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Unraveling genetic threads: Identifying novel therapeutic targets for allergic rhinitis through Mendelian randomization

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ABSTRACT

Background: Allergic rhinitis (AR) is a pervasive global health issue, and currently, there is a scarcity of targeted drug therapies available. This study aims to identify potential druggable target genes for AR using Mendelian randomization (MR) analysis.

Methods: MR analysis was conducted to assess the causal effect of expression quantitative trait loci (eQTL) in the blood on AR. Data on AR were collected from 2 datasets: FinnGen(R9) (11,009 cases and 359,149 controls) and UK Biobank (25,486 cases and 87,097 controls). Colocalization analysis was utilized to assess the common causal genetic variations between the identified drug target genes and AR. We also employed available genome-wide association studies (GWAS) data to gauge the impact of druggable genes on AR biomarkers and other allergic diseases.

Results: This study employs MR to analyze the relationship between 3410 druggable genes and AR. After Bonferroni correction, 10 genes were found to be significantly associated with AR risk ($P < 0.05/3410$). Colocalization analysis revealed a significant causal relationship between the expression variation of CFL1 and EFEMP2 genes and AR, sharing direct causal variants (colocalization probability PP.H3 + PP.H4 > 0.8), highlighting their importance as potential therapeutic targets for AR. The CFL1 gene showed a causal link with levels of thymic stromal lymphopoietin (TSLP), eosinophil count, and interleukin-13 (IL-13) ($P = 0.016, 7.45E\text{-}16, 0.00091$, respectively). EFEMP2 was also causally related to eosinophil count, IL-13, and interleukin-17 (IL-17) ($P = 0.00012, 0.00091, 0.032$, respectively). PheWAS analysis revealed significant associations of CFL1 with asthma, whereas EFEMP2 showed associations with both asthma and eczema. Protein-Protein Interaction (PPI) network analysis further unveiled the direct interactions of EFEMP2 and CFL1 with proteins related to immune regulation and inflammatory responses, with 77.64% of the network consisting of direct bindings, indicating their key roles in modulating AR-related immune and inflammatory responses. Notably, there was an 8.01% significant correlation between immune-related pathways and genes involved in inflammatory responses.

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Conclusion: These genes present notable associations with AR biomarkers and other autoimmune diseases, offering valuable targets for developing new AR therapies.

Keywords: Allergic rhinitis, Druggable target genes, Mendelian randomization

BACKGROUND

Allergic rhinitis (AR) a prevalent chronic disease, afflicts approximately 10%–20% of the global population, significantly deteriorating patients' quality of life by affecting sleep, daily activities, performance at school or work, and mental health.[1] Despite advancements in treatment methodologies, existing approaches exhibit noticeable limitations. The principal treatments for AR comprise drug therapy and allergen avoidance. Typically, drug therapy incorporates antihistamines, nasal steroids, and desensitizing drugs.[2] While these drugs proficiently manage symptoms, they neither cure AR nor are exempt from potential long-term side effects. Furthermore, although theoretically viable, complete allergen avoidance is practically implausible. Recently, a few biological agents have been utilized for AR treatment; however, the high costs currently limit the availability of targeted drugs. Consequently, the establishment of a new treatment strategy is paramount.[3]

In recent years, MR analysis has emerged as a pivotal tool for exploring the causal relationships between potential risk factors and disease outcomes by leveraging genetic variation.[4,5] Employing Mendelian randomization (MR) analysis of genome-wide association studies (GWAS) data enables a thorough examination of the underlying mechanisms of diseases, thereby enhancing drug targeting analysis. Expression quantitative trait locus (eQTL) analysis stands as a notable component of MR analysis in druggable target identification.[6,7] eQTLs, variations correlated with gene expression, can offer invaluable insights into genetic control. The expression levels of genes can be considered lifelong exposures, and eQTLs situated within the genomic region of druggable genes can act as proxies. Expressions of druggable genes, which encode proteins or enzymes, can significantly bolster the understanding of drug targets.[8] This approach to MR analysis has been applied to identify new drug targets for various diseases, including COVID-19 and Parkinson's Disease.[9,10]

Consequently, this study is poised to identify potential drug target genes for AR by amalgamating eQTL data and drug gene information, utilizing MR analysis. We anticipate that this genetics-based method will provide comprehensive insights into the etiology of AR, facilitating the development of new and more targeted treatment approaches. In this study, we leveraged the MR method and extensive GWAS data to pinpoint novel therapeutic targets for AR. This method integrates *cis*-eQTL and AR risk correlation data to establish a causal relationship between exposure and outcomes, thereby enhancing the prediction of drug efficacy. Additionally, we conducted a gene colocation analysis to identify common drivers between potential therapeutic targets and AR. This analysis assists in determining the causal relationship between treatment objectives and the disease while mitigating potential confounding factors. Moreover, our Phenome-wide association study (PheWAS) analysis[11] examines the relationship between potential therapeutic targets and other traits, providing invaluable insights into their multifunctionality and potential impact mechanisms for further research and development of related therapeutic strategies. Lastly, the construction of a protein-protein interaction (PPI) network reveals the functional characteristics and biological relevance of potential therapeutic targets, deepening our understanding of their role in the development and treatment of AR.

