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Mendelian randomization of plasma proteomics identifies novel ALS-associated proteins and their GO enrichment and KEGG pathway analyses

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Abstract

Background Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurological disorder with an increasing incidence rate. Despite advances in ALS research over the years, the precise etiology and pathogenic mechanisms remain largely elusive.

Objective To identify novel plasma proteins associated with ALS through Mendelian randomization methods in large-scale plasma proteomics and to provide potential biomarkers and therapeutic targets for ALS treatment.

Methods This study employed a large-scale plasma proteomic Mendelian randomization approach using genetic data from 80,610 individuals of European ancestry (including 20,806 ALS patients and 59,804 controls) derived from a genome-wide association study (GWAS). Protein quantitative trait loci (pQTLs) data were obtained from Ferkingstad et al. (2021), which measured 4,907 proteins in 35,559 Icelandic individuals. Multiple Mendelian randomization (MR) techniques were utilized, including weighted median, MR-Egger, Wald ratio, inverse-variance weighting (IVW), basic model, and weighted model. Heterogeneity was evaluated using Cochran's Q test. Horizontal pleiotropy was assessed through the MR-Egger intercept test and MR-PRESSO outlier detection. Sensitivity analysis was performed via leave-one-out analysis.

Results MR analysis revealed potential causal associations between 491 plasma proteins and ALS, identifying 19 novel plasma proteins significantly linked to the disease. Proteins such as C1QC, UMOD, SLITRK5, ASAP2, TREML2, DAPK2, ARHGEF10, POLM, SST, and SIGLEC1 showed positive correlations with ALS risk, whereas ADPGK, BTNL9, COLEC12, ADGRF5, FAIM, CRTAM, PRSS3, BAG5, and PSMD11 exhibited negative correlations. Reverse MR analyses confirmed that ALS negatively correlates with ADPGK and ADGRF5 expression. Enrichment analyses, including Gene Ontology (GO) functional analysis, indicated involvement in critical biological processes such as external encapsulating structure organization, extracellular matrix organization, chemotaxis, and taxis. KEGG pathway analysis

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highlighted significant enrichment in the PI3K-Akt signaling pathway, cytokine-cytokine receptor interactions, and axon guidance.

Conclusion This study enhances the understanding of ALS pathophysiology and proposes potential biomarkers and mechanistic insights for therapeutic development. Future research should explore the clinical translation of these findings to improve ALS patient outcomes and quality of life.

Keywords Amyotrophic lateral sclerosis, Plasma proteins, Mendelian randomization, GO functional analysis, KEGG pathway analysis, Drug target prediction, Protein quantitative trait loci, ALS

Introduction

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a progressive neurodegenerative disorder that affects motor neurons in the brain and spinal cord. Globally, two to three out of every 100,000 people develop ALS annually, with a higher prevalence among men [1]. ALS can be classified into familial and sporadic forms, with familial ALS accounting for approximately 10% of cases [2]. The disease is characterized by severe and progressive degeneration of motor neurons in the lower brainstem and upper cerebral cortex [3], leading to muscle atrophy, paralysis, stiffness, fasciculations, and spasticity. These symptoms result in difficulties with walking, hand coordination, speech, swallowing, and breathing [4]. Unfortunately, ALS is often diagnosed only one year after symptom onset [5]. Delayed diagnosis significantly hinders early therapeutic intervention, exacerbating disease progression and complicating treatment [6]. Furthermore, ALS progresses rapidly, with an average survival period of 2 to 4 years post-diagnosis, making it one of the most lethal motor neuron diseases [7]. By 2040, the global burden of ALS is projected to rise substantially, shifting from developed to developing nations and imposing a heavy strain on healthcare systems [8]. The lack of biomarkers for early diagnosis, clinical stratification, and treatment monitoring severely impedes the development of novel ALS therapies [9]. Although proteins encoded by genes such as SOD1, C9orf72, and FUS have been implicated in ALS pathogenesis, only tofersen—approved in the United States for adults with SOD1 mutations—has shown clinical efficacy [10]. Given the economic and clinical significance of ALS and the incomplete characterization of its genetic underpinnings, identifying key plasma proteins involved in ALS pathogenesis is critical for developing new therapeutic strategies.

To elucidate disease mechanisms, discover biomarkers, and uncover biological pathways, an increasing number of studies integrate proteomic and genomic data [11]. Plasma proteins play vital roles in immune regulation, molecular transport, signal transduction, tissue repair, and homeostasis maintenance [12]. As potential drivers of central nervous system disorders and major sources of drug targets, plasma proteins serve as diagnostic biomarkers and therapeutic intervention targets, holding significant value in human health and disease management [13]. Consequently, identifying disease-associated plasma proteins can deepen our understanding of pathophysiology and offer molecular targets for drug development.

Mendelian randomization (MR) is a statistical method that uses genetic variants as instrumental variables to infer causal relationships between exposures (e.g., proteomic factors) and outcomes (e.g., ALS). Unlike traditional observational studies, MR mitigates confounding bias through sensitivity analyses [14]. In MR, genetic variants associated with protein levels (protein quantitative trait loci, pQTLs) act as instrumental variables. By selecting cis-acting pQTLs (genetic variants near the target gene), MR provides functional annotations for disease-associated loci, prioritizes candidate genes from GWAS findings, and reveals tissue-specific disease mechanisms. Integrating expression quantitative trait loci (eQTL) data and gene network analyses further enhances the exploration of gene interactions [15–16]. MR has been widely applied to identify novel therapeutic targets and repurpose existing drugs [17]. Leveraging large-scale blood proteome datasets (e.g., Decode [18]), MR analyses can uncover genetic components of complex diseases influenced by circulatory factors.

Identifying proteins causally linked to ALS may improve our understanding of its genetic architecture and highlight potential therapeutic targets. Here, we employed a multiomics dataset to assess the causal effects of 4,907 plasma proteins on ALS, aiming to discover novel drug targets and dissect their pathophysiological roles. Subsequent enrichment analyses were conducted to identify pathways implicated in ALS pathogenesis, providing a theoretical foundation for developing effective therapies. This study seeks to advance therapeutic strategies for ALS, a disease with profound clinical challenges and limited treatment options.

Method

Data from ALS

ALS data come from the publicly accessible GWAS in the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/), The GWAS ID is ebi-a-GCST005647. In all, 80,610 people with European ancestry participated in this GWAS,

comprising 20,806 ALS patients and 59,804 controls. A total of 39,630,630 SNPs were examined (Fig. 1).

Data from plasma protein quantitative trait loci (pQTL)

The study by Ferkingstad et al. (2021), which produced the largest pQTL dataset to date, was the source of the pQTL data in this study [19]. In summary, 35,559 Icelanders participated in a genome-wide association study (GWAS) by Ferkingstad and colleagues, which examined plasma proteins using 4,907 aptamers. They found 18,084 sequence variations linked to plasma protein levels; uncommon variants minor allele frequency (MAF) < 1% accounted for 19% of these correlations. They discovered 257,490 connections by examining the relationships between plasma protein levels and 373 illnesses as well as other features. By combining pQTL data with genetic connections for traits and diseases, it was possible to identify 938 genes that could potentially be targets for drugs, and 12% of the lead variants in the GWAS catalog were in high linkage disequilibrium with pQTLs.

