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ORIGINAL RESEARCH

Identifying the Genetic Associations Between Diabetes Mellitus and the Risk of Vitiligo

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Purpose: While increasing observational studies have suggested an association between diabetes mellitus (DM) and vitiligo, the causal relationship and possible mechanism remain unclear.

Methods: Publicly accessible genome-wide association study (GWAS) was utilized to conduct a bidirectional two-sample Mendelian randomization (MR) analysis. GWAS data for diabetes and vitiligo were obtained from the UK Biobank Consortium (20203 cases and 388756 controls) and the current GWAS data with largest cases (GCST004785, 4680 cases and 39586 controls) for preliminary analysis, respectively. Inverse variance weighting (IVW) was used as the main analysis method. Several sensitivity analyses were utilized to test the pleiotropy or heterogeneity. To explore the possible mechanism of gene-generating effects represented by the final instrumental variables in the analysis, enrichment analysis was conducted using the DAVID and STRING database.

Results: IVW method showed a significant genetic causal association between DM and vitiligo (OR = 1.20, 95% CI: 1.08–1.33, P_{IVW} = 0.0009). Diabetes subtype analysis showed that T2D (type 2 diabetes) were associated with an increased risk of vitiligo (OR = 1.13, 95% CI: 1.00–1.27, P_{IVW} = 0.0432). Sensitivity analysis further confirmed the robustness of the results. The enrichment analysis revealed that the genetic inducing effects of diabetes mellitus on vitiligo were primarily about pancreatic secretion and protein digestion and absorption pathway.

Conclusion: Our findings provide genetic evidence that there is a notable association between T2D and an elevated risk of vitiligo in European populations. This result may explain why the co-presentation of T2D and vitiligo is often seen in observational studies, and emphasize the significance of vigilant monitoring and clinical evaluations for vitiligo in individuals diagnosed with T2D. The aberrant glucose and lipid metabolism and the primary nutrient absorption disorder of vitiligo brought on by diabetes may be the potential mechanisms behind this association.

Keywords: diabetes mellitus, type 2 diabetes, vitiligo, Mendelian randomization

Introduction

With an approximate global prevalence of 0.5% ~ 2.0%,[1] vitiligo is an acquired disorder of depigmentation defined by the destruction and disappearance of epidermal melanocytes. Diabetes mellitus (DM) is a chronic metabolic disease characterized by impaired blood sugar regulation. These patients currently bear a great burden because both of them are challenging to fully recover from. However, their comorbidity is currently being supported by an increasing amount of evidence. According to a recent retrospective study based on extensive national clinical databases of the United Kingdom, DM is the most frequent vitiligo complication.[2] To avoid their comorbidities and lessen the burden on patients, it is evident that determining their causal relationships is beneficial.

There are two main types of DM: Type 1 diabetes (T1D) and type 2 diabetes (T2D). Although both of them belong to the chronic disease caused by loss of functional β-cell mass, the pathogenesis and epidemiological characteristics of them are quite different. Basic pathogenic differences exist in the two forms of diabetes mellitus: T1D is immune mediated,

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while T2D is mediated by metabolic mechanisms.[3] The incidence of T1D is much lower than that of T2D, and the age of onset is usually earlier. The prevalence of antibody-mediated auto-immune disease including auto-immune thyroid disease, celiac disease and vitiligo is high among type 1 diabetes patients.[4] However, the clear causal relationship between the complex immune regulation and vitiligo remains uncertain.

The rise of the field of immune metabolism provides a new direction for the study of immune diseases. Metabolic homeostasis is the basic regulator of immune response in tissues and organs.[5] Researches have demonstrated the connection between a number of immune skin conditions including psoriasis and lichen planus, and metabolic disorders such as diabetes, hyperlipidemia and obesity.[6–9] There was a correlation between DM and vitiligo, according to the findings of a meta-analysis of the pertinent studies on the condition in conjunction with metabolic disorders.[10] In addition, some studies reported that lipid-lowering medications could reverse the depigmentation of vitiligo,[11,12] suggesting that the disorder of glucose and lipid metabolism was involved in the disease process of vitiligo. Therefore, it is plausible to hypothesize a potential causal association between DM and vitiligo. Furthermore, T2D, which is more metabolically related, may have a greater correlation than T1D.

