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ORIGINAL RESEARCH

From Phenotype to Molecules: Unveiling the Genetic and Immunological Bridges Between Autoimmune Diseases and Vitiligo

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Introduction: Vitiligo is an autoimmune disease characterized by the loss of skin pigmentation. This study aims to explore genetic associations between vitiligo and 21 autoimmune diseases using Mendelian randomization (MR) analysis, with a focus on identifying potential risk and protective factors.

Methods: We performed univariable and multivariable Mendelian randomization analyses to assess the causal associations between 21 autoimmune diseases and vitiligo. Confounding factors, including smoking, alcohol consumption, and Body Mass Index (BMI), were integrated into the multivariable analysis. Strongly associated single nucleotide polymorphisms (SNPs) were mapped to genes, followed by Summary-data-based Mendelian Randomization (SMR) analysis with expression Quantitative Trait Loci (eQTL) and methylation Quantitative Trait Loci (mQTL) data. Risk and protective factors were further identified by evaluating inflammatory mediators and immune cell phenotypes.

Results: The MR analysis identified seven autoimmune diseases with potential causal associations with vitiligo. However, after accounting for confounding factors, only Hashimoto's thyroiditis and type 1 diabetes maintained genetic associations with vitiligo. Gene mapping revealed 25 intersecting genes between these two diseases and vitiligo. SMR analysis confirmed *Sulfite Oxidase (SUOX)* as a protective gene across multiple tissues. Furthermore, several inflammatory factors were identified as risk factors, including C-X-C motif chemokine ligand 9 (CXCL9), C-X-C motif chemokine ligand 10 (CXCL10), Tumor Necrosis Factor (TNF), and Signaling Lymphocytic Activation Molecule (SLAM). In contrast, Osteoprotegerin (OPG) was identified as a protective factor.

Discussion: This study provides novel insights into the shared molecular mechanisms linking vitiligo with other autoimmune diseases. The identification of SUOX as a common protective gene and the discovery of specific inflammatory and immune-related factors may facilitate future therapeutic strategies.

Keywords: autoimmune diseases, causality, Mendelian randomization, sulfite oxidase, vitiligo

Introduction

Autoimmune diseases are a group of disorders characterized by the immune system erroneously attacking the body's normal tissues. This process is often due to genetic susceptibility and an imbalance in immune regulation.[1] These diseases encompass a wide range of clinical manifestations and complications, from diseases affecting specific organs such as Type 1 Diabetes and Hashimoto Thyroiditis to those impacting multiple systems across the body like Systemic Lupus Erythematosus. Vitiligo is a common, autoimmune, acquired pigmentary disorder of the skin, affecting approximately 0.5–2% of the global population.[2] While primarily characterized by the loss of skin pigment, the underlying causes of Vitiligo are far more complex than what meets the eye. The intricate interplay between genetic predisposition and immune system dysregulation may underlie the pathogenesis of autoimmune diseases and Vitiligo.

Previous studies have established a significant association between vitiligo and various autoimmune diseases. For instance, scholars from diverse geographical regions have consistently identified a link between vitiligo and Hashimoto Thyroiditis.[3–7] However, these studies also reveal inconsistencies. For instance, Rios-Duarte et al[7] reported a heightened likelihood of Primary Sclerosing Cholangitis (PSC) among Vitiligo patients compared to non-Vitiligo individuals. Conversely, a 2017 Systematic Review[8] suggested no substantial association between PSC and Vitiligo. Moreover, conflicting findings have also emerged regarding the association between Psoriasis and Vitiligo in prior research. For instance, Yen et al[9] identified an association between Psoriasis and Vitiligo through a systematic review and meta-analysis. However, a cross-sectional study conducted among a Chinese population[4] suggested no association between the two conditions. Furthermore, the precise mechanism linking Vitiligo and autoimmune diseases remains elusive. Many studies have not explored in depth the potential mechanisms underlying the comorbidity between Vitiligo and autoimmune diseases.

In recent years, Genome-Wide Association Studies (GWAS) have emerged as a powerful tool widely used to identify genetic variations associated with complex diseases across the entire genome. The genetic variants identified through GWAS may serve as new targets for disease prevention and treatment, providing a foundation for the development of novel drugs and therapeutic strategies. Previous studies have also suggested that single nucleotide polymorphisms (SNPs) related to vitiligo could provide potential genetic evidence for the links between vitiligo and other autoimmune diseases. For instance, Saevarsdottir et al[10] discovered that the SNP rs781745126 is associated with both autoimmune thyroid disease and vitiligo. Additionally, findings by Bottini[11] and Cantón[12] have revealed that SNP variations in the PTPN22 gene are simultaneously related to Type 1 diabetes and vitiligo.

In this study, we aimed to explore the potential genetic associations between vitiligo and autoimmune diseases by employing various analytical methods. Specifically, we utilized Mendelian randomization (MR), a genetic epidemiological approach that uses single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to investigate causal associations.[13] MR helps mitigate confounding biases and reverse causality effects that are common in traditional observational studies.[14] Additionally, we applied summary-data-based Mendelian randomization (SMR) to identify shared genetic loci and conducted the Heterogeneity in Dependent Instruments (HEIDI) test to determine whether the genetic associations between traits were due to shared causal variants or independent signals.[15]

Materials and Methods

Study Design

To determine the causal relationship between autoimmune diseases and Vitiligo, we conducted two-sample MR analyses using a combined dataset from genome-wide association studies (GWAS). Positive findings from the two-sample MR analyses were further subjected to multivariable MR analyses after adjusting for confounding factors. Additionally, we performed gene-based SMR analyses by mapping SNPs to genes, and MR analyses utilizing datasets of inflammatory factors and immune cells. The data used in this study were obtained from previously published research, which had obtained ethical approval from their respective committees, thus no additional ethical permission was required. The schematic diagram of the study design is illustrated in Figure 1.