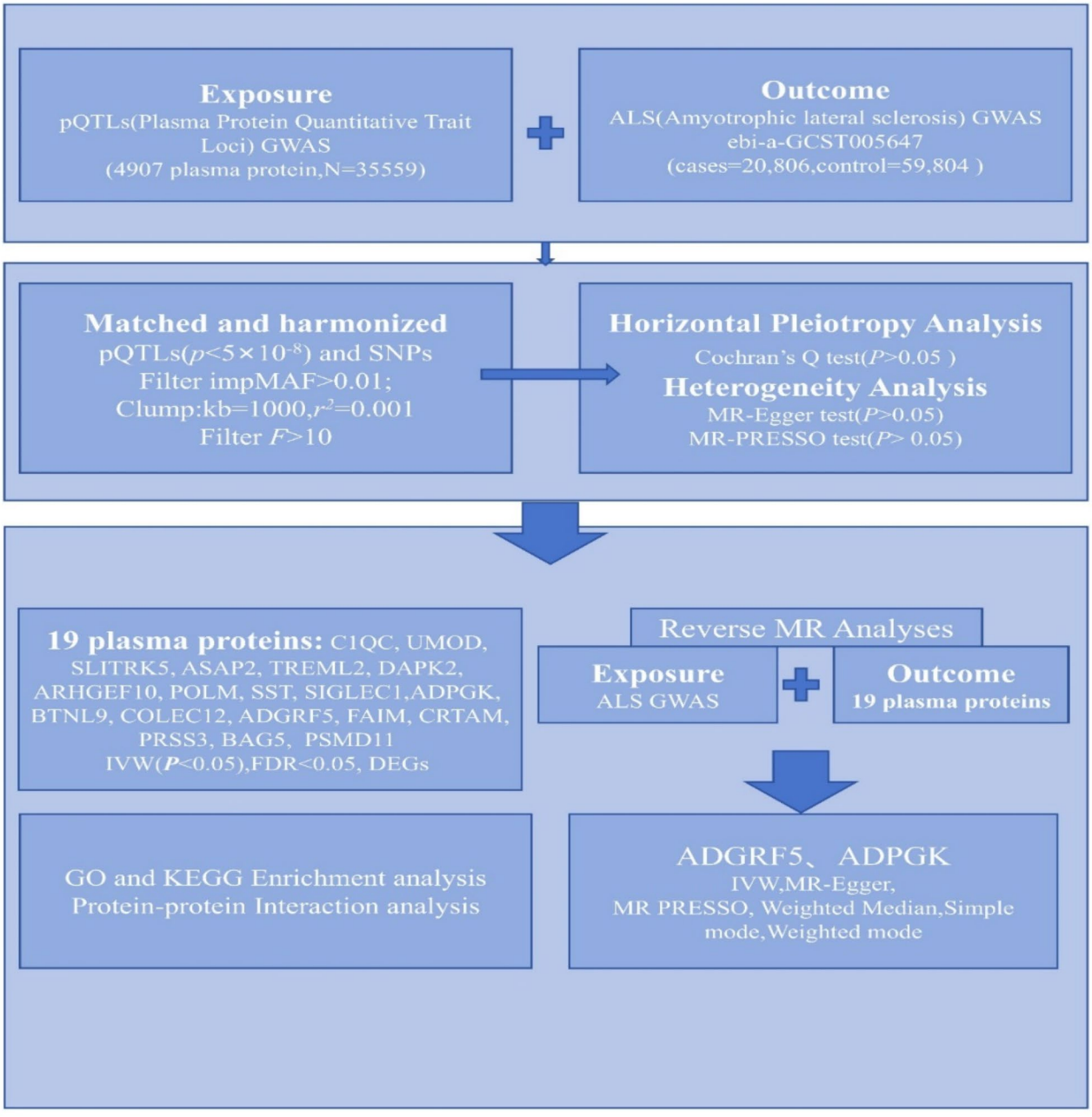

Fig. 1 The flowchart of this study

Selection of instrumental variables

We investigated the causal relationship between plasma proteins and ALS using dual-sample MR analysis [20, 21]. The MR method is based on the following assumptions: (i) instrumental variables are closely related to exposure (plasma protein levels); (ii) instrumental variables affect the outcome (ALS risk) only through their effect on exposure; (iii) instrumental variables are independent of any mixed factors.

In order to obtain single nucleotide polymorphisms (SNPs) that are closely related to exposure, we first set $p < 5 \times 10 - 8$ in accordance with the MR assumption [22]. Second, we determined the linkage disequilibrium between each exposed SNP using PLINK software, setting the threshold for linkage equilibrium at $r2 < 0.001$ (a distance of 10,00 kb) [23]. Minor Allele Frequency (MAF) was also considered in SNP selection to ensure that the instrumental variables used are common enough to avoid weak instrument bias. SNPs with low MAF (typically < 1%) are excluded as they may lead to imprecise estimates of the causal effect due to limited power [24]. Horizontal pleiotropy, heterogeneity and sensitivity analysis are important tools for quality control of MR analysis results [25]. We use MR-PRESSO and MR-Egger regression techniques to investigate possible horizontal pleiotropy among instrumental variables [26, 27]. Heterogeneity among selected instrumental variables was assessed using Cochran's Q statistic and its associated *p*-value [26, 28]. The presence or absence of heterogeneity is indicated by the *p* value ($p < 0.05$ indicates heterogeneity is present, $p > 0.05$ indicates no heterogeneity) [29]. To assess whether any particular SNP has an excessive impact on the overall causal relationship, a leave-one-out analysis is carried out by eliminating each SNP in turn and computing the combined effect of the remaining SNPs. Additionally, we computed the F statistic ($F = beta^2/se^2$), where beta is the allele's effect size and se is the standard error, to assess the validity of the included SNPs. If the F-statistic > 10, it suggests that the instrumental variable is robust; if F-statistic < 10, it is not [30] (Supplementary Table 1).

Mendelian randomization analysis

Mendelian randomization (MR) techniques, such as MR Egger, weighted median, inverse variance weighting (IVW), simple mode, and weighted mode, were mostly employed in this study [31]. IVW is the most critical method for evaluating analysis results in stochastic models. By integrating these different methods, we can verify hypothesized causal relationships from different perspectives, thereby increasing the credibility and accuracy of causal inferences. R software was used for all statistical analyses, and the TwoSampleMR and MendelianRandomization packages [32] were used for MR analysis. These packages provide tools for conducting MR analyses, testing hypotheses, and performing sensitivity analyses, providing a comprehensive framework for statistical assessment of causal relationships in genetic epidemiology. In addition, to solve the false positive problem caused by multiple comparisons, this study modified the false discovery rate (FDR) to the *P*-value to control the false positive rate in the multiple hypothesis test.By ranking all *P*-values and then correcting them, we ensure that false positive rates can still be effectively controlled at a high significance level. This revision process helps to improve the reliability of research results, especially in large-scale gene association studies, and effectively avoids the false negative problem caused by too strict revision methods.

Analysis of plasma protein differences associated with ALS

We performed differential expression analysis on positive results from forward MR analysis. Genes with $p < 0.05$ and |log fold change| (|logFC|) ≥ 1 are regarded as differential expression genes (DEGs). We used a volcano plot to display the common DEGs in plasma proteins, ultimately identifying a set of plasma protein genes associated with ALS. In the volcano plot, green indicates down regulated genes, and red indicates up regulated genes.

GO and KEGG enrichment analysis

We used the R software package clusterProfiler to conduct Gene Ontology (GO) and KEGG (Kyoto Encyclopedia of Genes and Genomes) analysis on differentially expressed plasma protein genes, successfully obtaining detailed information on cell components (CC), molecular functions (MF), biological processes (BP), and KEGG pathways. Based on this, we used two R packages, ggplot2 and circular, to visualize the results of the most representative parts of the analysis, specifically the top 30 KEGG pathways and the top 10 GO terms with the lowest *p*-values.

Result

Plasma proteins associated with ALS

After strictly following the instrumental variable selection criteria of the study, 1250 plasma proteins were finally included in the MR analysis, and the corresponding SNP information is detailed in Supplementary Table 2. Notably, among these 1250 plasma protein subgroups, MR based on the results of IVW or Wald ratio method ($p < 0.05$) and the corrected results (false discovery rate FDR < 0.05).The analysis revealed that 491 plasma proteins (Supplementary Table 3) may be associated with ALS. It is necessary to explain here that in this study, the Odds Ratio (OR) is used to measure the impact of plasma protein on ALS. When OR > 1, it indicates that the plasma protein is a risk factor; conversely, when OR < 1, it

means that it is a protective factor. The Confidence Interval (CI) reflects the uncertainty range of the estimated value, with a 95% CI typically used to evaluate the confidence level.Among the 491 ALS-associated plasma proteins, 95 plasma proteins were identified as potential risk factors for ALS ($\beta > 0$, OR > 1), while 396 plasma proteins were judged as potential protective factors for ALS ($\beta < 0$, OR < 1). We then performed an in-depth differential analysis of these plasma proteins associated with ALS. Among the top 20 most significantly different plasma proteins (Fig. 2), 11 of them are up-regulated genes, specifically covering C1QC, UMOD, SLITRK5, ASAP2, TREML2, DAPK2, F2, ARHGEF10, POLM, SST and SIGLEC1 et al. The down-regulated plasma protein genes include ADPGK, BTNL9, COLEC12, ADGRF5, FAIM, CRTAM, PRSS3, BAG5 and PSMD11. After completing the heterogeneity and horizontal pleiotropy analysis process, we excluded F2 from subsequent studies due to heterogeneity issues (Q < 0.05) (Supplementary Table 4).

