyses.

Differential gene expression analysis:

Differential expression between the BRCA-mutated groups and the non-mutated groups was analyzed using GEO2R. Statistical significance was determined using moderated t-tests with Benjamini-Hochberg false discovery rate correction. An adjusted *p*-value < 0.05 was considered statistically significant and was retained for downstream analyses (Benjamini & Hochberg, 1995).

Gene overlap and Target Prioritization:

Significant gene lists from each comparison (UpPrimaryovarian cancer, Downe Primary ovarian cancer, UpMets, DownMets) were compared using Venn diagram analysis to identify overlapping genes across the datasets and expression categories. CAV1 and KDR were prioritized because they were the overlapping targets identified through this comparative analysis. They were subsequently evaluated using protein-protein interaction and functional enrichment analyses. KDR was upregulated in both primary and metastatic datasets. CAV1 was downregulated in the primary dataset and upregulated in the metastatic dataset. Because of this, KDR showed consistent directional expression across disease stages, while

CAV1 showed a shared target with stage-dependent expression.

Protein-Protein Interaction Network/Network Centrality analysis:

Prioritized genes were analyzed using the STRING database to study potential protein-protein interactions and identify biologically relevant molecular networks. STRING combines both experimentally validated and computationally predicted protein interactions to create interaction networks and identify functionally related gene clusters. Network connectivity and functional associations were tested to pinpoint which genes occupied central positions within the interaction network and had greater biological significance. Protein interaction networks generated by STRING (*STRING: Functional Protein Association Networks*, n.d.) were further analyzed in Cytoscape (Otasek et al., 2019) to visualize the network architecture and identify highly connected hub genes.

Functional enrichment and network analysis:

Functional enrichment analysis was performed using STRING to identify biological processes and molecular functions that were enriched among the prioritized genes. Gene Ontology (GO) Biological Process and Molecular Function analyses were used to determine the biological pathways and molecular functions most strongly associated with BRCA-mutated ovarian cancer.

Survival Analysis:

Kaplan-Meier survival data for CAV1 and KDR were taken from the Human Protein Atlas (HPA) using The Cancer Genome Atlas (TCGA) ovarian cancer cohort. Patients were arranged into high and low-expression groups using the expression cutoff that was reported by HPA. The analysis is used as supplementary prognostic context rather than direct validation of the BRCA-associated findings as the cohort was not arranged by BRCA1/2 mutations.

RESULTS

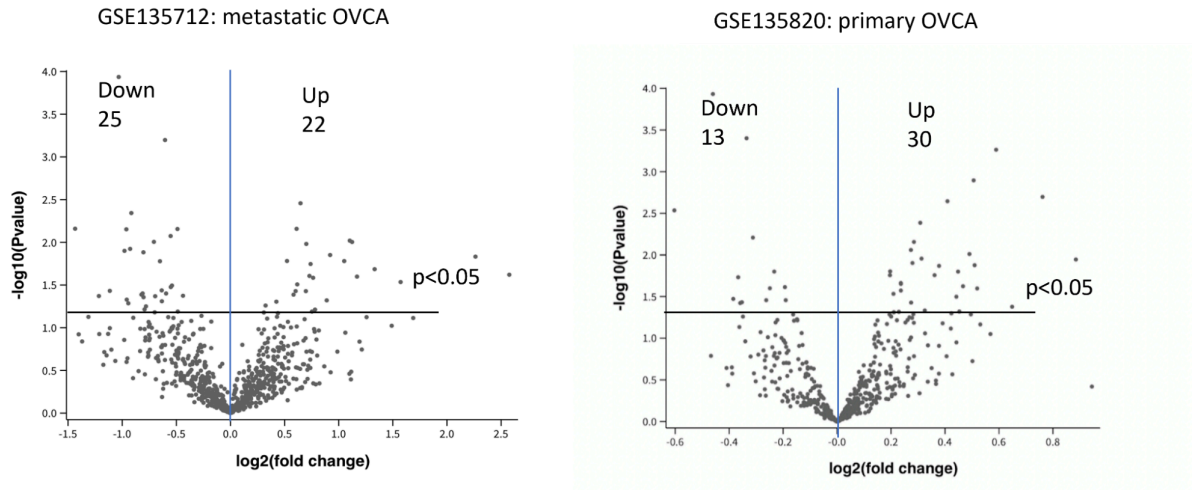


Figure 1: Volcano plots showing differential gene expression between BRCA1/2-mutated and non-mutated ovarian cancer samples in the metastatic ovarian cancer dataset GSE135712 (left) and primary ovarian cancer dataset GSE135820 (right). The Benjamini-Hochberg false discovery rate was used with an adjusted p-value < 0.05 to define the statistically significant differentially expressed genes.

