BRITISH JOURNAL OF HOSPITAL MEDICINE

ARTICLE

Investigating Potential Causal Relationships Between Plasma Protein Ratios and Alopecia Areata: A Bidirectional Mendelian Randomization Study

Xiaoqi Tan[1,2,3], Zhen Yin[4], Shiyu Zhu[4], Liehua Deng[1,3,*]

[1]Department of Dermatology, The First Affiliated Hospital of Jinan University and Jinan University Institute of Dermatology, Guangzhou, Guangdong, China
[2]Department of Dermatology, The Affiliated Hospital, Southwest Medical University, Luzhou, Sichuan, China
[3]Department of Dermatology, The Fifth Affiliated Hospital of Jinan University, Heyuan, Guangdong, China
[4]School of Clinical Medicine, Southwest Medical University, Luzhou, Sichuan, China
*Correspondence: liehuadeng@126.com (Liehua Deng)

Abstract

Aims/Background Several types of plasma protein ratios (PPRs) have been shown to have significant associations with alopecia areata (AA); however, their causal relationships remain to be elucidated. This study aimed to identify causal relationships of 2821 PPRs with AA.

Methods Data from the United Kingdom Biobank Pharma Proteomics Project (n > 54,000) and FinnGen R11 data (862 cases/432,686 controls) were used for a bidirectional Mendelian randomization (MR) analysis. Inverse-variance weighting (IVW), weighted median, simple mode, weighted mode and MR-Egger regression tests were used to estimate the causality between PPRs and AA. Sensitivity analyses were performed to ensure the robustness of our findings.

Results Our analysis showed that the agrin (AGRN)/heparan sulfate proteoglycan 2 (HSPG2) and 2,4-dienoyl-CoA reductase 1 (DECR1)/FK506-binding protein 1B (FKBP1B) ratios were significantly elevated in AA patients ($p < 0.05$). The IVW method revealed that for every one standard deviation (SD) increase in the AGRN/HSPG2 ratio, the risk of AA increased by 44.8% (odds ratio [OR] = 1.448, 95% confidence interval [CI]: 1.200–1.745, $p < 0.001$). Similarly, for every one SD increase in the DECR1/FKBP1B ratio, the risk of AA increased by 65.8% (OR = 1.658, 95% CI: 1.273–2.159, $p < 0.001$). In contrast, reverse MR analysis did not detect any significant causal effects of AA on these two PPRs ($p > 0.05$). Sensitivity analyses confirmed the robustness of our results and ruled out horizontal pleiotropy (MR-Egger intercept $p > 0.05$).

Conclusion This study uncovered the causal relationships between two types of PPRs and AA, offering new insights into the diagnosis, treatment, and underlying mechanisms of AA.

Key words: plasma protein; alopecia areata; Mendelian randomization analysis

Submitted: 29 April 2025 Revised: 17 July 2025 Accepted: 21 July 2025

How to cite this article:
Tan X, Yin Z, Zhu S, Deng L. Investigating Potential Causal Relationships Between Plasma Protein Ratios and Alopecia Areata: A Bidirectional Mendelian Randomization Study. Br J Hosp Med. 2025. https://doi.org/10.12968/hmed.2025.0405

Introduction

Alopecia areata (AA) is a common inflammatory, non-scarring hair loss disorder. The global prevalence of AA is approximately 2%, exhibiting a broad geographical distribution and affecting individuals across all age groups and both biological sexes (Lee et al, 2020). This disorder exhibits significant clinical heterogeneity, with manifestations ranging from localized, well-demarcated patchy hair

loss to complete scalp or even whole-body alopecia. It is often accompanied by multi-system damage involving the skin, immune system, eyes, nerves, and vasculature (Gau et al, 2025; Strazzulla et al, 2018). These symptoms not only markedly impair patients' quality of life but may also lead to psychological disorders such as anxiety and depression, in addition to the life-threatening risks in severe cases (Macbeth et al, 2022). Although studies have demonstrated that AA onset is closely associated with multiple factors, including genetics and environmental influences, its precise pathogenic mechanisms remain incompletely understood and warrant further investigation (Trüeb and Dias, 2018; Zhou et al, 2021).

Multiple other genetic factors have been shown to play important roles in the pathogenesis of AA (Zhou et al, 2021). Specifically, recent genome-wide association studies (GWAS) have achieved substantial progress in clarifying the underlying causes of AA; however, the detailed mechanisms by which altered activity of the products of these genes contributes to disease development remain unclear (Pietzner et al, 2021). Notably, compared to single protein markers, plasma protein ratios (PPRs) are often more sensitive indicators of pathological imbalances (İslamoğlu and Demirbaş, 2020; Kalaycı and Balta, 2022). Therefore, a comprehensive investigation of PPRs may provide important insights into the etiology or complications of AA.

In this study, we investigated a total of 2821 PPRs and focused on the potential biological significance of two key PPRs, the ratio of agrin (AGRN) to heparan sulfate proteoglycan 2 (HSPG2) and the ratio of 2,4-dienoyl-CoA reductase 1 (DECR1) to FK506-binding protein 1B (FKBP1B), in the context of immune regulation and hair follicle metabolism. AGRN, a basement membrane protein, interacts with HSPG2 to participate in extracellular matrix organization (Arikawa-Hirasawa, 2022), potentially influencing the homeostasis of the immune microenvironment surrounding hair follicles. As a critical member of the heparan sulfate proteoglycan family, HSPG2 modulates growth factor signaling pathways, such as fibroblast growth factor and vascular endothelial growth factor, thereby contributing to the dynamic regulation of the hair follicle cycle (Quarto and Amalric, 1994). DECR1, a key enzyme in mitochondrial fatty acid β-oxidation (Locke et al, 2024), may induce metabolic imbalance in hair follicle stem cells when its function is impaired, consequently affecting normal hair follicle physiology. FKBP1B, belonging to the immunophilin family, regulates T-cell activation and autoimmune responses via calcium ion signaling pathways (Kang et al, 2008). It may play a pivotal role in AA pathogenesis. These PPR changes may reflect dual dysregulation of hair follicle metabolism and immune homeland, providing novel insights into AA pathogenesis.

Mendelian randomization (MR) analysis is a method for causal inference that utilizes genetic variants as instrumental variables to approximate randomized controlled trials using data from observational studies. Its fundamental principle involves using genetic variants as instrumental variables to simulate random allocation between exposure and outcome. The present study employed a bidirectional MR analysis to explore the potential causality between PPRs and AA, aiming to

identify potential biomarkers for AA and establish a theoretical foundation for further research.

Methods

Study Design

A bidirectional MR analysis of the causality between PPRs and AA was performed in accordance with strengthening the reporting of observational studies in epidemiology using MR (STROBE-MR) (Skrivankova et al, 2021) recommendations and MR guidelines. The analysis was based on three core assumptions: (1) genetic instrumental variables are strongly associated with the exposure factor; (2) these instrumental variables are not correlated with any confounding factors; and (3) their effects on the outcome occur exclusively through the exposure factor (Fig. 1). Since this study utilized publicly available datasets, no specific ethical review was required.

