Clinical, Cosmetic and Investigational Dermatology

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Advances in Genetic Polymorphism Research in Rosacea: Mechanisms and Clinical Implications

Zhuangyi Wang, Zhengzhong Zhang

Department of Dermatology, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan Province, People's Republic of China

Correspondence: Zhengzhong Zhang, Department of Dermatology, Affiliated Hospital of North Sichuan Medical College, No. 1 Maoyuan South Road, Shunqing District, Nanchong City, Sichuan Province, 637000, People's Republic of China, Tel +8618080339898, Email laowaiaeo@163.com

Abstract: Rosacea is a chronic inflammatory skin disease primarily affecting the central region of the face. Typical manifestations include erythema, papules, or pustules on the cheeks, glabella, chin, and nose, with some patients experiencing ocular involvement. The pathogenesis of this disease is influenced by both polygenic inheritance and environmental factors, with abnormalities in innate immunity and neurovascular regulation playing a leading role. Recent genetic studies have identified several key genes, including Human Leukocyte Antigen (HLA), Toll-Like Receptor 2 (TLR2), Interleukin-17 (IL-17), Cathelicidin Antimicrobial Peptide (CAMP), and others, that are closely associated with rosacea onset and progression. This review summarized recent advances in rosacea-related genetic researches, aiming to reveal the genetic basis of the disease and provide support for early intervention and precision management of high-risk populations.

Keywords: Rosacea, susceptibility genes, gene polymorphism, genetic variants, genetics

Introduction

Rosacea is a common chronic inflammatory skin disorder primarily affecting the skin's blood vessels and sebaceous glands of hair follicles. It presents with a variety of clinical features, including central facial erythema, persistent redness, inflammatory papules, pustules, and telangiectasia, often accompanied by sensations of burning, stinging, plaques, edema, and ocular symptoms.[1,2] The condition is more prevalent among women, with the age of onset varying.[3] While it can affect individuals of all skin types, it is more common in those with lighter skin tones, which may be due to greater sensitivity to UV exposure, as well as erythema being more readily visualized on lighter skin.[3] Facial involvement in rosacea may lead to social embarrassment, further diminishing quality of life due to pigmentation changes or scarring, and have negative impact on both physical and psychological well-being. Despite advances in treatment options, current therapies often fail to provide inadequate relief for many patients, highlighting the need for a deeper understanding of the mechanism underlying rosacea. Research indicates that the pathogenesis of rosacea is influenced by a combination of genetic and environmental factors. Known triggers include abnormal neurovascular regulation, dysregulation of innate and adaptive immune functions, skin barrier impairment, microbial imbalance, temperature fluctuations, diet, and psychological stress.[4] In 2015, a study involving 233 pairs of monozygotic twins and 42 pairs of dizygotic twins, demonstrated that both genetic and environmental factors contribute approximately 50% each to the risk of developing the disease.[5] Recent genetic studies have uncovered several key genes that play crucial roles in the pathogenesis of rosacea (Table 1).[6,7] Among these, the Human Leukocyte Antigen (HLA) genes are involved in antigen presentation and the regulation of adaptive immune responses.[8] The Toll-Like Receptor 2 (TLR2) gene contribute to innate immunity and inflammatory cascades.[7] Interleukin-17 (IL-17) related genes are responsible for mediating pro-inflammatory cytokine production, which fuels chronic inflammation.[7] The Cathelicidin Antimicrobial Peptide (CAMP) gene encodes LL-37, a precursor antimicrobial peptide that regulates immune defense and inflammation.[7] Other genes, which are implicated in vascular regulation, pigmentation, and neuroinflammation, also contribute to the disease's progression. This review summarized these genetic factors and their mechanisms in rosacea development, with a focus on their potential as diagnostic biomarkers and therapeutic targets.

