

Genetically Predicted Serum miRNAs as Potential Causal Drivers of Atopic Dermatitis: Evidence from Large-Scale GWAS and Clinical Validation

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Background: Although dysregulated microRNAs (miRNAs) are implicated in Atopic Dermatitis (AD), their causal roles remain elusive due to potential confounding and reverse causation. We aimed to systematically identify causal miRNAs for AD and elucidate their underlying mechanisms.

Methods: We conducted a bidirectional two-sample Mendelian randomization (MR) study using large-scale GWAS summary statistics for 2083 miRNAs and AD. The findings were validated using independent trans- and cis-eQTL datasets, and consistency was assessed via correlation analysis. Bayesian colocalization was applied to distinguish pleiotropy from linkage disequilibrium. Downstream targets were analyzed via GO/KEGG enrichment, and clinical relevance was verified using differential expression analysis in two independent patient cohorts (GSE162926 and GSE217232).

Results: We identified six circulatory miRNAs causally associated with AD. Notably, miR-1908-5p, miR-148a-3p, miR-133a-3p were identified as a robust risk factor, while miR-125a-5p, miR-181b-5p, let-7e-5p exhibited a protective effect. Colocalization analysis revealed compelling evidence (PP.H4=0.99) for a shared causal variant (rs174561) between miR-1908-5p and AD. Reverse MR indicated no causal effect of AD on these miRNAs. Functional enrichment analyses revealed that downstream targets were predominantly enriched in the PI3K-Akt and MAPK signaling pathways, regulating biological processes critical for skin barrier integrity, wound healing, and oxidative stress response. Crucially, transcriptomic analysis in clinical cohorts corroborated the MR findings, showing significant dysregulation of the identified miRNAs in AD patients.

Conclusion: This study provides robust genetic and transcriptomic evidence for the causal involvement of specific circulating miRNAs, particularly miR-1908-5p, in AD pathogenesis. These findings offer potential novel biomarkers and therapeutic targets for precision medicine in AD.

Keywords: miRNAs, atopic dermatitis, Mendelian randomization, Bayesian colocalization, linkage disequilibrium

Introduction

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterized by eczematous lesions, intense pruritus, and substantial impairment in quality of life. Recent global modeling and Global Burden of Disease (GBD) analyses estimate that AD affects more than 100 million children and a similar number of adults worldwide, with pediatric prevalence around 3–5% and adult prevalence around 2%, making it one of the most common inflammatory skin disorders.¹ AD is now recognized as a systemic disease associated with sleep disturbance, mental health disorders, cardiometabolic comorbidities, and the “atopic march” to asthma, food allergy, and allergic rhinitis.² Its pathogenesis reflects a complex interplay between epidermal barrier dysfunction (eg filaggrin and tight junction defects), type 2-skewed immune responses involving Th2/Th22/Th17 axes, microbial dysbiosis, and environmental factors such as urbanization and pollutants.³ Despite the advent of targeted biologics and JAK inhibitors, many patients experience partial responses, relapses or treatment-limiting adverse events, underscoring the need to better define upstream molecular drivers and novel biomarkers for risk stratification and intervention.

MicroRNAs (miRNAs), ~19–25 nucleotide non-coding RNAs that repress gene expression post-transcriptionally, have emerged as important regulators of skin homeostasis and AD pathogenesis. Systematic reviews and focused studies consistently report dysregulation of numerous miRNAs—including miR-143, miR-146a, miR-155, miR-223, miR-10a-5p, and miR-29b—in lesional skin, peripheral blood mononuclear cells, and serum of AD patients, where they modulate NF- κ B-driven inflammation, keratinocyte proliferation, barrier protein expression, and T-cell differentiation.^{4–8} Beyond tissue, circulating miRNAs are stable in extracellular fluids and increasingly studied as minimally invasive AD biomarkers: elevated plasma miR-24 and miR-191, miR-628-3p, serum miR-155, and distinct plasma signatures including miR-451a, miR-143-3p and miR-223-3p have been reported to discriminate AD patients from healthy controls or correlate with disease severity.⁹ However, these observational data—whether from skin or circulation—cannot distinguish whether altered miRNA levels are causal drivers of AD, downstream consequences of chronic Th2-skewed inflammation, or epiphenomena related to treatment and comorbidities. This fundamental limitation motivates the application of causal inference approaches to circulating miRNAs in AD.

Mendelian randomization (MR) offers a powerful approach to address causality by leveraging germline genetic variants as instrumental variables (IVs) for modifiable exposures—here, circulating miRNA levels. Under core assumptions, genetic proxies are randomly allocated at conception and largely independent of environmental confounders and reverse causation, enabling causal inference from observational data.¹⁰ In AD, MR has already been used to implicate higher body mass index, altered gut microbiota, IL-18 signaling, gastroesophageal reflux disease and several psychiatric traits as causal risk factors or consequences, and to demonstrate bidirectional relationships between AD and asthma, diabetes and other comorbid conditions.¹⁰ Until recently, the lack of large-scale genetic instruments for circulating miRNAs precluded analogous analyses. This barrier has been overcome by genome-wide studies that map expression quantitative trait loci (eQTLs) for plasma miRNAs: Nikpay et al identified cis- and trans-miRQTLs for 143 circulating miRNAs in 710 Europeans, while recent work in the Framingham Heart Study (FHS) and Rotterdam Study extended ex-miRNA eQTL mapping to thousands of individuals and used MR to implicate extracellular miRNAs in diverse cardiometabolic traits.¹¹ Notably, MR leveraging circulating miRNA eQTLs has already been applied to other disease contexts, such as severe COVID-19,¹² demonstrating the feasibility of this approach. Furthermore, a systematic review of MR studies in AD has catalogued a growing body of causal evidence for this disease,¹⁰ though none of the reviewed studies employed circulating miRNAs as the exposure.¹³ Despite these advances, no study has systematically investigated whether genetically proxied plasma miRNAs causally influence AD susceptibility. Despite these advances, no study has systematically investigated whether genetically proxied plasma miRNAs causally influence AD susceptibility. Despite these advances, no study has systematically investigated whether genetically proxied plasma miRNAs causally influence AD susceptibility.

Against this backdrop, we designed a two-sample MR study to evaluate the causal effects of circulating miRNAs on AD risk. Leveraging cis-eQTLs from Nikpay et al for discovery, trans-eQTLs from the same study and independent cis-eQTLs from FHS for validation, and large-scale AD summary statistics from the FinnGen consortium (over 30,000 AD cases and 430,000 controls of European ancestry), we implemented a two-stage strategy to identify and replicate putatively causal miRNAs. We complemented primary MR analyses with Steiger directionality tests, phenome-wide pleiotropy scans, reverse MR treating AD as the exposure, and Bayesian colocalization to distinguish shared from distinct causal variants. Finally, we integrated experimentally validated miRNA–target interactions, pathway enrichment, and external expression profiling from independent AD transcriptomic datasets to elucidate potential biological mechanisms. This integrated genetic-epidemiologic and functional approach aims to move beyond association and provide robust evidence on which circulating miRNAs are genuinely involved in the etiology of AD.

Materials and Methods

Study Design and Data Sources

We employed a two-sample MR design to investigate the causal effect of circulating miRNAs on the risk of AD, adopting a rigorous two-stage strategy comprising a discovery phase and a validation phase. Summary statistics for miRNA expression were obtained from two large-scale genome-wide association studies (GWAS), utilizing the Nikpay et al Dataset (n=710) for both discovery (cis-eQTLs) and validation (trans-eQTLs),¹¹ and the FHS dataset (n= 5239) for additional validation (cis-eQTLs).¹⁴

All genomic coordinates were aligned to the GRCh38/hg38 reference genome. Genetic association data for the outcome, AD, were acquired from the FinnGen study (Release 12, Endpoint ID: L12_ATOPIC), which included 31,245 cases and 432,874 controls of European ancestry. Figure 1 illustrated the workflow of the study.

Ethical Statement

This study was based exclusively on publicly available, de-identified, summary-level data. All original studies had received ethical approval from their respective institutional review boards, and informed consent was obtained from all participants by the original investigators. No individual-level data were accessed, and no human participants were recruited or biological samples collected in the present study. In accordance with Article 32 (Items 1 and 2) of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects, issued by the National Health Commission of the People's Republic of China on February 18, 2023, this study is exempt from institutional ethical review, as it exclusively utilized legally obtained, publicly available, and fully anonymized summary-level data without causing harm to human subjects or involving sensitive personal information.

Instrumental Variable Selection and Statistical Analysis

To ensure the validity and biological plausibility of IVs, we implemented a rigorous screening and classification process. We defined cis-acting IVs as SNPs located within 250 kb of the corresponding miRNA gene region, while trans-acting IVs were defined as SNPs located beyond this range or on different chromosomes. SNPs associated with miRNA expression were selected at a significance threshold of $P < 5 \times 10^{-6}$. To ensure independence and mitigate linkage

