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Systematic Mendelian Randomization Using the Human Plasma Proteome to Discover Potential Biomarkers for Glioma

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Abstract: *Glioma is the most common malignant tumor in the central nervous system, and patients generally have a poor prognosis. In this article, we conducted a Mendelian randomization analysis between plasma proteins and glioma to explore the causal relationship between them. The results showed that 10 plasma proteins had a causal relationship with glioma, with five being risk factors (SIRPB1, RACGAP1, MLN, CHST9, TPST2) and five being protective factors (IL18R1, FCRL3, TAPBPL, ERAP1, TDGF1). Many of these are reported for the first time. Our study reports multiple biomarkers for glioma, which may provide reference for the diagnosis and treatment of glioma.*

Keywords: *Glioma, Plasma protein, Biomarker, Mendelian randomization*

1. Introduction

Glioma, a common primary brain tumor originating from glial cells or precursor cells, account for approximately 81% of malignant central nervous system tumors [1].The latest edition of World Health Organization (WHO) Classification of Tumors of the Central Nervous System (WHO CNS5) classifies adult diffuse glioma into three types: astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant; and 1p/19q-codeleted and glioblastoma, IDH-wildtype[2]. The median survival time for patients with the most malignant glioma, glioblastoma, is only 15 months, and only 2-5% of patients can survive more than three years [3, 4]. Currently, the standard treatment options for glioma include surgical resection, temozolomide, and radiation. However, these approaches fall short in the face of cancer progression [5]. In recent years, as related research has delved deeper, new treatment methods for glioma continue to emerge. Novel techniques, such as immunotherapy and molecular targeted therapy, have gradually been applied to glioma treatment and have achieved certain success. However, due to factors such as the high heterogeneity and invasiveness of glioma and the presence of the blood-brain barrier, existing treatment methods cannot significantly improve patient prognosis. Furthermore, glioma patients often do not exhibit specific symptoms in the early stages of the disease, making it difficult to diagnose them promptly [6, 7]. Moreover, the histopathological method, as the gold standard for diagnosis and classification, largely relies on the specific structural similarities between tumor cells and non-tumor glial cells. As a result, its accuracy and reproducibility are not entirely satisfactory [8]. In recent years, molecular markers have played an increasingly important role in the diagnosis and classification of gliomas. A complex set of methods integrating histologic and molecular markers for the diagnosis, classification, and grading of gliomas has been established in the WHO CNS5[9]. Proteins are direct effect molecules of life activities, and changes in their expression levels can reflect and affect a variety of complex pathological and physiological processes. Due to the fact that plasma flows through every organ and tissue in the human body, "sampling" the body's health status and its easily obtainable characteristics, it has become the most suitable material for proteomic analysis [10]. Therefore, research on the relationship between the disease and plasma proteomics is beneficial for elucidating the mechanisms of the disease, identifying new biomarkers, and discovering therapeutic targets. Plasma proteomics has been demonstrated to serve as a biomarker for various types of cancer [11]. A study led by Peddagangannagari Sreekanthreddy revealed that high concentrations of osteopontin in the blood are an unfavorable prognostic indicator for glioblastoma. Anders Carlsson and others have used recombinant antibody microarrays to study the plasma protein expression profiles of glioma patients. Still, due to the influence of factors such as the

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effect of the patient's treatment and the heterogeneity of the cohort, few differences were found compared to normal populations [12]. Therefore, a novel research methodology is required to elucidate the link between plasma proteins and glioma.

