Causal relationship between 731 immune cell immunophenotypes and giant cell arteritis: a Mendelian randomisation study

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Abstract

Objective

Giant cell arteritis (GCA) is the most common form of vasculitis among adults aged 50 and over, characterised by systemic inflammation and the potential for severe complications such as blindness and stroke. Despite its prevalence, the aetiology of GCA remains incompletely understood, with current treatments largely relying on corticosteroids, which carry significant side effects.

Methods

Our study utilised a bilateral Mendelian randomisation (MR) approach to investigate the causal impact of immune cells on GCA. By analysing 731 immune cell phenotypes from genome-wide association studies (GWAS) data of 3,757 European individuals, we aimed to identify genetic variants as instrumental variables for immune cell traits, thereby elucidating their role in GCA susceptibility. To ensure a robust examination, we used various MR techniques, including the inverse-variance weighted (IVW) method, and carried out sensitivity analyses to assess the dependability of our findings.

Results

Forward MR analysis identified three immune traits with significant associations with GCA: a protective effect from the absolute count of monocytic myeloid-derived suppressor cells and increased risks associated with HLA DR expression on CD14+ CD16-, and CD14+ monocytes. The sensitivity analyses yielded results consistent with the main findings. The reverse MR analysis yielded no statistically significant results.

Conclusion

The study advances our understanding of the immunological underpinnings of GCA, suggesting that specific immune cells significantly influence the disease's development. These insights pave the way for the exploration of new therapeutic targets that could offer more targeted and tolerable treatment options beyond the current reliance on corticosteroids. Further research is needed to validate these potential biomarkers and therapeutic targets in clinical settings.

Key words

giant cell arteritis, Mendelian randomisation, immune cell, genome-wide association studies, single nucleotide polymorphisms

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Introduction

Giant cell arteritis (GCA), commonly referred to as temporal arteritis, is a prominent type of vasculitis that mostly affects medium to large arteries, especially those originating from the aortic arch, such as the temporal arteries (1). This disorder is characterised by the presence of multinucleated giant cells in the inflamed walls of arteries. It is the most prevalent form of vasculitis in individuals who are 50 years old or older, which emphasises the complex connection between ageing, immunity, and vascular health (2, 3).

The clinical presentations of GCA exhibit a wide range of symptoms, indicative of the systemic nature of the disease and the variability in the affected arterial territories. These symptoms encompass severe headaches, jaw claudication, visual disturbances, as well as systemic manifestations like fever, weight loss, and polymyalgia rheumatica, a condition closely linked to GCA (4, 5).The potential ramifications of untreated GCA, such as permanent blindness caused by anterior ischaemic optic neuropathy, stroke, and aortic aneurysm, highlight the critical need for prompt diagnosis and care. The aetiology of GCA remains incompletely elucidated, with research indicating a multifaceted interaction between genetic susceptibility, environmental factors, and dysregulated immune responses. Epidemiologically, individuals of Northern European descent have a pronounced predilection for developing GCA; incidence rates rise with age, highlighting the convergence of genetic predisposition and age-related immune alterations (6, 7).

The diagnosis of GCA primarily relies on clinical evaluation, complemented by laboratory investigations and imaging modalities. Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are frequently observed but lack specificity (8). Recent advancements in non-invasive imaging modalities such as ultrasound, such as ultrasound, magnetic resonance imaging (MRI), and positron emission tomography (PET), have proven to be valuable tools for the diagnosis and monitoring of disease activity (9). As distinct histopathological characteristics such as inflammation, giant cell infiltration, and disruption of the internal elastic lamina are revealed by temporal artery biopsy, it remains the diagnostic gold standard (5, 7).

The primary approach to managing giant cell arteritis involves the prompt initiation of corticosteroids, which remain the foundation of treatment (10). High-dose glucocorticoids have been shown to significantly alleviate symptoms and decrease the occurrence of severe complications, such as vision loss (11-13). Nevertheless, the long-term use of corticosteroids is fraught with adverse effects, necessitating research into alternative therapeutic strategies (14). Recent progress has brought attention to the possibility of biologic medicines that focus on specific immune pathways, providing a glimpse into a future when more precise and well-tolerated treatments for GCA are possible (15-17).

The immune system involvement in GCA is intricate, encompassing both innate and adaptive immunological responses. T cells have a crucial role in coordinating the inflammatory response in arteries that are affected (18-20). The interplay among T cells, macrophages, and dendritic cells within the vascular wall stimulates the release of pro-inflammatory cytokines and growth factors, which in turn leads to the development of granulomatous inflammation (21-23).

