• Clinical Research •

Identification of novel drug targets for primary open angle glaucoma and its potential side-effects by human plasma proteome

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Abstract

● **AIM:** To explore whether plasma proteins serve as potential therapeutic targets for primary open angle glaucoma (POAG) based on a Mendelian randomization (MR) study.

● **METHODS:** Large-scale protein quantitative trait loci (pQTLs) data from the Icelandic deCODE database and two large POAG Genome-Wide Association Study (GWAS) summary datasets were used in this study. Causal associations between plasma proteins and POAG were identified using summary-data-based MR (SMR) analysis and the heterogeneity in dependent instruments (HEIDI) test. Colocalization analysis was then conducted to assess the genetic associations between these two factors. Phenotype-wide MR analysis was performed to validate protein targets as potential drug targets and to evaluate potential side effects. Finally, protein-protein interactions (PPI) were studied, and the Drug-Gene Interaction Database (DGIDb) was used to identify associations between drugs and the identified proteins.

● **RESULTS:** Four proteins (SVEP1, TMEM190, ROBO1, and ENPP5) were identified as potential drug targets in this study. Phenome-wide MR analysis showed that SVEP1, ROBO1, and ENPP5 were not associated with adverse effects, while TMEM190 was linked to nerve root and plexus disorders, as well as subarachnoid hemorrhage. Ticagrelor was suggested as a potential new drug for the treatment of glaucoma by regulating SVEP1.

● **CONCLUSION:** Four plasma proteins—SVEP1, TMEM190, ROBO1, and ENPP5—are identified as potential therapeutic targets for POAG through an MR approach. Phenome-wide MR analysis reveals that SVEP1, ROBO1, and ENPP5 are not associated with adverse effects, while TMEM190 is linked to nerve root and plexus disorders, as well as subarachnoid hemorrhage. Ticagrelor is proposed as a potential therapeutic drug for glaucoma by regulating SVEP1. These findings highlight the potential of plasma proteins as drug targets for POAG and provide valuable insights for further research.

● **KEYWORDS:** drug targets; mendelian randomization; proteome-wide Mendelian randomization; primary open angle glaucoma

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INTRODUCTION

Primary open angle glaucoma (POAG) is a chronic, progressive optic neuropathy in adults with a characteristic

acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons[1]. It is estimated that 53 million people worldwide will have POAG by 2020, with a prevalence of 3.0% in the population aged 40 to 80y[2]. Previous studies have shown that risk factors for POAG are associated with age, ethnicity, elevated intraocular pressure (IOP), family history of glaucoma, and type 2 diabetes, and a thin central cornea[3]. Existing guidelines have shown that lowering IOP can reduce the risk of POAG and slow disease progression. Currently, IOP is mainly reduced by drugs, lasers, and surgical interventions. Glaucoma is known to be a multifactorial disease, so finding treatment options other than lowering IOP is significant.

The plasma proteome encompasses all proteins present in blood plasma. Studying the plasma proteome helps us understand the association between proteins and diseases[4]. Mendelian randomization (MR) analysis is a popular tool for discovering new pathways for the use of licensed drugs and exploring new therapeutic targets for diseases[5-6]. Genome-Wide Association Study (GWAS) have identified specific single nucleotide polymorphisms (SNPs) that regulate protein expression. These SNPs are associated with quantitative traits of protein abundance, known as pQTLs[7]. MR uses pQTLs as instrumental variables to explore potential causal relationships between exposure and outcomes, including the screening of drug targets and biomarkers[8-9]. Compared to observational studies, MR can mitigate the effects of confounders and assess causality more reliably[10]. Additionally, by using phenome-wide association studies (PheWAS), it may be possible to predict adverse reactions associated with screening results corresponding to these targets[11]. Currently, several studies have used pQTLs to explore the corresponding drug targets for various diseases including those affecting the immune system[12], nervous system[13], cardiovascular system[14], and digestive system[15].