Mendelian randomization (MR) is an emerging method in genetic epidemiology research that uses single nucleotide polymorphisms (SNPs) associated with the exposure variable under investigation as instrumental variables(IVs). By randomly allocating study populations into high and low exposure groups through the random distribution of gametes during conception, the method investigates whether a causal relationship exists between exposure and outcome [13]. The MR method has been applied to many CNS tumor researches including glioma. Sheng Zhong et al. used MR methods found that genetically predicted herpes zoster caused by varicella-zoster virus infection can reduce the risk of low-grade glioma[14]. Another MR study led by Wenzhuo Yang suggests that schizophrenia can increase the risk of glioma. Currently, the whole genome association analysis (GWAS) of the human plasma proteome has reported associations between SNPs and the expression levels of thousands of circulating proteins, laying the foundation for using Mendelian randomization methods to study the relationship between the plasma proteome and disease. Zhiyun Zhang and colleagues investigated the association between multiple inflammation-related proteins in plasma and meningiomas using MR method and found that TNF-β, CXCL1 and IL-9 play an important role in the development of meningiomas. In this study, we used plasma protein quantitative trait loci (pQTLs) as instrumental variables in a two-sample Mendelian randomization analysis of plasma proteins and glioma. Our goal is to explore the association between plasma proteins and glioma and to identify new therapeutic targets and biomarkers for glioma.

2. Materials and Methods

2.1 Study design

We first conducted a two-sample Mendelian randomization analysis between plasma proteins and glioma, using plasma protein pQTLs from a European population as the instrumental variable. Subsequently, we replicated the significant results using plasma protein pQTLs from an Icelandic population and conducted a reverse Mendelian randomization analysis. Finally, we performed a phenome-wide association analysis using the Open Targets database to rule out confounding factors. The workflow of this study was showed in Figure 1.

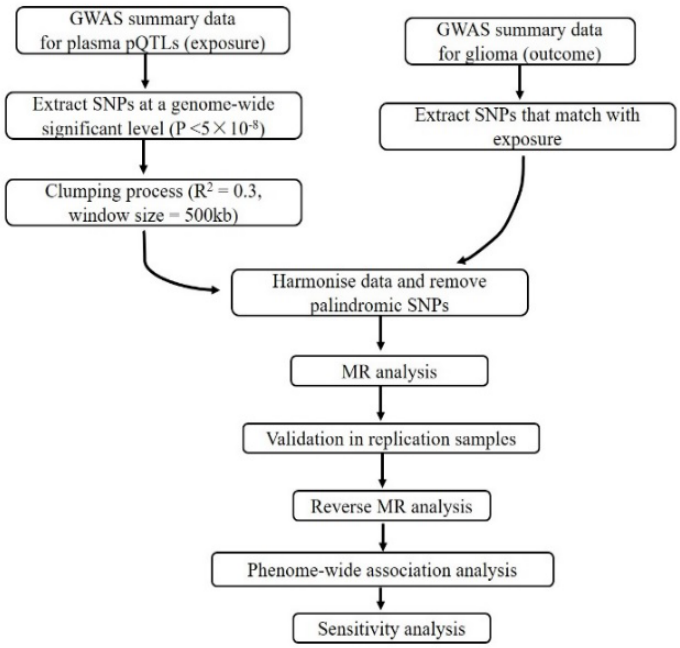

Figure 1: The whole workflow of this study.

2.2 Acquisition of GWAS summary data and ethical review

We acquired GWAS summary data for gliomas from the IEU GWAS database

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(https://gwas.mrcieu.ac.uk/), which included 1,856 cases and 4,955 controls from a European population. For the discovery phase, plasma protein pQTLs data was obtained from a study published in Nature led by Benjamin B. Sun, which measured 2,994 plasma proteins in 3,301 European participants using the SomaLogic SomaScan platform and reported a total of 10,572,788 genetic variants. For the replication phase, the plasma protein pQTLs data was obtained from another study led by Egil Ferkingstad, which measured 4,907 plasma proteins in 35,559 Icelanders and reported over 272 million genetic variants. The data used in this study were obtained from previously published research, and all of the original studies had obtained ethical approval from the respective institutions. Therefore, this study did not require an independent ethical review.

