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ORIGINAL RESEARCH

DNA Methylation at cg18095732 Modulates ZDHHC20 Expression and Decreases Acne Vulgaris Risk

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Background: Acne vulgaris is a common chronic inflammatory skin disorder involving lipid metabolism and immune dysregulation. Protein S-palmitoylation regulates lipid homeostasis, while DNA methylation has emerged as a potential contributor to acne pathogenesis. Yet, how DNA methylation and palmitoylation intersect in acne remains unclear.

Methods: The objective of this study was to investigate whether palmitoylation-related genes are causally linked to acne by integrating large-scale genetic and epigenetic datasets through Mendelian randomization and complementary analyses.

Results: Our MR and SMR analyses identified ZDHHC20, a gene encoding a palmitoyltransferase, as significantly and negatively associated with acne risk. Further mediation analysis revealed that hypermethylation at the CpG site cg18095732 was positively associated with ZDHHC20 expression and indirectly contributed to a reduced risk of acne. This methylation site accounted for 61.90% of the total effect via mediation. Robustness of the findings was confirmed through sensitivity analyses, which indicated no evidence of horizontal pleiotropy or heterogeneity.

Conclusion: This study provides supportive evidence for a regulatory pathway in which DNA methylation at cg18095732 up-regulates ZDHHC20 and is associated with lower acne susceptibility. Our findings highlight epigenetic regulation as a potential biomarker or intervention point for inflammatory skin disorders.

Plain Language Summary: Acne vulgaris, commonly known as acne, is a skin condition that causes pimples, blackheads, and inflammation. It affects many people, especially teenagers. While hormones, bacteria, and oil production are known to play roles, our understanding of the genetic and molecular causes of acne is still growing.

In this study, we explored how a specific chemical change to DNA, called DNA methylation, may protect against acne. DNA methylation is a natural process where small molecules attach to DNA and affect how genes work. We focused on a particular site on the DNA, called cg18095732, and examined its relationship with a gene named ZDHHC20. This gene helps control a process called palmitoylation, which can affect how skin cells function.

We used large databases and advanced genetic methods to study the connections between DNA methylation, ZDHHC20 gene activity, and acne risk. We found that higher methylation at cg18095732 was linked to increased activity of ZDHHC20 and a lower risk of acne. This suggests that DNA methylation at this site may help regulate gene function in a way that reduces acne.

Our findings may offer new clues for understanding acne and developing future treatments.

Keywords: acne vulgaris, DNA methylation, palmitoylation, ZDHHC20, Mendelian randomization

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Introduction

Acne vulgaris is a prevalent chronic inflammatory dermatosis that primarily impacts the pilosebaceous units. Clinically, it presents as pimples, papules, pustules, and nodules, and in severe cases, may lead to permanent scarring and psychosocial burden.[1] Globally, approximately 9% of the population is affected by acne, with prevalence rates reaching 85–90% among adolescents and young adults.[2] The pathogenesis of acne is multifactorial, involving excessive sebum production, aberrant follicular keratinization, Cutibacterium acnes (*C. acnes*) colonization, and inflammatory immune responses.[3,4] Among these factors, disturbances in lipid metabolism are increasingly recognized as key contributors to acne initiation and progression.[5–7]

S-palmitoylation is a reversible enzymatic modification in which palmitate, a saturated 16-carbon fatty acid, is covalently attached to cysteine residues through thioester bonds,[8,9] thereby influencing their stability, localization, and function.[10] Protein palmitoylation is crucial in various biological activities, particularly in protein-lipid interactions, and is defined by the presence of a zinc-finger aspartate-histidine-histidine-cysteine (ZDHHC) motif in the cysteine-rich structural domain.[11] In humans, the ZDHHC family includes 23 members, each with distinct substrate specificities and biological effects.[12] Although palmitoylation has been implicated in lipid metabolic regulation,[13,14] its potential contribution to acne pathogenesis—especially in the context of genetic and epigenetic regulation—remains inadequately elucidated.

DNA methylation serves as a principal epigenetic process that modulates gene activity without modifying the underlying DNA sequence, commonly involving the attachment of a methyl group to the 5′ carbon of cytosine or adenine residues.[15] In dermatology, DNA methylation has been implicated in several chronic inflammatory dermatoses, including hidradenitis suppurativa, atopic dermatitis, and psoriasis.[16–18] Additionally, emerging evidence indicates that individuals with acne may exhibit distinct methylation patterns.[19,20] Nonetheless, the precise regulatory link between DNA methylation alterations and gene expression relevant to acne pathogenesis remains largely unclear.

Given that DNA methylation is a key modulator of gene expression, and palmitoylation is crucial for lipid homeostasis, we systematically investigated the interplay among these pathways in acne. We integrated large-scale genetic, transcriptomic (eQTL), and epigenomic (mQTL) data using a multi-pronged analytical approach, including two-sample Mendelian Randomization (MR), Summary-data-based MR (SMR), and mediation analysis, to dissect their complex relationships.[21,22] This study was designed to test the central hypothesis that DNA methylation at specific loci regulates the expression of palmitoylation-related genes, thereby influencing susceptibility to acne vulgaris.