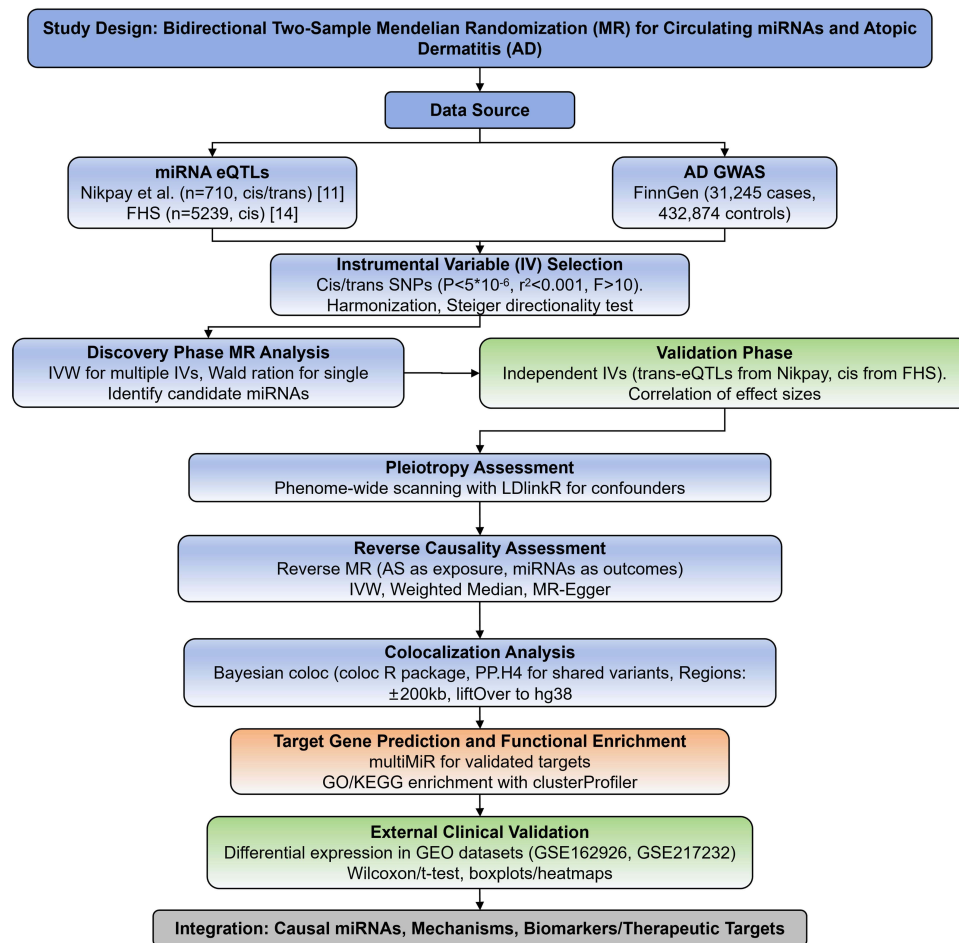


Figure 1 The workflow diagram of this study.

disequilibrium (LD), we performed clumping with a strict threshold of $r^2 < 0.001$ within a 10,000 kb window. We further calculated the F-statistic ($F = \beta^2 / SE^2$) for each SNP to assess instrument strength, excluding weak instruments with an F-statistic < 10 , and conducted the Steiger directionality test to rule out reverse causality by ensuring IVs explained significantly more variance in the exposure than in the outcome. Harmonization was performed to align effect alleles between exposure and outcome datasets, excluding palindromic SNPs with intermediate allele frequencies. The primary MR analysis was conducted using the Inverse Variance Weighted (IVW) method for exposures with multiple IVs and the Wald Ratio method for those with a single IV, with a nominal P-value of < 0.05 serving as the significance threshold in the discovery phase. All statistical analyses were performed using the TwoSampleMR package in R software.

Pleiotropy Assessment and Confounder Scanning

To rigorously assess potential horizontal pleiotropy and confounding factors beyond standard statistical heterogeneity, we implemented a phenome-wide scanning approach using the LDlinkR package. We queried the identified causal SNPs against the LDtrait database to screen for associations with potential confounders recorded in the GWAS Catalog. Specific keywords related to AD risk factors—including lifestyle factors (eg, smoking, BMI), immune-related traits (eg, inflammation, IgE), and allergic comorbidities (eg, asthma, rhinitis)—were used to flag suspicious SNPs. Any SNPs showing significant associations with these confounding traits were documented to evaluate potential violations of the MR independence assumption.

Leave-One-Out and Radial MR

To further evaluate the robustness of the causal estimates and identify potentially influential outlier variants, we conducted additional sensitivity analyses for miRNAs instrumented by multiple SNPs. First, we performed Leave-One-Out (LOO) analysis, in which the MR estimate was recalculated iteratively after excluding one SNP at a time. This analysis was used to assess whether the overall association was disproportionately driven by any single instrumental variant. Second, we applied a radial MR framework and generated MR radial plots to visually inspect SNP-specific contributions to heterogeneity and detect possible outlier instruments. Variants showing extreme deviation from the overall trend were considered potential outliers. These analyses were implemented in R using the TwoSampleMR and RadialMR packages. Associations that remained stable across LOO iterations and showed no influential outliers in radial analysis were considered more robust against pleiotropic bias.

Assessment of Reverse Causality

To exclude the possibility that the observed associations were driven by reverse causation (ie, AD influencing miRNA expression), we conducted a reverse MR analysis treating AD as the exposure and the candidate miRNAs identified in the forward analysis as outcomes. Genetic instruments for AD were extracted from the FinnGen summary statistics (Release 12) using a strict genome-wide significance threshold of $P < 5 \times 10^{-8}$. To ensure instrument independence, we performed clumping with a threshold of $r^2 < 0.001$ within a 10,000 kb window, utilizing the 1000 Genomes Project European reference panel to estimate linkage disequilibrium. Harmonization was conducted to align allele effects between the AD and miRNA datasets, excluding palindromic SNPs with intermediate allele frequencies. We extracted the corresponding summary statistics for the identified AD-associated SNPs from the Nikpay et al dataset. The causal estimates were calculated using the IVW method as the primary analysis, supplemented by the Weighted Median and MR-Egger regression methods to assess the robustness of the findings and detect potential pleiotropy. A nominal P-value < 0.05 in the reverse analysis was considered indicative of potential reverse causality.

Colocalization Analysis

To distinguish whether the observed causal associations were driven by a shared causal variant (pleiotropy) or distinct variants in LD, we performed Bayesian colocalization analysis using the coloc R package. We focused on the genomic regions surrounding the identified causal miRNAs (± 200 kb from the lead cis-eQTL). Summary statistics for AD (FinnGen R12) and miRNA expression (Nikpay et al) within these regions were extracted. Given the differences in genome builds, the coordinates of miRNA eQTLs were lifted over from hg19 to hg38 using the UCSC liftOver tool to

ensure alignment with the AD GWAS data. We assumed a single causal variant per region and calculated the posterior probabilities (PP) for five hypotheses: H0 (no association with either trait), H1 (association with miRNA only), H2 (association with AD only), H3 (association with both traits but distinct causal variants), and H4 (association with both traits sharing a single causal variant). Default priors were used ($p_1=10^{-4}$, $p_2=10^{-4}$, $p_{12}=10^{-5}$, $p_1=10^{-4}$, $p_2=10^{-4}$, $p_{12}=10^{-5}$). A high posterior probability for hypothesis 4 ($PP.H4 > 0.8$) was considered strong evidence of colocalization, indicating that the miRNA and AD likely share a common genetic etiology in the locus.

Target Gene Prediction and Functional Enrichment Analysis

To elucidate the potential biological mechanisms underlying the causal effect of the identified miRNAs on AD, we predicted downstream target genes using the multiMiR R package. To ensure the reliability of the bioinformatic predictions and reduce false positives, we restricted the query to experimentally validated miRNA-target interactions (MTIs) recorded in the validated database tables, excluding purely computational predictions. Gene symbols were mapped to Entrez IDs using the org.Hs.egdb database. Subsequently, we performed functional enrichment analyses, including Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis and Gene Ontology (GO) Biological Process annotation, utilizing the clusterProfiler package. Statistical significance was determined using the Benjamini-Hochberg (BH) method to control the false discovery rate, with an adjusted P-value threshold of <0.05 . To visualize the functional landscape and reduce redundancy among significant GO terms, we calculated semantic similarities using the enrichplot package and constructed a functional clustering tree (Treeplot). Furthermore, we generated gene-concept networks (Cnetplot) and heatmaps (Heatplot) to explicitly illustrate the linkage between shared target genes and AD-relevant pathways, specifically focusing on immune regulation, cytokine signaling, and skin barrier function.

External Validation of miRNA Expression in Clinical Datasets

To validate the clinical relevance of the causal miRNAs identified by MR analysis, we analyzed their expression levels in patients with AD using external transcriptomic datasets from the Gene Expression Omnibus (GEO) database. We selected two independent datasets: GSE162926 and GSE217232. For GSE162926, raw microarray data were obtained, and probe-level intensities were mapped to miRNA identifiers using the GPL21572 platform annotation. Probes corresponding to Homo sapiens miRNAs were retained, and expression values for replicate probes were averaged. For GSE217232, the processed expression matrix was directly retrieved. In both datasets, samples were stratified into AD cases and healthy controls (HC), excluding other conditions (eg, psoriasis). Expression data were log₂-transformed if not already normalized. The differential expression of the candidate miRNAs between AD and HC groups was evaluated using the Wilcoxon rank-sum test or Student's *t*-test, depending on the sample size and normality of distribution. Visualizations, including boxplots with statistical annotations and clustered heatmaps, were generated using the ggplot2 and pheatmap packages in R. A P-value <0.05 was considered statistically significant.