MATERIALS AND METHODS

The technical route of this study is depicted in Fig. 1, with further details on the utilized methods and materials provided below:

Initially, we integrate data from druggable genes and eQTLGen eQTLs to identify a set of

3410 druggable gene eQTLs. Subsequently, we evaluate the causal impacts of these blood-druggable eQTLs on AR using MR analysis. A subsequent colocalization analysis is performed to verify the robustness of eQTL expressions. Next, a replication study is conducted using a separate AR GWAS dataset to validate our findings. We then assess the causal linkage of prior expressions with AR biomarkers to explore potential underlying mechanisms. Additionally, we conduct a comprehensive PheWAS to examine potential side effects of targeting the identified druggable gene products for AR treatment. Lastly, we analyze the functional relationship between EFEMP2 and CFL1, 2 druggable genes related to AR, through PPI network analysis.

Identification of druggable gene eQTLs

A total of 5883 druggable genes were obtained by consolidating and deduplicating genes from the Drug-Gene Interaction Database (DGIdb)[12] and a review on "druggable" genes.[13] Blood eQTL data, encompassing 31,684 blood samples from healthy individuals of European descent, were retrieved from the eQTLGen website (https://eqtlgen.org/).[14] Single nucleotide polymorphisms (SNPs), within 1000 kb above and below the transcription start site of each gene and with a p-value less than 0.05, were selected as instrumental variables for expression levels. SNPs in each eQTL were screened using 1000 Genome European blood samples, adhering to an $r2<0.01$ criterion. Ultimately, 3410 genes, possessing available eQTL information and being susceptible to drug regulation, were identified (see Table S1).

Additionally, whole blood cis eQTLs from the Genotype Tissue Expression Project (GTEx, Version 8.0) were utilized to validate our findings, with the GTEx data being obtained from the website (https://www.gtexportal.org).

Outcome GWAS data

The outcome data for AR utilized in this study were derived from the FinnGen (R9) database, which comprises a cohort of 11,009 cases and

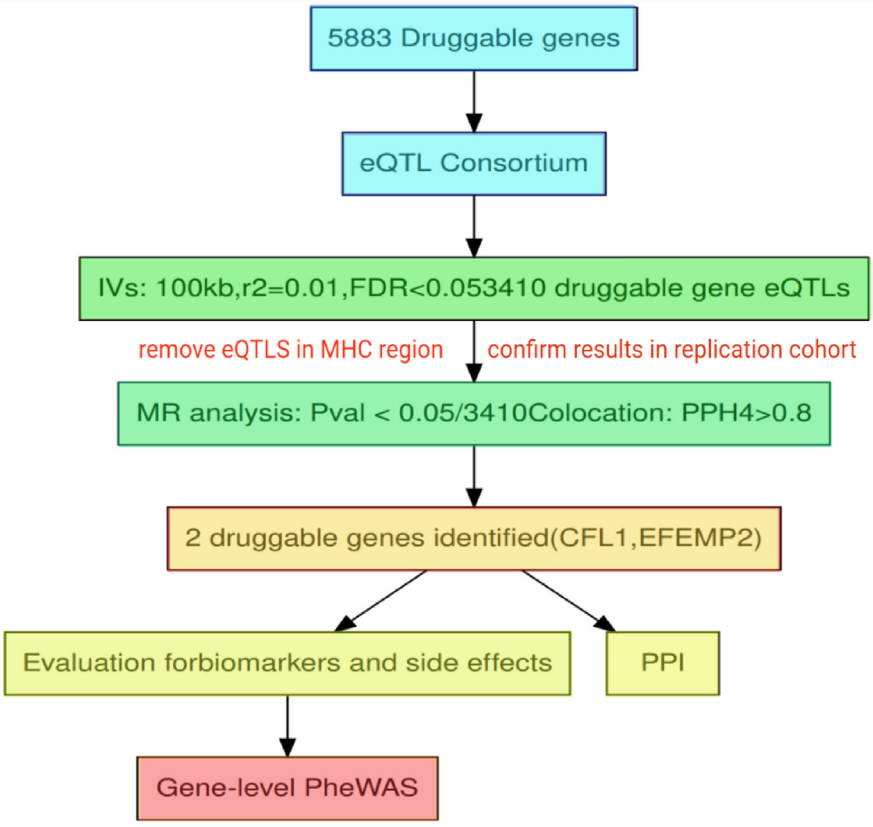

Fig. 1 Flow Chart Summarizing the Overall Analysis Procedure in This Study. This flow chart provides a step-by-step depiction of the analysis procedures used to assess the relationship between gene expression and Allergic Rhinitis (AR)

359,149 controls. The validation cohort was extracted from the AR dataset of UK Biobank, encompassing 25,486 cases and 87,097 controls. Table S2 provides a summary of all the outcome GWAS data.