Received: 27 February 2025
Accepted: 30 May 2025
Published: 5 June 2025

Table 1 Key Genetic Factors in Rosacea Pathogenesis

Gene/Locus	Key Findings	Mechanism	Clinical Implications	Reference
HLA-DRA /BTNL2 (rs763035)	Associated with rosacea susceptibility in individuals of European ancestry	Regulates antigen presentation and T-cell activation, enhancing inflammatory responses	Potential biomarker for disease risk; target for immunomodulatory therapies	[6]
HLA-DMA /DMB (rs57390839)	Correlated with rosacea symptom severity	Influences MHC class II antigen processing and presentation	May predict disease severity and guide treatment intensity	[9]
HLA-DQB1*03:03	Increased risk and severity in Asian populations	Mediates effects through neutrophil activation and HDL levels	Ethnic-specific risk assessment	[8]
HLA-DRB1*15	Associated with rosacea in Nordic populations	Enhances ER stress response and activates C/EBPα pathway	Population-specific risk profiling	[10]
TLR2	Upregulated in rosacea lesions	Triggers KLK5 production, LL-37 release, and NF-κB activation	Target for anti-inflammatory interventions	[11]
IL-17 pathway genes (IL17A, IL17F)	Elevated expression in rosacea tissues	Promotes inflammatory cytokine production and angiogenesis	Potential targets for biologic therapies (eg, secukinumab)	[12,13]
CAMP	Overexpressed in rosacea lesions	Promotes LL-37 production, activates TLR3/RIG-I pathways, enhances vascular adhesion	Biomarker for disease activity; target for therapeutic intervention	[14]

HLA Gene

In the immune system, the HLA gene activates T cells through antigen presentation, triggering adaptive immune responses and thereby playing a pivotal role in regulating inflammation.[15] Chang et al[6] conducted a comprehensive investigation into the genetic susceptibility to rosacea through a genome-wide association study (GWAS), analyzing data from approximately 53,000 individuals of European ancestry. The study consisted of a discovery cohort of 22,952 individuals (2,618 patients and 20,334 healthy controls) and a validation cohort of 29,481 individuals (3,205 patients and 26,262 healthy controls). After adjusting for potential confounders such as gender and age, the study identified the single nucleotide polymorphism (SNP) rs763035, located between the HLA-DRA and Butyrophilin Like 2 (BTNL2) genes on chromosome 6, suggesting its involvement in the pathophysiological process of rosacea. To validate the biological function of these genes, the researchers performed immunohistochemical examination of skin lesions from six rosacea patients. The results revealed strong positive expression of HLA-DRA in the inflammatory infiltrate around hair follicles, particularly in endothelial cells and epidermal dendritic cells, with almost no expression observed in healthy controls. This suggests that HLA-DRA may play a crucial role in the pathogenesis of rosacea by regulating the inflammatory response. Notably, the study also identified three HLA alleles significantly associated with rosacea, all of which belong to MHC class II molecules: HLA-DRB1**03:01, HLA-DQB1**02:01, and HLA-DQA1*05:01. This study was the first to establish a strong association between rosacea and HLA genes, providing compelling evidence for the genetic susceptibility of the disease. These HLA genes contribute to the recognition and response to foreign pathogens and self-antigens through antigen presentation within the immune system.[16,17]

Aponte et al[9] further investigated the critical role of HLA genes in rosacea through genome-wide association studies (GWAS) and gene expression analysis, with a particular focus on the SNP rs57390839 variant located at the 6p21.32 locus. This variant, found between the HLA-DMA and HLA-DMB genes, was significantly associated with the severity of rosacea symptoms. Xiao et al[8] were the first to apply mediation analysis, revealing the role of neutrophils and high-density lipoprotein (HDL) in the relationship between the HLA-DQB1 gene and rosacea risk and severity. Their findings suggest that the HLA-DQB1*03:03* allele may significantly increase the risk and severity of rosacea by influencing neutrophil and HDL levels. Their studies filled an important gap in previous genetic research on Asian populations and provides valuable data for comparing genetic mechanisms across different ethnic groups. A study conducted in a Nordic population also confirmed the association between rosacea and HLA gene polymorphisms. It was found that the *HLA-DRB1*15 allele is closely linked to the genetic risk of the disease. The proposed mechanism involves the enhancement of

the endoplasmic reticulum (ER) stress response, activation of the C/EBPα pathway in the skin, and the promotion of excessive production of antimicrobial peptide LL-37, ultimately leading to the overactivation of the inflammatory response and worsening of rosacea symptoms.[10]

The above findings offer significant implications for personalized medicine. Genotype screening can help to identify individuals at high risk, enabling the development of tailored treatment strategies based on the patient's immune genotype. Patients carrying high-risk HLA alleles can benefit from early therapeutic intervention, potentially alleviating disease severity through immunomodulatory treatments.