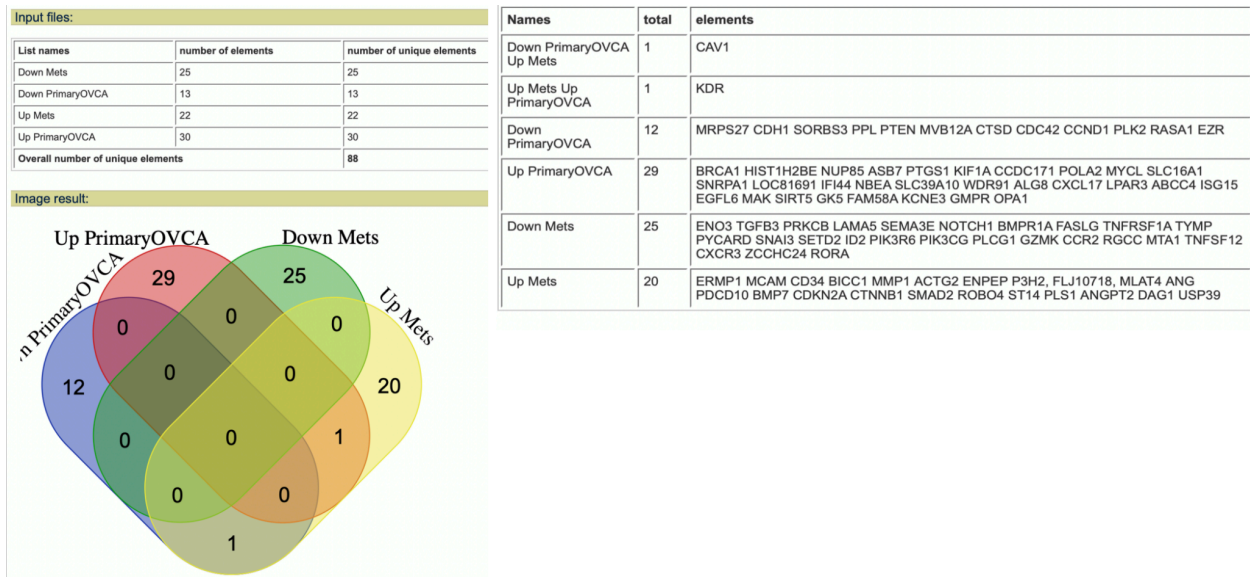


Figure 2. Venn diagram analysis of the statistically significant upregulated and downregulated genes from the primary and metastatic ovarian cancer datasets to find common targets associated with germline mutation (BRCA1 and BRCA2) among both datasets. The two prioritized molecular targets were caveolin

1 (CAV1) and kinase insert domain receptor (KDR). KDR showed consistent upregulation across datasets. CAV1 showed stage-dependent differential expression.

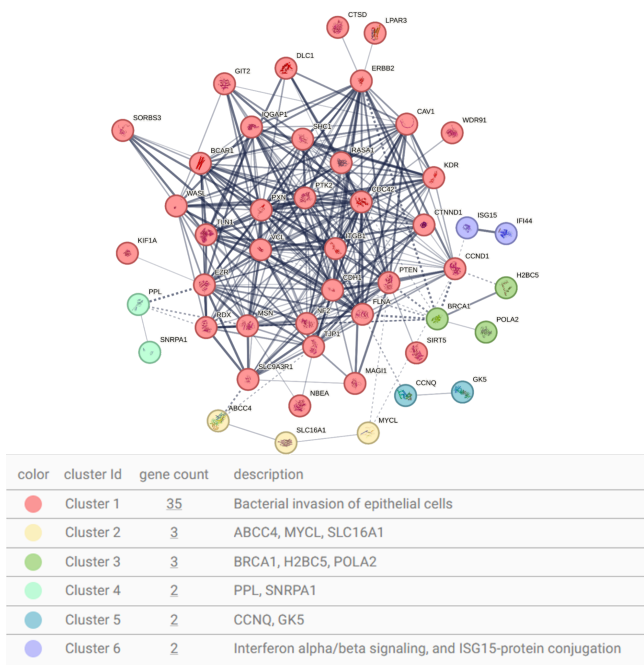


Figure 3. Protein-protein interaction (PPI) Network Analysis of Primary ovarian cancer dataset GSE 135820 using differentially expressed gene identified at an adjusted p-value <0.05. From the data, CAV1 and KDR were two prominent genes with high connectivity. This suggests that they may occupy central positions within the identified interaction network.