Multiple mendelian randomization analysis

R software (version 4.2.3) was utilized to compute MR results employing the "TwoSampleMR" package. Both exposure and outcome GWAS data were harmonized, with Phenoscanner (http://www.phenoscanner.medschl.cam.ac.uk/) being used to identify and omit SNPs associated with AR and AR-related traits, such as IgE. For estimating causal effects, the Wald ratio was used for a single SNP, while inverse variance weighted (IVW) was applied for more than 2 SNPs. IVW meta-analysis is the most commonly used method in two-sample MR analysis, integrating estimates from multiple genetic instruments to obtain accurate causal effect estimates between exposure and outcomes. IVW is chosen for its efficiency in providing effect estimates, especially in the absence of pleiotropic bias. To ensure the validity of the IVW analysis, we rigorously selected our instrumental variables, confirming their relevance, independence, and exclusivity to exclude SNPs directly related to the outcomes. The MR Egger test was conducted to evaluate pleiotropic effects, and the Cochran's Q test was applied to assess heterogeneity. A Bonferroni correction (0.05/3410) was utilized as the significance threshold. In the validation process using the UK Biobank cohort, a p-value <0.05 was considered statistically significant.

Notably, previous research has demonstrated that significant MR results can arise from SNPs in tight linkage disequilibrium, whereby the association between exposure SNPs and outcome SNPs is driven by different causal variants, potentially leading to false-positive results. To discern whether exposure and outcome possess the same causal SNP—when an SNP is significantly associated with both—colocalization analysis was utilized.[15] There is evidence suggesting that proteins identified through MR and colocalization have a higher likelihood of becoming drug targets,[6] thus, this study will perform colocalization analysis. The core assumption of colocalization analysis is that by assessing the association of individual SNPs within a specific region with 2 phenotypes (in this case, gene expression and the risk of AR), it is possible to determine whether there exists a shared causal variant.

For colocalization analysis, we used the "coloc" R package to examine each SNP within a 100 kb region upstream and downstream of the transcription start site of the corresponding gene. This method focuses on quantifying the support for 5 hypotheses: PPH0 (not associated with either trait), PPH1 (associated with gene expression but not with AR risk), PPH2 (associated with AR risk but not with gene expression), PPH3 (associated with both AR risk and gene expression, but with different causal variants), and PPH4 (associated with both AR risk and gene expression, with a shared causal variant). Genes with a sum of posterior probabilities greater than 0.8 for PPH3 (independent causal variation of 2 phenotypes) and PPH4 (shared causal variation of 2 phenotypes) were identified.[16]

Verification analysis

In the Summary-data-based Mendelian Randomization (SMR) analysis, the SMR software (1.3.1) with default settings was further utilized to explore the association between eQTLs of druggable genes (sourced from GTEx, Version 8.0) and AR.

Analysis of biomarkers related to AR

Initially, we curated AR-related biomarkers from the literature, which include Periostin, Thymic stromal lymphopoietin, Immunoglobulin E, Eosinophil counts, Interleukin-4, Interleukin-5, Interleukin-13, Interleukin-17, and TGF-β1, specifically selecting those markers for which GWAS data are available.[17,18] We conducted an MR analysis using eQTL as the exposure factor and biomarker GWAS as the outcome variable to evaluate the relationship between recognized genes and AR markers.

Phenome-wide association study (PheWAS)

To explore the potential impacts of druggable genes on various phenotypes, we utilized aggregated data from the ATLAS database (https://atlas.ctglab.nl/), which encompasses information on 3302 unique traits across 28 domains. This data served as the basis upon which we conducted an exhaustive phenotypic association study.[11]

Protein-protein interaction (PPI) network analysis

In this research, we employed the GeneMANIA network tool (http://www.genemania.org) to explore the functional network and interactions of genes involved in drug targeting.[19] GeneMANIA predicts gene function by constructing functional association networks derived from a multitude of bioinformatics data sources, including expression profiles, co-localization, co-evolution, protein-protein interactions, pathways, and gene ontology information. The network results generated by GeneMANIA facilitate the identification of the potential functions of druggable genes and their interactions with other genes.[19]

RESULTS

Identifying druggable genes for AR

The objective of our research was to pinpoint druggable genes associated with AR. Initially, we identified eQTLs for 3410 druggable genes. Subsequently, the two-sample MR method was utilized to thoroughly evaluate the causal relationships between these eQTLs and AR. Within the AR outcome data from the FinnGen(R9) database, we employed IVW meta-analysis to assess the effect estimation for each SNP. After employing a Bonferroni correction, we discerned that the predicted gene expression of 10 genes was significantly associated with the risk of AR ($P < 0.05/3410$; detailed in Fig. 2 and Table S3).

Colocalization analysis

To delve deeper into shared causal genetic variants between SNPs associated with eQTLs and AR, a colocalization analysis was undertaken. Notably, CFL1 and EFEMP2 exhibited robust evidence of colocation with AR. The eQTLs of these 2 druggable genes and AR shared a causal variation within the region (PP.H3 + PP.H4 > 0.8,[16] Table S3, Fig. 3A and B), pinpointing them as potential candidate drug target genes.

Validation analysis

In an endeavor to validate the research findings, a replication analysis was conducted, which scrutinized 2 identified genes utilizing the duplicate cohort from the UK Biobank. This cohort encompassed 25,486 cases and 87,097 controls. All MR results for these 2 genes achieved statistical significance ($P < 0.05$), thereby affirming their association with AR (refer to Table S4).