Materials and Methods

Data Source

This analysis utilised GWAS summary statistics for acne obtained from the FinnGen consortium (https://www.finngen.fi/en), a large public–private partnership launched in 2017 that integrates genomic and clinical data from approximately 500,000 Finnish biobank participants.[23] All participants provided informed consent for biobank research, and the study protocols were approved by the relevant Finnish ethics committees. The cohort is almost entirely of European (Finnish) ancestry, which reduces potential bias due to population stratification. The dataset used in this study was finngen_R12_L12_ACNE.gz, comprising 4617 patients with acne and 476,404 controls. The diagnosis of acne was determined according to the International Classification of Diseases, 10th Revision (ICD-10) code L70 (“Acne”), and all endpoints were clinically validated based on patient records and physician evaluations. The median age at first event was 24.57 years overall (26.72 years in females and 20.49 years in males). Further detailed information can be found at https://risteys.finngen.fi/endpoints/L12_ACNE. The online MRpower tool (https://shiny.cnsgenomics.com/mRnd) was applied to estimate statistical power and verify the adequacy of the sample size.

A total of 31 palmitoylation-related genes were compiled from prior literature, including studies by Li et al,[10] Chamberlain et al[24] and Chen et al.[25] These genes were cross-referenced with eQTL data from the eQTLGen database (https://eqtlgen.org),[26] resulting in the identification of 22 genes with available eQTL data, including PPT1, PPT2, and members of the ZDHHC gene family (Supplementary Table S1). Gene expression data were derived from 25,482 whole-blood and 6202 PBMC samples (total n = 31,684) in the eQTLGen consortium. Expression was measured by Illumina

HT-12, Affymetrix arrays and RNA-seq, harmonised across platforms and adjusted for covariates. After quantile normalization (Illumina/Affymetrix) or TMM normalization (RNA-seq), data were corrected for batch effects, PEER factors, age, sex and blood-cell composition, yielding residual expression values for downstream analyses, as described in the eQTLGen consortium study.

DNA-methylation quantitative trait loci (mQTL) data were obtained from the GoDMC consortium (https://www.godmc.org.uk/),[27] which aggregated cohorts of European ancestry. DNA methylation was measured in whole-blood samples (n = 27,750) using Illumina HumanMethylation450 BeadChip (with ~8.9% later run on MethylationEPIC and mapped back to the 450K backbone). Probes were annotated according to established resources, excluding cross-reactive and low-quality probes. Data underwent rigorous quality control, including functional normalization with the meffil R package, removal of samples with poor probe performance or sex/genotype mismatches, and adjustment for covariates such as age, sex, smoking status, blood cell counts, and technical factors (slide, plate, row). Outlier CpG values (>10 SD from the mean) were winsorised, and up to 20 non-genetic principal components were regressed out. The resulting residualised M-values (logit-transformed β) were used for downstream mQTL analysis, as described in the GoDMC study.

All datasets analyzed are publicly available summary statistics from eQTLGen, GoDMC, FinnGen and GEO. The original collections were conducted under IRB approval; our secondary analysis of anonymised, open-access data is exempt from further review under items 1–2 of Article 32 of the Ethical Review Measures for Life Science and Medical Research Involving Human Beings of the People's Republic of China (2023).

MR Analysis of the Relationship Between Palmitoylation and Acne Vulgaris

A two-sample MR analysis was conducted through the R package "TwoSampleMR" (version 0.6.9) to investigate the potential causal association between palmitoylation-related genes and acne vulgaris. The overall MR design is illustrated in Figure 1A. IVs were defined as single nucleotide polymorphisms (SNPs) strongly linked to gene transcription levels based on eQTL data, with inclusion criteria of genome-wide significance ($P < 5\times10^{-8}$) and an F-statistic > 10 to mitigate the influence of weak instrument bias. To guarantee the independence of instrumental SNPs, linkage disequilibrium (LD) pruning was then conducted using a stringent threshold of $r^2 < 0.001$ within a 10,000 kb window. For palmitoylation-related genes with a single available SNP, the Wald ratio method was applied to assess the causal impact; for genes with two or more SNPs, causal inference was conducted using multiple MR methods—including inverse variance weighting (IVW), MR-Egger, weighted median, simple mode, and weighted mode—and IVW was designated as the primary analytical framework. Within this framework, we computed the odds ratio (OR) for acne per one standard deviation (SD) elevation in the expression of palmitoylation-related genes. Additionally, steiger filtering was applied to exclude SNPs with ambiguous causal direction (exposure variance < outcome variance). Post-filtering IVW analyses on validated IVs ("TRUE" set) minimized reverse causality bias.