The pathophysiological mechanisms underlying GCA entail the activation of vascular dendritic cells, followed by the invasion of the arterial wall by $CD4^+$ T cells and macrophages, leading to the formation of giant cells (24, 25). The aforementioned cellular interactions lead to the secretion of growth factors and pro-inflammatory cytokines, which ultimately precipitate ischaemic symptoms, luminal constriction, and arterial wall injury (25, 26).

The clinical presentation of GCA encompasses a wide range of symptoms, from localised scalp tenderness and headaches to systemic manifestations like polymyalgia rheumatica, highlighting the systemic nature of this vasculitis. Ongoing research endeavours are

dedicated to investigating the intricate mechanisms driving the disease, with a specific emphasis on the discovery of novel biomarkers for early detection and the development of targeted therapeutic approaches. The complicated interplay between various immune cells and cytokines in the development of GCA is a challenging riddle that has to be solved in order to enhance therapeutic approaches.

Mendelian randomisation (MR) is an influential epidemiological technique that utilises genetic variants as instrumental variables to deduce causal connections between modifiable risk factors and health outcomes (27). This method leverages the random allocation of genes from parents to offspring during meiosis, which mirrors the randomisation process in controlled trials, to overcome the limitations of observational studies, such as confounding and reverse causation (28, 29). The emergence of genome-wide association studies (GWAS) has greatly strengthened the field of MR. GWAS have identified numerous genetic variants associated with specific traits and diseases, providing the necessary tools for MR analyses (30-33). The utility of MR resides in its capacity to furnish causal evidence in the absence of randomised controlled trials, which may be impractical or ethically questionable in the case of particular exposures. Through the clarification of causal linkages, MR can provide guidance for public health policy, offer insights for clinical practice, and pinpoint potential targets for therapeutic intervention.

The primary objective of our research is to utilise genetic variants as instrumental variables in order to definitively establish the causal influence of immune cells on GCA. Through this approach, we aim to address a significant knowledge deficit, potentially identifying novel biomarkers for GCA and discovering new therapeutic targets. This initiative not only offers the potential to advance our comprehension of GCA's immunopathogenesis but also to inform the development of more tailored and efficacious treatment approaches, thereby addressing a pressing requirement in the management of GCA.

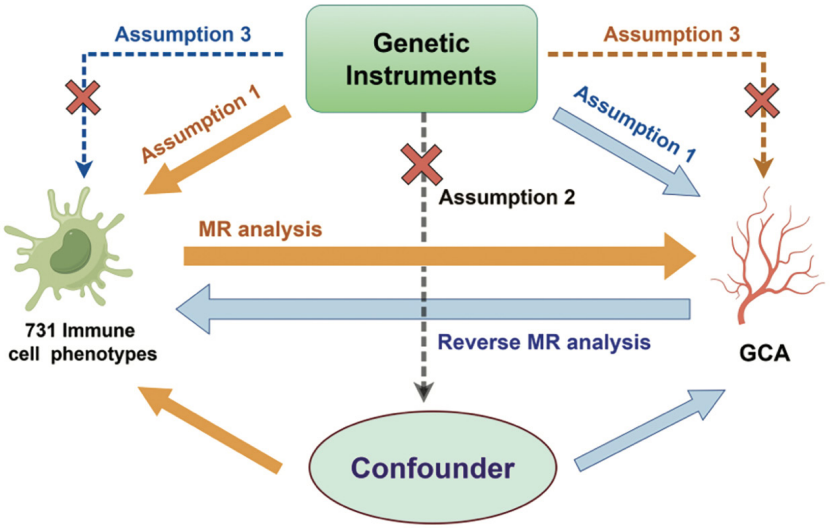

Fig. 1. Schematic diagram of our Mendelian randomisation assumptions. By Figdraw.

Materials and methods

Study design

To elucidate the causal relationship between giant cell arteritis and 731 immune cell signatures, which are systematically classified into seven distinct groups, we employed a two-sample MR analysis. This advanced statistical approach leverages genetic variations as instrumental variables (IVs), serving as proxies for the risk factors under investigation (34). The integrity of MR analysis hinges on satisfying three core criteria for the selection of valid instrumental variables: (i) a robust association must exist between the genetic variant and the immune cell signature of interest (the exposure); (ii) the genetic variant should not be linked to any confounders that could influence both the exposure and the outcome concurrently; and (iii) the influence of the genetic variant on GCA must be exclusively via its effect on the immune cell signature, with no indirect paths involved (Fig. 1).