Furthermore, the GTEx blood eQTL replication dataset was employed in this study to carry out SMR analysis. The objective was to ascertain the association between the identified genes and AR. The SMR results unveiled a notable correlation between the expression of CFL1 and EFEMP2 and AR ($P < 0.05$, delineated in Table S5).

Association between druggable genes and biomarkers

Several biomarkers are ubiquitously acknowledged in relation to AR, namely Periostin, Thymic Stromal Lymphopoietin, Immunoglobulin E, Eosinophil counts, Interleukin-4, Interleukin-5, Interleukin-13, Interleukin-17, and TGF-β1.[17,18] To explore the relationship between the identified pharmaceutical genes and these biomarkers, a

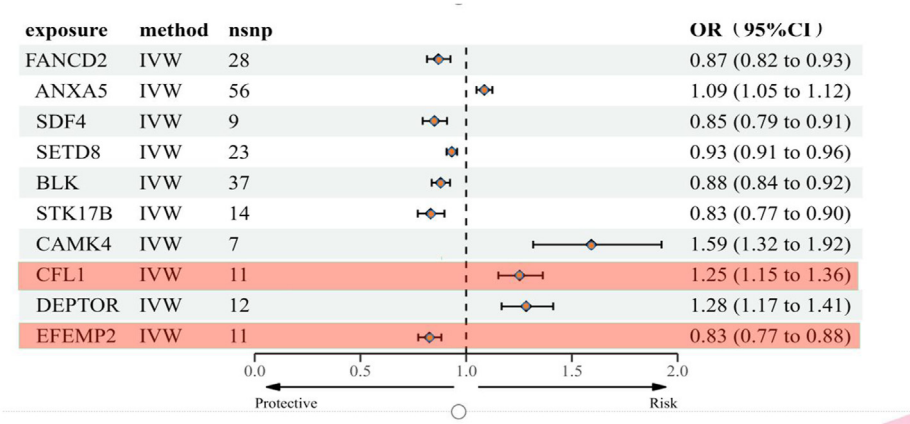

Fig. 2 Mendelian Randomization Results for the Association Between the Expression of Druggable Genes and AR. This figure illustrates the causal relationship inferred between gene expression levels and AR susceptibility using Mendelian randomization techniques