2.3 Selection of instrumental variables

In the forward Mendelian randomization analysis, we used pQTLs of plasma proteins from different sources as instrumental variables. To ensure the validity of the instrumental variables, the selected SNPs had to meet the following criteria: (1) the SNP selected should be significantly correlated with the expression level of the protein at the genome-wide level ($p<5\times10^{-8}$); (2) the SNP should not have horizontal pleiotropy, meaning that the SNP has no direct association with the outcome variable glioma and only affects the outcome through the exposure variable; (3) the SNP should have no relationship with confounding factors. Subsequently, we removed the linkage disequilibrium of the instrumental variables with an R^2 threshold of 0.3 within a 500kb window.

2.4 Mendelian randomization analysis

We performed MR analysis using five different models, including the Wald ratio model, inverse variance weighted (IVW) model, MR-Egger model, Weighted median model, and MRPRESSO model (MR Pleiotropy RESidual Sum and Outlier), with the R packages "TwoSampleMR" (version 0.5.6) and "MRPRESSO" (version 1.0). For situations where only a single SNP was available, we used the Wald ratio model to estimate its effect, while the IVW and Weighted median models were used for situations with multiple available SNPs. The IVW model used a meta-analysis approach to combine the Wald estimates of each SNP to obtain an overall estimate of the association between each plasma protein and glioma. We used Cochran's Q test to assess heterogeneity, and if significant heterogeneity was found ($P<0.05$), we used a random-effects model; otherwise, we used a fixed-effects model. We used the IVW model and weighted median model as the major analysis models, and if the result was positive in in both the IVW and weighted median models ($P<0.05$), we determined that there was a causal relationship between the protein and glioma. We also referred to the results of other models. If the positive result was replicated in the MR-Egger and MRPRESSO models, we considered it to be more robust.

Furthermore, to ensure the reliability of our results, we conducted sensitivity analyses using MR-Egger regression and the MRPRESSO method. MR-Egger regression was used to test for potential horizontal pleiotropy of the SNPs used as instrumental variables, and a non-zero intercept indicates the presence of horizontal pleiotropy, in other words, affected by confounding factors. We removed these results with significant level of horizontal pleiotropy to minimize the effect of confounding factors on the results. In addition, we used the MRPRESSO method to test and correct for horizontal pleiotropy by removing outliers. Moreover, to explore the presence of influential SNPs, we performed leave-one-out sensitivity analyses by sequentially excluding one SNP at a time to verify the reliability and stability of the causal effect estimates. We also performed Steiger directional tests to examine the consistency of the SNP effects on exposure and outcome

2.5 Reverse Mendelian randomization analysis

To investigate whether the changes in protein expression levels mentioned above were caused by glioma, we subsequently performed a reverse Mendelian randomization analysis with glioma as the exposure and the significant plasma proteins from the forward Mendelian randomization analysis as the outcome. Like the positive Mendelian randomization analysis, we selected SNPs with genome-wide significance ($p<5\times10^{-8}$) and removed linkage disequilibrium in a 500kb window with an R^2 threshold of 0.3 for the instrumental variables. Finally, we used four independent instrumental variables for the reverse Mendelian randomization analysis.

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2.6 Phenome-wide association analysis

We performed a phenome-wide association analysis of the IVs used in the positive results of the MR analysis with the api of the Open Targets database (https://platform.opentargets.org/, see Supplementary Material for code) to determine whether the IVs was also associated with other phenotypes. Subsequently, we excluded IVs associated with potential confounders at a genome-wide significance ($p < 5 \times 10^{-8}$) and performed the MR analysis again using the same parameters as before to further exclude the effect of confounding factors.

3. Results

3.1 40 glioma-associated plasma proteins were identified during the discovery phase

During the discovery phase, we conducted Mendelian randomization analysis on 2,994 plasma proteins to investigate their causal relationship with glioma. A total of 40 plasma proteins were identified as having a causal relationship with glioma, with 24 showing a negative correlation and 16 showing a positive correlation. All significant results showed consistent directional predictions in both the inverse variance weighted (IVW) and weighted median models, and none of them exhibited significant horizontal pleiotropy. Furthermore, the F-statistics were greater than 100 for all significant results, indicating sufficient instrument strength.

