Review Article

Genetics, Epigenetics, and Immunological Susceptibility in Psoriasis

Daniel Navarro Morales[1*], Álvaro Calvo Mondragon[2], Katherine Maroto Monge[3], Fabiola Alvarez Mora[4], Heizel Trejos Quiros[5]

[1, 2, 3, 4, 5]Independent Researcher and General Physician, Cartago, Costa Rica
[*]Corresponding author email: **506navarro@gmail.com**

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Abstract

Psoriasis is a chronic immune-mediated inflammatory disease characterized by marked clinical heterogeneity and a complex pathophysiology that extends beyond cutaneous involvement. Its development and progression result from the dynamic interplay between genetic susceptibility, epigenetic regulation, and immune dysregulation. Genome-wide association studies have identified numerous susceptibility loci, particularly within the major histocompatibility complex, highlighting the central role of antigen presentation and cytokine signaling pathways in disease pathogenesis. Variants affecting the IL-23/Th17 axis, tumor necrosis factor signaling, and keratinocyte differentiation contribute to both disease risk and variability in clinical phenotypes. Epigenetic mechanisms add a critical regulatory layer by modulating gene expression without altering the DNA sequence. Alterations in DNA methylation, histone modifications, and non-coding RNA expression influence immune activation and keratinocyte behavior, thereby shaping disease onset, severity, and persistence. These epigenetic changes are highly responsive to environmental and lifestyle factors such as infections, psychological stress, smoking, obesity, and seasonal variation, providing a mechanistic explanation for disease flares and fluctuating clinical activity. Immunological susceptibility in psoriasis is driven by sustained crosstalk between innate and adaptive immune compartments. Dendritic cells, innate lymphoid cells, T helper cell subsets, and keratinocytes interact within a self-amplifying inflammatory network dominated by the IL-23/Th17 pathway. This immune circuitry not only underlies chronic skin inflammation and epidermal hyperplasia but also contributes to systemic inflammation and associated comorbidities. Integrating genetic, epigenetic, and immunological insights has significant clinical implications. Although current biomarkers have limited predictive power, combined molecular and immune profiling holds promise for improved risk

stratification, therapeutic selection, and the advancement of personalized medicine approaches in psoriasis.

Key words

Psoriasis, immune dysregulation, IL-23/Th17 axis, Epigenetic regulation, Genetic susceptibility, Personalized therapy.

Introduction

Psoriasis has a well-established genetic basis, supported by genome-wide association studies that have identified more than one hundred susceptibility loci associated with disease development. These studies have expanded the understanding of psoriasis genetics by revealing novel loci linked to key therapeutic targets, including IL17RA and AHR, reinforcing the close relationship between genetic susceptibility and immune-mediated pathways involved in disease pathogenesis [1]. Among the identified genes, AIM2 has emerged as a particularly relevant factor, given its role in regulating inflammation and innate immune responses, thereby contributing to the chronic inflammatory state characteristic of psoriasis [2]. However, genetic predisposition alone is insufficient to fully explain disease expression, as it often requires interaction with environmental triggers that disrupt immune regulation and precipitate pathological immune responses [3].

Beyond fixed genetic variants, epigenetic mechanisms play a critical modulatory role in psoriasis by influencing gene expression without altering the underlying DNA sequence. Processes such as DNA methylation, histone modifications, and the action of non-coding RNAs contribute to dynamic changes in transcriptional activity within immune cells and keratinocytes, thereby shaping disease susceptibility and activity. These epigenetic alterations are particularly relevant in the context of disease onset and exacerbation, as environmental stimuli, including psychological stress and infections, can induce epigenetic changes that amplify inflammatory pathways and worsen clinical manifestations [4, 5]. Consequently, epigenetic research has provided a valuable framework for identifying novel genetic and molecular markers, while also opening avenues for the development of innovative therapeutic strategies aimed at modulating gene expression patterns associated with psoriasis [6].