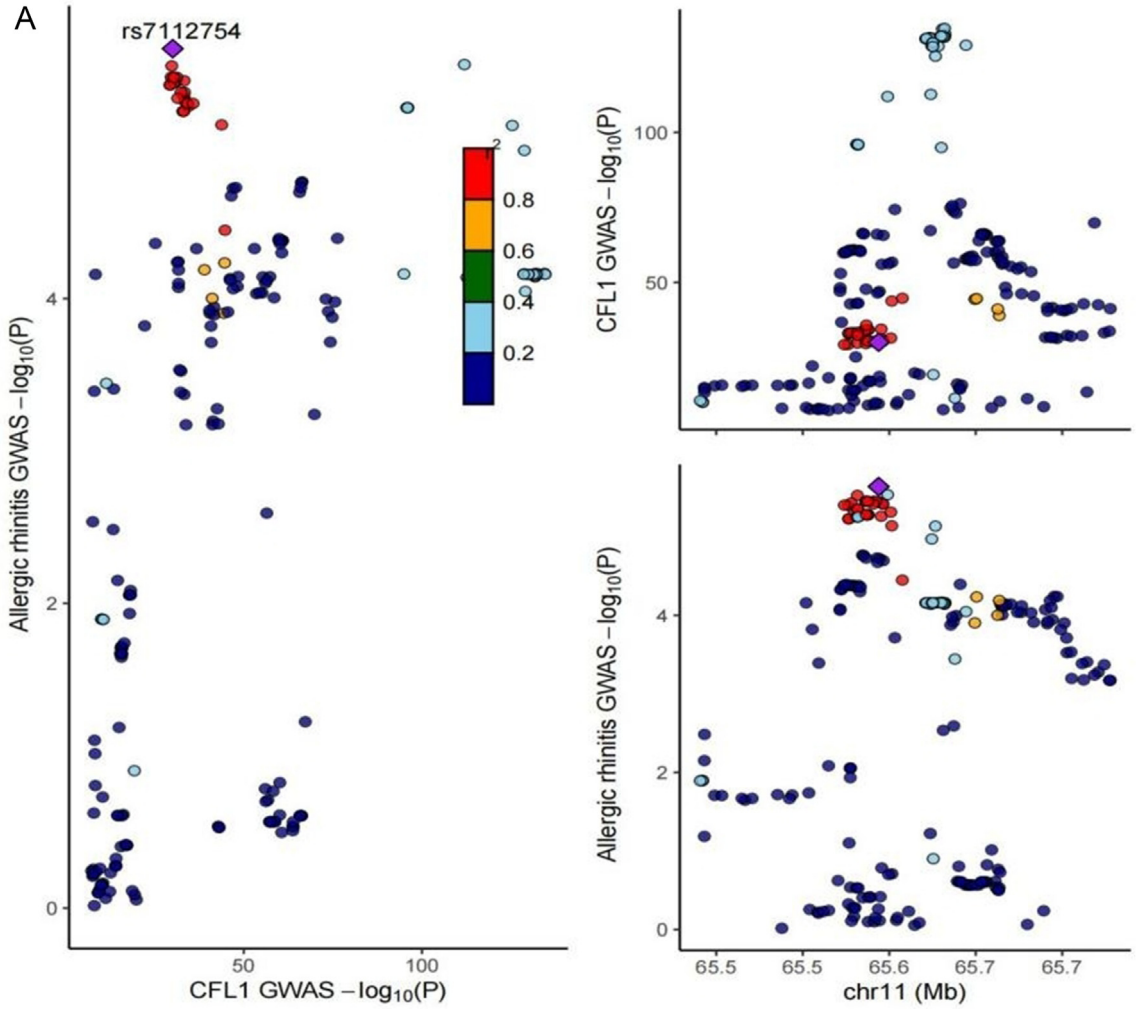

Fig. 3 A. The Colocalization Plot of CFL1 and AR. The plot demonstrates the spatial colocalization of CFL1 gene expression with AR. B. The Colocalization Plot of EFEMP2 and AR. Similar to Fig. 3A, this plot shows the colocalization of EFEMP2 gene expression with AR

MR analysis was performed on 2 samples within this study. The outcomes are illustrated in Fig. 4.

Blood expression of CFL1 displayed a causal association with the levels of Thymic Stromal Lymphopoietin ($P_{IVW} = 0.016$, beta (95%CI) = 0.77 to −0.97), Eosinophil Counts ($P_{IVW} = 7.45E\text{-}16$, beta (95%CI) = 1.08 to 1.14), and Interleukin-13 ($P_{IVW} = 0.00091$, beta (95%CI) = 0.73 to 0.92) (see Fig. 4). Concurrently, the blood expression of EFEMP2 demonstrated a causal association with the levels of Eosinophil Counts ($P_{IVW} = 0.00012$, beta (95%CI) = 0.94 to 0.98), Interleukin-13 ($P_{IVW} = 0.00091$, beta (95%CI) = 0.73 to 0.92), and Interleukin-17 ($P_{IVW} = 0.032$, beta (95%CI) = 1.01 to 1.24). These findings hint that CFL1 and EFEMP2 may exert an impact on these biomarkers in AR.

Safety evaluation of identified druggable genes

In an effort to elucidate potential associations between pharmacogenes and varied human phenotypes, a PheWAS was executed utilizing data derived from the ATLAS database, encompassing publicly accessible GWAS summary statistics. The PheWAS results disclosed distinct associations for each identified gene. Moreover, a potential causal linkage between 2 druggable genes and other autoimmune diseases was discerned. CFL1 revealed a pronounced correlation with both asthma and childhood asthma (refer to Fig. 5, Fig. S1, and Table S6), thereby identifying it as a risk factor. Conversely, EFEMP2 exhibited a significant correlation with asthma, childhood asthma, and eczema, designating it as a protective factor (refer to Fig. 5, Fig. S2, and Table S7).

