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Multi-omics investigation of prospective therapeutic targets for type 1 diabetes

Yue-Yang Zhang*, Qing-Tian Qiao*, Bing-Xue Chen* and Qin Wan

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Abstract

Background: In recent years, the incidence of type 1 diabetes has been rising steadily, positioning its prevention and treatment as a central focus of global public health initiatives. Previous Mendelian randomization (MR) studies have investigated the relationship between proteomics and type 1 diabetes. Consequently, this study aims to identify prospective therapeutic targets for type 1 diabetes through a comprehensive multi-omics analysis.

Methods: This study primarily utilized the MR method, drawing on genetic data from several large-scale, publicly accessible genome-wide association studies. Within this framework, we applied two-sample MR to evaluate the relationship between five omics components and type 1 diabetes. Finally, we conducted various sensitivity analyses and bidirectional MR to ensure the robustness and reliability of our findings.

Results: The inverse variance weighted method revealed that, following false discovery rate correction, 39 plasma proteins and 3 plasma protein ratios exhibited significant associations with type 1 diabetes. The genetically predicted risk of type 1 diabetes ranged from 0.05 for RBP2 to 394.51 for FMNL1. Furthermore, 4-chlorobenzoic acid levels demonstrated a potential association with type 1 diabetes.

Conclusion: Our research identified numerous omics components associated with type 1 diabetes. These findings offer novel insights into the disease's etiology, diagnosis, and treatment.

Keywords: immunophenotype, Mendelian randomization, multi-omics, plasma protein, type 1 diabetes

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Correspondence to:
Qin Wan
Department of Endocrinology and Metabolism, Affiliated Hospital of Southwest Medical University, No. 23 Taiping Street, Jiangyang District, Luzhou, Sichuan 646000, China

Metabolic Vascular Disease Key Laboratory of Sichuan Province, Luzhou, China

Sichuan Clinical Research Center for Diabetes and Metabolism, Luzhou, China

Sichuan Clinical Research Center for Nephropathy, Luzhou, China

Cardiovascular and Metabolic Diseases Key Laboratory of Luzhou, Luzhou, China
wanqin360@swmu.edu.cn

Yue-Yang Zhang
Qing-Tian Qiao
Department of Endocrinology and Metabolism, Affiliated Hospital of Southwest Medical University, Luzhou, China

Metabolic Vascular Disease Key Laboratory of Sichuan Province, Luzhou, China

Sichuan Clinical Research Center for Diabetes and Metabolism, Luzhou, China

Sichuan Clinical Research Center for Nephropathy, Luzhou, China

Cardiovascular and Metabolic Diseases Key Laboratory of Luzhou, Luzhou, China

Bing-Xue Chen
Department of Ultrasound Medicine, Affiliated Hospital of Southwest Medical University, Luzhou, China

*These authors made equal contributions to this work and they share the first authorship.

Introduction

Type 1 diabetes is a chronic autoimmune disorder characterized by absolute insulin deficiency and resulting hyperglycemia.[1] Although the pathophysiological mechanisms of type 1 diabetes may appear straightforward, research has shown that a deeper understanding often leads to a more nuanced comprehension of the disease. Initially, type 1 diabetes was thought to result from T cell-mediated damage to pancreatic β-cells; however, it is now understood to arise from interactions among genetic factors, environmental influences, microbiota, metabolic processes, and the immune system.

Type 1 diabetes is a hereditary polygenic disorder, exhibiting an incidence of 30%–70% among monozygotic twins,[2] 6%–7% among siblings, and 1%–9% among children with one diabetic parent,[3] with a significantly higher incidence in males compared to females.[4] Two HLA class II haplotypes associated with genetic susceptibility—HLA DRB10301-DQA10501-DQB10201 (DR3) and HLA DRB10401-DQA10301-DQB10301 (DR4-DQ8)—account for approximately 50% of the disease's heritability, a phenomenon predominantly observed in Caucasians.[5] In addition, several genome-wide association studies (GWAS) have identified more than 60 genetic loci associated with type 1 diabetes, revealing significant correlations with insulin gene expression in the thymus, T cell activation regulation, and viral responses.[6] Despite the increasing body of

research on type 1 diabetes, its global incidence continues to rise.[7] Since 2001, the annual incidence has been approximately 22.9 cases per 100,000 individuals.[8] Notably, observational studies indicate that the most significant increase in type 1 diabetes incidence is observed among individuals under the age of 15.[9] These changes are challenging to attribute solely to genetic variation, suggesting that multiple factors, including environmental and dietary influences, are closely associated with type 1 diabetes.[10] It is important to highlight that current clinical treatments for type 1 diabetes mellitus remain limited. Beyond the widely used insulin therapies, other potential treatments—such as preclinical interventions with teplizumab—primarily slow disease progression rather than providing a cure.[11]