Our methodological rigor extended to the ethical domain, where all included studies received approval from their respective institutional review boards, ensuring that participants were thoroughly briefed on the study's scope and provided their informed consent prior to participation.

Immunity-wide GWAS data sources

In the realm of genomics research, we procured pertinent summary statistics for each immune trait from the GWAS Catalogue, spanning accession numbers GCST0001391 to GCST0002121. This comprehensive dataset encompasses 731 distinct immunophenotypes, detailed as follows: 118 absolute cell counts (AC), 389 median fluorescence intensities (MFI) indicative of surface antigen levels, 32 morphological parameters (MP), and 192 relative cell counts (RC). This dataset intricately catalogues MFI, AC, and RC metrics across a variety of immune cells, including B cells, CDCs (dendritic cells), mature T cells, monocytes, myeloid cells, TBNK (T cells, B cells, natural killer cells), and Treg (regulatory T cells) panels, with MP attributes specifically delineating CDC and TBNK panels. The foundational genome-wide association studies (GWAS) that investigated these immune traits were conducted on a cohort of 3,757 European individuals, meticulously avoiding any overlap in cohorts (35). Leveraging a Sardinian sequence-based reference panel for the imputation process, the studies meticulously analysed approximately 22 million single nucleotide polymorphisms (SNPs), all genotyped using high-density arrays. To ensure the accuracy of association testing, covariate adjustments for sex, age, and the square of age were systematically applied.

Genome-wide association study (GWAS) data sources for GCA

The GWAS summary statistics pertinent to GCA were sourced from FinnGen's

most recent publication, labelled "DF10" and timestamped December 18, 2023. This database encapsulates an exhaustive examination of a cohort comprising 400,421 individuals of European descent, with 1,066 cases delineated alongside 399,355 controls (36). More detailed information on this data is available at https://r10.finngen.fi/.

Selection of instrumental variables

To select instrumental variables (IVs), we utilised single nucleotide polymorphisms (SNPs) to investigate the causal relationships between various immunophenotypes and susceptibility to GCA. This was accomplished using the "MRInstruments" package, which offers robust tools for identifying and validating genetic instruments essential for conducting MR analyses. The process was guided by a meticulously structured SNP selection protocol, anchored in stringent criteria to ensure the robustness of our causal inferences:

I. SNP Selection for Immune Traits: utilising the R software (v. 4.3.1), our initial SNP selection focused on those associated with immune cell traits, setting a significance threshold at P<5×10^-8.

II. Guaranteeing SNP independence: in order to preserve the autonomy of our instrumental variables, we eliminated SNPs that were in linkage disequilibrium (with a r^2 value of 0.001) within a radius of 10,000 kb. This step was crucial to minimise the risk of bias from correlated genetic variants.

III. Exclusion of SNPs linked to confounders: the PhenoScanner database, a comprehensive repository of SNP associations, was instrumental in identifying and excluding SNPs associated with potential confounders or directly with GCA outcomes (37). This precaution was taken to ensure the validity of our instrumental variables.

IV. Instrumental strength assessment: the strength of each SNP as an instrumental variable was quantified using the F statistic, with SNPs exhibiting an F statistic <10 being excluded from our analysis. This measure helped ensure that only SNPs with sufficient power to provide reliable causal estimates were included (38).

By adhering to these rigorous protocols, we aimed to establish a solid foundation for our Mendelian randomisation analysis, thereby enhancing the reliability and validity of our findings in elucidating the causal relationships between immune cell phenotypes and GCA susceptibility.