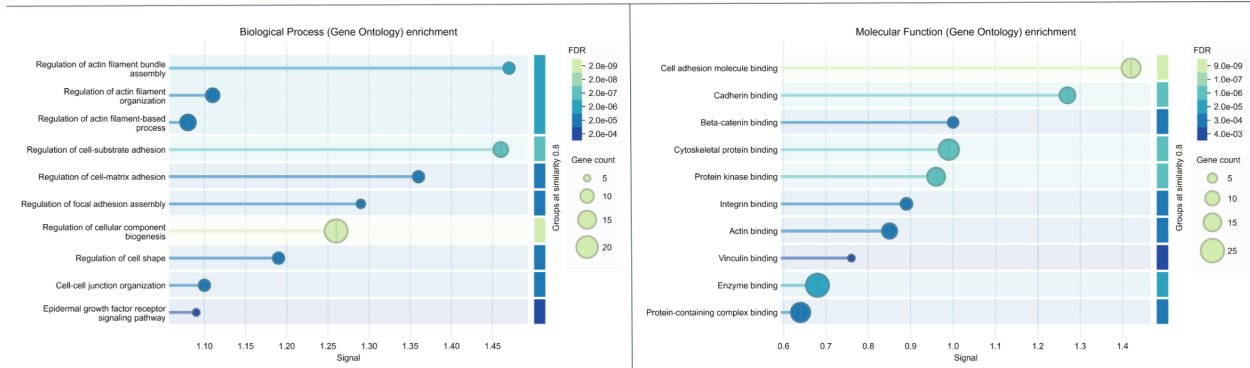


Figure 4. Functional Enrichment Analysis of Primary Ovarian Cancer (GSE135820). Dot plots display the top enriched Biological Processes (left) and Molecular Functions (right) for differentially expressed genes. The importance of “Epidermal growth factor receptor signaling pathway” and “Protein kinase binding” in these profiles indicates the potential involvement of the ERBB signaling pathway in BRCA-associated ovarian cancer.

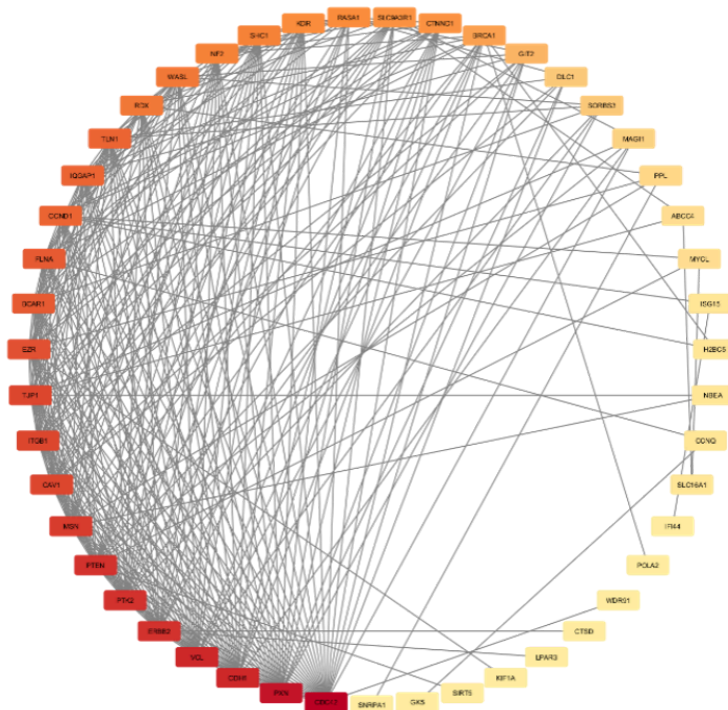


Figure 5. Cytoscape Network Centrality Analysis of the Primary ovarian cancer (dataset GSE 135820). The network shows the amount of connectivity among the expressed genes. Cytoscape showed CAV1 and members of the ERBB signaling pathway as “hub” genes, which had the highest degree of linkage to other nodes.