It is important to note that in the MR analysis of certain specific exposure factors (for example, ADPGK), we did not use the weighted median method. The reason is that the application of the weighted median method requires at least three independent SNPs as effective instrumental variables to ensure the reliability and statistical power of the analysis results. However, for genes like ADPGK, after detailed verification (Supplementary Table 2), the number of SNPs meeting this requirement was fewer than three, meaning the weighted median method could not be applied.In light of this, in the analysis of these specific exposure factors, we only selected other appropriate methods such as IVW to conduct research. However, it should be clear that although the IVW method is still applicable when the number of SNPs is small, it has certain limitations. When pleiotropy exists, the robustness

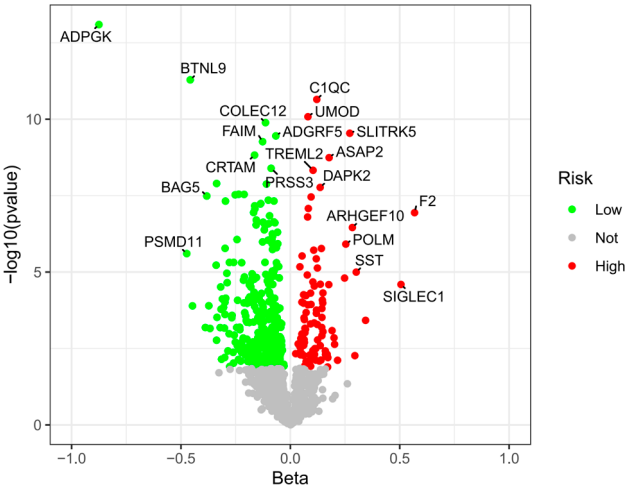

Fig. 2 Differential expression of plasma proteins associated with ALS. *Green represents downregulated genes, while red represents upregulated genes

of this method may be weakened to a certain extent, which in turn has a potential impact on the accuracy and reliability of the analysis results.

According to the MR analysis results (as shown in Fig. 3), the tabular data reveal that multiple proteins exhibit characteristics of potential risk factors for the disease (OR > 1), including SIGLEC1, SLITRK5, SST, among others. Notably, SIGLEC1 demonstrates the strongest risk effect, with an inverse-variance weighted OR of 1.658 (95% CI: 1.036–2.655, $p = 0.035$), suggesting that this protein may significantly promote disease progression, and its underlying mechanisms warrant further investigation. Additionally, SLITRK5 shows significant risk associations through both methods (weighted median OR = 1.258, $p = 0.029$; inverse-variance weighted OR = 1.318, $p = 0.003$), indicating the robustness of its pathogenic role. It is noteworthy that POLM, although analyzed only by the inverse-variance weighted method (nsnp = 2), still exhibits an OR of 1.289 ($p = 0.023$), highlighting its potential value as a novel risk factor. These results collectively unveil a complex disease risk regulatory network at the proteome level.

On the other hand, from the MR analysis results shown in Fig. 4 indicate that multiple proteins show the characteristics of potential protective factors for the disease (OR < 1), including ADGRF5, ADPGK, BTNLI9, FAIM, etc. Among them, ADPGK demonstrated the strongest protective effect, with an OR value of 0.417, which indicates that it may play a vital role in the prevention of the disease and holds significant value that should not be overlooked.

In addition, a reverse MR analysis was performed on these 20 genes, and two plasma proteins, ADPGK and ADGRF5, were successfully identified. It was found that these two genes were negatively correlated with ALS, meaning that the decrease in ADPGK and ADGRF5 levels was closely related to the progression of ALS. From the observation of the forest plot (Fig. 5A), it is evident that the CI for most individual SNPs cross zero, clearly indicating that the effects of individual SNPs are not statistically significant. Furthermore, the overall effect estimate (marked by the red line) is also close to zero, which strongly suggests that the causal effect of ALS on ADGRF5 may be weak or even non-significant. However, neither the MR Egger nor the IVW methods revealed significant horizontal pleiotropy. The Leave-One-Out plot (Fig. 5B) visually presents the sensitivity analysis results of sequentially removing each SNP, aiming to verify whether any specific SNP has a significant impact on the overall causal effect estimate. In this plot, the red dot represents the overall effect estimate, while the horizontal line indicates its confidence interval. It is evident from the figure that after each SNP is excluded, the change in the effect estimate is minimal and remains close to zero,

exposure	nsnp	method	pval	OR(95% CI)
ARHGEF10	4	Weighted median	**0.041**	1.312 (1.011 to 1.702)
	4	Inverse variance weighted	**0.011**	1.328 (1.068 to 1.651)
ASAP2	7	Weighted median	**0.004**	1.189 (1.058 to 1.336)
	7	Inverse variance weighted	**0.004**	1.190 (1.058 to 1.338)
C1QC	16	Weighted median	0.071	1.092 (0.993 to 1.201)
	16	Inverse variance weighted	**0.001**	1.126 (1.048 to 1.210)
DAPK2	6	Weighted median	**0.018**	1.129 (1.021 to 1.249)
	6	Inverse variance weighted	**0.005**	1.146 (1.042 to 1.260)
POLM	2	Inverse variance weighted	**0.023**	1.289 (1.036 to 1.603)
SIGLEC1	2	Inverse variance weighted	**0.035**	1.658 (1.036 to 2.655)
SLITRK5	10	Weighted median	**0.029**	1.258 (1.024 to 1.544)
	10	Inverse variance weighted	**0.003**	1.318 (1.099 to 1.581)
SST	4	Weighted median	0.060	1.389 (0.987 to 1.956)
	4	Inverse variance weighted	**0.026**	1.366 (1.037 to 1.798)
TREML2	10	Weighted median	0.052	1.094 (0.999 to 1.197)
	10	Inverse variance weighted	**0.004**	1.115 (1.036 to 1.200)
UMOD	30	Weighted median	**0.010**	1.089 (1.020 to 1.162)
	30	Inverse variance weighted	**0.001**	1.083 (1.031 to 1.137)

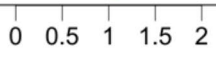

Fig. 3 Causal effect of plasma protein up-regulated gene on ALS. *OR: Odds Ratio; CI: Confidence Interval

exposure	nsnp	method	pval	OR(95% CI)
ADGRF5	24	Weighted median	**0.037**	0.945 (0.896 to 0.997)
	24	Inverse variance weighted	**0.002**	0.937 (0.899 to 0.976)
ADPGK	2	Inverse variance weighted	**<0.001**	0.417 (0.263 to 0.660)
BAG5	2	Inverse variance weighted	**0.006**	0.683 (0.521 to 0.895)
BTNL9	3	Weighted median	**0.008**	0.633 (0.451 to 0.888)
	3	Inverse variance weighted	**<0.001**	0.632 (0.482 to 0.830)
COLEC12	15	Weighted median	**0.026**	0.893 (0.808 to 0.986)
	15	Inverse variance weighted	**0.004**	0.897 (0.833 to 0.967)
CRTAM	13	Weighted median	0.122	0.910 (0.808 to 1.025)
	13	Inverse variance weighted	**0.003**	0.837 (0.743 to 0.942)
FAIM	10	Weighted median	**0.004**	0.875 (0.800 to 0.957)
	10	Inverse variance weighted	**0.002**	0.880 (0.812 to 0.954)
PRSS3	34	Weighted median	**0.005**	0.898 (0.832 to 0.968)
	34	Inverse variance weighted	**0.004**	0.917 (0.864 to 0.973)
PSMD11	3	Weighted median	0.308	0.782 (0.487 to 1.255)
	3	Inverse variance weighted	**0.019**	0.621 (0.418 to 0.923)