Statistical analysis

For comprehensive analysis, we utilised R software (v. 4.3.1) to explore the intricate causal relationships between 731 immunophenotypes and giant cell arthritis. This exploration was facilitated by leveraging the capabilities of the "TwoSampleMR" and "MRPRESSO" packages, which are instrumental in MR analysis (39, 40). Our methodology encompassed a variety of statistical techniques to ensure the reliability and validity of our findings:

1. In MR analyses, several statistical techniques are employed to estimate causal relationships, each suited to different assumptions about the genetic instruments used. Inverse variance weighting (IVW) is commonly used when all genetic variants are considered valid instruments, calculating a weighted average where weights are the inverse of the variance of each estimate. MR-Egger, in contrast, adjusts for pleiotropic effects by allowing for some invalid instruments, providing a test for directional pleiotropy alongside the causal estimate. The weighted median-based method offers a robust alternative, delivering a consistent estimate as long as at least 50% of the information comes from valid instruments. Mode-based estimation identifies the most frequently occurring estimate across variants, useful when dealing with heterogeneous instrument validity. Lastly, maximum likelihood employs a comprehensive likelihood function based on genetic associations, optimising efficiency under correct model assumptions and accommodating more complex MR scenarios, including multiple variables and nonlinear effects. Together, these methods provide a versatile toolkit for addressing a range of challenges in causal inference using genetic data.

2. Heterogeneity assessment: We employed Cochran's Q statistic along with corresponding *p*-values to evaluate heterogeneity among the selected instrumental variables. In instances where the null hypothesis was rejected, indicating significant heterogeneity, we transitioned from a fixed-effects model to a random-effects IVW model to better accommodate the variability among genetic instruments.

3. Addressing horizontal pleiotropy: the MR-Egger method was pivotal in our analysis for its ability to adjust for the effects of horizontal pleiotropy, where genetic variants might influence the outcome through pathways other than the exposure of interest. The intercept term of the MR-Egger regression provides an indication of the presence of horizontal pleiotropy.

4. Identification and correction of pleiotropic outliers: The MR-PRESSO approach was specifically utilised to detect and correct for horizontal pleiotropic outliers, ensuring that our causal estimates were not biased by such anomalies (41).

5. Robustness checks: To affirm the integrity of our results, funnel plots and scatter plots were employed to visually inspect the presence of outliers and assess the homogeneity of the instrumental variables. These plots served as a testament to the robustness of our correlation results.

6. Directionality validation: Lastly, the Steiger test was applied to confirm the correct directionality of the effects estimated by the SNPs, further solidifying the credibility of our causal inferences (42).

To evaluate the associations between variables, we calculated odds ratios (OR) and their corresponding 95% confidence intervals (CI). The OR is a measure of association that quantifies the relationship between an exposure and an outcome. Confidence intervals provide a range of values that are likely to contain the true OR, offering an indication of the precision of our estimates. Furthermore, the comprehensive multiple hypothesis testing necessitated the application of the False Discovery Rate (FDR) correction to safeguard against Type I errors, a critical measure given the extensive scope of our analysis (43). This statistical methodology, implemented through the "MendelianRan-

Exposure	N.of SNP	Method	OR(95% CI)	P_FDR
Mo MDSC AC	Inverse variance weighted	5	0.75 (0.67 to 0.85)	0.0015
	Weighted median	5	0.77 (0.67 to 0.89)	0.0214
	MR Egger	5	0.65 (0.36 to 1.15)	0.9680
	Maximum likelihood	5	0.75 (0.67 to 0.85)	0.0026
	Weighted mode	5	0.77 (0.66 to 0.90)	0.9936
HLA DR on CD14+ CD16− monocyte	Inverse variance weighted	5	1.26 (1.13 to 1.39)	0.0023
	Weighted median	5	1.26 (1.12 to 1.42)	0.0156
	MR Egger	5	1.15 (0.82 to 1.61)	0.9680
	Maximum likelihood	5	1.26 (1.13 to 1.40)	0.0028
	Weighted mode	5	1.23 (1.09 to 1.39)	0.9936
HLA DR on CD14+ monocyte	Inverse variance weighted	5	1.27 (1.14 to 1.41)	0.0023
	Weighted median	5	1.27 (1.13 to 1.43)	0.0156
	MR Egger	5	1.15 (0.81 to 1.64)	0.9680
	Maximum likelihood	5	1.27 (1.14 to 1.41)	0.0028
	Weighted mode	5	1.24 (1.09 to 1.41)	0.9936

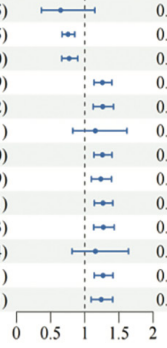

Fig. 2. The effect of immune cells on giant cell arteritis.
OR: odds ratio; CI: confidence interval.

domisation" and "stats" R packages, is essential for maintaining the integrity of our inferential conclusions. Initially, conduct individual MR analyses for each genetic variant to test their association with the outcome, resulting in a list of *p*-values. Collect and sort these *p*-values in ascending order. Apply the Benjamini-Hochberg procedure to calculate adjusted *p*-values, identifying the largest *p*-value where the adjusted *p*-value is less than or equal to the desired FDR level (0.05). Reject the null hypotheses for all tests with adjusted *p*-values below this threshold, identifying the significant genetic variants. By adjusting significance thresholds to consider the large number of statistical tests conducted, FDR correction ensures that our results are not merely artifacts of multiple tests but reflect true causal relationships. Finally, report the variants that remain significant after FDR correction, including the adjusted *p*-values and the significance threshold, thereby improving the scientific rigor of our conclusions regarding causal relationships.