Results

Causal Associations of Circulating miRNAs with AD in the Discovery Phase

In the discovery phase, we utilized cis-eQTLs identified from the Nikpay et al dataset to screen for miRNAs causally associated with AD. A total of 15 miRNAs were identified as potential causal factors for AD ([Figure 2](#) and [Supplementary materials: Table S1](#)). The strength of the genetic instruments was robust across all identified associations. The F-statistics for the selected IVs ranged from 22.10 (miR-146a-3p) to 148.16 (miR-1908-5p), all exceeding the threshold of 10, which indicates a low likelihood of weak instrument bias. Furthermore, the Steiger directionality test confirmed that the variance explained by the IVs in the exposure (miRNAs) was significantly greater than that in the outcome (AD) for all significant estimates ($P < 0.05$), supporting the direction of causality from miRNA expression to AD risk. Eleven miRNAs were identified to have a genetically predicted protective effect on AD (Odds Ratio [OR] < 1). Among them, let-7a-5p exhibited the strongest protective effect size (OR = 0.41, 95% CI: 0.21–0.81, $P = 0.0096$). miR-125a-5p showed a highly significant association, with a genetically predicted increase in expression associated with a 26% reduction in AD risk (OR = 0.74, 95% CI: 0.64–0.87, $P = 2.05 \times 10^{-4}$). Similarly, miR-941 (OR = 0.84, 95% CI:

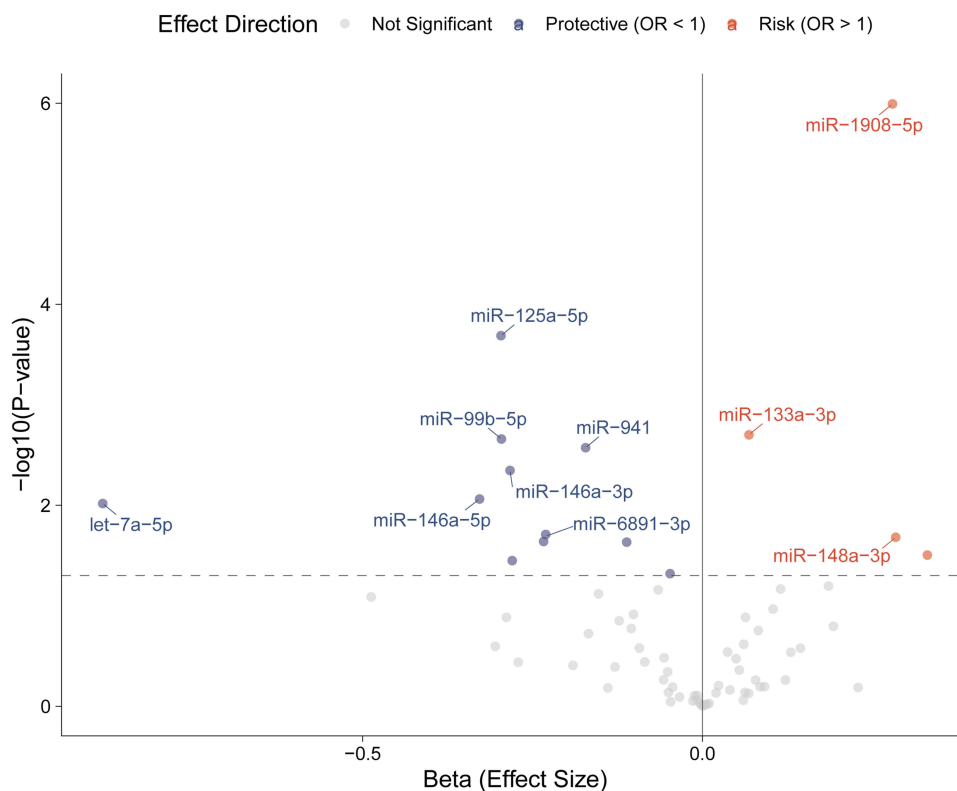


Figure 2 Causal associations of circulating miRNAs with Atopic Dermatitis in the discovery phase. A volcano plot illustrating the Mendelian Randomization (MR) results using cis-eQTLs from the Nikpay et al dataset. The x-axis represents the effect size (Beta) of the miRNA on AD risk, and the y-axis represents the statistical significance ($-\log_{10}$ P-value). The horizontal dashed line indicates the threshold for significance ($P < 0.05$). Points are color-coded based on the direction of the effect: red indicates risk factors (Odds Ratio > 1) and blue indicates protective factors (Odds Ratio < 1). A total of 15 miRNAs were identified as potential causal factors.

0.75–0.94, $P=0.0027$) and miR-99b-5p (OR = 0.74, 95% CI: 0.62–0.90, $P=0.0022$) were significantly associated with a decreased risk of AD. Notably, both the 5p and 3p strands of miR-146a, a key immune regulator, showed consistent protective effects (miR-146a-5p: OR = 0.72, 95% CI: 0.56–0.92, $P=0.0087$; miR-146a-3p: OR = 0.75, 95% CI: 0.62–0.92, $P=0.0045$). Other miRNAs showing protective associations included miR-4433b-5p (IVW method, OR = 0.95, $P=0.048$), miR-181b-5p (IVW method, OR = 0.89, $P=0.023$), let-7e-5p (OR = 0.76, $P=0.036$), miR-136-5p (OR = 0.79, $P=0.023$), and miR-6891-3p (OR = 0.79, $P=0.020$). Conversely, four miRNAs were identified as potential risk factors for AD (OR > 1). miR-1908-5p demonstrated the most significant association in the discovery phase; a genetically predicted increase in its expression was associated with a 1.32-fold increase in the risk of AD (OR = 1.32, 95% CI: 1.18–1.48, $P=1.02 \times 10^{-6}$). miR-33a-5p (OR = 1.39, 95% CI: 1.03–1.88, $P=0.031$) and miR-148a-3p (OR = 1.33, 95% CI: 1.04–1.69, $P=0.021$) also showed significant positive associations with AD risk. Additionally, miR-133a-3p, analyzed using the IVW method with 2 SNPs, was associated with an increased risk of AD (OR = 1.07, 95% CI: 1.03–1.12, $P=0.002$).

Validation of Causal Associations Using Independent Genetic Instruments

To assess the robustness of the findings from the discovery phase, we performed validation analyses using independent sets of IVs derived from trans-eQTLs (Nikpay et al) and cis-eQTLs from the FHS (Figure 3 and [Supplementary materials: Table S2](#)). Using trans-eQTLs as instruments, we successfully replicated the causal associations for four miRNAs. miR-1908-5p showed a robust risk effect consistent with the discovery phase, with a genetically predicted increase in expression associated with a 28% higher risk of AD (OR = 1.28, 95% CI: 1.11–1.47, $P=4.96 \times 10^{-4}$). Similarly, miR-133a-3p was confirmed as a risk factor (OR = 1.07, 95% CI: 1.03–1.12, $P=0.002$). Regarding protective factors, miR-181b-5p remained significantly associated with a reduced risk of AD (OR = 0.90, 95% CI: 0.83–0.97, $P=0.009$), and let-7e-5p also exhibited a significant protective effect (OR = 0.87, 95% CI: 0.76–0.99, $P=0.040$). In the validation

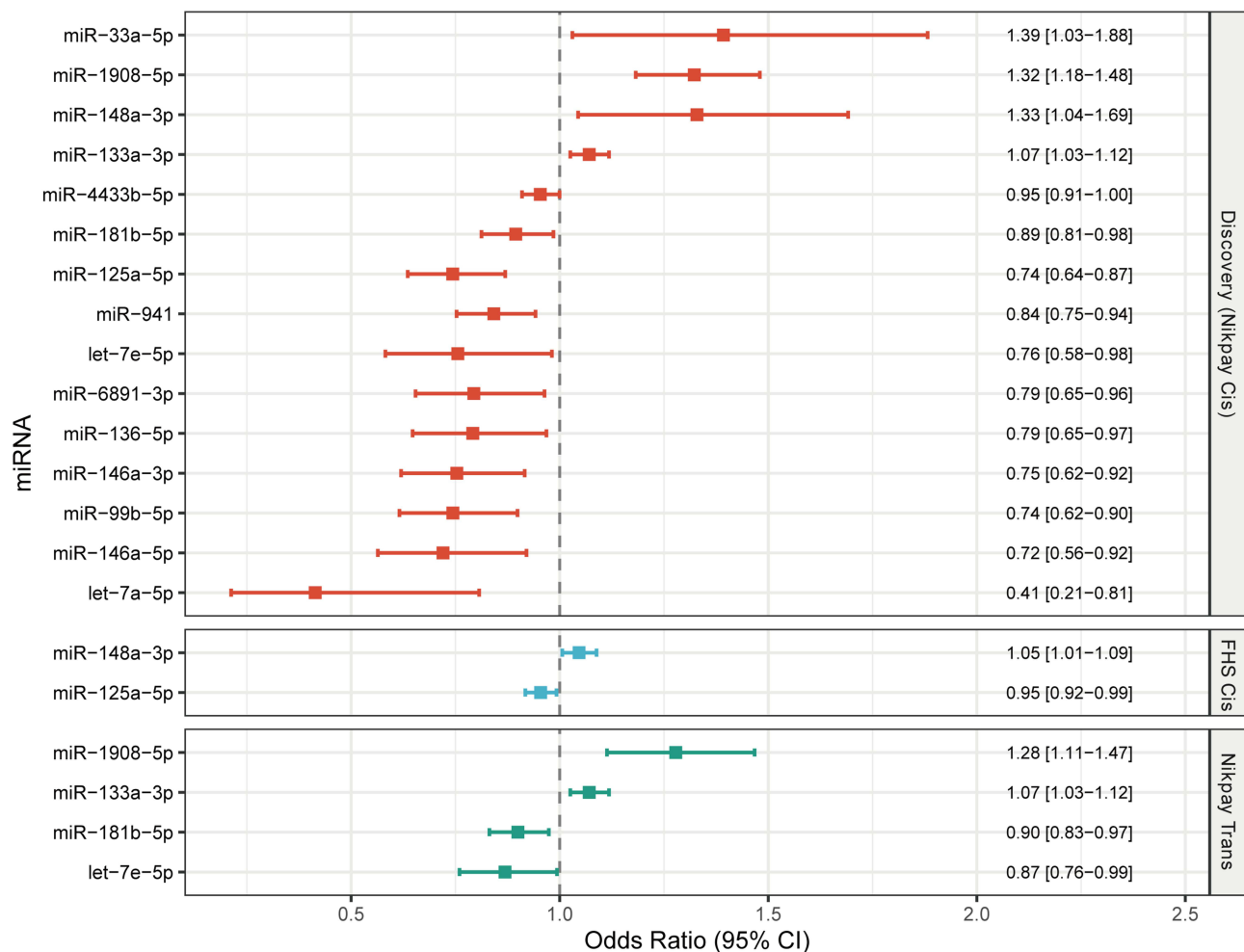


Figure 3 Validation of causal associations using independent genetic instruments. Forest plots summarizing the causal estimates (Odds Ratios and 95% Confidence Intervals) for the candidate miRNAs across the discovery and validation phases. The top panel displays the results from the discovery phase (Nikpay cis-eQTLs). The middle and bottom panels present the validation results using cis-eQTLs from the FHS dataset and trans-eQTLs from the Nikpay dataset, respectively. The vertical dashed line at OR = 1 represents the null effect. Error bars indicate the 95% confidence intervals. miR-1908-5p, miR-133a-3p, miR-181b-5p, let-7e-5p, miR-148a-3p, and miR-125a-5p were successfully validated in independent datasets.

