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Exploring the mechanism of comorbidity in patients with T1DM and COVID-19

Integrating bioinformatics and Mendelian randomization methods

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Abstract

During the coronavirus disease 2019 (COVID-19) pandemic, the incidence of type 1 diabetes mellitus (T1DM) has increased. Additionally, evidence suggests that individuals with diabetes mellitus may have increased susceptibility to severe acute respiratory syndrome coronavirus 2 infection. However, the specific causal relationships and interaction mechanisms between T1DM and COVID-19 remain unclear. This study aims to investigate the causal relationship between T1DM and COVID-19, utilizing differential gene expression and Mendelian randomization analyses. Differentially expressed gene sets from datasets GSE156035 and GSE171110 were intersected to identify shared genes, analyzed for functional enrichment. Mendelian randomization models were employed to assess causal effects, revealing no direct causal link between T1DM and COVID-19 in the European population ($P > .05$). Notably, DNA replication and sister chromatid cohesion 1 (DSCC1) showed negative causal associations with both diseases (T1DM: OR = 0.943, 95% CI: 0.898–0.991, $P = .020$; COVID-19: OR = 0.919, 95% CI: 0.882–0.958, $P < .001$), suggesting a protective effect against their comorbidity. This genetic evidence highlights DSCC1 as a potential target for monitoring and managing the co-occurrence of T1DM and COVID-19.

Abbreviations: ANKRD34B = ankyrin repeat domain 34B, CC = cellular component, COVID-19 = coronavirus disease 2019, DEGs = differentially expressed genes, DSCC1 = DNA replication and sister chromatid cohesion 1, eQTL = expression quantitative trait locus, eQTLs = expression quantitative trait loci, FasL = Fas ligand, GO = gene ontology, GWAS = genome-wide association study, HSV = herpes simplex virus, IVs = instrumental variables, IVW = inverse variance weighted, KEGG = Kyoto Encyclopedia of Genes and Genomes, MR = Mendelian randomization, OR = odds ratio, ROS = reactive oxygen species, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SNPs = single nucleotide polymorphisms, T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus.

Keywords: COVID-19, DSCC1, eQTL, Mendelian randomization, type 1 diabetes mellitus

1. Introduction

Type 1 diabetes mellitus (T1DM), an autoimmune disease characterized by hyperglycemia and insulin dependence, is influenced by a complex interplay of various environmental, microbial, genetic, metabolic, and immune factors. Viral infections, such as coxsackievirus, cytomegalovirus, and enterovirus infections, have been identified as potential triggers for the development of T1DM. Recent studies have focused on the potential connection between T1DM and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), suggesting a bidirectional relationship between the 2 conditions.[1–3] Both diseases seem to promote the other. However, the causal relationship between the 2 diseases has not been verified. Moreover, several studies have shown that the coronavirus disease 2019 (COVID-19) can lead to more complications and higher mortality in T1DM,[4–6] and T1DM is also associated with an increased risk of serious infections and higher mortality in patients with COVID-19,[7,8] highlighting the complex interplay between the 2 diseases and the burden it places on global healthcare systems. In addition to T1DM, type 2 diabetes mellitus (T2DM) represents the most common form of

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The datasets generated during and/or analyzed during the current study are publicly available.

Our study utilized publicly accessible data from the Gene Expression Omnibus (GEO) and genome-wide association study (GWAS) summary statistics. No original data were collected and no additional ethical approval was required.

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diabetes. The complex interplay between T2DM and COVID-19 has also attracted extensive research interest. This body of research encompasses bioinformatics analyses,[9,10] Mendelian randomization (MR) studies,[11,12] clinical observational research, and experimental studies. These investigations have elucidated common differentially expressed genes (DEGs) and enriched pathways that link T2DM and COVID-19. Moreover, they have explored the shared pathophysiological mechanisms underlying both diseases, such as immune dysregulation, chronic inflammation, aberrant expression of angiotensin-converting enzyme 2, and dysregulated cytokine expression.[13–16] Furthermore, the potential therapeutic implications of T2DM pharmacotherapy for COVID-19 have been examined.[17,18] Building upon this research, we posit that there may be also a genetic overlap between T1DM and COVID-19, which could be identified through the analysis of DEGs. This genetic overlap is hypothesized to be associated with a protective or aggravating effect on the concomitant occurrence of both diseases. Specifically, this study aims to analyze the shared DEGs associated with both T1DM and COVID-19 to elucidate the shared pathogenic pathways by employing integrated bioinformatics and enrichment analysis.

Additionally, MR, a reliable method for investigating causal relationships, was employed to explore the association between T1DM and COVID-19. This study employed a two-sample MR approach using single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to investigate the causal relationships between T1DM and COVID-19, and between insulin secretion function and COVID-19. Furthermore, this study integrated MR data with expression quantitative trait locus (eQTL) data obtained from the cis-eQTL open database to examine the causal relationship between the expression of shared DEGs and susceptibility to comorbid T1DM and COVID-19. The ultimate objective was to identify potential biomarkers for comorbidities and elucidate the underlying mechanism of the simultaneous occurrence of these 2 diseases.