Results

Investigating the impact of immunophenotypes on GCA

To determine the causal effect of immunophenotypes on GCA, we conducted a two-sample MR analysis using primarily the inverse variance weighting method. Critical to our analysis was the implementation of the false discovery rate correction to navigate the complexities of multiple testing, setting a stringent significance threshold at P_FDR<0.05. This meticulous approach led to the identification of three immune traits exhibiting a direct and statistically significant association with GCA, including one from the myeloid cell panel and two from the monocyte group, underscoring the nuanced role of immune cell dysregulation in GCA. Specifically, we observed a statistically significant association for monocytic myeloid-derived suppressor cells absolute count (OR=0.754, 95% CI: 0.670–0.850, P_FDR=0.0015), highlighting a potential protective effect against GCA. Conversely, increased levels of HLA DR on CD14$^+$ CD16- monocytes (OR=1.257, 95% CI: 1.333–1.394, P_FDR=0.0023) and HLA DR on CD14$^+$ monocytes (OR=1.265, 95% CI: 1.137–1.408, P_FDR=0.0023) were associated with a heightened risk of developing GCA. Figure 2 illustrates these findings.

The robustness of our findings on the causal links between immunophenotypes and giant cell arthritis was affirmed through comprehensive sensitivity analyses and additional MR techniques, detailed in Supplementary Tables S1 and S2. We effectively ruled out horizontal pleiotropy, as indicated by the MR-Egger intercept and MR-PRESSO global test (Suppl. Table S2), suggesting our genetic instruments were not influencing GCA through alternative pathways. Visual assessments via scatter and funnel plots (Fig. 3 and 4) further confirmed the stability of our results, showing no evidence of pleio-

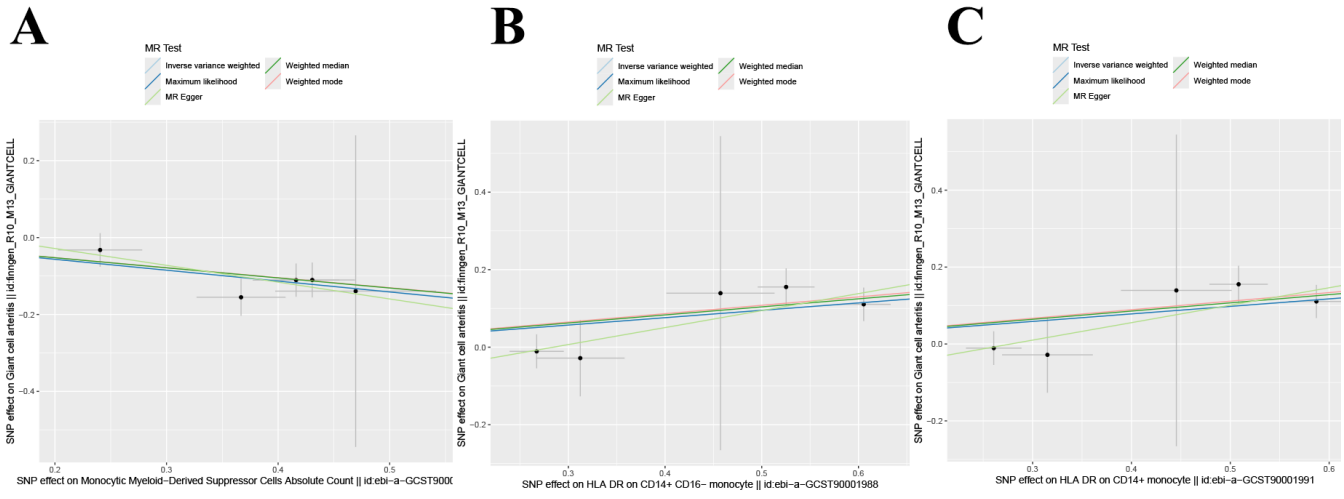

Fig. 3. Causal associations between immune cells (exposure) and GCA (outcome).
A: Scatter plot between monocytic myeloid-derived suppressor cells absolute count and GCA risk; **B**: Scatter plot between HLA DR on CD14+ CD16- monocytes and GCA risk; **C**: Scatter plot between HLA DR on CD14+ monocytes and GCA risk.