Mendelian randomization (MR) is a novel method for determining potential causality and confounding biases using genetic variants that are substantially related to exposure as instrumental variables (IVs).[13] To specifically investigate the potential causal relationship between diabetes and vitiligo, bidirectional MR was utilized in this study. The use of IVs in MR allows for the likely causal relationships between an exposure and a disease outcome to be inferred, and the bidirectional analysis of the exchange between exposure and outcome can further enhance the reliability of the conclusions. MR's strength is its utilization of the genotypes' random distribution at birth, which helps minimize confounding variables that frequently muddy the waters of interpretation in observational studies. It is well known that MR is useful in examining the potential causal relationships between diabetes and a variety of illnesses, including cancers.[14]

To ascertain whether DM is causally related to vitiligo, we therefore performed a bidirectional MR analysis, and we anticipate that our findings will add to the body of knowledge regarding the etiology, prophylaxis and management of vitiligo.

Materials and Methods

Study Design

MR is a novel method for determining causes and confounding biases using genetic variants that are substantially related to exposure as IVs. Publicly accessible genome-wide association study (GWAS) was utilized to conduct a bidirectional two-sample MR analysis. Inverse variance weighting (IVW) was used as the main analysis method. Several sensitivity analyses (Cochran's Q-test, leave-one-out analyses and MR-PRESSO) were applied to test pleiotropy or heterogeneity. For visual aids, refer to Figure 1a for an overview of the study design and Figure 1b for a detailed representation of the bidirectional two-sample MR study.

Data Sources Exposure

The GWAS data utilized for diabetes mellitus analysis were sourced from the UK Biobank applying scalable and accurate implementation of Generalized mixed model (SAIGE) (GWASID: ukb-saige-250), including 20203 cases and 388756 controls, and its two subtypes: type 1 diabetes (GWASID: ukb-saige-250.1, 2660 cases and 388756 controls), type 2 diabetes (ukb-saige-250.2, 18945 cases and 388756 controls). GWAS data for vitiligo were retrieved from the reported cohort of largest vitiligo cases (GCST004785, 4680 cases and 39586 controls). All the participants were of European ancestry.

Instrumental Variable Selection

To investigate potential associations between diabetes and vitiligo, it is necessary to select valid IVs that satisfy three key assumptions (Figure 1a): (1) the correlation hypothesis, (2) the exclusivity hypothesis, and (3) the independence assumption. (4) We selected single nucleotide polymorphisms (SNPs) as IVs up to the genome-wide significance