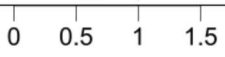

Fig. 4 Causal effect of Plasma protein down-regulated gene on ALS. *OR: Odds Ratio; CI: Confidence Interval

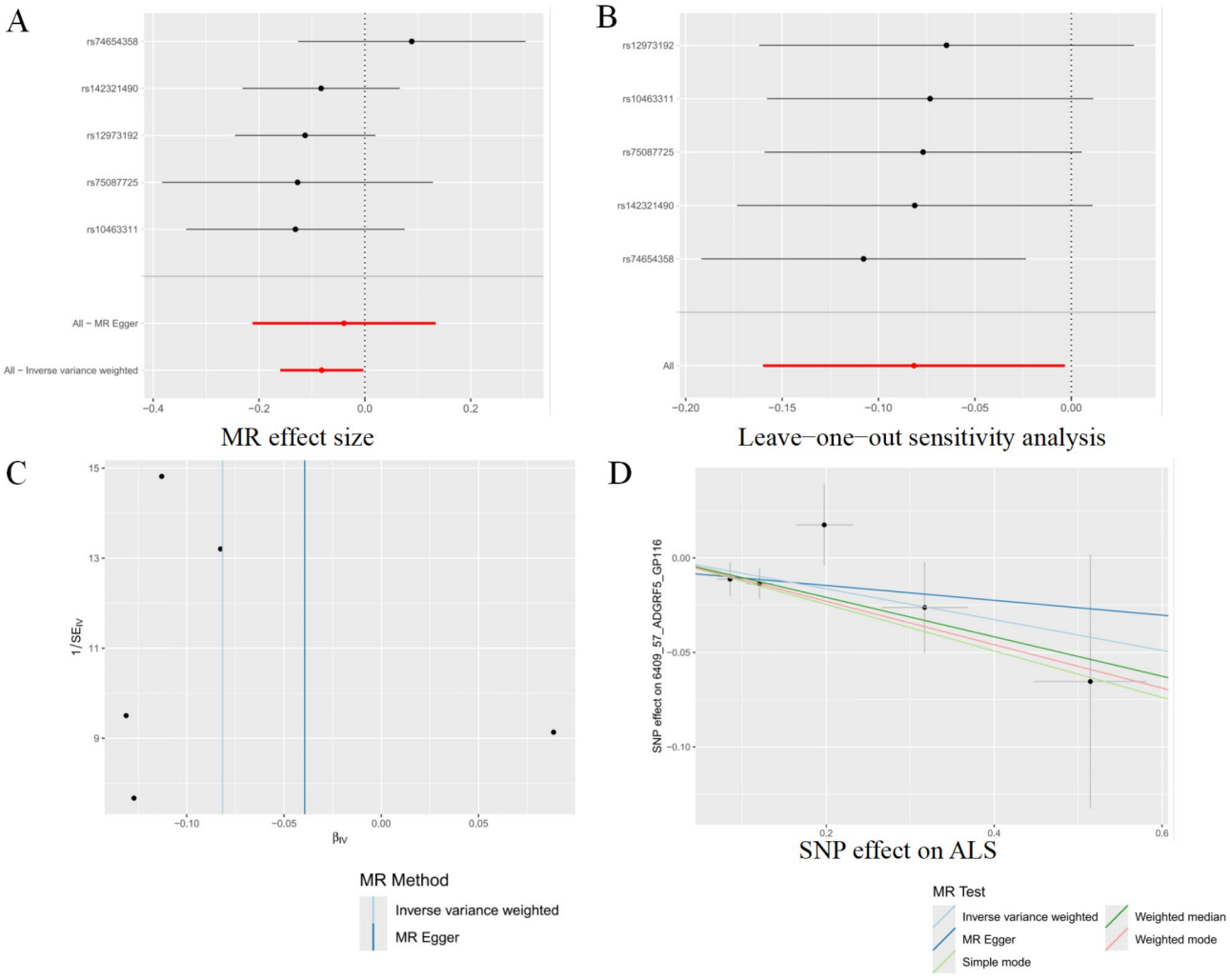

Fig. 5 Causal Effects of ALS on ADGRF5. (**A**. Forest Plot **B**. leave-one-out Plot **C**. funnal plot **D**. scatter Plot)

demonstrating that no single SNP significantly influences the causal effect estimate of ALS on ADGRF5. This stable estimate indicates the robustness of the causal effect. The Funnel Plot (Fig. 5C) is primarily used to assess potential bias in the MR analysis. The distribution of SNPs in the plot appears roughly symmetrical, without obvious skewness or aggregation, suggesting that the likelihood of horizontal pleiotropy or selection bias is low. The effect estimates of MR Egger and IVW methods on different SNPs are generally consistent, which further provides solid support for the reliability of causal effect analysis. The scatter plot clearly shows the relationship between the exposure effect and the outcome effect of each SNP. Among them, the fitting lines of different colors represent the effect estimates of different MR methods (such as IVW, MR Egger, weighted median, etc.). In Fig. 5D, the data points are mostly close to the zero value and relatively concentrated, which clearly indicates that the SNP effect is weak. The slopes of the fitting lines of different MR methods are close to zero, further confirming that the overall causal effect of ALS on ADGRF5 is small or does not have a significant effect. However, it is worth noting that the degree of directional consistency of the data fit is high, which strongly supports the robustness of the MR analysis."

Figure 6 presents the results of analyzing the causal effect of ALS on ADPGK using the MR method. The forest plots (Fig. 6A), Leave-One-Out plot (Fig. 6B), funnel plots (Fig. 6C), and scatter plots (Fig. 6D) all consistently indicate that the causal effect of ALS on ADPGK is weak or non-existent. Notably, both the scatter plot and funnel plot clearly show that there is no significant bias in the MR analysis, and the Leave-One-Out analysis further strengthens the robustness of the results. In summary, while the causal effect of ALS on ADPGK provides preliminary evidence, its significance has not been conclusively established, and further verification is needed to ensure the accuracy and reliability of the findings.