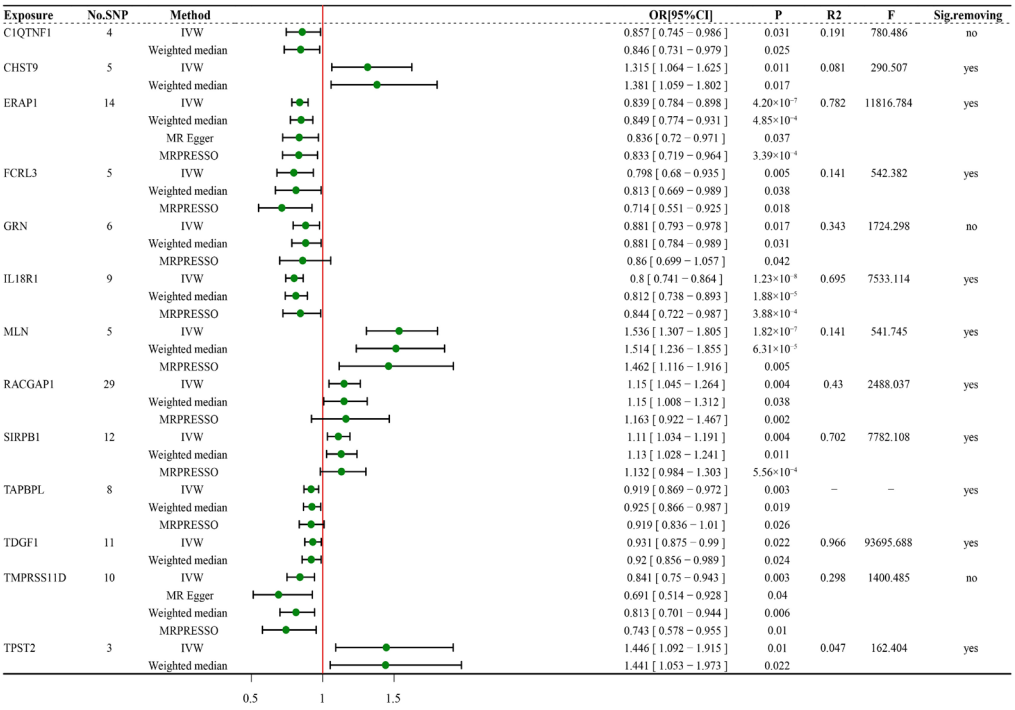

Figure 2: Forest plot of MR estimates (Discovery stage)

3.2 The replication phase successfully replicated 13 plasma proteins.

Subsequently, in the replication stage, we analyzed 39 of the 40 significant proteins in discovery stage (excluding C4A.C4B, which was missing in the Icelandic population data) and successfully replicated 13 proteins (CHST9, RACGAP1, IL18R1, FCRL3, ERAP1, GRN, MLN, TDGF1, SIRPB1, C1QTNF1, TAPBPL, TMPRSS11D, TPST2) that were associated with glioma. Among these, the expression levels of IL18R1 (IVW, odds ratio (OR) = 0.830, 95% confidence interval (CI) = [0.750–0.919], $p = 3.5\times10^{-4}$), FCRL3 (IVW, OR = 0.839, 95% CI = [0.742–0.948], $p = 0.005$), ERAP1 (IVW, OR = 0.926, 95% CI = [0.880–0.974], $p = 0.003$), GRN (IVW, OR = 0.826, 95% CI = [0.735–0.927], $p = 0.001$), TDGF1 (IVW, OR = 0.937, 95% CI = [0.894–0.984], $p = 0.008$), C1QTNF1 (IVW, OR = 0.781, 95% CI = [0.645–0.947], $p = 0.012$), TAPBPL (IVW, OR = 0.921, 95% CI = [0.875–0.970], $p = 0.002$), and TMPRSS11D (IVW, OR = 0.675, 95% CI = [0.527–0.866], $p = 0.002$) were negatively associated with glioma, whereas CHST9 (IVW, OR = 1.44, 95% CI = [1.17–1.77], $p = 6.51\times10^{-4}$), RACGAP1 (IVW, OR = 1.10, 95% CI

