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Potential drug targets for ovarian cancer identified through Mendelian randomization and colocalization analysis

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Abstract

Background The existing drugs for ovarian cancer (OC) are unsatisfactory and thus new drug targets are urgently required. We conducted proteome-wide Mendelian randomization (MR) and colocalization analysis to pinpoint potential targets for OC.

Methods Data on protein quantitative trait loci (pQTL) for 734 plasma proteins were obtained from large genome-proteome-wide association studies. Genetic associations with OC were derived from the Ovarian Cancer Association Consortium, which included 25,509 cases and 40,941 controls. MR analysis was performed to evaluate the association between the proteins and the OC risk. Colocalization analysis was conducted to check whether the identified proteins and OC shared causal variants. In addition, the phenome-wide MR analysis was performed to clarify protein associations across the phenotype, and drug target databases were examined for target validation.

Results Genetically predicted circulating levels of 44 proteins were associated with OC risk at Benjamini-Hochberg correction. Genetically predicted 17 proteins had evidence of the increased risk of OC (CLEC11A, MFAP2, TYMP, PDIA3, IL1R1, SPINK1, PLAU, DKK2, IL6ST, DLK1, LRRC15, CDON, ANGPTL1, SEMA4D, AKR1A1, TNFAIP6, and FCGR2B); 27 proteins decreased the risk of OC(SIGLEC9, RARRES1, SPINT3, TMEM132A, HAVCR2, CNTN2, TGFBI, GSTA1, HGFAC, TREML2, GRAMD1C, ASAH2, CPNE1, CCL25, MAPKAPK2, POFUT1, PREP, NTNG1, CA10, CACNA2D3, CA8, MAN1C1, MRC2, IL10RB, RBP4, GP5 and CALCOCO2). Bayesian colocalization demonstrated that GRAMD1C, RBP4, PLAU, PDIA3, MFAP2, POFUT1, MAN1C1 and DKK2 shared the same variant with OC. The phe-MR analyses assessed the side effects of these 44 identified proteins, and the drug target database offered information on both approved and investigational indications.

Conclusion This study provides proof of a causal relationship between genetically predicted 44 proteins associated with OC risk, which could serve as promising drug targets for OC.

Keywords Ovarian cancer, Mendelian randomization, Protein, Drug target

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Introduction

Ovarian cancer (OC) is a highly heterogeneous gynecologic malignancy and the seventh most common cancer in women. It has more pathological subtypes and mainly occurs in postmenopausal women after the age of 50 [1]. OC remains an enormous challenge in early diagnosis and medical treatment. 70% of OC cases are diagnosed as advanced when detected and usually accompanied by metastasis [2]. At present, the main treatment for OC is debulking surgery and platinum-based chemotherapy, but the effect is not satisfactory [3]. The methods of targeted therapy and immunotherapy also provide a new therapeutic approach for ovarian cancer. However, most patients experience relapse or progression after resistance, with a 5-year survival rate ranging between 30% and 40% [4]. Complex biological etiology of OC restricts development of new drugs. Hence, identifying new therapeutic targets is crucial for enhancing patient survival and prognosis.

The circulating proteins in human plasma can be directly secreted into circulation or overflow into the bloodstream from the organs of origin, and circulating proteins secreted or leaked into the bloodstream play a complex role in the biological processes involved in the development of various tumors, including colorectal and brain cancers, and are considered major targets for drug therapy [5–9]. In clinical practice, circulating proteins serve dual roles: they can function as biomarkers, such as N-terminal pro-brain natriuretic peptide in congestive heart failure [10], and as targets for drug therapy, such as proprotein convertase subtilisin/ kexin type 9 serine protease (PCSK9) used in the treating hypercholesterolemia [11]. Compared to invasive examinations, blood-derived protein tumour markers could present an alternative, non-invasive and cost-effective approach for improvement of cancer screening [12]. The study suggests that a protein drug target, supported by genetic evidence of its link to the disease, has double the likelihood of obtaining market approval [13]. Observational studies have identified a variety of circulating proteins with therapeutic potential related with the OC onset, progression and recovery [14]. CA125 and HE4 are the most widely applied biomarkers in blood tests for OC [15–17], increasing the sensitivity to 94.8% and specificity to 75% of the ROMA score (Ovarian Malignancy Risk Algorithm) in a cohort of patients with predominantly advanced OC [18]. However, observational studies are prone to confounding factors and reverse causality, and their associations need to be replicated and confirmed. Randomized controlled studies are unable to explore the relationship between thousands of proteins and OC.

Proteomic data can provide evidence for effective drug development for various diseases including OC. Recent studies increasingly indicate that proteomics play a significant role in predicting the success of drug trials [13]. Mendelian randomization (MR) analysis is now widely utilized in drug target development and drug repurposing. MR utilizes genetic variation as the instrumental variable to evaluate the causal relationship between measured protein levels and OC. MR can effectively avoid confounders due to the stable random assortment of genes from parents to offspring. Recently, MR analysis method has been applied to identify potential therapeutic targets for diseases like heart failure and inflammatory bowel disease [19]. Few MR studies have been reported on the integration of GWAS and protein quantitative trait loci (pQTL) data for OC.

In this study, we leverage recent pQTL data from genome-proteome-wide association studies to explore potential targets for OC [20]. We conducted MR and colocalization analyses to identify the causal influence of proteins. Additionally, we have performed phenome-wide MR (phe-MR) and retrieved their druggability to explore their potential as therapeutic targets for OC.