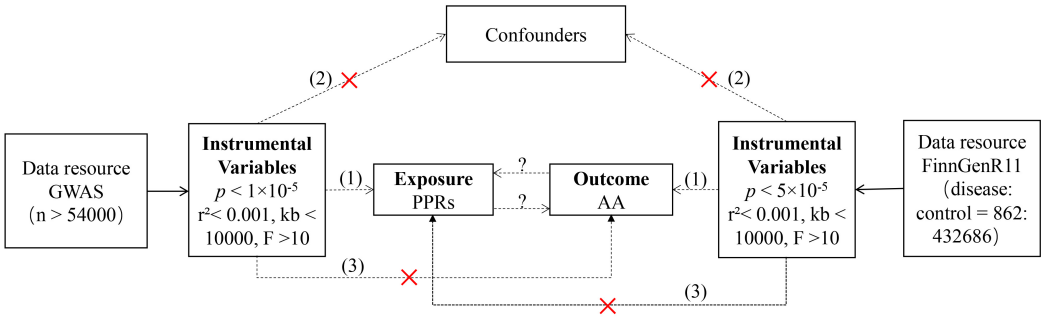

Fig. 1. The overall scheme design of bidirectional MR analysis. (1) Relevance hypothesis; (2) Independence hypothesis; (3) Exclusionary hypothesis. Abbreviations: AA, alopecia areata; GWAS, genome-wide association studies; MR, Mendelian randomization; PPRs, plasma protein ratios.

Data Sources

Sources of genetic data corresponding to the PPRs were derived from a GWAS conducted by Suhre (2024), which utilized data from the United Kingdom (UK) Biobank Pharma Proteomics Project. This project collected samples from more than 54,000 UK Biobank participants. The levels of nearly 1500 circulating blood proteins were quantified using the Olink Explore 1536 affinity proteomics platform (https://ukbiobank.dnanexus.com). The dataset included genetic information associated with 2821 distinct PPR levels.

Data for AA were derived from the R11 version of genomic data released by the FinnGen consortium on 24 June 2024, which comprise 862 European AA patients and 432,686 European control individuals (further details can be accessed at the official website: https://www.finngen.fi/en).

Selection of Instrumental Variables

The forward MR analysis identified single-nucleotide polymorphisms (SNPs) that were significantly associated with the exposure variable at the genome-wide

significance level, using a significance threshold of $p < 1 \times 10^{-5}$ (Li et al, 2022). To ensure a sufficient number of instrumental variables, a threshold of $p < 5 \times 10^{-5}$ was applied in the reverse MR analysis. The independence of selected SNPs was clustered using a pedigree linkage analysis tool (PLINK, version 1.9.0, NIH-NIDDK Bioinformatics Laboratory, Boston, MA, USA) for linkage disequilibrium (LD) ($r^2 < 0.001$, window size = 10,000 kb). Within each LD cluster, the SNPs with the strongest association (lowest *p*-value) were retained. The *F*-value was calculated (formula: $F = \beta^2/SE^2$) to exclude weak instrumental variables ($F < 10$).

Statistical Analysis

To evaluate the causal relationship between exposure factors and outcomes, this study primarily employed the inverse-variance weighting (IVW) method, supplemented by weighted median, simple mode, weighted mode, and MR-Egger regression tests to enhance the robustness of results. Abnormal SNPs were detected and removed using the MR-pleiotropy residual sum and outlier (MR-PRESSO) test ($p < 0.05$). To control the false positive rate in multiple testing, the Benjamini-Hochberg method was used to correct the false discovery rate (FDR). Specifically, all *p*-values were arranged in ascending order, and then the corrected critical value was calculated according to the Benjamini-Hochberg procedure. The significance threshold was set at 0.05. At the same time, horizontal pleiotropy was assessed via the MR-Egger regression intercept test, in which an intercept $p < 0.05$ indicated the presence of pleiotropy. Heterogeneity among SNPs in IVW and MR-Egger analyses was evaluated using Cochran's Q test ($p < 0.05$) (Zhang et al, 2024). To evaluate the effectiveness and potential multiplicity of the instrumental variables, a funnel plot was used to visualize the causal effect estimates of individual SNPs. The influence of individual SNPs on overall results was assessed using leave-one-out analysis. All statistical analyses were performed using the 'TwoSampleMR' package (version 0.6.7, the Biostatistics Research Team of the Medical Research Council, Bristol, UK) in R (version 4.4.1; R Core Team, Vienna, Austria).

Results

Forward MR Analysis of the Association of PPRs With AA

As illustrated in a volcano plot (Fig. 2), our analysis revealed that among 2821 PPRs, the AGRN/HSPG2 and DECR1/FKBP1B ratios were significantly elevated in AA patients ($p < 0.05$), selected for their robust statistical significance and biological relevance. With AA as the outcome variable and the AGRN/HSPG2 and DECR1/FKBP1B ratios as exposure variables, 41 and 22 strongly associated SNPs were identified, respectively (**Supplementary Table 1**).

A forest plot of data acquired using a forward MR analysis based on these methods further indicated the significant associations between these two PPRs and AA (Fig. 3). The IVW method demonstrated a significant association between the AGRN/HSPG2 ratio and AA (odds ratio [OR] = 1.448, 95% confidence interval [CI]: 1.200–1.745, $p < 0.001$). The weighted median method also detected a significant association (OR = 1.383, 95% CI: 1.121–1.707, $p = 0.003$), while the sim-