analysis utilizing cis-eQTLs from the FHS dataset, two additional miRNAs were successfully validated. miR-148a-3p was confirmed as a risk factor for AD (OR = 1.05, 95% CI: 1.01–1.09, $P=0.023$). Furthermore, the protective role of miR-125a-5p was corroborated, showing a significant reduction in AD risk (OR = 0.95, 95% CI: 0.92–0.99, $P=0.019$). To further evaluate the reliability of our MR findings, we performed a correlation analysis comparing the effect estimates (β coefficients) obtained from the discovery phase with those from the validation phase. As shown in Figure 4, we observed a significant positive correlation between the effect sizes of the miRNAs across the datasets (Pearson's $r = 0.766$, $P = 1.3e-4$). This high degree of concordance in both the direction and magnitude of the causal estimates supports the robustness of the identified miRNA-AD associations and suggests that the results are not driven by dataset-specific biases. Across all significant validation results, the genetic instruments demonstrated sufficient strength (F-statistics > 10, ranging from 22.08 to 91.85). The Steiger directionality test confirmed the correct causal direction (from miRNA to AD) for all replicated associations ($P<0.05$).

Assessment of Reverse Causality

To determine whether the identified associations were driven by reverse causation, we performed reverse MR analyses treating AD as the exposure and the candidate miRNAs as outcomes (Supplementary materials: Table S3). We utilized 22 SNPs associated with AD as IVs. No Causal Effect of AD on Circulating miRNAs The reverse MR analysis revealed no

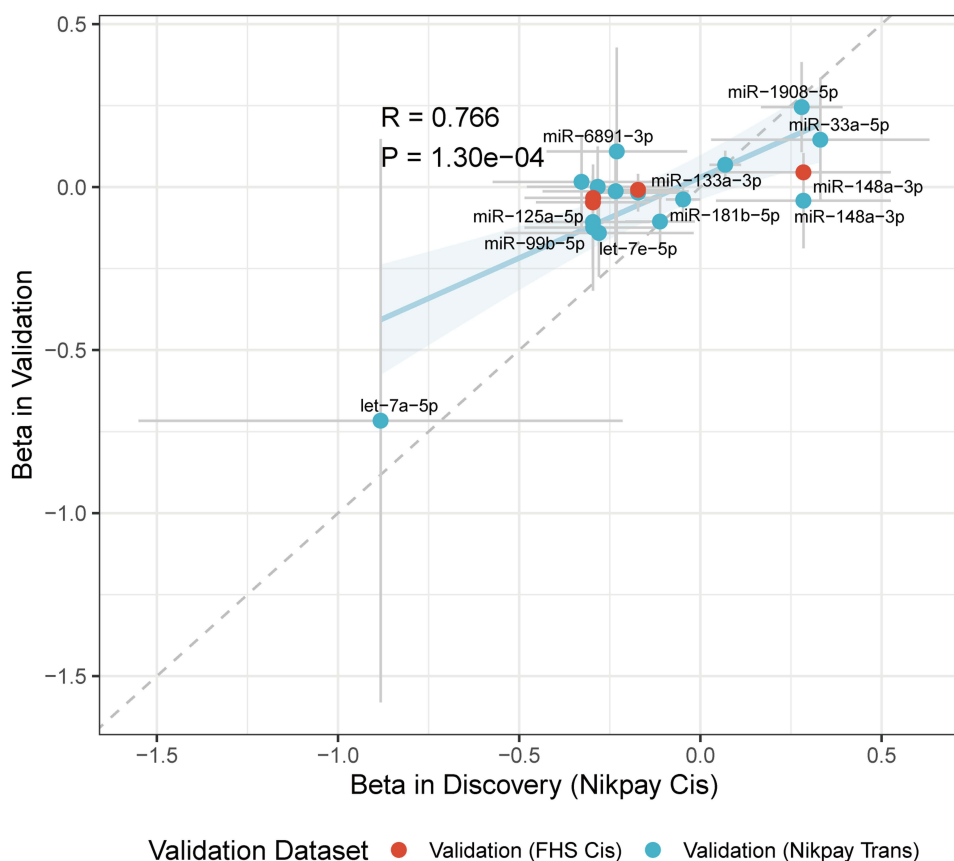


Figure 4 Correlation of causal estimates between discovery and validation phases. A scatter plot comparing the effect sizes (Beta values) obtained from the discovery phase (x-axis, Nikpay Cis) with those from the validation phase (y-axis). Data points represent individual miRNAs, colored by the source of the validation dataset (Red: FHS Cis; Blue: Nikpay Trans). The regression line (blue) with the shaded area (95% confidence interval) indicates the linear relationship between the estimates. A strong positive correlation (Pearson's $R=0.766$, $P=1.30e-4$) confirms the robustness and consistency of the identified causal directions across different datasets.

significant causal effect of genetically predicted AD on the expression levels of any of the 15 candidate miRNAs (all $P>0.05$). Sensitivity Analyses Consistent with the IVW results, sensitivity analyses using the Weighted Median and MR-Egger methods yielded no significant associations (all $P>0.05$). For instance, the MR-Egger regression for miR-181b-5p ($\beta=-0.287$, $P=0.051$) and miR-125a-5p ($\beta=-0.245$, $P=0.084$) approached marginal significance but did not cross the threshold, further supporting the lack of a robust reverse causal link. The consistency across multiple MR methods strengthens the conclusion that the causal relationships identified in the forward analysis (miRNA to AD) are unlikely to be confounded by reverse causality.

Colocalization of Genetic Variants Between miRNAs and AD

To further distinguish whether the identified associations were driven by a shared causal variant (pleiotropy) or merely by LD between distinct causal variants, we performed Bayesian colocalization analysis for the candidate miRNAs (Figure 5 and [Supplementary materials: Table S4](#)). We observed compelling evidence of colocalization for miR-1908-5p and AD. The posterior probability for a shared causal variant (PP.H4) was 0.99, far exceeding the standard threshold of 0.8. The analysis pinpointed rs174561 on chromosome 11 as the likely shared causal variant driving both miR-1908-5p expression and AD susceptibility. This finding strongly corroborates the MR results, suggesting a common genetic mechanism. Suggestive evidence of colocalization ($PP.H4 > 0.5$) was observed for three additional miRNAs located on chromosome 19. miR-125a-5p showed a high probability of sharing a causal variant with AD ($PP.H4 = 0.79$), mapped to the locus rs11673260. Similarly, the let-7e-5p and miR-99b-5p cluster exhibited moderate evidence of colocalization, with PP.H4 values of 0.70 and 0.62, respectively, both pointing to rs11084100 as the candidate variant. For other miRNAs such as miR-941 and miR-6891-3p, the analysis indicated a high probability of hypothesis 3 ($PP.H3 > 0.99$), suggesting that

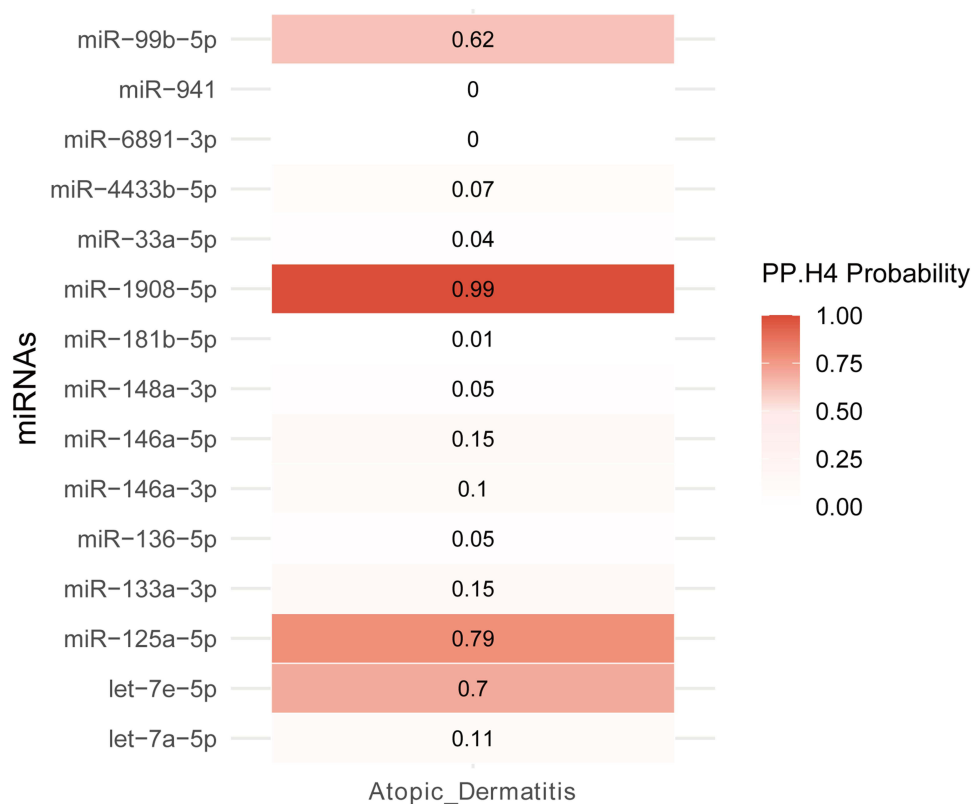


Figure 5 Bayesian colocalization analysis of candidate miRNAs and Atopic Dermatitis. A heatmap displaying the posterior probabilities of Hypothesis 4 (PP.H4), which represents the probability that the miRNA expression and Atopic Dermatitis share a single causal variant. The color intensity represents the magnitude of the PP.H4 value, with darker red indicating stronger evidence of colocalization. miR-1908-5p exhibited compelling evidence of colocalization (PP.H4 = 0.99), suggesting a shared genetic mechanism. miR-125a-5p, let-7e-5p, and miR-99b-5p showed suggestive evidence (PP.H4 > 0.5).

while these miRNAs are genetically associated with AD, the association is likely driven by distinct causal variants in linkage disequilibrium rather than a single shared variant. The remaining miRNAs showed limited evidence of colocalization (PP.H4 < 0.5) in this analysis, implying that their MR associations might be subject to complex genetic architectures or limited by the current sample size of the eQTL data.

