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Single nucleotide polymorphisms in ovarian cancer impacting lipid metabolism and prognosis: an integrated TCGA database analysis

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Abstract

Ovarian cancer (OC) stands as a formidable adversary among women, remaining a leading cause of cancer-related mortality owing to its aggressive and invasive nature. Investigating prognostic markers intricately linked to OC's molecular pathogenesis represents a critical avenue for enhancing patient outcomes and survival prospects. In this comprehensive study, we embarked on a bioinformatics journey, leveraging the vast repository of single nucleotide polymorphism (SNP) data from OC patients available within the TCGA database. Our overarching goal was to unearth the genetic underpinnings of OC, shedding light on potential prognostic markers that could significantly impact clinical decision-making and patient care. Our meticulous analysis led to the discovery of five mutated genes—APOB, BRCA1, COL6A3, LRP1, and LRP1B—engaged in the intricate world of lipid metabolism. These genes, previously unexplored in the context of OC, emerged as prominent figures in our investigation, showcasing their potential roles in OC progression. The intricate interplay between lipid metabolism and cancer development has garnered considerable attention in recent years, and our findings underscore the relevance of these genes in the context of OC. To fortify our discoveries, we delved into the realm of survival analysis, a pivotal component of our investigation. The results yielded compelling evidence of significant correlations between patient survival and the expression levels of the aforementioned genes. This critical insight underscores the potential utility of these genes as prognostic markers, illuminating a path toward more personalized and effective approaches to patient care. Our study represents a multifaceted approach to unraveling the complex molecular pathogenesis of OC. By harnessing the power of high-throughput data mining, we uncovered genetic insights that may reshape our understanding of this formidable disease. We complemented these findings with advanced techniques such as RT-qPCR and Western blot, further dissecting the intricacies of OC's molecular landscape. This holistic approach not only deepens our understanding but also provides essential bioinformatics information that holds promise in assessing patient prognosis. In summary, our study represents a significant stride in the quest to decode the molecular intricacies of ovarian cancer. Our findings spotlight the potential prognostic significance of APOB, BRCA1, COL6A3, LRP1, and LRP1B, inviting further exploration into their roles in OC progression. Ultimately, our research carries the potential to shape the future of OC management, offering a glimpse into a more personalized and effective approach to patient care.

Keywords Ovarian cancer, Prognostic markers, Single nucleotide polymorphism, Lipid metabolism, Patient prognosis

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Introduction

Ovarian cancer (OC) remains a formidable challenge in the realm of gynecologic malignancies due to its high lethality. It is characterized by a lack of reliable early diagnostic methods and specific warning signs, resulting in most OC cases being diagnosed at advanced stages with a grim prognosis [1]. Recent genome-wide association studies (GWAS) have identified common genetic susceptibility loci linked to ovarian cancer [2]. These susceptibility loci, particularly single nucleotide polymorphisms (SNPs) residing within genes participating in diverse biological pathways, have emerged as potential indicators of OC. These genetic variations contribute to differences in disease susceptibility and severity among individuals, underscoring the intricate mechanisms driving ovarian cancer development and progression [3].

Recent studies using radiolabeled substrates have unveiled the dynamic nature of lipid metabolism in cancer cells [4], particularly their active synthesis and uptake of lipids. The distinction in lipid metabolism between normal and cancer cells has long been considered a viable target for cancer therapy [5, 6]. Lipids of various classes, including fatty acids, glycerolipids, glycerophospholipids, sphingolipids, and sterol lipids, have been implicated in cancer development and chemotherapy [7–9]. Notably, in certain cancers like colon and ovarian cancer, endothelial cells have been found to induce metabolic reprogramming in cancer cells, leading to an overexpression of polyunsaturated fatty acids (PUFA) and glycerophospholipids [10, 11]. Additionally, recent research has illuminated the role of cancer-associated fibroblasts (CAFs) in enhancing lipid synthesis [12].

Despite the growing understanding of lipid metabolism's significance in cancer, the role of SNPs within the lipid metabolism pathway, their impact on genes influencing cancer progression, and their potential functional implications concerning tumor metastasis remain largely unexplored. This study aims to bridge this knowledge gap by utilizing publicly available TCGA datasets. Our objective is to conduct a comprehensive analysis of genes associated with the lipid metabolism pathway, investigating the associations between genetic variants within these genes and the survival outcomes of OC patients. This research endeavor strives to unravel the complex interplay between genetic polymorphisms, lipid metabolism, and the clinical trajectory of OC.

By delving into the associations between genetic variants in lipid metabolism-related genes and the survival of OC patients, this study seeks to contribute valuable insights to the field of ovarian cancer research. The identification of specific genetic markers and their potential influence on lipid metabolism may pave the way for more targeted therapeutic approaches and personalized treatment strategies for OC. Considering the therapeutic role of microRNAs in diseases such as tumors, inhibiting the expression of key genes involved in lipid metabolism in OC cells through microRNAs, thereby inhibiting tumor progression, may offer a potential therapeutic strategy [13–15].Additionally, understanding the genetic underpinnings of lipid metabolism in cancer could open doors to innovative interventions and prognostic tools that enhance our ability to combat this formidable disease.