Materials and methods

Exposure data

The summary-level statistics of genetic associations of plasma protein pQTL data were sourced from the study conducted by Zheng et al. [20], which involve the 5 studies previously published GWAS [21–25]. Only pQTLs that satisfy the criteria are considered: (a) was available at the genome-wide significant level ($P < 5E\text{-}08$); (b) were cis-pQTLs; (c) showed independent association [linkage disequili brium (LD) clumping $r^2 < 0.001$]. Cis-pQTLs are located near the gene encoding the target protein and are generally considered more reliable proxies due to their stronger biological evidence for direct and independent effects on proteins. Trans-pQTLs are more likely to exhibit pleiotropy because their indirect effects on proteins can potentially violate MR assumptions and introduce bias into the results [26]. Finally, a total of 738 cis-acting SNPs were included for 734 proteins. Further details on the GWAS are available in the original publication.

Outcome data

Summary-level data for the OC were available in Ovarian Cancer Association Consortium (OCAC) [27], which was involved 66,450 participants including 25,509 OC cases and 40,941 controls. All individuals of OCAC were of European ancestryand recruited from 14 countries. All sunmmary data were downloaded from the IEU OpenGWAS project.

Statistical analysis

Mendelian randomization analysis

In the main analysis, two-sample MR analysis was employed using the R package "TwoSampleMR" to investigate the relationship between circulating proteins and OC risk. Harmonization of data on exposure and outcome was performed to align the effects of SNPs on both, ensuring they correspond to the same allele. For proteins with a single cis-pQTL, MR estimates were calculated using the Wald ratio. For those with two or more genetic instruments, the inverse-variance weighted (IVW) method was applied, accounting for the weak LD among the instruments by using an LD matrix [28, 29]. For the primary analysis, the Benjamini-Hochberg correction was applied to reduce the false discovery rate (the *P* value of Benjamini-Hochberg correction was < 0.05). The MR findings were expressed as odds ratio (OR) and 95% confidence interval (95% CI) for the risk of OC. We performed the heterogeneity and pleiotropy analysis to assess the robustness of the results. In addition, we used linkage imbalance score regression analysis (LDSC) to estimate the co-genetic structure between plasma proteins and OC.

Colocalization analysis

To further investigate the causality of the observed MR associations, we carried out a colocalization analysis with the R package "coloc" to evaluate the likelihood that plasma proteins and OC share the same causal variant, and to remove the confounding caused by LD [30, 31]. SNP_S with significant genome-wide associations ($P < 5E\text{-}08$) in proteins and OC were selected. Duplicates and missing values were removed and SNPs with both exposure and outcome in overlap were extracted. For each locus, five hypotheses were considered about the shared presence of a single variant across two traits in the Bayesian co-localization analysis. Posterior probabilities were then calculated for each of these hypotheses: PPH0, no association with either trait; PPH1, associated with protein but not the OC trait; PPH2, linked to the OC trait but not protein; PPH3, related to both the OC trait and protein with different causal variants; PPH4, connected to both the OC trait and gene expression, sharing a causal variant [32]. The analysis was performed within a ± 100 kb window around the drug target gene. The shared genetic variant implicates that the protein itself contributes directly to the disease risk, rather than being altered by other biological processes. We defined genes as evidence that of co-localization based on the PPH4 > 50% [31].

Phenome-wide MR analysis

The Phe-MR analysis was used to discover significant associations between the identified pQTLs with other reported traits. Each of the cis-instruments from the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/) was selected and the association of variants with traits were retrieved for $P < 0.001$. The causal impact of each protein on the identified traits was explored using the same MR method.

Drug-target validation

To evaluate the potential for drug targeting of the identified proteins, we reviewed several drug-target databases including Drugbank, Therapeuutic Target Database, Clinical trial, along with previously established lists of druggable genes. We also searched for drugs currently being developed against identified potential proteins. To evaluate the potential for drug formability, we categorized these proteins into four groups: (a) approved (one or more drugs targeting a specific protein have been approved); (b) in clinical trials (the target drug is currently undergoing clinical trial); (c) preclinical (the target drug is in the preclinical research phase); (d) druggable (the protein is not be found in drug databases, but listed as a medicinal target).

Results

Screening the proteome for OC causal proteins

The study design was illustrated in Fig. 1. The research investigated the MR association between 734 proteins, each with available index pQTLs signals, and the risk of OC outcomes. MR analysis revealed 44 protein-OC causal relationships, meeting the Benjamini-Hochberg corrected threshold ($P_{\text{B–H adjusted}} < 0.05$) (Supplementary Table 1). Among the 44 proteins, 17 proteins are linked to a heightened risk of OC. The proteins with the most significant effects, in descending order, included CLEC11A, MFAP2, TYMP, PDIA3, IL1R1, SPINK1, PLAU, DKK2, IL6ST, DLK1, LRRC15, CDON, ANGPTL1, SEMA4D, AKR1A1, TNFAIP6, and FCGR2B. The other 27 risk-reducing proteins included SIGLEC9, RARRES1, SPINT3, TMEM132A, HAVCR2, CNTN2, TGFBI, GSTA1, HGFAC, TREML2, GRAMD1C, ASAH2, CPNE1, CCL25, MAPKAPK2, POFUT1, PREP, NTNG1, CA10, CACNA2D3, CA8, MAN1C1, MRC2, IL10RB, RBP4, GP5 and CALCOCO2 (Figs. 2 and 3). No heterogeneity and pleiotropy were detected in the analyzed proteins (Supplementary Table 2). No statistically significant genetic association was found on LDSC results (Supplementary Table 3).