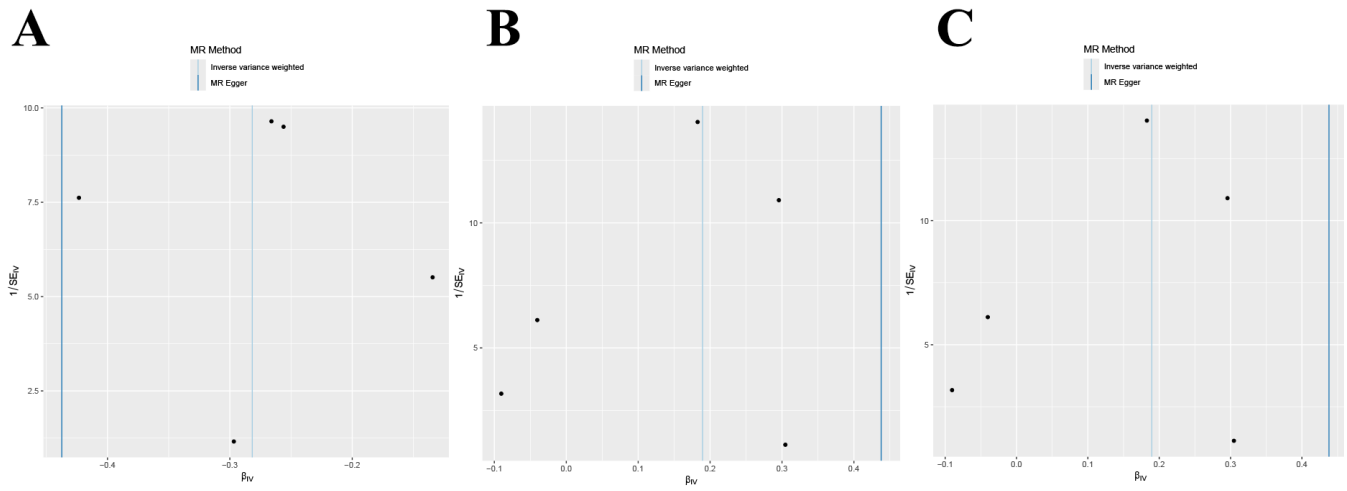

Fig. 4. Funnel plot for the overall heterogeneity between immune cells and GCA.
A: Funnel plot between monocytic myeloid-derived suppressor cells absolute count and GCA risk; **B**: Funnel plot between HLA DR on CD14+ CD16- monocytes and GCA risk; **C**: Funnel plot between HLA DR on CD14+ monocytes and GCA risk.