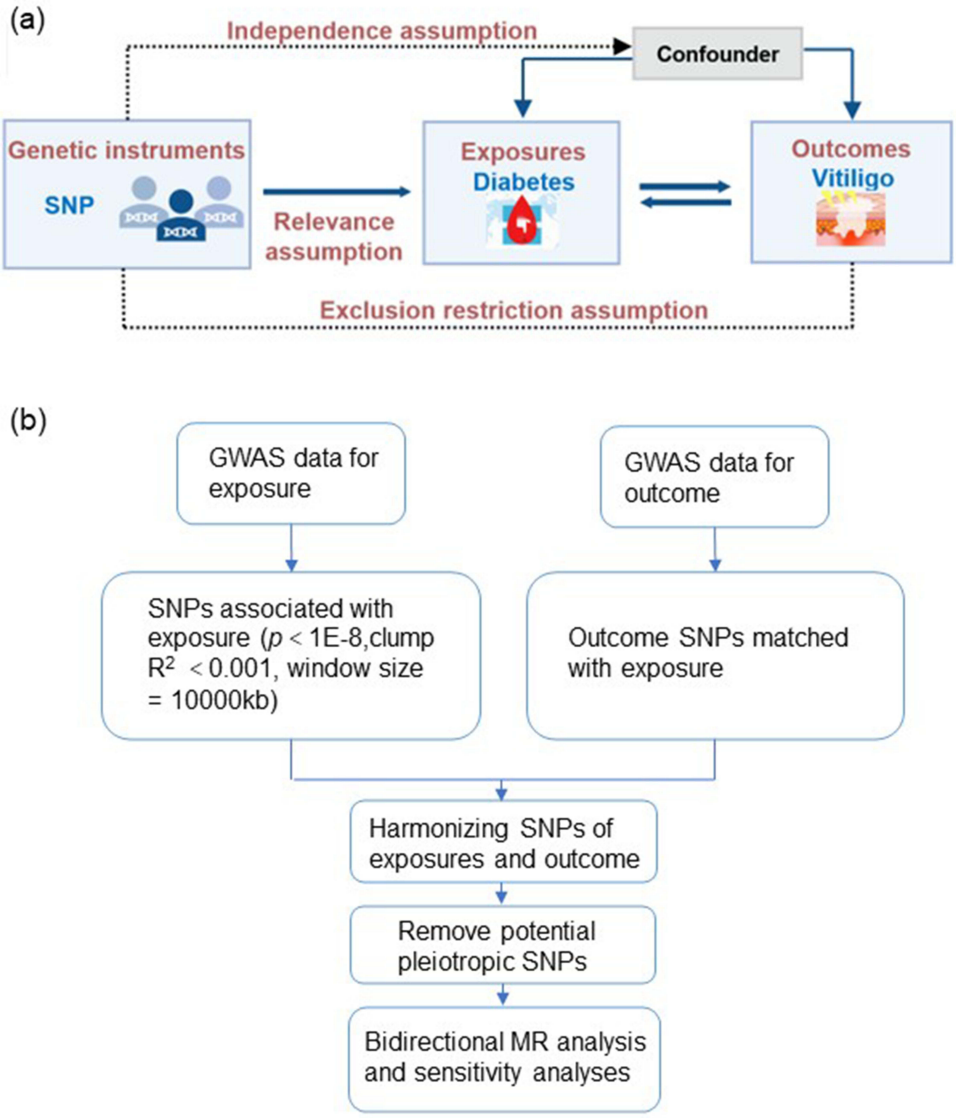

Figure 1 (**a**) An overview of the study design. (**b**) comprehensive schematic representation of the bidirectional two-sample MR estimation.
Abbreviations: MR, Mendelian randomizations; SNPs, single nucleotide polymorphisms.

threshold ($P < 5\times10^{-8}$) (If the amount of SNP is too small, $P< 5\times10^{-5}$). (5) In order to verify the independence of every single SNP, we utilized a clumping window width (kb) of 10000 and a linkage disequilibrium (LD) factor (r2) of 0.001. (6) Subsequently, we extracted information on SNPs associated with diabetes in vitiligo or vitiligo in diabetes. The minor allele frequency (MAF) was set at 0.01 and missing SNPs were eliminated.

We adopted strict inclusion and exclusion criteria for SNPs by evaluating the potential influence of confounding factors, and used Phen Scanner V2 to determine the trait of each SNP. If SNPs showed associations with known confounders of diabetes with vitiligo, these were excluded from the analysis. Seven SNPs ("rs1613299", "rs515071", "rs34715063", "rs780093", "rs6062322", "rs4804833", "rs4688760") were excluded from the final SNPs used for MR analysis (diabetes in vitiligo). "rs1613299", "rs515071" and "rs34715063" were the three SNPs with the greatest heterogeneity (P<0.05), and were excluded as outliers. "rs780093" had the most complex secondary phenotypes which are primarily focused on lipid metabolism was excluded as a potential confounder.[15] Several studies have shown that patients with vitiligo commonly have anemia complications,[16–18] the secondary phenotypes of "rs6062322" and

"rs4804833" are related to anemia, so they should be excluded. Similarly, several studies have suggested that insomnia may be a confounding factor in the disease of vitiligo,[19,20] so "rs4688760" should be excluded.

Eight SNPs ("rs60135207", "rs2111485", "rs706779", "rs72928038", "rs78037977", "rs11021232", "rs2111485", "rs7137828") were excluded from the final SNPs used for MR analysis (vitiligo in diabetes). "rs60135207" were the SNP with the greatest heterogeneity (P<0.05), and was excluded as outliers. "rs2111485", "rs706779", "rs72928038" and "rs78037977" are directly related to the outcome diabetes, so that they were excluded. Previous studies have shown that many diabetic patients are complicated with dyslipidemia,[21] and traits of these SNPs ("rs11021232", "rs2111485", "rs7137828") include cholesterol-related lipid metabolism abnormalities, thus they should be excluded.