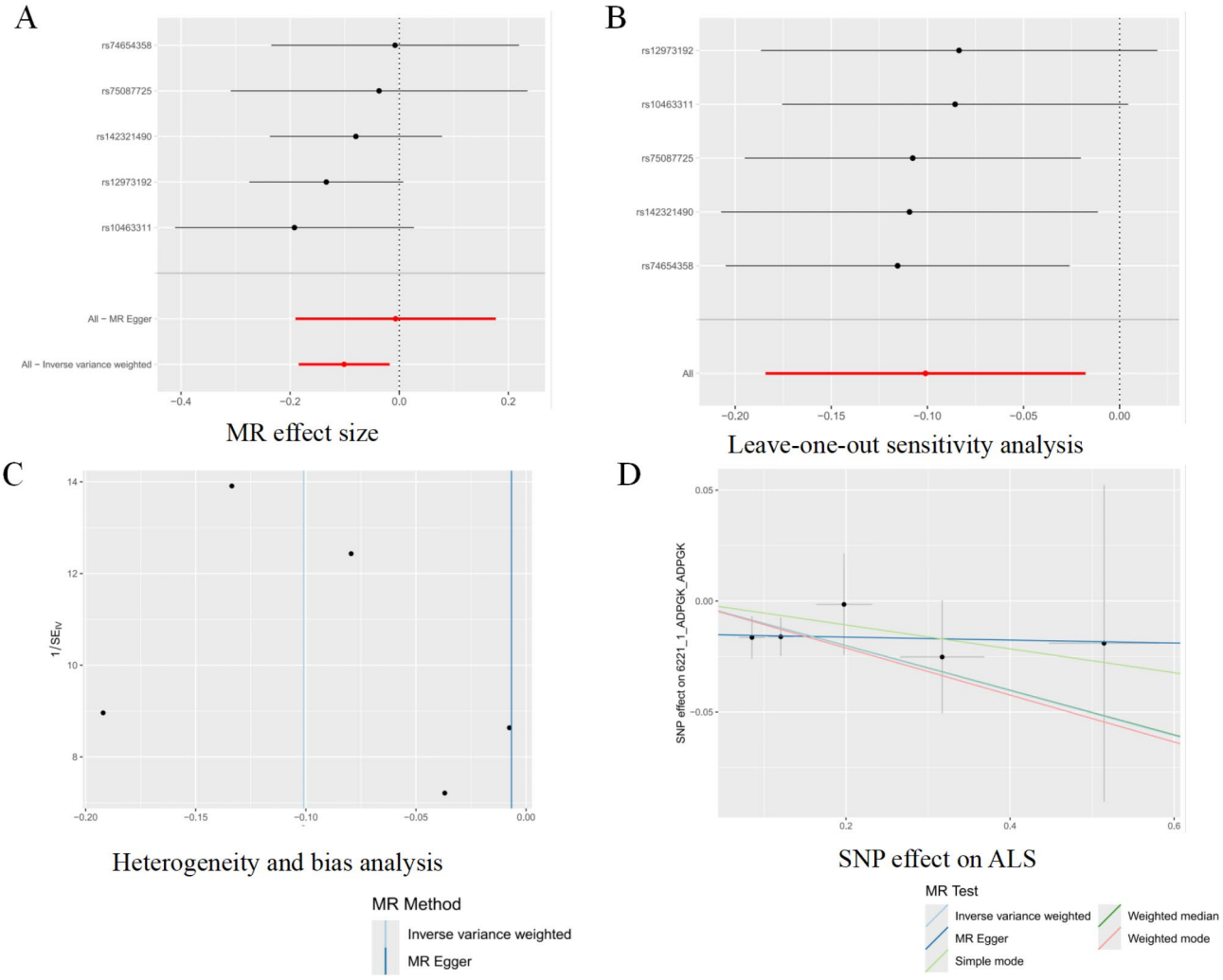

Fig. 6 Causal Effects of ALS on ADPGK. (**A**. Forest Plot **B**. leave-one-out Plot **C**. funnal plot **D**. scatter Plot)

Analysis of gene ontology and KEGG pathway enrichment

We performed GO analysis on the positive plasma protein genes found in the forward MR study using the clusterProfiler R package. The results revealed significant enrichment in 60 CC, 143 MF, and 982 BP, all of which were statistically significant ($P < 0.05$) (Supplementary Table 5). Figure 7A shows a circular graph summarizing the results of the GO analysis of positive plasma protein genes identified in forward MR)studies. The diagram consists of four concentric circles: First, the outer ring shows the top 18 enriched categories of GO analysis. Different colors represent the GO category: purple for MF, yellow for CC, and green for BP. The second circle represents the total number of genes in the genomic background, as well as the Q values of up-regulated genes in a particular biological process. Notably, GO: 0062023 (extracellular matrix containing collagen) had the highest number of genes (429) and the most significant enrichment. The third circle shows the number of differential genes in each enrichment pathway. As can be seen from the figure, the collagen-containing extracellular matrix in CC and the negative regulation of the response to external stimuli in BP show the highest gene counts, indicating their important role in ALS pathogenesis. The fourth circle shows the enrichment factor for each GO. The concentration of GO: 35580 (specific granular cavity) was the highest, suggesting a potential immune-related mechanism in ALS. Based on the lowest *P* values, Fig. 7B displays the top 10 biological processes in the GO analysis.The top five CC are collagen-containing extracellular matrix, cytoplasmic vesicle lumen, vesicle lumen, secretory granule lumen, and specific granule lumen. The top five MF are glycosaminoglycan binding, peptidase inhibitor activity, sulfur compound binding, endopeptidase regulator activity, and endopeptidase inhibitor activity. The top five BP are external encapsulating structure organization, extracellular matrix organization, extracellular structure organization, chemotaxis, and taxis.

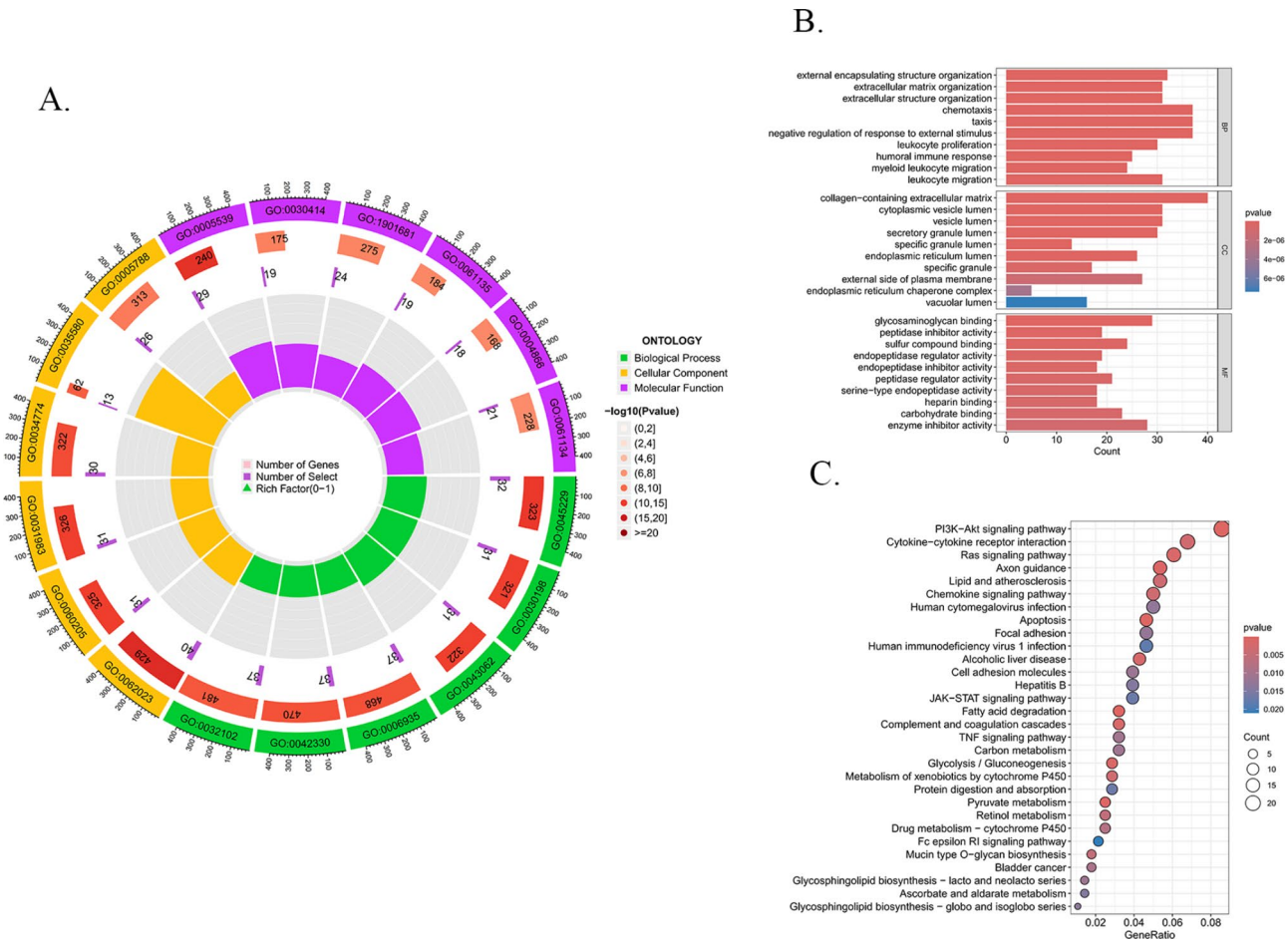

Fig. 7 GO and KEGG enrichment of plasma protein genes (**A**. The cycle diagram of GO enrichment **B**. The barplot of GO enrichment **C**. The bubble diagram of KEGG enrichment)

Through KEGG Pathway analysis, we identified 50 signaling pathways ($P < 0.05$) (Supplementary Table 6). The top six signaling pathways are: PI3K-Akt signaling pathway, cytokine-cytokine receptor interaction, axon guidance, lipid and atherosclerosis, chemokine signaling pathway. These pathways are involved in the development and course of the disease because they collectively control inflammatory response, cell survival, axon guidance, and metabolic processes (Fig. 7C).

