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Exploring the Causality and Pathogenesis of Immune Cells in Allergic Diseases: A Bidirectional Mendelian Randomization Study

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Abstract: ***Increasing evidence suggests a substantial correlation between immune cells and allergic diseases; however, the causal relationship remains to be elucidated. Objective: To explore the Causality and Pathogenesis of Immune Cells in Allergic Diseases through bidirectional Mendelian randomization. Methods: Leveraging comprehensive publicly accessible summary-level data from genome-wide association studies (GWAS), this study employed the bidirectional MR research method to investigate causal relationships among 731 immune cell phenotypes (seven groups) and three allergic diseases (ADs). Various sensitivity analysis methods were systematically employed to ensure the robustness of the results. Results: After FDR adjustment, we indicate that 16 types of immune cells show potential causal relationships with allergic conjunctivitis (AC), 5 types of immune cells show potential causal relationships with allergic contact dermatitis (ACD), 12 types of immune cells show potential causal relationships with ACD caused by drug contact with the skin. Conclusion: Our study elucidates the close genetic associations between immune cells and nine allergic diseases, thereby providing valuable insights for future research endeavors and clinical applications.***

Keywords: Mendelian randomization, Immune cells, Allergic diseases**.**

1. Introduction

Allergic disease (AD) represents a category of disorders characterized by complex pathogenesis, with a rising incidence in recent years, and has emerged as the sixth most costly chronic condition in the United States [1]. Allergic conjunctivitis (AC), Allergic contact dermatitis (ACD) and Allergic contact dermatitis caused by drug contact with the skin represent the more prevalent forms of ADs. Treatment typically involves allergen avoidance, pharmacotherapy (antihistamines, corticosteroids) and immunotherapy [2]. ADs are associated with genetic, dietary, and environmental factors such as air pollution and exposure to allergens; however, their underlying causes remain elusive [3].

In recent years, extensive research has been conducted on the relationship between immune cells and ADs. Lymphocytes primarily encompass innate lymphocytes (T cells and B cells) and adaptive lymphocytes (natural killer (NK) cells). Innate lymphoid cells (ILCs) predominantly are poised to respond rapidly to environmental pathogens and insults. ILCs do not express rearranged antigen-specific receptors and are activated by cytokines and other mediators released by epithelial cells, macrophages, and dendritic cells (DCs). Upon activation, ILCs secrete substantial quantities of cytokines that recruit additional immune and inflammatory cells, activate adaptive immune responses, and mediate both physiological and pathological processes. There are three main subsets of ILCs: ILC1, ILC2, and ILC3 [4]. ILC2s are likely most relevant subset in ADs, although other ILCs may also be implicated [5]. Observational studies have shown that DCs is involved in the recognition and presentation of allergens through the expression of TLRs (Toll-like receptors) in allergic diseases. By interacting with T cells, DCs can promote Th2 cell differentiation and IgE production. The absence of Tregs is a hallmark of the pathogenesis of allergic diseases. Pathogenesis of allergic diseases and implications for therapeutic interventions DCs play critical roles in ADs by orchestrating both innate and adaptive immune responses [6]. Observational studies have shown that monocytes have direct protective and pathogenic activities during immune regulation [7].

However, the absence of evidence from randomized controlled trials (RCTs) leaves the causal relationship between immune cells and these three ADs uncertain. Given that genetic variants are randomly assigned at conception prior to disease onset, Mendelian randomization (MR) has emerged as an effective tool for identifying causal relationships while controlling for confounding factors and mitigating reverse causation [8]. MR has been extensively utilized in AD research, revealing numerous causative factors associated with various ADs [9] [10]. In this study, we performed a bidirectional MR analysis utilizing a recently published genome-wide association study (GWAS) database to explore potential causal relationships between immune cell populations and ADs, thereby offering a novel perspective on the targeted modulation of specific immune cell subsets for the prevention of these conditions.