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= [1.04–1.16], $p = 4.44\times10^{-4}$), MLN (IVW, OR = 1.22, 95% CI = [1.11–1.35], $p = 6.05\times10^{-5}$), SIRPB1 (IVW, OR = 1.08, 95% CI = [1.02–1.13], $p = 0.007$), and TPST2 (IVW, OR = 1.98, 95% CI = [1.38–2.84], $p = 2.22\times10^{-4}$) were positively associated with glioma. All significant results were consistent in both the IVW and weighted median models, and none of them exhibited significant horizontal pleiotropy in MR-Egger regression and MRPRESSO test. After performing the FDR (false discovery rate) correction on the *p*-values, there were three significant results (IL18R1, MLN, PRDM1) of the discovery stage remained, of which two (IL18R1, MLN) were successfully replicated in the replication stage. The F statistics for all successfully replicated results were greater than 1000. Figure 2 shows the detailed results of these 13 proteins in discovery stage. Figure 3 shows the detailed results of these 13 proteins in replication stage.

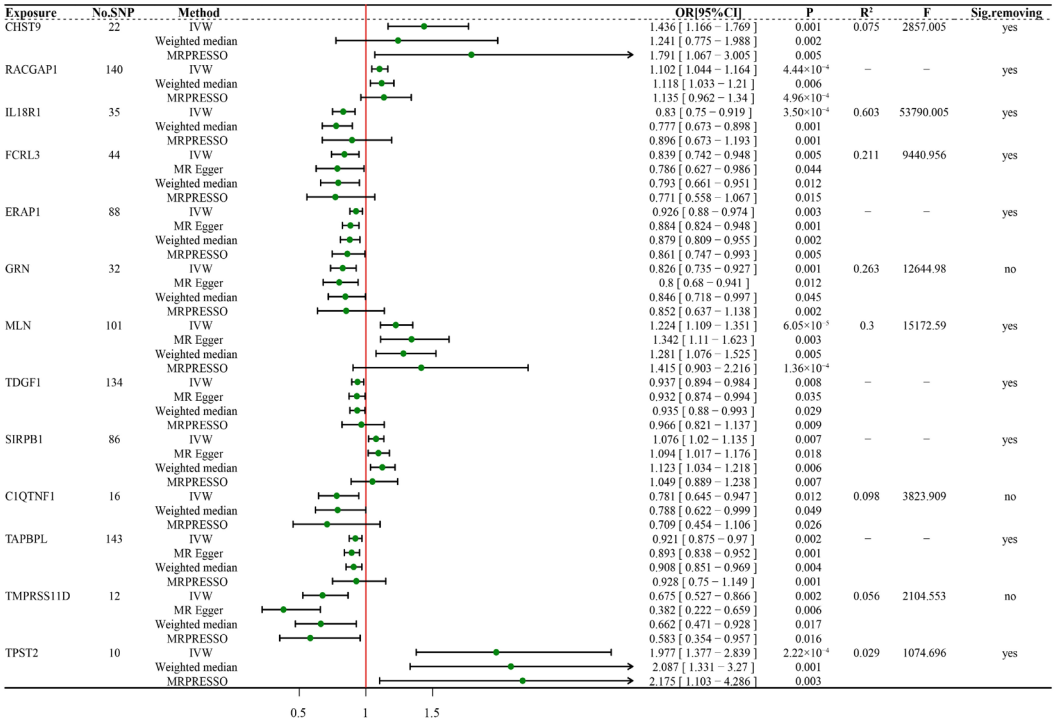

Figure 3: Forest plot of MR estimates (Replication stage)

3.3 Reverse Mendelian randomization suggests no reverse causality between significant plasma proteins and glioma

In the reverse Mendelian randomization analysis, we found no significant results for all 39 proteins (including the 13 proteins that were replicated in the replication phase), indicating that there is no reverse causality between changes in the expression levels of these plasma proteins and glioma.