Materials and methods

Data processing and analysis

As data of SNPs in the Cancer Genome Atlas (TCGA) (https://portal.gdc.cancer.gov/) is not open, we analysis the condition of SNPs in OC via cBioportal database [16]. We also downloaded the normal ovarian surface epithelium and the expression profiles of OC from UCSCXena (https://xena.ucsc.edu) on May 14, 2024.The difference data were analyzed to integrate and standardize raw data using edgeR soft packages (version 4.3.0) and to obtain different expression genes and their expression levels.

Functional enrichment and pathway analysis of mutant genes

In order to better understand the dysfunction caused by these mutant genes, we used the DAVID (https://david.ncifcrf.gov/) database on May 22, 2024 to perform gene ontology (GO) and Kyoto Gene and Genome Encyclopedia (KEGG) enrichment analysis on genes with more than 20 mutant samples. As an open source platform, DAVID can be used to determine the relationship between target molecules. By selecting GO items and KEGG pathway, and using P-value < 0.05 as the cut-off condition, molecular function (MF), biological process (BP), cell component (CC) and KEGG pathway screening can be completed in mutant genes enrichment.

Construction of mutant gene PPI network and gene expression analysis

The construction of biological networks can be expanded in the form of actual system scales and provide a visual representation of molecular interactions. We use the STRING database (https://string-db.org) on May 27, 2024 to characterize the protein–protein interaction (PPI) network base on mutant genes, the confidence score > 0.9 was regarded as the cut-off criterion. We visualized the generated PPI network by using R language software (version 4.3.0).

Mapping of Kaplan–Meier survival curve of mutant genes and screening of prognostic biomarkers

We used the Kaplan–Meier plotter (https://kmplot.com) on June 4, 2024 to evaluate the progression-free survival (PFS) and overall survival (OS) of patients with ovarian cancer. This online tool can be used for meta-analysis and biomarker identification. By drawing a Kaplan–Meier diagram, we assessed the impact of mutant genes on the prognosis of OC patients, and screened mutant genes that can be used as prognostic biomarkers for OC.

Cell Lines and culturing

Human OC cell lines OVCAR3, OVCAR5, OVCAR8, OV90, and CAOV3 were all purchased from Cell Bank of the Chinese Academy of Sciences (Shanghai, China). Immortalized human ovarian epithelial cell line IOSE80 was from American Type Culture Collection (ATCC, Manassas, VA). All of the cells were cultured following the instructions of ATCC.

Reagents

The antibodies used in this study were against apolipoprotein-B (APOB) (ab27626, Abcam, Cambridge, MA, USA), breast cancer susceptibility gene (BRCA1) (ab238983, Abcam, Cambridge, MA, USA), Collagen Type VI Alpha 3 Chain (COL6A3) (ab231025, Abcam, Cambridge, MA, USA), LDL Receptor Related Protein 1 (LRP1) (#64,099, Cell Signaling Technology), LRP1B (LDL Receptor Related Protein 1B) (PA5-47,836, Invitrogen, USA) and β-actin (GB11001, Servicebio, Wuhan, China) for western blotting. Secondary antibodies were purchased from Jackson ImmunoResearch (West Grove, PA, USA).

Quantitative real-time PCR

Total RNA was extracted from the cells in each group using Trizol kits. The qualified RNA samples were then reverse transcribed to synthesize complementary DNA (cDNA) with the PrimeScript™RT reagent Kit (RR047A, TAKARA, Japan). The specific reaction conditions were set to 37 °C for 30 min followed by 85 °C for 30 s. For quantitative analysis, the ABI 7500 fluorescence PCR amplification instrument (Applied Biosystems; Thermo Fisher Scientific, Inc.) was employed. Ribosomal Protein S18 (RPS18) served as an internal control, and the Ct values were analyzed using the $2^{-\Delta\Delta}$Cq method. The primer sequences used in this experiment are detailed in Table 1.

Western blotting analysis

For western blotting, total protein was extracted from cells using RIPA lysis buffer supplemented with a protease inhibitor (Beyotime, Jiangsu, China). Equal amounts of protein (60 μg per lane) were separated on 10% or 8% SDS–polyacrylamide gels and subsequently transferred onto Pure Nitrocellulose Blotting membranes (Pall Life Science, AZ, USA). The membranes were then blocked with 5% non-fat milk for 1 h and incubated overnight at 4 °C with primary antibodies targeting APOB, BRCA1, COL6A3, LRP1, LRP1B, and β-actin. After washing, the membranes were treated with secondary antibodies. Immunoreactive bands were visualized using the Odyssey Infrared Imaging System (Gene Company Limited, Hong Kong, China).