Mendelian Randomization and Sensitivity Analysis

We standardized the exposure and outcome data by aligning the effect alleles to the forward strands before performing the analysis. Palindromic genetic variants were excluded from next MR analysis. We employed four distinct approaches, including IVW, MR–Egger, weighted median, and weighted mode,[22] to conduct the MR analysis and assess the associations between diabetes mellitus and vitiligo.[23] IVW MR, based on inverse variance weighting, was used as the main analysis. Cochran's Q-test was utilized to assess IVs heterogeneity, with a P value more than 0.05 indicating the absence of heterogeneity.[24] In cases where the heterogeneity test indicated the existence of heterogeneity within the analysis, the primary approach to address the heterogeneity was to utilize the random-effects model.[25] Furthermore, leave-one-out analyses were conducted by sequentially excluding each SNP and employing the IVW approach on the remaining SNPs to assess the potential impact of variants on the results. To evaluate the extent of horizontal pleiotropy, MR-PRESSO was used to aggregate the residuals for each SNP, enabling the identification of outlier SNPs contributing to overall pleiotropy.[26] IF the P value of MR-PRESSO Global Test is more than 0.05, the result is considered to have no significant horizontal pleiotropy. For each instrumental variable on exposures and outcomes, we used MR Steiger filtering to verify the direction of causality. By classifying an instrument's direction as "TRUE" if it satisfies the criteria and "FALSE" otherwise, the Steiger filtering method assumes that a valid IV should explain more variation in exposure than in outcome.[27]

Enrichment Analysis

We selected the final SNPs that were significantly associated with exposure and outcome variables and carried out gene annotation for these SNPs using the PhenoScanner V2 online tool. This led us to identify important genes for enrichment analysis. Enrichment analysis was conducted using the DAVID and STRING database.

Statistical Analysis

All MR analyses were performed using the R (version 4.3.0) computational environment [https://www.R-project.org/], utilizing the "TwoSampleMR",[28] "MVM R"[29] and "MR-PRESSO"[26] packages. The R package "forestploter" and "ggplot2" was employed to generate certain figures. Statistical significance for associations was determined using a p value threshold of less than 0.05.

Results

IVW method showed a significant genetic causal association between DM and vitiligo (OR = 1.20, 95% CI: 1.08–1.33, P_{IVW} = 0.0009). Diabetes subtype analysis showed that T2D was associated with an increased risk of vitiligo (OR = 1.13, 95% CI: 1.00–1.27, P_{IVW} = 0.0432) (Figure 2 and Table 1). The remaining negative results are shown in Figure S1. Detailed SNP information for the analysis can be found in Tables S1–S3.

Cochran's Q-test and MR-Egger regression intercept and MR-PRESSO Global Test analysis showed no significant heterogeneity or horizontal pleiotropy among the IVs (Table S1). Visual representations of these findings, including scatter diagrams and leave-one-out charts, are presented in Figure 3a and b, for the other results in Figure S2.

In bidirectional MR analysis, MR showed genetic predisposition to vitiligo not elevate the risk of developing diabetes and its two subtypes (Figures S1 and S3). Detailed SNP information for the analysis can be found in Tables S4–S6.

Exposure	Outcome	No. of SNP	Method	OR (95% CI)	P
Diabetes mellitus	Vitiligo	32	IVW	1.20 (1.08 to 1.33)	0.0009
		32	MR egger	1.44 (1.14 to 1.82)	0.0051
		32	Weighted median	1.31 (1.12 to 1.53)	0.0007
		32	Weighted mode	1.29 (1.07 to 1.55)	0.0118
Type 2 diabetes	Vitiligo	31	IVW	1.13 (1.00 to 1.27)	0.0432
		31	MR egger	1.42 (1.11 to 1.82)	0.0098
		31	Weighted median	1.26 (1.09 to 1.47)	0.0025
		31	Weighted mode	1.30 (1.09 to 1.55)	0.0057

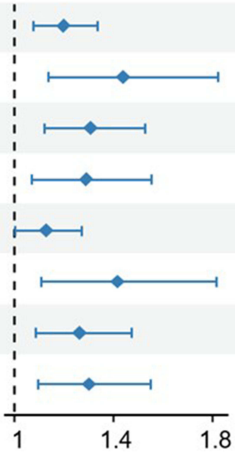

Figure 2 The positive results of MR analysis. The forest plots for the associations of genetic susceptibility between DM/T2D and vitiligo using different MR analysis.
Abbreviations: MR, Mendelian randomizations; IVW, inverse variance weighting; DM, diabetes mellitus; T2D, type 2 diabetes.