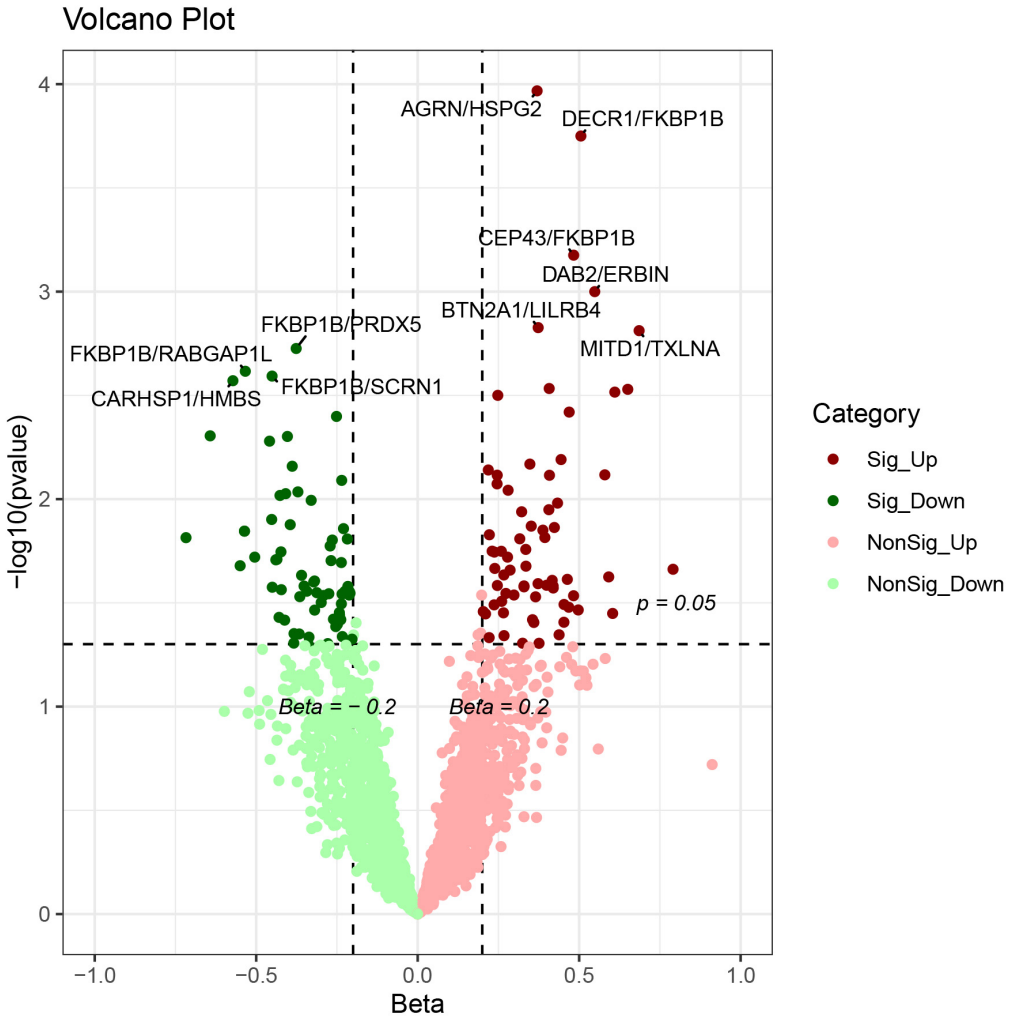

Fig. 2. A volcano plot illustrating the effect size of each PPR in relation to AA. The horizontal axis of the volcano plot represents the beta value (effect quantity), the vertical axis represents –log10 (*p*-value), and the dashed line represents $p = 0.05$. Abbreviations: AA, alopecia areata; PPR, plasma protein ratio; AGRN/HSPG2, agrin/heparan sulfate proteoglycan 2; DECR1/FKBP1B, 2,4-dienoyl-CoA reductase 1/FK506-binding protein 1B.

ple mode method did not detect any significant correlation (OR = 1.382, 95% CI: 0.753–2.538, $p = 0.303$). Similarly, for the DECR1/FKBP1B ratio and AA, both the IVW (OR = 1.658, 95% CI: 1.273–2.159, $p < 0.001$) and weighted median methods (OR = 1.610, 95% CI: 1.155–2.244, $p = 0.005$) indicated significant associations, whereas the simple mode method could not uncover significant correlations between the DECR1/FKBP1B ratio and AA (OR = 1.756, 95% CI: 0.773–3.992, $p = 0.193$). The failure of the simple mode method in detecting statistically significant associations is probably attributed to its lower statistical power compared to the IVW and weighted median methods. However, the results from the other methods were largely consistent, supporting the robustness of the causal relationship. The Benjamin-Hochberg method for FDR correction was applied, and the significance threshold was set to 0.05 after correction. After correction, the results from multiple tests indicated an FDR of 0.251 for both PPRs, suggesting a potential risk of false positives, possibly due to limited AA case numbers.

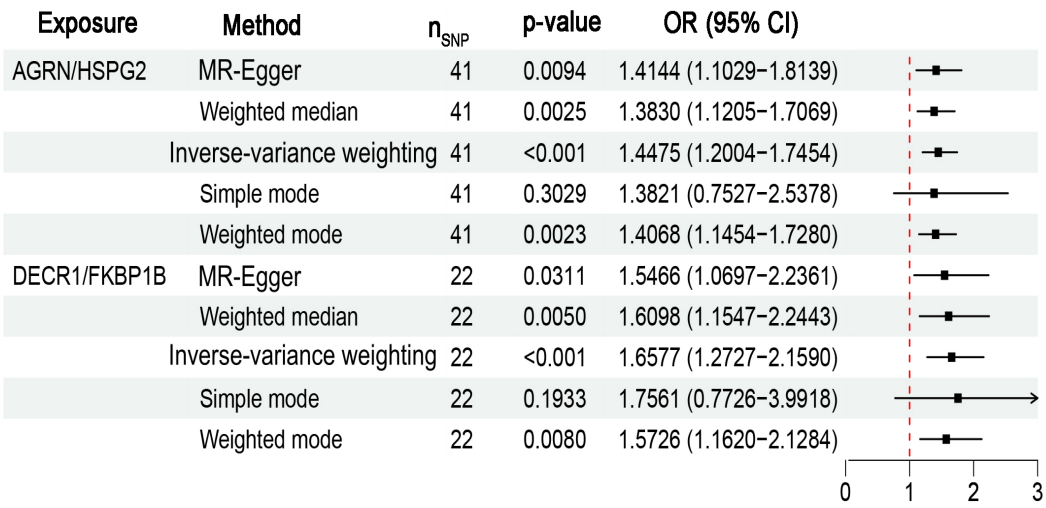

Fig. 3. A forest plot of forward MR analysis data illustrating the causal relationship of AGRN/HSPG2 and DECR1/FKBP1B ratios with AA. Abbreviations: AA, alopecia areata; CI, confidence interval; MR, Mendelian randomization; OR, odds ratio; SNP, single-nucleotide polymorphism.

Table 1. Sensitivity analysis results for bidirectional MR of PPRs and AA.

Exposure	Outcome	n_{SNP}	Heterogeneity	Pleiotropy	
			Cochran's Q test (*p*-value)	MR-PRESSO (*p*-value)	MR-Egger intercept (*p*-value)
AGRN/HSPG2	AA	41	0.221	0.347	0.780
DECR1/FKBP1B	AA	22	0.555	0.617	0.602
AA	AGRN/HSPG2	5	0.040	0.147	0.807
AA	DECR1/FKBP1B	5	0.521	0.556	0.383

Abbreviations: AA, alopecia areata; MR, Mendelian randomization; PRESSO, pleiotropy residual sum and outlier; PRRs, plasma protein ratios; SNP, single-nucleotide polymorphism.

Results of sensitivity analyses, presented in the form of scatter plots and forest plots, provided further support for the conclusion that increased levels of AGRN/HSPG2 and DECR1/FKBP1B PPRs are risk factors for AA. The symmetry of the funnel plot suggested that the SNP effects are relatively uniform, supporting the reliability of causal estimates. A leave-one-out analysis validated the robustness of the findings (Figs. 4,5). Heterogeneity tests revealed no significant heterogeneity among the selected SNPs. Neither MR-PRESSO nor MR-Egger analyses detected evidence of horizontal pleiotropy (Table 1).