In this study, we first identified the association between serum proteins and POAG using summary-data-based MR (SMR) analysis and the heterogeneity in dependent instruments (HEIDI) test. We then identified gene variant sites through colocalization analysis, which led to serum protein drug targets for the potential treatment of POAG. Finally, we explored their potential adverse effects.

MATERIALS AND METHODS

Ethical Approval The data used for the study were publicly available, and the corresponding ethical consent was approved in the original study. This study did not involve individual patient information and therefore did not require additional ethical review or informed consent from the patients.

Study Design The research workflow diagram was shown in Figure 1. In summary, we used SMR and the HEIDI test to determine the causal relationship between plasma proteins and POAG. Colocalization analysis was then employed to assess the genetic association between proteins and POAG. By integrating the aforementioned analyses, we performed protein-protein interactions (PPI) analysis and evaluated the drug's side effects and druggability.

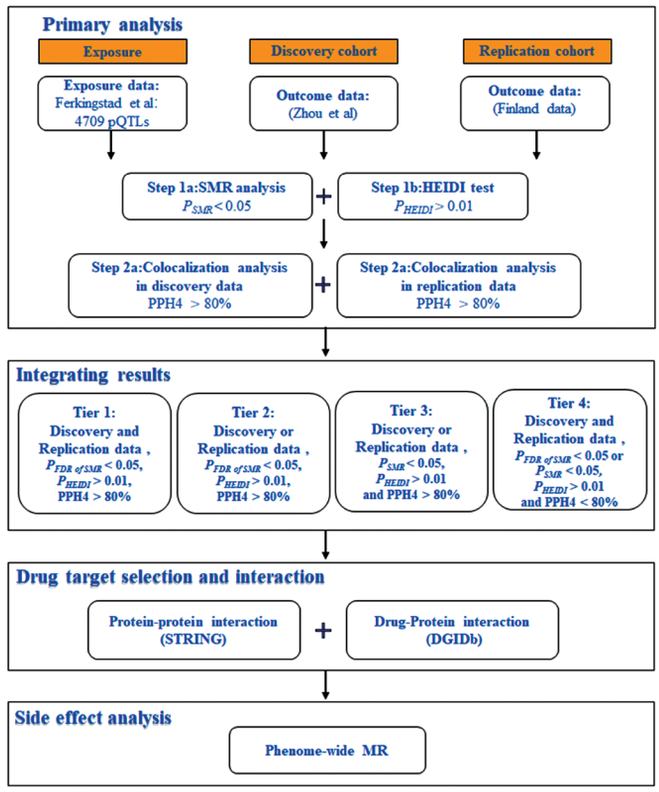

Figure 1 The flowchart of study SMR: Summary-data-based Mendelian randomization; HEIDI: Heterogeneity in dependent instruments; PPH4: Posterior probability of H4; DGIDb: the Drug-Gene Interaction Database; MR: Mendelian randomization.

Data Source of Proteomic Data and POAG For pQTLs, large-scale proteomic data were used[16]. Ferkingstad *et al*'s[17] study included 35 559 individuals from Iceland and ultimately contained 4709 proteins using the SomaScan multiplex aptamer assay (version 4). For POAG, Meta-analysis data from a GWAS (Aggregating 23 biobanks from four continents, POAG: 26 848 cases) were included in the discovery dataset[18]. A GWAS summary data, comprising 8530 cases and 391 275 controls, was then obtained from Finland data as replication data[19]. All POAG data are derived exclusively from the European population. Detailed information on all GWAS data can be found in Table 1.

