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ORIGINAL RESEARCH

Exploring the Relationship Between Immune Cells and Non-Scarring Hair Loss: A Mendelian Randomization Study

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Background: Non-scarring hair loss (NSHL) is a global health concern with increasing prevalence due to lifestyle changes and an aging population. It can cause psychological distress and affect quality of life.

Objective: This study aimed to identify the associations between NSHL and immune cell phenotypes using a two-sample Mendelian randomization (MR) analysis, offering insights for future immune-based therapies for NSHL.

Methods: We obtained immunocyte data from the IEU Open GWAS Project and NSHL data from the same database and used MR analysis to evaluate the causal association between each immunophenotype and NSHL. Three statistical methods were employed: the MR-Egger regression, weighted median estimation, and inverse variance weighting (IVW).

Results: The MR resonance imaging identified 31 immunocyte phenotypes associated with NSHL. Among these, 19 immunocyte phenotypes were negatively associated with NSHL, indicating their protective effects. The remaining 12 immunocyte phenotypes were positive association. Sensitivity analyses suggested the robustness of all MR findings.

Conclusion: These findings highlight a clear correlation between NSHL and immunity, demonstrating the significant role of certain immune cell phenotypes. This study offers a new direction for immune-based therapies in the treatment of NSHL.

Keywords: non-scarring hair loss, immune cell, Mendelian randomization, immunotherapy

Introduction

Hair loss (HL) is a global issue and its prevalence continues to increase with human lifespan and lifestyle changes.[1] In particular, non-scarring hair loss (NSHL) causes great distress and has an adverse psychological impact on many individuals.[2] Currently, the main methods for treating NSHL are medications, such as minoxidil and finasteride, and surgical interventions, such as hair transplantation. However, these methods have potential side effects, including rashes, headaches, and sexual dysfunction.[3,4] In addition to genetic factors, changes in human lifestyle are believed to be among the main contributors to the increased prevalence of hair loss. Factors, such as poor dietary habits, lack of exercise, and significant psychological stress, are associated with hair loss. Furthermore, on a global scale, environmental factors, such as air pollution and exposure to ultraviolet radiation, have been found to be closely correlated with the incidence of hair loss.[5,6] Understanding the etiology and mechanisms of illness is crucial for disease treatment. Changes in lifestyle habits and stress can lead to alterations in human immune function.[7,8] Studies are currently examining the relationship between hair loss and the immune system.[9,10] This provides a new direction for the future implementation of immunotherapy for the treatment of NSHL. However, a key prerequisite for successful immunotherapy is the identification of immune cells associated with NSHL.

Mendelian randomization (MR) is a methodology used to assess causality in observational studies. This method is based on Mendelian inheritance principles, which suggest that the inheritance of genetic variation occurs randomly. Consequently, the genetic variations associated with specific diseases may have influenced the variables under

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consideration. The MR investigates the correlation between exposure and outcomes by contrasting populations with distinct genetic variations. This approach provides superior control over potential confounding factors compared with conventional observational studies, thereby enhancing the reliability of the conclusions.[11]

Therefore, our study aimed to examine the association between NSHL and immune cells using two-sample MR analysis.

Materials and Methods

Acquired Data

We acquired immunocyte data from the Ieu Open Gwas Project (http://gwas.mrcieu.ac.uk), a genome-wide association studies database.[12] These data were used as exposure data in this study. The identification numbers for the data ranged from GCST0001391 to GCST0002121. In this study, we conducted a genome-wide association analysis of 629 blood immune cell-related traits in 272,100 individuals from the European general population. The study included 731 immunophenotypes.[13] We obtained the NSHL data[ID: finn-b-L12_HAIRLOSSNONSCAR, Year:2021, Population: European, Sex: Males and Females, n(case):81, n (control): 211,139, Number of SNPs: 16,380,450] as the outcome using the same method.

MR Analysis

Following data acquisition, we conducted separate evaluations for two associations: 1) between SNPs and exposure, and 2) between each SNP and outcome. Subsequently, an MR analysis was performed to evaluate the causal association between each immunophenotype and NSHL.