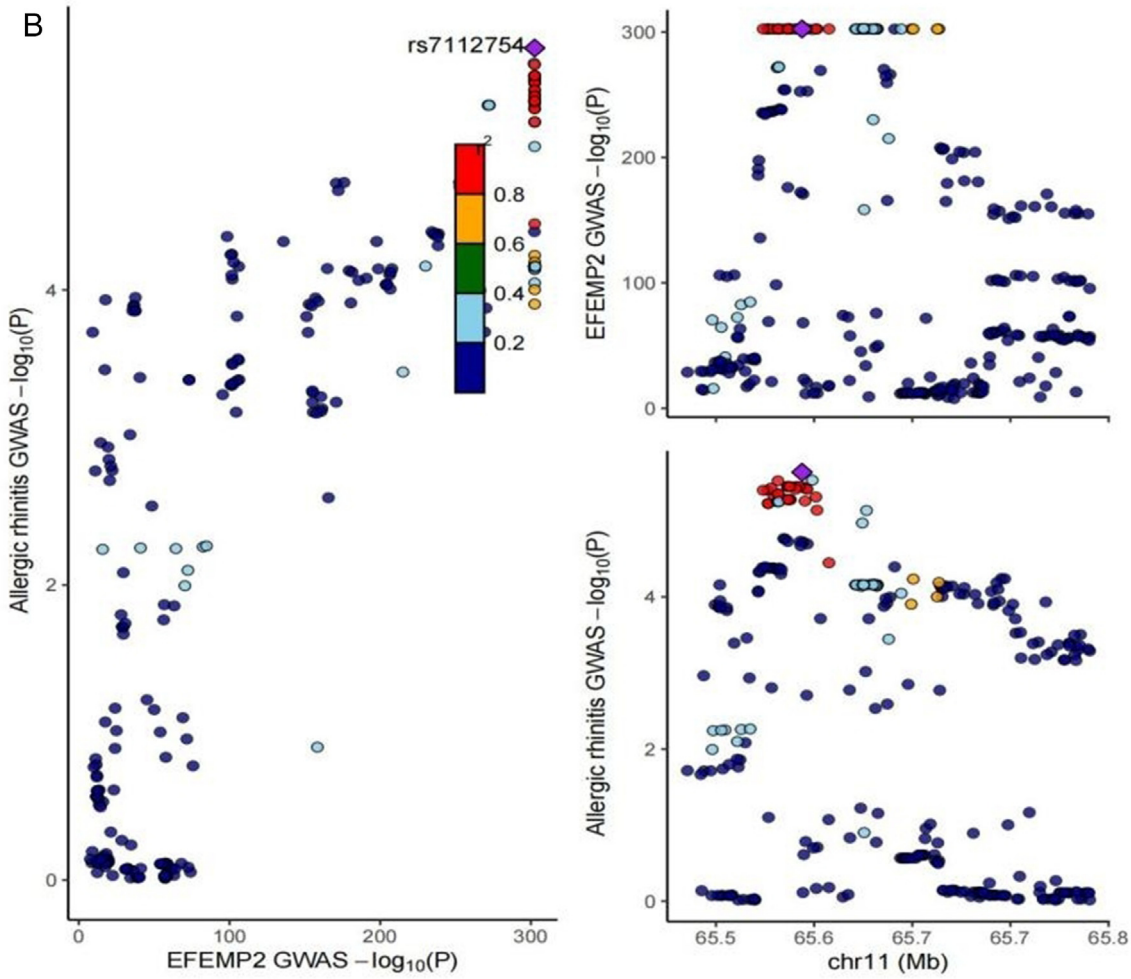

Fig. 3 Continued

PPI network analysis

Using PPI Network Analysis, we explored the functional relationships between EFEMP2 and CFL1, 2 druggable genes associated with AR. Our network analysis unveiled key effector sites directly interacting with EFEMP2 and CFL1, as well as members of the immune pathway that are highly co-expressed. Moreover, we identified a relationship between EFEMP2 and CFL1 and several proteins involved in DNA damage repair and cell proliferation (Fig. 6). Specifically, a substantial majority of the EFEMP2 and CFL1 networks (77.64%) were comprised of direct physical bindings, indicating their potential role in regulating allergic reactions by interacting with various signal transduction proteins (e.g., small G protein ARRB1/2) and effector proteins (eg, actin regulatory protein CFL1/2). Furthermore, a significant correlation (8.01%) was observed between EFEMP2, CFL1, immune-related pathways, and inflammatory response genes, suggesting their involvement in modulating the allergic inflammatory response.

DISCUSSION

In this study, CFL1 and EFEMP2 were identified as 2 druggable genes associated with AR by exploring drug-gene databases and executing MR analysis. This study delved into the pharmacogenomics database and utilized MR analysis to identify CFL1 and EFEMP2 as key therapeutic target genes closely related to the pathogenesis of AR. By employing two-sample MR analysis, colocalization, and SMR methods, we not only confirmed a direct causal relationship between the expression level changes of these genes and the risk of AR but also laid the groundwork for developing new AR

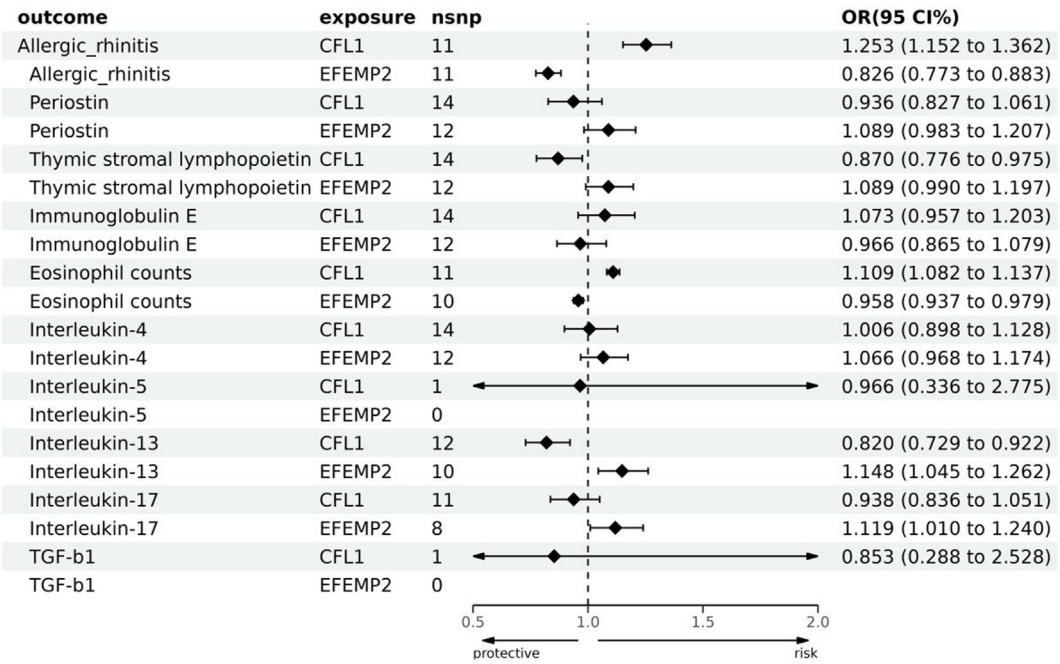

Fig. 4 Mendelian Randomization Results for the Association Between the Expression of Druggable Genes and Biology Markers of AR. The forest plot presents the Mendelian randomization effect estimates and corresponding 95% confidence intervals for the expression of 2 identified druggable genes and 9 AR biomarkers, providing evidence for potential therapeutic targets

treatment regimens by regulating the expression of these genes. Moreover, our findings highlight the significant advantages of the MR method in identifying potential therapeutic targets for AR, especially in strengthening causal inference and overcoming confounding factors, compared to traditional gene expression analysis and transcriptional regulatory network construction.[20,21]