Mendelian randomization (MR) was initially regarded as a promising alternative to randomized controlled trials, utilizing genetic instruments as reliable proxies for exposure and disease. According to Mendelian genetics, genetic information is randomly allocated at conception, before the onset of any disease, thereby minimizing confounding biases from various sources.[12] Previous MR studies have investigated the associations between clinically relevant circulating proteins and type 1 diabetes, yet have not addressed multi-omics components.[13] Consequently, this study investigates potential associations between multi-omics components—such as blood cells, cerebrospinal fluid (CSF) proteins, immune phenotypes, proteomics, and plasma protein-to-protein ratios—and type 1 diabetes using MR.

Methods

Study design

This study primarily utilizes MR methods to investigate the causal relationships between type 1 diabetes and a range of multi-omics components, including 91 blood cell types, 338 CSF proteins, 731 immune phenotypes, 1001 plasma proteins, and 2821 plasma protein-to-protein ratios, drawing on multiple independent large-scale human GWAS. Subsequently, various sensitivity analysis techniques and bidirectional MR were employed to evaluate the robustness of the findings. In all MR analyses, three fundamental assumptions must be rigorously met: first, the selected genetic instruments must be strongly associated with the exposure factors; second, they must be independent of confounding variables; and third, their impact on the outcome must be entirely mediated through the specific exposure factors.[14] Figure 1 depicts the fundamental design framework of this study.

Data sources

All data utilized in this study are sourced from global GWAS conducted in European populations and are entirely derived from publicly accessible summary datasets (refer to Table S1).

The genetic data concerning blood cell perturbation phenotypes are derived from a GWAS encompassing 2600 samples. This study employed human peripheral blood, along with physical, chemical, and pharmacological perturbations, and flow cytometry-based functional assays to elucidate underlying cellular processes.[15] The genetic data on CSF proteins originate from a GWAS focusing on two distinct cohorts.[16] Immune cell phenotypes are derived from a GWAS analysis involving 3757 Sardinian participants, covering 731 immune cell phenotypes.[17] Genetic data on plasma proteins and plasma protein ratios are obtained from the most recent Olink proteomics dataset, encompassing 54,000 samples from the UK Biobank. This dataset identifies 1001 and 2821 genetic loci associated with various plasma proteins and plasma protein ratios, respectively.[18] In addition, genetic data on type 1 diabetes were sourced from two distinct GWAS. Data from Chiou et al.,[19] comprising 520,580 samples, were utilized for initial exploration, whereas genetic data from the FinnGen DF4 version, encompassing 189,113 samples, were employed for secondary validation. The FinnGen study represents a large-scale genomic project that analyzed over 500,000 Finnish biobank samples, correlating genetic variation with health data to elucidate disease mechanisms and susceptibility.[20] Importantly, when comparing the five omics datasets with the two type 1 diabetes genetic datasets, only minimal sample overlap was observed.

Instrument selection

To ensure an adequate number of single-nucleotide polymorphisms (SNPs) for subsequent statistical analyses, we established a significance threshold of 1×10^{-5} for the five omics components. We subsequently utilized the European