Data Sources

The data can be broadly categorized into exposure data and outcome data. The outcome data related to Vitiligo is sourced from the latest and most comprehensive Finnish database, R10 version (https://www.finngen.fi/en/access_results).[16] We identified 21 autoimmune diseases potentially associated with Vitiligo through a review of relevant literature, all sourced from IEU-OpenGWAS (https://gwas.mrcieu.ac.uk/). Additionally, the original data for inflammatory factors and immune cells were obtained from the GWAScatalog database. The expression Quantitative Trait Loci and methylation Quantitative Trait Loci (eQTL and mQTL) datasets required for SMR analysis were sourced from https://yanglab.westlake.edu.cn/software/smr/. Among these, the eQTL data were derived from the CAGE[17] eQTL summary data and the V8 release of the GTEx[18] eQTL summary data, while the mQTL data were obtained from the mQTL summary data provided by McRae et al[19] For a detailed description of the GWAS data and information on the sample sizes, please refer to Supplementary Table S1.
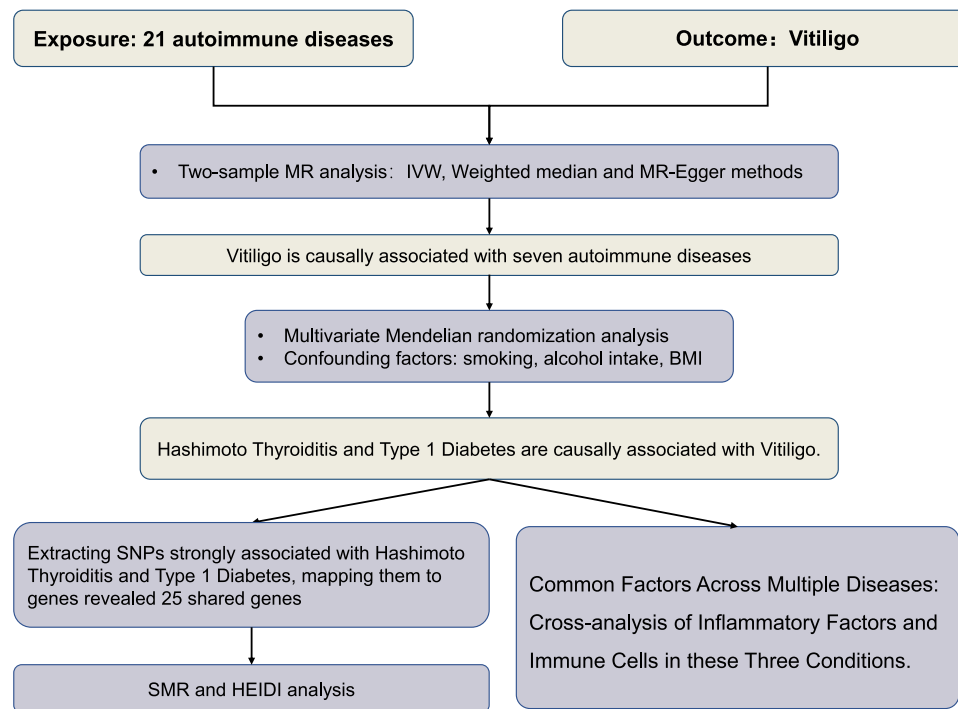
Figure 1 Study design overview.

Inclusion and Exclusion Criteria

In this study, we have focused our analysis on leveraging the most extensive and up-to-date GWAS data derived from European populations. To minimize potential ethnic biases that may confound our results, we have deliberately excluded GWAS data from non-European ancestries.

The final selection of 21 autoimmune diseases encompasses the following conditions: Celiac Disease, Hashimoto's Thyroiditis, Multiple Sclerosis, Primary Sclerosing Cholangitis, Psoriasis, Rheumatoid Arthritis, Type 1 Diabetes Mellitus, Ankylosing Spondylitis, Autoimmune Hepatitis, Crohn's Disease, Graves' Disease, Immunoglobulin A Nephropathy, Juvenile Idiopathic Arthritis, Membranous Nephropathy, Myasthenia Gravis, Polymyositis, Primary Biliary Cholangitis, Sarcoidosis, Sjögren's Syndrome, Systemic Lupus Erythematosus, and Ulcerative Colitis.

Genetic Instrumental Variable Selection

IV selection criteria in this study:

Identification of SNPs Significantly Associated with the Phenotype

Initially, we identified SNPs significantly associated with the phenotype using a stringent threshold (P<5E-08).[20] However, for some exposures, an insufficient number of SNPs (less than or equal to 2) were obtained at the threshold of 5E-08. In such cases, the threshold was adjusted to 5E-06.[21] All adjustments to the threshold are clearly noted in the Supplementary Table S1.

Removal of Linkage Disequilibrium (LD)

Removal of LD by applying quality control standards: r2 < 0.001, kb > 10,000.

Correction of Palindromic SNPs

Integration and concordance of the exposure-outcome dataset, along with correction of palindromic SNPs with an ambiguous strand based on allele frequency information.

Assessment of Instrumental Variable (IV) Strength

To evaluate the strength of the instrumental variables, we calculated the F-value. We excluded potentially weak IVs by setting a threshold (F > 10) to mitigate bias between the instrumental variables and exposure factors.[22]

Confounding Factor Screening

We screened potential confounding factors using the LDlink website (https://ldlink.nci.nih.gov/?tab=ldtrait) to be included in the multivariable MR analysis.

Two-Sample MR Analysis and Sensitivity Analysis

We utilized the "Two-Sample MR" package in R 4.1.0 software to conduct our analysis. The primary method employed was the Inverse Variance Weighted (IVW) method,[23] which calculated the odds ratio (OR) and its 95% confidence interval (CI), enabling the assessment of potential genetic associations between exposure and outcome. Supplementary analyses were also carried out using MR-Egger regression[24] and the Weighted Median Method (WME)[25] to further explore the robustness of our findings. Subsequently, sensitivity analyses were performed to ensure the validity of our results.For heterogeneity assessment, Cochran's Q test was utilized to examine SNP heterogeneity. If the resulting p-value was less than 0.05, indicating heterogeneity, a random-effects model was applied; otherwise, a fixed-effects model was used. To evaluate horizontal pleiotropy, we employed the MR-Egger method. Additionally, to address the issue of multiple testing, we utilized the Benjamini-Hochberg method, which incorporates the false discovery rate (FDR). All statistical tests employed bilateral analysis, and a significance threshold of $P<0.05$ was considered statistically significant.