Colocalization analysis of cis-pQTLs

MR analysis revealed a causal association between 44 proteins and OC. Steiger filtering further ensures directionality. Colocalization analyses were performed to distinguish between causal relationships from linkage disequilibrium. The PPH4 for 10 of the 44 cis-pQTLs

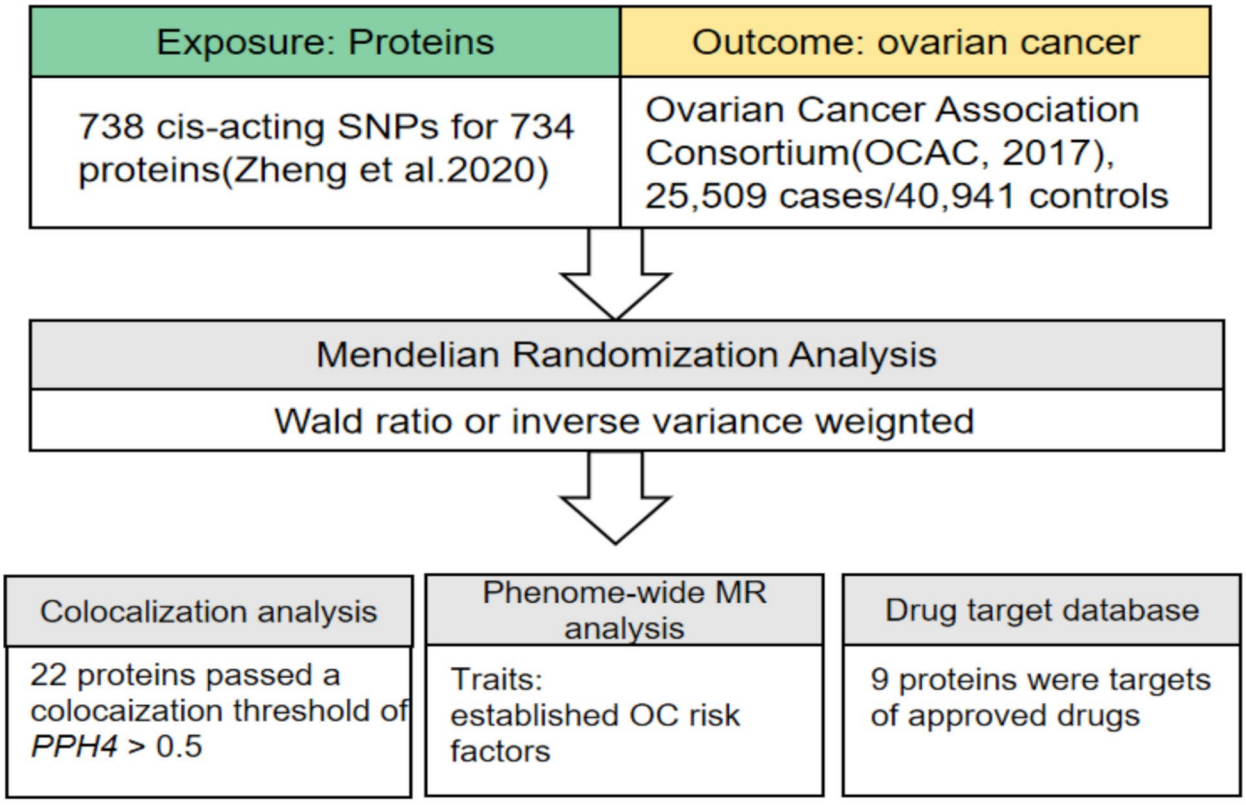


Fig. 1 Study design. OC: ovarian cancer; SNP: single nucleotide polymorphism

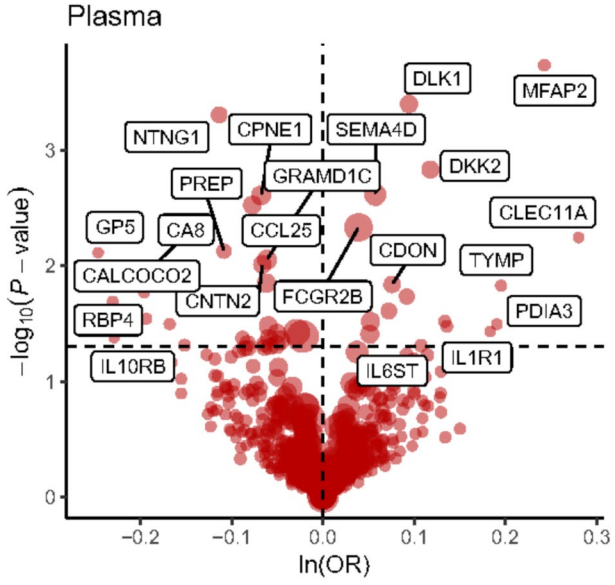


Fig. 2 Volcano plot of the MR results for plasma proteins and OC risk

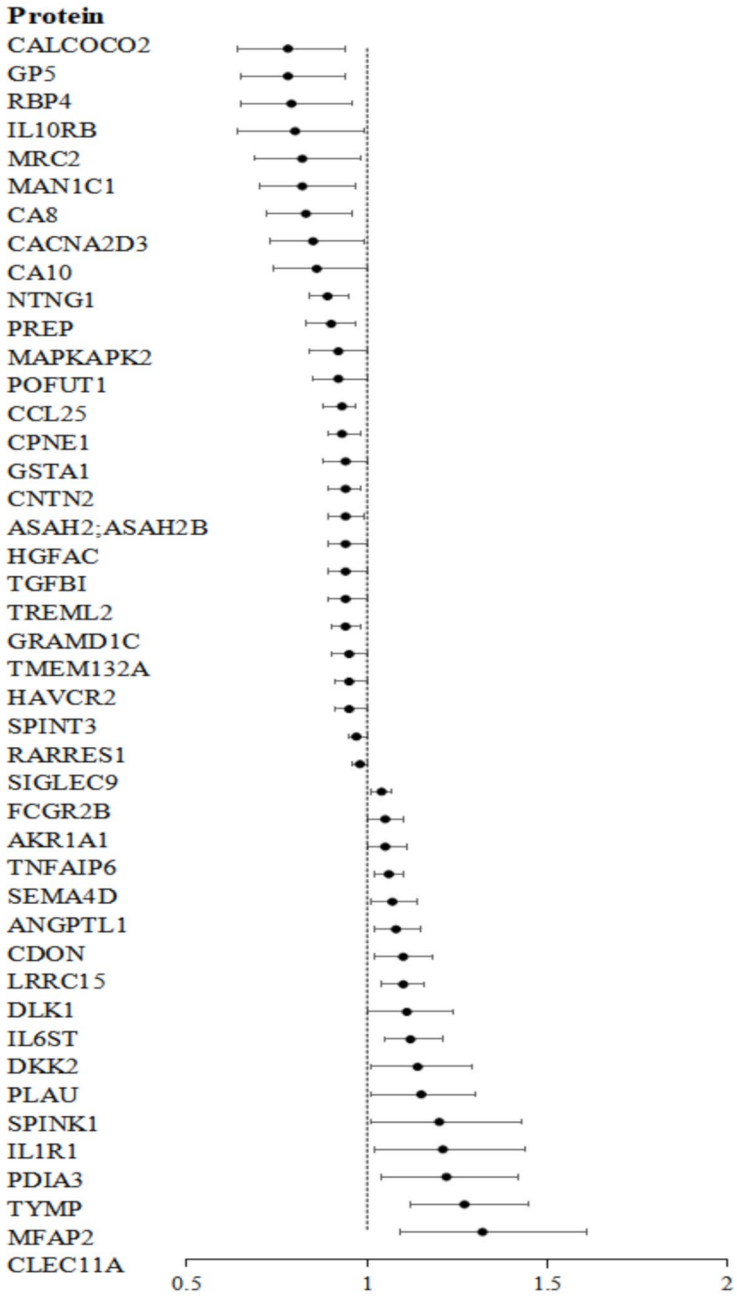
with MR evidence exceeded 0.5 (SPINK1, IL1R1, CCL25, MAPKAPK2, TYMP, IL6ST, CDON, AKR1A1, PREP and RARRES1), in 4 proteins were >0.75(GP5, CA10, CLEC11A and CACNA2D3), and in 8 proteins were >0.95(GRAMD1C, RBP4, PLAU, PDIA3, MFAP2, POFUT1, MAN1C1 and DKK2) (Fig. 4; Supplementary Table 4).

Drug-target validation and repurposing

Phenome-wide MR

To delve deeper into the comprehensive indications and side effects of the 44 proteins, phe-MR studies were conducted, revealing important safety and efficacy findings that could provide the treatment of OC (Supplementary Table 5). A significant number of identified proteins influenced risk factors for OC, such as anthropometric traits (weight, height, body mass index, hip or waist circumference, and fat mass), metabolic traits (triglycerides, cholesterol, urate, and calcium), and female reproductive traits (menstrual cycle, sex hormones). Beyond the aforementioned well-known factors, certain proteins also impact a variety of other traits, including basal metabolic rate, breast cancer, birth weight, and blood cell count. Notably, both breast cancer and basal metabolic rate have been linked to the risk of OC [33–35].

