

# Association of NLRP1 and NLRP3 gene polymorphism with psoriasis

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## ABSTRACT

Psoriasis is a global health problem and one of the most frequent chronic, relapsing inflammatory skin diseases. With a prevalence of 1–3% worldwide, it is typically observed in patients 20–30 years old, with a second peak occurring at 55 to 60. Its pathogenesis is unclear but there is strong genetic influence associated. Several genes have been found to be linked with an altered immune system resulting in the development of psoriasis. This literature review is aimed at the current knowledge and the role of inflammasomes in psoriasis with regard to the NLRP1 and NLRP3 gene polymorphism associated with the pathogenesis of the disease.

**Key words:** NLRP1; NLRP3; psoriasis; gene polymorphism

## INTRODUCTION

With a prevalence of 1–3% worldwide, psoriasis is one of the most common, inflammatory cutaneous diseases in genetically predisposed individuals [1]. It is a noncontagious, relapsing condition usually affecting the elbows, knees, lumbosacral areas, intergluteal clefts, and glans penis. Triggered by various factors, such as infections and the environment, psoriasis also affects the joints in 10–30% of patients. The disease has a characteristic bi-modal peak and presents itself between the ages of 20 and 30 and between 55 and 60. Males and females are affected at equal rates with not much variation seen in the prevalence of psoriasis [2]. Although psoriasis affects all races, it has a higher prevalence in Caucasians (2.5%) than in African Americans (1.3%). Psoriasis is a debilitating condition affecting the quality of life even in its early stages and, if present along with other comorbidities, can lead to death [3]. Around 15–20% of patients suffer from moderate to severe cases of the disease and require intensive and vigorous treatment plans that negatively impact their lives. Psoriasis not only presents itself with skin and joint manifestations but is increasingly

seen in conjunction with other systems such as cardiovascular disease, chronic obstructive pulmonary disease (COPD), and even gastrointestinal disease. Additionally, due to the social stigma associated with the appearance of psoriatic patients, depression is frequently diagnosed together with unhealthy habits, such as excessive smoking and alcohol intake [4]. Due to these multiple comorbidities, there is a 50% increased risk of mortality among patients with severe cases of the disease as compared to patients with milder psoriasis [3].

Clinically, psoriasis vulgaris can easily be diagnosed by observing the skin lesions with the naked eye. The characteristic erythematous and scaly plaques found over the extensor surfaces on the arms and legs help in distinguishing psoriasis from other scaly, cutaneous diseases. Another important finding is the changes observed in nails usually accompanying skin lesions. The Auspitz's sign—a common indicator appearing as numerous fine bleeding points after the removal of psoriatic scales—can further aid in the differentiation of psoriasis from other scaly-plaque diseases. However, if clinical doubt arises, a biopsy specimen can be taken

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from the site of the lesion and a histological diagnosis can be made.

Prior to the commencement of treatment, it is essential to categorize patients according to the severity of their lesions as this helps provide them with appropriate treatment. To this end, several scoring systems have been employed based on factors such as the extent and location of lesions, the severity of inflammation, treatment responsiveness, and the impact on the quality of life. One example, and probably the gold standard in clinical trials, is the Psoriasis Area and Severity Index (PASI) score [5] invented by Fredriksson and Pettersson in 1978. According to the European S3 Guidelines on the systemic treatment of psoriasis vulgaris, a PASI score of more than 10 is interpreted as a moderate to severe case of psoriasis [6]. However, systemic treatment may also be provided in lower PASI scores if accompanied by visibly affected sites and severe symptoms such as itching. Other scoring systems include the body surface area (BSA) and the Physician Global Assessment (PGA).

With regards to treatment, patients with mild cases of psoriasis are usually administered topical measures. These have fewer side effects and are the most favorable. Depending on severity, patients can be given systemic treatment with steroids and/or biologics along with phototherapy. Topical corticosteroids, with their anti-inflammatory properties and suppression of the immune system, are commonly prescribed and highly favored for use in mild to moderate psoriasis [7]. These are usually prescribed for short-term treatment to control flares. Other topical medications include vitamin A derivatives, such as retinoids, that help control the inflammation. Oral preparations are also available; however, they are accompanied by side effects such as hair loss and birth defects. Vitamin D analogues and calcineurin inhibitors are also commonly prescribed. Moisturizers and creams may help alleviate the symptoms of itching and dryness.