2. Materials and methods

2.1. Dataset preparation

For this study, we utilized the gene expression omnibus database, which is a comprehensive and publicly available resource containing gene expression data for various diseases. Based on the Agilent-072363 SurePrint G3 Human GE v3 8 × 60K Microarray 039494-based platform, the GSE 156035 dataset contains gene chip expression data acquired from 20 fresh blood samples of T1DM patients and 20 healthy controls.[19] The GSE171110 dataset consists of whole blood gene expression profiles from 44 COVID-19 patients and 10 healthy donors obtained using high-throughput sequencing technology based on the Illumina HiSeq 2500 platform.[20]

The genome-wide association study (GWAS) data for T1DM, Fasting insulin, and COVID-19 patients were obtained from the IEU OpenGWAS Project database with the IDs ebi-a-GCST90014023, ebi-a-GCST90002238, and ebi-a-GCST011071, respectively. Additionally, we obtained summary datasets of expression quantitative trait loci (eQTLs) from the cis-eQTL dataset (https://gtexportal.org/home/datasets). From the eQTL dataset, we extracted relevant information such as SNP chromosome positions, alleles, eQTL sample numbers, and p-values.

2.2. Identification of shared DEGs between T1DM and COVID-19

The "limma" package in R software (v 4.2.0) was used to filter DEGs with absolute values of logFC > 1 and FDR < 0.05. Then, shared DEGs between GSE 156035 and GSE 171110 were obtained using the online Jvenn analysis tool (http://jvenn.toulouse.inra.fr/app/example.html).

2.3. Functional annotation and pathway enrichment analysis

To characterize the function of shared DEGs between T1DM and COVID-19, gene enrichment analysis was performed using the Enrichr online website (https://maayanlab.cloud/Enrichr/) to acquire a detailed characterization of the biological mechanisms and signaling pathways. Gene ontology (GO) analysis includes 3 terms: biological process, molecular function, and cellular component. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis was utilized to identify metabolic pathways and thus to analyze the potential functions of shared DEGs.[21]

2.4. Analysis of immune infiltrating cells

The CIBERSORT algorithm was used to assess the relative composition and function of different immune cells on the basis of immunogenomic mRNA expression data. The corrplot package was employed to plot relevant heatmaps. The Wilcoxon test was performed to evaluate the fraction of infiltrating immune cells, and the results are displayed in a box plot. Spearman's rank correlation analysis in R software was used to explore the correlation between genes and immune cells. The "ggplot2" software package was applied to visualize the association information.

2.5. Mendelian randomization analysis

2.5.1. IVs extraction. To investigate the potential causal relationships among T1DM, COVID-19, and gene expression, we performed two-sample MR analyses. These analyses involved using pairs of T1DM, fasting insulin, COVID-19, and eQTL data as exposures and outcomes. We extracted SNPs that were closely associated with the exposures using a significance threshold of $P < 1 \times 10^{-5}$. Subsequently, we removed SNPs that exhibited linkage disequilibrium ($r^2 < 0.1$ within 500 kb), palindromic SNPs, and those that were strongly correlated with the outcome.

2.5.2. Statistical analysis. Five MR models were used to assess the causal associations, including inverse variance weighted (IVW), MR-Egger, weighted median, simple mode and weighted mode. Among them, the test was mainly based on the results of the IVW. However, if there is heterogeneity and no pleiotropy, weighted median method is preferred.

2.5.3. Sensitivity analysis. Sensitivity analysis was conducted to evaluate the robustness of our findings. This involved performing heterogeneity tests, pleiotropy tests, and a "leave-one-out" analysis. The Cochran Q test was used to assess heterogeneity and identify invalid IVs. The MR-Egger intercept was employed to evaluate horizontal pleiotropy. Additionally, a "leave-one-out" analysis was conducted to examine the impact of individual SNPs on the MR estimates.

3. Results

3.1. Shared DEGs between T1DM and COVID-19

A total of 95 DEGs were screened from the T1DM dataset, including 58 upregulated genes and 37 downregulated genes. Similarly, we identified 3169 DEGs in the COVID-19 dataset, including 1446 upregulated genes and 1723 downregulated genes. After cross-comparative analysis on the Jvenn analysis online website, 10 shared DEGs were identified for further

analysis, including ankyrin repeat domain 34B (ANKRD34B), DNA replication and sister chromatid cohesion 1 (DSCC1), ESCO2, FAM221B, KIF14, KIF4A, KRT86, NEK2, HPD, and ZNF547 (Fig. 1).