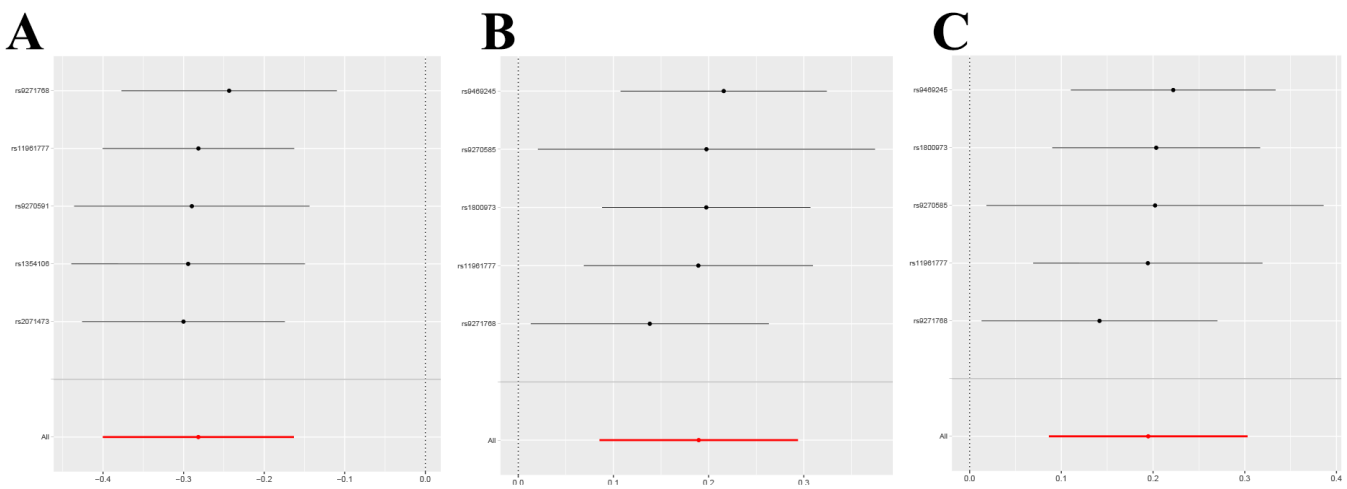

Fig. 5. The leave-one-out analysis of causal impacts of immune cell traits on GCA.
A: The leave-one-out analysis of causal impacts of monocytic myeloid-derived suppressor cells absolute count on GCA; **B**: The leave-one-out analysis of causal impacts of HLA DR on CD14+ CD16- monocytes on GCA; **C**: The leave-one-out analysis of causal impacts of HLA DR on CD14+ monocytes on GCA.

tropic bias.

Further, a leave-one-out analysis (Fig. 5) demonstrated the robustness of our results, showing that no single SNP disproportionately influenced the causal estimates, indicating a lack of pleiotropic bias. Lastly, the MR Steiger test, detailed in Supplementary Table S5, confirmed the correct directionality of the associations for all analysed SNPs, indicating that these genetic variants were indeed more strongly associated with the immunophenotypes (the exposure) than with GCA (the outcome). This final layer of validation ensures that our analysis accurately reflects the true nature of these complex biological relationships, providing a solid foundation for future research and potential therapeutic interventions targeting these immune traits in GCA.

Exploration of the causal effect of GCAon immunophenotypes

We performed a comprehensive reverse MR with GCA as exposure and 731 immune cell traits as outcome. In instances where the pool of eligible SNPs fell below 3, we adjusted our criteria, extending the *p*-value threshold to less than $5x10^{-6}$. This modification, while broadening the eligibility criteria, was implemented without compromising the foundational principles essential to MR analyses. Multiple MR techniques were employed, and the findings suggested no convincing proof to substantiate a causal impact of GCA on immunophenotypes (all P-FDR values were greater than 0.05). The results of the four methods and sensitivity analysis are presented in Supplementary Tables S3 and S4.

Discussion

By revealing both protective and risk factors associated with the disease, the forward MR analysis that we have implemented in an innovative manner in our research has yielded significant insights into the causal relationship between three distinct immune cells and GCA. This study is significant as it represents a pioneering application of MR

in elucidating the intricate interactions between immune cell dysregulation and GCA. The results of what we found correspond with and enhance the existing body of research, specifically highlighting the involvement of monocytic myeloid-derived suppressor cells, HLA DR on CD14+ CD16- monocytes, and HLA DR on CD14+ monocytes.

In contrast, our reverse MR analysis did not conclusively show causal linkages, despite identifying giant cell arteritis as the exposure that influences immune cell traits. This finding suggests that while some immune cells may influence the vulnerability to GCA, the development of GCA may not have a substantial effect on the characteristics of these immune cells through genetic pathways. It also emphasises the necessity for further investigation to clarify the causal relationship between GCA and changes in the immune system.

The distinct roles of the immune cells identified in our study have been previously explored to varying extents in GCA research. For example, Monocytic Myeloid-Derived Suppressor Cells (M-MDSCs), as a subset of myeloid-derived suppressor cells, have been recognised for their potent immunosuppressive functions, which are critical in the context of chronic inflammation or stress, known for their potent immunosuppressive capabilities, primarily function to mitigate immune responses, a trait that is beneficial in controlling non-resolving inflammation and immunopathology seen in various diseases (44, 45). The protective effect of monocytic myeloid-derived suppressor cells absolute count against GCA, as indicated by our analysis (OR=0.754, 95% CI: 0.670–0.850, P-FDR=0.0015), introduces a potential counter-regulatory mechanism within the pathophysiology of GCA. Given the inflammatory onslaught characteristic of GCA, where immune cells infiltrate and damage the arterial wall, the immunosuppressive nature of M-MDSCs could represent a physiological attempt to dampen such responses, thus reducing the risk of developing GCA (46). Further research is warranted to examine the participation of M-MDSCs in GCA, as this could reveal novel diagnostic indicators or therapeutic targets that have a substantial bearing on the management of this vasculitis.