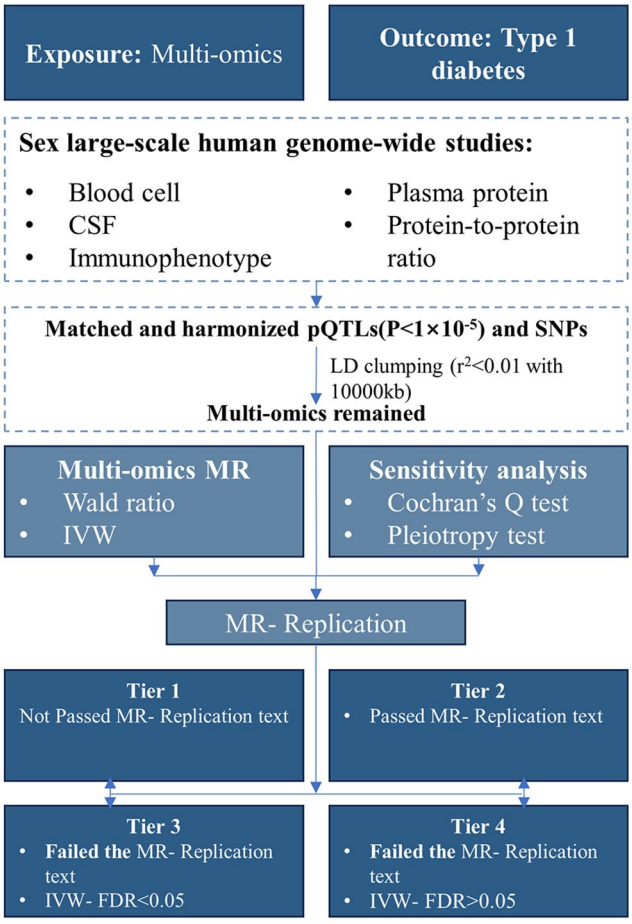

Figure 1. Study flow chart.

1000 Genomes panel to select SNPs exhibiting relative independence, specifically those within a 10,000 base pair genomic region and with a linkage disequilibrium threshold (r^2) below 0.01. In addition, we assessed the statistical robustness of all SNPs using the *F*-statistic, excluding those with an *F*-statistic below 10 to mitigate bias introduced by weak instrumental variables.[21]

Statistical analysis

This study primarily employs the inverse variance weighted (IVW) method to investigate potential associations between five omics components and type 1 diabetes. In addition, four sensitivity analysis techniques—weighted median, simple mode, weighted mode, and MR-Egger test—are employed to ensure the robustness of the IVW analysis results. The research process is as follows: First, the associations between 91 blood cell types, 338 CSF proteins, 731 immune phenotypes, 1001 plasma proteins, and 2821 plasma protein ratios and type 1 diabetes in the initial exploratory cohort are assessed separately. Cochran's *Q* test assesses the heterogeneity of genetic instruments ($p < 0.05$), whereas the MR-Egger intercept test elucidates directional pleiotropy ($p < 0.05$).[22] The false discovery rate (FDR) is employed for multiple testing correction, with an IVW-FDR < 0.05 set as the significance threshold. Subsequently, the associations between the five omics components and type 1 diabetes in the secondary validation cohort are examined to enhance the generalizability and accuracy of the findings. Third, the study investigates the reverse causal relationship between the five omics components identified as being associated with type 1 diabetes and type 1 diabetes itself.

All statistical analyses are conducted using the TwoSampleMR package (version 0.5.6) within