Central to the clinical and molecular expression of psoriasis is immune susceptibility driven by dysregulation of both innate and adaptive immune responses. Dendritic cells, T lymphocytes, and keratinocytes interact within a complex immunological network dominated by the IL-23/Th17 axis, which sustains chronic inflammation and epidermal hyperproliferation [3]. Within this framework, cytokine circuits involving tumor necrosis factor alpha, interleukin 23, and interleukin 17 play a pivotal role in disease pathophysiology, a finding that has directly informed the development and clinical success of targeted biologic therapies [7]. Moreover, disruption of the skin's epithelial immune microenvironment has been identified as a defining feature of psoriasis, underscoring the importance of maintaining immune homeostasis at the epithelial level for effective disease control and long-term management [8].

Environmental and lifestyle factors further modulate genetic, epigenetic, and immunological susceptibility, contributing to disease variability and progression. Elements such as seasonality and psychological stress, along with lifestyle choices including smoking and alcohol consumption, have been shown to exert a significant influence on psoriasis activity and severity. These factors not only exacerbate clinical symptoms but may also interact with underlying genetic and epigenetic mechanisms to alter disease trajectories over time. As a result, their recognition is essential for understanding individual disease expression and for

implementing personalized management strategies tailored to the specific risk profile and environmental exposures of each patient [5].

The objective of this article is to analyze the interplay between genetic factors, epigenetic mechanisms, and immunological susceptibility in the pathogenesis of psoriasis, emphasizing how their interaction contributes to disease onset, clinical heterogeneity, and progression, as well as to discuss the implications of this integrated framework for risk stratification and the development of targeted and personalized therapeutic strategies.

Methodology

For the preparation of this review on the genetic, epigenetic, and immunological determinants of psoriasis, a structured and integrative analysis of the scientific literature was carried out with the objective of examining the molecular mechanisms underlying disease susceptibility and immune dysregulation. The methodological approach was designed to explore how inherited genetic variants, epigenetic regulation, and immune pathways converge to influence disease onset, clinical variability, and progression, with particular emphasis on their relevance to targeted and personalized therapeutic strategies.

The literature search was conducted using established biomedical databases, including PubMed, Scopus, and Web of Science, selected for their broad coverage of dermatology, immunology, genetics, and molecular medicine. Inclusion and exclusion criteria were defined to ensure scientific rigor and relevance. Peer-reviewed articles published between 2021 and 2026 in English or Spanish were considered eligible if they addressed key aspects of psoriasis genetics, epigenetic regulation, immune susceptibility, or their interactions. Studies focusing on genome-wide association analyses, epigenetic profiling, immune signaling pathways, and translational implications were prioritized, while publications with incomplete data, lack of peer review, or redundant findings were excluded. The search strategy incorporated keywords such as: *Psoriasis, immune dysregulation, IL-23/Th17 axis, epigenetic regulation, genetic susceptibility, personalized therapy.*

The initial search yielded 28 relevant publications, including original research articles, narrative and systematic reviews, and translational studies addressing molecular and immunological mechanisms of psoriasis. These sources were systematically reviewed to extract and synthesize information related to susceptibility loci, epigenetic modifications, immune cell interactions, and cytokine networks implicated in disease pathophysiology.

Artificial intelligence–assisted tools were employed as complementary resources to support literature organization, thematic grouping, and identification of conceptual links across studies. Their use facilitated efficient integration of multidisciplinary evidence and contributed to maintaining logical coherence and continuity throughout the review.

A qualitative and integrative analytical approach was applied, allowing the findings to be organized into thematic domains encompassing genetic predisposition, epigenetic modulation, and immune susceptibility. This framework enabled the identification of convergent mechanisms, areas of clinical relevance, and existing knowledge gaps, while providing a coherent and up-to-date overview of the molecular basis of psoriasis and its implications for future research and personalized management strategies.