Additionally, phe-MR has identified several proteins as promising drug targets for different indications that align with the same therapeutic direction as OC. Proteins implicated in OC also contribute to elevated risks



Protein	OR(95%CI)	*P* value	*P* adjust
CALCOCO2	0.78 (0.64, 0.94)	0.0104	0.0305
GP5	0.78 (0.65, 0.94)	0.0077	0.0305
RBP4	0.79 (0.65, 0.96)	0.0203	0.0425
IL10RB	0.80 (0.64, 0.99)	0.0416	0.0498
MRC2	0.82 (0.69, 0.98)	0.0286	0.0498
MAN1C1	0.82 (0.70, 0.97)	0.0168	0.0389
CA8	0.83 (0.72, 0.96)	0.0098	0.0305
CACNA2D3	0.85 (0.73, 0.99)	0.0316	0.0498
CA10	0.86 (0.74, 1.00)	0.0485	0.0498
NTNG1	0.89 (0.84, 0.95)	0.0005	0.0072
PREP	0.90 (0.83, 0.97)	0.0074	0.0305
MAPKAPK2	0.92 (0.84, 1.00)	0.0422	0.0498
POFUT1	0.92 (0.85, 1.00)	0.0468	0.0498
CCL25	0.93 (0.88, 0.97)	0.0030	0.0186
CPNE1	0.93 (0.89, 0.98)	0.0024	0.0179
GSTA1	0.94 (0.88, 1.00)	0.0471	0.0498
CNTN2	0.94 (0.89, 0.98)	0.0097	0.0305
ASAH2;ASAH2B	0.94 (0.89, 0.99)	0.0141	0.0362
HGFAC	0.94 (0.89, 1.00)	0.0329	0.0498
TGFBI	0.94 (0.89, 1.00)	0.0498	0.0498
TREML2	0.94 (0.89, 1.00)	0.0418	0.0498
GRAMD1C	0.94 (0.90, 0.98)	0.0088	0.0305
TMEM132A	0.95 (0.90, 1.00)	0.0479	0.0498
HAVCR2	0.95 (0.91, 1.00)	0.0440	0.0498
SPINT3	0.95 (0.91, 1.00)	0.0386	0.0498
RARRES1	0.97 (0.95, 1.00)	0.0375	0.0498
SIGLEC9	0.98 (0.96, 1.00)	0.0408	0.0498
FCGR2B	1.04 (1.01, 1.07)	0.0046	0.0255
AKR1A1	1.05 (1.00, 1.10)	0.0303	0.0498
TNFAIP6	1.05 (1.00, 1.11)	0.0390	0.0498
SEMA4D	1.06 (1.02, 1.10)	0.0024	0.0179
ANGPTL1	1.07 (1.01, 1.14)	0.0245	0.0490
CDON	1.08 (1.02, 1.15)	0.0144	0.0362
LRRC15	1.10 (1.02, 1.18)	0.0184	0.0405
DLK1	1.10 (1.04, 1.16)	0.0004	0.0072
IL6ST	1.11 (1.00, 1.24)	0.0489	0.0498
DKK2	1.12 (1.05, 1.21)	0.0015	0.0161
PLAU	1.14 (1.01, 1.29)	0.0301	0.0498
SPINK1	1.15 (1.01, 1.30)	0.0333	0.0498
IL1R1	1.20 (1.01, 1.43)	0.0368	0.0498
PDIA3	1.21 (1.02, 1.44)	0.0319	0.0498
TYMP	1.22 (1.04, 1.42)	0.0148	0.0362
MFAP2	1.27 (1.12, 1.45)	0.0002	0.0072
CLEC11A	1.32 (1.09, 1.61)	0.0057	0.0278