SMR and HEIDI Test The use of SMR to analyze the association between proteome and POAG allows for the simultaneous analysis of gene expression and epigenetic data, providing a more comprehensive assessment of gene causality for complex traits than traditional MR. In addition, SMR relies on cis-QTLs associated with up-regulated genes, which provides higher statistical efficacy in large sample sizes[20]. The

Table 1 Information of GWAS summary data

Data source	Population	No. of cases	No. of controls	Total	PMID
pQTLs					
4709 proteins	Iceland	35559	-	35559	34857953
Discovery data					
Zhou *et al*[18]	European	16355	1156550	1172905	36777996
Replication data					
Kurki *et al*[19]	European	8530	391275	3998055	-

pQTL: Large-scale protein quantitative trait loci; GWAS: Genome-Wide Association Study Catalog.

HEIDI test was used to exclude possible nonspecific effects of genetic variants and was used to improve the robustness of the results[20]. Linkage disequilibrium was excluded when the *P*-value of the HEIDI test was less than 0.01, indicating that associations between pQTLs and POAGs were not affected by this effect[21]. SMR analyses and the HEIDI test were performed using the SMR software tool (v1.3.1), with all parameters at default values. To eliminate the possibility of false positives, the results of the multiplex assays were corrected using the false discovery rate (FDR). $P_{FDR\ of\ SMR}$<0.05 were considered as significantly associated proteins, P_{SMR}<0.05 were considered as suggestively associated proteins, and P_{SMR}>0.05 were considered as non-associated proteins. All significant and suggestive associations had to fulfill the criterion of P_{HEIDI} greater than 0.01. Significant results of MR analysis and HEIDI testing are shown in Table 2.

Colocalization Analysis Colocalization analysis to determine whether POAG and plasma proteins share causal variants was performed with the "coloc" package (v5.2.2) downloaded from GitHub (https://github.com/chr1swallace/coloc)[22]. The analysis was based on five hypotheses: 1) POAG and plasma proteins have no causal variants at the genetic locus (H0); 2) Only proteins have causal variants (H1); 3) Only POAG has causal variants (H2); 4) Proteins and POAG have two distinct causal variants (H3); 5) Proteins and POAG share the same causal variant (H4)[23]. We selected SNPs within ±1000 kb of each protein's pQTLs and Colocalization analysis was performed using default parameters[23]. When the posterior probability of H4 (PPH4) was higher than 80%, it provided strong evidence for colocalization[22].

Result Integration To comprehensively identify potential drug targets for POAG, we categorized the results of primary analysis into four tiers based on the following criteria: 1) Tier 1: Significantly associated proteins ($P_{FDR\ of\ SMR}$<0.05, P_{HEIDI}>0.01, PPH4>80%) in both discovery and replication data; 2) Tier 2: Significantly association proteins ($P_{FDR\ of\ SMR}$<0.05, P_{HEIDI}>0.01, PPH4>80%) in discovery or replication data; 3) Tier 3: suggestive association proteins (P_{SMR}<0.05, P_{HEIDI}>0.01) and PPH4 >80% in either discovery or replication data. 4) Tier 4: significant or suggestive association proteins ($P_{FDR\ of\ SMR}$<0.05 or P_{SMR}<0.05, P_{HEIDI}>0.01) and PPH4<80% in both discovery and replication data. Consequently, we excluded proteins that showed inconsistent estimates between the discovery and replication cohorts. This ensures that we avoid potentially contradictory results.

Protein-Protein Interaction and Druggability Evaluation We constructed a PPI network using the STRING database (https://string-db.org/) to estimate the interactions between identified proteins. We also queried the Drug-Gene Interaction Database (DGIDb, v4.2.0, https://www.dgidb.org/) to determine whether the identified proteins could be potential therapeutic targets and to learn about the drug information associated with the identified proteins[24].

Phenome-wide MR To further investigate the potential side effects after pharmacological modulation of plasma proteins, a Phenome-wide MR analysis of the top SNPs identified in the SMR was conducted. The GWAS data for diseases were acquired from the UK Biobank. These data addressed the unbalanced case-control ratios using the Scalable and Accurate Implementation of a Generalized Mixed Model (SAIGE, version 0.29)[25]. Disease phenotypes with fewer than 500 cases were subsequently excluded to ensure adequate statistical power, resulting in 783 diseases were filtered. Then, 779 non-POAG phenotypes were selected. Summary data related to the top SNPs can be downloaded from the SAIGE GWAS at https://www.leelabsg.org/resources[25]. Causal associations between four proteins and other phenotypes were estimated using the Wald ratio method. Results were considered significant when the *P*-value was less than 0.05/779.