Light therapy or phototherapy can be used alone or in combination with other medications. This involves use of artificial ultraviolet A (UVA) or ultraviolet B (UVB) light. In spite of the potential side effects, such as premature skin aging and the development of skin cancer, phototherapy is still considered one of the safest therapeutic measures for moderate to severe cases of psoriasis. If the skin lesions are of increased severity or even if mild but resistant and with symptoms that do not lessen with topical treatment and phototherapy,

systemic drugs—oral or injected—can be considered; these include methotrexate, retinoids, cyclosporine, apremilast, and biologic agents. Due to their strong side effects of renal damage, hepatotoxicity, marrow suppression, and birth defects, caution needs to be exercised in the administration of these drugs and the patient's blood parameters need to be monitored regularly.

## Pathogenesis

The etiopathogenesis of psoriasis has been studied for decades. From altered cell cycles and dysfunctional keratinocytes to T-cell involvement, much progress has been made to identify the components responsible for this inflammatory, cutaneous condition. An imbalance has been found between innate and adaptive immunity with subsequent infiltration of leukocytes into psoriatic skin lesions. T cells, constantly stimulated by keratinocytes, and members of the innate immune system play a major role in inflammation accompanying psoriasis [8]. Antigen-presenting cells such as dendritic cells (myeloid and plasmacytoid DCs), Langerhans' cells, neutrophils, macrophages, and cytokines produced by Th1-type cells all contribute to the pathogenesis of psoriasis. The role of IL-23/Th-17 cell lineage likewise proves to have prime importance. Other factors, such as vascular endothelial growth factor (VEGF) and keratinocyte growth factor (KGF), contribute to the angiogenesis and dyskeratosis commonly seen in psoriasis.

Besides the immune system, genetic, epigenetic, and environmental factors, such as infection, trauma, obesity, and vitamin D<sub>3</sub> deficiency have also been found to contribute to the presentation of the disease, although the exact mechanism is still not fully understood [9,10].

## Genetics in psoriasis

Psoriasis can be linked to multiple genes associated with linkage disequilibrium in genetically susceptible individuals. Over the past four decades, with the help of genome-wide association studies (GWASs) with large cohorts, much light has been shed on the role of genetics in the pathogenesis of psoriasis. Besides GWA studies, population-based epidemiological studies, association studies with human leukocyte antigens (HLAs), genome-wide linkage scans, and candidate-gene studies within and outside the major histocompatibility complex (MHC) region have also generated much information to establish

a definitive genetic background of psoriasis [11]. Psoriasis is associated with familial recurrence, and disease concordance is higher in monozygotic than in dizygotic twins [12]. Through genetic studies, more than 60 psoriasis susceptibility loci have been discovered, with PSORS1—located in the major histocompatibility complex (MHC, chromosome 6p21.3)—being the major susceptibility locus for psoriasis vulgaris (PV) [13]. The nine different regions of Psoriasis Susceptibility (PSORS) 1–9 are linked with disease susceptibility [14]. Several HLA alleles have been linked with psoriasis, particularly, HLA-B13, HLA-B37, HLA-B46, HLA-B57, HLA-Cw1, HLA-Cw6, HLA-DR7, and HLA-DQ9 [10]. Many of these alleles are in linkage disequilibrium with HLA-Cw6, which has demonstrated the highest relative risk of psoriasis in Caucasian populations [11]. Besides the MHC, other genes have been studied to determine their role; these include ERAP1, IL12Bp40, IL23Ap19, IL4, IL13, and TNFAIP3 [15]. The genes that have been studied so far and whose role is well established in the pathogenesis of psoriasis may be grouped and related to different immune pathways. These include antigen presentation (HLA-C and ERAP1), innate antiviral signaling (IFIH1, DDX58, TYK2, RNF114), innate immunity (NF- $\kappa$ B), and, being of particular importance, Th17 cell activation [13,16].

### Environmental factors

Psoriasis may be triggered by exogenous or endogenous environmental stimuli. These include group A streptococcal pharyngitis, viremia, allergic drug reactions, withdrawal of systemic corticosteroids, local trauma (Köbner phenomenon), and emotional stress [16]. A correlation has been found between streptococcal throat infections and guttate psoriasis, the former preceding any outbreak of the disease [9,17]. In one study [18], 17% of psoriatic patients with newly-developed or aggravated symptoms were associated with staphylococcal super-antigens. Drugs can also trigger the presentation of psoriatic symptoms; those most commonly triggering include lithium, beta-blockers, antimalarials, non-steroidal anti-inflammatory drugs, and tetracyclines [16].