Multivariable MR Analysis

Conducting a multivariable MR analysis by extracting positive results from two-sample MR analysis and incorporating confounding factors such as Body Mass Index (BMI), Current Tobacco Smoking, and Alcohol Intake Frequency. Multivariable MR analysis[26] suggests genetic associations for the identified exposures, followed by validation in an independent dataset to substantiate the conclusions.

SNP Mapping to Genes

Using the SNP2GENE module in the FUMA website (https://fuma.ctglab.nl/),[27] inputting SNPs highly correlated with positive exposure in multivariable MR analysis, and mapping them to genes at a threshold of 5e-08, resulted in 25 intersecting genes. These genes may play a crucial role in mediating autoimmune diseases and Vitiligo.

SMR Analysis

SMR analysis was utilized to validate the causal associations between genes and Vitiligo, examining them through the perspectives of eQTL and mQTL.[28] This validation across multiple tissues contributes to bolstering the reliability and generalizability of our conclusions. The HEIDI test, employing multiple SNPs within a region, served to distinguish genes associated with Vitiligo risk attributable to a shared genetic variant versus genetic linkage. Both the SMR and HEIDI tests were conducted using SMR software (version 1.3.1).

Results

The Outcomes of Instrumental Variable (IV) Selection

All SNPs included in this study are detailed in Supplementary Table S2, with F values exceeding 10. Through the LDlink website, six SNPs associated with smoking (rs11611029, rs13195040, rs1648153, rs1776616, rs4759229, rs62397561), four SNPs associated with alcohol consumption (rs13195040, rs2110451, rs2638281, rs9277654), and thirteen SNPs associated with BMI were identified (rs10797431, rs1108618, rs11875687, rs13195040, rs13415465, rs142144003, rs151233, rs2499714, rs3184504, rs35139284, rs4364506, rs62397561, rs9266775).

Results of Two-Sample MR Analysis and Sensitivity Analysis

Among 21 autoimmune diseases, we identified a causal relationship between Vitiligo and seven autoimmune diseases (Celiac Disease, Hashimoto Thyroiditis, Multiple Sclerosis, Primary Sclerosing Cholangitis, Psoriasis, Rheumatoid
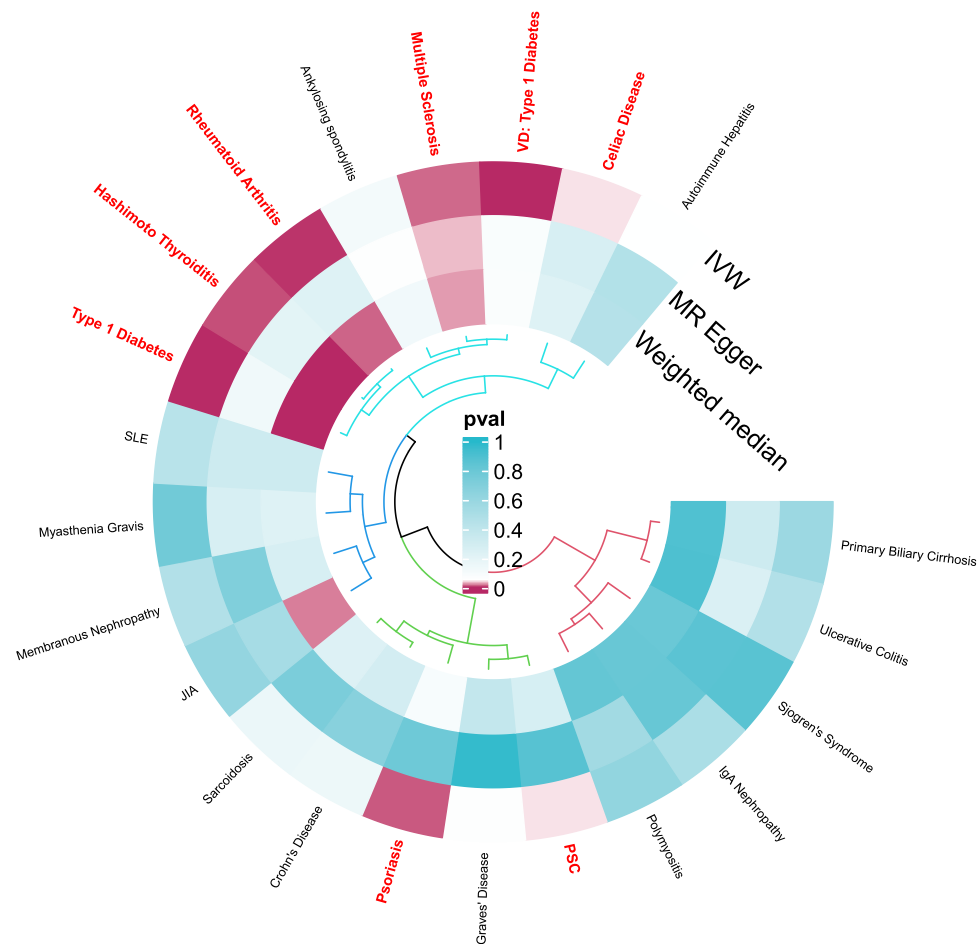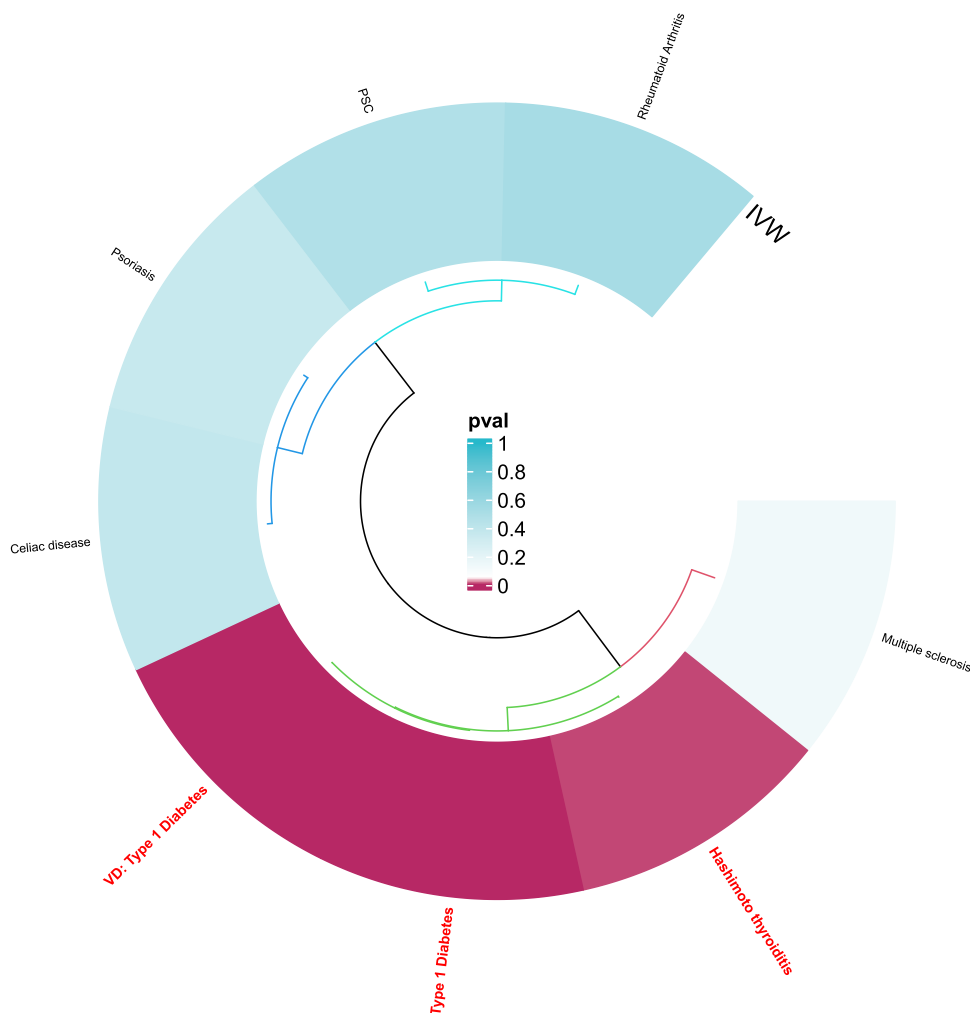
Figure 2 The circular diagram illustrates the genetic associations between 21 autoimmune diseases and Vitiligo, with exposures reaching significant levels highlighted in red. The two-sample Mendelian Randomization analysis suggests a genetic associations between vitiligo and the following seven diseases: Celiac Disease, Hashimoto Thyroiditis, Multiple Sclerosis, Primary Sclerosing Cholangitis, Psoriasis, Rheumatoid Arthritis, and Type 1 Diabetes. VD, Validation Dataset.

