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Original Research

Potential genetic associations of acne scar phenotypes: IL1A in fibrotic scarring and CYB5R1 in atrophic scarring

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ABSTRACT

Introduction: Nearly half of individuals diagnosed with acne vulgaris develop scarring. This study aimed to investigate the genetic associations between acne scarring and six selected gene variants (*CYB5R1*, *IL1A*, *TLR4*, *FLG*, *SPINK5*, and *TNF*). **Methods:** We conducted a cross-sectional study at the University of Medicine and Pharmacy Hospital and the Vietnam National Hospital of Dermatology and Venereology from September 2023 to December 2024. A total of 202 acne patients were recruited and categorized into either a non-scarring cohort (n = 55) or a scarring cohort (n = 147). Patients with scars were further classified into atrophic (n = 56), hypertrophic (n = 46), and keloid (n = 45) subgroups. **Results:** No significant demographic or clinical differences were observed between the groups ($p > 0.05$). Variants in *CYB5R1* were more frequent in the scarred group than in the non-scarred group (38.1% vs. 23.6%, $p = 0.05$; OR = 1.99, 95% CI: 1.00–4.15), with the highest proportion observed in patients with atrophic scars. In contrast, *IL1A* variants were enriched in hypertrophic and keloid (fibrotic) scars ($p < 0.05$). The remaining evaluated genes (*TNF*, *TLR4*, *FLG*, and *SPINK5*) demonstrated no significant association with acne scarring. **Conclusion:** This study suggests a potential association between *CYB5R1* and atrophic scarring, as well as between *IL1A* and fibrotic scarring. These findings support the polygenic nature of acne scarring, although further validation in larger cohorts is required.

Key words: Acne Scar, Genetics, CYB5R1, IL1, Atrophic scar, Fibrotic scar

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INTRODUCTION

Acne vulgaris is the eighth most common skin disease globally [1], affecting up to 85% of adolescents and often persisting into adulthood [2]. While inflammatory lesions may resolve, nearly half of affected individuals with acne suffer from develop scarring [3], which can lead to result in low self-esteem, social isolation, anxiety, and depression [4]. Scar formation can be broadly categorized divided into two primary phenotypes: those resulting from excessive tissue deposition, leading to hypertrophic or keloid scars, and those characterized by tissue loss or destruction, resulting in atrophic scars. Despite advances in acne treatment, the prevention and management of scarring remain therapeutic challenges hurdle [3,5], highlighting the critical need for research into acne scar morphogenesis and the early identification of individuals at elevated risk.

Current evidence indicates that acne scarring results from prolonged inflammation and dysregulated wound healing, where with genetic predisposition potentially plays may play a pivotal role [3,5]. Candidate genes implicated in inflammatory and immunological pathways, such as interleukin-1 (*IL1*), interleukin-6 (*IL6*), tumor necrosis factor (*TNF*), and toll-like receptor 4 (*TLR4*), have been associated with acne severity and inflammatory phenotypes [6–9]. Moreover, genes involved in skin barrier integrity and repair, including filaggrin (*FLG*) and serine protease inhibitor Kazal-type 5 (*SPINK5*), may influence scar formation by modulating epidermal homeostasis and inflammation resolution [10,11]. Additionally, the *CYB5R1* gene, which encodes a member of the cytochrome b5 reductase family involved in oxidative stress and ferroptosis pathways, emerges as presents a novel candidate potentially affecting extracellular matrix remodeling in acne lesions [12,13]. Collectively, these six genes represent biologically plausible candidates for investigating the genetic basis of acne scarring.

However, despite growing interest in acne genetics, most research has targeted targets acne susceptibility rather than scarring outcomes [6–8]. To date, no comprehensive study has evaluated whether polymorphisms in *IL1A*, *TLR4*, *TNF*, *FLG*, *SPINK5*, and *CYB5R1* predispose individuals to distinct acne scar phenotypes. Therefore, this study aims to investigate the correlation between these six genetic variants and acne scarring utilizing with detailed phe-

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notypic scar characterization. By addressing this knowledge gap, our research seeks to enhance the understanding of acne scar pathogenesis and support the development of personalized approaches to in dermatological care.