3.2. Functional correlation analysis

The results of GO analysis of shared DEGs were mainly related to the tyrosine catabolic process, protein acetylation, oxidoreductase activity, and microtubule motor activity (Fig. 2A–C). The results of KEGG analysis showed enrichment in specific pathways, including ubiquinone and other terpenoid-quinone biosynthesis pathways, the phenylalanine metabolism pathway, the tyrosine metabolism pathway, and the herpes simplex virus 1 infection pathway (Fig. 2D).

3.3. Immune infiltration analysis

The extent of immune cell infiltration in T1DM and COVID-19 samples was calculated by the CIBERSORT algorithm. First, the composition of 22 kinds of immune cells in each sample was presented in stacked histograms. Second, the immune cells in each sample are shown in normalized absolute abundance in heatmaps. Third, correlation heatmaps were drawn to assess the correlation between 22 kinds of immune cells. In T1DM, activated memory CD4(+) T cells were positively correlated with activated dendritic cells and negatively correlated with monocytes. In COVID-19, activated mast cells were positively correlated with neutrophils. Memory B cells were negatively correlated with naive B cells. Resting dendritic cells were negatively correlated with neutrophils. Last, as seen in the box plot of immune cell infiltration, there were significant differences in the abundance values of 2 immune cell subsets. In T1DM group, 2 immune cell subsets were significantly different from those in control group ($P < .05$), including a significantly higher number of activated mast cells and a significantly lower number of naive B cells. In COVID-19 group, 13 immune cell subsets were significantly different from those in control group ($P < .05$). Among them, neutrophils, memory B cells, M0 macrophages, monocytes, plasma cells, activated mast cells, resting NK cells, and naive CD4(+) T cells were significantly increased in COVID-19 samples. Resting dendritic cells, resting memory CD4(+) T cells, CD8(+) T cells, naive B cells, and gamma delta T cells were significantly reduced in COVID-19 samples. Comparison of the relative composition of immune cells between T1DM and COVID-19 samples and control samples showed that the abundance of activated mast cells was higher and the abundance of naive B cells was lower in both T1DM and COVID-19.

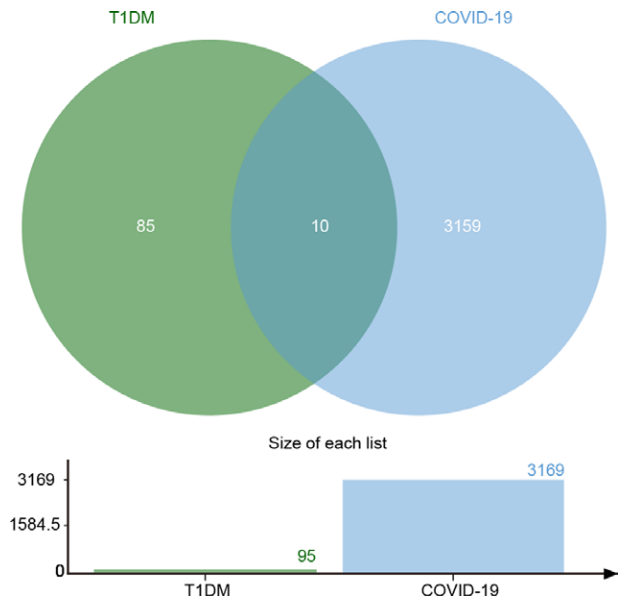

Figure 1. Shared DEGs representation through a Venn diagram. 10 genes were found as shared DEGs from 95 DEGs of T1DM and 3169 DEGs of COVID-19. COVID-19 = coronavirus disease 2019, DEGs = differentially expressed genes, T1DM = type 1 diabetes mellitus.

3.4. Mendelian randomization analysis

3.4.1. Causality of the eQTL of genes on T1DM and COVID-19. To examine the causal effects of gene expression on T1DM and COVID-19, we analyzed eQTL data for 10 shared DEGs: ANKRD34B, DSCC1, ESCO2, FAM221B, KIF14, KIF4A, KRT86, NEK2, HPD, and ZNF547. Six genes with no cis-eQTL information were excluded, and eQTL records were retrieved for 4 genes: ANKRD34B, DSCC1, HPD, and KIF4A. The causal effects of these eQTLs on T1DM and COVID-19 were primarily assessed using the IVW method. Statistically significant causal associations were identified for DSCC1 with both T1DM and COVID-19. The odds ratio (OR) for DSCC1 in patients with T1DM was 0.943 (95% CI: 0.898–0.991, $P = .020$), and that in patients with COVID-19 was 0.946 (95% CI: 0.910–0.984, $P = .006$). Because of heterogeneity ($P = .044 < .05$), the weighted median method was used to analyze the effect of DSCC1 on COVID-19, with an OR of 0.919 (95% CI: 0.882–0.958, $P < .001$). The OR for ANKRD34B in patients with T1DM was 1.005 (95% CI: 0.969–1.042, $P = .780$), and that in patients with COVID-19 was 0.995 (95% CI: 0.974–1.017, $P = .674$) (Fig. 3). Due to the absence of SNPs in HPD and KIF4A following harmonization with either T1DM or COVID-19, MR analysis could not be conducted for these genes and is therefore not depicted in the figure.