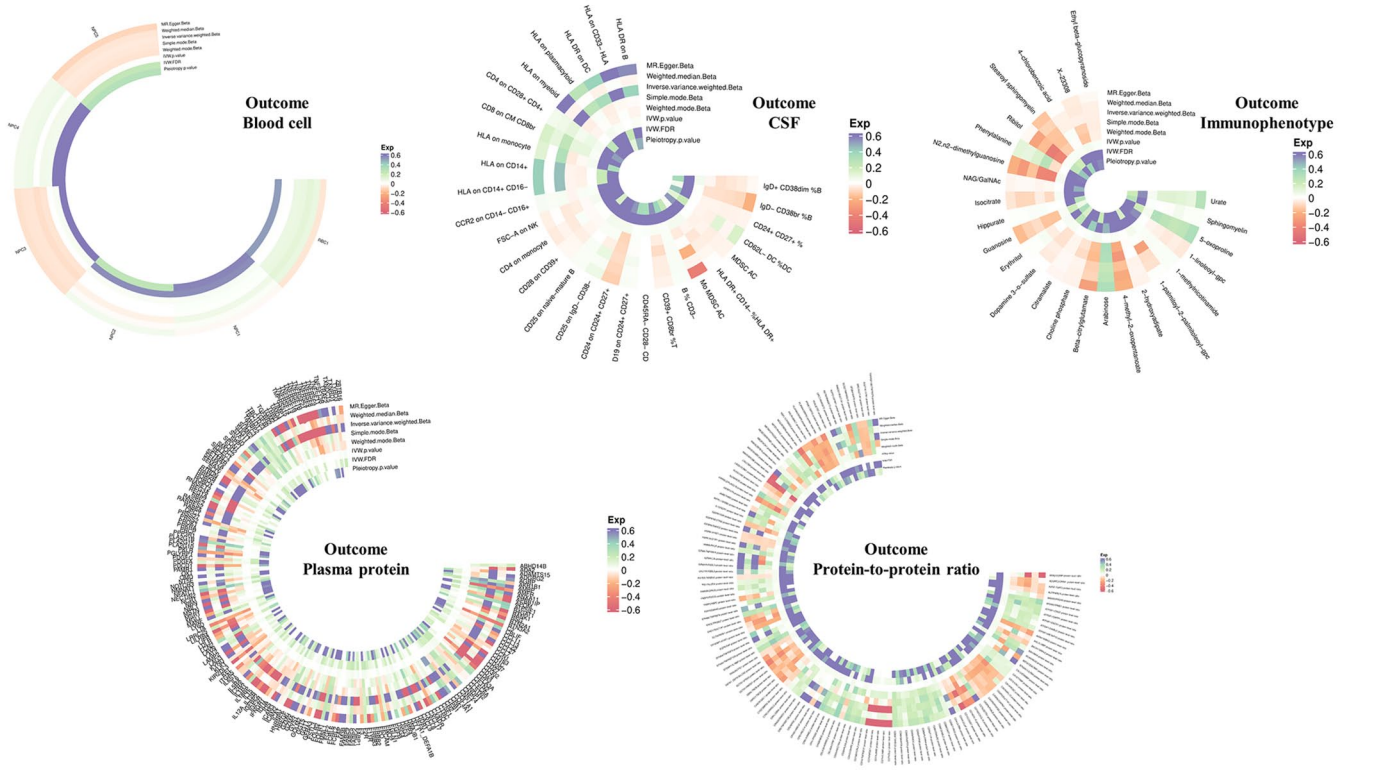

Figure 2. Heat map of the sensitivity analysis carried out by applying various MR analysis models.
MR, Mendelian randomization.

the R software environment (version 4.3.3). Significance is assessed using stringent two-tailed statistical criteria.

Results

Instrument selection

As illustrated in Table S2, researchers selected between 5 and 409 SNPs using stringent selection criteria to investigate the association between five omics components and type 1 diabetes. All selected genetic instruments had an *F*-statistic exceeding 10, indicating that the study can minimize bias from weak instrumental variables.

The correlation between 91 blood cell phenotypes and type 1 diabetes

Table S2 and Figure 2 present the IVW results, revealing that only six blood cell phenotypes are significantly associated with type 1 diabetes ($p < 0.05$). Following FDR correction, only two blood cell phenotypes remained significantly associated with type 1 diabetes (IVW-FDR < 0.05). Specifically, neutrophil perturbation response (the forward scatter coefficient of variation of neutrophil 1 in response to Pam3CSK4 perturbation, measured by WDF dye) was negatively associated with type 1 diabetes risk, while Red blood cell perturbation response (the forward scatter standard deviation of RBC in response to rotenone perturbation, measured by reticulocyte dye) was positively associated with type 1 diabetes risk, with odds ratio (OR) values of 0.94 (0.9, 0.97) and 1.12 (1.06, 1.18), respectively. Cochran's *Q* test and MR-Egger intercept regression analyses revealed no significant heterogeneity or horizontal pleiotropy (Tables S3 and S5). The MR-Egger, weighted median, simple mode, and weighted mode sensitivity analysis methods generally exhibited directional consistency with the IVW results. Unfortunately, during the replication phase, we did not observe an association between these two blood cell phenotypes and type 1 diabetes.

The correlation between 338 CSF proteins and type 1 diabetes

Table S2 and Figure 2 present the IVW results, indicating that 25 CSF proteins are significantly associated with type 1 diabetes ($p < 0.05$). Unfortunately, following FDR correction, no blood cell phenotypes were found to retain a significant association with type 1 diabetes (IVW-FDR < 0.05). Notably, in both the discovery and validation cohorts, levels of 4-chlorobenzoic acid were negatively associated with type 1 diabetes, showing consistent OR values. Cochran's Q test and MR-Egger intercept regression analyses similarly revealed no significant heterogeneity or horizontal pleiotropy (Tables S3 and S5). The MR-Egger, weighted median, simple mode, and weighted mode sensitivity analysis methods similarly exhibited directional consistency with the IVW results, suggesting a potential association between 4-chlorogenic acid levels and type 1 diabetes.