Three statistical methods were used to investigate the relationship between immunophenotypes and NSHL: MR-Egger regression, weighted median estimation, and inverse variance weighting (IVW). MR-Egger regression, employed in MR studies, is a statistical method used to detect and account for pleiotropic effects. Pleiotropy refers to the phenomenon in which a genetic variant influences outcomes through multiple pathways. The MR-Egger approach incorporates instrumental variables to estimate the causal effect of exposure on the outcome while accounting for potential pleiotropic effects.[14] The weighted median estimator is a statistical technique used to estimate the representative value of a population by calculating the median score of a weighted sample. In this method, individual data points in a sample are assigned weights that reflect their relative importance or influence the overall estimation of population parameters. This approach is particularly advantageous when dealing with outliers in data distribution, as it offers a more robust measure of central tendency than conventional methods, such as the arithmetic mean.[15] IVW is a statistical methodology frequently used in meta-analyses to combine the effect size estimates obtained from multiple studies. The weight assigned to each study in IVW was determined based on the inverse of its variance, which represented the precision of the effect estimate. By considering both sample size and variability in effect sizes across studies, the IVW approach generates a pooled effect size that incorporates information from the entire body of evidence.[16]

To ensure the accuracy of MR analysis, it is crucial that the genetic variation of the instrumental variables chosen exhibit a strong correlation with the risk factors. Therefore, we set the significance level at $p<5x10^{-8}$ as the criterion for screening instrumental variables.[13,17]

Sensitivity Analysis

The IVW method was used to calculate the Q value[18] to assess the heterogeneity between SNPs, and the Q *P*-value was calculated to determine heterogeneity. Additionally, we conducted a "leave-one-out" analysis to investigate the potential influence of individual SNPs on the causal association. Furthermore, we applied the MR-Egger regression tests to monitor the presence of potential horizontal pleiotropy effects.

Statistical Analysis

MR analysis was conducted using the "TwoSampleMR" package in R (V4.2.3).[19] Calculation of the causal association between each immunophenotype and NSHL is reported as an odds ratio (OR) with a corresponding 95% confidence interval (CI). The threshold for statistical significance was set at $p<0.05$.

Results

MR

The MR Results are presented in Tables 1 and 2 with a threshold of $p<0.05$, defining a causal relationship. When the IVW method yields significance ($p < 0.05$), even if the other methods do not, a positive result can be considered provided that the beta values of the other methods align in the same direction.[20] Based on these results, 31 immunocyte phenotypes associated with NSHL were identified. Among these, 19 immunocyte phenotypes were negatively associated with NSHL (Table 1), indicating their protective effects against NSHL. In contrast, the remaining 12 immunocyte phenotypes were positively associated with NSHL (Table 2). Details regarding each SNP are shown in Supplementary Table S1.

Sensitivity Analysis

The results of the heterogeneity tests indicated no heterogeneity among the SNPs in all MR Analyses (Q_p>0.05) (Tables 1 and 2). In this study, we conducted all MR analyses using a "leave-one-out" approach. After sequential removal of each SNP, the direction of the beta values calculated using the IVW method remained consistent across all analyses (Figure 2). This indicates the stability of all MR findings.[21] Furthermore, we subjected all intercept terms (egger_intercept) of the MR-Egger method to statistical testing, and the resulting p-values were >0.05. Therefore, we concluded that there was no evidence of horizontal pleiotropy (Figures 1 and 2).[22]

Discussion

Immunotherapy has been utilized to treat numerous diseases, especially with the advent of Chimeric antigen receptor (CAR)-T-cell therapy,[23] which has brought hope to patients with malignant tumors owing to its exceptional therapeutic efficacy. Furthermore, its success has provided insights into the application of immunotherapy in the treatment of other diseases. Currently, there is limited research focusing on immunotherapy for the treatment of NSHL,[24] which raises questions regarding the specific immune cells to be targeted for investigation, potential immune cells that may confer a protective effect against NSHL, and immune cells that might be implicated in the exacerbation of NSHL. Further investigations are required to address these questions.

We sorted all immune cell phenotypes based on their OR values according to IVW; the top three phenotypes that were most negatively correlated with NSHL were CD4+ CD8dim T cell % leukocytes, CD4+ CD8dim T cell % lymphocytes, and CD86+ plasmacytoid dendritic Cell (Table 1). Thus, it can be inferred that CD4+ CD8dim T cells play a significant role in the protection against NSHL. CD4+ CD8dim T cells are a special type of immune cells belonging to the T cell family. In the immune system, leukocytes are an important type of cell that play a crucial role in protecting the body from infections.[25] "% leukocyte" represents the percentage of this cell type within the leukocyte population. The percentage of leukocytes can be used to measure the relative abundances of different cell types in the immune system. CD4+ CD8dim T cell leukocytes indicates the proportion of this specific type of T-cell within the leukocyte population. Typically, changes in this proportion may be associated with immune system function and disease status. CD86+ plasmacytoid dendritic cells are important components of the immune system that contribute to the regulation and coordination of immune responses, particularly in the context of viral infections.[26] It can be inferred that in-depth investigations of the immune cells closely associated with NSHL are crucial for advancing research on immunotherapy for this condition. In the context of NSHL immunotherapy, targeting and inhibiting immunosuppressive immune cells are considered a critical step towards augmenting the immune response against baldness and improving treatment outcomes. Therefore, a comprehensive exploration of the immune cells closely linked to the immune response in NSHL is pivotal in determining the potential of immunotherapy and developing efficacious treatment modalities.