Arthritis, Type 1 Diabetes) (Figure 2). After FDR correction, "Celiac Disease" and "Primary Sclerosing Cholangitis" no longer showed significant p-values, suggesting a potential causal relationship with Vitiligo. The remaining five diseases are considered to have a significant causal relationship with Vitiligo. The detailed results of the two-sample MR analysis can be found in Supplementary Table S3. During sensitivity analysis, no evidence of horizontal pleiotropy was detected. Although some analyses exhibited heterogeneity, a random effects model was employed in such cases. For a comprehensive overview of these results, please refer to Supplementary Table S4.

Results of Multivariable MR Analysis

After adjusting for confounding factors such as smoking, alcohol consumption, and BMI, among the seven autoimmune diseases, only Hashimoto Thyroiditis and Type 1 Diabetes remained causally associated with Vitiligo, with p-values still below 0.05 after FDR correction (Figure 3). We also established a validation set to confirm the relationship between Hashimoto Thyroiditis and Type 1 Diabetes with Vitiligo. Unfortunately, we could not find an additional large dataset for Hashimoto Thyroiditis, so we only validated Type 1 Diabetes. The results from the validation set demonstrated a significant causal relationship between Type 1 Diabetes and Vitiligo, confirmed by both two-sample MR analysis and multivariable MR analysis. The detailed results of the multivariable MR analysis can be found in Supplementary Table S5.

Figure 3 The circular diagram illustrates the true genetic associations between seven autoimmune diseases with positive Mendelian analysis in two samples, after controlling for confounding factors, and Vitiligo, with exposures reaching significant levels highlighted in red. Multivariable Mendelian Randomization analysis suggests that, after adjusting for potential confounders, there is a significant genetic association between Hashimoto Thyroiditis and Type 1 Diabetes and vitiligo.
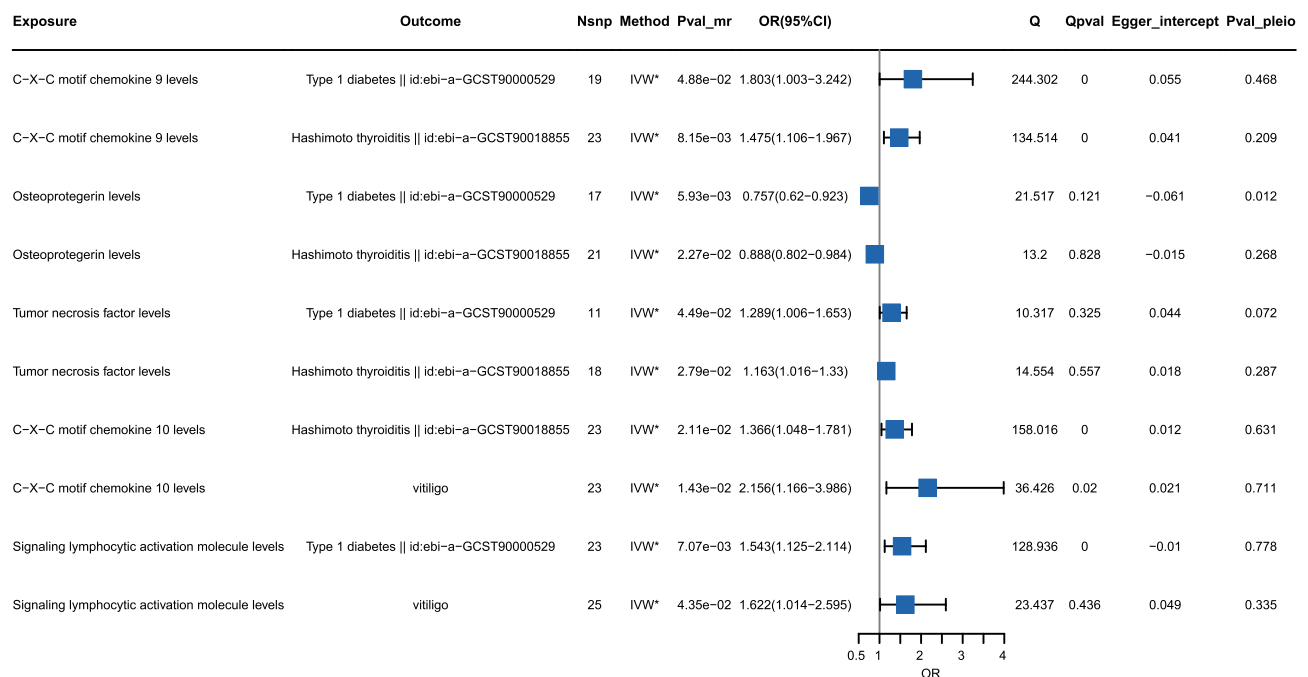**Abbreviation**: VD, Validation Dataset.