Reverse MR Analysis of AA for PPRs

In a reverse MR analysis, AA was treated as the exposure variable, while the AGRN/HSPG2 and DECR1/FKBP1B ratios were considered outcome variables. Five strongly associated SNPs were identified for each PPR (**Supplementary Table 2**). Upon application of the IVW method (Fig. 6), no significant association

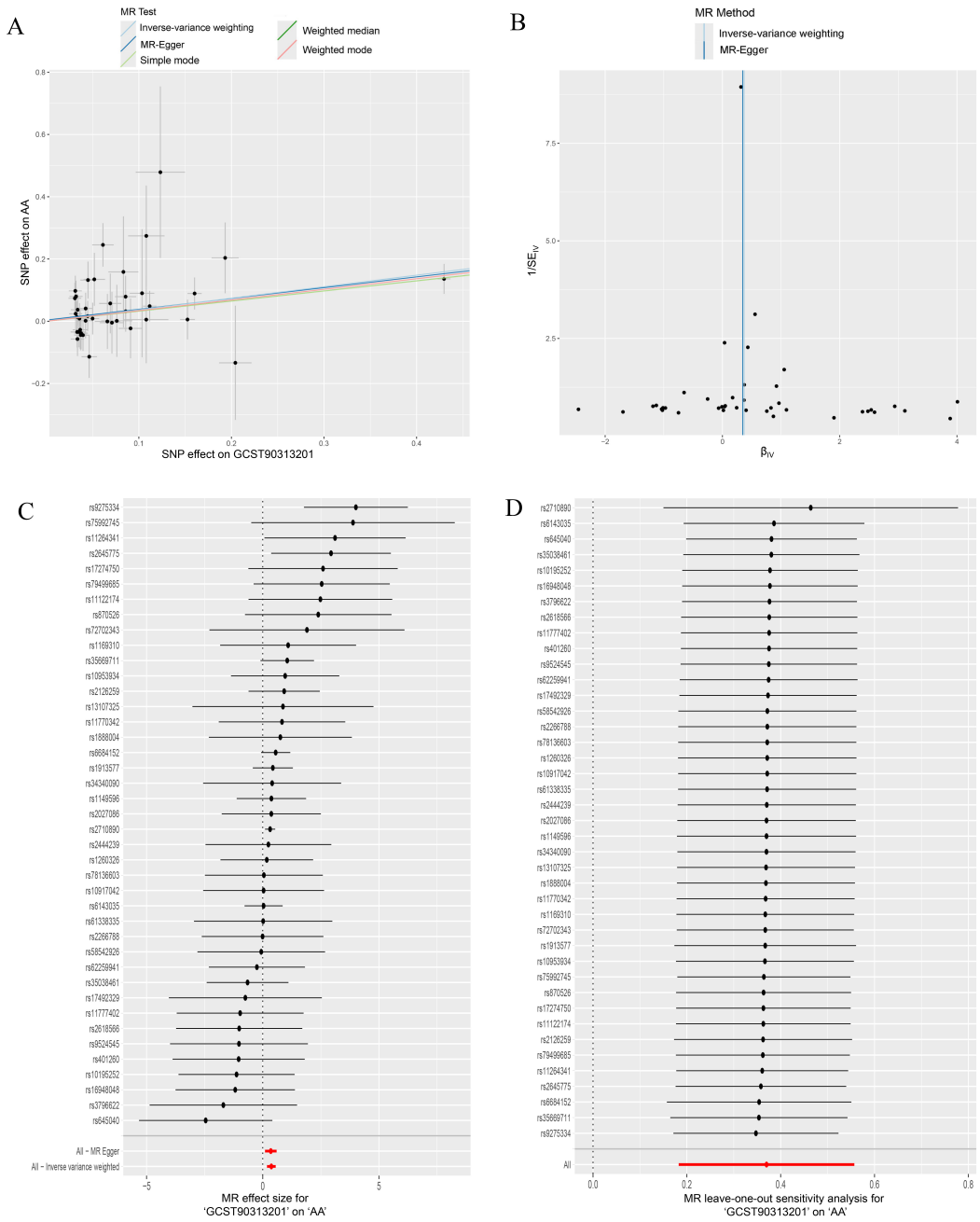

Fig. 4. Sensitivity analysis of forward MR analysis data depicting the causal relationship between the AGRN/HSPG2 ratio and AA. (A) Scatterplot. (B) Funnel plot. (C) Forest plot. (D) Leave-one-out analysis. Abbreviations: AA, alopecia areata; MR, Mendelian randomization; SNP, single-nucleotide polymorphism.

was identified between AA and either ratio (AGRN/HSPG2: OR = 1.014, 95% CI: 0.976–1.052, $p = 0.477$; DECR1/FKBP1B: OR = 0.989, 95% CI: 0.966–1.013, $p = 0.352$).

Scatter plots and forest plots stemming from the sensitivity analyses similarly indicated no significant causal relationship between AA and either PPR. A leave-one-out analysis demonstrated that no specific SNPs significantly influenced the outcome variables (Figs. 7,8). The results of a Cochran's Q test showed no evi-