Fig. 3 Association between 44 identified drug targets and risk for ovarian cancer. Association between 44 identified drug targets and risk for ovarian cancer. Forest plot showing 44 proteins with strong evidence of causality in MR analysis. Odds ratios per standard deviation (s.d.) of the protein and 95% confidence intervals (CI) are shown. CALCOCO2: calcium binding and coiled-coil domain 2; GP5: glycoprotein V platelet; RBP4: retinol binding protein 4; IL10RB: interleukin 10 receptor subunit beta; MRC2: mannose receptor C type 2; MAN1C1: mannosidase alpha class 1 C member 1; CA8: carbonic anhydrase 8; CACNA2D3: calcium voltage-gated channel auxiliary subunit alpha2delta 3; CA10: carbonic anhydrase 10; NTNG1:netrin G1; PREP: prolyl endopeptidase; MAPKAPK2: MAPK activated protein kinase 2; POFUT1: protein O-fucosyltransferase 1; CCL25: C-C motif chemokine ligand 25; CPNE1: copine 1; GSTA1: glutathione S-transferase alpha 1; CNTN2: contactin 2; ASAH2;ASAH2B: N-acylsphingosine amidohydrolase 2; HGFAC: HGF activator; TGFBI: transforming growth factor beta induced; TREML2: triggering receptor expressed on myeloid cells like 2; GRAMD1C: GRAM domain containing 1 C; TMEM132A: transmembrane protein 132 A; HAVCR2: hepatitis A virus cellular receptor 2; SPINT3: serine peptidase inhibitor, Kunitz type 3; RARRES1: retinoic acid receptor responder 1; SIGLEC9: sialic acid binding Ig like lectin 9;FCGR2B: Fc gamma receptor IIb; AKR1A1: aldo-keto reductase family 1 member A1; TNFAIP6: TNF alpha induced protein 6; SEMA4D: semaphorin 4D; ANGPTL1:angiopoietin like 1; CDON: cell adhesion associated, oncogene regulated; LRRC15: leucine rich repeat containing 15; DLK1: delta like non-canonical Notch ligand 1; IL6ST: interleukin 6 cytokine family signal transducer; DKK2: dickkopf WNT signaling pathway inhibitor 2; PLAU: plasminogen activator, urokinase; SPINK1: serine peptidase inhibitor Kazal type 1; IL1R1: interleukin 1 receptor type 1; PDIA3: protein disulfide isomerase family A member 3; TYMP: thymidine phosphorylase; MFAP2: microfibril associated protein 2; CLEC11A: C-type lectin domain containing 11 A