MATERIALS AND METHODS

Patient Recruitment and Clinical Assessment

This cross-sectional study was conducted at the University of Medicine and Pharmacy Hospital, and the Vietnam National Hospital of Dermatology and Venereology between September, 2023 and December, 2024. The study protocol was approved by the Institutional Review Board of the School of Medicine (approval number #MEDVNU-093) and adhered to the principles of the Declaration of Helsinki.

A total of 202 patients with clinically diagnosed acne vulgaris were consecutively recruited during their outpatient dermatology visits. Eligible participants were at least 16 years of age, had a confirmed clinical diagnosis of acne vulgaris, and provided written informed consent. Patients with systemic inflammatory conditions, endocrine disorders, current immunosuppressive or systemic corticosteroid therapy, or a history of isotretinoin use within the preceding six months were excluded.

Participants were stratified into two groups based on their scar status: 55 patients with acne but without visible scars (the non-scarring cohort), and 147 patients with acne scars (the scarring cohort). Clinical characteristics, including age, sex, acne phenotype (comedonal, cystic, inflammatory, or mixed), and pore size (small, medium, or large), were recorded.

All patients were independently evaluated by two board-certified dermatologists, and any diagnostic discrepancies were resolved via consensus. Acne phenotypes were classified according to the criteria established by Sebastian Cruz et al. (2023)[14]. Scar assessment was performed by the same two board-certified dermatologists utilizing the morphological classification system (atrophic, hypertrophic, and keloid) as described by Jacob et al. (2001)[15] and Kravvas et al. (2017)[16]. Additionally, scar severity was graded according to the Goodman & Baron qualitative global scarring grading system (2006)[17] to ensure inter-rater reliability. Any further discrepancies were resolved by consensus. Clinical assessment and peripheral blood collection were performed concurrently to ensure phenotypic-genotypic concordance for downstream association analyses.

Sample Collection and DNA Extraction

Peripheral venous blood samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes and processed according to standardized molecular laboratory protocols. Genomic DNA was extracted using validated commercial extraction kits. DNA concentration and purity were assessed via spectrophotometric and fluorometric methods. Samples that failed to meet quality control thresholds were excluded from subsequent analyses.

Single Nucleotide Polymorphism Selection and Targeted Sequencing

A targeted next-generation sequencing (NGS) approach was employed, focusing on preselected single nucleotide polymorphisms (SNPs) and pathogenic variants chosen based on biological plausibility and prior clinical evidence. The six selected gene variants (*CYB5R1*, *IL1A*, *TLR4*, *FLG*, *SPINK5*, and *TNF*) represent three principal biological axes implicated in acne pathogenesis: the inflammatory response, epidermal barrier function, and lipid metabolism.

Variant selection was informed by published evidence from the ClinVar and dbSNP databases, pathogenicity classification according to the American College of Medical Genetics and Genomics (ACMG) guidelines, and putative associations with inflammatory phenotypes, nodulocystic acne, and scar formation (Table 1). For variants without assigned reference SNP cluster IDs (rsIDs), genomic coordinates and Human Genome Variation Society (HGVS) nomenclature are provided to ensure reproducibility. High-depth NGS was performed to ensure the reliable detection of both rare and common variants within the targeted loci.

Genetic Analysis

Genetic analysis was designed based on recent genome-wide association studies (GWAS) of acne vulgaris, which have identified more than 25 susceptibility loci across diverse populations[8,18]. To capture the genetic architecture relevant to acne and scarring, we selected two complementary SNP panels. First, we compiled index SNPs and their proxies ($r^2 \geq 0.8$) reported in large meta-GWAS of acne vulgaris (including loci near *FADS2*, *LGR5*, *FASN*, *ZNRF3-KREMEN1*, *HLA-C*, and *FLG*)[8,18]. These SNPs represent established risk loci implicated in sebaceous gland biology, hair follicle development, immune regulation, and wound healing.