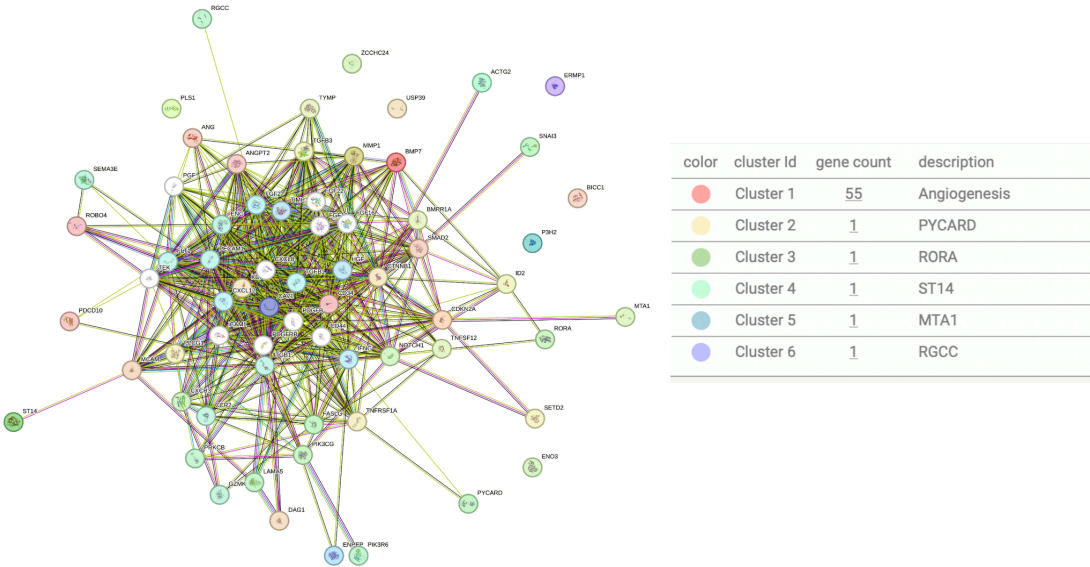


Figure 6. Protein-Protein (PPI) network analysis of metastatic ovarian cancer. From the STRING analysis METS ovarian cancer (Dataset GSE 135712), cluster 1 (red) contains 58 genes that are primarily associated with angiogenesis. This provides the basis for prioritizing KDR and CAV1 as central nodes.

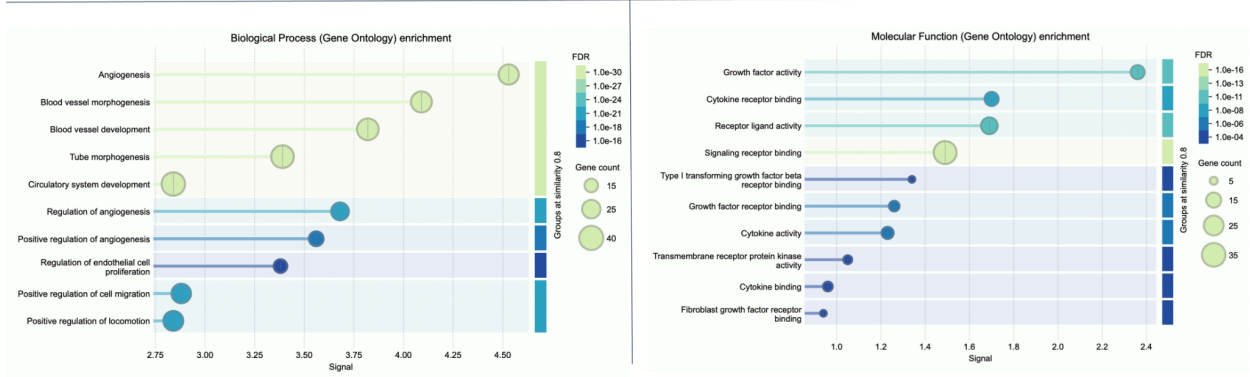


Figure 7. Functional Enrichment Analysis of Prioritized Targets. Dot plots show the top-enriched biological processes and molecular functions. Through the analysis, there is significant enrichment in angiogenesis, blood vessel morphogenesis, and growth factor activities, which identify biological processes associated with the prioritized targets KDR and CAV1.