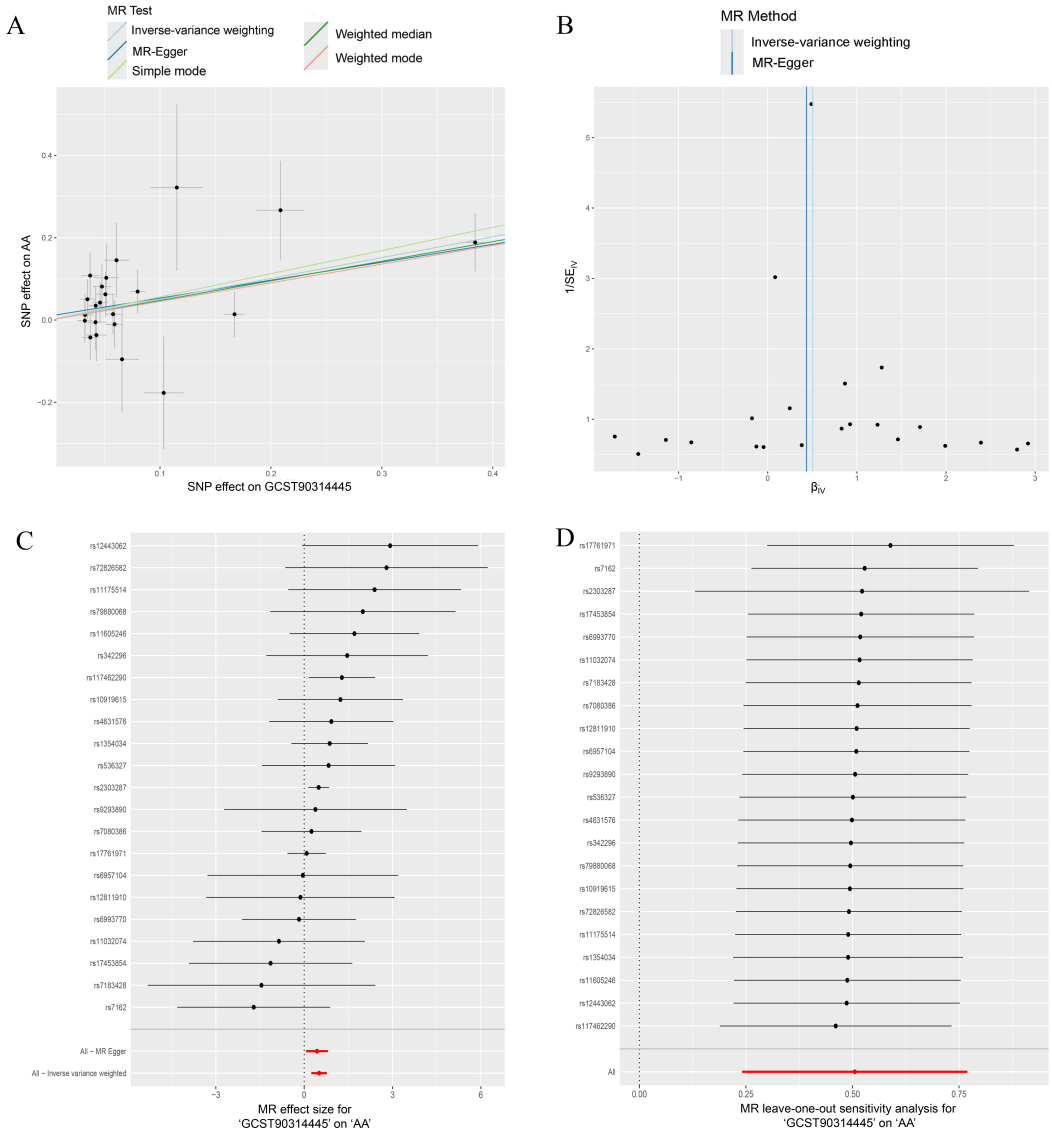

Fig. 5. Sensitivity analysis of forward MR analysis data depicting the causal relationship between the DECR1/FKBP1B ratio and AA. (A) Scatterplot. (B) Funnel plot. (C) Forest plot. (D) Leave-one-out analysis. Abbreviations: AA, alopecia areata; MR, Mendelian randomization; SNP, single-nucleotide polymorphism.

dence of heterogeneity for the association between AA and DECR1/FKBP1B. However, some heterogeneity was observed for the association between AA and AGRN/HSPG2 (Table 1). Horizontal pleiotropy tests revealed *p*-values greater than 0.05 for both AGRN/HSPG2 and DECR1/FKBP1B in MR-PRESSO and MR-Egger intercept analyses, indicating no evidence of horizontal pleiotropy (Table 1).

Discussion

By utilizing bidirectional MR analysis, we identified causal relationships of AGRN/HSPG2 and DECR1/FKBP1B PPRs with AA. Our forward MR analysis demonstrated that elevated levels of the AGRN/HSPG2 or DECR1/FKBP1B PPRs are risk factors for AA. Conversely, a reverse MR analysis revealed no significant

Exposure	Method	n_{SNP}	p-value	OR (95% CI)
AGRN/HSPG2	MR-Egger	5	0.6279	1.0241 (0.9389−1.1172)
	Weighted median	5	0.7552	1.0055 (0.9712−1.0411)
	Inverse-variance weighting	5	0.4774	1.0137 (0.9764−1.0523)
	Simple mode	5	0.3573	1.0387 (0.9669−1.1157)
	Weighted mode	5	0.8507	0.9962 (0.9598−1.0340)
DECR1/FKBP1B	MR-Egger	5	0.6956	1.0106 (0.9633−1.0603)
	Weighted median	5	0.7876	0.9959 (0.9664−1.0263)
	Inverse-variance weighting	5	0.3522	0.9889 (0.9658−1.0125)
	Simple mode	5	0.8047	0.9945 (0.9543−1.0363)
	Weighted mode	5	0.9212	0.9984 (0.9682−1.0294)

Fig. 6. A forest plot of reverse MR analysis data illustrating the causal relationship of AGRN/HSPG2 and DECR1/FKBP1B ratios with AA. Abbreviations: AA, alopecia areata; CI, confidence interval; MR, Mendelian randomization; OR, odds ratio; SNP, single-nucleotide polymorphism.

association between AA and these two PPRs. These results suggested that the PPRs have causal relationships with AA. It is worth noting that even after the FDR correction, the result was still greater than 0.05, indicating a potential risk of false positives. This might be due to the limited number of AA cases (n = 862) and the burden of multiple comparisons in the large-scale proteomics analysis. Additionally, the AA subtypes may not have been adequately stratified, diluting the effect value. A limited sample size may also increase the risk of false negatives; therefore, future large-scale validation is needed to address the multiple testing burden. Despite the lack of FDR significance, the directionally consistent effects across MR methods and biological relevance underscore the need for a mechanistic investigation.

While our analyses do not directly address the nature of these causal relationships, carefully considering the known roles of the proteins suggests how they might influence AA. AGRN and HSPG2 are associated with the basement membrane (Arikawa-Hirasawa, 2022; Burgess et al, 2000). AGRN may promote hair follicle regeneration by enhancing WNT signaling, and HSPG2 may enhance the activity of the anagen phase of hair follicles by stabilizing fibroblast growth factor 2 or promoting its binding to receptors (Colin-Pierre et al, 2022). A study has shown that AGRN is significantly correlated with the functions of immune cells (such as paracrine inflammatory responses and type I interferon responses) (Lv et al, 2023). The changes to the expression of HSPG2 or its structure have been shown to lead to abnormal T-cell migration to sites of inflammation (Gao et al, 2021). The relative stability of the protein suggests that developmental signals primarily regulate its expression, while inflammation-related factors exert limited immediate regulatory effects at the transcriptional level (Warren et al, 2014). Alterations in the hair follicle microenvironment have been linked to AA onset, with changes in the extracellular matrix influencing hair follicle development and immune regulation (Šutić Udović et al, 2024; Trüeb and Dias, 2018). Therefore, for AA, we speculate that changes to the expression of HSPG2 could weaken the barrier function of the hair