Similarly, heightened HLA-DR expression on monocytes has been linked to increased antigen-presenting functions, potentially intensifying the inflammatory response in GCA (47). The presence of HLA-DR on monocytes is indicative of immune activation and has been implicated in the pathogenesis of several autoimmune and inflammatory conditions (48). These findings are supported by research demonstrating the participation of monocytes and myeloid cells in the inflammatory environment of giant cell arteritis, indicating their dual functions as both contributors and regulators of the disease progression (49).

Furthermore, a significant association was found between the presence of HLA-DR on CD14+ CD16- monocytes and the susceptibility to GCA development. This discovery is significant as it highlights the intricate involvement of immune cell dysregulation in the onset of GCA, an area that has been lacking in existing literature. Prior studies have confirmed the increase in HLA-DR expression in systemic inflammatory situations, suggesting its role in enhancing the ability of monocytes to present antigens and activating autoimmune responses (50, 51). Our work corroborates these findings by suggesting that heightened HLA-DR expression on CD14+ CD16- monocytes may play a role in the vascular inflammation associated with GCA, potentially serving as a biomarker for disease severity or a target for therapeutic interventions.

Additionally, the findings indicate that an up-regulation of HLA DR expression on CD14+ monocytes correlate with a heightened vulnerability to GCA. This correlation is significant due to the pivotal role of monocytes in immune responses, specifically in antigen presentation and cytokine production, which play a crucial role in the pathogenesis of GCA. The granulomatous inflammation seen in GCA, marked by the infiltration of activated immune cells into the arterial wall, serves as the foundation for the disease' systemic and vascular symptoms (52, 53). The selective increase in HLA DR expression on CD14+ monocytes implies an augmented capacity for antigen presentation, potentially contributing to the pathogenesis of the aberrant immune response targeting arterial walls in GCA. Consequently, the predominant therapeutic approach for GCA, centred on glucocorticoid administration, offers insight into the underlying disease mechanisms. The effectiveness of glucocorticoids in alleviating symptoms and averting complications underscores the inflammatory nature of GCA, with dysregulation of monocytes playing a pivotal role. The modulation of monocyte subsets post-treatment hints at their contribution to disease pathology and remission (54, 55).

The study we conducted marks significant progress toward clarifying the onset of giant cell arteritis by using bilateral MR analysis to investigate the causal connections between distinct immune cells and GCA. This methodology has identified three immune phenotypes that are closely linked to GCA, providing novel perspectives on the immunopathological mechanisms that drive the disease.

Comparatively, prior studies have primarily concentrated on the inflammatory pathways and the efficacy of conventional immunosuppressive therapies in treating GCA. Our discovery of immune cells associated with GCA enhances our comprehension of the disease, indicating that targeting these immune cell functions could present new treatment options or supplementary therapies to existing glucocorticoid treatments, potentially reducing their negative side effects and enhancing patient outcomes.

While our work provides a fresh viewpoint to GCA research, it is crucial to recognise its limitations. The reverse MR analysis conducted did not definitively establish a causal relationship between GCA and immune cell phenotypes, probably due to the complex nature of interactions within the immune system that may not be completely understood simply via genetic connections. Additionally, our analysis is restricted by the genetic homogeneity of the population studied, predominantly of European descent, which may limit

the generalisability of the results to other ethnic groups (35). Subsequent research efforts should strive to include a more diverse cohort in order to enhance the overall applicability of the findings. Based on the findings of our study, further study should focus on figuring out the molecular processes via which the immune cells detected in GCA affect the disease. This may be achieved by conducting clinical and laboratory investigations to validate possible treatment targets. On top of that, conducting longitudinal studies that investigate the chronological development of the alterations in immune cells in connection to the start and advancement of GCA might offer beneficial insights into the deeper roots of the disease and the efficacy of treatment.

Conclusion

In conclusion, our investigation into the role of immune cells in GCA offers a glimpse into the intricate dynamics of immune regulation within vasculitis, setting the stage for future research that could provide critical insights into the immunopathology of GCA. This discovery can aid in clinical decision-making regarding disease prognosis and treatment options. It also offers a new avenue for drug development.

Acknowledgments

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