Second, to expand genomic coverage, we included a custom array panel of approximately 4,500 SNPs,

Table 1: Selected gene variants information

Gene variants	rsID	Database
IL1A	rsID: Not available IL1A(NM_000575.5):c.586C>T p.(Gln196Ter)	ACMG: PVS1, PM2, PP3
TNF	rs281865419 (NM_000594.4(TNF):c.322C>T (p.Arg108Trp))	ClinVar, Pathogenic
TLR4	rsID: Not available TLR4(NM_138557.3):c.1390del p.(Cys464AlafsTer2)	ACMG: PVS1, PM2
SPINK5	rs771730802 (NM_006846.4(SPINK5):c.81+5G>A)(intron variant)	ClinVar, Pathogenic
FLG	rs775253166 NM_002016.2(FLG):c.11033_11036del (p.Ser3678fs)	ClinVar, Pathogenic
CYB5R1	rsID: Not available CYB5R1(NM_016243.3):c.706C>T p.(Arg236Cys) CYB5R1(NM_016243.3):c.624C>A p.(Cys208Ter)	ACMG: PVS1, PM2

incorporating variants previously reported in dermatologic genetics studies and polymorphisms in inflammation-related, barrier-related, and extracellular matrix remodeling genes[6,19]. This panel was designed to facilitate exploratory association testing beyond the known GWAS hits, with a specific focus on genes potentially involved in scarring.

Genotyping was performed using the Illumina Infinium Global Screening Array (GSA) supplemented with custom content, with quality control assessments conducted by Macrogen Inc. (Seoul, Korea). In brief, DNA samples (≥50 ng/μL, A260/280 ratio 1.8–2.0) were processed according to the manufacturer's protocols. Quality control procedures followed standard GWAS pipelines[20]. Specifically, samples with call rates <95%, sex discordance, or cryptic relatedness (pi-hat >0.2) were excluded. SNP-level filters included a call rate <98%, a Hardy–Weinberg equilibrium of $p < 1 \times 10^{-6}$, and a minor allele frequency (MAF) <0.01. After quality control, approximately 4,300 SNPs remained for downstream analysis.

Statistical association analyses were conducted using PLINK v1.9 software. Additive genetic models were tested using logistic regression, adjusted for age, sex, and acne severity. Principal component analysis (PCA) was employed to control for population stratification, and the first five principal components (PCs) were included as covariates. Variants showing a suggestive association ($p < 1 \times 10^{-4}$) were further annotated using ANNOVAR against the dbSNP, gnomAD, and GTEx eQTL databases. Enrichment analyses of significant SNPs were performed to identify biological pathways relevant to scar pathogenesis.

Statistical Analyses

IBM SPSS Statistics version 26.0 and R version 4.5.1 were utilized for the statistical analyses. Independent t-tests were used to compare continuous variables between groups, and chi-square tests were used to assess categorical relationships, with statistical significance set at $p < 0.05$. The R programming language was used to visualize gene variant distributions and odds ratios using forest plots and heatmaps.

RESULTS

Demographic Characteristics and Prevalence of Acne Scarring

Over a 16-month period, the study recruited 202 patients receiving acne treatment at the Vietnam National Hospital of Dermatology and Venereology. The participants were stratified into two groups based on scar status: a non-scarring cohort (n = 55) and a scarring cohort (n = 147). Subsequently, gene analysis was conducted, and clinical features were assessed by dermatologists. Detailed data are presented in Table 2.