Sensitivity Analysis

We systematically implemented complementary sensitivity frameworks to verify the stability of causal estimates across analytical assumptions. Specifically, heterogeneity across genetic instruments was quantified using Cochran's Q statistic, with a *p-value* above 0.05 indicating the absence of statistically significant heterogeneity. The MR-Egger regression intercept was performed to probe for horizontal pleiotropy, where a non-significant intercept ($P > 0.05$) was interpreted as evidence against pleiotropic distortion. To further identify outlier variants potentially driving pleiotropy, we applied the MR Pleiotropy Residual and Outlier (MR-PRESSO) method; a non-significant global test ($P > 0.05$) was interpreted as evidence against the presence of pleiotropic outliers. Finally, a leave-one-out sensitivity analysis was implemented by iteratively excluding one IV and repeating the MR analysis to assess the impact of individual SNPs on the aggregate association (Figure 1C).

SMR Analysis

We applied SMR using SMR software (v1.3.1) to determine whether cis-eQTLs controlling palmitoylation-related gene expression colocalize with acne GWAS loci, thereby revealing shared causal mechanisms in acne pathogenesis. To address the SMR assumption of a single causal variant per locus, we applied the Heterogeneity in Dependent Instruments

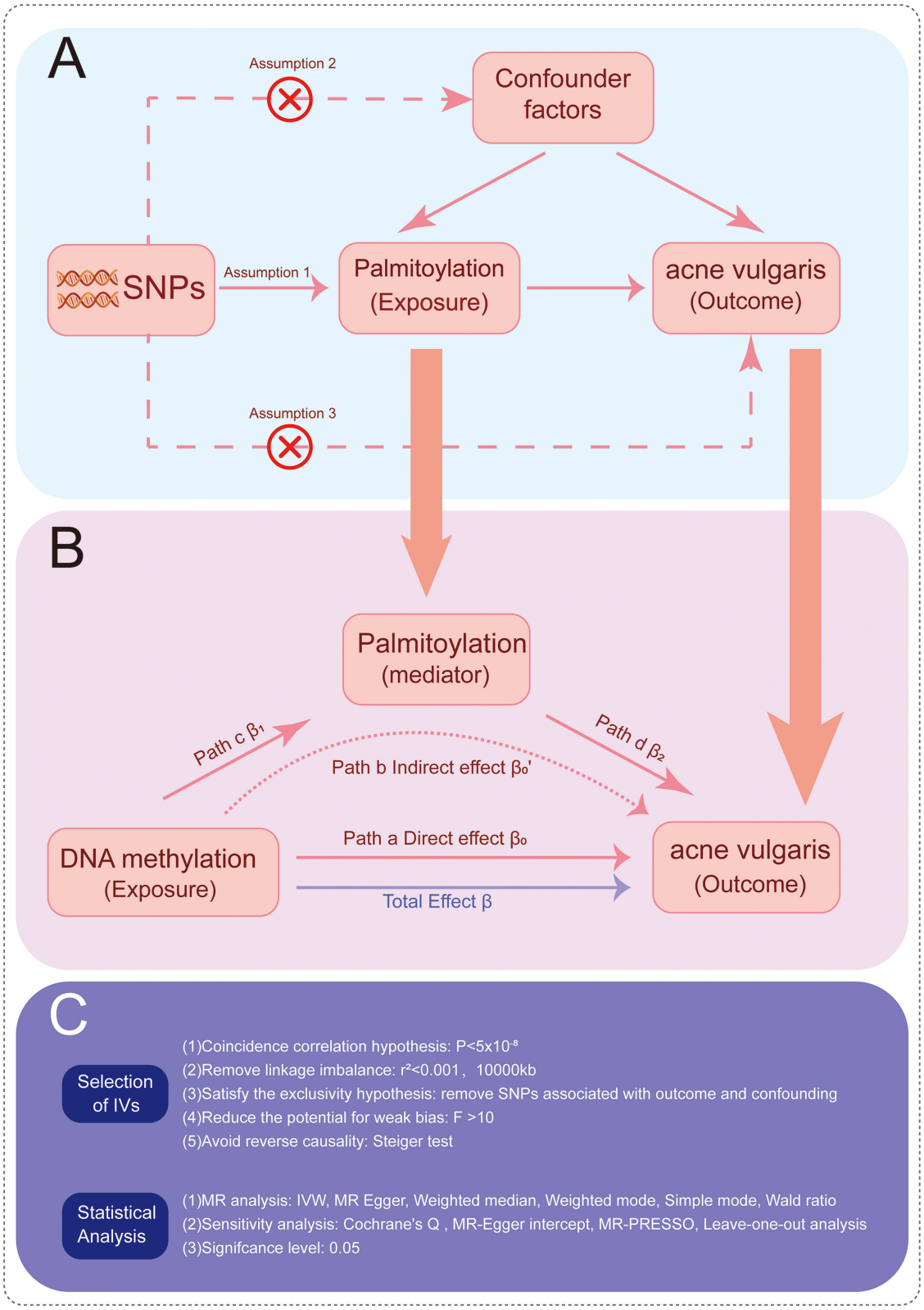

Figure 1 Overview of the analytical workflow investigating the relationship among DNA methylation, ZDHHC20 expression and acne using Mendelian Randomisation (MR) and mediation analysis. (**A**) Assumptions of MR; (**B**) Conceptual diagram of mediation analysis: The total effect (β) of DNA methylation on acne is partitioned into a direct effect (β_0) and an indirect effect (β_0': $\beta_1 \times \beta_2$) mediated through ZDHHC20 expression; (**C**) Statistical methods used in the study: instrumental variables (IVs) selection and statistical analysis.