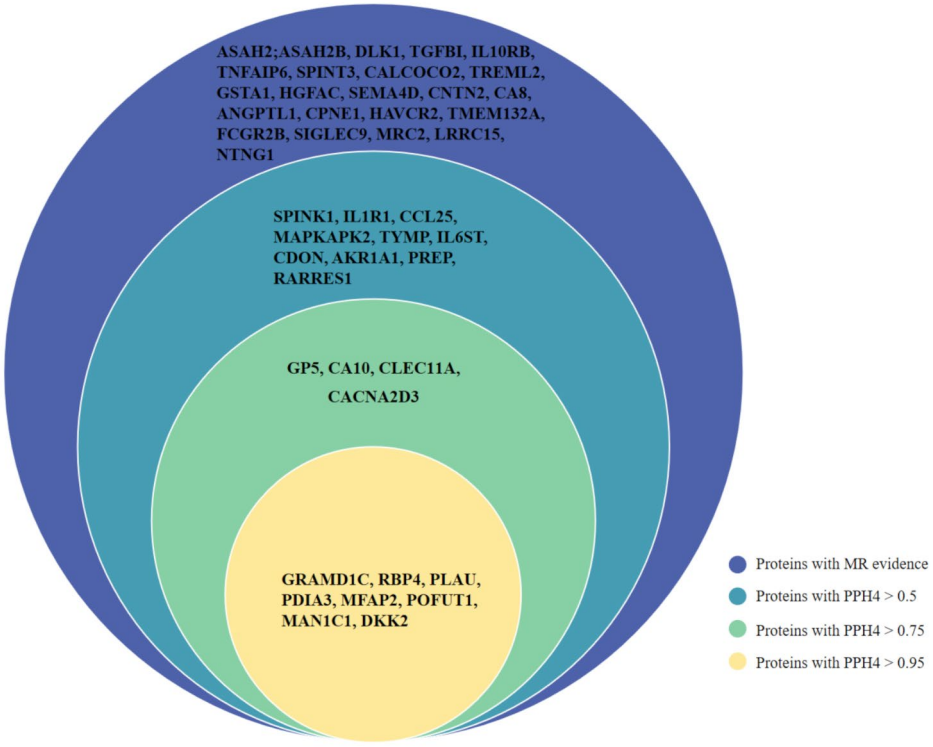


Fig. 4 Proteins with MR and colocalization evidence

for various disorders affecting both the female reproductive and non-reproductive systems. Genetically determined MAPKAPK2, MFAP2, and PLAU increased the risk of rheumatoid arthritis in non-female reproductive and breast diseases. Genetic determined CALCOCO2 and DLK1 increased the Type 2 diabetes risk. As for cancer, CPNE1 and TGFBI increased the risk of breast cancer, while MAN1C1 and PDIA3 reduced it. GRAMD1C reduces the risk of pharyngeal cancer, CA8 decreased the skin cancer risk, and CALCOCO2 increases the risk of carcinoma in situ of cervix uteri. When considering proteins as targets for OC, it is crucial to also evaluate their safety. For example, CA8 reduced OC but increased the risk of varicose veins. MAPKAPK2 decreased the risk of OC but increased inflammatory bowel disease and ulcerative colitis risk. CPNE1 increased the risk of asthma. These adverse side effects should be taken into consideration when evaluating its preventive effect on OC.

Druggability of identified proteins

44 proteins identified as possible drug targets in MR analysis were searched in the drug databases to uncover records of past or ongoing clinical drug development programs associated with these proteins. Among these 44 proteins, 9 (20.45%) proteins were identified as targets under investigation in clinical trials. These 9 proteins include SEMA4D, HAVCR2, CACNA2D3, MAPKAPK2, PREP, FCGR2B, TYMP, PLAU and DLK1. Their indications include huntington disease (SEMA4D), alzheimer disease (SEMA4D), myelodysplastic syndrome (HAVCR2), Generalized anxiety disorder (CACNA2D3), solid tumor/cancer (SEMA4D, HAVCR2), mesothelioma (MAPKAPK2), airway inflammation (MAPKAPK2), coeliac disease (PREP), influenza virus infection (PREP), Autoimmune diabetes (FCGR2B), Chronic lymphocytic leukaemia (FCGR2B), inborn errors of metabolism (TYMP), ovarian cancer (PLAU), and Amyotrophic lateral sclerosis (DLK1).

There are 9 proteins that are already approved drug targets. Amlodipine and nilvadipine, both inhibitors of CACNA2D3, are used to treat hypertension and angina; Tretinoin, an agonist of RARRES1, is employed for the treatment of acne vulgaris and promyelocytic leukemia; Anakinra, an antagonist of IL1R1, is used to treat the rheumatoid arthritis and coronavirus disease 2019 (COVID-19); Ritlecitinib, substrate of GSTA1, is utilized for the treatment of alopecia areata.

None of them were found to be drug targets for OC. No information was available for SIGLEC9, CLEC11A, DKK2, MRC2, ASAH2; ASAH2B, MAN1C1, POFUT1, LRRC15, GRAMD1C, TREML2, NTNG1, CDON, TMEM132A, caloco2, SPINT3, GP5, PDIA3, AKR1A1, RBP4, SPINK1, CCL25, HGFAC, TGFBI, IL6ST, CNTN2, and ANGPTL1 in searched databases. Although only one protein for OC target was identified in the databases,

they may provide new and promising targets for OC (Table 1).

Discussion

To the best of our knowledge, this study represents the inaugural attempt to leverage plasma proteomic data for identifying the causal proteins associated with OC through the utilization of two-sample MR and Bayesian colocalization methodologies. In this study, 738 cis-acting SNPs across 734 plasma proteins were analyzed for causal associations with OC through two-sample MR. Ultimately, we pinpointed 44 proteins as potential drug targets for OC. Among them, 27 proteins were negatively correlated with the risk of OC, while 17 of which increased the risk. To constrain the bias of pleiotropy, we exclusively employed cis-pQTLs as instruments, given their direct involvement in the transcription and/or translation of relevant genes. The results did not reveal heterogeneity or pleiotropy. We also calculated the LDSC as the complementary analysis to explore the genetic relationship between plasma protein and OC, although the LDSC results were not statistically significant. LDSC evaluates the shared genetic architecture between traits, identifying genetic correlations that provide insights into potential biological pathways. However, it does not infer causal relationships [36]. On the other hand, MR complements LDSC by using genetic variants as instrumental variables to infer causal effects, thereby providing directional evidence [37, 38]. Our findings contributed to the determination of circulating protein biomarkers that hold promise for early-stage detection and diagnosis of OC in clinical settings. These associations encompassed previously reported incident OC connections, such as CNTN2 and HAVCR2 [39–41], proteins like SEMA4D, which have documented links to prognosis, invasion, and metastasis [42, 43], and proteins such as DLK1 promoting tumorigenesis and epithelial-mesenchymal transition [44].

MR analysis plays an important role in drug target development. Multi-omics research has demonstrated the value of pQTLs in reusing existing targets for other indications and prioritizing new drug targets [20]. Compared to trans-acting pQTLs that may act through indirect mechanisms, cis-acting pQTLs are generally accorded greater biological significance and commonly utilized in the screening of drug targets [20, 45]. MR employs genetic variation as an instrumental variable for probing the causal impacts of exposure on outcomes, and the target indication that links target genes to related phenotypes is a potential cost-effective method for prioritizing the development of drug targets. Compared with observational studies, MR circumvents the impact of confounding variables. It has streamlined the discovery of prospective therapeutic targets across various conditions, including atrial fibrillation and Alzheimer's disease [31, 46].