### Immunological interactions

In the last 30 years, several important subsets of immune cells have been identified and proven to play a role in the pathogenesis not only of psoriasis but of other autoimmune diseases as well. An imbalance

in the regulation of innate immunocytes mediated by antigen-presenting cells (including natural killer T lymphocytes, Langerhans' cells, and neutrophils) and acquired or adaptive immunocytes mediated by mature CD4+ and CD8+ T lymphocytes in the skin are mainly responsible for the characteristic clinical plaques and histological patterns seen in psoriasis [11]. These include Th1, Th2, T-reg, and Th17 cells and their corresponding cytokines, such as IFN- $\gamma$ , TNF- $\alpha$ , IL-23, and IL-17 [9]. The early phase of psoriatic plaques may be linked to autoinflammation due to its association with neutrophils and cytokines related to the interleukin-1 (IL-1) family, such as IL-1 $\alpha$ , IL-1 $\beta$ , and IL-36 [19]. Hence, similarities between psoriasis and other classic autoinflammatory diseases such as pyogenic arthritis, acne, and pyoderma gangrenosum (PAPA) syndrome may be inferred because of the same involvement of cytokines and their pathogenesis resulting from mutations in similar genes that are involved in innate immunity [20,21]. The roles of different cell lineages in both innate and adaptive immunity with respect to psoriasis are described below.

#### a) Th1 and Th2 cells

Initially, psoriatic plaques are associated with Th1 cells and increased levels of Th1 cytokines such as c-interferon (IFN-c), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukin (IL)-12 [22]. Under such influence, dysregulated keratinocytes release a rich source of AMP and IL-1 family cytokines, including IL-1 $\beta$  and IL-18, which are further involved in the differentiation of Th1 and Th17 cells, respectively [23]. This may suggest a role of Th17 cells along with Th1 in the pathogenesis of psoriasis. IL-1 $\beta$  plays an important role in upregulating IL6, IL-8, TNF- $\alpha$ , and hBD2 expression, differentiation of Th17 and Th22 cells, and stimulation of IL-17 and IL-22 secretion [24].

#### b) Th17 cells

Th17 cells are crucial in the secretion of IL-17, IL-12, IL-22, and IL-9, all of which directly or indirectly promote the inflammatory response of keratinocytes. High levels of IL-17 mRNA have been recorded in psoriatic skin lesions, but not in non-lesional skin, indicating its possible role in the pathogenesis of the disease [16]. IL-17 also leads to an increased release of IL-6 and IL-8 in keratinocytes leading to an inflammatory condition and exaggeration of psoriatic lesions [25]. Dysregulated IL-17 signaling and Th17 cell pathway function, thus, promote the chronic inflammation in psoriasis.

### c) IL-23

The role of IL-23 in the pathogenesis of psoriasis has been studied in both humans and mice. In humans, exaggerated levels of IL-23p19 and IL-12p40 (IL-12/23p40) were observed in psoriatic skin lesions, and most of the IL-23p19 was released by mature DCs, monocytes, and monocyte-derived DCs in the papillary dermis [26]. IL-23 is also essential for the development and maintenance of Th17 immune cells.

Several innate immune cells have also been linked with the pathogenesis of psoriasis. Neutrophils, found in the early phase of psoriasis, are present in the stratum corneum of psoriatic skin. Both plasmacytoid DCs and myeloid DCs are accumulated in psoriatic skin lesions and, by producing IFN- $\alpha$  and TNF- $\alpha$ , respectively, play important roles in the development of lesions [10]. Innate immunity is associated with the production of proinflammatory or primary cytokines. The most important of them are IL-1 $\alpha$  and TNF- $\alpha$ .

### d) TNF

Tumor necrosis factor plays a vital role in the pathogenesis of psoriasis. Besides activation of the nuclear-factor (NF- $\kappa$ B) signal pathway, which affects cell survival, proliferation, and the anti-apoptotic effects of lymphocytes and keratinocytes, it also causes Th17 to produce proinflammatory cytokines through the NF- $\kappa$ B pathway [27,28].

### e) Interleukin 1

Due to their role and function in innate immunity, members of the IL-1 family constitute an integral part of the development of several inflammatory diseases. The IL-1 family is comprised of three subfamilies, including IL-1, IL-36, and IL-18 [29]. IL-1 is an essential pro-inflammatory cytokine and is strongly expressed by monocytes, tissue macrophages, and dendritic cells, and also produced by B lymphocytes, NK cells, and epithelial cells [30]. It helps regulate T helper cell polarization and the release of various pro-inflammatory cytokines that engage in apoptosis/pyroptosis, resulting in tissue damage. IL-1 $\alpha$  (IL-1F1) and IL-1 $\beta$  (IL-1F2) are the two members of the IL-1 family that were discovered first. The secretion of IL-1 $\beta$  is mediated by various stimuli, such as microbial pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns or endogenous signals, e.g., ATP and uric acid crystals. These stimuli result in the activation of specific inflammasomes such as NLRP3 inflammasomes, which further activate Caspase-1, which, in turn, cleaves pro-IL-1 $\beta$  to produce mature IL-1 $\beta$  [31].