2. Materials and Methods

2.1 Study Design

We assessed the causal relationship between 731 immune cell signatures (seven groups) and three ADs based primarily on TSMR analysis. MR uses genetic variation to represent risk factors, and a valid instrumental variable (IV) in causal inference must satisfy three fundamental assumptions [11] 1. Correlation assumption: The SNPs exhibit strong associations with the exposure; 2. Exclusion assumption: The chosen SNP is not related to the outcome; 3. Independence assumption: The chosen SNP is not related to confounding variables. All studies included in our analysis received approval from

relevant institutional review boards, and informed consent was obtained from participants. Based on the MR Results, the Venn diagram was used to find AA and AR intersecting cells.

2.2 Data Sources and Selection of Instrumental Variables

2.2.1 Source of immune cell data

The immune cell genome-wide association study (GWAS) data were obtained from an investigation into the genetic characteristics of immune cells. In this study, researchers performed analyses on a substantial number of genetic variations to identify those associated with immune cell traits and to further elucidate the impact of these variations on immune system functionality. The research encompassed 539 independent tests aimed at identifying genetic variants linked to immune cell characteristics while also exploring their functional implications. Utilizing flow cytometry for measurement, 731 immune cell phenotypes were categorized into four distinct groups: absolute cell counts (AC) (n=118), median fluorescence intensity reflecting surface antigen levels (MFI) (n=389), morphological parameters (MP) (n=32), and relative cell counts (RC) (n=192). Specifically, the seven types of immune cells examined in our research include T cells, B cells, dendritic cells (DCs), monocytes, other myeloid cells, natural killer cells, and regulatory T cells [12] [14].

2.2.2 Source of Allergic diseases data

The ADs primarily encompass allergic conjunctivitis, allergic contact dermatitis, allergic purpura, and allergic contact dermatitis caused by drugs in contact with the skin. The GWAS statistics utilized in this analysis are derived from data published by FinnGen Research (https://r11.finngen.fi) in June 2024. Details of GWAS are shown in Table 1.

Table1: Information on the GWAS data cohort used to conduct the MR analysis

Phenotype	Cases	Controls	Sample size	Population	Phenocode
ACD	5 331	394 476	399 807	European	L12_ALLERGICCONTACT
ACD caused by drug contact with the skin	707	453 026	453 733	European	ALLERGIC_CONTACT_DERMA_DRUGS_CONTACT_W_SKIN
AC	26 125	427 608	453 733	European	H7_ALLERGICCONJUNCTIVITIS

2.3 Selection of IVs

We refined the inclusion criteria for instrumental variables (IVs) to enhance the accuracy and effectiveness of the causal relationship between immune cells and the risk of ADs. Firstly, only SNPs with a pval <1×10-5 were considered as exposure and outcome IVs in the MR study [15]. Secondly, the TSMR package was employed with parameters set to r^2 = 0.001 and kb = 10 000 to ensure the independence of selected instrumental variables (IVs) and minimize violations of random allele distribution resulting from linkage disequilibrium effects. Only single nucleotide polymorphisms (SNPs) that met the P-value criteria and were cleared of linkage disequilibrium were eligible for matching with exposure [16]. Additionally, to mitigate bias arising from weak instrumental variables, we utilized the F-statistic to evaluate the statistical strength of the correlation between each SNP and its respective exposures. IVs with an F-statistic greater than 10 were classified as strong instruments, while those with an F-statistic less than 10 were considered indicative of a weak correlation between SNPs and exposures [17]. During each analysis, SNPs with palindromic structures were automatically excluded. The F-statistic was calculated using the formula: $F = (\frac{N-K-1}{K})\left(\frac{R^2}{1-R^2}\right)$ [18], where N represents sample size, K denotes the number of instrumental variables (IV), and R^2 indicates the proportion of exposure variability explained by IV.