RESULTS

Results of Primary Analysis The 105 proteins were significantly associated with POAG, meeting the conditions (P_{SMR}<0.05 and P_{HEIDI}>0.01) in the discovery data. The 127 proteins were significantly associated with POAG, meeting the conditions (P_{SMR}<0.05 and P_{HEIDI}>0.01) in the replication data. We then selected proteins that met the criteria in both the discovery and replication data. This resulted in 17 proteins: BRSK2, DCI, DNAJA4, DUSP13, G6B, IL18R1, ITIH1, ITIH3, JUND, LILRB1, NAAA, RGMA, ROBO1, SFTPD, SVEP1, TIMP3 and TMEM190. Then, in discovery data three significant ($P_{FDR\ of\ SMR}$<0.05) associated proteins (SVEP1, ENPP5 and TMEM190) were filtered (Figure 2A).

Table 2 Significant results of SMR analysis and HEIDI test

Gene	Type of results	Top-SNP	Beta±SE	P_{SMR}	P_{HEIDI}	$P_{FDR\ of\ SMR}$
Discovery data						
SVEP1	Tier1	rs78742138	0.213±0.047	6.14×10^{-6}	0.252	[a]4.808×10^{-3}
ENPP5	Tier2	rs1047153	0.082±0.018	1.02×10^{-5}	0.055	[a]5.319×10^{-3}
TMEM190	Tier2	rs35791293	-0.049±0.013	1.160×10^{-4}	0.294	[a]4.539×10^{-2}
ROBO1	Tier3	rs6807536	0.142±0.067	3.338×10^{-2}	0.299	6.469×10^{-1}
TIMP3	Tier4	rs2899194	-0.042±0.018	2.102×10^{-2}	0.310	5.873×10^{-1}
BRSK2	Tier4	rs7932863	-0.167±0.080	3.766×10^{-2}	0.307	6.476×10^{-1}
DCI	Tier4	rs11541763	-0.185±0.089	3.698×10^{-2}	0.815	6.475×10^{-1}
DNAJA4	Tier4	rs12591810	-0.403±0.190	3.414×10^{-2}	0.251	6.469×10^{-1}
DUSP13	Tier4	rs6480768	-0.224±0.084	7.820×10^{-3}	0.020	4.868×10^{-1}
G6B	Tier4	rs144347886	-0.246±0.123	4.659×10^{-2}	0.437	6.606×10^{-1}
IL18R1	Tier4	rs6753717	-0.044±0.021	3.653×10^{-2}	0.283	6.475×10^{-1}
ITIH1	Tier4	rs1042779	0.079±0.025	1.554×10^{-3}	0.790	2.432×10^{-1}
ITIH3	Tier4	rs2071044	-0.062±0.027	2.095×10^{-2}	0.146	5.873×10^{-1}
JUND	Tier4	rs4531856	-0.490±0.230	3.288×10^{-2}	0.718	6.469×10^{-1}
LILRB1	Tier4	rs138131257	0.036±0.016	2.645×10^{-2}	0.325	6.403×10^{-1}
NAAA	Tier4	rs10518142	-0.062±0.022	5.542×10^{-3}	0.796	4.630×10^{-1}
RGMA	Tier4	rs11074135	-0.211±0.076	5.630×10^{-3}	0.956	4.630×10^{-1}
SFTPD	Tier4	rs12357764	-0.057±0.024	1.957×10^{-2}	0.297	5.778×10^{-1}
Replication data						
SVEP1	Tier1	rs61751937	0.321±0.047	9.211×10^{-12}	0.120	[a]1.648×10^{-8}
ENPP5	Tier2	rs1047153	0.026±0.024	2.687×10^{-1}	0.072	7.809×10^{-1}
TMEM190	Tier2	rs4806666	-0.040±0.016	1.170×10^{-2}	0.367	3.968×10^{-1}
ROBO1	Tier3	rs6807536	0.315±0.083	1.498×10^{-4}	0.499	6.447×10^{-2}
TIMP3	Tier4	rs2899194	-0.095±0.023	4.214×10^{-5}	0.060	[a]2.513×10^{-2}
BRSK2	Tier4	rs4255564	-0.298±0.098	2.243×10^{-3}	0.283	1.953×10^{-1}
DCI	Tier4	rs11541763	-0.310±0.104	2.961×10^{-3}	0.592	2.207×10^{-1}
DNAJA4	Tier4	rs4887023	-0.510±0.243	3.542×10^{-2}	0.651	5.307×10^{-1}
DUSP13	Tier4	rs4746262	-0.210±0.106	4.784×10^{-2}	0.072	5.560×10^{-1}
G6B	Tier4	rs144347886	-0.298±0.099	2.510×10^{-3}	0.470	1.953×10^{-1}
IL18R1	Tier4	rs6753717	-0.066±0.029	1.991×10^{-2}	0.301	4.686×10^{-1}
ITIH1	Tier4	rs1042779	-0.089±0.032	5.422×10^{-3}	0.426	2.977×10^{-1}
ITIH3	Tier4	rs2071044	-0.120±0.033	2.797×10^{-4}	0.397	6.447×10^{-2}
JUND	Tier4	rs10406080	-0.643±0.296	2.965×10^{-2}	0.907	5.307×10^{-1}
LILRB1	Tier4	rs138131257	0.044±0.020	3.299×10^{-2}	0.283	5.307×10^{-1}
NAAA	Tier4	rs10518142	-0.069±0.029	1.607×10^{-2}	0.567	4.492×10^{-1}
RGMA	Tier4	rs11074135	-0.325±0.093	4.848×10^{-4}	0.921	7.618×10^{-2}
SFTPD	Tier4	rs12357764	-0.078±0.031	1.209×10^{-2}	0.637	3.968×10^{-1}