Discussion

To investigate potential associations between 4,907 circulating plasma proteins and ALS, this study employed MR methods and identified 19 proteins significantly linked to ALS risk. Among these, 11 proteins—C1QC, UMOD, SLITRK5, ASAP2, TREML2, DAPK2, ARHGEF10, POLM, SST, and SIGLEC1—were identified as potential risk factors for ALS. Conversely, eight proteins—ADPGK, BTNL9, COLEC12, ADGRF5, FAIM, CRTAM, PRSS3, BAG5, and PSMD11—may act as protective factors. Reverse MR analyses were subsequently conducted on these 19 proteins. Finally, GO enrichment and KEGG pathway analyses provided novel insights into ALS pathophysiology, highlighting potential therapeutic targets and mechanistic pathways.

ALS is a neurodegenerative disease characterized by key neuropathological features, including endoplasmic reticulum stress, chronic neuroinflammation, impaired autophagy, mitochondrial dysfunction, oxidative stress, and DNA damage. These features are also shared with other neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) [33]. Additional ALS-associated mechanisms include Golgi apparatus fragmentation, excitotoxicity, axonal transport defects, deficient neurotrophic factors, altered glial function, viral infections, and genetic mutations [34, 35]. A pathological hallmark of ALS is the presence of neuronal cytoplasmic inclusions containing misfolded SOD1 aggregates in oligodendrocytes [34]. Conformational changes in *SOD1* are linked to accelerated aging processes and are observed in other age-related neurodegenerative diseases, including PD and AD [36, 37]. These

findings suggest shared mechanisms involving SOD1 aggregation across ALS, PD, and AD. Notably, our study identified overlapping proteins implicated in the pathophysiology of PD and AD, supporting the existence of common molecular pathways among these disorders.

The C1QC gene encodes the C1QC protein, a component of the complement system's C1 complex. This protein initiates the classical complement pathway, which is essential for pathogen clearance and removal of apoptotic cells [38]. Complement activation was first reported in ALS cases as early as the 1990s [39]. Recent pathological studies have shown that C1q co-localizes with HLA-DR-positive microglia and GFAP-positive astrocytes in spinal cord tissues of deceased ALS patients, with upregulated expression in spinal neurons and glial cells [40]. Evidence suggests that C1QC plays a critical role in synaptic pruning [33]. Animal studies demonstrate that C1q alone can activate microglia into a pro-inflammatory state, leading to blood-brain barrier disruption [41]. Furthermore, the C1Q complement gene is implicated in both AD and PD [42]. In this study, C1QC was significantly upregulated and positively associated with ALS risk, suggesting that inhibiting complement signaling may represent a novel therapeutic strategy for ALS.

UMOD (uromodulin), also known as the Tamm-Horsfall protein, encodes uromodulin [43]. Researchers have found that mutant UMOD expression strongly upregulates mesencephalic astrocyte-derived neurotrophic factor (MANF). Notably, mutant uromodulin induces the unfolded protein response (UPR), disrupting endoplasmic reticulum (ER) function and proteostasis [44]. UMOD mutations cause autosomal dominant tubulointerstitial kidney disease (ADTKD-UMOD), which—like ALS—is classified as an ER storage disorder and proteinopathy due to protein misfolding [44]. Our findings further support that elevated UMOD expression may contribute to ALS pathogenesis, reinforcing its potential role as a risk factor.

SLIT and NTRK-like protein 5 (SLITRK5) and its family members are neural transmembrane proteins that are widely expressed in the central nervous system (CNS) [45]. SLITRK5 is believed to be a key factor in regulating essential functions such as neurite outgrowth, dendritic refinement, synapse development, and neuronal signaling in the CNS [46, 47]. Research by Salesse et al. found that overexpression of SLITRK5 in neurons induced more inhibitory inputs and promoted the formation of inhibitory synapses, which may reduce neuronal activity and inhibit dendritic growth [48]. This led to a decrease in the number and length of neurites [49]. Consistent with these findings suggesting SLITRK5's involvement in CNS diseases including PD [50], our research indicates that the inhibitory effects of SLITRK5 may affect neural development and synaptic function, promoting ALS-related neurodegenerative changes.

ASAP2, part of the ArfGTPase activating protein family, is involved in actin-based endocytosis, macrophage macropinocytosis, and phagocytosis, acting as a regulator of actin [51]. The ASAP2 gene (ADP Ribosylation Factor GTPase Activating Protein 2) encodes a GTPase-activating protein that primarily participates in intracellular membrane trafficking, cytoskeletal dynamics, and signal transduction. Neuroinflammation in ALS is characterized by lymphocyte and macrophage infiltration, activation of microglia and reactive astrocytes, and complement involvement [52]. ASAP2 may regulate the involvement of macrophages in the development of neuroinflammation in ALS and impact skeletal muscle function, warranting further investigation.

The TREML2 genomic region has recently been associated with AD susceptibility and encodes the TREML2 protein [53]. Research by Wang et al. found that in the context of AD, the upregulation of TREML2 may exert pro-inflammatory and proliferative effects on microglia [54]. They provided the first evidence that TREML2 modulates inflammation by regulating microglial polarization and NLRP3 inflammasome activation [55]. Song et al. discovered that TREML2 can amplify the immune-related neuroinflammatory response, exacerbating this pathological process [56].These findings align with our study, where upregulation of TREML2 may exacerbate the development of neuroinflammation, increasing the risk of ALS.

Death-associated protein kinase 2 (DAPK2) belongs to the pro-apoptotic Ca^{2+}/calmodulin-regulated serine/threonine kinase family [57]. It plays roles in autophagy, secretory pathways, and transforming growth factor-beta (TGF-β) signal transduction through protein-protein interactions [58]. Studies demonstrate that transient overexpression of DAPK2 promotes apoptosis [59]. Studies indicate that neutrophils are highly activated in rapidly progressing ALS [60]. DAPK2 activity has a pro-inflammatory effect and can positively regulate granulocyte migration. Increased DAPK2 activity may be one of the mechanisms inducing neuroinflammation in ALS [61].

The ARHGEF10 gene encodes the ARHGEF10 protein, which is a Rho family small GTPase activating protein (GEF) with functions in regulating the cytoskeleton and cell motility. It has been reported that missense mutations in ARHGEF10 contribute to various central nervous system diseases and affect the expression of certain neurotransmitters, such as serotonin and norepinephrine [62]. ARHGEF10 regulates the actin cytoskeleton and microtubule dynamics and participates in neuronal morphogenesis processes, including cell migration, axonal growth and guidance [63]. Additionally, it plays an

important role in myelination. Mutations in ARHGEF10 cause myelin to become thinner and nerve conduction to slow down [64]. ARHGEF10 has been confirmed to activate RhoA, and a large number of studies have shown that the RhoA/Rho kinase pathway can exacerbate inflammation and oxidative stress [65]. Therefore, overexpression of ARHGEF10 may increase the risk of ALS.

The POLM protein encoded by the POLM gene, also known as DNA polymerase μ, plays a crucial role in DNA repair, especially in the non-homologous end joining (NHEJ) process of repairing DNA double-strand breaks (DSBs). In postmitotic cells, DNA double-strand breaks (DSBs) are repaired through the classic nonhomologous end joining (NHEJ) pathway. This process may lead to genome structural variations and disruption of three-dimensional genome organization, potentially contributing to promoting the progression of neurodegenerative diseases [66, 67]. Excess POLM may lead to imbalanced DNA repair, genomic instability, and neuroinflammation, thereby increasing the risk of ALS.

The SST protein encoded by the SST gene is also known as somatostatin or growth hormone release inhibitory factor. This cyclic peptide can effectively inhibit hormone secretion and neuronal excitability [68]. Research has found that in neurodegenerative diseases such as ALS, overactive somatostatin-positive interneurons (SST-ins) disinhibit layer 5 pyramidal neurons (L5 PNs), promoting their excitotoxicity. Hyperactivity of somatostatin interneurons can lead to inhibitory imbalances, leading to glutamate excitotoxicity and further neuronal damage [69]. Research also recommends drug development targeting somatostatin receptor subtype 4 (SST4), as it has been shown to mediate analgesic, antidepressant, and anti-inflammatory effects without endocrine effects [70]. Consistent with our findings, overexpression of somatostatin may lead to glutamate-induced excitotoxicity, a key mechanism leading to neuronal death in ALS.