3.4 Phenome-wide association analyses further excluded the effects of confounding factors

We performed a phenome-wide association analyses of 919 SNPs of the 13 proteins that were successfully replicated at the replication stage, and a total of 64 of them were found to be horizontally pleiotropic. We performed MR analysis between these 13 proteins and gliomas again in both discovery and replication cohorts after excluding these IVs with horizontal pleiotropy. The results showed that, in both cohorts, ten proteins, excluding the GRN, C1QTNF1 and TMPRSS11D, were still significantly causally associated with gliomas.

4. Discussion

We employed Mendelian randomization to systematically investigate the association between genetically predicted plasma protein levels and glioma and demonstrated causal relationships between 13 plasma proteins (CHST9, RACGAP1, IL18R1, FCRL3, ERAP1, GRN, MLN, TDGF1, SIRPB1, C1QTNF1, TAPBPL, TMPRSS11D, TPST2) and glioma. Specifically, five of them were identified as

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risk factors (SIRPB1, RACGAP1, MLN, CHST9, TPST2) while eight were protective factors (TMPRSS11D, C1QTNF1, GRN, IL18R1, FCRL3, TAPBPL, ERAP1, TDGF1). Three significant results (IL18R1, MLN, PRDM1) of the discovery stage remained after performing FDR correction on the *p*-values, of which two (IL18R1, MLN) were successfully replicated in the replication stage. After excluding SNPs with horizontal pleiotropy, 10 proteins other than GRN, TMPRSS11D and C1QTNF1 remained significantly causally associated with gliomas. Many of these were reported for the first time.

Among the 5 risk proteins, motilin (MLN) is a small molecular peptide that regulates gastrointestinal contraction and peristalsis [15]. It is associated with various digestive system tumors [16], but there is currently no research on its relevance to glioma. Since it remains significantly causally associated with glioma after FDR correction, the role it plays in glioma deserves further investigation. Rac GTPase activating protein 1 (RACGAP1) is a member of the Rho GTPase activating protein (GAP) family and plays an important role in processes such as cell proliferation. Studies have shown that the expression of RACGAP1 could increase the malignant potential of tumors, and is a biomarker for lymph node metastasis and poor prognosis in colorectal cancer. Another study showed that RACGAP1 is significantly upregulated in both glioblastoma and LGG and is associated with poor prognosis in LGG. Signal regulatory protein beta 1 (SIRPB1) is a signal regulatory protein member of the immunoglobulin superfamily. A study by Qiong Song et al. reported that it can promote prostate cancer cell proliferation through Akt activation. The protein encoded by carbohydrate sulfotransferase 9 (CHST9) belongs to the sulfotransferase 2 family, and catalyzes the transfer of sulfate to the 4th position of non-reducing N-acetylgalactosamine (GalNAc) residues in N- and O-glycans. Several members of the CHST family have been reported as oncogenes in glioma. Literature has reported that inhibition of CHST11 and CHST3, key enzymes in the synthesis of chondroitin sulfate 4-sulfate (C4S) and chondroitin sulfate 6-sulfate (C6S), can inhibit the cell viability, migration, and invasion of glioma. A study by Juan Wang et al. showed that knocking down carbohydrate sulfotransferase 12 can reduce the proliferation and motility of glioblastoma cells through the WNT/β-catenin pathway. Tyrosine protein sulfotransferase (TPST) is mainly divided into two subtypes, TPST1 and TPST2 [17]. A study led by Juan Xu showed that TPST-1 mediates nasopharyngeal carcinoma metastasis through the sulfation of CXCR4 [18]. It shows that SIRPB1, RACGAP1, CHST9, and TPST2 usually play pro-tumorigenic roles. Our MR analysis also found that the above proteins increased the risk of glioma, which is consistent with previous findings.