3.4.2. Causality between T1DM and COVID-19. There was no causal relationship between T1DM and COVID-19. The OR for the effect of T1DM on COVID-19 incidence was 0.984 (95% CI: 0.966–1.004, $P = .109$), indicating no significant association. Similarly, the OR for the effect of COVID-19 on T1DM was 1.111 (95% CI: 0.853–1.447, $P = .434$), also suggesting no significant causal link. In addition, no bidirectional causal relationship was observed between fasting insulin and COVID-19. The OR for fasting insulin on COVID-19 was 1.146 (95% CI: 0.940–1.397, $P = .179$), while the OR of the reverse test was 1.027 (95% CI: 0.989–1.066, $P = .170$) (Fig. 3). These findings suggest that there is no established causal link between COVID-19 and pancreatic beta cell function.

Moreover, the outcomes of both heterogeneity and pleiotropy assessments for all MR analyses are depicted in Figure 3. Notably, none of the MR analyses revealed evidence of directional pleiotropy (pleiotropy test $P > .05$). For the analyses of DSCC1 on COVID-19, T1DM on COVID-19, COVID-19 on T1DM, and COVID-19 on fasting insulin, significant heterogeneity was observed (heterogeneityn test $P < .05$). To mitigate potential bias, the weighted median method was selectively applied to these analyses. For the remainder of the MR analyses that did not demonstrate heterogeneity, the IVW method was utilized, as previously mentioned in the section 2.5.2.

3.5. Correlation analysis between DSCC1 and infiltrating immune cells

In T1DM patients, DSCC1 expression was negatively correlated with the number of naive B cells (Fig. 4A). In patients with COVID-19, DSCC1 expression was positively correlated with the number of plasma cells and memory B cells but negatively correlated with the number of naive B cells and resting memory