No significant differences were observed between the groups regarding gender distribution, age, and clinical features ($p > 0.05$). Genetic analysis revealed

Table 2: Demographic characteristics of the study groups

	No scar (n=55)	Scar (n=147)	p-value
Gender			
Female	23 (41.8)	72 (49.0)	0.454
Male	32 (58.2)	75 (51.0)	
Age, years			
Mean (SD)	29.3 (7.00)	28.4 (7.33)	0.435
Median (IQR)	28 (17 - 42)	28 (17 - 42)	
Acne phenotypes (%)			
Comedonal	18 (32.7)	40 (27.2)	0.883
Cystic	12 (21.8)	33 (22.4)	
Inflammatory	12 (21.8)	34 (23.1)	
Mixed	13 (23.6)	40 (27.2)	
Pore size (%)			
Small	26 (47.3)	55 (37.4)	0.246
Medium	18 (32.7)	46 (31.3)	
Large	11 (20.0)	46 (31.3)	
***SPINK5* (%)**			
Found	19 (34.5)	37 (25.2)	0.185
None	36 (65.5)	110 (74.8)	
***TNF* (%)**			
Found	14 (25.5)	46 (31.3)	0.419
None	41 (74.5)	101 (68.7)	
***IL1A* (%)**			
Found	18 (32.7)	54 (36.7)	0.597
None	37 (67.3)	93 (63.3)	
***CYB5R1* (%)**			
Found	13 (23.6)	56 (38.1)	0.05
None	42 (76.4)	91 (61.9)	
***FLG* (%)**			
Found	13 (23.6)	50 (34.0)	0.156
None	42 (76.4)	97 (66.0)	
***TLR4* (%)**			
Found	24 (43.6)	46 (31.3)	0.101
None	31 (56.4)	101 (68.7)	

† Abbreviations: SD, standard deviation; IQR, interquartile Range; all asterisks "*" indicate statistically significant differences: *p < 0.05

no significant differences in the proportion of variants in *SPINK5*, *TNF*, *IL1A*, *FLG*, and *TLR4* (p > 0.05) between the non-scarring and scarring cohorts. In contrast, *CYB5R1* variants, though not statistically significant, demonstrated a borderline association with the scarring cohort (p = 0.05).

Genetic Associations with Scarring and Non-Scarring Outcomes

This genetic association study investigated the relationship between scarring risk and selected gene variants (Figure 1). Notably, *CYB5R1* variants exhibited the strongest observed association with scarring (OR = 1.99, 95% CI: 1.00 - 4.15); however, because the confidence interval includes unity, this finding does not reach conventional statistical significance.

Although *FLG*, *IL1A*, and *TNF* variants showed odds ratios greater than 1, their wide confidence intervals overlapping with unity indicated a lack of statistical significance. Conversely, *TLR4* (OR = 0.59, 95% CI: 0.31 - 1.12) and *SPINK5* (OR = 0.64, 95% CI: 0.33 -