The enrichment analysis revealed that the genetic inducing effects of diabetes mellitus on vitiligo were primarily about pancreatic secretion and protein digestion and absorption pathway (represent genes include ADCY5, CTRB1, CTRB2, KCNQ1) (Figure 4a). The protein-protein interaction networks showed that the proteins expressed by these key genes have strong interaction with each other (Figure 4b and c).

Discussion

In order to lessen the computational load of Phenome-wide association studies in large cohorts, like the UK Biobank, a tractable method called SAIGE has been proposed to control for sample relatedness and case-control imbalance.[30] The DM GWAS data from the UK Biobank in our study are well suited to this approach. For the reliability of the analysis, we leveraged the vitiligo GWAS data with the largest number of cases from the cohort studies by Ying Jin et al.[31] Based on reliable and representative data sources, our bidirectional two-sample MR study firstly revealed significant associations between DM or T2D and the increased risk of vitiligo.

The autoimmune disease T1D causes the beta cells in the pancreas that produce insulin to be destroyed. According to certain research, T and B cells are essential for the pathophysiology of many diseases.[32] Early histological examination of vitiligo lesions showed a significant increase in the concentration of melanocyte-specific CD8+ cells.[33] These cells were also able to kill and pigmented cells in vitro through the generation of clones.[34] Therefore, the expansion of CD8+ T cells induced by T1D may play a mediating role in the effect of T1D on the development of vitiligo. However, this positive result was not found in our analysis, and a recently published MR study[35] based on European and Asian populations was consistent with our findings and did not find an association between T1D and vitiligo. The possible reason is that the complex immune regulation may not be a direct risk factor, or the current sample size is not large enough.

Previously, the onset of T2D is more common in the middle-aged and elder population,[36] while vitiligo is often earlier. Nonetheless, trends in T2D show an increase in prevalence along with younger age of onset,[37] and their age distribution of first events are closer than ever according to Risteys FinnGen R10 (https://r10.risteys.finngen.fi/endpoints/L12_VITILIGO). Furthermore, there is a long incubation period before the formal diagnosis of T2D,[38] and the altered physiological functions at this stage may have exacerbated the risk of vitiligo. A retrospective study[39] with a sample size of 535 indicated that patients with a family history of diabetes had a significantly higher comorbidity risk of vitiligo and diabetes (OR = 18.82, 95% CI: 7.59–46.64, P<0.001), which also suggests that genetic susceptibility to DM may play an important role in the occurrence of vitiligo. Different from previous small sample clinical studies, in this statistical analysis of a large sample, an OR value of 1.1 to 1.2 already implies a higher risk factor for a multifactorial disease like vitiligo.

Table 1 Detail Information of MR Analysis Results

Exposure	Outcome	Method	No. of SNPs	OR	OR_lci95	OR_uci95	MR-Pval	Cochran's Q-test	Egger intercept Pval	Global Test Pval
Diabetes mellitus	Vitiligo	IVW	32	1.20	1.08	1.33	0.0009	0.786	0.099	0.771
		MR Egger	32	1.44	1.14	1.82	0.0051	0.865		
		Weighted median	32	1.31	1.12	1.53	0.0007			
		Weighted mode	32	1.29	1.07	1.55	0.0118			
Type 1 diabetes	Vitiligo	IVW	62	1.05	0.99	1.10	0.0989	0.997	0.083	0.083
		MR Egger	62	1.14	1.02	1.26	0.0219	0.999		
		Weighted median	62	1.06	0.98	1.14	0.1617			
		Weighted mode	62	1.12	0.92	1.38	0.2641			
Type 2 diabetes	Vitiligo	IVW	31	1.13	1.00	1.27	0.0432	0.224	0.053	0.053
		MR Egger	31	1.42	1.11	1.82	0.0098	0.120		
		Weighted median	31	1.26	1.09	1.47	0.0025			
		Weighted mode	31	1.30	1.09	1.55	0.0057			
Vitiligo	Diabetes mellitus	IVW	28	1.01	0.99	1.03	0.3066	0.416	0.161	0.400
		MR Egger	28	0.97	0.91	1.03	0.3094	0.472		
		Weighted median	28	1.01	0.98	1.04	0.4041			
		Weighted mode	28	1.01	0.97	1.06	0.5468			
Vitiligo	Type 1 diabetes	IVW	27	1.09	1.03	1.16	0.0031	0.053	0.726	0.051
		MR Egger	27	1.06	0.88	1.28	0.5474	0.042		
		Weighted median	27	1.09	1.01	1.18	0.0299			
		Weighted mode	27	0.97	0.81	1.16	0.7299			
Vitiligo	Type 2 diabetes	IVW	28	1.01	0.98	1.03	0.5875	0.198	0.115	0.115
		MR Egger	28	0.96	0.90	1.02	0.1827	0.271		
		Weighted median	28	1.01	0.98	1.04	0.6092			
		Weighted mode	28	1.02	0.96	1.10	0.4773			