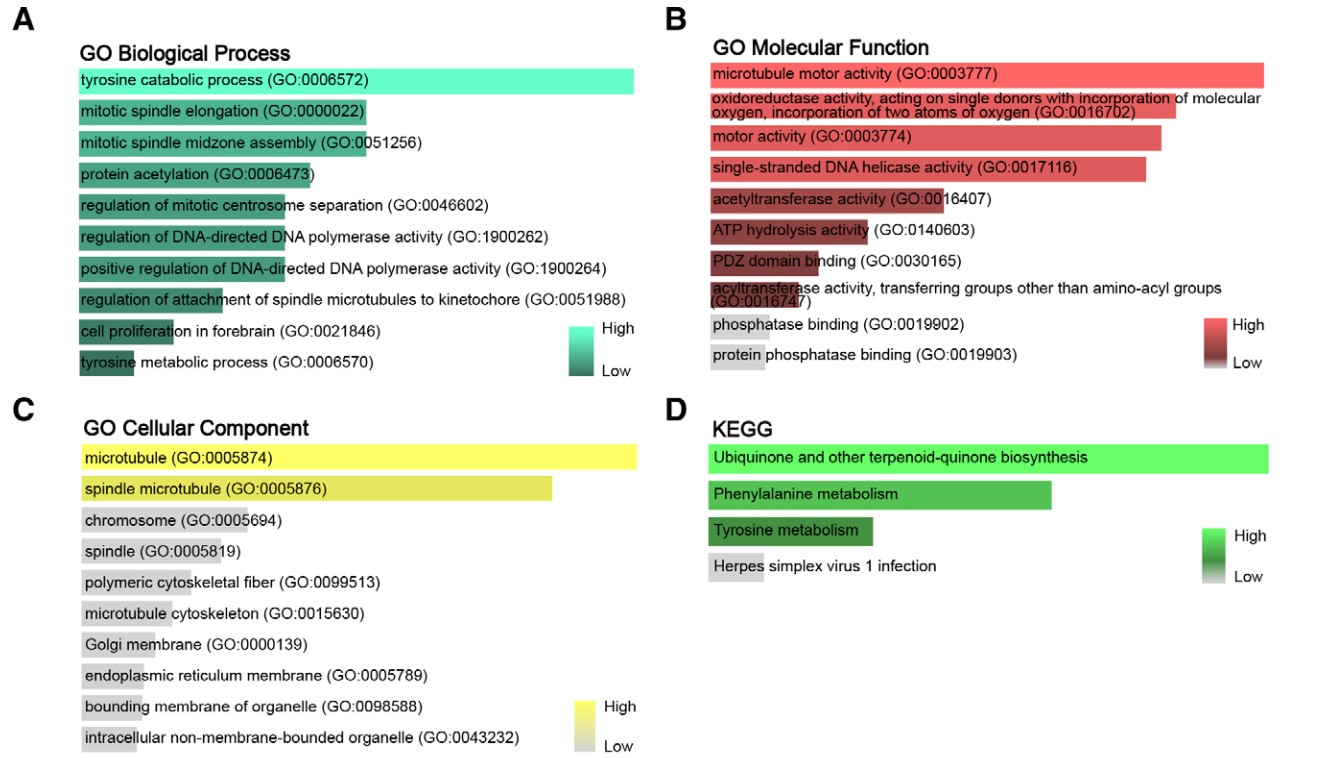

Figure 2. The top items of genes enrichment of the shared DEGs. (A) The enrichment analysis results of GO (biological processes); (B) The enrichment analysis results of GO (molecular functions); (C) The enrichment analysis results of GO (cellular components); (D) The enrichment analysis results of KEGG Pathway. DEGs = differentially expressed genes, GO = gene ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes.

CD4 T cells (Fig. 4B). Our findings revealed a consistent negative correlation between DSCC1 expression and the number of naive B cells in both T1DM patients and COVID-19 patients.

4. Discussion

Although SARS-CoV-2 may act as an etiological factor influencing the pathogenesis of both T1DM and T2DM within susceptible populations,[22] T1DM appears to be subjected to a more severe threat. Clinical evidence indicates that, compared to patients with T2DM or those without diabetes, individuals with T1DM exhibit worse prognoses and higher mortality rates following COVID-19 infection.[23] Furthermore, during the COVID-19 pandemic, T1DM patients exhibited higher levels of hyperglycemia compared to T2DM patients,[24] implying that glucose control may be more challenging to achieve in T1DM patients. Consequently, the exploration of the pathogenic mechanisms underlying the co-occurrence of T1DM and COVID-19 is of paramount clinical relevance.

The COVID-19 pandemic has highlighted a complex relationship between T1DM and SARS-CoV-2 infection. While the pandemic has led to an increase in hyperglycemia, diabetic ketoacidosis, and new diabetes cases, the role of SARS-CoV-2 as a trigger for T1DM remains debated. Some studies suggest a possible link,[25] while others argue that the increased T1DM incidence during the pandemic cannot be solely attributed to COVID-19.[26] It has also been suggested that this correlation varies by country and age.[1] Whether diabetic patients are more susceptible to SARS-CoV-2 infection is also controversial. It has been suggested that diabetic patients are more susceptible to SARS-CoV-2 infection.[7,8] However, there are also studies showing that the effect of diabetes on susceptibility to SARS infection has not passed rigorous multiple testing for correction.[27] However, both diseases can lead to disease exacerbation. COVID-19 has been associated with a greater incidence and severity of diabetic ketoacidosis in patients with T1DM,[4] and several studies have demonstrated that diabetes mellitus is associated with an increased risk of serious infections and elevated mortality in patients with COVID-19.[8] The potential for mutual exacerbation underscores the importance of further research to understand the mechanisms underlying this comorbidity and develop effective strategies for managing these conditions.

To investigate the potential mechanisms underlying the comorbidity of T1DM and COVID-19, we first identified 10 shared DEGs from 2 gene expression omnibus datasets. These shared DEGs were then subjected to GO and KEGG enrichment analyses. The main enriched GO terms were tyrosine catabolic process, protein acetylation, oxidoreductase activity, and microtubule motor activity. KEGG analysis showed that shared DEGs were mainly enriched in the following pathways: the ubiquinone biosynthesis pathway and other terpenoid-quinone biosynthesis pathways, the phenylalanine metabolism pathway, the tyrosine metabolism pathway, and the herpes simplex virus 1 infection pathway. The enrichment analysis revealed many alterations in biological processes, molecular functions, and cellular components in both diseases. Additionally, several signaling pathways were found to be involved in pathogenesis. Tyrosine metabolism and serum tyrosine levels are altered in both T1DM animals and SARS-CoV-2-infected patients.[28] The metabolism of phenylalanine affects the course of diabetic nephropathy and is also associated with higher renal plasma flow in T1DM.[29] Moreover, as a marker of COVID-19 illness severity,[30] phenylalanine enhances angiotensin-converting enzyme 2 binding.[31] Protein acetylation is also involved in the development of both diseases. Acetylation of H3 group proteins induces beta cell dysfunction, which inhibits insulin secretion in T1DM.[32] Acetylation of SARS-CoV-2 nucleocapsid proteins also plays a crucial role in the function of the virus.[33] Additionally, the oxidoreductive process is linked to 2 diseases. Reactive oxygen