In contrast, the three immune cell phenotypes that exert the strongest promoting effects on NSHL are phenotypes PDL-1 on CD14- CD16+ monocyte, CX3CR1 on CD14- CD16+ monocyte, and CD25 on resting CD4 regulatory T cell. The functional mechanisms of these immune cells are currently unclear, and studying these immune cells will help understand the pathogenic mechanisms of NSHL.

Table 1 Results of Mendelian Randomization of 19 Immune Cell Phenotypes Negatively Associated with NSHL

ID	Immune Cell Phenotype	Method	nsnp	b	se	pval	or	95% CI		Q_pval (heterogeneity)	Egger_ intercept	se	pval (pleiotropy)
ebi-a-GCST90001611	CD4+ CD8dim T cell %leukocyte	MR Egger	13	−0.746	0.658	0.281	0.474	0.131	1.722	0.251	0.027	0.121	0.830
		Weighted median	13	−0.722	0.292	0.013	0.486	0.274	0.861				
		IVW	13	−0.617	0.284	0.030	0.540	0.309	0.941	0.375			
ebi-a-GCST90001610	CD4+ CD8dim T cell %lymphocyte	MR Egger	18	−0.587	0.351	0.114	0.556	0.280	1.107	0.233	0.012	0.070	0.869
		Weighted median	18	−0.639	0.235	0.007	0.528	0.333	0.837				
		IVW	18	−0.537	0.183	0.003	0.585	0.409	0.836	0.287			
ebi-a-GCST90001399	IgD- CD27- B cell %B cell	MR Egger	18	−0.587	0.351	0.114	0.556	0.280	1.107	0.901	0.094	0.069	0.196
		Weighted median	18	−0.639	0.235	0.007	0.528	0.333	0.837				
		IVW	18	−0.537	0.183	0.003	0.585	0.409	0.836	0.839			
ebi-a-GCST90001466	CD86+ plasmacytoid Dendritic Cell	MR Egger	20	−0.218	0.273	0.435	0.804	0.471	1.373	0.661	−0.045	0.065	0.498
		Weighted median	20	−0.465	0.224	0.038	0.628	0.405	0.974				
		IVW	20	−0.368	0.165	0.025	0.692	0.501	0.956	0.691			
ebi-a-GCST90002028	CD19 on B cell	MR Egger	22	−0.124	0.206	0.553	0.883	0.589	1.323	0.691	−0.075	0.053	0.178
		Weighted median	22	−0.316	0.217	0.146	0.729	0.476	1.116				
		IVW	22	−0.339	0.138	0.014	0.713	0.544	0.934	0.626			
ebi-a-GCST90001670	CD39+ CD8+ T cell %T cell	MR Egger	20	−0.608	0.244	0.023	0.544	0.337	0.878	0.375	0.103	0.069	0.152
		Weighted median	20	−0.545	0.221	0.014	0.580	0.375	0.895				
		IVW	20	−0.326	0.160	0.041	0.722	0.528	0.987	0.301			
ebi-a-GCST90001791	CD25 on naive-mature B cell	MR Egger	23	−0.116	0.205	0.578	0.891	0.596	1.331	0.825	−0.069	0.050	0.179
		Weighted median	23	−0.267	0.207	0.197	0.766	0.511	1.148				
		IVW	23	−0.323	0.140	0.021	0.724	0.550	0.953	0.770			
ebi-a-GCST90002113	HLA DR on HLA DR+ T cell	MR Egger	18	−0.448	0.120	0.002	0.639	0.505	0.808	0.506	0.075	0.045	0.112
		Weighted median	18	−0.409	0.166	0.014	0.664	0.480	0.919				
		IVW	18	−0.319	0.095	0.001	0.727	0.603	0.876	0.383			
ebi-a-GCST90001672	CD39+ CD8+ T cell	MR Egger	23	−0.451	0.149	0.006	0.637	0.476	0.853	0.757	0.070	0.054	0.206
		Weighted median	23	−0.205	0.165	0.215	0.815	0.590	1.126				
		IVW	23	−0.314	0.105	0.003	0.731	0.595	0.898	0.710			
ebi-a-GCST90001591	CD4+ T cell %T cell	MR Egger	22	−0.088	0.248	0.726	0.916	0.564	1.488	0.381	−0.072	0.063	0.265
		Weighted median	22	−0.210	0.212	0.322	0.810	0.534	1.228				
		IVW	22	−0.310	0.155	0.045	0.733	0.541	0.993	0.362			
ebi-a-GCST90001656	CD28+ CD4-CD8- T cell %CD4-CD8 - T cell	MR Egger	27	−0.114	0.171	0.511	0.892	0.638	1.248	0.820	−0.057	0.044	0.202
		Weighted median	27	−0.112	0.169	0.506	0.894	0.642	1.244				
		IVW	27	−0.278	0.117	0.017	0.757	0.602	0.952	0.781			
ebi-a-GCST90002018	CCR2 on granulocyte	MR Egger	16	−0.202	0.174	0.266	0.817	0.580	1.150	0.498	−0.028	0.055	0.615
		Weighted median	16	−0.238	0.200	0.235	0.788	0.532	1.167				
		IVW	16	−0.262	0.130	0.044	0.770	0.596	0.993	0.554			