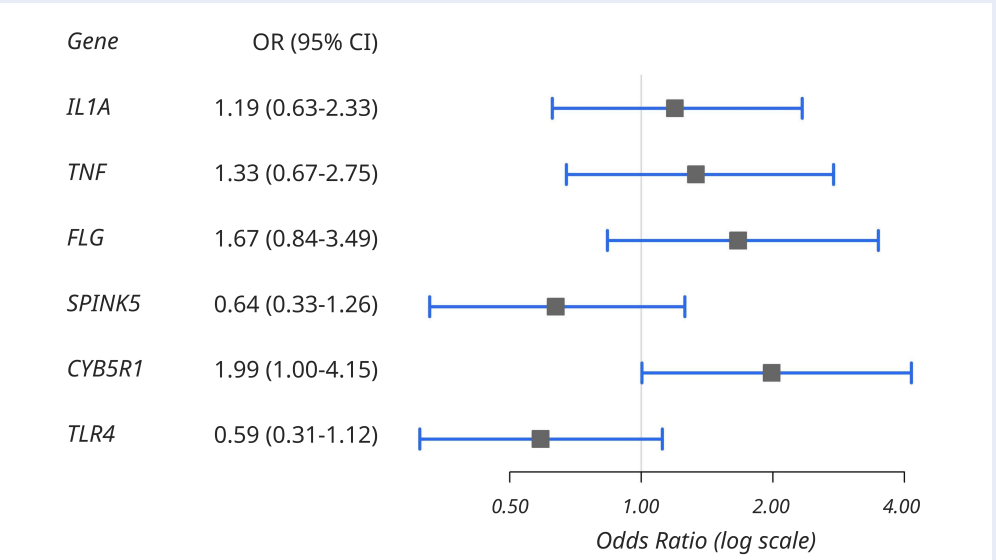

Figure 1: Association of genetic variants with the risk of acne scarring. This forest plot illustrates the odds ratios (OR) and 95% confidence intervals (CI) for the association between acne scarring and variants in the *IL1*, *TNF*, *FLG*, *SPINK5*, *CYB5R1*, and *TLR4* genes. An OR > 1 indicates an increased risk of scar formation, whereas an OR < 1 suggests a protective effect. The vertical gray line represents the null value (OR = 1), indicating no statistical association.

1.26) were associated with reduced odds, but these findings were also not statistically significant.

Genetic Associations with Specific Scar Phenotypes

Participants in the scarring cohort were stratified into three scar types of increasing severity: atrophic (n = 56), hypertrophic (n = 46), and keloid (n = 45). The study examined the odds ratios and the distribution of gene variants across these three scar types. Detailed data are presented in Table 3. Significant differences in variant proportions were observed across scar types for *IL1A* (p = 0.020) and *CYB5R1* (p = 0.042). No significant differences were found for *TLR4*, *FLG*, *SPINK5*, or *TNF* (p > 0.05) across the scar phenotypes.

The proportions of patients harboring specific gene variations across various scar types were illustrated via heatmap analysis (Figure 2). The proportion of the *CYB5R1* gene variant in atrophic scars was found to be 0.48. The proportion of the *IL1A* gene variant was 0.43 in hypertrophic scars and 0.49 in keloid scars. In patients without scars, the proportion of the *TLR4* gene variant was 0.44. Hypertrophic scars demonstrated an *FLG* gene variant proportion of 0.39, while keloid scars showed a variant proportion of 0.36. In patients without scars, the proportion of the *SPINK5* gene variant was 0.35. With values of 0.32 in atrophic scars, 0.37 in hypertrophic scars, 0.24 in keloid scars, and 0.25 in the non-scarring cohort, the *TNF* gene variant exhibited moderate proportions across all groups.

DISCUSSION

This study found no significant associations between demographic factors (gender, age), clinical acne phenotypes, or pore size and the presence of acne scarring. These findings align with previous reports indicating that such variables often have limited predictive value for scarring outcomes. Moreover, we observed a potential association between *CYB5R1* variants and acne scarring, highlighting a possible genetic predisposition to this condition. This variant is more prevalent in the scarred cohort, presenting mostly with atrophic scars, and carries nearly double the odds of scarring (OR 1.99; CI 1.00 - 4.15), while the other gene variants showed no significant association. However, this finding was borderline and should be interpreted cautiously.

According to meta-analyses, between 75 and 90 percent of acne scars are atrophic[3,21], with hypertrophic and keloidal scars accounting for only a small minority. Indeed, Cheng et al. discovered that approximately 78% of scars in acne patients were atrophic[3], consistent with older estimates of

Table 3: Distribution of Gene Variants Across Diverse Scar Phenotypes

Gene Variant	*IL1A*		*TLR4*		*FLG*		*SPINK5*		*CYB5R1*		*TNF*	
	Found (n=72)	None	Found (n=70)	None	Found (n=63)	None	Found (n=56)	None	Found (n=69)	None	Found (n=60)	None
No Scars (n = 55)	18	37	24	31	13	42	19	36	13	42	14	41
Atrophic (n = 56)	12	44	20	36	16	40	16	40	27	29	18	38
Hyper-trophic (n = 46)	20	26	11	35	18	28	11	35	16	30	17	29
Keloid (n = 45)	22	23	15	30	16	29	10	35	13	32	11	34
p-value	**0.020***		0.225		0.335		0.511		**0.042***		0.495	