Exposure	Outcome	Method	nSNP	Pvalue	OR (95%CI)	Heterogeneity test P	Pleiotropy test P
ANKRD34B	T1DM	MR Egger	11	0.973	1.001(0.922−1.088)	0.999	0.621
		Weighted median	11	0.569	1.014(0.967−1.063)		
		Inverse variance weighted	11	0.780	1.005(0.969−1.042)		
		Simple mode	11	0.624	1.021(0.943−1.105)		
		Weighted mode	11	0.615	1.016(0.958−1.077)		
ANKRD34B	COVID-19	MR Egger	13	0.531	0.984(0.937−1.034)	0.169	1.000
		Weighted median	13	0.798	0.996(0.967−1.026)		
		Inverse variance weighted	13	0.674	0.995(0.974−1.017)		
		Simple mode	13	0.766	1.007(0.963−1.053)		
		Weighted mode	13	0.915	0.998(0.966−1.031)		
DSCC1	T1DM	MR Egger	12	0.068	0.182(0.036−0.932)	0.729	0.076
		Weighted median	12	0.046	0.937(0.879−0.999)		
		Inverse variance weighted	12	0.020	0.943(0.898−0.991)		
		Simple mode	12	0.215	0.937(0.850−1.032)		
		Weighted mode	12	0.232	0.937(0.847−1.036)		
DSCC1	COVID-19	MR Egger	12	0.667	0.725(0.174−3.015)	0.044	0.721
		Weighted median	12	<0.001	0.919(0.882−0.958)		
		Inverse variance weighted	12	0.006	0.946(0.910−0.984)		
		Simple mode	12	0.011	0.919(0.871−0.970)		
		Weighted mode	12	0.007	0.919(0.874−0.966)		
T1DM	COVID-19	MR Egger	78	0.277	0.987(0.964−1.010)	<0.001	0.811
		Weighted median	78	0.109	0.984(0.966−1.004)		
		Inverse variance weighted	78	0.146	0.989(0.975−1.004)		
		Simple mode	78	0.148	0.976(0.944−1.008)		
		Weighted mode	78	0.071	0.985(0.969−1.001)		
COVID-19	T1DM	MR Egger	7	0.726	1.200(0.458−3.145)	0.010	0.949
		Weighted median	7	0.434	1.111(0.853−1.447)		
		Inverse variance weighted	7	0.343	1.164(0.850−1.594)		
		Simple mode	7	0.069	1.806(1.070−3.049)		
		Weighted mode	7	0.692	1.068(0.784−1.455)		
Fasting insulin	COVID-19	MR Egger	38	0.369	0.754(0.410−1.386)	0.545	0.163
		Weighted median	38	0.179	1.225(0.911−1.647)		
		Inverse variance weighted	38	0.179	1.146(0.940−1.397)		
		Simple mode	38	0.786	1.092(0.579−2.060)		
		Weighted mode	38	0.615	1.145(0.679−1.930)		
COVID-19	Fasting insulin	MR Egger	7	0.636	1.035(0.905−1.185)	0.035	0.924
		Weighted median	7	0.170	1.027(0.989−1.066)		
		Inverse variance weighted	7	0.114	1.028(0.993−1.065)		
		Simple mode	7	0.629	0.982(0.916−1.053)		
		Weighted mode	7	0.138	1.067(0.991−1.148)		

Figure 3. Forest plot for the causality of ANKRD34B and DSCC1 on T1DM and COVID-19, the bidirectional causality between T1DM and COVID-19, and the bidirectional causality between fasting insulin and COVID-19. ANKRD34B = ankyrin repeat domain 34B, CI = confidence interval, COVID-19 = coronavirus disease 2019, DSCC1 = DNA replication and sister chromatid cohesion 1, MR = Mendelian randomization, OR = odds ratio, SNP = single nucleotide polymorphism, T1DM = type 1 diabetes mellitus.