Functional Enrichment Analysis of Downstream Targets

To elucidate the potential biological mechanisms underlying the causal effects of the identified miRNAs on AD, we predicted their downstream target genes and performed functional enrichment analyses. Collectively, we identified a total of 2587 unique target genes for the 4 causal miRNAs. Specifically, let-7e-5p was predicted to regulate the largest number of targets (n = 2491), followed by miR-181b-5p (n = 164), miR-133a-3p (n = 10), and miR-148a-3p (n = 6) ([Supplementary materials: Table S5](#)). Functional clustering of these targets via Gene Ontology (GO) analysis highlighted their critical roles in skin tissue remodeling and cellular homeostasis. As illustrated in [Figure 6](#), the target genes were significantly enriched in biological processes essential for barrier maintenance, including epithelial cell proliferation, wound healing, and cell-substrate adhesion. Furthermore, the analysis revealed a strong involvement in environmental stress adaptation and cell survival, characterized by clusters related to response to oxidative stress, response to hypoxia, and the regulation of apoptotic signaling pathway. At the molecular level, these processes appeared to be driven by the regulation of kinase activity and protein phosphorylation. Consistent with these biological functions, KEGG pathway analysis ([Figure 7](#)) demonstrated that the targets were predominantly enriched in pivotal signaling cascades associated with inflammation and cell-matrix interactions. The PI3K-Akt signaling pathway and MAPK signaling pathway emerged as the top enriched terms, followed by Focal adhesion, FoxO signaling pathway, and Cellular senescence. These findings

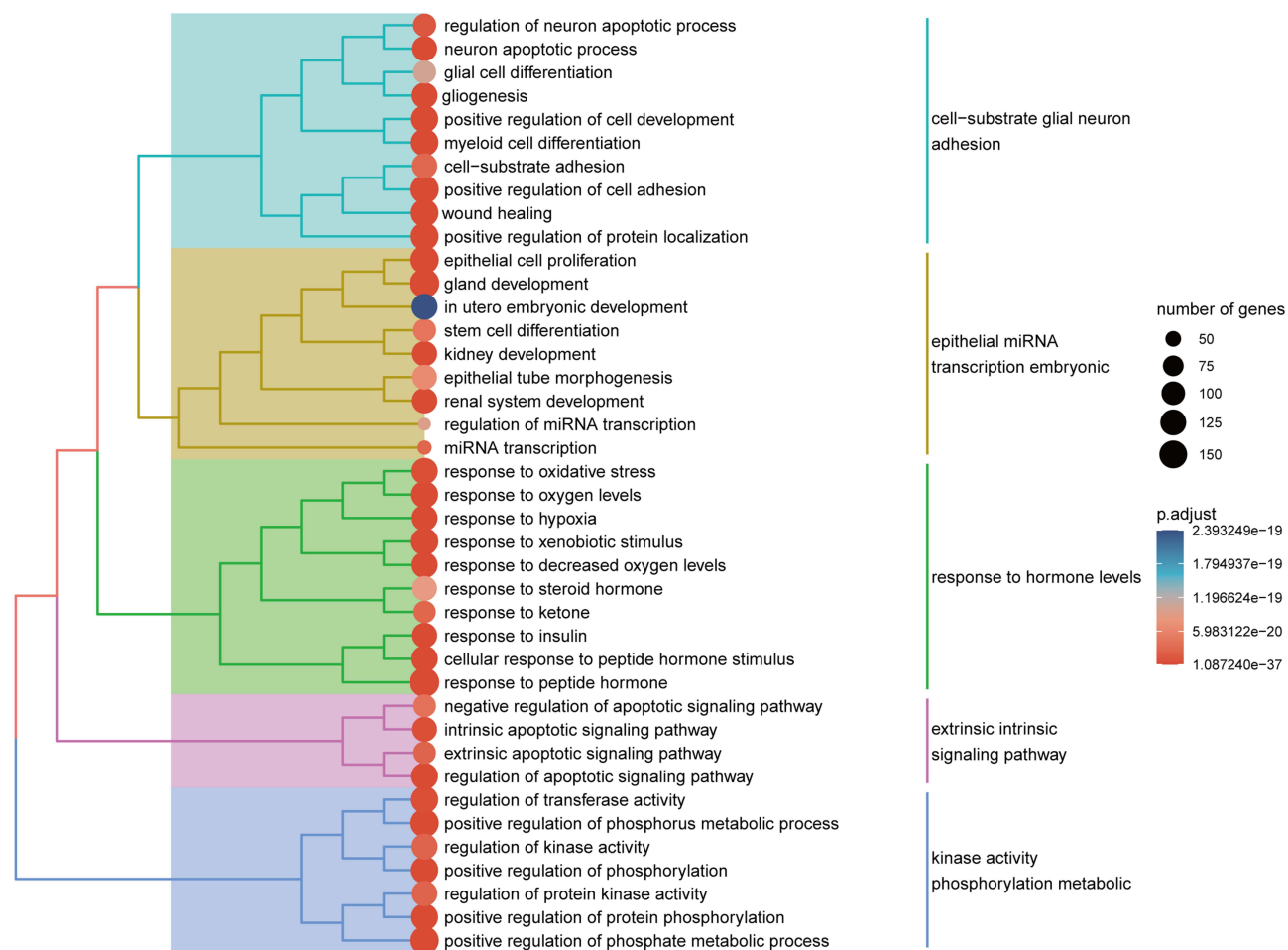


Figure 6 Functional clustering of predicted miRNA targets via Gene Ontology (GO) analysis. A treemap visualization of the biological process (BP) enrichment analysis for the targets of the validated causal miRNAs.

suggest that the identified miRNAs may modulate AD pathogenesis by influencing gene networks governing immune responses, skin barrier integrity, and oxidative stress regulation.

Additional Sensitivity Analyses

Additional sensitivity analyses were conducted using LOO and radial MR for the replicated miRNAs, where applicable. LOO analysis was performed only for associations instrumented by at least two SNPs (Table S6). For miR-133a-3p and miR-1908-5p in the validation stage, as well as miR-133a-3p in the discovery stage, the causal estimates remained stable across leave-one-out iterations, suggesting that these associations were not driven by any single SNP. For miR-181b-5p, let-7e-5p, and miR-125a-5p, the effect direction remained consistent after sequential exclusion of individual SNPs, although modest attenuation in effect size was observed, indicating overall robustness with some sensitivity to instrument composition. In contrast, the LOO results for miR-148a-3p suggested potential sensitivity to individual SNP exclusion, and this association should therefore be interpreted with greater caution.

Radial MR analyses were performed for miRNAs instrumented by at least three SNPs (Table S7). For several associations, particularly those involving miR-125a-5p, miR-148a-3p, and miR-181b-5p in the validation stage, radial MR suggested potential outlier signals. However, some radial IVW analyses showed instability or software-related boundary errors, indicating limited robustness of radial model fitting under sparse instrument settings. Therefore, the radial MR results were treated as exploratory outlier-screening evidence rather than definitive proof of pleiotropic bias.