Overview of Psoriasis Pathophysiology

Psoriasis is initiated and sustained by a complex immunopathogenic network involving dendritic cells, T lymphocytes, and keratinocytes, in which the IL-23/Th17 pathway plays a central role [3]. Within this framework, dendritic cells act as key initiators of the inflammatory cascade by producing tumor necrosis factor alpha and

interleukin 23, which promote the differentiation of naïve T cells into Th17 effector cells. These Th17 cells subsequently secrete proinflammatory cytokines such as interleukin 17, interferon gamma, and interleukin 22, driving keratinocyte activation, epidermal hyperplasia, and sustained skin inflammation characteristic of psoriatic lesions [9]. Beyond cutaneous involvement, this persistent immune activation is associated with systemic inflammation and the development of comorbid conditions, including cardiovascular disease and metabolic syndrome, underscoring the systemic nature of psoriasis [10].

The immunopathogenesis of psoriasis is further shaped by the dynamic interaction between innate and adaptive immunity. Innate lymphoid cells type 3 and Th17 cells are particularly central to this process, as innate lymphoid cells can induce psoriatic skin changes independently of classical T-cell receptor and antigen interactions, highlighting the importance of innate immune mechanisms in disease initiation [10]. This crosstalk between innate and adaptive immune compartments establishes a self-amplifying inflammatory loop that perpetuates immune activation and exacerbates disease severity over time (Kamata & Tada, 2023). In addition to these key players, other immune cell populations, including neutrophils and gamma delta T cells, contribute to the inflammatory milieu through the release of cytokines and effector molecules, further reinforcing the chronic inflammatory environment observed in psoriatic skin [8].

Keratinocytes play an active and multifaceted role in this immunopathogenic framework and should not be regarded merely as passive targets of immune-mediated damage. In psoriasis, keratinocytes actively secrete antimicrobial peptides, chemokines, and cytokines such as interleukin 36 and interleukin 23, thereby directly participating in immune activation and amplification of inflammation. Through continuous interaction with immune cells, keratinocytes influence immune cell differentiation, recruitment, and proliferation, effectively sustaining the inflammatory cycle that characterizes the disease [11]. Moreover, keratinocytes are implicated in phenotypic switching and disease relapse, reflecting their role in disease persistence and recurrence and representing a significant challenge for long-term therapeutic control [12].

Genetic Susceptibility in Psoriasis

Psoriasis demonstrates a strong heritable component supported by consistent epidemiological evidence. Familial aggregation studies and twin analyses have shown markedly higher concordance rates among monozygotic twins compared with dizygotic twins, indicating that genetic factors play a substantial role in disease susceptibility [13]. This observation is reinforced by population-based studies, which have reported that individuals with a positive family history of psoriasis carry a significantly increased risk of developing the disease, underscoring the importance of inherited genetic liability in its pathogenesis [14].

Within this genetic framework, several major susceptibility loci have been identified, with the PSORS loci holding historical and scientific relevance. Among them, PSORS1, located within the major histocompatibility complex region, remains the locus most strongly associated with psoriasis and has served as a cornerstone for understanding the genetic architecture of the disease [1]. A key variant within this region is the HLA-C*06:02 allele, which is widely recognized as a robust genetic marker for psoriasis. This allele plays a crucial role in antigen presentation and modulation of immune responses and has also been linked to differential therapeutic responses, particularly a more favorable outcome with certain biologic agents such as interleukin 12 and interleukin 23 inhibitors [15].

Beyond the major histocompatibility complex, non-HLA genetic variants contribute substantially to psoriasis susceptibility. Variants in genes involved in antigen processing and

presentation, particularly those within the major histocompatibility complex class I region, influence immune system function and shape the inflammatory responses characteristic of the disease [16]. In parallel, genetic alterations affecting cytokine signaling pathways, including those related to interleukin 23, interleukin 17, and tumor necrosis factor, have been consistently implicated in psoriasis pathogenesis. The clinical relevance of these findings is highlighted by the fact that these same pathways are targeted by several highly effective therapeutic agents currently used in clinical practice. Additionally, genes regulating keratinocyte differentiation and epidermal barrier integrity have been associated with psoriasis, as certain variants may compromise skin structure and contribute to disease development and persistence [1, 12].