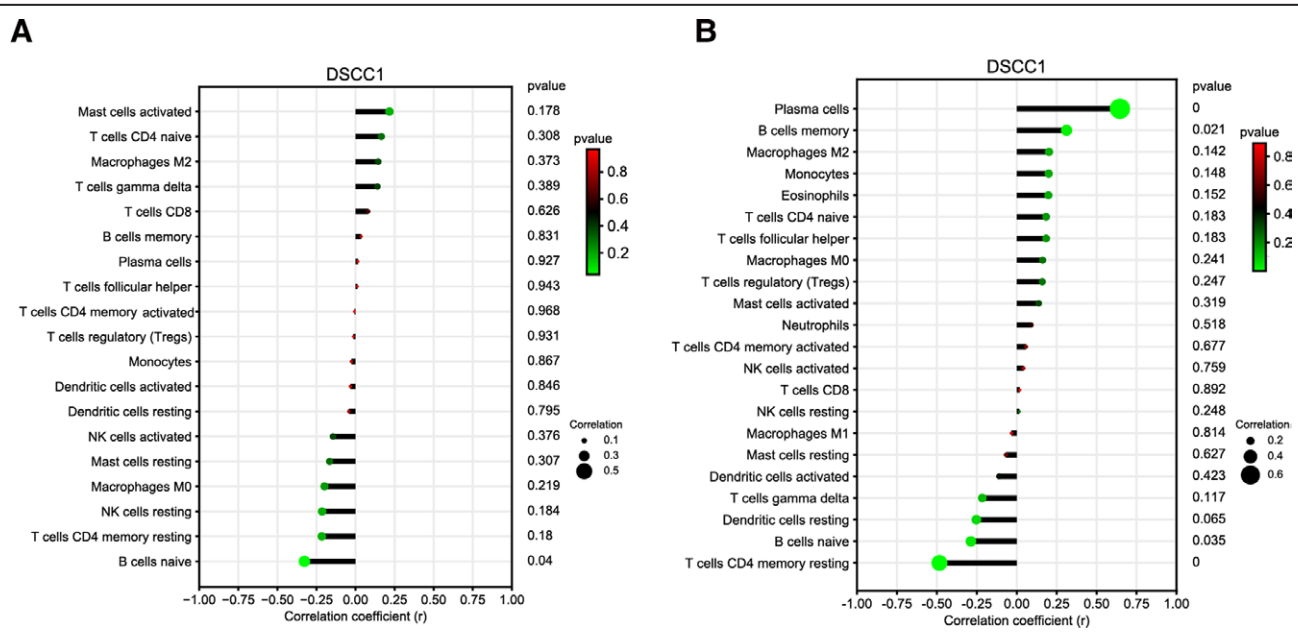

Figure 4. Correlation between DSCC1 with immune infiltrating cells in T1DM (A) and COVID-19 (B). DSCC1 = DNA replication and sister chromatid cohesion 1.

species (ROS) and nicotinamide adenine dinucleotide phosphate act as important signaling molecules in the oxidoreductive process, which is essential for the survival of the organism. Under the circumstances of immune dysregulation, mitochondrial ROS are involved in T1DM pancreatic beta cell damage.[34]. SARS CoV protein affects mitochondrial membrane potential and mitochondrial autophagy by increasing ROS levels, which may be a key factor in the outcome of SARS-CoV infection.[35]

Additionally, reduced nicotinamide adenine dinucleotide phosphate increases susceptibility to SARS-CoV-2 infection, causing disruption of redox homeostasis and contributing to severe pneumonia and death.[36] Microtubules (MTs), as key structures for intracellular material transport and maintenance of cellular morphology, are frequently hijacked by viruses during viral infections, including SARS-CoV-2.[37] Microtubule dynamics and microtubule-based motility are also involved in pancreatic beta cell autophagy in T1DM.[38] Furthermore, herpes simplex virus (HSV) infection may be an independent predictive risk factor for T1DM.[39] Additionally, COVID-19 oral mucosal changes are associated with herpes simplex virus type 1 (HSV1) reactivation.[40]

The causal relationship between T1DM, fasting insulin, and COVID-19 was then explored by MR analysis, which did not reveal a causal relationship. The current study was conducted in a European population and is consistent with previous clinical observations.[1] MR was also used to identify genes that were causally associated with both diseases as a means of exploring the mechanism of comorbidity of the 2 diseases. The DSCC1 gene was causally associated with both diseases, suggesting that the role of DSCC1 expression in the pathogenesis of comorbidities of these 2 diseases should not be ignored.

The potential role of DSCC1 in the comorbidity of T1DM and COVID-19 is explored here. Previous studies on DSCC1 have focused mostly on tumor diseases, and DSCC1 may be closely related to basic cell biological processes such as cell cycle regulation, chromosome stability, DNA replication, and cell division.[41] DSCC1 has antiapoptotic effects.[42] In T1DM, the main mechanism of decreased pancreatic beta cell mass is increased beta cell apoptosis.[43] Similarly, SARS-CoV-2 infection triggered apoptosis in a variety of cell types, including alveolar type 1 and type 2 cells, vascular endothelial cells, macrophages, and T cells, in infected nonhuman primate lungs.[44] Similarly, SARS-CoV-2 infection triggered apoptosis in a variety of cell types, including alveolar type 1 and type 2 cells, vascular endothelial cells, macrophages, and T cells, in infected nonhuman primate lungs.

Since immune disorders are involved in both diseases,[45,46] we analyzed the immune infiltration of the 2 diseases separately and found that DSCC1 expression was negatively correlated with naive B cells in both diseases; therefore, it was speculated that DSCC1 might be involved in the comorbidity of the 2 diseases by regulating the generation of naive B cells. Dysregulation of B-cell signaling can affect naive B cells, leading to the production of autoantibodies, which are involved in the pathogenesis of T1DM.[47] Naive B cells bind to the SARS-CoV-2 receptor binding domain and produce a subset of recombinant antibodies that protect the organism.[48] herefore, disruption of naive B cells could affect the interaction between viruses and hosts. In summary, naive B cells may be involved in the pathogenesis of T1DM combined with COVID-19, possibly by promoting the production of autoantibodies in T1DM patients on the one hand and in the body's defense against the SARS-CoV-2 virus on the other hand, and the role of naive B cells in comorbidities is affected by the expression of the DSCC1 gene.