(HEIDI) test to rule out LD–driven confounding. A HEIDI *p-value* exceeding 0.05 was interpreted as evidence that the detected associations were unlikely to result from LD artifacts, thereby reinforcing the inference of a genuine causal effect of gene expression on acne risk.

Differentially Gene Expression Analysis

To investigate acne pathogenesis at the transcriptomic level, we analyzed curated RNA-sequencing data from the Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo/) accession number GSE53795, based on the GPL570 platform, comprising clinically validated paired lesional/non-lesional skin specimens with rigorous quality control metrics.[28,29] This dataset includes expression profiles from 12 acne lesions and 12 corresponding normal skin samples (n = 24). Differential gene expression analysis was conducted using the "limma" package in R, with genes defined as differentially expressed if they exhibited an absolute log fold change (|logFC|) greater than 0.3 and a *p-value* less than 0.05.

Mediation Analysis of DNA Methylation-Palmitoylation-Acne Relationship

We investigated the potential mechanistic link between DNA methylation and palmitoylation in acne susceptibility by performing a two-sample MR analysis followed by causal mediation analysis to decompose the total effect into direct and indirect (methylation-mediated) pathways. In this framework, we decomposed the total causal impact of DNA methylation on acne into (1) a direct pathway reflecting methylation's independent influence, and (2) an indirect pathway mediated through changes in palmitoylation (Figure 1B). The mediation proportion—calculated as the ratio of indirect-to-total effect estimates—quantified the degree to which palmitoylation pathways operationalize DNA methylation's influence on disease susceptibility. To mitigate unmeasured confounding inherent in mediation models, genetic instruments were used as proxies for exposure, and additional sensitivity analyses were conducted to evaluate the robustness of our findings.

Results

MR Analysis of the Relationship Between Palmitoylation and Acne Vulgaris

Employing IVW method as our primary analytical framework, we uncovered robust causal links connecting multiple palmitoylation-related genes with acne susceptibility. Power calculations, incorporating the effective sample size and the explanatory strength of the selected genetic instruments, demonstrated over 99% power to support a valid causal inference with high confidence. A total of 90 SNPs were selected as IVs (Supplementary Table S2). Detailed variant-level associations with acne are provided in Supplementary Table S3 and illustrated in Supplementary Figures S1a–S3a. Each instrument exhibited an F-statistic above 10, confirming the strength and validity of our genetic proxies. Among these, three ZDHHC family members—ZDHHC14, ZDHHC19, and ZDHHC20—were significantly associated with acne (Figure 2). Results from MR-Egger, weighted median, weighted mode, and simple mode methods are presented in Supplementary Table S4 and Supplementary Figures S1b–S3b.

Figure 2 presents the causal effects of palmitoylation-related genes in relation to acne susceptibility based on estimates derived from the IVW method. Notably, ZDHHC14, ZDHHC19, and ZDHHC20 demonstrated inverse associations with acne, indicating their potential protective roles.

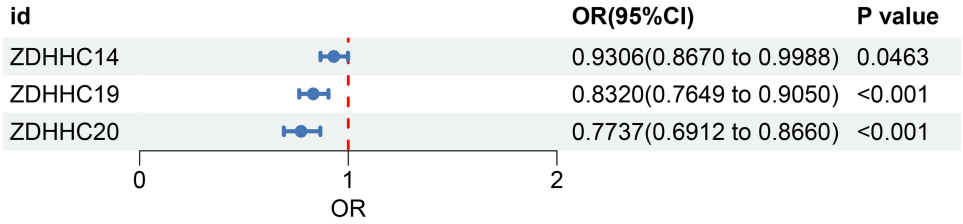

Figure 2 Causal effect of palmitoylation-related genes on acne risk estimated via the Inverse Variance Weighting method.

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Sensitivity Analysis

Multiple sensitivity analyses were performed to evaluate potential biases in the IVW method. Cochran's Q test yielded *p-values* > 0.05 for all models, signifying no significant heterogeneity. Visual inspection via funnel plots likewise showed symmetric distributions without outlying variants (Supplementary Figures S1c–S3c), justifying the application of an IVW fixed-effects estimator. The MR–Egger intercept was close to zero ($P > 0.05$), and similarly, the MR-PRESSO global test also returned a non-significant result ($P > 0.05$), together indicating no detectable horizontal pleiotropy or outlier influence. Moreover, leave-one-out analysis indicated that no single instrument drove the association (Supplementary Figures S1d–S3d), hence confirming the stability of our MR findings (Supplementary Table S5).