† Abbreviations: all asterisks "*" indicate statistically significant differences: *p < 0.05

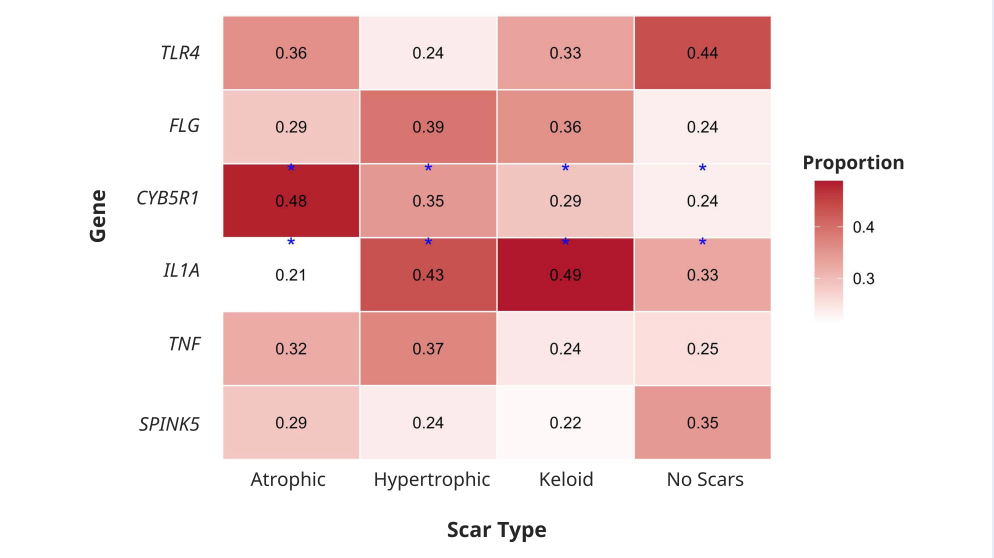

Figure 2: Proportion of gene variants across acne scar phenotypes. This heatmap illustrates the proportion of individuals in the atrophic, hypertrophic, keloid, and non-scarring cohorts who harbored variants in the *TLR4*, *FLG*, *CYB5R1*, *IL1*, *TNF*, and *SPINK5* genes. Greater proportions are represented by darker red shading. Statistically significant differences ($p < 0.05$) are indicated by asterisks (*).

80-90%[21]. Therefore, genes that affect the development of atrophic scars are of significant clinical relevance in acne pathogenesis.

CYB5R1 encodes NADH-cytochrome b5 reductase 1, a ubiquitous oxidoreductase involved in lipid metabolism, steroid biosynthesis, and drug metabolism, with strong expression in keratinocytes and mitochondria across multiple tissues. Crucially, recent mechanistic work implicates *CYB5R1* in the generation of reactive oxygen species (ROS) and lipid peroxidation—especially in the context of ferroptosis (iron-dependent lipid peroxidation)[22]. *CYB5R1* is predicted to localize to the mitochondria and the endoplasmic reticulum and shares 63% sequence identity with the well-known *CYB5R3* isoform. Recent data indicate that *CYB5R1* can drive mitochondrial electron leakage to generate ROS[12].