2.4 Statistical Analysis

Data analyses were performed using the MRPRESSO and TwoSampleMR packages within R software (version 4.3.2). Utilizing five Mendelian Randomization (MR) analysis methods, with the Inverse Variance Weighted (IVW) method as the primary approach, evaluate the causal relationship between exposure and outcome. To ensure robustness, sensitivity analyses were conducted employing methods that incorporate different assumptions regarding horizontal pleiotropy, including MR-Egger and MR-Presso. The MR-Egger analysis assessed instrumental variable pleiotropy, where a non-zero intercept indicates potential bias in IVW estimates [19]. MR-PRESSO identified horizontal pleiotropy through a global test and, when necessary, corrected for potential pleiotropy by removing outliers [20]. Additionally, we employed the "leave-one-out" method to exclude abnormal SNPs, thereby preventing undue influence of individual SNPs on the causal relationship between exposure and outcome. Furthermore, heterogeneity was assessed using the Cochran Q test, with a P-value below 0.05 indicating the presence of heterogeneity. In such instances, we utilized the IVW random-effects model to estimate causal effects; in the absence of heterogeneity, the IVW fixed-effects model was deemed appropriate for reporting results from the IVW method. Moreover, considering multiple MR analyses involving different exposures and a single outcome, we controlled for potential false-positive results arising from multiple hypothesis testing by applying the false discovery rate (FDR) [21]. Finally, we visually represented our findings through forest plots, funnel plots, scatter plots, and "leave-one-out" plots.

2.5 Ethical Approval

The GWAS data utilized in this research were publicly available de-identified datasets. The ethics committee granted approval for these data; consequently, no additional ethical clearance was required [22].

3. Results

3.1 Causal Effects of Immune Cells on ACD

After FDR adjustment (adjust P<0.05), Our research results indicate that 5 types of immune cells show potential causal

relationships with ACD (as shown in Figure 6). Among them, only CD4+ CD8dim %leukocyte (in the TBNK, OR 95%CI= 0.89 (0.82,0.96)) shows a negative association with ACD. The BAFF-R on IgD+ CD38dim (in the B cells, OR 95%CI= 1.03 (1.00,1.05)), CD86+ myeloid DC (in the cDCs, OR 95%CI= 1.05 (1.02,1.09)), CD86 on myeloid DC (in the cDCs, OR 95%CI= 1.07 (1.01,1.13)) and CD40 on CD14- CD16+ monocyte (in the Monocytes, OR 95%CI= 1.05 (1.02,1.09)) show a positive correlation. In the reverse MR results of immune cells and ACD, all MR analysis pvals and adjust P are greater than 0.05, indicating that ACD has no effect on the included immune cells (shown in the Supplementary material).

Panel	Trait.type	Trails	method	nsnp	pval	OR(95%CI)	adjustP
B cell	MFI	BAFF−R on IgD+ CD38dim	Inverse variance weighted	25	0.0495	1.03 (1.00−1.05)	0.049544550
cDC	Absolute count	CD86+ myeloid DC	Inverse variance weighted	21	0.0042	1.05 (1.02−1.09)	0.007038666
cDC	MFI	CD86 on myeloid DC	Inverse variance weighted	22	0.0307	1.07 (1.01−1.13)	0.038419724
Monocyte	MFI	CD40 on CD14− CD16+ monocyte	Inverse variance weighted	27	0.0032	1.05 (1.02−1.09)	0.016102068
TBNK	Relative count	CD4+ CD8dim %leukocyte	Inverse variance weighted	14	0.0036	0.89 (0.82−0.96)	0.008878708

Figure 6: Forest plots showed the causal associations between immune cell traits and ACD by using Inverse variance weighted. CI: confidence interval