Table 1 The oligonucleotide sequence of primers used in this experiment

Genes	Forward primer (5′–3′)	Reverse primer (5′–3′)
APOB	ACAGCTGATTGAGGTGTCCA	AGCCACTGGAGGATGTGAGT
BRCA1	ACCTGATACCCCAGATCCCC	TTTGGAAGTGTTTGCTACCAGG
COL6A3	GGTTCCCTGCAAGTGCTC	ACCAGGATAGCCTCGGTAGC
LRP1	ACCACCCCTCCCGCCAGCCCA	AGCCCGAGCCGTCGCCTTGC
LRP1B	CCCCAAAGAGCAGCAAGTCT	CCAAGAGGACGAGAGGCACA
RPS18	CAGCCAGGTCCTAGCCAATG	CCATCTATGGGCCCGAATCT

Results

Data processing and analysis

We identified 407 genes that mutated in more than 20 samples in TCGA database. Of the 407 genes, 20 mutated in more than 50 samples (Fig. 1). Finally, 6145 differentially expressed genes that were up-regulated (log2 fold change > 2 and *P*-value < 0.01) in OC were obtained (Fig. 2).

Gene ontology and KEGG enrichment analysis of mutanted genes

To further understand the function of the mutated genes in the OC, we performed the GO and KEGG enrichment analysis for the identified 407 gene using David online tools. Analysis of GO shows that the BP gene is involved in the transcriptional regulation and signal transduction process, including the positive regulation of RNA polymerase II promoter transcription and intracellular signaling. Mutation genes affect ATP binding in the MF group. In the CC group, the mutant gene was specific to the cell membrane (Table 2). KEGG based analysis revealed the enrichment of mutant genes in many signal transduction pathways of cancer including the calcium signaling pathway and mitogen activated protein kinase (MAPK) signaling pathway (Fig. 3).