Abbreviations: IVW, Inverse variance weighted. MR, Mendelian randomization.

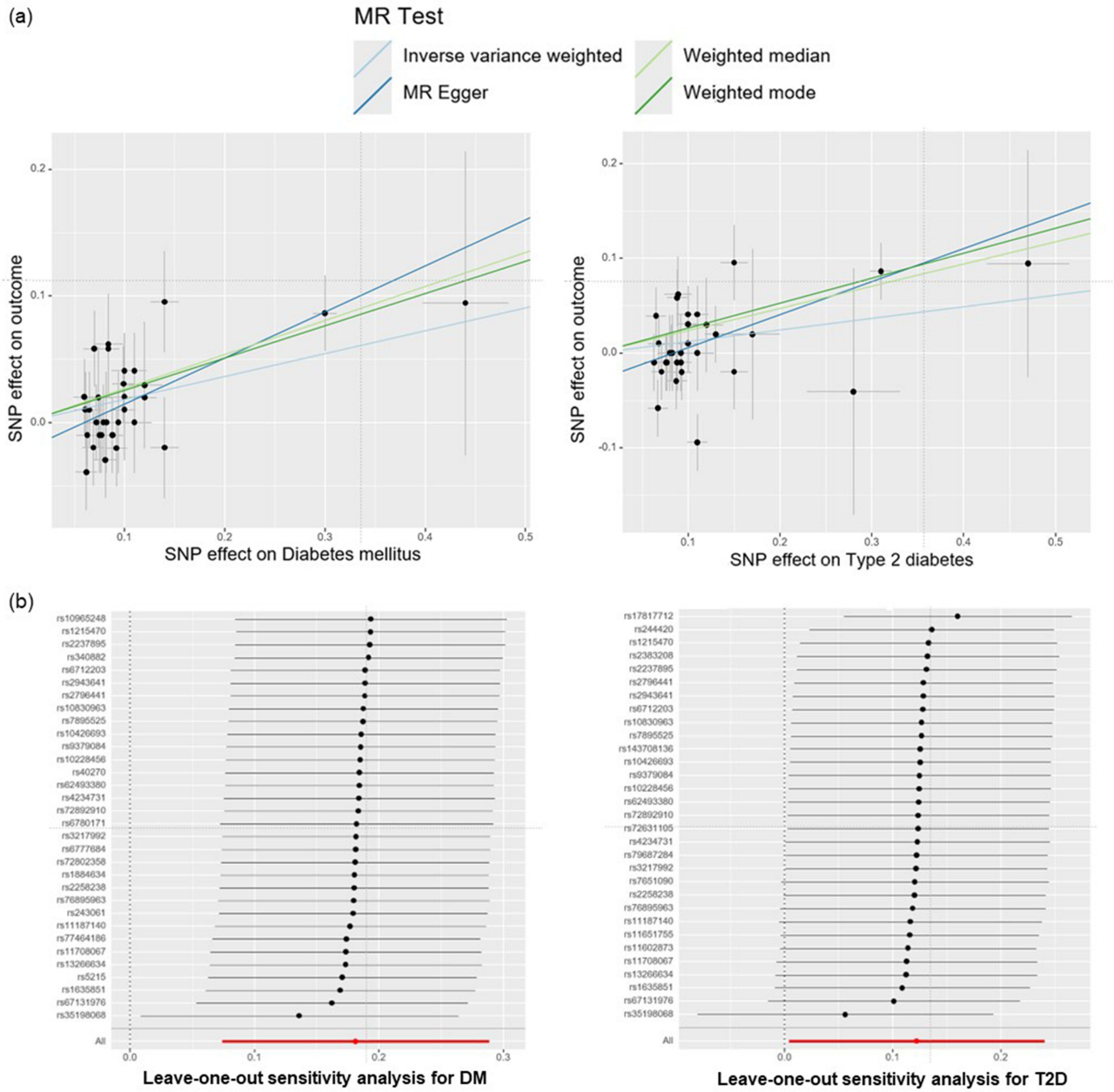

Figure 3 (**a**) scatter plots for the causality between DM/T2D and vitiligo. (**b**) leave-one-out plots for the causality between DM/T2D and vitiligo.
Abbreviations: MR, Mendelian randomizations; DM, diabetes mellitus; T2D, type 2 diabetes; SNP, single nucleotide polymorphism.

Pancreas secretes insulin and pancreatic enzymes to regulate the body's glucose and lipid metabolism. The primary result of enrichment analysis (pancreatic secretion) also supported the correlation between disrupted glucose and lipid metabolism and the risk of vitiligo, which is consistent with previous researches[10] and may help to explain why lipid-lowering drugs can reverse depigmentation of vitiligo.[11,12] Due to the high glucose environment brought on by diabetes mellitus, the body may produce more succinic acid, which then stimulates the release of inflammatory factors such as CRT, IL-1β, CXCL9, and CXCL10 by binding with the melanocyte receptor SUCNR1. This, in turn, causes CD8+T cells to migrate and become activated, which ultimately damages melanocytes through immune response.[40] Such new mechanisms can also inspire the clinical prevention and management of vitiligo, since diabetes or high blood sugar can be controlled with medications or lifestyle changes.