3.2 Causal Effects of Immune Cells on ACD Caused by Drug Contact with the Skin

After FDR adjustment (adjustP<0.05), Our research results indicate that 12 types of immune cells show potential causal relationships with ACD caused by drug contact with the skin (as depicted in Figure 7). In the B cells, BAFF-R on IgD- CD38br (OR 95%CI= 0.83 (0.69,0.99)) and CD19 on IgD- CD38br (OR 95%CI= 0.81 (0.68,0.96)) has a negative correlation with ACD caused by drug contact with the skin. In the cDCs, only CD62L- myeloid DC %DC (OR 95%CI= 1.13 (1.03,1.25)) has a positive correlation with ACD caused by drug contact with the skin. In the Monocytes, both CCR2 on CD14+ CD16- monocyte (OR 95%CI= 1.08 (1.02,1.13)) and CCR2 on monocyte (OR 95%CI= 1.13 (1.06,1.21)) has a positive correlation with ACD caused by drug contact with the skin. In the Myeloid cell, only HLA DR on CD33dim HLA DR+ CD11b- (OR 95%CI= 0.89 (0.80,0.99)) has a negative correlation with ACD caused by drug contact with the skin. In the TBNKs, HLA DR+ T cell%T cell (OR 95%CI= 0.93 (0.86,1.00)), DN (CD4-CD8-) NKT (OR 95%CI= 0.70 (0.54,0.91)) and HLA DR+ NK (OR 95%CI= 0.78 (0.67,0.92)) has a negative correlation with ACD caused by drug contact with the skin. Only SSC-A on lymphocyte (OR 95%CI= 1.26 (1.05,1.51)) has a positive correlation with ACD caused by drug contact with the skin. In the Tregs, CD28+ CD45RA+ CD8dim (OR 95%CI= 1.03 (1.01,1.05)) has a positive correlation and CD3 on T cell (OR 95%CI= 0.91 (0.83,0.99)) has a negative correlation with ACD caused by drug contact with the skin. In the reverse MR results of immune cells and ACD caused by drug contact with the skin, all MR analysis pvals and adjustP are greater than 0.05, indicating that ACD caused by drug contact with the skin has no effect on the included immune cells (shown in the Supplementary material).

Panel	Trait.type	Trails	method	nsnp	pval	OR(95%CI)	adjustP
B cell	MFI	BAFF−R on IgD− CD38br	Inverse variance weighted	15	0.0431	0.83 (0.69−0.99)	0.046979931
B cell	MFI	CD19 on IgD− CD38br	Inverse variance weighted	18	0.0170	0.81 (0.68−0.96)	0.025461699
cDC	Relative count	CD62L− myeloid DC %DC	Inverse variance weighted	24	0.0075	1.13 (1.03−1.25)	0.017910578
Monocyte	MFI	CCR2 on CD14+ CD16− monocyte	Inverse variance weighted	27	0.0040	1.08 (1.02−1.13)	0.012069268
Monocyte	MFI	CCR2 on monocyte	Inverse variance weighted	24	<0.001	1.13 (1.06−1.21)	0.003215736
Myeloid cell	MFI	HLA DR on CD33dim HLA DR+ CD11b−	Inverse variance weighted	18	0.0274	0.89 (0.80−0.99)	0.032910874
TBNK	Relative count	HLA DR+ T cell%T cell	Inverse variance weighted	31	0.0455	0.93 (0.86−1.00)	0.045510030
TBNK	Absolute count	DN (CD4−CD8−) NKT	Inverse variance weighted	10	0.0078	0.70 (0.54−0.91)	0.015559561
TBNK	Absolute count	HLA DR+ NK	Inverse variance weighted	18	0.0034	0.78 (0.67−0.92)	0.013654449
TBNK	Morphological parameter	SSC−A on lymphocyte	Inverse variance weighted	21	0.0150	1.26 (1.05−1.51)	0.025680552
Treg	Absolute count	CD28+ CD45RA+ CD8dim	Inverse variance weighted	49	0.0023	1.03 (1.01−1.05)	0.013850773
Treg	MFI	CD3 on T cell	Inverse variance weighted	31	0.0267	0.91 (0.83−0.99)	0.035605013

Figure 7: Forest plots showed the causal associations between immune cell traits and ACD caused by drug contact with the skin by using Inverse variance weighted. CI: confidence interval