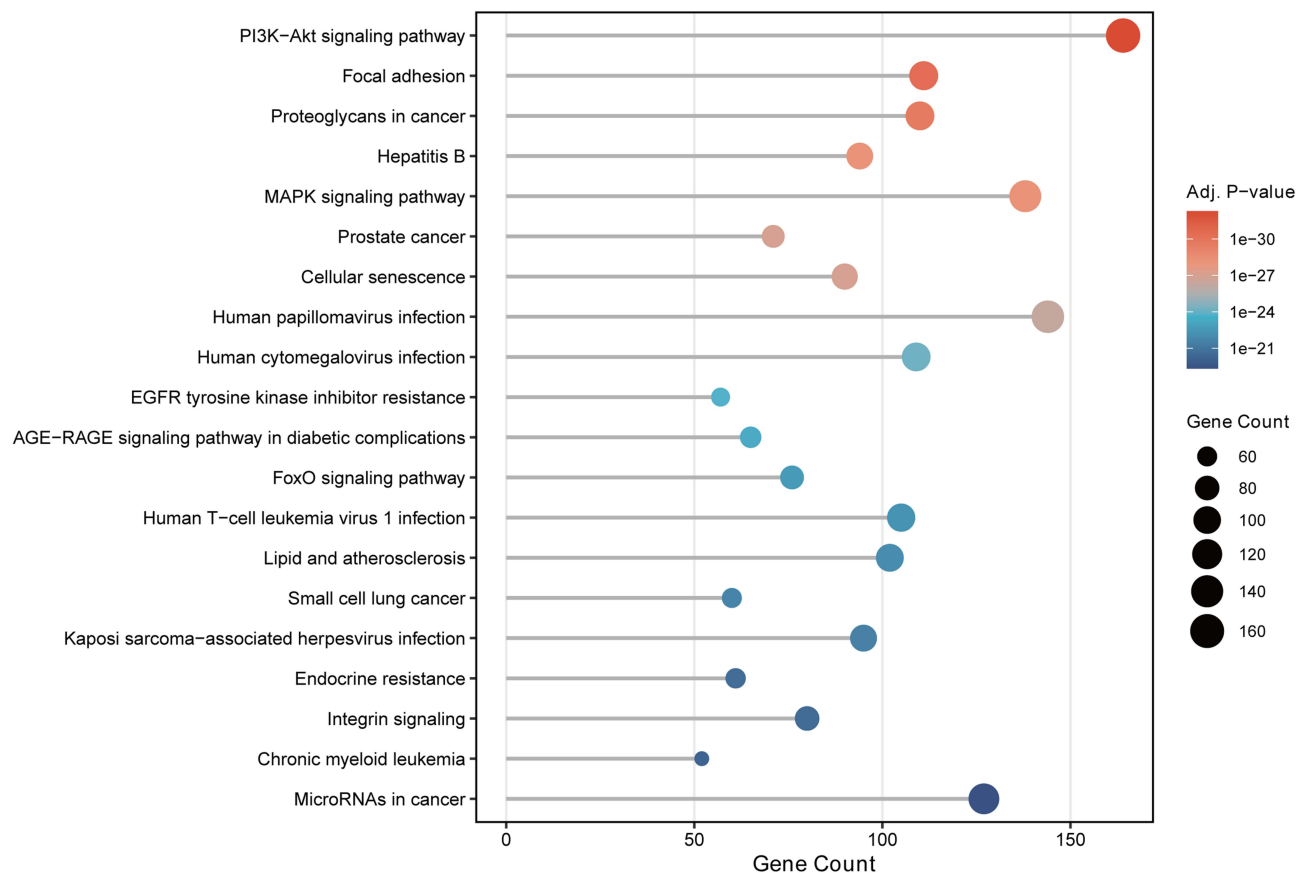


Figure 7 KEGG pathway enrichment analysis of downstream targets. A lollipop chart showing the top enriched KEGG pathways for the target genes of the causal miRNAs.

Overall, these additional sensitivity analyses support the robustness of most replicated associations, while indicating that the findings for miR-148a-3p warrant more cautious interpretation.

Phenome-Wide Screening of Instrumental Variants for Potential Confounding

To further evaluate the independence assumption of MR, we performed a phenome-wide screening of the instrumental SNPs using LDlinkR and the LDtrait database, focusing on predefined AD-related confounding domains, including smoking, body mass index (BMI), alcohol-related traits, immune and inflammatory phenotypes, eosinophil-related traits, IgE/allergic phenotypes, and atopic comorbidities such as asthma and allergic rhinitis ([Supplementary Materials: Table S8](#)). This analysis showed that the degree of potential pleiotropy varied across loci. Several instrumental variants were associated with lifestyle-related traits, such as BMI and smoking behavior, whereas a larger number of variants were linked to immune-related or allergic phenotypes, particularly eosinophil count, asthma, allergic disease, rhinitis, and eczema. Notably, the lead variant for miR-1908-5p (rs174561) showed multiple associations with eosinophil traits, asthma-related phenotypes, and inflammatory conditions, while the instrument for miR-181b-5p was strongly linked to eosinophil-related traits. The instrument for miR-148a-3p also showed associations with adiposity-related traits, including waist-to-hip ratio and BMI-related phenotypes. These findings indicate that, although the selected instruments are biologically relevant to AD-related pathways, residual horizontal pleiotropy cannot be completely excluded and should be considered in interpretation.

External Validation of miRNA Expression in Clinical Cohorts

To verify the clinical relevance of our MR findings and assess whether the genetically predicted causal effects translate into observable transcriptional changes in patients, we analyzed miRNA expression profiles in two independent AD datasets (GSE162926 and GSE217232). In the GSE162926 dataset, we compared the expression levels of the candidate miRNAs

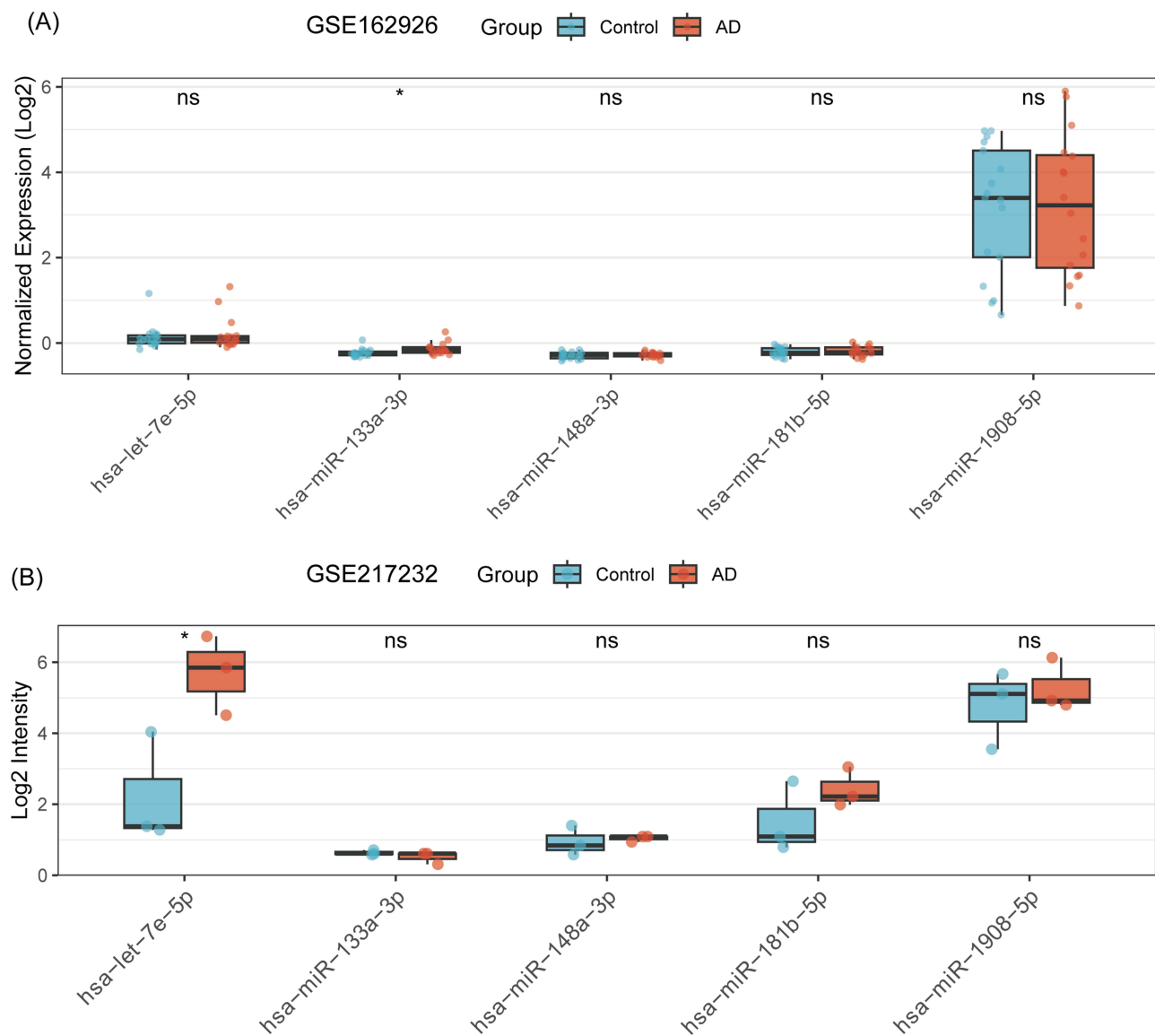


Figure 8 External validation of candidate miRNA expression in independent clinical cohorts. Boxplots comparing the expression levels of causally identified miRNAs between Atopic Dermatitis (AD) patients and healthy controls in two independent datasets. **(A)** In the GSE217232 dataset, hsa-let-7e-5p showed significantly higher expression in AD patients compared to controls. **(B)** In the GSE162926 dataset, hsa-miR-133a-3p was significantly upregulated in the AD group. Statistical significance was assessed using the Wilcoxon rank-sum test. * $P < 0.05$, ns = not significant.

between AD patients and healthy controls. As illustrated in [Figure 8A](#), the analysis revealed a statistically significant upregulation of hsa-miR-133a-3p in the AD group compared to controls ($P < 0.05$). However, no significant differences were observed for the other candidate miRNAs in this cohort. We further extended our validation to the GSE217232 dataset to corroborate these findings. Notably, hsa-let-7e-5p exhibited a significant elevation in expression levels in AD patients relative to the control group ([Figure 8B](#), $P < 0.05$). While other miRNAs, such as hsa-miR-181b-5p, showed discernible trends of altered expression, they did not reach statistical significance, possibly due to the limited sample size and biological heterogeneity between cohorts. Collectively, these transcriptomic analyses provide supportive clinical evidence for the involvement of specific MR-identified miRNAs—particularly hsa-miR-133a-3p and hsa-let-7e-5p—in the pathophysiology of AD.

Discussion

In this two-sample MR study, we systematically evaluated the causal relationships between circulating miRNAs and AD using large-scale miRNA eQTL resources and FinnGen GWAS data. In the discovery phase we identified 15 candidate

plasma miRNAs with putative causal effects on AD, including 11 showing genetically predicted protective effects and 4 associated with increased risk. Six miRNAs—miR-1908-5p, miR-133a-3p, miR-148a-3p, miR-181b-5p, let-7e-5p and miR-125a-5p—were robustly replicated using independent instrument sets (trans-eQTLs from Nikpay et al and cis-eQTLs from FHS), with consistent directions of effect and no evidence for reverse causation. Colocalization further supported shared causal variants for miR-1908-5p and several chromosome 19 miRNAs (miR-125a-5p, let-7e-5p, miR-99b-5p), while our enrichment and external-expression analyses linked their validated targets to immune regulation, cytokine signaling and barrier-relevant pathways central to AD pathogenesis. These results expand the current miRNA landscape in AD beyond the well-studied miR-146a, miR-155, miR-151a and miR-223, and provide genetically anchored evidence for a set of circulating miRNAs that likely participate in the etiology of AD rather than merely reflecting secondary inflammatory changes.⁷ Additional Leave-One-Out and radial MR analyses further strengthened the robustness assessment of our findings. Most replicated associations remained directionally consistent after sequential SNP exclusion, although some attenuation was observed for several multi-SNP instruments. Notably, the association for miR-148a-3p appeared more sensitive to instrument composition, and the exploratory radial MR analyses for several miRNAs suggested possible outlier signals under sparse instrument settings. These findings underscore the need for cautious interpretation and future validation using larger miRNA eQTL resources.