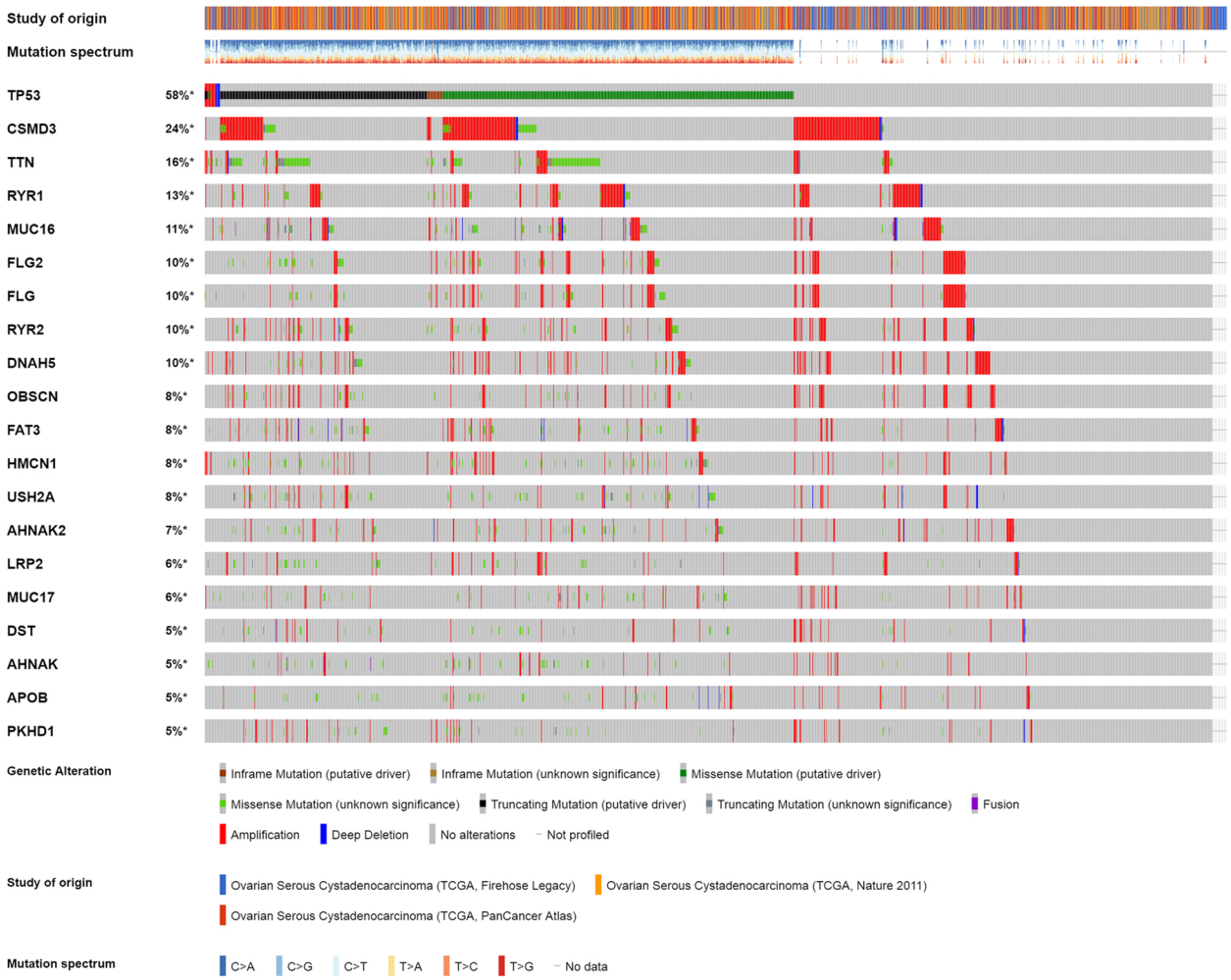

Fig. 1 A waterfall map of 20 genes that mutant in more than 50 samples derived from cBioPortal

Construction of PPI network of mutant genes associated with lipid metabolism

To further study the potential interaction between these mutant genes, the STRING was used to construct interactions between these mutant genes. As a result, a complex PPI network was constructed using a circlize package containing 42 genes [17] (Fig. 4).

In order to further explore the impact of lipid metabolism-related gene mutations on ovarian cancer, we selected the genes or a gene-set involved in the lipid metabolism pathway through the Molecular Signatures Database (http://software.broadinstitute.org/gsea/msigdb/index.jsp) on June 5, 2024, by the keyword "lipid" and "metabolism". After removal of duplicated genes and exclusion of genes on the X chromosome, 5 genes (*APOB*, *BRCA1*, *COL6A3*, *LRP1* and *LRP1B*) remained as candidate genes for further analysis. Among them, the expression levels in the mutant samples were decreased (Fig. 5). We also detect the expression of these genes by RT-qPCR and western blot in ovarian cancer cell lines (OVCAR3, OVCAR5, OVCAR8, OV90, and CAOV3) and normal ovarian epithelial cell line IOSE80 and found that they were all up-regulated in ovarian cancer cell lines (Fig. 6).

Kaplan–Meier survival curve analysis of mutant genes and screening of prognostic biomarkers

According to the Kaplan–Meier plotter, patients were divided into high expression groups and low expression groups according to the median expression value. The overall survival (OS) and progression-free survival (PFS) curves of five expression-related mutant genes are drawn. Taking P-value < 0.05 as the significance level, OS and PFS curves showed that regardless of whether potential confounding factors (e.g., age, stage, or treatment regimens) are taken into account, the high expression of *APOB*, *COL6A3*, *LRP1* and *LRP1B* in patients with ovarian cancer is related to the difference between OS and PFS, whereas the expression of *BRCA1* was only affect the PFS of patients (Fig. 7).

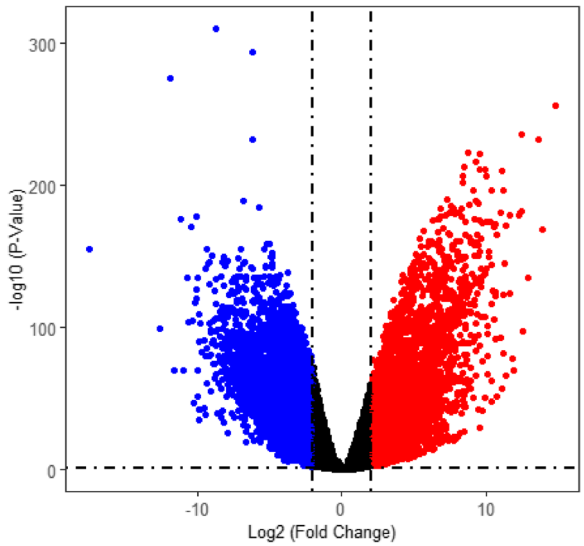

Fig. 2 The volcano diagram about differentially expresses mRNAs. Red dots represent up-regulated mRNA and blue dots represent down-regulated mRNA

Discussion

Ovarian cancer (OC) stands as a formidable adversary, maintaining its status as one of the most common causes of cancer-related mortality in women across the globe. Its insidious nature is compounded by the absence of reliable early diagnostic methods and the subtle manifestation of specific warning symptoms [18]. Often, OC patients receive their diagnosis at an advanced stage, significantly impacting prognosis. Recent advancements in genomics, particularly genome-wide association studies (GWAS), have illuminated a path toward understanding this formidable disease better. These studies have unveiled a multitude of common genetic susceptibility loci linked to OC [19, 20]. Single nucleotide polymorphisms (SNPs) within genes that regulate various biological pathways have emerged as potential markers for OC, offering a glimpse into the genetic variations that contribute to distinct susceptibilities and disease severities among individuals [21–23].