ebi-a-GCST90001966	FSC-A on granulocyte	MR Egger	20	−0.366	0.178	0.054	0.693	0.489	0.983	0.501	0.053	0.056	0.357
		Weighted median	20	−0.213	0.171	0.214	0.808	0.578	1.131				
		IVW	20	−0.239	0.116	0.040	0.788	0.628	0.989	0.508			
ebi-a-GCST90001511	CD25++ CD45RA- CD4 not regulatory T cell %CD4+ T cell	MR Egger	24	−0.171	0.102	0.109	0.843	0.690	1.030	0.278	−0.039	0.052	0.467
		Weighted median	24	−0.229	0.113	0.043	0.796	0.638	0.993				
		IVW	24	−0.214	0.083	0.010	0.808	0.686	0.950	0.299			
ebi-a-GCST90001512	CD25++ CD45RA- CD4 not regulatory T cell %T cell	MR Egger	28	−0.120	0.088	0.182	0.887	0.746	1.053	0.366	−0.070	0.047	0.150
		Weighted median	28	−0.207	0.098	0.035	0.813	0.671	0.985				
		IVW	28	−0.199	0.072	0.006	0.820	0.712	0.943	0.305			
ebi-a-GCST90001711	BAFF-R on IgD- CD27- B cell	MR Egger	17	−0.053	0.121	0.671	0.949	0.748	1.203	0.426	−0.101	0.056	0.089
		Weighted median	17	−0.141	0.113	0.209	0.868	0.696	1.083				
		IVW	17	−0.197	0.098	0.045	0.821	0.677	0.996	0.282			
ebi-a-GCST90001955	CD33 on Immature Myeloid-Derived Suppressor Cells	MR Egger	22	−0.042	0.124	0.738	0.959	0.752	1.223	0.361	−0.078	0.056	0.182
		Weighted median	22	−0.125	0.094	0.185	0.883	0.734	1.062				
		IVW	22	−0.175	0.080	0.028	0.839	0.717	0.982	0.308			
ebi-a-GCST90001953	CD33 on CD33dim HLA DR-	MR Egger	19	−0.131	0.117	0.280	0.877	0.697	1.104	0.856	−0.009	0.059	0.884
		Weighted median	19	−0.153	0.086	0.077	0.858	0.724	1.017				
		IVW	19	−0.144	0.073	0.048	0.866	0.750	0.999	0.893			
ebi-a-GCST90001510	CD25++ CD45RA- CD4 not regulatory T cell	MR Egger	19	−0.133	0.094	0.176	0.875	0.727	1.053	0.687	0.001	0.098	0.990
		Weighted median	19	−0.140	0.084	0.096	0.870	0.738	1.025				
		IVW	19	−0.132	0.062	0.033	0.876	0.776	0.989	0.747			

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Table 2 Results of Mendelian Randomization of 12 Immune Cell Phenotypes Positive Associated with NSHL