[a]$P_{FDR\ of\ SMR}<0.05$. SMR: Summary-data-based Mendelian randomization; HEIDI: Heterogeneity in dependent instruments; SNPs: Single nucleotide polymorphisms.

In replication data, two significant ($P_{FDR\ of\ SMR}<0.05$) associated proteins (SVEP1 and TIMP3) were filtered the results displayed in Figure 2B. ENPP5 exhibited correlation only in the discovery cohort, but this association was not replicated in the validation data ($P_{SMR}<0.05$ and $P_{HEIDI}>0.01$). In summary, the 18 proteins were selected for follow-up analysis.

Colocalization Analysis and Result Integration We performed colocalization analysis on the 18 proteins identified in the initial analysis. In the discovery data, three proteins (SVEP1, ENPP5 and TMEM190) were found to share genetic variants with POAG, with PPH4 of 99.602%, 87.619% and 97.724%, respectively. In the replication data, two proteins (ROBO1 and SVEP1) were found to share genetic variants with POAG, with PPH4 of 88.725% and 99.936% respectively. Detailed results of the colocalization analysis can be found in. By integrating the results of the primary and colocalization

analyses, we identified SVEP1 as the protein with tier 1 evidence, as it exists in both datasets. Meanwhile, TMEM190 and ENPP5 were identified as tier 2 evidence ($P_{FDR\ of\ SMR}$<0.05, and P_{HEIDI}>0.01). ROBO1 was identified as tier 3 evidence. TIMP3, BRSK2, DCI, DNAJA4, DUSP13, G6B, IL18R1, ITIH1, ITIH3, JUND, LILRB1, NAAA. RGMA, and SFTPD were identified as tier 4 evidence.