Several studies have reported HAVCR2 as a biomarker for OC [47]. HAVCR2, best known as TIM3, is described co-inhibitory molecule and expresses in cellular membranes. HAVCR2, through its interaction with galectin-9, facilitates T cell apoptosis and consequently promotes immunosuppression. Additionally, by recognizing nucleic acids released from apoptotic tumor cells via Toll-like receptors (TLRs), it further diminishes chemotherapeutic efficacy [48, 49]. PLAU, also called urokinase-type plasminogen activator (uPA, Urokinase), is a serine protease involved in the regulation of numerous cellular signaling pathways and the induction of diverse responses. There is now clear evidence that PLAU is expressed in primary and metastatic OC. Its overexpression correlates with the invasive metastatic potential of ovarian cancer and predicts a worse prognosis [50–52].

In this study, we found that GRAMD1C, RBP4, PLAU, PDIA3, MFAP2, POFUT1, MAN1C1 and DKK2 exhibited the most compelling evidence of MR and colocalization (PPH4 > 0.95). PLAU, PDIA3, MFAP2, and DKK2 were found to increase the risk of OC. The protein disulphide isomerase (PDI) family comprises multifunctional endoplasmic reticulum (ER) enzymes that are often elevated in multiple cancer types [53]. The oncogenic effects of PDI are facilitated through the UPR signaling pathway and the regulation of apoptosis [54, 55], which may be responsible for the development and progression of OC. MFAP2, the inaugural member of the MFAP family subfamily, manifests in both membrane and soluble forms. In OC, MFAP2 modulates the FOXM1/β-catenin signaling axis to enhance cell proliferation and glycolysis [56]. DKK2, a secreted proteins, acts as a Wnt signaling antagonist by binding to LDL receptor-related protein 5/6 (LRP5/6), thereby inhibiting its interaction with the Wnt-Frizzled complex [57].

In a subsequent analysis, the 44 OC drug targets underwent evaluation in databases, with exploration of their associated side effects. For instance, TNFAIP6, derived from TNF, has been linked to elevated susceptibility to various cancers, such as OC, as well as several autoimmune diseases. TNFAIP6 can promote cell migration and have anti-inflammatory property by binding to the chemokine CXCL8 [58]. TNFAIP6 has already a target for pain, inflammation, and Alzheimer's Disease [59, 60]. FCGR2B had the function of inhibiting the overactivation of immune cells and associated with a variety of autoimmune diseases [61]. MGD010, a developed drug targeting autoimmune diseases, is currently undergoing phase II clinical trials to

Table 1 Potential repurposing opportunities of approved drugs and novel drugs under development

Protein info		Indication info of drugs under development / approved drugs			
Protein	**Protein_full name**	**Indications**	**Direction**	**Clinical Status**	**Drug name**
SIGLEC9	sialic acid binding Ig like lectin 9	NA	NA	NA	NA
CLEC11A	C-type lectin domain containing 11 A	NA	NA	NA	NA
DKK2	dickkopf WNT signaling pathway inhibitor 2	NA	NA	NA	NA
MRC2	mannose receptor C type 2	NA	NA	NA	NA
CA10	Carbonic anhydrase-related protein 10	Partial-Onset Seizures	Inhibitor	Approved	Zonisamide
ASAH2;ASAH2B	N-acylsphingosine amidohydrolase 2	NA	NA	NA	NA
MAN1C1	mannosidase alpha class 1 C member 1	NA	NA	NA	NA
POFUT1	protein O-fucosyltransferase 1	NA	NA	NA	NA
SEMA4D	semaphorin 4D	Huntington disease; Squamous head and neck cell carcinom;	Inhibitor	Clinical Trial Phase 1	VX-15
		Alzheimer Disease	Inhibitor	Clinical Trial Phase 1	Pepinemab
LRRC15	leucine rich repeat containing 15	NA	NA	NA	NA
HAVCR2	Hepatitis A virus cellular receptor 2	Myelodysplastic syndrome	Inhibitor	Clinical Trial Phase 3	MBG453
		Solid tumour/cancer	Inhibitor	Clinical Trial Phase 1/2	MBG453
CACNA2D3	Voltage-dependent calcium channel subunit alpha-2/delta-3	hypertension and angina	Inhibitor	Approved	Amlodipine
		hypertension	Inhibitor	Approved	Nitrendipine
		Chronic obstructive pulmonary disease	Inhibitor	Approved	Pregabalin
		hypertension	Inhibitor	Approved	Diltiazem
		hypertension	Inhibitor	Approved	Lercanidipine
		Peripheral neuropathy	Inhibitor	Registered	Mirogabalin
		Generalized anxiety disorder	Inhibitor	Clinical Trial Phase 3	Imagabalin
IL10RB	interleukin 10 receptor subunit beta	Neuropathic pain; Inflammatory bowel disease;	Modulator	Investigative	VT-310
TNFAIP6	TNF alpha induced protein 6	pain, inflammation, Alzheimer's Disease	Inhibitor	Approved	Acetylsalicylic acid, Hyaluronic acid, Donepezil
MFAP2	NA	NA	NA	NA	NA
RARRES1	Retinoic acid receptor responder protein 1	acne vulgaris, promyelocytic leukemia	agonist	Approved	Tretinoin
SPINT3	NA	NA	NA	NA	NA
MAPKAPK2	MAP kinase-activated protein kinase 2	Mesothelioma	Inhibitor	Clinical Trial Phase 1/2	CBP-501
		Airway inflammation	Inhibitor	Clinical Trial Phase 1	MMI-0100
PREP	Prolyl endopeptidase	Coeliac disease	Inhibitor	Clinical Trial Phase 2	ALV-003
		Influenza virus infection	Inhibitor	Clinical Trial Phase 2	BAICALEIN
		Cognitive impairment	Inhibitor	Clinical Trial Phase 2	ONO-1603
		Cognitive impairment	Inhibitor	Clinical Trial Phase 1	S-17092-1
GP5	glycoprotein V platelet	NA	NA	NA	NA
CA8	carbonic anhydrase 8	partial seizures	inhibitor	Approved	Zonisamide
FCGR2B	Fc gamma receptor IIb	Autoimmune diabetes	Modulator	Clinical Trial Phase 2	Xmab 5871
		Chronic lymphocytic leukaemia	Modulator	Clinical Trial Phase 1/2	BI 1206
		Autoimmune disease	Modulator	Clinical Trial Phase 1	MGD010
PDIA3	protein disulfide isomerase family A member 3	NA	NA	NA	NA
TYMP	thymidine phosphorylase	Inborn Errors of Metabolism	substrate	Clinical Trial Phase 2	NA
		Depression	Inhibitor	Approved	Uridine
IL1R1	interleukin 1 receptor type 1	Rheumatoid arthritis; coronavirus disease 2019 (COVID-19)	antagonist	Approved	Anakinra
AKR1A1	aldo-keto reductase family 1 member A1	NA	NA	NA	NA