We hypothesize about the mechanisms underlying *CYB5R1*'s impact on scarring given its redox involvement. Our findings are consistent with new research that links *CYB5R1* to hydrogen peroxide production and membrane damage during ferroptotic cascades[22], pointing to a mechanism by which its variants increase the oxidative burden in

acne-prone skin. Although ferroptosis is known to trigger inflammatory pathways, an overproduction of ROS may affect the viability or function of dermal fibroblasts, resulting in inadequate collagen deposition and cutaneous atrophy[22]. Likewise, fibroblasts or endothelial cells in the regenerating skin may directly undergo cell death as a result of *CYB5R1*-mediated ferroptosis. On the other hand, hypertrophic/keloid scars are indicative of increased matrix and fibroblast activity; hence, a pro-oxidative bias may specifically predispose individuals to the atrophic phenotype. The association of *CYB5R1* adds a new redox-mediated dimension to scar morphogenesis, which is distinct from well-established genes like *IL1A* and *TNF*, which are well-documented in acne pathogenesis[23]. Future research should examine whether individuals harboring the *CYB5R1* variant actually exhibit elevated oxidative stress or compromised fibroblast remodeling during the healing of acne lesions. Nevertheless, despite its role in regulating ferroptosis and oxidative stress—processes essential to lipid peroxidation and cellular death [12,23]—*CYB5R1* has not previously been studied in dermatological settings like acne or skin fibrosis.

The cytokines of the IL-1 family are well-known mediators of acne inflammation and scarring. Historically, *IL1A* had been found to be particularly important because IL-1α activity is detected early in comedogenesis and can help initiate the inflammatory response in acne lesions[24]. Previously, IL-1 protein levels were shown to be significantly higher in fibrotic scars, such as keloids, which indicates persistent wound inflammation[25]; however, previous genetic research did not find any link to acne scarring[26]. Consequently, our discovery of a significant *IL1A* gene variant association (p=0.020) offers compelling evidence that IL-1α signaling affects scar risk. Interestingly, *IL1B* was previously recognized as a major cytokine in acne[26]; subsequently, our findings are consistent with known biology, but they also point to a new polymorphism or regulatory mechanism in the *IL1A* gene that was missed by previous SNP investigations.

TNF-α is also a key inflammatory mediator in acne. In keloid tissues, the TNF-α protein is increased, and TNF-α mediates the immediate acne lesion response[25]. However, SNPs in the *TNF* promoter, such as -308G/A, have not reliably predicted the severity or amount of scarring[26,27]. All scar types in our group had modest frequencies (0.24–0.37) of *TNF* variants. This is consistent with the complex body of evidence, as meta-analyses only find minor, population-specific effects of *TNF* SNPs on acne. Though its genetic contribution to scarring seems widespread and most likely involves numerous regulatory alleles rather than a single common variant, *TNF*'s key inflammatory role remains evident overall[25,26].

For *TLR4*, the pattern was intriguing. TLR4 is an innate immune receptor that initiates MyD88/NF-κB signaling, which causes dermal fibroblasts to produce IL-6, IL-8, and MMP-1[28]. In fact, fibroblasts exposed to UV-A exhibit elevated TLR4 expression and subsequent production of IL-6, IL-8, and MMP-1[28]. The importance of 3′-UTR SNPs in *TLR4* linked to acne susceptibility has been confirmed by recent GWAS on acne[7]. According to our study, the no-scar group had the highest proportion of the *TLR4* variant (44%), indicating a protective polymorphism that inhibits fibrotic/inflammatory signaling. This observation aligns with biological mechanisms; for instance, in skin models, inhibiting TLR4 reduces pro-fibrotic cytokines. Therefore, by suggesting that specific alleles may reduce scar development, our findings expand on *TLR4*'s recognized role in acne[7,28].