SMR Analysis

SMR analysis pinpointed ZDHHC20 as the sole gene with a statistically significant association to acne (*b*-SMR=−0.263, *p*-SMR= 5.69E-03), suggesting a potential inhibitory role of ZDHHC20 in acne pathogenesis. We then applied the HEIDI test to exclude bias from horizontal pleiotropy; a non-significant outcome ($P > 0.05$) confirmed that the ZDHHC20–acne link was not confounded by pleiotropic instruments, thereby reinforcing the credibility of our SMR findings (Supplementary Table S6).

Differentially Gene Expression Analysis

From the acne dataset GSE53795, we identified a total of 4538 differentially expressed genes (DEGs), comprising 2057 upregulated genes and 2481 downregulated genes (Supplementary Figures 4 and 5).

Among them, ZDHHC20 was significantly downregulated in acne samples relative to controls (*P-value* = 0.004), indicating a potential inhibitory effect on acne development (Figure 3).

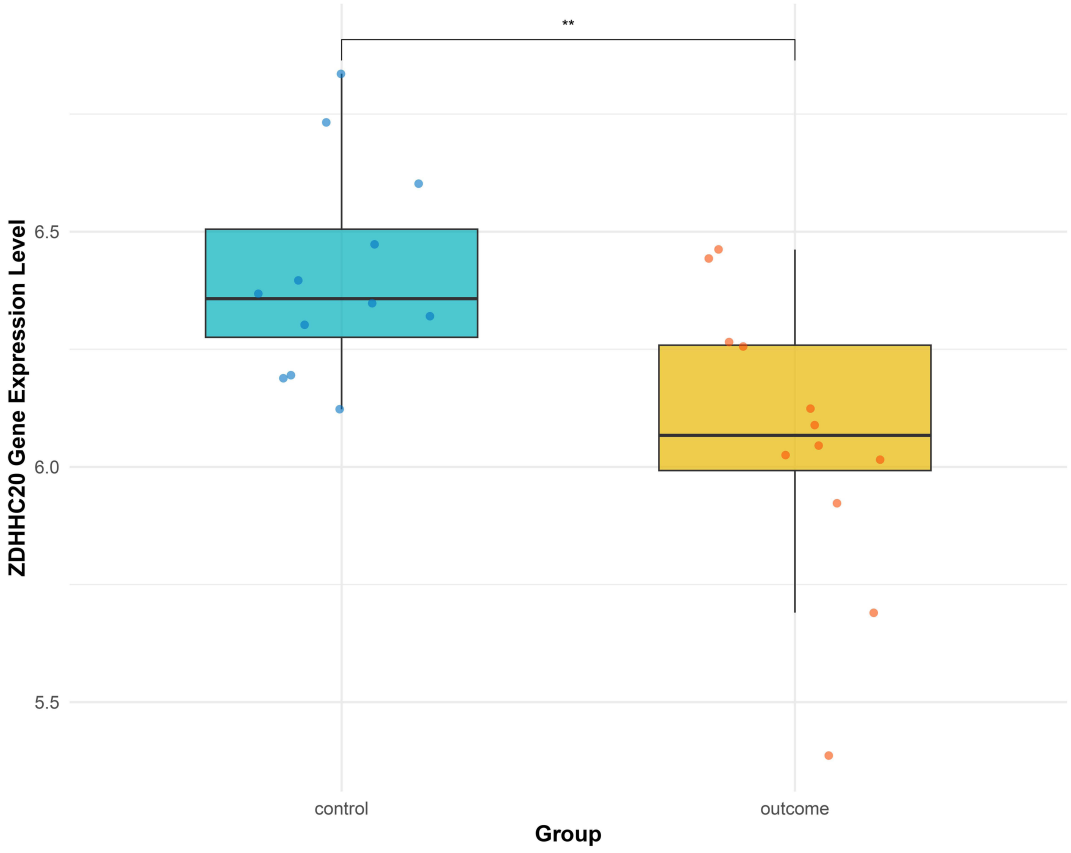

Figure 3 Expression levels of representative DEGs in acne lesions and normal skin samples. ** indicates $P < 0.01$ (Wilcoxon rank-sum test, two-sided).