TLR2 Gene

TLR2 is a pattern recognition receptor located on human chromosome 4 and belongs to the Toll-like receptor family. It plays a critical role in the innate immune system by recognizing pathogen-associated molecular patterns (PAMPs), thus activating the immune response.[18,19] TLR2 plays a significant regulatory role in various skin diseases, including rosacea. Yamasaki et al[11] were the first to discover that marked upregulation of TLR2 gene expression increases the skin's sensitivity to microorganisms (such as *Propionibacterium acnes*) and environmental stimuli (such as ultraviolet light). This heightened sensitivity triggers a strong inflammatory response by promoting the production of serine proteases (e.g Kallikrein-5) in keratinocytes and the release of antimicrobial peptide LL-37. The increased expression of TLR2 also leads to enhanced calcium ion influx, further exacerbating inflammation. These mechanisms ultimately contribute to the characteristic symptoms of rosacea, such as erythema, pustules, and telangiectasia.[20]

Sun et al[21] analyzed the gene expression datasets of rosacea patients and healthy controls in the GEO database (eg, GSE65914) and identified 359 differentially expressed genes (DEGs). Further KEGG pathway analysis indicated that the TLR signaling pathway is one of the key pathways involved in rosacea, suggesting that the aberrant expression of TLR2 may be closely linked to inflammatory processes associated with innate immunity. The study also found that the overactivation of TLR2 promotes the cleavage of the cathelicidin precursor protein via calcium-dependent KLK5, leading to the generation of active antimicrobial peptide LL-37, which significantly aggravates skin inflammation. Dysregulated activation of TLR2 also induces the release of inflammatory cytokines (eg, IL-1β, TNF-α, IL-6), which further amplify the inflammatory response via the downstream NF-κB signaling pathway, exacerbating rosacea symptoms.[21]

Karpouzis et al[22] demonstrated that the high expression of TLR2 is especially pronounced in patients with papulopustular rosacea. The upregulated TLR2 activity not only makes the skin more susceptible to excessive reactions to microorganisms and environmental stimuli, but also triggers the release of pro-inflammatory cytokines and antimicrobial peptide LL-37 by activating the NF-κB signaling pathway. LL-37 exerts a potent pro-angiogenic and pro-inflammatory effect in rosacea patients, further worsening local erythema and pustules. TLR2 works synergistically with other pro-inflammatory factors (e.g substance P), inducing the degranulation of mast cells and the subsequent release of histamine, causing vasodilation and exacerbating inflammation. The dysregulated activity of TLR2 may also enhance the local immune response through its interaction with vitamin D-dependent mechanisms.[22] Meanwhile, Buhl et al[23] found that the upregulation of TLR2 gene expression activates the Th1/Th17 immune pathway, perpetuating inflammation associated with adaptive immunity.

Future studies should further investigate the precise functions of the TLR2 gene and how its polymorphisms influence susceptibility to rosacea, with the goal of developing targeted therapies for the TLR2 signaling pathway.