Protein-Protein Interaction and Druggability Evaluation Next, we explored the interactions between the four proteins that were successfully colocalized using PPI analysis (Figure 3). We queried whether these four proteins could be potential drug targets in the Drug-Gene Interaction Database (DGIdb, v4.2.0, https://www.dgidb.org/)[24]. The result showed that SVEP1 was affected by a drug called TICAGRELOR, while other proteins were not affected by any drugs. TICAGRELOR is a novel antiplatelet agent that can prevent thrombosis by inhibiting platelet aggregation, thereby improving the cardiovascular status of patients[26].

Phenome-wide MR We performed Phenome-wide MR using Top-SNPs from the successful colocalization data (SVEP1: rs78742138; TMEM190: rs35791293; ENPP5: rs1047153; ROBO1: rs6807536) to investigate potential side effects when using identified proteins as drug targets. The results showed that with a threshold of P<0.05/779, SVEP1 and ROBO1 were not associated with any adverse reactions, while TMEM190 was linked to two diseases or symptoms: Nerve root and plexus disorders, and Subarachnoid hemorrhage (Figure 4).

DISCUSSION

In this study, we systematically investigated the causal relationship between plasma proteins and POAG. Our study identified an association between four proteins (SVEP1, TMEM190, ROBO1, and ENPP5) and POAG, providing new insights for drug development against POAG.

SVEP1 is a protein found in the extracellular matrix that circulates in plasma and is expressed in the vasculature[27], lymphatics[28], adipose[29], and bone marrow[30]. Analysis of human genomic and proteomic data suggests that SVEP1 is involved in the development of several chronic diseases in humans, such as cardiovascular disease, dementia, glaucoma, *etc*. SVEP1 is a modifier of TEK-related primary congenital glaucoma[31]. An experimental study demonstrated that under-expression of SVEP1 in mouse neural crest cells may lead to Schlemm's canal defects and increased IOP, possibly by a mechanism whereby the protein affects lymphangiogenesis through its interaction with angiopoietin 2, which in turn affects the development of Schrems' canals, suggesting that under-expression of SVEP1 may lead to primary congenital glaucoma[32]. Future studies are dedicated to determining whether chronic excess of SVEP1 is also sufficient to disrupt Schrems' canal as well as to determine how SVEP1 affects

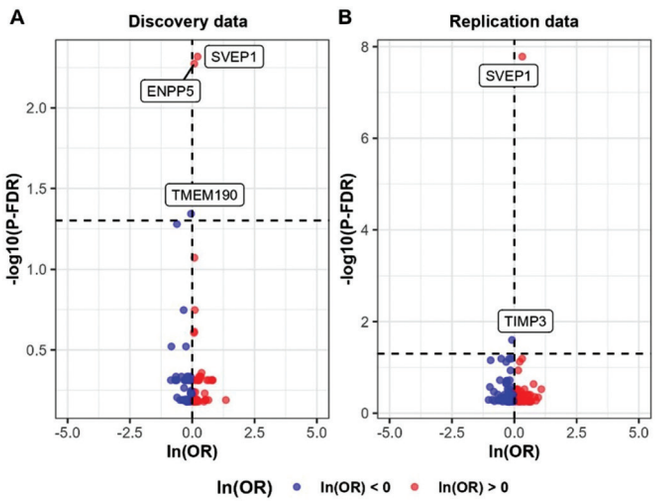

Figure 2 The results of primary analysis In the discovery cohort, SVEP1, ENPP5 and TMEM190 were found to meet the criteria of the FDR less than 0.05 and HEIDI test was greater than 0.01. In the replication cohort, SVEP1 and TIMP3 were identified as satisfying the same requirements. FDR: False discovery rate; HEIDI: Heterogeneity in dependent instruments.