Genetic heterogeneity further explains the variability observed in clinical presentation and disease course. Distinct differences in susceptibility loci have been identified between early-onset and late-onset psoriasis, suggesting that these subtypes may arise from partially divergent genetic backgrounds [17]. Moreover, evidence indicates that specific clinical forms, such as pustular psoriasis, display unique genetic features, including oligogenic inheritance patterns and transethnic differences in susceptibility, reinforcing the concept that psoriasis encompasses a spectrum of genetically heterogeneous disorders rather than a single uniform entity [18].

Epigenetic Mechanisms in Psoriasis

Epigenetic regulation represents a fundamental layer of control in psoriasis pathogenesis, with DNA methylation emerging as one of the most extensively studied mechanisms. Both global and gene-specific methylation alterations have been consistently observed in psoriatic tissues, indicating widespread epigenomic remodeling in affected individuals. Aberrant methylation patterns can lead to dysregulation of genes involved in immune responses and keratinocyte function, thereby contributing to the initiation and maintenance of chronic inflammation characteristic of psoriasis [4, 19].

In this context, DNA methylation alterations exert a significant impact on immune-related and keratinocyte-associated genes. Genes regulating immune activation and epidermal proliferation, particularly those involved in the IL-17 signaling pathway, are subject to epigenetic modulation through differential methylation, which directly influences their transcriptional activity [20, 21].

Complementing DNA methylation, histone modifications constitute another critical epigenetic mechanism implicated in psoriasis. Alterations in histone acetylation and methylation patterns have been documented in psoriatic skin, affecting chromatin structure and gene expression programs related to inflammation and cellular proliferation [20, 21]. These modifications modulate the accessibility of DNA to transcription factors and regulatory proteins, thereby fine-tuning the expression of genes involved in immune responses. In particular, increased histone acetylation has been associated with the activation of pro-inflammatory pathways, facilitating sustained cytokine production and epidermal hyperplasia observed in psoriatic lesions [21, 22].

Non-coding RNAs further expand the epigenetic landscape of psoriasis by introducing an additional level of post-transcriptional and transcriptional regulation. MicroRNAs play a prominent role in controlling immune cell activation and keratinocyte proliferation, and their dysregulated expression has been closely linked to psoriasis pathogenesis [4, 23]. Through the modulation of target mRNAs, these microRNAs influence key inflammatory pathways and cellular behaviors, thereby contributing to disease persistence. Alongside microRNAs, long non-coding RNAs such as MALAT1 and HOTAIR have been implicated in psoriasis through their ability to modulate transcriptional networks and interact with microRNAs, ultimately affecting keratinocyte proliferation and immune responses [24].

The relevance of epigenetic mechanisms in psoriasis is further underscored by their interaction with environmental and lifestyle factors. External stimuli such as infections, psychological stress, smoking, and obesity have been shown to trigger or exacerbate psoriasis by inducing epigenetic changes that alter DNA methylation and histone modification patterns [4, 25]. These environmentally driven epigenetic alterations can amplify inflammatory signaling pathways and precipitate disease flares. Importantly, the intrinsic plasticity and reversibility of epigenetic modifications suggest that gene expression in psoriasis can be dynamically reshaped in response to environmental influences, providing a mechanistic explanation for the episodic and fluctuating nature of the disease [19, 23].

Immunological Susceptibility

Innate immune dysregulation constitutes a fundamental component of psoriasis pathogenesis, with dendritic cells occupying a central role in the initiation and perpetuation of cutaneous inflammation. Acting as professional antigen-presenting cells, dendritic cells orchestrate early immune activation through the production of key cytokines such as tumor necrosis factor alpha and interleukin 23, which are essential for the differentiation and maintenance of Th17 cells, a pivotal immune population in psoriasis [9, 26]. This process is further intensified by the activation of pattern recognition receptors expressed on dendritic cells, which detect damage-associated molecular patterns released by stressed or injured keratinocytes. The engagement of these receptors amplifies innate immune signaling and reinforces inflammatory cascades within psoriatic skin [27].