Results of SNP Mapping to Genes

Using the FUMA website, we mapped strongly correlated SNPs from Hashimoto Thyroiditis and Type 1 Diabetes to genes, resulting in 25 intersecting genes: ACAD10, ALDH2, ATXN2, ASCC2, BACH2, BRAP, CDK2, CTLA4, ERBB3, HECTD4, HORMAD2, ICOS, MAPKAPK5, MTMR3, NAA25, PHTF1, PMEL, PTPN22, RAB5B, RPL6, RPS26, RSBN1, SH2B3, SUOX, and TRAFD1.

MR Analysis of 91 Inflammatory Factors and 731 Immune Cell Phenotypes

In our investigation, we analyze 91 inflammatory factors and 731 immune cell phenotypes as potential influencing factors. We designate Hashimoto Thyroiditis, Type 1 Diabetes, and Vitiligo as the outcomes of interest. Our objective is to identify shared pathogenic or protective factors and immune cell phenotypes across these three diseases, with the goal of elucidating the potential mechanisms contributing to the comorbidity of autoimmune diseases and Vitiligo. The results indicate that C-X-C motif chemokine 9 (CXCL9) and Tumor necrosis factor may be common pathogenic factors for Hashimoto Thyroiditis and Type 1 Diabetes, while Osteoprotegerin is their common protective factor. However, no significant causal relationship was found between these three factors and Vitiligo. Additionally, C-X-C motif chemokine 10 (CXCL10) is a common pathogenic factor for Hashimoto Thyroiditis and Vitiligo, while Signaling lymphocytic activation molecule is a common pathogenic factor for Type 1 Diabetes and Vitiligo. Please refer to Figure 4 for details.

Exposure	Outcome	Nsnp	Method	Pval_mr	OR(95%CI)		Q	Qpval	Egger_intercept	Pval_pleio
C−X−C motif chemokine 9 levels	Type 1 diabetes || id:ebi−a−GCST90000529	19	IVW*	4.88e−02	1.803(1.003−3.242)		244.302	0	0.055	0.468
C−X−C motif chemokine 9 levels	Hashimoto thyroiditis || id:ebi−a−GCST90018855	23	IVW*	8.15e−03	1.475(1.106−1.967)		134.514	0	0.041	0.209
Osteoprotegerin levels	Type 1 diabetes || id:ebi−a−GCST90000529	17	IVW*	5.93e−03	0.757(0.62−0.923)		21.517	0.121	−0.061	0.012
Osteoprotegerin levels	Hashimoto thyroiditis || id:ebi−a−GCST90018855	21	IVW*	2.27e−02	0.888(0.802−0.984)		13.2	0.828	−0.015	0.268
Tumor necrosis factor levels	Type 1 diabetes || id:ebi−a−GCST90000529	11	IVW*	4.49e−02	1.289(1.006−1.653)		10.317	0.325	0.044	0.072
Tumor necrosis factor levels	Hashimoto thyroiditis || id:ebi−a−GCST90018855	18	IVW*	2.79e−02	1.163(1.016−1.33)		14.554	0.557	0.018	0.287
C−X−C motif chemokine 10 levels	Hashimoto thyroiditis || id:ebi−a−GCST90018855	23	IVW*	2.11e−02	1.366(1.048−1.781)		158.016	0	0.012	0.631
C−X−C motif chemokine 10 levels	vitiligo	23	IVW*	1.43e−02	2.156(1.166−3.986)		36.426	0.02	0.021	0.711
Signaling lymphocytic activation molecule levels	Type 1 diabetes || id:ebi−a−GCST90000529	23	IVW*	7.07e−03	1.543(1.125−2.114)		128.936	0	−0.01	0.778
Signaling lymphocytic activation molecule levels	vitiligo	25	IVW*	4.35e−02	1.622(1.014−2.595)		23.437	0.436	0.049	0.335

OR scale: 0.5 1 2 3 4

Figure 4 The forest plot illustrates the inflammatory factors that have shared pathogenic or protective effects with at least two diseases.