Mediation Analysis of DNA Methylation-Palmitoylation-Acne Relationship

A total of 17 CpG sites were mapped to ZDHHC20 gene using the Illumina 450k reference annotation provided by the R package IlluminaHumanMethylation450kanno.ilmn12.hg19. These sites were subsequently evaluated for their associations with gene expression and acne (Supplementary Table S7). To assess whether methylation at the ZDHHC20 locus exerts a causal effect on acne risk, we performed MR analysis (Figure 1B, Path a β_0). The IVW analysis showed that only cg18095732 was significantly associated with acne, showing a negative correlation (OR = 0.920, 95% CI: 0.867–0.976, P = 0.006) (Supplementary Table S8). Sensitivity analyses indicated no evidence of heterogeneity or horizontal pleiotropy. This site included 19 SNPs as IVs (Supplementary Table S9), with individual variant effect estimates on acne detailed in Supplementary Table S10 and visualised in Supplementary Figure S6a–c. All examined SNPs had F-statistics > 10, confirming their suitability as robust IVs. The MR results are presented in Supplementary Table S11.

Subsequently, we evaluated the impact of this DNA methylation site on ZDHHC20 expression by MR analysis (Figure 1B, Path c β_1). The findings showed a robust positive association between cg18095732 and ZDHHC20 gene expression (OR = 1.223, 95% CI: 1.085–1.379, P = 0.001), with no indication of heterogeneity or horizontal pleiotropy observed in the sensitivity analysis (Supplementary Table S12). This site included 20 SNPs as IVs, with the details shown in Supplementary Table S13. Individual SNP effect estimates on ZDHHC20 expression appear in Supplementary Table S14, while the complete MR outcomes are showed in Supplementary Table S15.

Ultimately, we conducted mediation MR analysis to assess how this methylation site affects acne pathogenesis via the regulation of ZDHHC20 expression. Based on the aforementioned results, we decomposed the total effect (β) into the direct effect (β_0) and the indirect effect (β_0') and quantified the mediation proportion. Our findings reveal that increased methylation at cg18095732 lowers acne risk primarily through upregulation of ZDHHC20, with this indirect pathway mediating 61.90% of the overall effect (Table 1 and Figure 4).

Sensitivity analyses indicated an absence of heterogeneity (Cochran's Q test) and directional pleiotropy (MR-Egger intercept), with no outliers detected by the MR-PRESSO global test. Additionally, leave-one-out analysis demonstrated that the causal estimates were not disproportionately influenced by any single SNP, providing further support for the reliability of our MR findings (Supplementary Figure S6d).

Discussion

Utilizing an integrative framework of two-sample MR, SMR, differentially gene expression analysis, and mediation analysis, we uncovered a DNA methylation–mediated link between ZDHHC20 expression and reduced acne susceptibility. Our results might provide new light on acne pathophysiology by highlighting epigenetic control mechanisms and suggest that ZDHHC20 methylation may serve as a potential molecular indicator and therapeutic target in acne management.

Our MR and SMR analyses consistently supported an inverse association between ZDHHC20 expression and acne risk. This association was further supported by differential expression analysis, which revealed significantly reduced ZDHHC20 levels in acne lesions compared to healthy skin. S-palmitoylation in mammals is mediated by 23 members of the ZDHHC family of protein acyltransferases,[30] with ZDHHC20 uniquely distinguished by having a resolved crystal

Table 1 Results of the Mediation Analysis Involving DNA Methylation Sites, ZDHHC20 Expression and Acne Risk

CpG site	Path a Direct Effect β_0	Path b Indirect Effect $\beta_{0'}$	Path c β_1	Path d β_2	Total Effect β	Proportion Mediated (%)
cg18095732	−0.032	−0.052	0.201	−0.257	−0.083	61.90%

Notes: Mediation analysis of the effect of DNA methylation at cg18095732 on acne risk through ZDHHC20 expression. Path a (direct effect) β_0: methylation → acne without mediator. Path b (indirect effect) β_0': methylation → ZDHHC20 expression → acne. Path c β_1: effect of cg18095732 methylation on ZDHHC20 expression. Path d β_2: effect of ZDHHC20 expression on acne. Total effect $\beta = \beta_0 + \beta_0'$; proportion mediated = $\beta_0' / (\beta_0 + \beta_0')$.

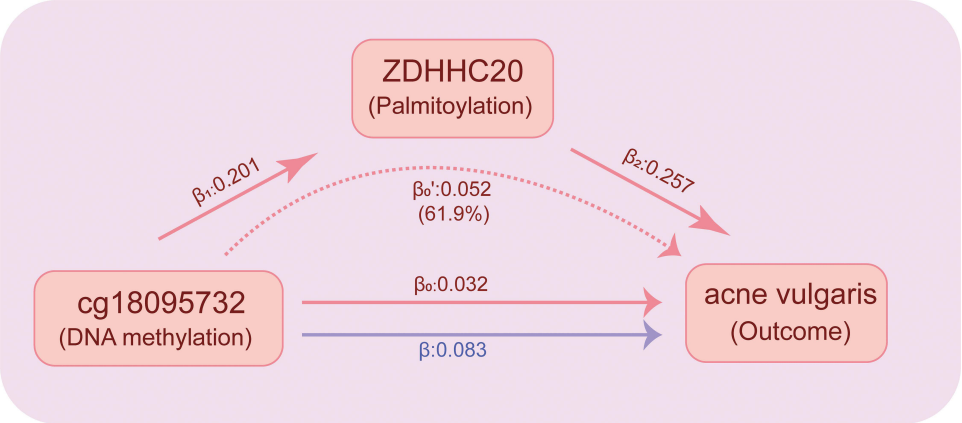

Figure 4 Mediation analysis results demonstrating the proportion of the total effect of DNA methylation on acne risk mediated by ZDHHC20 expression.