Within this innate immune environment, antimicrobial peptides emerge as potent immune activators rather than merely antimicrobial effectors. Molecules such as LL-37 are markedly overexpressed in psoriatic lesions and contribute directly to immune activation by forming complexes with self-DNA. These complexes are internalized and recognized by dendritic cells, triggering the production of type I interferons and a broad spectrum of pro-inflammatory cytokines that further enhance immune activation and sustain inflammation [3, 27].

The adaptive immune response builds upon this innate immune foundation and plays a decisive role in maintaining chronic inflammation. Central to this process is the IL-23/Th17 axis, with Th17 cells producing interleukin 17 and interleukin 22, cytokines that directly promote keratinocyte proliferation, inflammatory mediator release, and epidermal hyperplasia [3, 12]. In parallel, Th1 cells contribute to the inflammatory milieu through the secretion of interferon gamma, while Th22 cells further reinforce keratinocyte hyperproliferation via interleukin 22 production, collectively shaping the complex cytokine environment characteristic of psoriatic lesions [9, 28].

These immune cell populations are interconnected through an intricate cytokine network dominated by tumor necrosis factor alpha, interleukin 17, and interleukin 23, which sustains chronic inflammation and drives disease persistence. The centrality of this network is underscored by the clinical success of biologic therapies targeting these cytokines, which have significantly improved disease control by interrupting key inflammatory pathways and restoring immune balance in many patients [26, 29].

Genetic–immune crosstalk further refines immune responses in psoriasis by shaping immune cell behavior and cytokine production. Genetic predispositions, including variants in genes such as IL-36RN, influence immune signaling pathways and cytokine release, thereby contributing to disease susceptibility and severity [26, 28]. More broadly, susceptibility genes modulate the expression of cytokines, receptors, and signaling molecules, affecting immune cell activation, differentiation, and persistence within psoriatic skin [8].

Epigenetic mechanisms provide an additional regulatory layer that integrates genetic susceptibility with immune function. DNA methylation patterns and histone modifications regulate the transcription of genes involved in immune signaling pathways, influencing the magnitude and duration of inflammatory responses. These epigenetic alterations can modulate disease severity and progression by shaping immune cell behavior and cytokine expression profiles, further illustrating the dynamic interplay between genetics, epigenetic regulation, and immune dysregulation in psoriasis [8, 12].

Integration of Genetics and Epigenetics in Disease Expression

Genetic and epigenetic mechanisms jointly contribute to the development and clinical expression of psoriasis, forming a complex regulatory framework that shapes immune susceptibility. Genetic factors play a central role, as genome-wide association studies have consistently linked psoriasis to specific susceptibility genes, particularly those located within the major histocompatibility complex, underscoring the importance of antigen presentation and immune regulation in disease pathogenesis [2]. Complementing these inherited variants, epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNAs modulate gene expression without altering the underlying DNA sequence, thereby influencing both disease onset and progression [4]. These epigenetic alterations may be either heritable or acquired throughout life and are frequently shaped by external influences, including diet, microbiota composition, and therapeutic interventions, highlighting their dynamic and adaptable nature [30].

Environmental factors further interact with genetic and epigenetic susceptibility to trigger or exacerbate psoriasis. Stress, infections, and lifestyle-related exposures can act as precipitating factors by inducing epigenetic changes that amplify immune dysregulation and inflammatory signaling [4]. Seasonal variability represents another important modulator, as fluctuations in solar radiation and humidity have been shown to influence the genetic and epigenetic landscape of the skin, contributing to well-recognized seasonal patterns in disease activity [5]. At the molecular level, immune-related transcriptomic differences observed in psoriatic skin further emphasize the relevance of immune–environment interactions, with specific hub genes correlating with both disease severity and responsiveness to treatment [31].

This multilayered interaction between genetic, epigenetic, and immune factors contributes to the marked variability in disease severity and therapeutic response observed among patients with psoriasis. The expression profiles and circulating levels of immune-related molecules such as CCL20, interleukin 6, and CXCL8 have emerged as potential biomarkers capable of predicting disease activity and response to targeted therapies, particularly biologic agents directed against tumor necrosis factor alpha and interleukin 23 [31]. Consequently, integrating genetic, epigenetic, and immune data offers a promising approach for refining personalized management strategies, with the potential to optimize treatment selection and improve clinical outcomes in individuals affected by psoriasis [5, 31].