Table 2 Gene ontology analysis of 407 mutant genes in ovarian cancer

Category	Term	Count	*P*-value
GOTERM_BP_DIRECT	Membrane depolarization during action potential	13	1.3E-12
GOTERM_BP_DIRECT	Homophilic cell adhesion via plasma membrane adhesion molecules	14	6.01E-06
GOTERM_BP_DIRECT	Intracellular signal transduction	16	0.001528
GOTERM_BP_DIRECT	Heart development	9	0.002533
GOTERM_BP_DIRECT	Neuromuscular process controlling balance	6	0.002851
GOTERM_BP_DIRECT	Cell adhesion	10	0.005417
GOTERM_BP_DIRECT	Post-embryonic development	7	0.005467
GOTERM_BP_DIRECT	Cell proliferation	9	0.009558
GOTERM_BP_DIRECT	Protein autophosphorylation	8	0.010021
GOTERM_CC_DIRECT	Plasma membrane	58	5.51E-05
GOTERM_CC_DIRECT	Proteinaceous extracellular matrix	19	1E-08
GOTERM_CC_DIRECT	Myosin complex	10	9.69E-08
GOTERM_CC_DIRECT	Sarcolemma	10	2.59E-07
GOTERM_CC_DIRECT	Intracellular membrane-bounded organelle	9	0.004137
GOTERM_CC_DIRECT	Dendrite	9	0.008819
GOTERM_CC_DIRECT	Postsynaptic density	8	8.49E-05
GOTERM_CC_DIRECT	Cell–cell junction	8	0.007445
GOTERM_CC_DIRECT	Axon	8	0.008749
GOTERM_CC_DIRECT	Voltage-gated sodium channel complex	7	3.89E-07
GOTERM_MF_DIRECT	ATP binding	70	1.49E-13
GOTERM_MF_DIRECT	Calcium ion binding	40	2.03E-09
GOTERM_MF_DIRECT	Atpase activity	14	1.23E-07
GOTERM_MF_DIRECT	Microtubule motor activity	10	2.61E-06
GOTERM_MF_DIRECT	Motor activity	8	6.83E-06
GOTERM_MF_DIRECT	Extracellular matrix structural constituent	8	1.29E-05
GOTERM_MF_DIRECT	Transcription regulatory region DNA binding	8	0.007267
GOTERM_MF_DIRECT	Voltage-gated sodium channel activity	7	6.17E-07
GOTERM_MF_DIRECT	Transmembrane receptor protein tyrosine kinase activity	6	3.18E-05
GOTERM_MF_DIRECT	Atpase activity, coupled to transmembrane movement of substances	6	0.001185

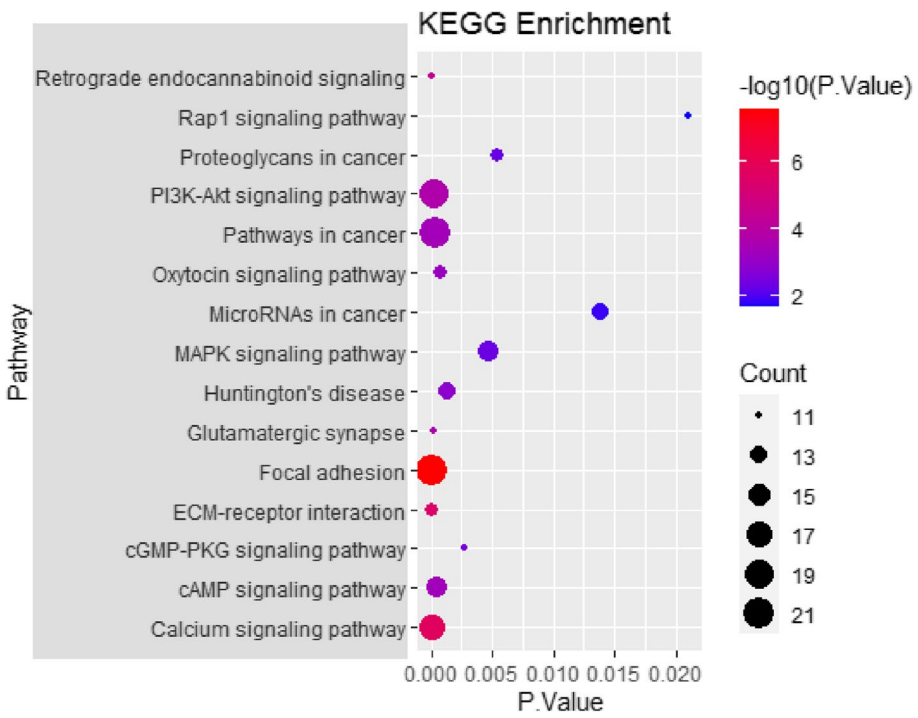

Fig. 3 Pathways enrichment map of 407 mutant genes. The top 20 terms with the lowest *P* value were selected. Count: the number of enriched genes in each term