Table 1 (continued)

Protein info		Indication info of drugs under development / approved drugs			
Protein	**Protein_full name**	**Indications**	**Direction**	**Clinical Status**	**Drug name**
RBP4	retinol binding protein 4	NA	NA	NA	NA
SPINK1	serine peptidase inhibitor Kazal type 1	NA	NA	NA	NA
PLAU	plasminogen activator, urokinase	rheumatoid arthritis, Thrombin deficiency; Breast cancer;	Inhibitor	Approved	Pro-urokinase
		ovarian cancer	agonist	Clinical Trial Phase 2	Urokinase-Derived Peptide A6
CCL25	C-C motif chemokine ligand 25	NA	NA	NA	NA
HGFAC	NA	NA	NA	NA	NA
CPNE1	copine 1	asthma, COPD,	NA	Approved	Theophylline
DLK1	delta like non-canonical Notch ligand 1	Amyotrophic lateral sclerosis	Inhibitor	Clinical Trial Phase 1	GDC0134
GSTA1	glutathione S-transferase alpha 1	alopecia areata,	substrate	NA	Ritlecitinib
		breast cancer	inhibitor	Not Applicable	Curcumin
TGFBI	transforming growth factor beta induced	NA	NA	NA	NA
IL6ST	interleukin 6 cytokine family signal transducer	NA	NA	NA	NA
CNTN2	contactin 2	NA	NA	NA	NA
ANGPTL1	angiopoietin like 1	NA	NA	NA	NA
GRAMD1C	GRAM domain containing 1 C	NA	NA	NA	NA
TREML2	triggering receptor expressed on myeloid cells like 2	NA	NA	NA	NA
NTNG1	netrin G1	NA	NA	NA	NA
CDON	cell adhesion associated, oncogene regulated	NA	NA	NA	NA
TMEM132A	transmembrane protein 132 A	NA	NA	NA	NA
CALCOCO2	calcium binding and coiled-coil domain 2	NA	NA	NA	NA

assess its efficacy. Our pQTL-MR study identified that PLAU (rs2227551) significantly increased the risk of OC, which consistent with previous study reports. The clinical trial of PLAU has been initiated for OC treatment in the United States (NCT00939809), which is a multicenter phase II study to access the efficacy and tolerability of urokinase-derived peptide (A6) in managing persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. This study showed that A6 exhibited good tolerability but showed limited efficacy in patients with persistent or recurrent OC [62]. Whether PLAU merits consideration as a drug target for OC warrants investigation in forthcoming animal studies and clinical trials.

There were several strengths in this analysis. Firstly, Using MR analysis to assess the correlation between 734 proteins and OC reduced the biases caused by confounders and reverse causality. Colocalization analysis explored how specific loci exert pleiotropic effects across multiple traits. The innovative combination of proteomic data with MR analysis for OC presents a pioneering approach to pinpoint potential therapeutic targets. This advancement enhances our comprehension of ovarian cancer biology and propels future research and clinical applications. Secondly, large samples of GWAS have sufficient statistical validity to present a relationship between proteins and ovarian cancer. Thirdly, as additional analyses, the phe-MR and drug target databases improved the completeness and reliability of our findings. Fourthly, our analysis was restricted to Europeans, which minimized population stratification bias. However, there are still limitations. First, only European populations were studied, limiting the generalization of this study to other populations. Second, plasma proteins were selected instead of direct tissue samples for numerous human disorders. Interventions involving plasma proteins may not directly affect particular tissues. Thirdly, MR analysis was not a complete substitute for clinical trials. Our analysis suggested a biological relationship between the proteins and OC, offering evidence solely for the initial stage of drug development. Fourthly, the drug targets assessed in this study represented by a limited range of instruments, implying that the

inferred causal effects hinge on a small set of genetic instruments. Thus, these associations indicate causality and do not confirm it definitively. Additionally, in MR analysis addressing LD is achieved by employing the generalized IVW method to gauge the effect sizes, potentially enhancing the power of MR results.

Conclusions

In summary, this study identified 44 proteins that may be attractive drug targets for OC via MR and colocalization analysis using population-based proteomic data. Additional research is warranted to confirm our discoveries and delve into the functions of these protein candidates in OC.

Abbreviations

IVs	Instrumental variables
IVW	Inverse variance weighted
LD	Linkage disequilibrium
LDSC	Linkage imbalance score regression analysis
MR	Mendelian randomization
OC	Ovarian Cancer
OCAC	Ovarian Cancer Association Consortium
OR	Odds ratio
SNP	Single nucleotide polymorphism

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

LSC, ZQ and ZK conceived the idea for the study and performed the data analyses and interpreted the results of the data analyses. LSC and LH obtained the genetic data. LSC, ZK, LH, ZQ and SY wrote the manuscript. LSC, ZQ and LH revised, polished, and verified the results of the manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Not applicable.

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