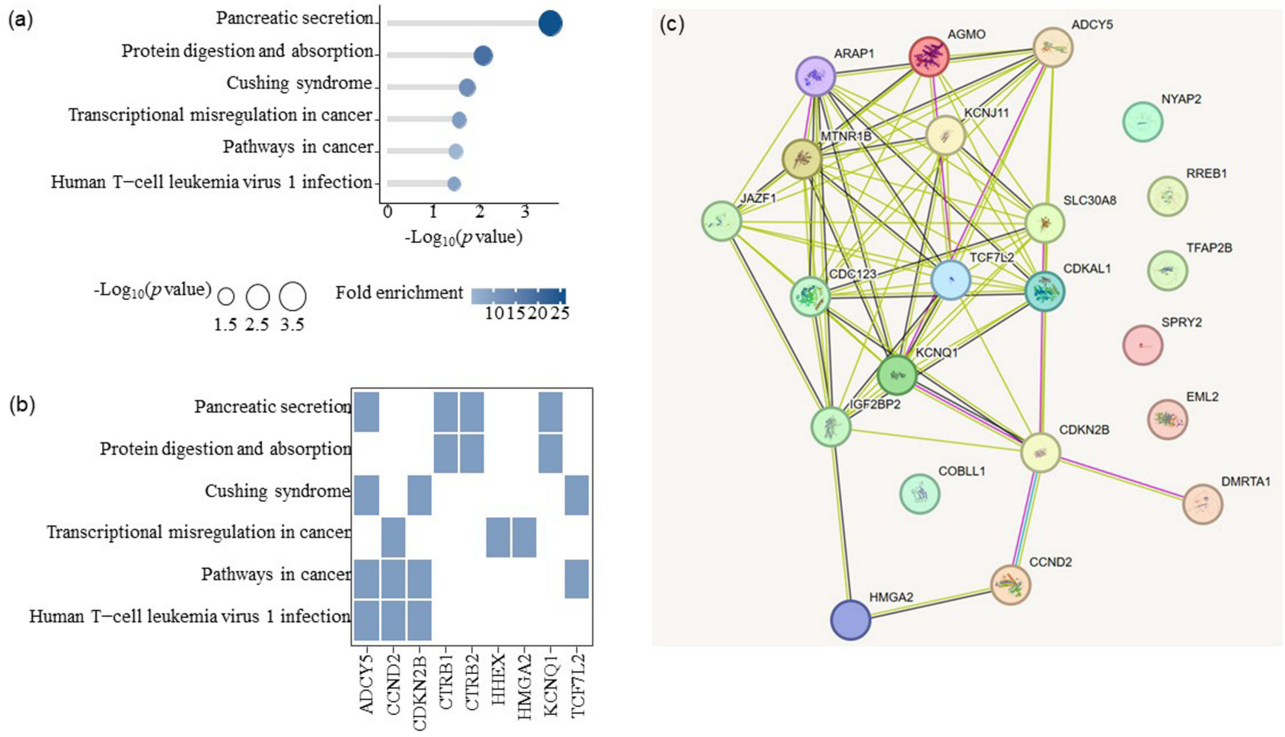

Figure 4 Enrichment analysis of SNPs for diabetes with vitiligo using the DAVID and STRING database. (**a**) the 6 KEGG-Pathway routes after enrichment analysis using the DAVID database. (**b**) the pathways enriched by important SNPs represented by the gene. (**c**) targeting genes with coding functions represented by the important SNPs, the protein-protein interaction networks (PPI) were constructed using STRING database. The nodes represent proteins, and the lines between nodes represent associations. **Abbreviations**: SNPs, single- nucleotide polymorphism; KEGG, Kyoto encyclopedia of genes and genomes.

DM is often accompanied by gastrointestinal dysfunction, significantly affecting the body's digestive function.[41] Numerous studies have demonstrated that dietary intake of micronutrients, including calcium, magnesium, zinc, potassium and vitamin D, is highly probable in individuals with diabetes and plays a significant role in the onset and progression of T2D.[42] The absorption of various nutrients plays an important role in the occurrence and development of vitiligo, and supplementing these nutrients will help the treatment of patients with vitiligo.[43,44] Based on the enrichment analysis, the abnormal protein digestion and absorption caused by T2D may directly or indirectly affect the absorption of key nutrients in the development of vitiligo including vitamins.[45] On the other hand, the occurrence and development of T2D can be prevented or controlled through diet and other means.[46] This also means that this risk factor for vitiligo can be effectively controlled at the early stage. Therefore, for patients at risk of their comorbidities, it would be beneficial to strengthen relevant dietary management.