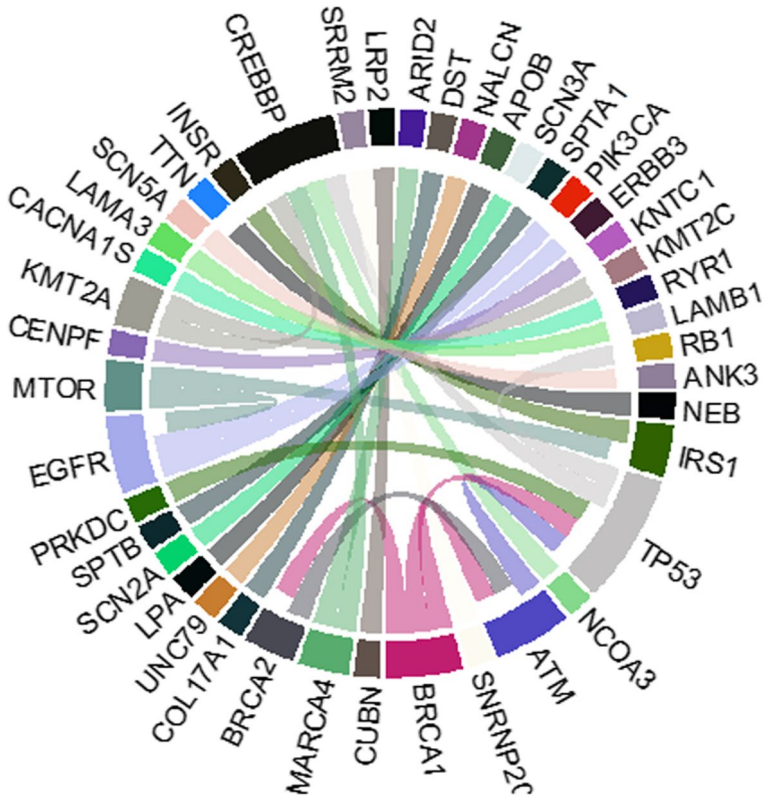

Fig. 4 The PPI network of the 42 mutant genes in ovarian cancer

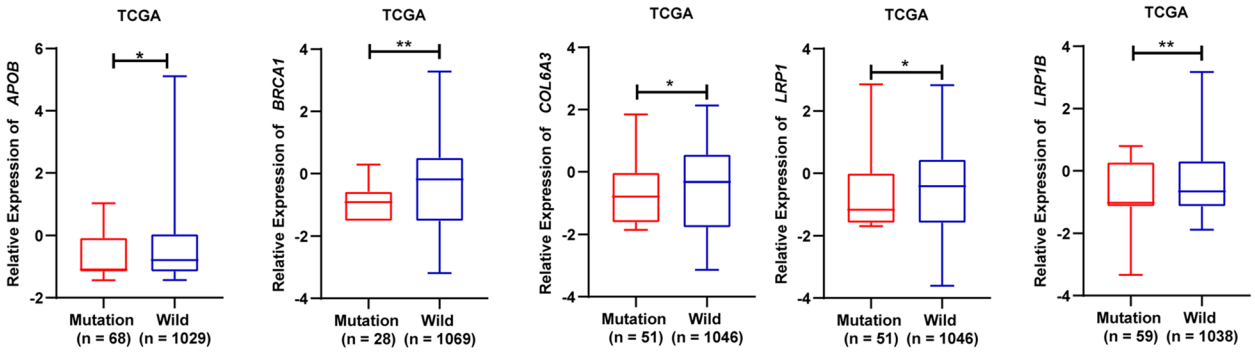

Fig. 5 The relationship between mutation and expression about 5 genes

The relevance of genetic polymorphisms in shaping the prognosis of ovarian cancer patients has gained substantial attention. These genetic variations hold promise as potential tumor biomarkers, offering an invaluable tool for clinicians to tailor patient treatment strategies and predict prognosis accurately. The identification of specific SNP variant genes could represent a paradigm shift in how we approach the management of ovarian cancer patients, ushering in a new era of precision medicine.

Among the genetic players in OC, apolipoprotein B (*APOB*) emerges as a prominent candidate. APOB plays a pivotal role in the realm of atherogenic lipoproteins, serving as the major apolipoprotein component in chylomicrons and low-density lipoproteins [24]. It is intriguing to note that genetic polymorphisms within APOB have demonstrated significant associations with gallbladder cancer (GBC). Notably, the C allele of the APOB polymorphism exhibits a notably higher frequency in GBC patients compared to both gallstone (GS) patients and healthy individuals [25, 26]. Furthermore, a distinct pattern is observed among the genotypes, with the C/T and T/T variants being associated with a reduced risk of GBC in comparison to the C/C genotype. These findings imply that the APOB rs693 polymorphism may confer susceptibility to GBC under specific environmental conditions, hinting at the intricate interplay between genetic factors and disease risk [27].

The compelling link between *BRCA1* mutations and cancer susceptibility, particularly in breast and ovarian cancer, has been the subject of intense scrutiny. Recent breakthroughs have unveiled a nuanced connection between BRCA1 mutations and fatty acid biosynthesis, offering a unique perspective on the molecular underpinnings of these cancers [28–30]. It has come to light that BRCA1 mutations disrupt the interaction between BRCA1 and acetyl-CoA carboxylase alpha (ACACA), a pivotal enzyme in fatty acid synthesis. This disruption, especially concerning BRCA1's interaction with phosphorylated ACACA (p-ACACA), exerts a profound influence on ACACA's activity by hindering the dephosphorylation of p-ACACA. This intricate relationship underscores the intricate balance between adipogenesis and tumor development, providing crucial insights into the genesis of BRCA1-related breast cancer [31].