Among eight protective proteins, interleukin-18 receptor 1 (IL18R1) is a cytokine receptor belonging to the interleukin 1 receptor family, which specifically binds to interleukin 18 (IL18). It has been reported that IL-18 combined with IL-12 can activate cytotoxic T cells (CTL) and natural killer (NK) cells to produce IFN-γ, thereby promoting tumor immunity [19]. Clinical trials have shown that intravenous injection of IL-18 can inhibit the progression of multiple cancers by enhancing immunity. IL-18 can regulate Th1 and Th2 responses[20], and the study by Yasuo Takashima et al. demonstrated that low Th2 balance and low activity of the PD-L1/PD-1 axis predicts good prognosis in glioblastoma[21]. Our results also confirmed a strong causal relationship between IL18R1 and glioma, which remained significant even after FDR correction. Teratoma-derived growth factor 1 (TDGF1), also known as Cripto-1 (CR-1), plays a crucial regulatory role in early embryonic development and participates in cell migration and other activities [22]. H. Huang et al. used cDNA expression arrays to analyze the gene expression profile of 11 diffuse astrocytomas and found that TDGF1 was downregulated to below 11% of normal levels in 64-100% of cases. The N-terminal amino acid residue trimming of peptides in the endoplasmic reticulum is the final step for the generation of most MHC class I binding peptides and involves the collaborative action of two endoplasmic reticulum aminopeptidases, ERAP1 and ERAP2. Studies have shown that low expression or imbalanced expression of ERAP1 and ERAP2 may lead to incorrect antigen processing, thereby promoting tumor escape from immune surveillance. Similarly, TAP Binding Protein Like (TAPBPL) is also associated with MHC class I molecules, and studies have shown that it can use peptide traps to promote antigen loading on MHC class I molecules, thus promoting the body's immune response to tumor cells. Our MR study confirms that ERAP1, TAPBPL, and IL18R1 can reduce the risk of glioma, which may be achieved by promoting anti-tumor immunity. Fc receptor-like protein (FCRL) is a marker for multiple B-cell tumors, but its relationship with non-lymphatic system tumors such as glioma is still unclear, which requires further research. In addition to the five proteins previously discussed, the remaining three proteins (GRN, C1QTNF1 and TMPRSS11D) also demonstrated potential causal associations with glioma. Granulin precursor (GRN) can stimulate cell proliferation, migration, malignancy, as well as cancer cell drug resistance and immune evasion. LM Liao et al. used cDNA microarray analysis and found that GRN was highly expressed in glioblastoma. Our MR analysis indicates that GRN is associated with a lower risk of glioma. Therefore, the role of GRN in glioma remains to be further studied. C1q/TNF-related protein 1 (C1QTNF1) is a poor prognostic biomarker and oncogene in human glioblastoma, and studies have shown that it can promote tumor progression by

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regulating CCL2 expression. However, this study only focused on glioblastoma, and there may be some differences in the results in other types of glioma. Transmembrane serine protease 11D (TMPRSS11D) is a pancreatic enzyme-like serine protease released from submucosal serous glands onto mucosal surfaces and plays a role in mucosal immunity. Studies have shown that it is a poor prognostic marker for non-small cell lung cancer, but there is currently a lack of research on its relationship with glioma. However, after excluding potential pleiotropic SNPs, the causal effects between these three proteins and glioma disappeared, which suggested that its causality may be driven by confounding factors.

Data availability statement

The original contributions presented in the study and further inquiries can be directed to the corresponding author.

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