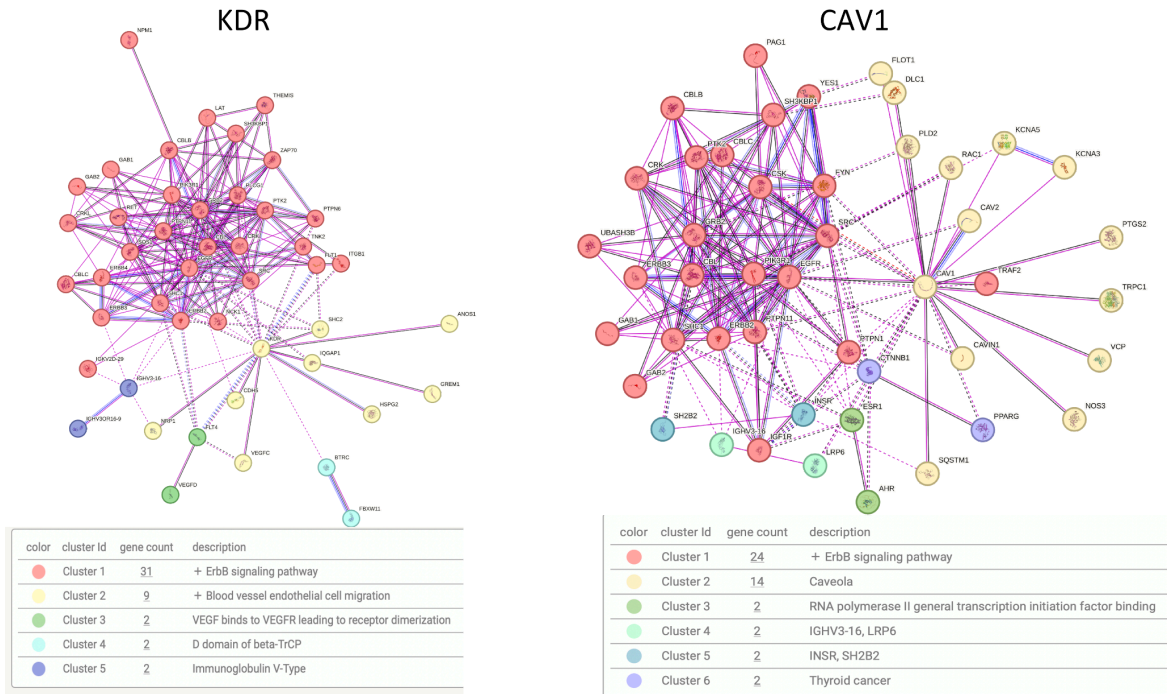


Figure 8. Protein-protein interaction (PPI) network analysis of the two prioritized targets, KDR and CAV1, in ovarian cancer associated with BRCA1/BRCA2 mutations. On the left is KDR, which shows a dense cluster (n=31) that is associated with the ERBB signaling pathway and significant involvement in endothelial cell migration, which is consistent with an association with angiogenesis-related processes. The right side represents the CAV1 STRING network, which shows a dense cluster (n=24) that is associated with the ERBB signaling pathway.