Several limitations should be observed in this study. Firstly, there is an absolute lack of GWAS data on DM and vitiligo in non-European populations in this study. As such, extra care needs to be taken when extrapolating these results to other racial or ethnic groups. Second, even though we applied strict inclusion and exclusion criteria for SNPs, there may still be some potential confounding factors that we did not detect. Finally, even though our study sheds light on the aetiology of DM and vitiligo, we were unable to perform more subgroup analyses for the classification of DM or vitiligo due to the lack of comprehensive participant demographic and clinical data.

Conclusion

In brief, our results offer genetic proof of a significant correlation between T2D and a higher incidence of vitiligo in European populations. This finding may clarify the frequent co-occurrence of T2D and vitiligo in observational studies and highlight the need of vigilant monitoring and clinical evaluations for vitiligo in people with T2D diagnoses. The association may be explained by the primary nutrient element absorption disorder of vitiligo caused by diabetes, as well as the aberrant metabolism of glucose and lipid. Therefore, it would also seem prudent to strengthen dietary management

and monitoring of body glucose and lipid metabolism. Furthermore, we anticipate that additional research from different ethnic groups will verify our findings.

Abbreviations

DM, diabetes mellitus; IVs, instrumental variables; T2D, type 2 diabetes; SAIGE, scalable and accurate implementation of Generalized mixed model; GWAS, genome-wide association study; IVW, inverse variance-weighted; MR, Mendelian randomization; OR, odds ratio; SNP, single nucleotide polymorphism; KEGG, Kyoto encyclopedia of genes and genomes.

Data Sharing Statement

All data are available from the corresponding author by request.

Ethics Statement

This study is exempt from ethical review as per Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Beings (National Science and Technology Ethics Committee, China). The exemption is based on the use of non-harmful, non-sensitive data from open, legal databases.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

None to declare.

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