	Immune Cell Phenotype	Method	nsnp	b	se	pval	or	95% CI		Q_pval(heterogeneity)	Egger_intercept	se	pval(pleiotropy)
ebi-a-GCST90001999	PDL-1 on CD14- CD16+ monocyte	MR Egger	17	0.663	0.306	0.047	1.940	1.065	3.536	0.171	−0.098	0.088	0.284
		Weighted median	17	0.277	0.195	0.155	1.319	0.901	1.932				
		IVW	17	0.371	0.159	0.020	1.450	1.061	1.981	0.154			
ebi-a-GCST90002012	CX3CR1 on CD14- CD16+ monocyte	MR Egger	17	0.663	0.306	0.047	1.940	1.065	3.536	0.621	−0.047	0.056	0.411
		Weighted median	17	0.277	0.195	0.155	1.319	0.901	1.932				
		IVW	17	0.371	0.159	0.020	1.450	1.061	1.981	0.638			
ebi-a-GCST90001937	CD25 on resting CD4 regulatory T cell	MR Egger	20	0.250	0.185	0.193	1.285	0.894	1.846	0.364	0.012	0.048	0.812
		Weighted median	20	0.259	0.194	0.183	1.295	0.885	1.896				
		IVW	20	0.281	0.132	0.033	1.325	1.023	1.714	0.424			
ebi-a-GCST90001653	CD28- CD4-CD8- T cell %CD4-CD8- T cell	MR Egger	27	0.114	0.171	0.511	1.121	0.801	1.568	0.820	0.057	0.044	0.202
		Weighted median	27	0.112	0.175	0.522	1.119	0.794	1.577				
		IVW	27	0.278	0.117	0.017	1.320	1.050	1.660	0.781			
ebi-a-GCST90001748	CD25 on resting CD4 regulatory T cell	MR Egger	25	0.161	0.154	0.308	1.175	0.868	1.589	0.893	0.031	0.044	0.485
		Weighted median	25	0.187	0.166	0.259	1.206	0.871	1.670				
		IVW	25	0.236	0.112	0.035	1.267	1.017	1.577	0.904			
ebi-a-GCST90001852	CD3 on CD39+ resting CD4 regulatory T cell	MR Egger	25	0.161	0.154	0.308	1.175	0.868	1.589	0.466	0.079	0.059	0.201
		Weighted median	25	0.187	0.166	0.259	1.206	0.871	1.670				
		IVW	25	0.236	0.112	0.035	1.267	1.017	1.577	0.419			
ebi-a-GCST90002000	PDL-1 on CD14- CD16-	MR Egger	25	0.287	0.150	0.069	1.332	0.992	1.789	0.604	−0.021	0.044	0.635
		Weighted median	25	0.154	0.172	0.368	1.167	0.834	1.633				
		IVW	25	0.240	0.115	0.037	1.272	1.015	1.594	0.647			
ebi-a-GCST90001772	CD24 on unswitched memory B cell	MR Egger	21	0.218	0.097	0.036	1.244	1.029	1.504	0.896	−0.035	0.045	0.445
		Weighted median	21	0.176	0.106	0.097	1.193	0.969	1.469				
		IVW	21	0.172	0.077	0.026	1.188	1.021	1.383	0.903			
ebi-a-GCST90001778	CD25 on IgD+ CD24+ B cell	MR Egger	26	0.111	0.086	0.213	1.117	0.943	1.323	0.254	0.024	0.041	0.562
		Weighted median	26	0.133	0.094	0.159	1.142	0.949	1.374				
		IVW	26	0.140	0.070	0.046	1.150	1.003	1.318	0.283			
ebi-a-GCST90002108	HLA DR on CD33+ HLA DR+ CD14-	MR Egger	24	0.109	0.085	0.211	1.115	0.945	1.317	0.408	0.022	0.055	0.697
		Weighted median	24	0.117	0.084	0.165	1.124	0.953	1.326				
		IVW	24	0.134	0.056	0.016	1.143	1.026	1.275	0.458			
ebi-a-GCST90001964	FSC-A on plasmacytoid Dendritic Cell	MR Egger	26	0.130	0.085	0.138	1.139	0.964	1.346	0.995	−0.001	0.040	0.986
		Weighted median	26	0.152	0.090	0.089	1.165	0.977	1.388				
		IVW	26	0.129	0.065	0.046	1.138	1.002	1.292	0.997			
ebi-a-GCST90001987	CD64 on CD14+ CD16- monocyte	MR Egger	33	0.107	0.051	0.044	1.113	1.007	1.230	0.994	−0.011	0.038	0.767
		Weighted median	33	0.095	0.062	0.125	1.100	0.974	1.242				
		IVW	33	0.100	0.044	0.025	1.105	1.013	1.206	0.996			