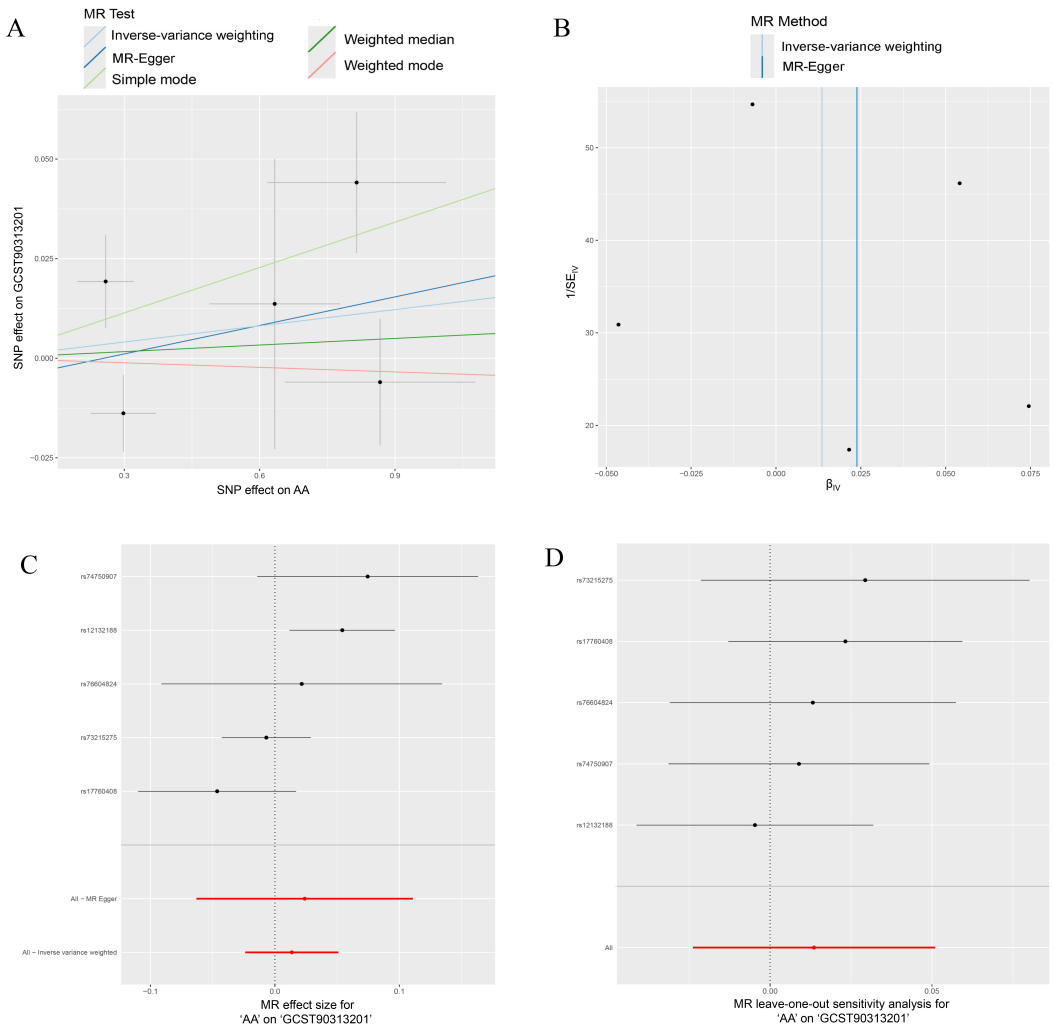

Fig. 7. Sensitivity analysis of reverse MR analysis data depicting the causal relationship between AA and AGRN/HSPG2 ratio. (A) Scatterplot. (B) Funnel plot. (C) Forest plot. (D) Leave-one-out analysis. Abbreviations: AA, alopecia areata; MR, Mendelian randomization; SNP, single-nucleotide polymorphism.

follicle basement membrane, enabling immune cells to infiltrate the hair follicle microenvironment and trigger autoimmune attacks. Disruption of the AGRN/HSPG2 ratio may compromise the immune privilege of the hair follicle and further disturb its microenvironmental homeostasis.

DECR1 participates in fatty acid metabolism, whereas FKBP1B regulates protein folding and calcium homeostasis. Abnormal fatty acid metabolism has been shown to alter hair follicle cells' energy supply and membrane structure composition, thereby affecting their normal physiological functions (Dong et al, 2025; Fujiwara, 2024). Imbalances in protein homeostasis may induce stress responses and immune activation in hair follicle cells (Chen et al, 2025). Reduced mitochondrial fatty acid β-oxidation capacity in dermal papilla cells has been found to correlate with excessive reactive oxygen species production and inhibition of the WNT/β-catenin signaling pathway (Chew et al, 2022). Impaired DECR1 function would shift fatty acid metabolism toward the peroxisomal pathway, generating