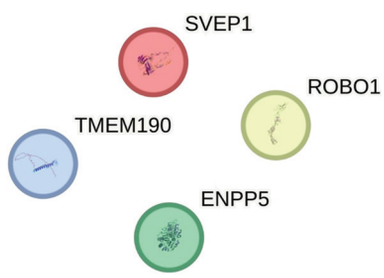

Figure 3 Protein-protein interaction analysis showed that there was no direct correlation between the four proteins.

Schrems' canal development. Our study showed that SVEP1 is positively correlated with POAG, and that SVEP1 and POAG share genetic variants. Drug-related analyses suggest a potential association between an antithrombotic drug (Ticagrelor) and POAG. Notably, increasing SVEP1 protein expression by drugs may affect hepatic and renal function.

In addition, we found an association between three other proteins (TMEM190, ROBO1, and ENPP5) and POAG. Unfortunately, previous literature has not mentioned the targeted interactions between these proteins and POAG. TMEM190 is a transmembrane protein is present in the cell membrane. However, its function in the cell is not fully understood. Previous studies have suggested that TMEM190 may be involved in biological processes such as cell signaling, cell adhesion, and intracellular transport, and may also play a role in brain function[33-34]. A study found that methylation levels of TMEM190 differed among heavy cannabis users, suggesting that TMEM190 may be involved in neural pathways associated with cannabis use. In addition, TMEM190 has also been associated with several other neural-related genes (*e.g.*, *MUC3L*, *CDC20*, and *SP9*), which further supports a potential

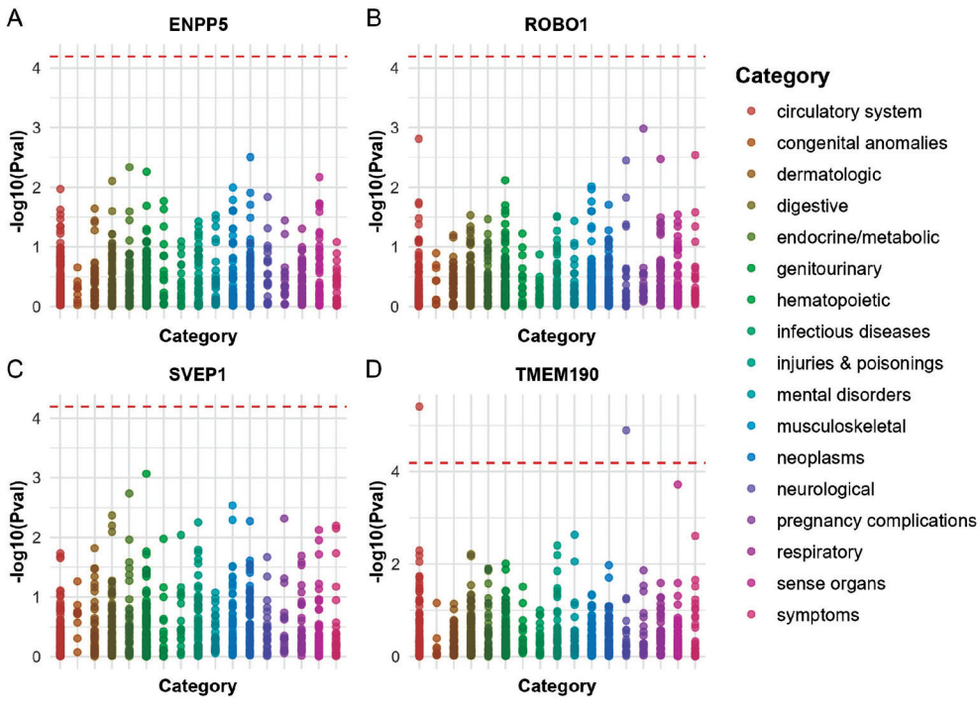

Figure 4 The results from the Phenome-wide Mendelian randomization indicate that SVEP1, ENPP5 and ROBO1 had no adverse actions, and TMEM190 was associated with 2 diseases or symptoms The X-axis shows the disease classification, and the Y-axis shows the $\log_{10}$(Pval) of the MR analysis results. The red dotted line for the $\log_{10}$(0.05/779).