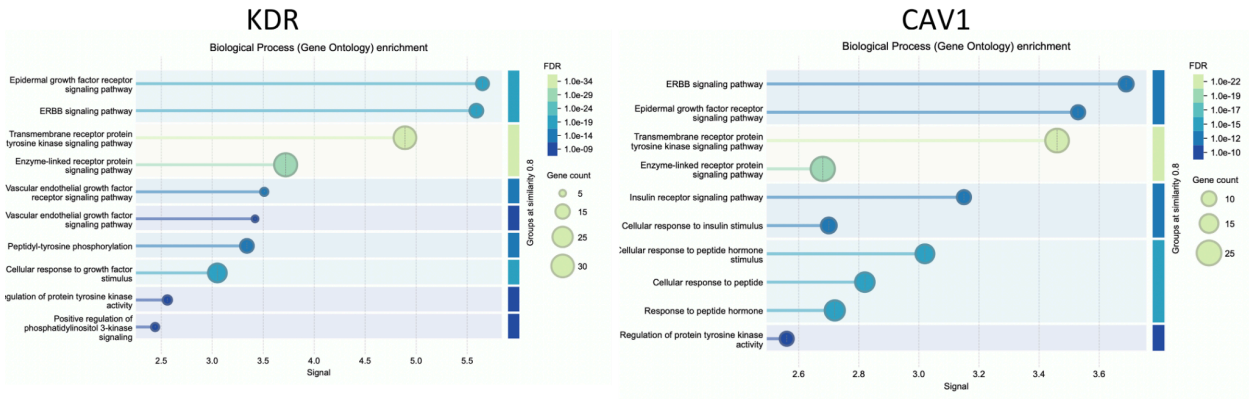


Figure 9. Gene Ontology (GO) Functional enrichment analysis of KDR and CAV1 determined that the most significant biological process was associated with the ERBB signaling pathway ($FDR < 1.0e^{-22}$) among both prioritized targets in ovarian cancer associated with BRCA1 and BRCA2 mutations. This

suggests that the ERBB signaling pathway may represent an important pathway associated with BRCA1/2-mutated ovarian cancer.

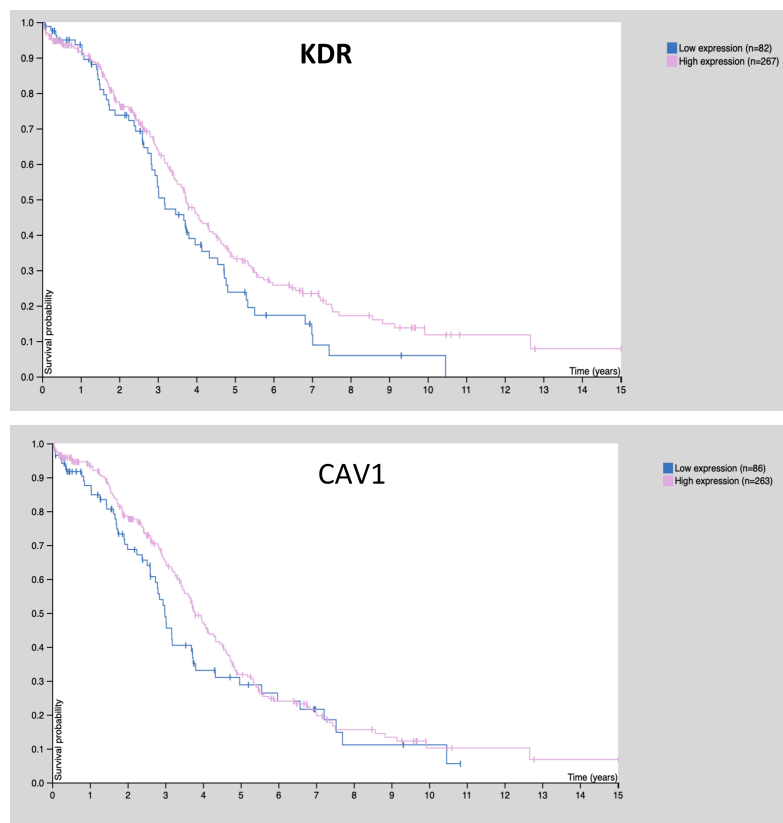


Figure 10. Kaplan-Meier survival curves of CAV1 (right) and KDR (left) from the Human Protein Atlas. The curve were obtained from the Human Protein Atlas using the TCGA ovary serous cystadenocarcinoma cohort compare overall survival between patients with high and low CAV1 or KDR expression. The groups were evaluated using the log-rank test. CAV1 and KDR were classified by HPA as not prognostic on this cohort. These analysis give supplementary prognostic context and do not directly validate the BRCA-associated findings as the TCGA cohort was not stratified by BRCA1/2 mutations.

DISCUSSION

This study investigated the molecular mechanism associated with BRCA1 and BRCA2 mutations in ovarian cancer through bioinformatic analyses of two publicly available gene expression datasets representing primary and metastatic ovarian tumors. Across different analyses, CAV1 and KDR emerged as prioritized molecular targets, while functional enrichment analyses repeatedly identified the ERBB signaling pathway as one of the most significantly enriched biological pathways. KDR was upregulated in both primary and metastatic datasets, while CAV1 was downregulated in primary tumor and upregulated in metastatic tumor. This shows there is a stage-dependent differential expression of CAV1.