Previous studies have shown a strong positive correlation between DSCC1 expression and CD8(+) T cells, CD4(+) T cells and B cells in the tumor microenvironment.[49] In contrast, the above immune cell dysregulation was also present in T1DM and COVID-19 patients. In T1DM, both CD8(+) and CD4(+) T-cell populations exhibit autoreactivity to specific islet antigen peptides.[50] In addition, T1DM autoantibody production is closely related to the production and activation of follicular helper T cells in vivo, and follicular helper T cells are a distinct subpopulation of CD4(+) T cells.[47] B-cell depletion slows disease progression in patients with newly diagnosed T1DM. Loss of tolerance of islet antigen-responsive B cells occurs early in the disease, and the number of pancreatic CD20(+) B cells correlates with beta cell loss.[51] In COVID-19, dysregulation of the immune response is also considered a very important feature of SARS-CoV-2 infection, manifested by a decrease in the absolute number of CD4(+) and CD8(+) T cells, which correlates with the severity of the disease. Fas ligand (FasL) expression on CD4(+) and CD8(+) T cells was significantly greater in COVID-19 patients than in healthy controls, resulting in apoptosis. Furthermore, FasL expression on the surface of B cells in COVID-19 lymph nodes indicated that SARS-CoV-2 promotes B-cell apoptosis.[44] It is inferred that DSCC1 causes the loss of pancreatic beta cell function and autoantibody production by interfering with CD8(+) T cells, CD4(+) T cells and B cells, which are immune cells, while promoting apoptosis and exacerbating the severity of COVID-19.

DSCC1 expression is associated with p53 and β-catenin in breast cancer,[52] and both p53 and β-catenin signaling are associated with both T1DM and COVID-19. Studies have shown that p53 accumulates in patients with T1DM as well as in rat models of T1DM.[53] Moreover, in T1DM, intervention with p53 affects T-cell apoptosis and influences pancreatic beta-cell function.[54] In COVID-19, the p53 protein directly reduces epithelial cell proliferation and differentiation, thereby increasing the severity of the disease.[55] Increased levels of p-β-catenin have hypoglycemic and antioxidant effects and protect the kidneys of T1DM rats from damage and fibrosis.[56] Activation of p-β-catenin by Wnt ligands inhibited alveolar macrophage proliferation and stemness and promoted inflammatory activity. The p-β-catenin-HIF-1α axis is conserved in human alveolar macrophages and enhances macrophage inflammation in patients with COVID-19.[57] Overall, we hypothesize that DSCC1 regulates p53 expression and β-catenin signaling in both diseases and mediates the onset of comorbidities in both diseases.

Despite providing novel insights into the genetic association between T1DM and COVID-19, this study has several limitations. First, although we only conducted our study in a European population, which limits the possibility of generalizing our study to other populations, our conclusions are consistent with clinical observations in European populations.[1] If data from other racial populations are available, it would be best to go ahead and do more studies to explore other races and populations. Second, to determine the appropriate number of SNPs, we relaxed the threshold of P ($P < 1 \times 10^{-5}$), but we verified the robustness of the MR statistics by sensitivity analysis. Third, if this study could be combined with clinical validation, more evidence could be added to the conclusions. Nevertheless, our study elucidated the association between T1DM and COVID-19 at the genetic level for the first time by combining bioinformatics and MR, which previous studies have not addressed. This study provides new insights for exploring the relationship between these 2 diseases and provides valuable information for investigating their underlying mechanisms.

5. Conclusions

In conclusion, this study highlights the potential role of DSCC1 in the comorbidity of T1DM and COVID-19. Although a causal relationship between the 2 diseases was not established through Mendelian randomization analysis, the differential expression of DSCC1 in patients with both conditions suggests a potential mechanistic link. Our findings suggest that DSCC1, through its influence on immune cell function and cellular signaling pathways, may contribute to the development of comorbidities by affecting processes such as pancreatic beta cell apoptosis, autoantibody production, and immune dysregulation. This finding opens new avenues for understanding the etiology, screening, and management of these comorbidities. However, to fully elucidate the underlying pathophysiological mechanisms, large-scale randomized controlled trials and basic experimental studies are necessary to validate these findings. Further investigation of the

specific role of DSCC1 and the complex interplay of immune and cellular processes in both T1DM and COVID-19 is crucial for developing effective therapeutic strategies to address this growing public health concern.

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