SIGLEC1 (sialic acid-binding Ig-like lectin 1), also known as CD169, is a member of the glycoprotein family that plays a vital role in the immune system. SIGLEC1 is mainly expressed on the surface of immune cells such as macrophages and dendritic cells. Its main function includes recognizing and binding sialic acid-modified glycans, thereby playing a role in immune responses [71]. Soluble SIGLEC-1 (sSIGLEC-1) has been reported as a novel circulating plasma biomarker of type I interferon (IFN) activity in systemic autoimmune, inflammatory, and infectious diseases [72, 73]. Studies have shown that in ALS transgenic mice, there is a significant increase in SIGLEC1-positive macrophages in the peripheral nervous system, which is closely related to disease progression and neuronal degeneration [74]. Recently, Taylor et al. reported that SIGLEC1 perivascular macrophages in the central nervous system are highly correlated with vascular amyloid deposition following Aβ immunotherapy [75]. This finding aligns with previous research suggesting that marginal zone macrophages regulate aging and neurodegeneration through extracellular matrix remodeling [76]. Previous studies on SIGLEC1 have provided evidence suggesting that elevated SIGLEC1 expression may serve as a risk factor for ALS, consistent with our findings.

ADP-dependent glucokinase, or ADPGK, is a glycolytic enzyme that plays a critical role in maintaining energy and metabolic homeostasis in cells by converting glucose to glucose-6-phosphate during a critical step in glycolysis [77]. Ongoing exploration of ALS metabolic pathways suggests that genes involved in cellular energy production and metabolic regulation, such as ADPGK, may affect neuronal survival and function by influencing glycolytic pathways [78]. In 2019, Imle et al. found that knocking out ADPGK promoted apoptosis and increased endoplasmic reticulum stress in Jurkat T cells. Experimental validation in zebrafish embryos showed that the absence of the ADPGK gene led to increased cell apoptosis, further metabolic imbalance, and phenotypes such as shortened body axis and elongated dorsum [79]. These studies align with our findings that low levels of ADPGK may lead to metabolic dysregulation and increased neuronal damage in ALS. Reverse MR analysis indicates that ALS progression may lead to reduced ADPGK levels. Glucose metabolism is related to muscle function, and a study found that elite strength athletes carry more strength-related alleles, including the ADPGK gene [80, 81]. Therefore, the downregulation of the ADPGK gene after ALS onset may contribute to muscle atrophy. Additionally, studies have shown reduced glucose utilization in the primary motor cortex and other brain regions of ALS patients [82], which may be related to decreased ADPGK levels following ALS onset. These results suggest that ADPGK is a viable target for ALS treatments in the future because it has a bidirectional causal relationship with ALS.

BTNL9 (Butyrophilin-like 9) is a member of the butyrophilin and butyrophilin-like (BTNL) family, which regulates T cell activity and influences inflammatory diseases and cancer [83]. Functional enrichment analysis shows that BTNL9 is involved in immune and tumor regulatory signaling pathways [84]. Co-expression analysis by Zheng, P. et al. indicates that BTNL9 is associated with reduced immune responses [85]. The immune system is a crucial component of ALS pathogenesis [86], and changes in immune responses can contribute to the disease mechanisms in both human and mouse models of ALS [87]. BTNL1 and BTNL9 are reported to have high homology. In autoimmune and asthma mouse, administration of neutralizing antibodies against BTNL1 enhances T cell activation and exacerbates the disease

[88]. These findings are consistent with our study, where reduced expression of BTNL9 leads to decreased immune responses. This reduction in immune response may predispose the central nervous system to autoimmune reactions, potentially increasing the risk of ALS.

The COLEC12 gene expresses COLEC12 (collectin subfamily member 12, also referred to as CL-12 or CL-P1), a pattern recognition molecule in the innate immune system [89]. Bioinformatic analysis suggests that COLEC12 expression is strongly correlated with several immune infiltrating cells, including M2 macrophages, dendritic cells (DCs), neutrophils, and regulatory T cells (Tregs) [90]. Research findings indicate that knocking out COLEC12 significantly activates inflammatory functions, increasing inflammation in osteosarcoma both in vivo and in vitro [91]. COLEC12 encodes a member of the C-type lectin family, a scavenger receptor that plays a crucial role in the binding and clearance of amyloid-beta (Aβ) [92]. This study suggests that COLEC12 plays a role in intercellular signaling and inflammatory responses, and as a possible protective factor, its downregulation may lead to reduced clearance of misfolded proteins in ALS, potentially exacerbating neuroinflammation and accelerating neurodegeneration.

ADGRF5(Adhesion G Protein-Coupled Receptor F5), or GPR116 (G Protein-Coupled Receptor 116), is a transmembrane protein that belongs to the adhesion G protein-coupled receptor (GPCR) family of transmembrane proteins. The ADGRF5 protein is involved in regulating various physiological processes, including immune responses and inflammation [93]. Recent exciting discoveries have shown that adhesion-GPCRs can regulate neuronal precursor migration, axon guidance, axon myelination, brain angiogenesis, and synapse formation [94]. Kubo et al. observed that ADGRF5 knockout mice exhibited increased neutrophil development and enhanced type II immune response activity [95]. This suggests that downregulation of ADGRF5 may lead to neurodegeneration and amplified inflammation, potentially being a risk factor for ALS, consistent with our findings. Additionally, research has shown that the lack of ADGRF5 in quiescent muscle stem cells (MuSC pool) results in time-dependent depletion and impaired tissue regeneration [96]. Increased ALS risk leading to downregulation of ADGRF5 manifests in clinical symptoms such as muscle atrophy and paralysis, supporting the findings of our reverse MR analysis. Therefore, in our MR study, ADGRF5 expression shows bidirectional causality with ALS risk, and ADGRF5 may be a promising new target for anti-ALS drugs.

FAIM (Fas Apoptosis Inhibitory Molecule) is a highly evolutionarily conserved 20 kDa protein that possesses anti-apoptotic and pro-survival properties. FAIM-L has been demonstrated to shield neural cells from Fas-induced apoptosis and is exclusively expressed in neural tissues [97]. Kaku et al. discovered that FAIM counteracts the intracellular accumulation of mutant SOD1 protein aggregates by preventing protein aggregation and degrading cytotoxic substances [98, 99]. This is in line with our findings, which suggest that FAIM may be a protective factor for ALS.FAIM holds promise as a novel therapeutic target, potentially improving the condition of ALS patients by blocking or disrupting protein aggregation.

CRTAM (Class-I Restricted T cell Associated Molecule) is a transmembrane protein highly expressed in activated T cells and natural killer (NK) cells, primarily involved in cell adhesion and signal transduction processes. CRTAM is highly expressed in the human cerebellum, particularly in Purkinje neurons [100]. It has been reported that CRTAM-deficient mice exhibit reduced cytokine production of IFN-γ and IL-17 in CD4 T cells, as well as defects in cell polarity [101]. Damage to the blood-brain barrier is a characteristic of several neurodegenerative diseases, including ALS. CRTAM plays a crucial role in the migration of neural stem cells induced by glioma cells, by promoting migration and regulating blood-brain barrier permeability [102]. This is consistent with our findings that CRTAM may be one of the protective factors in ALS.

The PRSS3 gene encodes trypsinogen and trypsinogen 4, with trypsin playing an important role in neurodevelopment, plasticity, and neurodegeneration [103]. Research has shown that astrocytes play a crucial role in neurodegenerative diseases such as ALS, and mesotrypsin may selectively activate protease-activated receptor-1 (PAR-1) to regulate the function of astrocytes [104]. Data from one study showed that axial symptoms in patients with Parkinson's disease 5 years after deep brain stimulation were associated with PRSS3 [105]. Therefore, PRSS3 is enriched in the brain, and the trypsin it encodes may affect signal transduction. Downregulation of PRSS3 may significantly impact the development and degeneration of ALS motor neurons, suggesting its potential as a therapeutic target for ALS.