CAV1 was found to be one of the most prominent genes within both ovarian cancer datasets. CAV1 encodes caveolin-1, a membrane-associated scaffolding protein involved in signal transduction, cell proliferation, and regulation of multiple intracellular signaling pathways (Wiechen et al., 2001). Previous studies have shown CAV1 to function as either a tumor suppressor or an oncogene depending on the tissue type and stage of tumor development (Chatterjee et al., 2015; Fu et al., 2017). In this study, CAV1 was downregulated in primary ovarian tumors but upregulated in metastatic tumors. This stage-dependent expression patterns shows that the association between CAV1 expression and BRCA-associated ovarian cancer may change between primary and metastatic disease. Experimental validation is still needed to determine the biological significance of this expression pattern.

KDR also emerged as a highly prioritized target across multiple analyses. KDR encodes vascular endothelial growth factor receptor 2 (VEGFR2), a receptor that plays a central role in angiogenesis through regulation of endothelial cell proliferation, migration, and new blood vessel formation (Marques et al., 2024). Increased KDR activity has been associated with tumor progression because rapidly growing tumors require an adequate blood supply to sustain continued growth and metastasis (Edelbauer et al., 2010). Because KDR was upregulated in both the primary and metastatic ovarian cancer datasets, it suggests a consistent association between KDR expression and angiogenic-related signaling across both disease stages.

One of the major findings of this study was the repeated enrichment of the ERBB signaling pathway across multiple bioinformatic analyses. Members of the ERBB receptor family regulate numerous cellular processes, including proliferation, differentiation, survival, migration, and apoptosis (Appert-Collin et al., 2015). BRCA1 and BRCA2 mutations have traditionally been associated with defects in homologous recombination-mediated DNA repair, but through the study, the findings identify an association between BRCA1/2 mutation status and enrichment of the growth factor-related pathways. However, the study does not establish a causal relationship between BRCA mutations and these signaling alterations.(Bhat-Nakshatri et al., 2024). Through differential gene expression analysis, protein-protein interaction networks, and functional enrichment analysis, the ERBB signaling pathway was repeatedly identified, which is consistent with the hypothesis that dysregulation of this pathway represents a biologically meaningful association with BRCA mutation status.

Identifying molecular pathways consistently associated with BRCA-mutated ovarian cancer may contribute to biomarker discovery and inform the development of different personalized therapeutic strategies. Identification of additional pathways associated with BRCA-mutated ovarian cancer may contribute to future biomarker research and therapeutic investigation. The repeated identification of ERBB signaling, CAV1, and KDR in these computational analyses provides hypotheses for future studies evaluating their potential therapeutic relevance. (Rojas-Salazar et al., 2024). Experimental validation is needed before therapeutic implications can be established.

Many strengths of this study include that two independent ovarian cancer datasets representing both primary and metastatic disease were analyzed to compare molecular targets across different stages of

tumor progression. In addition, there were multiple bioinformatic approaches, including differential gene expression analysis, protein-protein interaction network analysis, network centrality analysis, and functional enrichment analysis, used to compare biologically relevant targets. The convergence of findings across these approaches strengthens the prioritization of CAV1, KDR, and ERBB signaling. Despite these strengths, there are still limitations. This study was fully computational and would need laboratory validation to confirm the biological significance of CAV1, KDR, and ERBB signaling in ovarian cancer.

FUTURE DIRECTIONS

Future studies should focus on validating these computational findings using experimental approaches such as immunohistochemistry, quantitative PCR, or RNA sequencing to evaluate protein and gene expression in ovarian tumor tissues. These studies could potentially provide additional evidence regarding the therapeutic potential of these molecular targets.

CONCLUSION

This study integrated bioinformatic analyses to test molecular changes that are associated with BRCA1 and BRCA2 mutations in ovarian cancer. Through different analyses such as differential gene expression analysis, protein-protein interaction network analysis, and functional enrichment, CAV1 and KDR were prioritized as molecular targets, and the ERBB signaling pathway was identified through functional enrichment analysis. Even though there needs to be laboratory validation, these findings improve the understanding of the molecular landscape of BRCA-mutated ovarian cancer and identify CAV1, KDR, and ERBB signaling as candidates for future investigations.

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