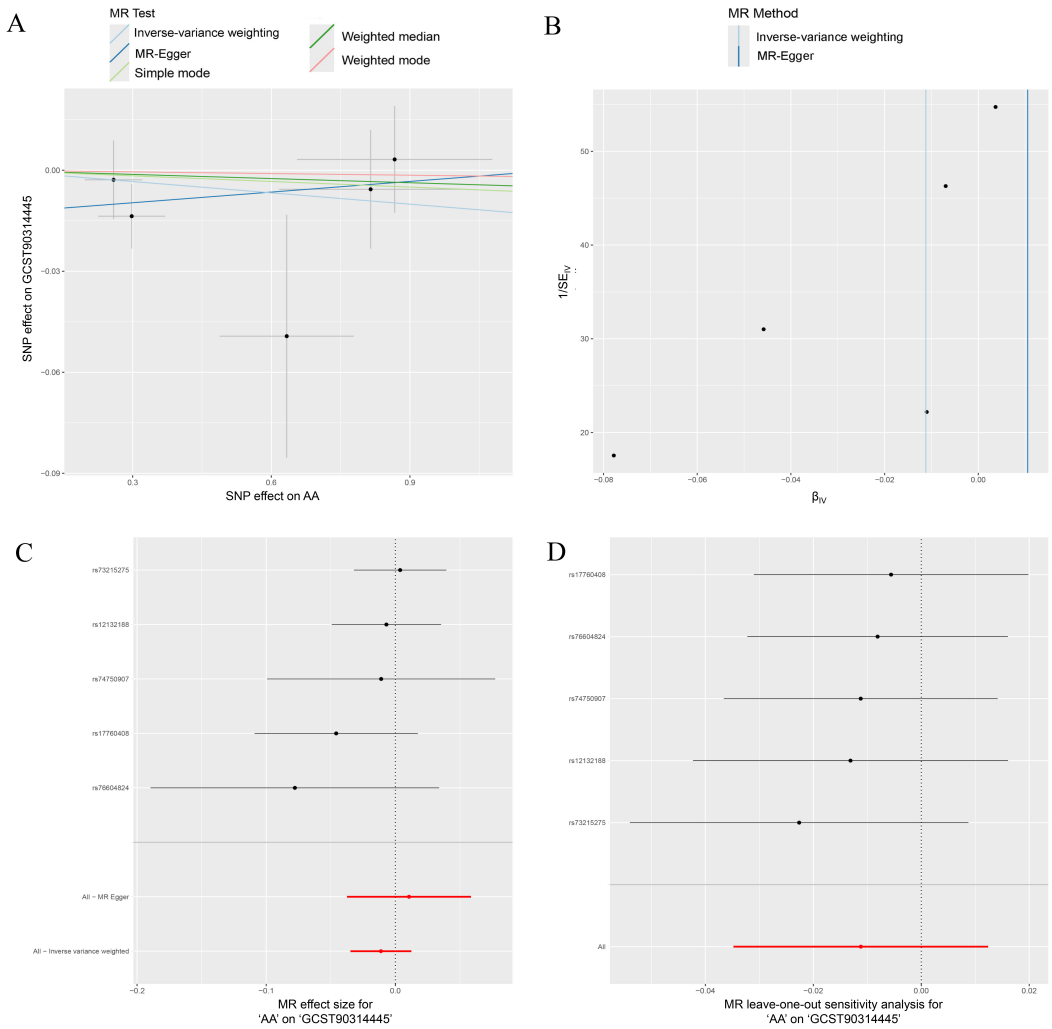

Fig. 8. Sensitivity analysis of reverse MR analysis data depicting the causal relationship between AA and DECR1/FKBP1B ratio. (A) Scatterplot. (B) Funnel plot. (C) Forest plot. (D) Leave-one-out analysis. Abbreviations: AA, alopecia areata; MR, Mendelian randomization; SNP, single-nucleotide polymorphism.

excessive hydrogen peroxide (H_2O_2) and triggering endoplasmic reticulum stress (Lu et al, 2025). Conversely, alteration of the ability of FKBP1B to regulate ryanodine receptor calcium channels would disrupt mitochondrial-endoplasmic reticulum calcium ion homeostasis and enhance sustained activation of the inositol-requiring enzyme 1α-X-box-binding protein 1 signaling pathway (Roy Chowdhury et al, 2020). This metabolic-stress positive feedback loop may promote the transformation of hair follicle keratinocytes into antigen-presenting cells through the release of damage-associated molecular patterns such as mitochondrial DNA, ultimately initiating an autoimmune response (Fetter et al, 2023). Therefore, we speculate that changes to the DECR1/FKBP1B ratio may influence intracellular metabolism and protein homeostasis. During the progression of AA, abnormal changes in the DECR1/FKBP1B ratio are indicative of hair follicle damage exacerbation.

This study extends the mechanistic understanding of AA beyond traditional immune cell infiltration perspectives to a dual-engine-driven model encompassing both extracellular matrix remodeling and metabolic reprogramming. We propose that the AGRN/HSPG2 ratio serves as a dynamic biomarker for hair follicle immune barrier integrity, while the DECR1/FKBP1B ratio reflects metabolic adaptive reserves in hair follicle stem cells. Therapeutically, targeting the glycosaminoglycan modification of HSPG2 or the supply of the DECR1 cofactor nicotinamide adenine dinucleotide phosphate hydrogen offers novel strategies for combined metabolic and immunological therapies for AA. Tacrolimus, an FKBP1B inhibitor, promotes hair regrowth in AA local treatment, potentially by inhibiting FKBP1B-mediated T-cell activation and interleukin-23/T helper cells 17 pathways (Freyschmidt-Paul et al, 2001). Consequently, these PPRs may serve as potential clinical biomarkers and therapeutic targets, offering new possibilities for the early diagnosis and treatment of AA.

This study is associated with several limitations. Firstly, the underlying data were primarily sourced from the European populations, potentially impacting the generalizability of the results. Besides, we could not completely rule out reverse causality in the results based on the case data gleaned from FinnGen's cross-sectional study. Secondly, GWAS data do not take into account post-translational modifications, and it is challenging for MR methods to fully control for interference attributable to epigenetic changes that might occur under extreme environmental stress. Thirdly, the number of SNPs in the reverse MR was relatively small, and there may be publication bias, which could potentially affect the validity of our results. Finally, a high FDR value suggests the possibility of a false positive. Future works could further expand the sample size to include individuals of different racial and ethnic origins, conduct multi-omics research, and carry out more biological experiments to verify the potential molecular mechanisms.

Conclusion

This study utilized bidirectional MR analyses to identify causal relationships of AGRN/HSPG2 and DECR1/FKBP1B ratios with AA at the genetic level. These PPRs may serve as potential clinical biomarkers for early risk prediction of AA and provide a molecular basis for the development of therapies. In the future, it will be necessary to increase the sample size and conduct in-depth biological experiments to clarify the specific mechanism of action.

Key Points

- The association between plasma protein ratios and alopecia areata remains controversial in observational studies.
- Increased AGRN/HSPG2 and DECR1/FKBP1B ratios significantly elevate the risks of alopecia areata at the genetic level.
- No bidirectional causality links exist between plasma protein ratios and alopecia areata.
- Our findings highlight the importance of plasma protein ratios as clinical biomarkers of the risk of alopecia areata.

Availability of Data and Materials

All data included in this study are available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization, LD; methodology, XT; software, ZY; validation, XT, ZY, SZ; formal analysis, ZY, SZ; investigation, SZ; resources, LD; data curation, XT; writing—original draft preparation, XT, SZ; writing—review and editing, XT, LD; visualization, ZY, SZ; supervision, LD; project administration, LD. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgement

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2025.0405.

References

Arikawa-Hirasawa E. Impact of the heparan sulfate proteoglycan perlecan on human disease and health. American Journal of Physiology. Cell Physiology. 2022; 322: C1117–C1122. https://doi.org/10.1152/ajpcell.00113.2022

Burgess RW, Skarnes WC, Sanes JR. Agrin isoforms with distinct amino termini: differential expression, localization, and function. The Journal of Cell Biology. 2000; 151: 41–52. https://doi.org/10.1083/jcb.151.1.41

Chen H, Liu C, Cui S, Xia Y, Zhang K, Cheng H, et al. Intermittent fasting triggers interorgan communication to suppress hair follicle regeneration. Cell. 2025; 188: 157–174.e22. https://doi.org/10.1016/j.cell.2024.11.004

Chew EGY, Lim TC, Leong MF, Liu X, Sia YY, Leong ST, et al. Observations that suggest a contribution of altered dermal papilla mitochondrial function to androgenetic alopecia. Experimental Dermatology. 2022; 31: 906–917. https://doi.org/10.1111/exd.14536

Colin-Pierre C, El Baraka O, Danoux L, Bardey V, André V, Ramont L, et al. Regulation of stem cell fate by HSPGs: implication in hair follicle cycling. NPJ Regenerative Medicine. 2022; 7: 77. https://doi.org/10.1038/s41536-022-00267-y

Dong TR, Li YJ, Jin SY, Yang FL, Xiong RX, Dai YQ, et al. Progress on mitochondria and hair follicle development in androgenetic alopecia: relationships and therapeutic perspectives. Stem Cell Research & Therapy. 2025; 16: 44. https://doi.org/10.1186/s13287-025-04182-z

Fetter T, de Graaf DM, Claus I, Wenzel J. Aberrant inflammasome activation as a driving force of human autoimmune skin disease. Frontiers in Immunology. 2023; 14: 1190388. https://doi.org/10.3389/fimmu.2023.1190388

Freyschmidt-Paul P, Ziegler A, McElwee KJ, Happle R, Kissling S, Sundberg JP, et al. Treatment of alopecia areata in C3H/HeJ mice with the topical immunosuppressant FK506 (Tacrolimus). European Journal of Dermatology. 2001; 11: 405–409.