3.3 Causal Effects of Immune Cells on AC

After FDR adjustment (adjust P<0.05), Our research results indicate that 16 types of immune cells show potential causal relationships with AC (as shown in Figure 9). In the B cells, IgD+ CD38- (OR 95%CI= 0.93 (0.89,0.98)), CD19 on CD20- CD38- (OR 95%CI= 0.96 (0.94,0.99)) and CD38 on IgD+ CD24- (OR 95%CI= 0.97 (0.93,1.00)) has a negative correlation with AC. Both Transitional %B cell (OR 95%CI= 1.10 (1.03,1.16)) and CD25 on IgD+ CD38- (OR 95%CI= 1.01 (1.00,1.02)) has a positive correlation with AC. In the cDCs, only Plasmacytoid DC (OR 95%CI= 1.02 (1.01,1.04)) has a positive correlation with AC. In the Myeloid cells, only CD45 on Gr MDSC (OR 95%CI= 0.97 (0.95,0.99)) has a negative correlation with AC. In the TBNKs, HLA DR++ monocyte %leukocyte (OR 95%CI= 0.96 (0.93,1.00)), CD8br %leukocyte (OR 95%CI= 0.93 (0.88,0.99)), FSC-A on CD14+ monocyte (OR 95%CI= 0.97 (0.95,0.99)) and CD19 on B cell (OR 95%CI= 0.98 (0.96,1.00)) has a negative correlation with AC. Only SSC-A on T cell (OR 95%CI= 1.04 (1.01,1.06)) has a positive correlation with AC. In the Tregs, only CD28 on CD39+ CD8br (OR 95%CI= 1.02 (1.00,1.03)) has a positive correlation with AC. CD3 on CD45RA+ CD4+ (OR 95%CI= 0.98 (0.96,1.00)), CD25 on CD28+ CD4+ (OR 95%CI= 0.93 (0.88,0.99)) and CD4 on CD39+ secreting Treg (OR 95%CI= 0.98 (0.96,1.00)) has a positive correlation with AC. In the reverse MR results of immune cells and AC, all MR analysis pvals and adjust P are greater than 0.05, indicating that AC has no effect on the included immune cells (shown in the Supplementary material).

Panel	Trait.type	Trails	method	nsnp	pval	OR(95%CI)	adjustP
B cell	Absolute count	IgD+ CD38−	Inverse variance weighted	17	0.0031	0.93 (0.89−0.98)	0.009905730
B cell	Relative count	Transitional %B cell	Inverse variance weighted	15	0.0022	1.10 (1.03−1.16)	0.008761384
B cell	MFI	CD19 on CD20− CD38−	Inverse variance weighted	19	0.0068	0.96 (0.94−0.99)	0.015507741
B cell	MFI	CD25 on IgD+ CD38−	Inverse variance weighted	28	0.0105	1.01 (1.00−1.02)	0.020921826
B cell	MFI	CD38 on IgD+ CD24−	Inverse variance weighted	17	0.0299	0.97 (0.93−1.00)	0.036832388
cDC	Absolute count	Plasmacytoid DC	Inverse variance weighted	30	0.0062	1.02 (1.01−1.04)	0.016461583
Myeloid cell	MFI	CD45 on Gr MDSC	Inverse variance weighted	18	0.0019	0.97 (0.95−0.99)	0.010267745
TBNK	Relative count	HLA DR++ monocyte %leukocyte	Inverse variance weighted	8	0.0327	0.96 (0.93−1.00)	0.037319291
TBNK	Relative count	CD8br %leukocyte	Inverse variance weighted	16	0.0165	0.93 (0.88−0.99)	0.023933909
TBNK	Morphological parameter	FSC−A on CD14+ monocyte	Inverse variance weighted	23	0.0016	0.97 (0.95−0.99)	0.012757056
TBNK	MFI	CD19 on B cell	Inverse variance weighted	24	0.0467	0.98 (0.96−1.00)	0.049837775
TBNK	Morphological parameter	SSC−A on T cell	Inverse variance weighted	22	0.0016	1.04 (1.01−1.06)	0.025490521
Treg	MFI	CD3 on CD45RA+ CD4+	Inverse variance weighted	31	0.0181	0.98 (0.96−1.00)	0.024132903
Treg	MFI	CD28 on CD39+ CD8br	Inverse variance weighted	20	0.0139	1.02 (1.00−1.03)	0.024712364
Treg	MFI	CD25 on CD28+ CD4+	Inverse variance weighted	5	0.0149	0.93 (0.88−0.99)	0.023825651
Treg	MFI	CD4 on CD39+ secreting Treg	Inverse variance weighted	22	0.0470	0.98 (0.96−1.00)	0.047044443

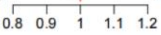

Figure 9: Forest plots showed the causal associations between immune cell traits and AC by using Inverse variance weighted. CI: confidence interval

3.5 Sensitivity Analysis

In sensitivity analysis, we conducted heterogeneity and pleiotropy analyses for the types of immune cells included in our study and the corresponding ADs. Our results all yielded pvals greater than 0.05, indicating the absence of heterogeneity and pleiotropy SNPs. Additionally, we performed leave-one-out analysis, which also demonstrated a stability of our results. Heterogeneity results, pleiotropy analysis results, the scatter plots and the leave-one-out plots can all be found in the supplementary materials.