Furthermore, there were notable patterns in the genes related to skin barrier function. Filaggrin, or *FLG*, is necessary for epidermal cornification and hydration; ichthyosis and severe eczema result from null variants[29]. We found *FLG* variants in approximately 36–39% of hypertrophic and keloid scars, despite the fact that they were previously considered to be unrelated to overall acne risk. According to this new association, barrier abnormalities may make people more likely to experience excessive fibrosis during the healing process. Similarly, *SPINK5* produces the protease inhibitor LEKTI, which is necessary for cornification; variants in *SPINK5* result in Netherton syndrome, which is characterized by scaly, irritated skin[30,31]. Interestingly, the *SPINK5* variant was enriched in those without scars (35%), suggesting that some *SPINK5* alleles may reduce inflammation that promotes scarring. These findings raise novel questions about how barrier gene variation can affect scar outcomes, because *FLG* and *SPINK5* polymorphisms have not, to our knowledge, been connected to acne scarring previously[29].

This study has several strengths, including its detailed phenotypic characterization of acne scars (atrophic, hypertrophic, and keloid subtypes) by board-certified dermatologists using standardized classification systems, which enhances the clinical relevance of the findings. The use of a custom-expanded

genotyping array allowed for the exploration of biologically plausible candidate genes beyond established GWAS loci, providing insights into potential redox-mediated mechanisms in acne scarring pathogenesis. Additionally, the cross-sectional design enabled efficient recruitment and simultaneous assessment of genetic variants and scar outcomes in a Vietnamese hospital-based cohort, where such data remain limited. However, the relatively small sample size, particularly within the scar subgroups (n = 202 overall, with scar subgroups of n = 45-56), reduces statistical power and increases the risk of type II errors. The primary association for *CYB5R1* variants was borderline (p = 0.050, OR = 1.99, 95% CI: 1.00-4.15), rendering it nominally significant and exploratory rather than confirmatory. The cross-sectional design prevents causal inference, and findings require replication in larger, independent cohorts for confirmation and generalizability.

Conclusion

In conclusion, our findings suggest a possible distinct role for *CYB5R1* and *IL1A* variants in atrophic and fibrotic scarring, respectively. Hypothetical mechanisms are suggested to involve oxidative stress and ferroptosis pathways, which represents a paradigm-shifting novelty, connecting redox biology with acne pathophysiology, even though the findings regarding *TNF*, *FLG*, *SPINK5*, and *TLR4* collectively build upon established inflammatory and barrier pathways in dermatology. These discoveries support the polygenic character of acne scarring and open the door for tailored treatments, such as ferroptosis inhibitors, to lessen scar formation in people who are genetically predisposed.

ABBREVIATIONS

CYB5R1: Cytochrome B5 reductase 1; SPINK5: Serine peptidase inhibitor Kazal type 5; FLG: Filaggrin; TNF: Tumor necrosis factor; IL: Interleukin; SNP: Single Nucleotide Polymorphisms; ROS: Reactive Oxygen Species; NGS: Next-generation sequencing; GWAS: Genome-wide association studies; PCA: Principal component analysis; OR: Odds ratio; CI: Confidence Interval; SD: Standard deviation; IQR: Interquartile range

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AUTHOR CONTRIBUTIONS

Conceptualisation: Duy-Khang Nguyen, Quynh-Giang Nguyen, Dong Kha To. Data analysis and methodology: Duy-Khang Nguyen, Quynh-Giang Nguyen, Chi-Bao Bui. Acquisition of clinical data: Tuan-Khoi Duong, Dang-Khoa Nguyen, Dong Kha To. Writing - original draft preparation: Duy-Khang Nguyen, Quynh-Giang Nguyen, Hoang-Dung Nguyen. Writing - review & editing: Duy-Khang Nguyen, Chi-Bao Bui, Quynh-Giang Nguyen, Dong Kha To. Supervision: Chi-Bao Bui, Dong Kha To. All authors have read and agreed to the published version of the manuscript.

COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ETHICS APPROVAL

The study protocol was approved by the Institutional Review Board of School of Medicine (approval number #MEDVNU-093) and adhered to the principles of the Declaration of Helsinki.

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DATA AVAILABILITY STATEMENT

On reasonable request, the associated author will provide the data used in this article.

CONSENT FOR PUBLICATION

Not applicable.

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