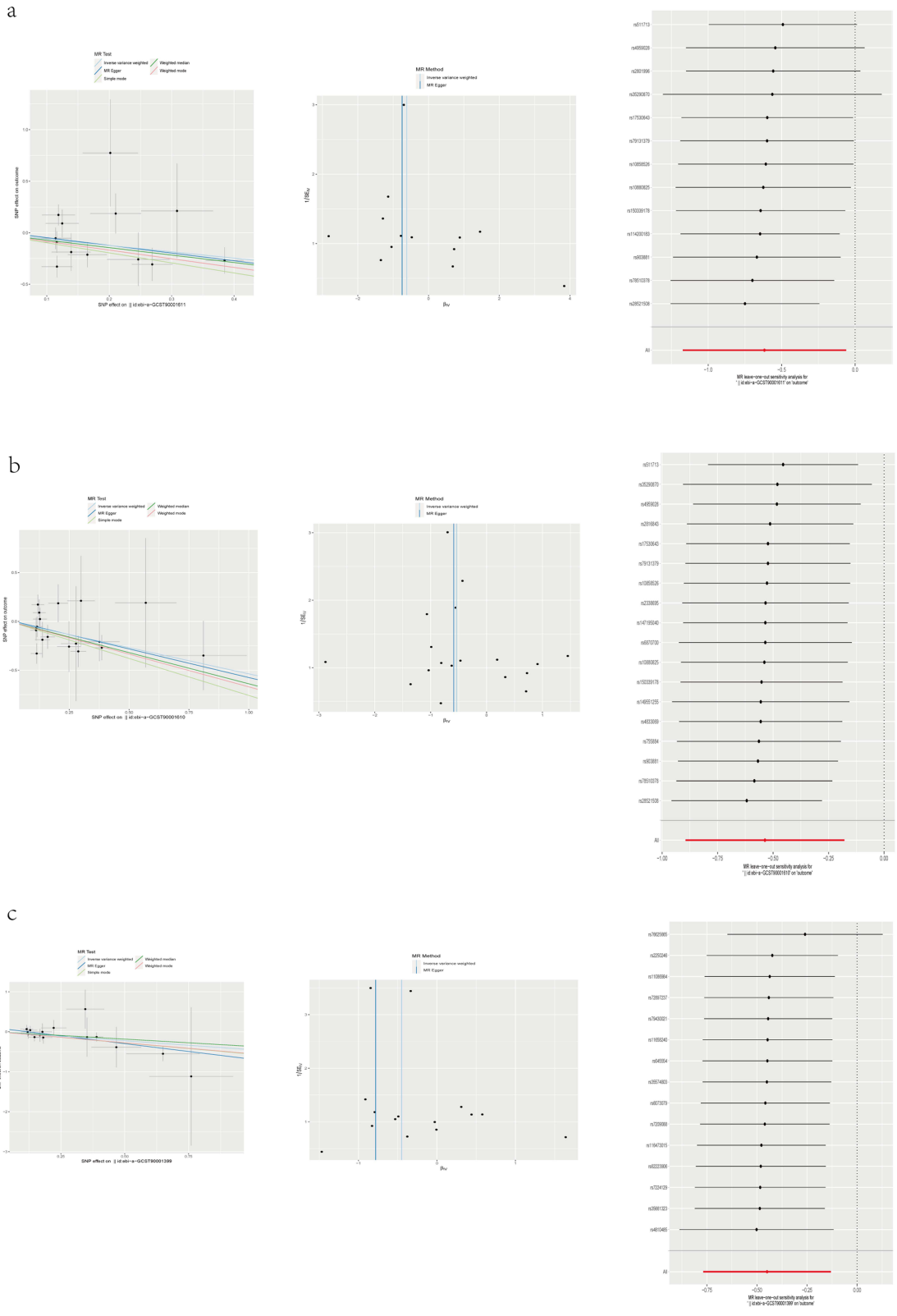

Figure 1 Sensitive analysis of the top 3 positively correlated immune cell phenotypes, (**a**) ebi-a-GCST90001611, (**b**) ebi-a-GCST90001610, (**c**) ebi-a-GCST90001399.