IL-17-Related Gene

IL-17 is a crucial pro-inflammatory cytokine produced by Th17 cells, playing a pivotal role in various inflammatory diseases, and is typically highly expressed in patients with rosacea.[24] Genetic polymorphisms in the IL-17 gene may significantly influence patient responses to inflammatory stimuli, with certain variants potentially triggering hypersensitivity reactions in the immune system, thereby exacerbating disease severity.[24,25] Polymorphisms in IL-17-related genes have been shown to exert similar effects in other inflammatory skin conditions (e.g psoriasis and pustulosis), further highlighting its potential importance in rosacea.[24]

Ali et al[26] revealed the critical role of IL-17-related genes, such as Interferon Regulatory Factor 4 (IRF4) and Signal Transducer and Activator of Transcription 3 (STAT3), in rosacea through a multidimensional research approach. Abnormal expression and genetic polymorphisms of these genes promote chronic inflammation and vascular damage in rosacea by regulating Th17 cell differentiation and IL-17 production. Dysregulation of the IL-17 signaling pathway not only exacerbates the inflammatory response but also worsens erythema and capillary dilation in rosacea patients through angiogenic factors. The study by Hayran et al[12] further affirmed the role of IL-17 in rosacea. Serum analysis of 60 rosacea patients and 60 healthy controls revealed significantly higher IL-17 levels in the patients' serum, indicating the important role of IL-17 in rosacea pathogenesis. The generation and secretion of IL-17 are controlled by genes such as RAR-related Orphan Receptor gamma-t (RORγt), STAT3, and IRF4, which enhance IL-17 levels by promoting Th17 cell differentiation and activity, and increase the production of pro-inflammatory cytokines (such as IL-6, IL-1β) and chemokines. Polymorphisms in the IL17A and IL17F genes are strongly correlated with inflammatory severity in rosacea. IL-17 also exacerbates capillary dilation and erythema symptoms by activating the expression of angiogenic factors, such as Vascular Endothelial Growth Factor (VEGF).[27,28] These findings solidify the central role of IL-17-related genes in the pathogenesis of rosacea. Kumar et al[13] further validated the potential of the IL-17 signaling pathway as a therapeutic target. They evaluated the efficacy of the IL-17A inhibitor secukinumab in patients with moderate to severe papulopustular rosacea (PPR). The results showed a significant reduction in the number of papules and pustules, providing preliminary evidence for its therapeutic potential in treating inflammatory manifestations of rosacea.[29]

CAMP Gene

The CAMP gene plays a pivotal role in immune regulation by encoding the precursor hCAP-18 for the antimicrobial peptide LL-37, which is converted to LL-37 via KLK5 cleavage. It is involved in innate immune defense, inflammation regulation, and tissue repair.[30] Dysregulated expression of the CAMP gene is crucial in the pathophysiology of rosacea.[14,31] Kulkarni et al[14] comprehensively demonstrated through cell-based assays, gene knockout techniques, in vivo mouse models, and UV-induced experiments that overexpression of the CAMP gene significantly elevates LL-37 levels. LL-37 activates the Toll-like receptor 3 (TLR3) and RIG-I-like receptor (RIG-I) signaling pathways by binding to small non-coding double-stranded RNA (dsRNA), which subsequently upregulates inflammation-related genes and promotes the expression vascular cell adhesion molecule 1 (VCAM1) and intercellular adhesion molecule 1 (ICAM1) in endothelial cells, exacerbating the inflammatory response and immune cell migration. LL-37 also triggers vasculitis and erythema formation, which are closely related to the hallmark symptoms of rosacea. These findings elucidate the role of the CAMP gene in rosacea. Sun et al[21] analyzed the expression levels of the CAMP gene in rosacea by utilizing skin tissue samples from rosacea patients and healthy controls extracted from the GSE65914 database. The mRNA expression of the CAMP gene in rosacea patients was significantly higher than in the healthy control group. Enrichment analysis indicated that the CAMP gene is closely associated with the TLR signaling pathway and the cytokine–cytokine receptor interaction pathway. Immunohistochemical analysis demonstrated that the CAMP gene product, LL-37, is predominantly expressed in areas of inflammation and co-localizes with inflammatory markers such as ICAM1 and VCAM1, highlighting the crucial role of the CAMP gene in local inflammation. The study suggested that local inflammatory factors and cytokines further enhance CAMP gene expression, establishing a positive feedback loop that perpetuates and exacerbates inflammation.[21] Deng et al[20] revealed the central role of the CAMP gene in the inflammatory positive feedback mechanism. They discovered that the CAMP gene promotes the generation of LL-37 through the mTORC1 signaling pathway, and LL-37, by activating the NF-κB pathway, upregulates pro-inflammatory factors (such as IL-1β and TNF-α). By binding to dsRNA, LL-37 induces further production of pro-inflammatory cytokines and chemokines, worsening the skin inflammation and erythema symptoms of rosacea. As a potential biomarker for rosacea, the CAMP gene can assist in evaluating disease activity and severity, and it may also provide personalized treatment strategies for patients.