4. Discussion

Leveraging a substantial repository of publicly accessible genetic data, our study investigated the causal relationships between 731 immune cell phenotypes and 3 ADs. To our knowledge, this is the first MR analysis to investigate the causal relationships between multiple immune phenotypes and ADs.

BAFF-R serves as a critical receptor for B cells and plays a significant role in the regulation of allergic reactions [23]. BAFF-R on IgD+ CD38dim is positively correlated with ACD, indicating that an increase in this cell population may elevate the risk of ACD. Studies have demonstrated that CD4+CD8dim assume a unique function in controlling chronic viral infections [24]. Our findings corroborate this observation. Myeloid DCs are the primary antigen-presenting cells involved in ACD, capturing and presenting allergens to T cells to initiate an immune response [25]. CD86, a costimulatory molecule expressed by DCs, provides additional signals to activate T cells and promotes the development of immune responses [26]. In cases of ACD, allergens are initially captured and processed by these activated DCs before migrating to lymph nodes where they activate specific T cell populations, ultimately triggering skin inflammation. Our study proves this point through both Absolute count and MFI methods. Numerous studies have indicated that the CD40 molecule on CD14-CD16+ monocytes in non-canonical monocytes signals macrophages to a large extent in favor of expressing genes involved in pro-inflammatory responses and tissue remodeling [27] [28] [29]. This aligns with our findings.

Allergic contact dermatitis caused by drug contact with the skin is a specific type of ACD that refers to an allergic reaction caused by skin contact with a pharmaceutical ingredient, such as a topically applied ointment, liquid, or patch [30]. According to our observations, the types of immune cells associated with ACD caused by drug contact with the skin are essentially similar to those of ACD. Notably, HLA-DR plays a critical role in mediating the pathogenesis of ACD caused by drug contact with the skin. Numerous studies have substantiated this association: varying levels of HLA-DR expression can influence the risk of ACD caused by drug contact with the skin [31]. Therefore, for effective prevention and treatment of ACD caused by drug contact with the skin, we should pay more attention to HLA-DR on the basis of the prevention and treatment of ACD.

Macrophages, dendritic cells, and mast cells play crucial roles in the innate immune response to allergens that penetrate the conjunctival epithelium. During this response, dendritic cells and mast cells act as intermediaries between innate and adaptive immunity [32]. Immunoglobulin D (IgD) is a type of antibody expressed on the surface of B cells [33]. CD38 is a multifunctional cell surface protein involved in nicotinamide adenine dinucleotide (NAD) homeostasis in types of cells and tissues, which can be found in many immune cells and non-immune cells. Previous studies have demonstrated that CD38 significantly influences the regulation of innate immunity [34] [35]. Consequently, IgD+ CD38- exhibit protective effects against AC. CD25 is the α chain of the IL-2 receptor and is often seen as a hallmark of cell activation [36]. CD25 on IgD+ CD38- is positive, indicating that IgD+ CD38- is activated, affecting AC exacerbation. CD45 on Gr MDSC affects the pathogenesis of AC by inhibiting T cell activity and promoting immune tolerance [37]. Plasmacytoid DCs represent a specialized subset with significant capacity for producing large quantities of type I interferon (IFN) [38], which may indirectly influence allergic responses through modulation of Th1/Th2 cell balance. Our research findings align with these observations by targeting the regulation of immune cell populations throughout the natural history of AC for early prevention and intervention.

5. Conclusion

Based on the findings of this study, we have identified potential causal associations between 731 immune cell signatures and various ADs. Our research offers novel

biomarkers and therapeutic targets for the clinical prevention and treatment of ADs, thereby opening new avenues for future interventions.

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