Collagen VI, encoded by *COL6A1*, *COL6A2*, and *COL6A3*, is a vital component in skeletal muscle health and has been implicated in muscular dystrophy. Recently, its role has expanded to encompass cancer progression. Specifically, COL6A3 has garnered attention due to its upregulation in white adipose tissue and the liver, implicating its involvement in lipid metabolism [32]. Furthermore, *COL6A3*'s overexpression has been documented across various cancers, including breast cancer [33–36]. While the bulk of research has concentrated on COL6A3 in the context of breast cancer, its relevance to OC remains a tantalizing area for exploration. The potential insights that may emerge from this avenue hold the promise of a more profound understanding of OC's intricate biology.

LRP1 and *LRP1B*, members of the low-density lipoprotein receptor family, play integral roles in maintaining lipid homeostasis [37]. Their overexpression in adipose tissue in obesity underscores their importance in controlling intracellular cholesterol accumulation and fatty acid synthesis [38]. In previous studies, LRP1 has emerged as a crucial mediator in colon cancer, where it establishes molecular interactions in close proximity to Discoidin Domain Receptor 1 (DDR1) within cancer cell plasma membranes. The LRP1-mediated endocytosis of DDR1 is shown to promote cell cycle progression and augment cell proliferation while dampening apoptosis [39]. On a parallel front, LRP1B assumes a unique role as a tumor suppressor. Frequently targeted for deletion and subject to epigenetic silencing across a spectrum of cancers, including urothelial and esophageal cancers, LRP1B's functions in OC and its implications for lipid metabolism warrant profound exploration.