Among all candidates, miR-1908-5p showed the strongest and most consistent risk signal. In both cis- and trans-instrument analyses, genetically higher plasma miR-1908-5p was associated with a ~30% increase in AD risk, and Bayesian colocalization yielded compelling evidence (PP.H4 = 0.99) that a single variant, rs174561 on 11q12 within the FADS1 locus, jointly drives variation in miR-1908-5p expression and AD susceptibility. Critically, this locus has direct relevance to AD pathogenesis. rs174561 is one of several FADS gene cluster SNPs that have been shown to strongly modulate blood PUFA composition in children and adults;¹⁵ in pooled birth cohort studies (KOALA and LISA, n=879), rs174561 and adjacent FADS variants were directly tested for association with eczema in the first two years of life, confirming the FADS cluster as a regulator of PUFA metabolism relevant to atopic disease.¹⁶ A Swedish birth cohort study further demonstrated that FADS minor allele carriers had reduced capacity to desaturate n-6 PUFAs, which was nominally associated with a reduced risk of developing atopic eczema.¹⁷ Since FADS1 catalyzes the Δ 5-desaturation step critical for arachidonic acid (AA) formation—and AA-derived eicosanoids (prostaglandins, leukotrienes) are central mediators of allergic inflammation in AD skin¹⁸—the miR-1908-5p–FADS1 axis likely influences AD susceptibility by altering the balance of pro-inflammatory and pro-resolving lipid mediators. In a large circulating-miRNA eQTL study, carriers of the rs174561-C allele had higher plasma miR-1908-5p levels; mechanistic experiments showed that miR-1908-5p directly represses BMP1 and dampens TGF- β 1 signaling.¹⁹ TGF- β signaling is directly implicated in AD, where it influences fibrosis and tissue remodeling in chronic lichenified lesions, and BMP signaling participates in epidermal differentiation. We acknowledge, however, that direct experimental evidence linking miR-1908-5p to keratinocyte barrier function or Th2-driven inflammation in AD models is currently lacking and represents a priority for future investigation. The very strong colocalization at rs174561 reduces concern that the MR signal is driven by linkage disequilibrium with a neighboring, non-miRNA mechanism.

miR-148a-3p emerged as a replicated risk miRNA in our analyses. Importantly, miR-148a-3p has been directly studied in the context of inflammatory skin disease. In psoriasis, plasma exosomal miR-148a-3p was highly expressed in both exosomes and CD4⁺ T cells of patients and was correlated with abnormal CD4⁺ T cell subset proportions and cytokine levels; plasma exosomal miR-148a-3p targeted Bim to affect the dysfunction of CD4⁺ T cells in psoriatic mice, aggravating psoriasis-like symptoms.²⁰ Since AD and psoriasis both involve CD4⁺ T-cell-driven chronic skin inflammation—and AD skin contains even more T cells than peripheral blood, with a dynamic Th-subset pattern²¹—the finding that miR-148a-3p directly modulates CD4⁺ T-cell function in inflammatory skin disease provides a mechanistic framework more directly relevant to AD than studies in non-dermatological conditions alone. Furthermore, miR-148a-3p has been identified as a repressor of IKBKB and NF- κ B signaling in human cells,²² and NF- κ B is a central driver of keratinocyte chemokine production and immune activation in AD skin.⁶ miR-148a-3p was also elevated in both psoriasis and vitiligo patient plasma, further supporting its role as a dysregulated miRNA in autoimmune skin diseases.²³ In an immunological context, miR-148a can disrupt B-cell tolerance by downregulating Gadd45 α , PTEN, and Bim,²⁴ which may be relevant to the high total and allergen-specific IgE and autoantibody

production characteristic of extrinsic AD, but direct evidence in AD B cells remains lacking. The enrichment of miR-148a target genes in MAPK, PI3K-Akt and cytokine-receptor pathways in our functional analysis is consistent with AD-relevant signaling. We note, however, that AD-specific expression studies of miR-148a-3p in Th2 cells or lesional skin are still needed to confirm the proposed mechanisms.

We identified miR-133a-3p as a replicated risk miRNA. This finding is particularly noteworthy when considered alongside direct skin-tissue data. Early microarray studies showed that miR-133a is downregulated in lesional skin of both AD and psoriasis patients,²⁵ suggesting local suppression of this miRNA in inflamed skin. miR-133a-3p was also investigated alongside miR-146a-5p and let-7b-5p in a study of psoriatic patients examining cardiovascular risk miRNAs in inflammatory skin disease,^{6,26,27} further connecting this miRNA to cutaneous inflammation. Our MR finding that genetically higher systemic miR-133a-3p increases AD risk while local skin expression is reduced may reflect tissue-compartment-specific effects: MR captures the impact of life-long genetic perturbation of plasma miR-133a-3p, which primarily reflects muscle and adipose expression; its systemic effects on metabolism or vascular tone could indirectly predispose to AD even as local skin expression is downregulated as a compensatory change. In allergic airway disease, miR-133a reduces PI3K/Akt/mTOR signaling and airway remodeling,²⁶ indicating a broader role in atopic conditions sharing Th2-driven inflammation. Nevertheless, the convergence of AD and psoriasis data showing downregulated cutaneous miR-133a highlights this miRNA family as part of a shared inflammatory/epidermal remodeling signature, and direct functional studies in AD keratinocytes and Th2-stimulated models are needed to clarify the mechanism.

miR-181b-5p was replicated as a protective factor, with higher genetically proxied plasma levels associated with lower AD risk. Crucially, miR-181b-5p has been directly studied in skin biology. In human epidermal keratinocytes (HEKs), high expression of miR-181b-5p inhibited keratinocyte proliferation through modulating TLR4 signaling.²⁸ Further work demonstrated that miR-181b-5p was downregulated in psoriasis skin tissues, and that Akt3 was a direct target of both miR-125b-5p and miR-181b-5p; upregulation of these miRNAs inhibited HEKs proliferation by targeting Akt3, with Akt/mTOR signaling involved in the inhibitory effect.²⁸ This is directly relevant to AD, where keratinocyte hyperproliferation driven by Akt/mTOR signaling contributes to epidermal acanthosis in chronic lesions, and NF- κ B-dependent chemokine production by keratinocytes is a key driver of immune cell recruitment into AD skin.⁶ In endothelial cells, miR-181b targets importin- α 3 to inhibit NF- κ B nuclear translocation, reducing TNF- α -induced VCAM-1 and E-selectin expression,²⁹ a mechanism that could also contribute to reduced immune cell infiltration in AD. In the context of allergic disease, miR-181b-5p targets SPP1 (osteopontin) in bronchial epithelial cells and attenuates IL-13-induced eosinophil recruitment,³⁰ and IL-13 is now recognized as the key type 2 cytokine driving AD inflammation locally.³¹ Our MR finding that genetically higher miR-181b-5p reduces AD risk is therefore consistent with a role in restraining both pathological keratinocyte responses and type 2-biased inflammation—the two pillars of AD pathogenesis. Individuals with a genetic profile favoring higher baseline miR-181b-5p may be more resistant to the chronic inflammatory milieu required for AD initiation and maintenance.

let-7e-5p emerged as a replicated protective miRNA, with moderate colocalization evidence at rs11084100 on chromosome 19. The let-7 family is directly relevant to AD pathogenesis through its regulation of IL-13, which is now recognized as the primary type 2 cytokine driving peripheral inflammation in AD—overexpressed in both lesional and non-lesional AD skin and directly linked to disease severity.³¹ IL-13 is the target of approved AD biologics (tralokinumab, lebrikizumab) and drives skin barrier dysfunction, filaggrin downregulation, and IgE production.³² The let-7 family (including let-7e-5p) directly targets IL-13 mRNA, providing a mechanistically direct link between this protective miRNA and the central cytokine axis of AD. Furthermore, let-7e is part of the conserved miR-125a~99b~let-7e cluster induced in monocytes by TLR4 ligands in an IL-10-dependent manner, which exerts broad negative feedback on TLR signaling by targeting TLR4, CD14, IRAK1, and multiple effector cytokines (TNF- α , IL-6, CXCL8)³³—all of which are upregulated in AD skin and contribute to keratinocyte activation and immune cell recruitment. In allergic rhinitis—an atopic comorbidity sharing the Th2 endotype with AD—let-7e is downregulated in nasal mucosa and serum; overexpression reduces histamine, IgE, and TNF- α .³⁴ Our MR findings suggest that individuals with genetically higher circulating let-7e-5p are better able to restrain IL-13-driven barrier dysfunction and innate immune activation that otherwise favor AD development. The observed elevation of let-7e-5p in AD sera (GSE217232) mirrors the situation for miR-146a—a “protective” miRNA upregulated in active AD as part of compensatory

negative feedback—and is biologically plausible: MR captures constitutional susceptibility, whereas cross-sectional expression reflects responses to ongoing inflammation.

miR-125a-5p was another replicated protective miRNA, with colocalization ($PP.H4 \approx 0.79$) at rs11673260 on chromosome 19. Importantly, miR-125a-5p has direct relevance to skin biology and inflammatory skin disease. In a bioinformatic analysis of AD transcriptomic datasets, miR-125a-5p was identified among miRNAs predicted to target differentially expressed genes in AD lesional skin.³⁵ In psoriasis—which shares CD4⁺ T-cell-driven chronic skin inflammation with AD—miR-125b-5p (a closely related family member) and miR-181b-5p were both downregulated in lesional skin and directly inhibited keratinocyte proliferation by targeting Akt3,²⁸ suggesting a conserved anti-proliferative role for the miR-125 family in inflammatory skin diseases. At the immunological level, miR-125a-5p is inducible in Tregs upon TCR activation and upregulated by GATA3; it targets IL-6R and STAT3, decreasing Treg sensitivity to IL-6-mediated conversion into Th17-like cells.³⁶ This is directly pertinent to AD, where Treg insufficiency and Th2/Th17 imbalance are hallmarks of disease pathogenesis, and IL-6/STAT3 signaling is elevated in both lesional skin and serum. Perturbations in the GATA3-miR-125a-5p-IL-6R axis were specifically documented in Tregs from asthma patients,³⁶ linking this pathway to the atopic disease spectrum that includes AD. miR-125a-5p also promotes M2 macrophage polarization by targeting TRAF6/TAK1,³⁷ which may favor pro-resolving tissue responses in AD. Our MR result suggesting that constitutional elevation of miR-125a-5p lowers AD risk is consistent with stabilized Treg function and restrained keratinocyte hyperproliferation—both directly relevant to AD pathobiology.