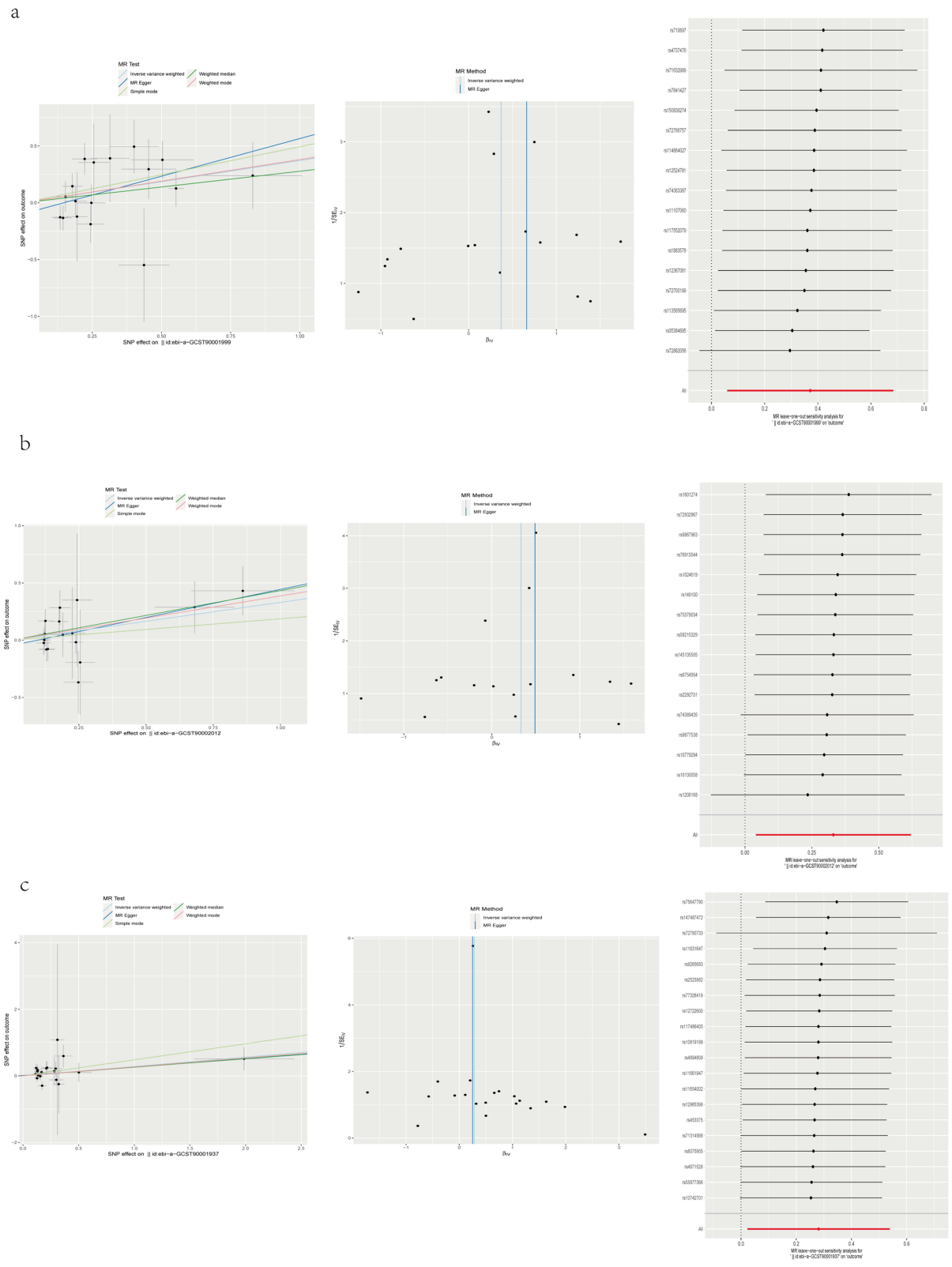

Figure 2 Sensitive analysis of the top 3 negative correlated immune cell phenotypes, (**a**) ebi-a-GCST90001999, (**b**) ebi-a-GCST90002012, (**c**) ebi-a-GCST90001937.

Although this study yielded rich results, it has certain limitations. Our data came exclusively from Europeans, and the causes of hair loss may vary among ethnic groups.[27] Therefore, larger, more globally representative datasets are required to support our findings.

Conclusion

This study revealed a correlation between NSHL and the immune system by utilizing MR analysis, identifying 31 immune cell phenotypes associated with NSHL. Our findings may provide a research direction for immune-based therapies for NSHL and establish a foundation for understanding the pathogenesis of NSHL.

Ethical Approval and Consent

This study has been approved by the Ethics Committee of the Second Affiliated Hospital of Guangxi Medical University. Approval Number:2024-KY(0500).