The correlation between 731 immunophenotype and type 1 diabetes

Table S2 and Figure 2 present the IVW results, revealing that 28 immunophenotypes are significantly associated with type 1 diabetes ($p < 0.05$). However, following FDR correction, no immune cell phenotypes were found to retain a significant association with type 1 diabetes (IVW-FDR < 0.05). Cochran's Q test revealed some evidence of heterogeneity. However, given that the MR-Egger, weighted median, simple mode, and weighted mode sensitivity analyses exhibited directional consistency with IVW, the observed heterogeneity is considered negligible. MR-Egger intercept regression analyses did not detect significant horizontal pleiotropy (Tables S3 and S5). Unfortunately, in the validation cohort, we did not observe any immunophenotype associated with type 1 diabetes either.

The correlation between 1001 plasma proteins and type 1 diabetes

Table S2 and Figure 2 present the IVW results, revealing that 203 plasma proteins are significantly associated with type 1 diabetes ($p < 0.05$). Following FDR correction, 93 plasma proteins were found to retain a significant association with type 1 diabetes (IVW-FDR < 0.05). Among these, 45 proteins, such as APOM and BTN2A1, were negatively associated, while 48 proteins, including AGRP and AMBP, were positively associated. The genetically predicted risk of type 1 diabetes varied from 0.05 for RBP2 to 394.51 for FMNL1. Cochran's Q test revealed evidence of some heterogeneity. However, given that the MR-Egger, weighted median, simple mode, and weighted mode sensitivity analyses exhibited directional consistency with IVW, this heterogeneity is considered negligible. MR-Egger intercept regression analyses identified significant horizontal pleiotropy for 37 plasma proteins, including ADA2, AMBP, and ANXA11, about type 1 diabetes (Tables S3 and S5). In the validation cohort, we identified 147 plasma proteins associated with type 1 diabetes, of which 39 proteins, including AGRP and B4GAT1, were confirmed to be closely related to the disease. In addition, reverse MR analyses identified inverse associations between type 1 diabetes and AGRP, CD207, NBN, PPP3R1, RARRES2, and SETMAR (Table S6).

The correlation between 2821 plasma protein-to-protein ratios and type 1 diabetes

Table S2 and Figure 2 present the IVW results, revealing that 130 protein-to-protein ratios are significantly associated with type 1 diabetes ($p < 0.05$). Following FDR correction, only eight protein-to-protein ratios retained a significant association with type 1 diabetes (IVW-FDR < 0.05). Among these, four ratios, such as the CASP3/SULT1A1 protein level ratio and the CD74/JAM2 protein level ratio, were negatively associated, whereas four ratios, including the CD69/CNST protein level ratio and the CDSN/NECTIN4 protein level ratio, were positively associated. The genetically predicted risk of type 1 diabetes varied from 0.12 for the CD74/JAM2 protein level ratio to 1.38 for the CD69/CNST protein level ratio. Cochran's Q test revealed evidence of some heterogeneity. However, given that MR-Egger, weighted median, simple mode, and weighted mode sensitivity analyses exhibited directional consistency with IVW, the heterogeneity is considered negligible. MR-Egger intercept regression analyses identified significant horizontal pleiotropy solely for the CD74/JAM2 protein level ratio about type 1 diabetes (Tables S3–S5). In the validation cohort, we identified 31 plasma protein ratios associated with type 1 diabetes, of which 3 ratios, including the CDSN/NECTIN4 protein level ratio, the LTA/LTBR protein level ratio, and the SCG2/TMPRSS15 protein level ratio, were confirmed to be closely

related to type 1 diabetes. Additionally, reverse MR analyses identified inverse associations between type 1 diabetes and the CDSN/NECTIN4 protein level ratio, as well as the LTA/LTBR protein level ratio (Table S6).

Discussion

This MR study utilized a range of sensitivity analysis methods to evaluate the associations between 91 blood cell types, 338 CSF proteins, 731 immune phenotypes, 1001 plasma proteins, and 2821 protein-to-protein ratios and the risk of type 1 diabetes. The study identified 39 plasma proteins and 1 plasma protein ratio that were strongly associated with type 1 diabetes. In addition, we observed a potential association between 4-chlorobenzoic acid levels and type 1 diabetes. The study also investigated reverse causal associations between these omics components and type 1 diabetes. These findings may offer new insights into the prevention and treatment of type 1 diabetes.