structure.[31] Previous studies have associated ZDHHC20-mediated palmitoylation with various malignancies and metabolic disorders, including liver cancer, pancreatic cancer, melanoma, and obesity.[32–35]

Nonetheless, the specific contribution of ZDHHC20 to acne development continues to be poorly characterised. Emerging evidence suggests that ZDHHC20 regulates lipid metabolism by mediating fatty acid synthase (FASN).[32] FASN is a pharmacological target in multiple lipid-related disorders,[36,37] and serves as a key enzyme in sebaceous glands, responsible for synthesizing long-chain fatty acid synthesis.[38] Fatty acids are major components of sebum, and their overproduction is believed to contribute to acne development. FASN expression also reflects sebocyte differentiation status, exhibiting elevated levels during the mid-differentiation stage of cortical cells and diminished levels at later stages.[39] Furthermore, FASN may engage in inflammatory regulation by modulating the PI3K/AKT/NF-κB signaling pathway, thereby suppressing oxidative stress and inflammation.[40] Taken together, ZDHHC20 is hypothesized to modulate FASN activity, thereby reducing sebum production and potentially mitigating follicular obstruction and inflammation.[41] This palmitoylation-dependent mechanism may represent a key pathway through which ZDHHC20 contributes to acne pathogenesis. However, the specific role of ZDHHC20 in sebocyte proliferation, differentiation, and inflammatory response remains poorly understood. Given that acne pathogenesis involves not only excess sebum production but also dysregulated sebocyte differentiation, inflammatory responses, and altered microbial composition, future studies should aim to elucidate the downstream functional consequences of ZDHHC20 upregulation in acne-relevant cellular contexts.

Our mediation analysis suggested that methylation at cg18095732 may upregulate ZDHHC20 expression and potentially influence acne risk through an indirect pathway. This CpG site is located within a CpG island and annotated as TSS1500, though its potential role in acne pathogenesis remains unexplored in prior studies. Epigenetic modifications bridge genetics and environmental exposure by dynamically adjusting gene expression patterns, all without changing the underlying DNA sequence.[42] Among these, DNA methylation is the most prevalent and well-characterized epigenetic modification.

DNA methylation has been mechanistically associated with the development of inflammatory dermatoses, such as atopic dermatitis, psoriasis, and hidradenitis suppurativa,[16,17] which has garnered heightened interest as a critical research frontier in dermatology. DNA methylation may contribute to acne vulgaris pathogenesis by affecting key biological processes such as inflammatory activation, genetic interactions, immune dysregulation, and skin barrier impairment. First, the hypomethylation of inflammatory genes, including IL1B, TNF, and TLR4, in acne lesions has been linked to their transcriptional upregulation, activation of the NLRP3 inflammasome, and enhanced neutrophil infiltration.[19] Moreover, DNA methylation also interacts with genotype. For instance, differential methylation of PDGFD (eg, cg03020863) may influence immune-related genes such as CXCR4, thereby affecting neutrophil recruitment and the inflammatory microenvironment.[20] Future studies may explore whether methylation-related regulation of CXCR4 and other immune genes contributes to local neutrophil activity and inflammatory microenvironment in acne lesions. In

addition, immunological dysregulation in acne may be subject to epigenetic modulation. Decreased NK cell proportions and elevated granulocytes in peripheral blood have been linked to differential methylation of SH2D6 and CAPG.[43] Collectively, our findings support the hypothesis that DNA methylation may represent a contributing factor to acne development through the modulation of inflammatory responses, immune pathways, gene regulation, and barrier function.

Interestingly, although promoter methylation is classically associated with transcriptional repression by preventing transcription factor binding or facilitating the recruitment of inhibitory complexes,[44,45] our results suggested a positive association between cg18095732 (within the ZDHHC20 promoter) and increased ZDHHC20 expression. This finding challenges the conventional model of promoter methylation-mediated gene silencing and suggests that cg18095732 may participate in an alternative or context-dependent regulatory mechanism that enhances ZDHHC20 expression. Such non-canonical regulation may involve mechanisms including enhancer hijacking, bidirectional promoter activity, or methylation-sensitive insulator disruption—all of which have been proposed to facilitate gene activation despite promoter methylation.[46–48] Additional experimental studies and mechanistic investigations are warranted to elucidate the biological function of this regulatory methylation event in the context of acne pathogenesis.