Fujiwara H. Dynamic duo: Cell-extracellular matrix interactions in hair follicle development and regeneration. Developmental Biology. 2024; 516: 20–34. https://doi.org/10.1016/j.ydbio.2024.07.012

Gao G, Chen S, Pei YA, Pei M. Impact of perlecan, a core component of basement membrane, on regeneration of cartilaginous tissues. Acta Biomaterialia. 2021; 135: 13–26. https://doi.org/10.1016/j.actbio.2021.08.032

Gau SY, Chen CW, Wang YH, Chi CC, Wei JCC. Increased risk of incident alopecia areata among patients with hidradenitis suppurativa: A multicenter cohort study in the United States. Biomedical Journal. 2025; 48: 100837. https://doi.org/10.1016/j.bj.2025.100837

İslamoğlu ZGK, Demirbaş A. Evaluation of complete blood cell and inflammatory parameters in patients with alopecia areata: Their association with disease severity. Journal of Cosmetic Dermatology. 2020; 19: 1239–1245. https://doi.org/10.1111/jocd.13131

Kalaycı BN, Balta İ. Evaluation of the serum C-reactive protein-albumin ratio and its relationship with disease severity IN alopecia areata: A prospective case-control study. Journal of Cosmetic Dermatology. 2022; 21: 7194–7199. https://doi.org/10.1111/jocd.15460

Kang CB, Hong Y, Dhe-Paganon S, Yoon HS. FKBP family proteins: immunophilins with versatile biological functions. Neuro-Signals. 2008; 16: 318–325. https://doi.org/10.1159/000123041

Lee HH, Gwillim E, Patel KR, Hua T, Rastogi S, Ibler E, et al. Epidemiology of alopecia areata, ophiasis, totalis, and universalis: A systematic review and meta-analysis. Journal of the American Academy of Dermatology. 2020; 82: 675–682. https://doi.org/10.1016/j.jaad.2019.08.032

Li P, Wang H, Guo L, Gou X, Chen G, Lin D, et al. Association between gut microbiota and preeclampsia-eclampsia: a two-sample Mendelian randomization study. BMC Medicine. 2022; 20: 443. https://doi.org/10.1186/s12916-022-02657-x

Locke TM, Fields R, Gizinski H, Otto GM, MacEwen MJS, Rusnac DV, et al. High-throughput identification of calcium-regulated proteins across diverse proteomes. Cell Reports. 2024; 43: 114879. https://doi.org/10.1016/j.celrep.2024.114879

Lu QB, Sun HT, Zhou K, Su JB, Meng XY, Chen G, et al. Therapeutic Targeting of Decr1 Ameliorates Cardiomyopathy by Suppressing Mitochondrial Fatty Acid Oxidation in Diabetic Mice. Journal of Cachexia, Sarcopenia and Muscle. 2025; 16: e13761. https://doi.org/10.1002/jcsm.13761

Lv R, Duan L, Gao J, Si J, Feng C, Hu J, et al. Bioinformatics-based analysis of the roles of basement membrane-related gene AGRN in systemic lupus erythematosus and pan-cancer development. Frontiers in Immunology. 2023; 14: 1231611. https://doi.org/10.3389/fimmu.2023.1231611

Macbeth AE, Holmes S, Harries M, Chiu WS, Tziotzios C, de Lusignan S, et al. The associated burden of mental health conditions in alopecia areata: a population-based study in UK primary care. The British Journal of Dermatology. 2022; 187: 73–81. https://doi.org/10.1111/bjd.21055

Pietzner M, Wheeler E, Carrasco-Zanini J, Cortes A, Koprulu M, Wörheide MA, et al. Mapping the proteo-genomic convergence of human diseases. Science. 2021; 374: eabj1541. https://doi.org/10.1126/science.abj1541

Quarto N, Amalric F. Heparan sulfate proteoglycans as transducers of FGF-2 signalling. Journal of Cell Science. 1994; 107: 3201–3212. https://doi.org/10.1242/jcs.107.11.3201

Roy Chowdhury A, Srinivasan S, Csordás G, Hajnóczky G, Avadhani NG. Dysregulation of RyR Calcium Channel Causes the Onset of Mitochondrial Retrograde Signaling. iScience. 2020; 23: 101370. https://doi.org/10.1016/j.isci.2020.101370

Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: The STROBE-MR Statement. JAMA. 2021; 326: 1614–1621. https://doi.org/10.1001/jama.2021.18236

Strazzulla LC, Wang EHC, Avila L, Lo Sicco K, Brinster N, Christiano AM, et al. Alopecia areata: Disease characteristics, clinical evaluation, and new perspectives on pathogenesis. Journal of the American Academy of Dermatology. 2018; 78: 1–12. https://doi.org/10.1016/j.jaad.2017.04.1141

Suhre K. Genetic associations with ratios between protein levels detect new pQTLs and reveal protein-protein interactions. Cell Genomics. 2024; 4: 100506. https://doi.org/10.1016/j.xgen.2024.100506

Šutić Udović I, Hlača N, Massari LP, Brajac I, Kaštelan M, Vičić M. Deciphering the Complex Immunopathogenesis of Alopecia Areata. International Journal of Molecular Sciences. 2024; 25: 5652. https://doi.org/10.3390/ijms25115652

Trüeb RM, Dias MFRG. Alopecia Areata: a Comprehensive Review of Pathogenesis and Management. Clinical Reviews in Allergy & Immunology. 2018; 54: 68–87. https://doi.org/10.1007/s12016-017-8620-9

Warren CR, Grindel BJ, Francis L, Carson DD, Farach-Carson MC. Transcriptional activation by NFκB increases perlecan/HSPG2 expression in the desmoplastic prostate tumor microenvironment. Journal of Cellular Biochemistry. 2014; 115: 1322–1333. https://doi.org/10.1002/jcb.24788

Zhang YY, Chen BX, Yang Q, Wan Q. The causal relationship between plasma protein-to-protein ratios and type 2 diabetes and its complications: Proteomics mendelian randomization study. Diabetes, Obesity & Metabolism. 2024; 26: 4410–4417. https://doi.org/10.1111/dom.15792

Zhou C, Li X, Wang C, Zhang J. Alopecia Areata: an Update on Etiopathogenesis, Diagnosis, and Management. Clinical Reviews in Allergy & Immunology. 2021; 61: 403–423. https://doi.org/10.1007/s12016-021-08883-0