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Gan DC, Sinclair RD. Prevalence of male and female pattern hair loss in Maryborough. *J Investig Dermatol Symp Proc*. 2005;10(3):184–189. doi:10.1111/j.1087-0024.2005.10102.x
2. Cash TF. The psychosocial consequences of androgenetic alopecia: a review of the research literature. *Br J Dermatol*. 1999;141(3):398–405. doi:10.1046/j.1365-2133.1999.03030.x
3. Randolph M, Tosti A. Oral minoxidil treatment for hair loss: a review of efficacy and safety. *J Am Acad Dermatol*. 2021;84(3):737–746. doi:10.1016/j.jaad.2020.06.1009
4. York K, Meah N, Bhoyrul B, Sinclair R. A review of the treatment of male pattern hair loss. *Expert Opin Pharmacother*. 2020;21(5):603–612. doi:10.1080/14656566.2020.1721463
5. Gokce N, Basgoz N, Kenanoglu S, et al. An overview of the genetic aspects of hair loss and its connection with nutrition. *J Prev Med Hyg*. 2022;63 (2 Suppl 3).
6. Phillips TG, Slomiany WP, Allison R. Hair Loss: common Causes and Treatment. *Am Fam Physician*. 2017;96(6):371–378.
7. Snyder BK, Roghmann KJ, Sigal LH. Stress and psychosocial factors: effects on primary cellular immune response. *J Behav Med*. 1993;16 (2):143–161. doi:10.1007/BF00844890
8. Friedman SM. Lifestyle (Medicine) and Healthy Aging. *Clin Geriatr Med*. 2020;36(4):645–653. doi:10.1016/j.cger.2020.06.007
9. Sterkens A, Lambert J, Bervoets A. Alopecia areata: a review on diagnosis, immunological etiopathogenesis and treatment options. *Clin Exp Med*. 2021;21(2):215–230. doi:10.1007/s10238-020-00673-w
10. Watson VE, Faniel ML, Kamili NA, Krueger LD, Zhu C. Immune-mediated alopecias and their mechanobiological aspects. *Cells Dev*. 2022;170:203793. doi:10.1016/j.cdev.2022.203793
11. Sekula P, Del Greco MF, Pattaro C, Köttgen A. Mendelian Randomization as an Approach to Assess Causality Using Observational Data. *J Am Soc Nephrol*. 2016;27(11):3253–3265. doi:10.1681/ASN.2016010098
12. Elsworth B, Lyon M, Alexander T, et al. The MRC IEU OpenGWAS data infrastructure. *bioRxiv*. 2020.
13. Orrù V, Steri M, Sidore C, et al. Complex genetic signatures in immune cells underlie autoimmunity and inform therapy. *Nat Genet*. 2020;52 (10):1036–1045. doi:10.1038/s41588-020-0684-4
14. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44(2):512–525. doi:10.1093/ije/dyv080
15. Yang S. The Weighted Kernel Estimators of Nonparametric Regression Function with Censored Data. *Acta Mathematica Sinica*. 1999.
16. Jack B, George DS, Stephen B. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44(2).
17. Auton A, Brooks LD, Durbin RM, et al. A global reference for human genetic variation. *Nature*. 2015;526:7571.
18. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ*. 1997;315(7121):1533–1537. doi:10.1136/bmj.315.7121.1533
19. Dessau RB, Pipper CB. "R"–project for statistical computing. *Ugeskr Laeger*. 2008;170(5):328–330.
20. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol*. 2017;32 (5):377–389. doi:10.1007/s10654-017-0255-x
21. Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity Analyses for Robust Causal Inference from Mendelian Randomization Analyses with Multiple Genetic Variants. *Epidemiology*. 2017;28(1):30–42. doi:10.1097/EDE.0000000000000559
22. Hemani G, Bowden J, Davey Smith G. Evaluating the potential role of pleiotropy in Mendelian randomization studies. *Hum Mol Genet*. 2018;27 (R2):R195–R208. doi:10.1093/hmg/ddy163

23. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. *Blood Cancer J*. 2021;11(4):69. doi:10.1038/s41408-021-00459-7
24. Okada M, Tashiro-Yamaji J, Takahashi T, et al. Regulation of hair regrowth in alopecic site of IFN-gamma-/- mice by macrophages infiltrating into allograft in IFN-gamma+/+ mice. *J Interferon Cytokine Res*. 2005;25(9):564–574. doi:10.1089/jir.2005.25.564
25. Lambert C, Ibrahim M, Iobagiu C, Genin C. Significance of unconventional peripheral CD4+CD8dim T cell subsets. *J Clin Immunol*. 2005;25(5):418–427. doi:10.1007/s10875-005-5257-x
26. Suzuki M, Yokota M, Matsumoto T, Ozaki S. Synergic Effects of CD40 and CD86 Silencing in Dendritic Cells on the Control of Allergic Diseases. *Int Arch Allergy Immunol*. 2018;177(2):87–96. doi:10.1159/000489862
27. Lee WS, Lee HJ. Characteristics of androgenetic alopecia in asian. *Ann Dermatol*. 2012;24(3):243–252. doi:10.5021/ad.2012.24.3.243