BAG5 (BCL2-associated athanogene 5) is a member of the BAG family and plays a regulatory role in apoptosis and protein folding. BAG5 interacts with Hsp70 and Hsp90 to prevent the refolding of misfolded proteins and the aggregation of intracellular proteins. It plays a role in regulating apoptosis and protein folding. Role in regulating ubiquitination, protein aggregation and cell death makes it a potential therapeutic target for neurodegenerative diseases such as Parkinson's disease [106]. BAG5 can also serve as a nucleotide exchange factor for Hsp70, promoting protein refolding [107]. In addition, BAG5 protects cells from mitochondrial oxidative damage by regulating the degradation of the mitochondrial

protective protein PINK1 (PTEN-induced kinase 1) [108]. Therefore, BAG5 may exert protective effects by maintaining protein homeostasis, alleviating the pathological progression of ALS, and reducing the risk of disease progression, suggesting its potential role as a protective factor in ALS.

PSMD11 is an important component of the proteasome complex, responsible for protein degradation and maintenance of cellular proteostasis. It plays a key role in various physiological and pathological processes such as cell cycle regulation, apoptosis, DNA repair and signal transduction. Under the regulation of cAMP/PKA, overexpression of PSMD11 can activate proteasome function and reduce the degradation of certain aggregated proteins [109]. Phosphorylated PSMD11 enhances proteasome activity and improves its ability to degrade misfolded proteins [110]. PSMD11 is involved in the degradation of ubiquitinated proteins, and lack of PSMD11 will lead to increased levels of ubiquitinated proteins in cells [111]. This finding is consistent with our study suggesting that PSMD11 acts as a protective factor in ALS by maintaining proteasome activity and preventing the accumulation of misfolded proteins in cells.This emphasizes the importance of PSMD11 in protein quality control in ALS disease.

Finally, we performed GO function and KEGG pathway enrichment analysis on significantly different proteins. The top three biological processes (BP) are "external envelope structural organization", "extracellular matrix organization" and "extracellular structural organization". Within the cellular component (CC) category, "collagen-containing extracellular matrix"is emphasized, involved in the formation, assembly, and maintenance of all extracellular structures, including the extracellular matrix (ECM), cell walls, and capsules. In the MF category, "glycosaminoglycan binding" refers to the ability to bind glycosaminoglycans (GAGs). GAGs are long-chain polysaccharides composed of repeating disaccharide units, widely present in the ECM. Hyaluronic acid (a type of GAG and a major component of the extracellular matrix) has been shown to increase in the serum and skin of patients with longer ALS durations [112, 113]. The ECM comprises proteins and polysaccharides, providing structural support and signaling functions, whose changes may affect neuronal growth, survival, and regeneration abilities [114]. For instance, SIGLEC1 is involved in regulating ECM remodeling and neurodegeneration; TREML2, ASAP2, C1QC, and COLEC12 regulate neuroinflammation by upregulating immune cells; PSMD11 and BAG5 are involved in the degradation of ubiquitinated proteins; CRTAM and ADGRF5 mainly participate in cell adhesion and signal transduction; C1QC and CRTAM regulate blood-brain barrier permeability in ALS. By understanding the changes and mechanisms of these biological processes, researchers can gain a deeper understanding of the pathogenesis of ALS and develop potential treatments targeting these changes. These strategies may include stabilizing ECM components, suppressing inflammatory responses, and repairing the blood-brain barrier to slow or halt the progression of ALS.

Through KEGG Pathway analysis, we identified the three most important signaling pathways: PI3K-Akt signaling pathway, Cytokine – cytokine receptor interaction, and Axon guidance. The PI3K-Akt pathway is a crucial intracellular signaling pathway that facilitates growth, angiogenesis, metabolism, proliferation, and cell survival by reacting to extracellular cues. In recent years, many researchers have found that the PI3K/AKT signaling pathway is closely related to ALS. Activation of the PI3K/AKT pathway has been shown to protect the cerebral cortex and astrocytes of ALS patients, reduce damage caused by oxidative stress, and improve cell survival and mitochondrial function [115]. In addition, the PI3K/AKT signaling pathway is also involved in the adhesion and migration of reactive astrocytes [116]. In addition, the PI3K/AKT signaling pathway is also involved in the adhesion and migration of reactive astrocytes [117]. The Cytokine-Cytokine Receptor Interaction pathway is a crucial route for intercellular communication and is essential in the immune system, involved in regulating the activation, proliferation, and differentiation of immune cells. Some cytokines activate their receptors, triggering signaling pathways within neurons that lead to oxidative stress, mitochondrial dysfunction, and apoptosis [118]. In ALS, elevated levels of pro-inflammatory cytokines (such as TNF-α, IL-1β, IL-6) can lead to neuronal damage and death [119]. The cytokine-cytokine receptor interaction pathway influences neuronal survival and function in ALS by regulating neuroinflammation, cell stress responses, and apoptosis. The Axon Guidance pathway refers to the precise growth of neuronal axons to their target areas during development. This process is guided by a series of molecular signals to ensure correct connections within the complex neural network.

According to some researchers, ALS is also a distal axonopathy [120], and the pathological alterations in motor axons and nerve terminals that are central to the ALS pathogenesis may be caused by abnormalities in the expression or function of axon guidance proteins [121]. Lesnick et al. found that specific axon guidance pathway genes or their transcripts or proteins are associated with the pathogenesis of ALS [122]. Körner et al. also found evidence of increased axon guidance protein signaling in the motor cortex of ALS patients [123]. In our study, ARHGEF10, ADGRF5, and others are involved in the Axon Guidance pathway. It is evident that abnormalities in the Axon Guidance pathway in ALS may lead to axon

degeneration, abnormal neural network connections, and neuronal dysfunction.

Limitation

Our study has several limitations. First, all participants in the GWAS were derived from European populations, predominantly of European ancestry. While this provides valuable insights into the genetic architecture of ALS in this demographic, the limited population diversity may introduce potential biases. Therefore, validating protein associations and their relevance to ALS in non-European populations is essential to evaluate the generalizability of our findings.Second, publicly available datasets are inherently constrained and may lack comprehensive information. For instance, due to the absence of individual-level data, we could not perform additional analyses such as population stratification or disease risk stratification. Third, although MR is a robust method for causal inference, its findings require further validation through clinical and experimental studies to confirm causality and elucidate underlying mechanisms. Specifically, in vivo (e.g., animal models) and in vitro (e.g., cellular assays) experiments are needed to validate the roles of these proteins in ALS pathogenesis. Additionally, large-scale longitudinal studies and clinical trials in patient cohorts are necessary to assess the potential of these identified proteins as biomarkers.

Conclusion

This study identified 19 novel plasma proteins associated with ALS, including C1QC, UMOD, SLITRK5, ASAP2, TREML2, DAPK2, ARHGEF10, POLM, SST, SIGLEC1, ADPGK, BTNL9, COLEC12, ADGRF5, FAIM, CRTAM, PRSS3, BAG5, and PSMD11. Additionally, we performed GO functional analysis and KEGG pathway enrichment analysis. GO functional analysis revealed that these proteins are involved in several important biological processes, including external encapsulating structure organization, extracellular matrix organization, and extracellular structure organization. KEGG pathway analysis demonstrated significant enrichment of these proteins in key pathways, including the axon guidance signaling pathway, cytokine-cytokine receptor interactions, and the PI3K-Akt signaling pathway.In summary, our findings provide genetic evidence supporting the potential of these 19 proteins as novel biomarkers for ALS and their involvement in disease-related mechanistic pathways. Further clinical and experimental studies are warranted to validate these results.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

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Author contributions

CL Contributed to the design, analysis and interpretation of the work, and the drafting and revising of the manuscript. XXH contributed to data acquisition, methodology and results, and revisions. CNL, and MH wrote, reviewed, and discussed the final version. JWX was responsible for the quality control and guidance of data and papers.All authors read and approved the final version of the manuscript.

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Data availability

The datasets used in this study are publicly available and can be accessed from decode and ebi-a. All relevant metadata, including [PMID]34857953, are provided in the dataset and can be accessed according to the terms of use. The data are available upon request or via the data infrastructure provided by the IEU OpenGWAS project. All data sharing complies with the terms and conditions outlined by the dataset providers. Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

According to institutional and local regulations, ethical review and approval were not necessary for the study that used publicly accessible databases. According to institutional policies and national law, patients/participants or their legal guardians/next of kin were not required to give written informed consent in order to take part in this study. Clinical trial number: not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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