This study has several notable strengths. First, we applied Mendelian Randomization (MR) to explore potential causal relationships, thereby minimizing confounding and reverse causation inherent to observational studies. While MR strengthens the plausibility of causal inference, it relies on untestable assumptions that should be acknowledged. Second, through the integration of MR, SMR, mediation analysis, mQTL and eQTL data, we systematically examined the potential involvement of ZDHHC20 in acne pathogenesis and its epigenetic modulation via DNA methylation. This multidimensional analytical approach enhances the consistency and interpretability of our findings. Third, we utilized large-scale publicly available data resources, including multiple population cohorts from the Finngen database and the eQTL/mQTL database, to increase the generalizability and reproducibility of our results. Importantly, our exploration of the epigenetic regulation of ZDHHC20 may offer novel insights into acne pathogenesis and lay the groundwork for future molecular investigations.

Nevertheless, this study has certain limitations.First, experimental validation remains the major weakness of this study. While our MR and mediation analyses provide supportive evidence for the cg18095732–ZDHHC20–acne axis, functional studies are required to establish causality. Potential directions include: (i) skin-biopsy cohorts to quantify cg18095732 methylation and ZDHHC20 expression in matched lesional and non-lesional tissues; (ii) in vitro assays using sebocyte models with targeted epigenetic editing or demethylation to assess effects on ZDHHC20 expression, lipid metabolism, and inflammatory cytokine release; and (iii) in vivo validation in acne models to evaluate the therapeutic potential of modulating cg18095732 methylation. Only through such functional data can the clinical relevance of our findings be firmly established. Second, our analysis primarily relied on datasets from individuals of European ancestry, which may limit the generalizability of the findings; therefore, future studies should aim to validate these results in more ethnically diverse populations, and caution is warranted when extrapolating these results to non-European populations. Third, as the FinnGen cohort is based on biobank participants, potential GWAS selection bias cannot be excluded when compared with the general population. Fourth, given the heterogeneous clinical presentations of acne (eg, inflammatory vs comedonal subtypes), future studies should explore whether ZDHHC20 exerts differential effects across acne subtypes, particularly with respect to immune responses and sebaceous gland activity.

Beyond elucidating a novel molecular pathway, our findings hold considerable translational implications for the management of acne vulgaris. The identification of cg18095732 methylation and ZDHHC20 expression as potential regulators of acne risk opens the door for their development as novel biomarkers. For instance, the methylation status of this locus could potentially be used for early risk assessment or for stratifying patients into subtypes more likely to benefit from specific treatments. More ambitiously, the ZDHHC20-mediated pathway itself represents a promising therapeutic target. Future drug discovery efforts could focus on developing small molecules or epigenetic-based therapies as a new, non-antibiotic approach to acne treatment. Such targeted interventions could potentially normalize lipid metabolism and mitigate inflammation with greater specificity and fewer side effects than current systemic therapies.

Conclusion

This study provides supportive evidence that DNA methylation at cg18095732 may regulate ZDHHC20 expression and contribute to acne susceptibility. Convergent findings across multiple analytic frameworks—including MR, SMR, mediation, and differential expression analyses—consistently pointed to this regulatory link, underscoring the robustness of our integrative approach and highlighting the potential role of DNA methylation in inflammatory skin disorders. Beyond mechanistic insights, our results indicate that ZDHHC20 could serve as a biomarker or therapeutic target for acne. Future research should validate these associations in multi-ancestry cohorts, perform functional experiments in acne-relevant cells and tissues, and assess whether ZDHHC20 exerts differential effects across acne subtypes.

Abbreviations

C. acnes, Cutibacterium acnes; ZDHHC, zinc-finger aspartate-histidine-histidine-cysteine; MR, Mendelian Randomization; SMR, Summary-data-based Mendelian Randomization; GWAS, Genome-Wide Association Studies; mQTL, Methylation quantitative trait loci; eQTL, expression quantitative trait locus; ICD, International Classification of Diseases; GEO, Gene Expression Omnibus; SNPs, Single nucleotide polymorphisms; IVs, Instrumental Variables; LD, Linkage Disequilibrium; IVW, Inverse variance weighting; OR, odds ratio; SD, standard deviation; MR-PRESSO, The MR Pleiotropy Residuals and Outlier; HEIDI, Heterogeneity in Dependent Instruments; DEGs, Differential expressed genes; FASN, fatty acid synthase.

Data Sharing Statement

All datasets used for analysis in this research are openly freely available and have been cited appropriately within the manuscript. Their use complies with the ethical standards and data-sharing protocols of the original studies. Further information is available upon request from the corresponding author.

Ethics Approval

According to Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Beings adopted by the National Science and Technology Ethics Committee of the People's Republic of China, this study qualifies for exemption as it relies solely on publicly available, anonymised summary data that pose no risk to individuals and contain no sensitive personal or commercial information.

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Disclosure

The authors affirm that there are no conflicts of interest—financial or otherwise—relevant to the present study.

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