Other Related Genes

Research has shown that the elevated expression of inflammation-related genes, such as C-C Chemokine Receptor Type 2 (CCR2) and C-C Motif Chemokine Ligand 2 (CCL2), may exacerbate the inflammatory response in rosacea by promoting monocyte recruitment and the release of inflammatory mediators (e.g High Mobility Group Box 1 (HMGB-1), IL-1β, TNF-α).[32,33] The Melanocortin 1 Receptor (MC1R) gene, which regulates melanin synthesis, may also contribute to the pathophysiology of rosacea.[9,33] Certain genetic variations in the HERC2-OCA2 and SLC45A2 genes, which are involved in skin pigmentation, might

influence skin reactivity, barrier function, and the development of erythema in rosacea patients.[33] The Methyltransferase Like 3 (METTL3) gene exhibits significantly increased expression in both rosacea patients and animal models, potentially contributing to the disease's development by enhancing inflammation.[34] Additionally, the Tachykinin Receptor 3 (TACR3) gene, which encodes neurokinin receptor 3 (NK3R), plays a unique role in the neuroinflammation and vascular abnormalities characteristic of rosacea.[35] Polymorphism studies have identified a strong association between the G allele at the rs3733631 locus and papulopustular rosacea, particularly in male patients, highlighting the genetic influence on disease manifestation.[22]

Conclusion and Perspectives

This review has elucidated the significant roles of key genetic factors in rosacea pathogenesis, with particular emphasis on HLA, TLR2, IL-17, and CAMP genes, which collectively regulate critical aspects of immune function, inflammatory responses, and vascular homeostasis (Figure 1). The identification of specific genetic variants associated with rosacea