Clinical Implications

Risk stratification and early identification in psoriasis have increasingly focused on the use of genetic markers to predict disease behavior and therapeutic response. Single nucleotide polymorphisms have been associated with variability in treatment outcomes, and specific variants, such as those identified in IRAK3 and CD84, have shown potential as stratification biomarkers for biologic therapies. These findings suggest that genetic profiling may help identify patients more likely to benefit from particular therapeutic agents, although robust validation in larger and more diverse cohorts remains necessary before routine clinical implementation

[32]. Despite these advances, the overall predictive value of currently available genetic markers remains limited, as many associations have yet to be consistently replicated. Furthermore, the polygenic nature of psoriasis and the complex interplay between multiple genetic variants pose significant challenges to accurate risk stratification and early prediction of treatment response [33].

Genetic and epigenetic insights have also informed the development of targeted therapeutic strategies, shaping contemporary approaches to psoriasis management. Therapies directed against interleukins and intracellular signaling molecules, including interleukin 23 and tyrosine kinase 2 inhibitors, are grounded in genetic evidence highlighting the central role of these pathways in disease pathogenesis. In parallel, biologic agents targeting tumor necrosis factor, interleukin 12 and 23, and interleukin 17 pathways have revolutionized clinical outcomes for patients with moderate to severe psoriasis. The integration of genetic markers into therapeutic decision-making holds promise for guiding the selection of these biologic and small-molecule therapies, with the potential to enhance efficacy and minimize unnecessary treatment exposure [13, 32].

The pursuit of personalized medicine in psoriasis increasingly relies on pharmacogenomic approaches aimed at aligning therapeutic choices with individual genetic profiles. By tailoring treatments according to genetic variability, pharmacogenomics seeks to reduce treatment failures and adverse effects while optimizing clinical response. Variants in genes such as tumor necrosis factor alpha and MYD88 have been associated with differential responses to tumor necrosis factor inhibitors, supporting the feasibility of genotype-guided therapy in selected patient populations [33]. Looking forward, epigenetic biomarkers represent a promising extension of personalized medicine, as they may capture dynamic disease states and environmental influences not reflected by static genetic markers. However, the clinical utility of epigenetic biomarkers in psoriasis remains under active investigation, and further research is required to establish their reliability, reproducibility, and practical applicability in routine clinical care [34].

Conclusion

Psoriasis emerges as a prototypical immune-mediated inflammatory disease in which genetic susceptibility, epigenetic regulation, and immune dysregulation converge to drive disease initiation, persistence, and systemic involvement. The central role of the IL-23/Th17 axis, sustained by complex interactions between dendritic cells, T lymphocytes, keratinocytes, and innate immune mechanisms, explains both the chronicity of cutaneous inflammation and the frequent association with systemic comorbidities, reinforcing the concept of psoriasis as a systemic disorder rather than a skin-limited condition.

The substantial heritable component of psoriasis, characterized by major susceptibility loci such as PSORS1 and HLA-C*06:02 alongside numerous non-HLA variants, is further refined by epigenetic mechanisms that dynamically modulate gene expression in response to environmental and lifestyle factors. DNA methylation, histone modifications, and non-coding RNAs integrate genetic predisposition with external stimuli, providing a mechanistic explanation for disease heterogeneity, episodic flares, and variability in clinical phenotypes and severity.

The integration of genetic, epigenetic, and immunological insights has direct clinical relevance, offering a framework for improved risk stratification, biomarker development, and personalized therapeutic strategies. While current genetic and epigenetic markers remain insufficient for routine clinical prediction, their continued investigation, combined with immune and transcriptomic profiling, holds promise for optimizing treatment selection, enhancing therapeutic response, and advancing precision

medicine approaches in the management of psoriasis.

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