Recent research using the MR approach in conjunction with an upper airway epithelial cell (AEC) model identified key genes related to asthma and allergic diseases, echoing our findings. This study demonstrated the enrichment of disease-associated GWAS SNPs in AECs, revealing the critical role of functional variations in a specific biological context, further emphasizing the unique

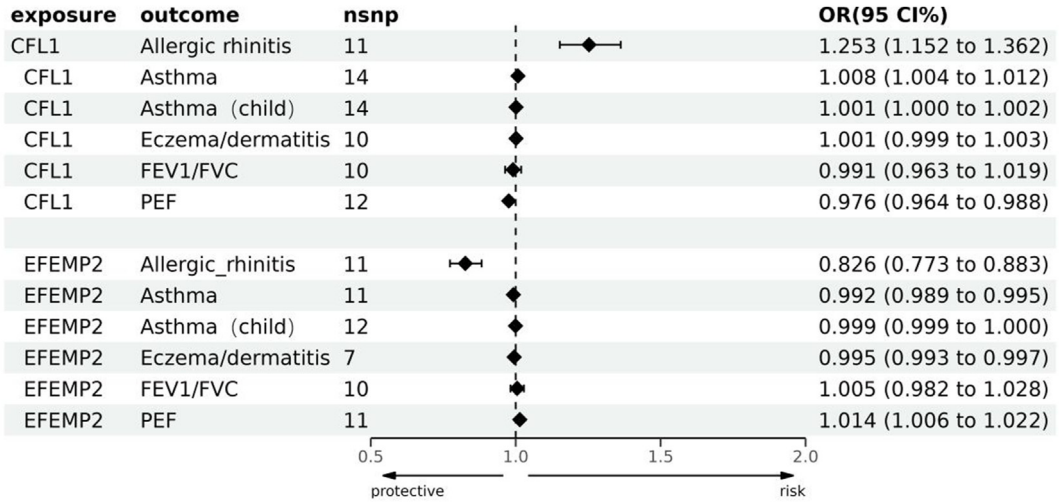

Fig. 5 Mendelian Analysis Showing the Association Between the Expression of Druggable Genes and Other Autoimmune Diseases. This forest plot illustrates the Mendelian randomization results between eQTL and the susceptibility to other autoimmune diseases, suggesting a shared genetic etiology

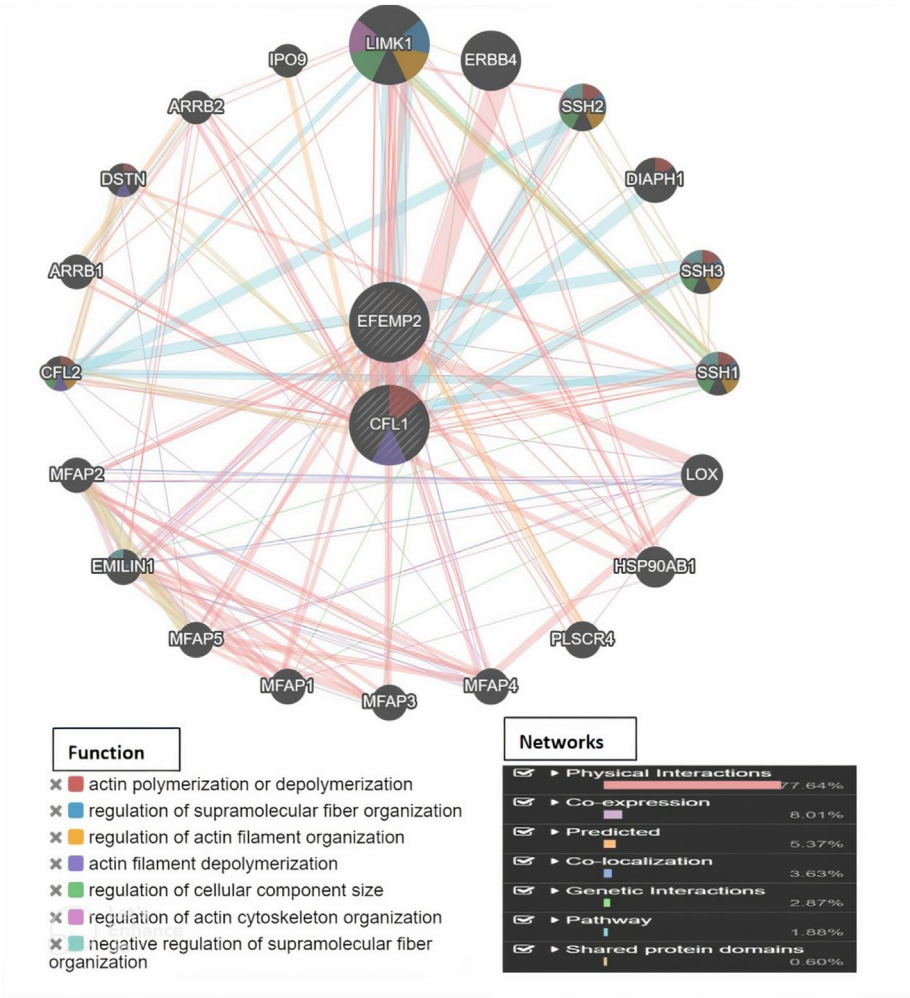

Fig. 6 PPI Network Constructed by GeneMANIA. The protein-protein interaction (PPI) network, generated using GeneMANIA, highlights the functional pathways associated with each gene involved in AR, with each circle color-coded to represent different pathways