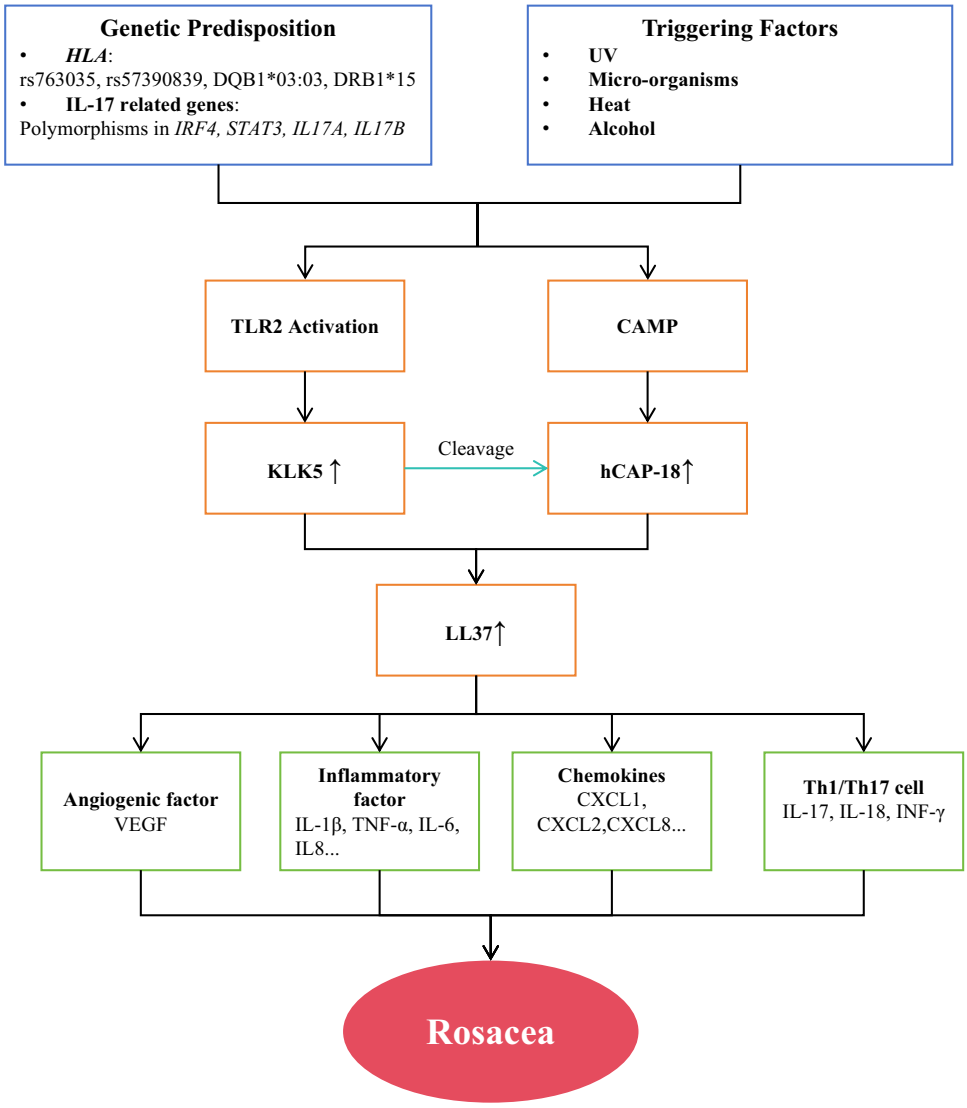

Figure 1 Mechanisms of Key Genetic Factors in Rosacea Pathogenesis. The integrated pathways involved in rosacea pathogenesis, highlighting the interactions between genetic predisposition factors and environmental triggers. The diagram demonstrates how HLA variants (rs763035, rs57390839, DQB103:03, DRB115) and IL-17 related gene polymorphisms (in IRF4, STAT3, IL17A, IL17F) create susceptibility that, when combined with external triggers (UV radiation, microorganisms, heat, alcohol), leads to activation of two primary pathways: TLR2 signaling and CAMP expression. These pathways converge on increased production of the antimicrobial peptide LL-37, which drives the characteristic inflammatory, vascular, and immune responses seen in rosacea through multiple downstream effector mechanisms.
Abbreviations: HLA: Human Leukocyte Antigen, IL-17: Interleukin-17, IRF4: Interferon Regulatory Factor 4, STAT3: Signal Transducer and Activator of Transcription 3, IL17A: Interleukin-17A, IL17B: Interleukin-17B, UV: Ultraviolet, TLR2: Toll-like Receptor 2, CAMP: Cathelicidin Antimicrobial Peptide.