Among the 731 immune cell phenotypes, only CD25 on IgD-CD38-B cells is a common risk factor for these three diseases. Meanwhile, CD64 on CD14-CD16, HLA DR on plasmacytoid Dendritic Cell and Dendritic Cell are common risk factors for Hashimoto thyroiditis and Vitiligo. Please refer to Figure 5 for details. The complete MR results of inflammatory factors and immune cells are detailed in Supplementary Tables S6-S11.
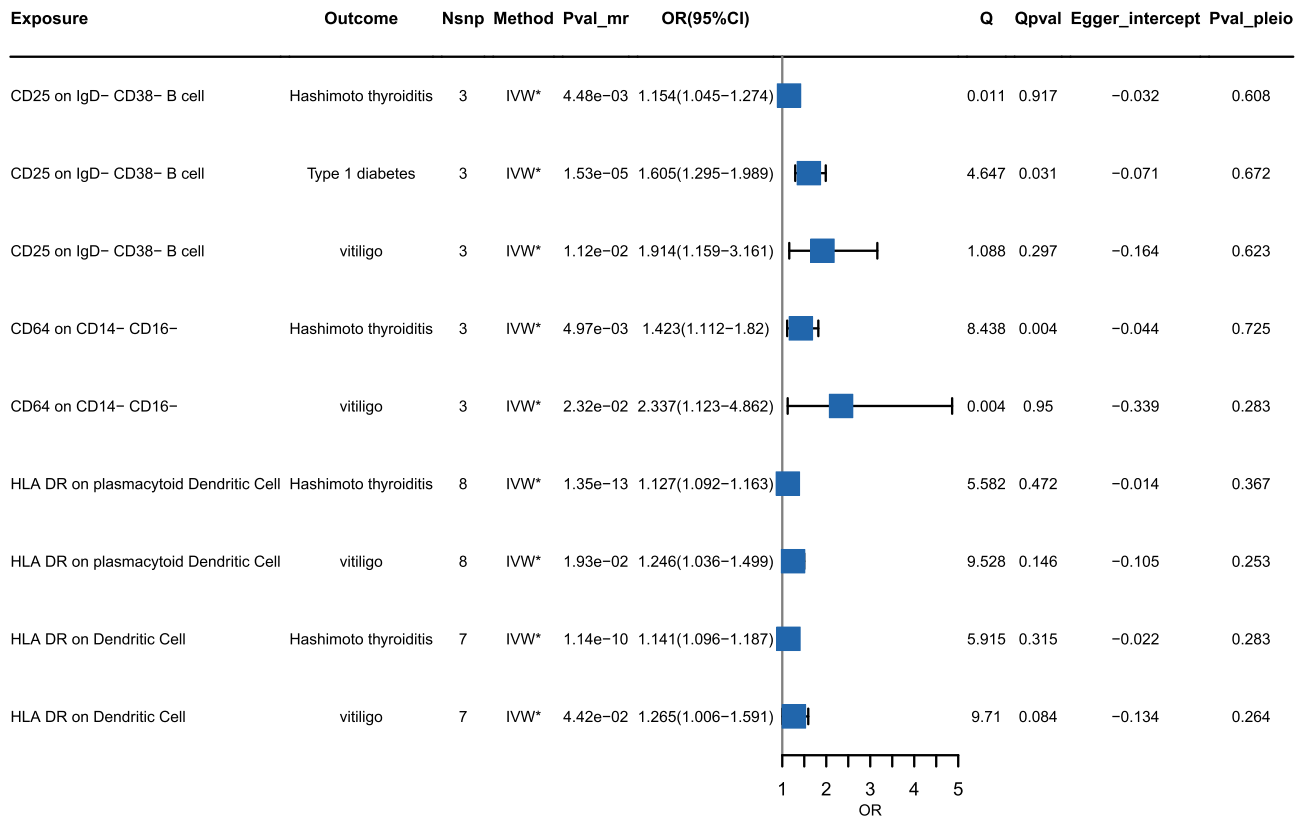
Results of SMR Analysis

To explore the potential causal relationship between the 25 intersecting genes and Vitiligo, we performed SMR analysis using eQTL and mQTL data. The findings suggest that Sulfite Oxidase (SUOX) might serve as a shared protective gene for these three conditions, a conclusion validated across various tissues. For additional information, please consult Figure 6 and Supplementary Table S12-S15.

Discussion

In this study, we systematically evaluated the causal relationship between various autoimmune diseases and Vitiligo through MR analysis. At the same time, by utilizing eQTL and mQTL data, inflammation factors, and immune cell data, we thoroughly explored the underlying mechanisms of comorbidity and obtained some important findings.

Among the 21 autoimmune diseases, we ultimately found that only Hashimoto Thyroiditis and Type 1 Diabetes were causally related to Vitiligo. This finding is consistent with previous observational studies but also presents some differences. After adjusting for smoking, alcohol consumption, and BMI, the genetic associations between Celiac Disease, Multiple Sclerosis, PSC, Psoriasis, and Rheumatoid Arthritis and Vitiligo are no longer significant. This resolves the controversy in previous studies regarding the existence of genetic associations between these five diseases and Vitiligo.[7,9,29–31] We hypothesize that the previous clinical studies claiming a significant relationship between these five diseases and Vitiligo may have yielded biased results due to uncorrected confounding factors.

The relationship between Vitiligo and autoimmune thyroid diseases has become a clinical consensus. The International Vitiligo Task Force recommends screening Vitiligo patients for anti-thyroid antibodies and thyroid function.[32] Our study strongly confirms this view: genetic prediction of Hashimoto Thyroiditis increases the risk of Vitiligo. However, we did not find a causal relationship between Graves' disease and Vitiligo. This may suggest that thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TGAb) are more important factors for the onset of

Exposure	Outcome	Nsnp	Method	Pval_mr	OR(95%CI)		Q	Qpval	Egger_intercept	Pval_pleio
CD25 on IgD− CD38− B cell	Hashimoto thyroiditis	3	IVW*	4.48e−03	1.154(1.045−1.274)		0.011	0.917	−0.032	0.608
CD25 on IgD− CD38− B cell	Type 1 diabetes	3	IVW*	1.53e−05	1.605(1.295−1.989)		4.647	0.031	−0.071	0.672
CD25 on IgD− CD38− B cell	vitiligo	3	IVW*	1.12e−02	1.914(1.159−3.161)		1.088	0.297	−0.164	0.623
CD64 on CD14− CD16−	Hashimoto thyroiditis	3	IVW*	4.97e−03	1.423(1.112−1.82)		8.438	0.004	−0.044	0.725
CD64 on CD14− CD16−	vitiligo	3	IVW*	2.32e−02	2.337(1.123−4.862)		0.004	0.95	−0.339	0.283
HLA DR on plasmacytoid Dendritic Cell	Hashimoto thyroiditis	8	IVW*	1.35e−13	1.127(1.092−1.163)		5.582	0.472	−0.014	0.367
HLA DR on plasmacytoid Dendritic Cell	vitiligo	8	IVW*	1.93e−02	1.246(1.036−1.499)		9.528	0.146	−0.105	0.253
HLA DR on Dendritic Cell	Hashimoto thyroiditis	7	IVW*	1.14e−10	1.141(1.096−1.187)		5.915	0.315	−0.022	0.283
HLA DR on Dendritic Cell	vitiligo	7	IVW*	4.42e−02	1.265(1.006−1.591)		9.71	0.084	−0.134	0.264

Figure 5 The forest plot illustrates the immune cell phenotypes that have shared pathogenic or protective effects with at least two diseases.