Several variants were linked to eosinophil-related traits, asthma, allergic disease, rhinitis, eczema, and, for some loci, BMI- or smoking-related phenotypes. These associations are biologically plausible, as AD is established as the first occurrence of the atopic march, with shared variants mapped across cytokine and T cell-mediated pathways modulating type 2 immune responses and epithelial barrier dysregulation, underpinning a pleiotropic inflammatory axis.³⁸ Indeed, the majority of identified AD loci overlap reported atopic-march-associated loci, supporting the known shared genetic architecture of AD with other atopic-march phenotypes.³⁹ However, such cross-trait associations indicate that horizontal pleiotropy, where the SNP influences the exposure and outcome through independent pathways, cannot be fully excluded. For miR-1908-5p, the lead variant rs174561 showed associations with eosinophil traits, asthma, and other inflammatory phenotypes, consistent with the broad immunometabolic architecture of the FADS locus. However, the strong colocalization signal ($PP.H4 = 0.99$) provides important reassurance, since genetic colocalization methods evaluate whether two traits share the same causal variant, and thus the use of colocalization in MR can be valuable to eliminate at least some unreliable associations.⁴⁰ For miR-181b-5p, enrichment for eosinophil-related traits is consistent with the hypothesis that blood eosinophil counts and atopic diseases share a genetic architecture,⁴¹ but also suggests that the observed effect may partly reflect a broader type 2 inflammatory genetic background. For miR-148a-3p, associations with adiposity-related traits align with the greater instability observed in sensitivity analyses, warranting a more cautious interpretation. Overall, this phenome-wide scan enhances the transparency of our causal inference framework by demonstrating that pleiotropy is likely widespread in the human genome, and a core limitation of MR is the unprovable assumption that pleiotropic associations reflect vertical rather than horizontal pleiotropy.⁴⁰

Beyond the six replicated miRNAs, our discovery phase recovered several miRNAs already implicated in AD pathogenesis, supporting the validity of our screen. Most notably, both strands of miR-146a (miR-146a-5p and miR-146a-3p) showed protective causal effects. This dovetails with extensive functional and clinical data: miR-146a is consistently upregulated in lesional AD skin and keratinocytes, where it suppresses NF- κ B-dependent chemokines (eg. CCL5, CCL8, UBD) and upstream adapters IRAK1/TRAF6; miR-146a-deficient mice develop more severe AD-like dermatitis, and serum miR-146a levels correlate with IgE and disease severity in patients.⁶ Our genetic evidence that higher baseline miR-146a reduces AD risk therefore reinforces the interpretation of miR-146a as an endogenous “brake” on chronic skin inflammation rather than a pathogenic driver. Other discovery-phase candidates (miR-99b-5p, miR-941, miR-6891-3p, miR-136-5p, miR-181b-5p, let-7a-5p) showed biologically plausible associations but either failed replication with independent instruments or had colocalization patterns suggesting distinct linked variants. For example, miR-6891 is encoded within HLA-B intron 4 and has been shown (for its 5p strand) to modulate IgA heavy chain expression, providing an intriguing mechanistic link to mucosal immunity and the epithelial-barrier/IgA axis that may also be relevant in AD.⁴² However, for these miRNAs, our current data do not yet support firm causal claims.

In two independent serum/plasma datasets (GSE162926 and GSE217232), most of the 15 candidate miRNAs did not show statistically significant case–control differences, with the exception of miR-223-3p in GSE162926 and let-7e-5p in GSE217232. This is broadly consistent with earlier serum profiling in adult AD, where only a subset of miRNAs—such as miR-151a, miR-223, miR-146a and miR-24—show robust dysregulation, while many others display modest or variable changes.⁴³ For the six replicated MR miRNAs, the absence of strong expression differences should not be over-interpreted. First, MR reflects life-long genetic predisposition, whereas transcriptomic data represent a single time-point influenced by disease activity, treatment and comorbidities. Protective miRNAs (miR-146a, miR-125a-5p, miR-181b-5p, let-7e-5p) may be secondarily upregulated in active disease as part of endogenous negative feedback, obscuring baseline genetic differences. Second, serum miRNA concentrations are influenced by release and clearance from multiple tissues; skin-derived signals may be diluted or overshadowed. Third, our sample sizes in GEO cohorts were modest relative to FinnGen, limiting power to detect small expression shifts. The discordant direction observed for some miRNAs (eg. MR risk signal vs. lower serum expression in cases) echoes similar findings for miR-223-3p, which is upregulated in whole blood cells of AD patients and modulates histamine-N-methyltransferase, but may behave differently in serum vs cellular compartments.⁴ Overall, these discrepancies illustrate why genetic and expression data should be viewed as complementary: MR strengthens causal inference, while expression profiles inform tissue specificity and dynamic regulation.

We acknowledge that, for several of the identified miRNAs, direct experimental evidence in AD-specific models (Th2 cytokine-stimulated keratinocytes, lesional AD tissue, or AD mouse models) remains limited. While we have prioritized skin-relevant and atopic-disease data wherever possible—including keratinocyte studies for miR-181b-5p and miR-125a/b-5p, FADS-eczema birth cohort studies for miR-1908-5p, CD4+ T-cell studies in inflammatory skin disease for miR-148a-3p, and IL-13 targeting data for let-7e-5p—some mechanistic interpretations necessarily draw on evidence from related inflammatory conditions sharing key pathways (NF- κ B, IL-6/STAT3, PI3K-Akt, TLR signaling) with AD. These extrapolations should be regarded as hypothesis-generating rather than definitive. Direct functional validation of each miRNA in AD-relevant cell types using Th2 cytokine (IL-4/IL-13/IL-31) stimulation paradigms is essential to confirm the proposed mechanisms and to determine whether the causal effects observed genetically translate into actionable therapeutic targets.

Major strengths of this work include the large AD sample size (over 30,000 cases and 430,000 controls in FinnGen), the use of independent miRNA eQTL sources (Nikpay cis and trans, FHS cis) with strong instrument strength, and the two-stage design with replication and cross-dataset effect-size correlation. The Steiger directionality tests and reverse MR provided no evidence that genetic liability to AD drives changes in circulating miRNA levels, reducing concerns about reverse causation. Colocalization further distinguished miRNAs where the same variant likely drives both miRNA expression and AD risk from those where LD with neighboring causal variants is more plausible. Nonetheless, important limitations should be acknowledged. All underlying GWAS and eQTL datasets were derived from individuals of European ancestry; miRNA regulation and AD genetics differ across populations, so our findings may not generalize to other ethnic groups. Some miRNAs were instrumented by a relatively small number of SNPs, restricting the ability to robustly detect and correct for horizontal pleiotropy. The reliance on blood/plasma eQTLs may not fully capture skin- or immune cell-specific regulation; future intestinal and cutaneous miR-eQTL resources will be invaluable to refine tissue-specific causal maps. Colocalization assumes a single causal variant per region, which may not hold in complex loci. Finally, while our functional annotations and literature review provide biologically plausible mechanisms, direct experimental validation of these six miRNAs in keratinocytes, T cells and innate immune cells from AD patients is still needed. From a translational standpoint, our results nominate miR-1908-5p and miR-148a-3p as genetically supported risk miRNAs whose inhibition might be beneficial, and miR-125a-5p, miR-181b-5p and let-7e-5p as protective miRNAs that could be harnessed or mimicked therapeutically—analogue to the way miR-124 is being exploited by obefazimod in ulcerative colitis.⁴⁴ Given that several of these miRNAs also regulate central axes in asthma, allergic rhinitis and autoimmunity, they may help explain shared genetic architecture and comorbidities across the “atopic march” and autoimmune spectrum, and could potentially serve as biomarkers of systemic inflammatory set-points rather than disease activity alone.

Conclusion

By integrating large-scale miRNA eQTL data, FinnGen AD GWAS and multiple sensitivity analyses, this study provides genetic evidence that a discrete set of circulating miRNAs—miR-1908-5p, miR-148a-3p, miR-133a-3p, miR-181b-5p, let-7e-5p and miR-125a-5p—play causal roles in modulating AD susceptibility. Our findings prioritize a small number of plasma miRNAs as promising candidates for mechanistic follow-up and, potentially, for development as biomarkers or RNA-based therapeutics in AD. Future studies should prioritize functional validation of these miRNAs in AD-relevant cell models (eg, Th2 cytokine-stimulated keratinocytes and T-cell co-cultures), replication in multi-ethnic cohorts, and long-itudinal clinical investigation of their utility as predictive biomarkers for disease onset, severity, and therapeutic response.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available in the GEO repository (GSE162926 and GSE217232) and GWAS summary statistics are available from the original publications referenced in the article.

Ethics Approval and Consent to Participate

This study used only publicly available, de-identified, summary-level data. In accordance with Article 32 (Items 1 and 2) of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (February 18, 2023, China), this research is exempt from institutional ethical review. All original studies had obtained ethical approval and informed consent from participants.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no relevant financial or non-financial interests to disclose.

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