role for TMEM190 in brain function[33]. However, further research is still needed to determine the specific function of TMEM190 and its role in cannabis use. Currently, no study has found a direct relationship between TMEM190 and POAG. Our study identified for the first time a reduced expression of this protein in plasma, which may increase the risk of developing POAG and is also associated with common genetic variants. Therefore, it could be considered as a potential therapeutic target. Unfortunately, drug-related analyses have shown that no drugs have been developed against this protein.

ROBO1 is a protein that belongs to an important class of the Slit-Robo signaling pathway, which mainly plays a role in embryonic development and the nervous system[35-36]. Previous studies have confirmed that during cardiac development, ROBO1 is involved in processes such as migration, alignment, and lumen formation of cardiac cells[37]. Mutations in the *ROBO1* gene may lead to abnormal axon guidance, which could affect reading ability[38]. Abnormal expression of ROBO1 has been associated with tumor development and angiogenesis. *ROBO1* has been found to act as a tumor suppressor gene in a variety of cancers [9,39-40]. In summary, *ROBO1* plays important regulatory roles in several biological processes. Our study identified for the first time an increased expression of this protein in plasma, which may increase the risk of developing POAG and is also associated with common genetic variants. Therefore, it could be considered as a potential therapeutic target. Unfortunately, it was shown by drug-related analyses that there are no drugs developed against this protein.

Ectonucleotide pyrophosphatase/phosphodiesterase 5 (ENPP5) is an enzyme primarily expressed in the nervous system and a member of the ENPP family involved in extracellular nucleotide metabolism and signaling. ENPP5 is one of least studied members of the ENPP family and shows no activity towards many known ENPP substrates. It has been demonstrated that ENPP5 can hydrolyze nicotinamide adenine dinucleotide (NAD), suggesting a potential role in NAD-based neurotransmission[41]. However, this hypothesis requires further investigation. Oral vitamin B3 (nicotinamide) has been shown to provide precursor substances for NAD+, which plays a role in intervening and protecting against the development of glaucomatous disease[42]. Our study is the first to identify that increased plasma expression of this protein may elevate the risk of developing POAG and that it is associated with a common genetic variant. Combined with existing research, these findings suggest that ENPP5 could be a potential new therapeutic target for the treatment of POAG. Unfortunately, there are currently no licensed drugs targeting ENPP5 in our drug-related analyses.

Furthermore, the results of proteins classified under Tier 4 in this study may suggest an association with glaucoma, where there may be potential drug targets for the treatment of glaucoma as well as possible markers for POAG that could be used to test for the disease. However, our review of previous studies revealed no existing literature supporting the association of these Tier 4 proteins with POAG. Thus, further research is necessary to explore the relationship between

POAG and these proteins.

Our study also has some limitations. First, we only explored the causal relationship between plasma proteins and POAG and did not investigate the underlying mechanisms. Second, we only utilized data from European populations, so further studies are needed to determine whether these findings apply to different populations, such as those in East Asia or Africa. Finally, although our study reported for the first time the association of SVEP1, TMEM190, ENPP5 and ROBO1 with POAG, these proteins lack experimental validation. Therefore, further studies are needed to investigate the potential therapeutic effects of these proteins on POAG.

In summary, our study systematically explored the causal relationship between serum proteins and POAG, while four proteins (SVEP1, TMEM190, ROBO1, ENPP5) were identified as potential drug targets. The Phenome-wide MR analysis showed that SVEP1, ROBO1 and ENPP5 had no adverse reactions, and TMEM190 was associated with nerve root and plexus disorders and subarachnoid hemorrhage. Ticagrelor may act as a new drug for the treatment of glaucoma by modulating SVEP1.

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