Vitiligo compared to thyrotropin receptor antibodies (TRAb). According to a retrospective study,[33] 72% of Graves' disease patients tested positive for TPOAb, while 54% tested positive for TgAb. These data suggest that there is a significant association between Graves' disease and Vitiligo, as reported in some previous studies,[6,34–36] possibly due to the presence of TPOAb and TgAb. In contrast, TRAb may play a smaller role in this association.

CXCL10 is a chemokine initially identified as interferon (IFN)-γ-induced. It exerts its function through binding to the C-X-C motif chemokine receptor 3 (CXCR3). Our research indicates that CXCL10 is a common pathogenic factor in both Hashimoto Thyroiditis and Vitiligo. The expression levels of CXCL10 are elevated in the peripheral blood[37] and thyroid tissue[38] of patients with Hashimoto Thyroiditis. CXCL10 may participate in thyroid inflammation and contribute to thyroid tissue damage by promoting immune cell infiltration and activation.[39] Interestingly, IFNγ can also induce keratinocytes to secrete CXCL9 and CXCL10, with CXCL10 inducing apoptosis in melanocytes through its interaction with CXCR3B.[40–42] Therefore, CXCL10 is considered a promising common therapeutic target for both Hashimoto Thyroiditis and Vitiligo, and interventions targeting its activity may help alleviate inflammation and tissue damage. Previous studies have shown that HLA-DR plays an important role in the pathogenesis of Hashimoto Thyroiditis[43] and Vitiligo.[44] Our study further indicates that this effect may be mediated by dendritic cells and plasmacytoid dendritic cells (pDCs).

A single-center study in France has shown that Vitiligo is the most commonly occurring additional autoimmune disease (AAD) among children with Type 1 Diabetes,[45] which aligns with our results. Additionally, we identified Signaling Lymphocytic Activation Molecule (SLAM, also known as SLAMF1) as a common pathogenic factor in both Type 1 Diabetes and Vitiligo. Magnusson et al[46] observed that individuals with long-standing Type 1 Diabetes demonstrated elevated plasma levels of SLAMF1 when compared to the healthy control group. However, we did not uncover any prior studies documenting the association between SLAM and Vitiligo. Additional research is warranted to validate the relationship between SLAM and Vitiligo. Another finding of this study is that the presence of CD25 on IgD-
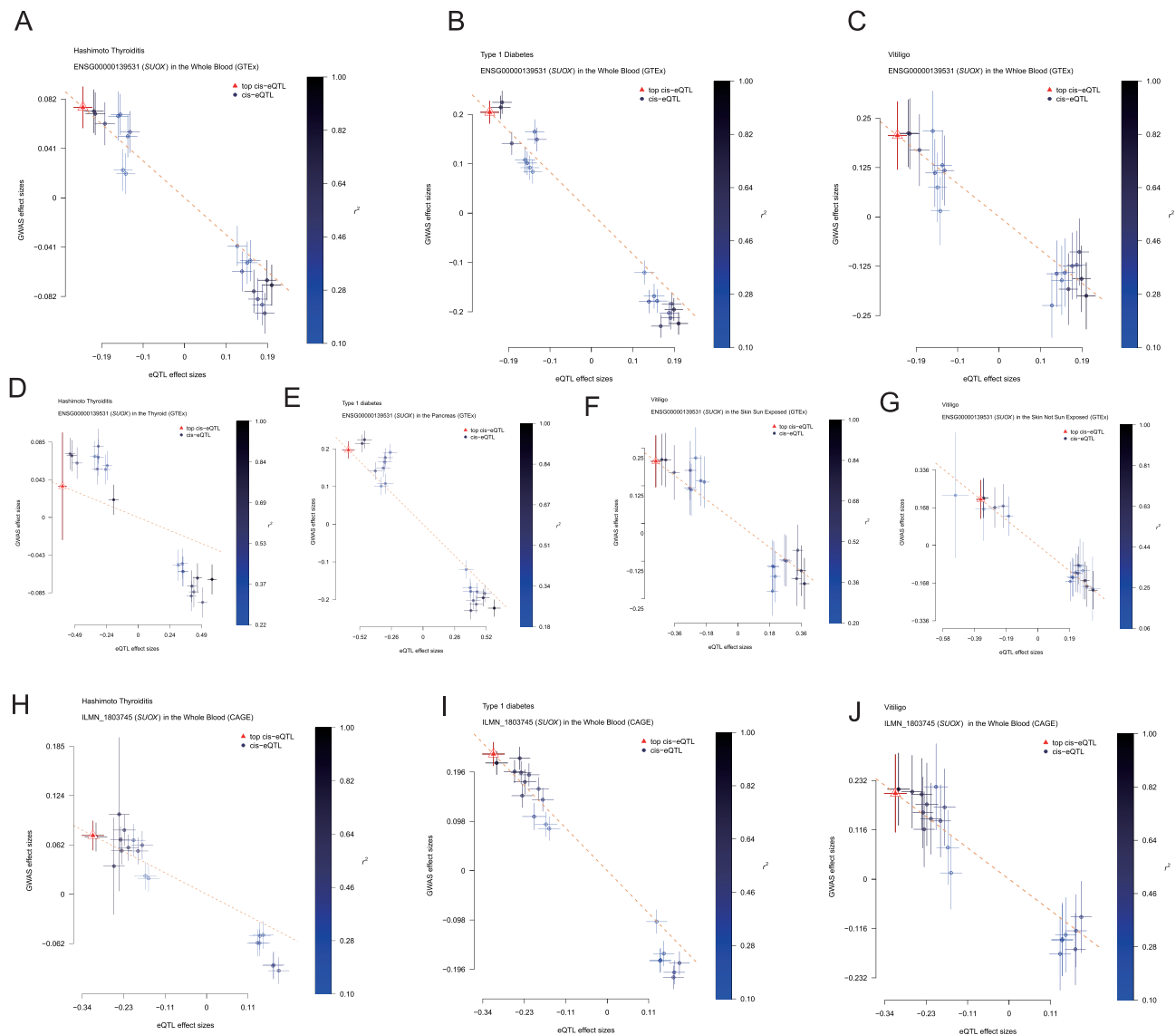
Figure 6 The relationship between SUOX's eQTL levels in various tissues and Hashimoto Thyroiditis, Type 1 Diabetes, and Vitiligo (with GTEx as the discovery set and CAGE as the validation set). (**A**) Negative association between SUOX expression and Hashimoto Thyroiditis in the GTEx Whole Blood tissue. (**B**) Negative association between SUOX expression and Type 1 Diabetes in the GTEx Whole Blood tissue. (**C**) Negative association between SUOX expression and Vitiligo in the GTEx Whole Blood tissue. (**D**) Negative association between SUOX expression and Hashimoto Thyroiditis in the GTEx Thyroid tissue. (**E**) Negative association between SUOX expression and Type 1 Diabetes in the GTEx Pancreas tissue. (**F**) Negative association between SUOX expression and Vitiligo in the GTEx Skin (Sun-Exposed) tissue. (**G**) Negative association between SUOX expression and Vitiligo in the GTEx Skin (Not Sun-Exposed) tissue. (**H**) Negative association between SUOX expression and Hashimoto Thyroiditis in the CAGE Whole Blood tissue. (**I**) Negative association between SUOX expression and Type 1 Diabetes in the CAGE Whole Blood tissue. (**J**) Negative association between SUOX expression and Vitiligo in the CAGE Whole Blood tissue.