susceptibility and severity represents a major advance though results are often influenced by factors such as case sources, environmental variables, and ethnic differences. Future research should prioritize more precise clinical diagnoses and multi-center population studies across diverse ethnicities, while investigating gene-environment interactions that may modify disease expression. The practical implications of these genetic insights include potential identification of high-risk individuals before clinical manifestation, stratification of patients into distinct pathogenic subgroups for personalized treatment, and development of novel therapeutic strategies targeting specific pathways. As our understanding of the genetic architecture of rosacea continues to evolve, these genes and their functional implications not only provide deeper insights into disease pathogenesis but also offer promising directions for developing clinically applicable genetic biomarkers and precision medicine approaches for this challenging condition.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Gether L, Overgaard LK, Egeberg A, Thyssen JP. Incidence and prevalence of Rosacea: a systematic review and meta-analysis. *Br J Dermatol*. 2018;179(2):282–289. doi:10.1111/bjd.16481
2. Tüzün Y, Wolf R, Kutlubay Z, Karakuş O, Engin B. Rosacea and Rhinophyma. *Clin Dermatol*. 2014;32(1):35–46. doi:10.1016/j.clindermatol.2013.05.024
3. Alexis AF, Callender VD, Baldwin HE, Desai SR, Rendon MI, Taylor SC. Global epidemiology and clinical spectrum of Rosacea, highlighting skin of color: review and clinical practice experience. *J Am Acad Dermatol*. 2019;80(6):1722–1729.e7. doi:10.1016/j.jaad.2018.08.049
4. Geng RSQ, Bourkas AN, Mufti A, Sibbald RG. Rosacea: pathogenesis and therapeutic correlates. *J Cutan Med Surg*. 2024;28(2):178–189. doi:10.1177/12034754241229365
5. Aldrich N, Gerstenblith M, Fu P, et al. Genetic vs environmental factors that correlate with Rosacea: a cohort-based survey of twins. *JAMA Dermatol*. 2015;151(11):1213–1219. doi:10.1001/jamadermatol.2015.2230
6. Chang ALS, Raber I, Xu J, et al. Assessment of the genetic basis of rosacea by genome-wide association study. *J Invest Dermatol*. 2015;135(6):1548–1555. doi:10.1038/jid.2015.53
7. Yang F, Wang L, Song D, et al. Signaling pathways and targeted therapy for Rosacea. *Front Immunol*. 2024;15:1367994. doi:10.3389/fimmu.2024.1367994
8. Xiao W, Li J, Huang X, et al. Tang Y. mediation roles of neutrophils and high-density lipoprotein (Hdl) on the relationship between Hla-Dqb1 and Rosacea. *Ann Med*. 2022;54(1):1530–1537. doi:10.1080/07853890.2022.2077427
9. Aponte JL, Chiano MN, Yerges-Armstrong LM, et al. Assessment of Rosacea symptom severity by genome-wide association study and expression analysis highlights immuno-inflammatory and skin pigmentation genes. *Hum Mol Genet*. 2018;27(15):2762–2772. doi:10.1093/hmg/ddy184
10. Melnik BC. Rosacea: the blessing of the Celts - an approach to pathogenesis through translational research. *Acta Derm Venereol*. 2016;96(2):147–156. doi:10.2340/00015555-2220
11. Yamasaki K, Kanada K, Macleod DT, et al. Tlr2 expression is increased in rosacea and stimulates enhanced serine protease production by keratinocytes. *J Invest Dermatol*. 2011;131(3):688–697. doi:10.1038/jid.2010.351
12. Hayran Y, Şen O, Fırat Oğuz E, et al. Serum Il-17 levels in patients with Rosacea. *J Cosmet Dermatol*. 2022;21(3):1147–1153. doi:10.1111/jocd.14169
13. Kumar AM, Chiou AS, Shih YH, Li S, Chang ALS. An exploratory, open-label, investigator-initiated study of interleukin-17 blockade in patients with moderate-to-severe papulopustular Rosacea. *Br J Dermatol*. 2020;183(5):942–943. doi:10.1111/bjd.19172
14. Kulkarni NN, Takahashi T, Sanford JA, et al. Innate immune dysfunction in Rosacea promotes photosensitivity and vascular adhesion molecule expression. *J Invest Dermatol*. 2020;140(3):645–655.e6. doi:10.1016/j.jid.2019.08.436
15. Medhasi S, Chantratita N. Human leukocyte antigen (Hla) system: genetics and association with bacterial and viral infections. *J Immunol Res*. 2022;2022:9710376. doi:10.1155/2022/9710376
16. Holmes AD, Steinhoff M. Integrative concepts of rosacea pathophysiology, clinical presentation and new therapeutics. *Exp Dermatol*. 2017;26(8):659–667. doi:10.1111/exd.13143
17. Dursun R, Daye M, Durmaz K. Acne and Rosacea: what's new for treatment? *Dermatol Ther*. 2019;32(5):e13020. doi:10.1111/dth.13020
18. Colleselli K, Stierschneider A, Wiesner C. An update on toll-like receptor 2, its function and dimerization in pro- and anti-inflammatory processes. *Int J Mol Sci*. 2023;24(15):12464. doi:10.3390/ijms241512464
19. Tsukidate T, Hespen CW, Hang HC. Small molecule modulators of immune pattern recognition receptors. *RSC Chem Biol*. 2023;4(12):1014–1036. doi:10.1039/D3CB00096F
20. Deng Z, Chen M, Liu Y, et al. A positive feedback loop between Mtorc1 and Cathelicidin promotes skin inflammation in Rosacea. *EMBO Mol Med*. 2021;13(5):e13560. doi:10.15252/emmm.202013560
21. Sun Y, Chen LH, Lu YS, et al. Identification of novel candidate genes in Rosacea by bioinformatic methods. *Cytokine*. 2021;141:155444. doi:10.1016/j.cyto.2021.155444
22. Karpouzis A, Avgeridis P, Tripsianis G, Gatzidou E, Kourmouli N, Veletza S. Assessment of Tachykinin Receptor 3' gene polymorphism Rs3733631 in Rosacea. *Int Sch Res Notices*. 2015;2015:469402. doi:10.1155/2015/469402
23. Buhl T, Sulk M, Nowak P, et al. molecular and morphological characterization of inflammatory infiltrate in Rosacea reveals activation of Th1/Th17 pathways. *J Invest Dermatol*. 2015;135(9):2198–2208. doi:10.1038/jid.2015.141