value of MR analysis in elucidating the complex pathogenesis of airway diseases.[22] Our study's pharmacogenetic target-focused MR analysis, a data-driven approach, allowed us to systematically assess genetic variations related to the risk of AR, uncovering previously overlooked therapeutic targets. This opens new directions for AR treatment.

We explored the crucial role of CFL1 in the pathogenesis of AR,[23] revealing its significant association with the pathological processes of AR. As a core protein regulating actin dynamics, CFL1 plays a role in various cellular functions, especially important in the migration and morphological changes of immune cells such as eosinophils.[24] Our findings confirmed a significant causal relationship between CFL1 and eosinophil counts, and PPI analysis revealed CFL1's direct involvement in regulating molecules required for inflammation activation. Previous proteomic studies further validated this, showing significant changes in CFL1 expression among birch pollen allergy sufferers and in conditions of fibrinogen deficiency associated with allergic diseases.[24,25] Additionally, our analysis uncovered CFL1's significant associations with key regulatory factors in AR, such as TSLP and IL-13, and other allergic diseases like asthma and eczema. These results not only broaden our understanding of CFL1's role in allergic pathology but also highlight its potential as a therapeutic target for allergic diseases.

In this study, we innovatively explored the relationship between the EFEMP2 gene and AR, revealing a negative correlation with AR, suggesting

its potential protective role against the development of AR. EFEMP2, widely expressed in various human tissues and coding for a protein involved in extracellular matrix formation, is crucial for maintaining the structure and function of epithelial cells.[26] The epithelium, as the primary barrier between the body and the external environment, plays a key role in defending against allergens and pathogens, with its dysfunction closely related to the occurrence of allergic diseases like AR.[27] This aligns with research by Wei Luo et al,[28] who analyzed eQTLs of airway epithelial cells and their application in GWAS results for asthma and related phenotypes, underscoring the importance of epithelial cells in studying the molecular mechanisms of asthma and other airway diseases. Our findings further confirm the roles of EFEMP2 in the pathogenesis of AR by modulating key biomarkers such as eosinophil counts and levels of IL-13 and IL-17. This not only reveals the importance of further in-depth research into the molecular basis of epithelial cells in AR and asthma but also emphasizes the protective role of EFEMP2 by enhancing the integrity of the nasal mucosal barrier, potentially reducing allergen invasion. Additionally, PheWAS studies revealed the association of the EFEMP2 gene with other allergic diseases such as asthma and eczema, expanding its potential role in allergic pathology. PPI analysis indicated that EFEMP2 is related to DNA repair and cytoskeletal proteins, essential for maintaining immune cell function.

While this study marks significant progress in identifying potential therapeutic targets for AR, there are limitations to consider. Firstly, despite its strength, MR analysis is constrained by potential genetic confounding and the selection of instrumental variables. Secondly, reliance on genetic data without inclusion of animal model validations limits a comprehensive understanding of the mechanisms of action of the identified genes. Additionally, the scope of the sample population necessitates validation of our findings in a broader cohort. Future studies are required to further validate these results and explore the efficacy and safety of CFL1 and EFEMP2 through *in vitro* experiments and animal models. A series of preclinical and clinical trials will provide a solid foundation for translating these findings into practical treatment strategies, paving the way towards the development of more effective and less adverse AR treatment options.

In summary, through druggable gene MR analysis, we identified CFL1 and EFEMP2 as 2 new candidate therapeutic targets for AR, laying a foundation for the development of AR therapy targeting these genes. Our research also demonstrates that the druggable gene MR analysis method is an effective strategy for identifying disease treatment targets. Subsequent studies are needed to further elucidate the precise mechanisms of both genes in AR through functional verification.

Abbreviations

AR: Allergic Rhinitis; MR: Mendelian Randomization; eQTL: Expression Quantitative Trait Locus; SNP: Single Nucleotide Polymorphism; GWAS: Genome-Wide Association Study; PheWAS: Phenome-Wide Association Study; PPI: Protein-Protein Interaction; IVW: Inverse Variance Weighted; SMR: Summary-data-based Mendelian Randomization; GTEx: Genotype Tissue Expression project; DGIdb: Drug-Gene Interaction Database.

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Availability of data and materials

The data supporting this study's findings are available in public data sources or on request from the corresponding authors.

Authors' contributions

XR H and RY S conceptualized and designed the study, performed formal analyses, and were involved in collecting and interpreting the data. XR H drafted the initial manuscript. Z Z supervised this work. All authors approved the final submitted version.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors approved the final version and its submission.

Declaration of competing interest

All authors have no relevant financial interests to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100927.

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