CD38- B cells is positively correlated with three diseases. Previous studies have mainly focused on the role of CD25 on the surface of T cells.[47] However, our study provides a new perspective, but further verification is also needed.

After conducting SMR analysis on the intersection of 25 genes, we found that only SUOX is causally related to three diseases, and this relationship has been validated in multiple tissues. The protective effect of SUOX on these three diseases has aroused our curiosity. It is noteworthy that the direction of the effect of SUOX methylation on Vitiligo susceptibility, the impact of SUOX methylation on gene expression, and the effect of gene expression on Vitiligo susceptibility are consistent in our analysis. For example, cg22580629 is positively causally associated with SUOX gene expression in various tissues, and both cg22580629 and SUOX are suggested to be protective factors for Vitiligo in various tissues. In our study, we postulate that SUOX plays a pivotal role in mitigating the detrimental effects of sulfite accumulation. Specifically, SUOX catalyzes the conversion of sulfite to sulfate, culminating in the final stage of oxidative

degradation of sulfur-containing amino acids such as cysteine and methionine.[48] Deficiency in SUOX has been identified as the primary cause of isolated sulfite oxidase deficiency (ISOD), a condition associated with impaired sulfite metabolism.[49] The accumulation of sulfite has been extensively linked to various adverse health outcomes, including neurological disorders, progressive brain atrophy, and premature mortality.[50] Drawing upon this understanding, we hypothesize a potential mechanism by which sulfite-induced oxidative stress triggers apoptotic pathways in melanocytes, islet β cells, and thyroid cells. This may opens novel avenues for future therapeutic strategies.

The primary strength of this study lies in its utilization of MR methodology to evaluate the genetic associations between genetic predisposition to 21 autoimmune diseases and Vitiligo. Additionally, the study employs SNP mapping to genes to delve deeper into the underlying mechanisms of these genetic associations. By sidestepping the biases introduced by confounding factors and reverse causation inherent in traditional observational studies, it provides a robust framework for causal inference. However, the study is not without its limitations. Firstly, the availability of GWAS data on Vitiligo primarily focuses on European populations in public databases, constraining our ability to explore the relationships between autoimmune diseases and East Asian populations. Secondly, despite incorporating 21 auto-immune diseases, many others remain unexamined due to a lack of suitable GWAS data (such as Alopecia Areata). Additionally, among these 21 autoimmune diseases, the classification of psoriasis as an autoimmune disease is still a matter of debate, with some experienced dermatologists considering it a chronic inflammatory multisystemic disease. Nevertheless, given the common occurrence of psoriasis in dermatology and its potential clinical significance in exploring genetic links with vitiligo, it was still included in our study. Thirdly, although efforts were made to identify potential confounding factors using the LDlink website, it's crucial to acknowledge the possibility of undiscovered confounders without corresponding SNPs, making it challenging to exclude them through LDlink analysis.

Conclusion

In this study, we applied Mendelian Randomization analysis to assess the genetic susceptibility between vitiligo and a range of autoimmune diseases. Utilizing extensive GWAS data, we identified significant genetic associations between vitiligo and Hashimoto Thyroiditis, as well as Type 1 Diabetes, even after adjusting for potential confounding factors. The genetic overlap between vitiligo and these autoimmune conditions was further supported by the identification of 25 intersecting genes, with SUOX emerging as a potential protective factor. Our findings underscore the genetic predisposition linking vitiligo with specific autoimmune diseases, highlighting the need for further research to explore these genetic connections in diverse populations and to uncover the underlying immunological mechanisms. This research contributes to the understanding of the genetic architecture of vitiligo and its co-occurrence with certain autoimmune diseases.

Data Sharing Statement

All summary statistics data used in this work were from genome-wide association studies. Please refer to Supplementary Table S1 for all original data sources.

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.

Acknowledgments

Disclosure

The author(s) report no conflicts of interest in this work.

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