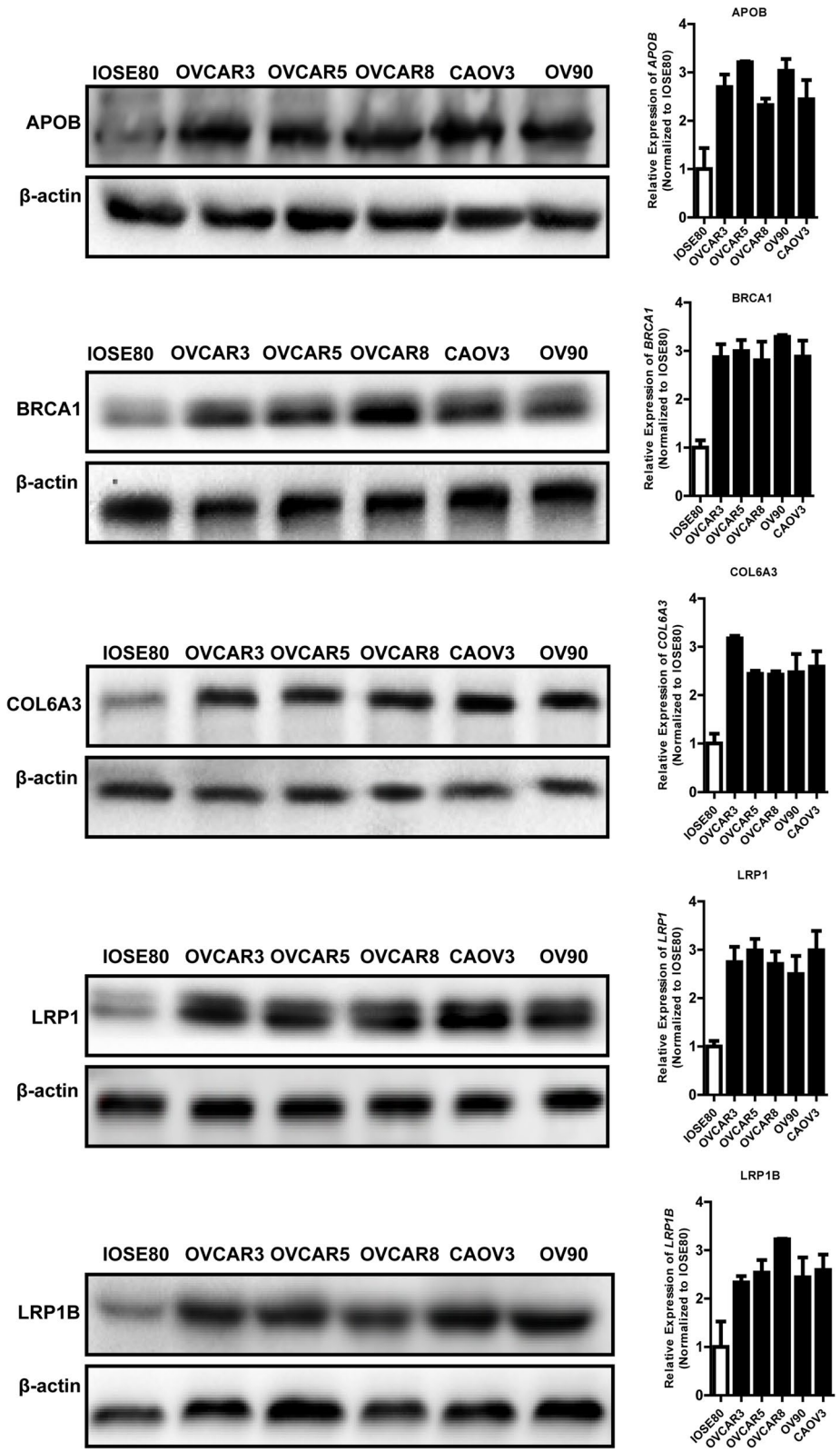

Fig. 6 The expression of 5 mutant genes in ovarian cancer cell lines

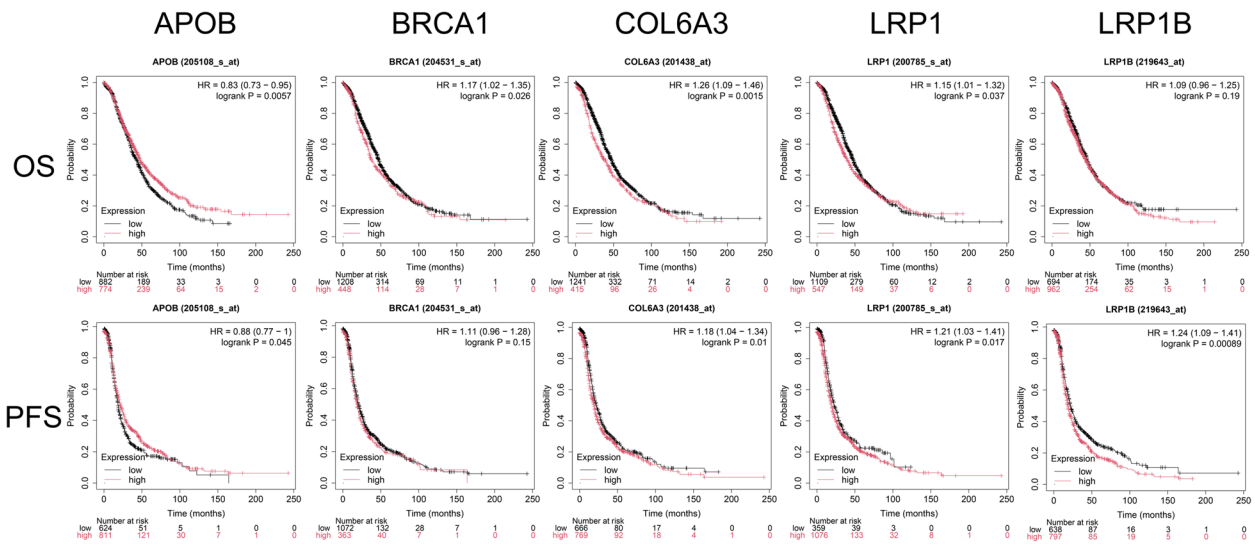

Fig. 7 Kaplan–Meier survival curves of the 5 mutant genes

However, several aspects of the previously mentioned genes (APOB, BRCA1, COL6A3, LRP1, and LRP1B) remain to be explored: the biochemical mechanisms by which their mutations affect lipid metabolism in OC cells; whether their mutations have predictive value for the efficacy of specific OC treatments; whether these gene mutations are common in other tumor types or specific to OC; and whether the use of lipid metabolism-targeting drugs as adjuvant therapy for OC would be beneficial. We hope that this study can provide valuable insights and clues for research on lipid metabolism in OC.

Conclusions

Overall, bioinformatics analysis revealed that SNPs of five genes related to lipid metabolism (*APOB*, *BRCA1*, *COL6A3*, *LRP1* and *LRP1B*) were significantly associated with the corresponding expression levels and were involved in multiple pathways involved in OC development. In addition, analysis showed that SNP is an important factor affecting the expression of these genes. Besides, OS and PFS analysis showed that the expression of *APOB*, *BRCA1*, *COL6A3*, *LRP1* and *LRP1B* were closely related to the survival of OC patients. These findings require validation in a large-scale clinical study to determine the accuracy and sensitivity of tumorigenesis and to predict patient outcomes. The theoretical basis related to the important bioinformatics basis leading the follow-up study on the OC was still necessary.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13841-6.

Supplementary Material 1

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Authors' contributions

All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by H.W; T.T., L.Y., Z.L., H.L. provided help and advice on the study. The first draft of the manuscript was written by Haoyu Wang and all authors commented on previous versions of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Data availability

Data is provided within the manuscript or supplementary information files.All data and materials are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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