24. Bernardini N, Skroza N, Tolino E, et al. Potenza C. Il-17 and its role in inflammatory, autoimmune, and oncological skin diseases: state of art. *Int J Dermatol*. 2020;59(4):406–411. doi:10.1111/ijd.14695
25. Salah S, Sadeq YI, Mosaad YM, Elmenshawi IEH, Tawhid ZME. Association of interleukin-17f (Rs763780) single nucleotide polymorphism with multiple sclerosis and optic neuritis. *Sci Rep*. 2024;14(1):13643. doi:10.1038/s41598-024-62736-2
26. Amir Ali A, Vender R, Vender R. The role of Il-17 in Papulopustular Rosacea and future directions. *J Cutan Med Surg*. 2019;23(6):635–641. doi:10.1177/1203475419867611
27. Woo YR, Lim JH, Cho DH, Park HJ. Rosacea: molecular mechanisms and management of a chronic cutaneous inflammatory condition. *Int J Mol Sci*. 2016;17(9):1562. doi:10.3390/ijms17091562
28. Liang J, Chen Y, Wang Z, et al. Exploring the association between Rosacea and acne by integrated bioinformatics analysis. *Sci Rep*. 2024;14 (1):3065. doi:10.1038/s41598-024-53453-x
29. Dai X, Zhang C, Yin Z. Therapy outcomes of Il-17 and Jak inhibitors in Rosacea: a systematic review. *J Biomed Res*. 2024;25:1–2.
30. Yang B, Good D, Mosaiab T, et al. Significance of Ll-37 on immunomodulation and disease outcome. *Biomed Res Int*. 2020;2020:8349712. doi:10.1155/2020/8349712
31. Melnik BC. Endoplasmic reticulum stress: key promoter of Rosacea pathogenesis. *Exp Dermatol*. 2014;23(12):868–873. doi:10.1111/exd.12517
32. Gao C, Ge L, Chen D, et al. Increased frequency of circulating classical monocytes in patients with Rosacea. *Clin Cosmet Invest Dermatol*. 2021;14:1629–1636. doi:10.2147/CCID.S336194
33. Mitchell BL, Saklatvala JR, Dand N, et al. Genome-wide association meta-analysis identifies 29 new acne susceptibility Loci. *Nat Commun*. 2022;13(1):702. doi:10.1038/s41467-022-28252-5
34. Zhang S, Wu M, Xue W. Decoding the role of M(6)a regulators in identifying and characterizing molecular subtypes of Rosacea. *Heliyon*. 2023;9 (12):e23310. doi:10.1016/j.heliyon.2023.e23310
35. Deng Z, Chen M, Zhao Z, et al. Whole genome sequencing identifies genetic variants associated with neurogenic inflammation in Rosacea. *Nat Commun*. 2023;14(1):3958. doi:10.1038/s41467-023-39761-2