Our study initially validated several previously established associations between plasma proteins and type 1 diabetes, such as AGRP and BANK1,[23–25] underscoring the high reliability of the data sources utilized. BANK1 is an adaptor protein consisting of 785 amino acids, predominantly expressed in B cells, and is involved in the mobilization of calcium from intracellular stores following B cell receptor activation.[26] In pancreatic β-cells, apoptosis induced by glucose and IL-1β necessitates calcium flux,[27] while B cells contribute significantly to the development of type 1 diabetes through their role as antigen-presenting cells.[28] Furthermore, prior research has established that the *BANK1* gene is linked to genetic susceptibility to several autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis.[29,30]

A study conducted on an Iranian cohort observed significantly elevated levels of CCL11 in patients with type 1 diabetes,[31] corroborating our findings. CCL11 is a powerful chemotactic and activating factor that targets eosinophils, basophils, and Th2 lymphocytes via the chemokine receptor CC chemokine receptor 3 (CCR3) present in the serum. The CCL11 promoter harbors common binding sites that overlap with transcription factors such as nuclear factor-kappa B and signal transducer and activator of transcription 6.[32] These interactions can mediate responses to tumor necrosis factor-alpha and IL-4, potentially contributing to the development of type 1 diabetes. CD27 is a transmembrane dimer expressed on immune cells, including B cells and NK cells, and is crucial for both the generation and sustained maintenance of T cell immunity.[33] Numerous in vitro studies have demonstrated that CD27-deficient mice exhibit heightened susceptibility to a range of viruses and cancers,[34,35] while recent animal experiments have underscored the significant role of CD27 in type 1 diabetes.[36]

Furthermore, we identified several omics components that have yet to be demonstrated as being associated with type 1 diabetes. LCN2 is a lipid carrier protein primarily involved in the transport of lipids and small hydrophobic molecules, including steroid hormones. It plays a critical role in innate immunity by limiting bacterial growth through iron binding.[37] Existing research has established a significant association between LCN2 and both mild cognitive impairment and dementia.[38] We also identified a potential association between 4-chlorobenzoic acid and type 1 diabetes. Previous observational studies have suggested that 4-chlorobenzoic acid could serve as a potential biomarker for COVID-19.[39] However, its specific associations with various diseases remain ambiguous and warrant further investigation. Although our study did not identify any strongly associated components among the 731 immune cell phenotypes, this does not preclude the possibility of a potential association with type 1 diabetes. We identified associations between certain immune cell phenotypes and type 1 diabetes in two distinct populations; however, the generalizability of these findings may be constrained by population differences.

This study boasts several notable advantages. First, the genetic data for the five omics components and type 1 diabetes are derived from large-scale, population-based GWAS. These studies are methodologically robust and minimize sample overlap, thereby mitigating potential confounding effects due to shared samples across datasets. Second, all selected genetic instruments possess *F*-statistics greater than 10, indicating robust instrument strength that effectively mitigates bias from weaker tools and enhances the reliability of the instrumental variables utilized in the analysis. Finally, the application of multiple sensitivity analysis methods has further reinforced the reliability of the study's findings.

Although this study is relatively comprehensive, several limitations must be acknowledged, which could impact the interpretation of our findings. First, it is crucial to acknowledge that MR has inherent limitations, including trait heterogeneity and compensatory development issues, which may influence the accuracy and applicability of our findings.[40] Second, our reliance on summary-level data constrains our capacity to perform stratified analyses or conduct a thorough investigation of individual-level data. Third, given that our study participants are predominantly of European descent, caution is warranted when generalizing the findings to other racial groups, such as those of Asian descent. Further research is essential to validate the applicability of our findings across diverse racial groups. Finally, although we identified potential causal relationships between numerous omics components and type 1 diabetes, our comprehension of the underlying mechanisms remains incomplete, necessitating further basic research to elucidate these complex pathways.

Conclusion

In summary, this extensive multi-omics MR study identified numerous omics components closely associated with type 1 diabetes, offering promising targets for elucidating the pathogenesis, diagnosis, and therapeutic strategies for the disease. Nevertheless, additional fundamental experiments are crucial for assessing the true effects of these candidate targets.

Declarations

Ethics approval and consent to participate

This study is based on publicly available summarized data. Ethical approval and informed consent had been obtained in all original studies.

Consent for publication

Not applicable.

Author contributions

Yue-Yang Zhang: Formal analysis; Methodology; Writing – original draft.

Qing-Tian Qiao: Project administration; Resources; Software; Writing – original draft.

Bing-Xue Chen: Data curation; Investigation; Visualization; Writing – original draft.

Qin Wan: Funding acquisition; Validation; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

ORCID iD

Qin Wan https://orcid.org/0000-0001-7765-1416

Supplemental material

Supplemental material for this article is available online.

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