## ROLE OF IL-1 IN PSORIASIS

Clinical findings show that the IL-17/IL-1 axis plays an important role in the pathogenesis of psoriasis [30,32]. IL-1 cytokines have been reported to be highly expressed in psoriatic skin lesions, leading to Th17 cell development and a subsequent release of IL-17 [33-35]. IL-1 $\beta$ , together with IL-23 and IL-6, plays a major role in the differentiation of human naïve T cells into IL-17 producing cells [31]. IL-17 further continues the cascade by causing keratinocyte activation and a further release of IL-1-family members. This enhances inflammation and exaggerated immune response, which may lead to psoriatic skin lesions. After the treatment of skin lesions in psoriasis patients, the levels of IL-1 $\beta$  substantially decrease. This may also suggest the role of the IL-1 family in the inflammatory changes exhibited by psoriatic patients [36,37].

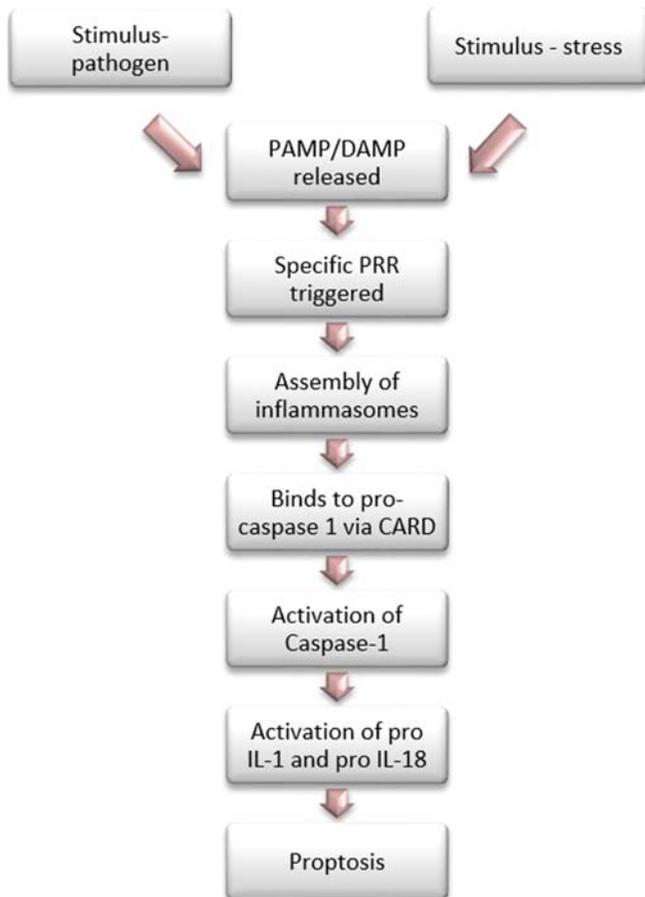
## NLRP GENE

The NLRP gene is linked with the production of the members of the nucleotide-binding domain and leucine-rich repeat containing (NLR) family of proteins. These NLR proteins are important mediators of the immune system and are mainly found in white blood cells and in cartilage-forming cells. These proteins become activated after being exposed to injury, toxins, or foreign particles, and help in the formation of multimeric protein complexes called inflammasomes that take part in and regulate inflammatory processes [38].

The two most extensively studied NLRP genes are the NLRP1 NLRP3 genes. The NLRP1 gene is located at position 13.2 of the short (p) arm of chromosome 17 (17p13.2) while the NLRP3 gene is located at position 44 of the long (q) arm of chromosome 1 (1q44). The latter specifically provides instructions for making a protein called cryopyrin, one of the members of the NLR protein family that is necessary for the formation of inflammasomes.

### *What is an inflammasome?*

Inflammasomes, first described in 2002, are cytosolic multimeric protein complexes that form an integral part of the innate immune system and are responsible for the activation of inflammatory responses via IL-1 $\beta$  and IL-18 [39]. Excessive inflammasome activation can result in an immunological imbalance, thus causing various autoimmune and metabolic disorders. Hence, it is important to understand the various physiological and pathological mechanisms of inflammasomes [40].



**Figure 1:** Mechanism of action of an inflammasome in response to both pathogenic and external stimuli.

### Structure and components

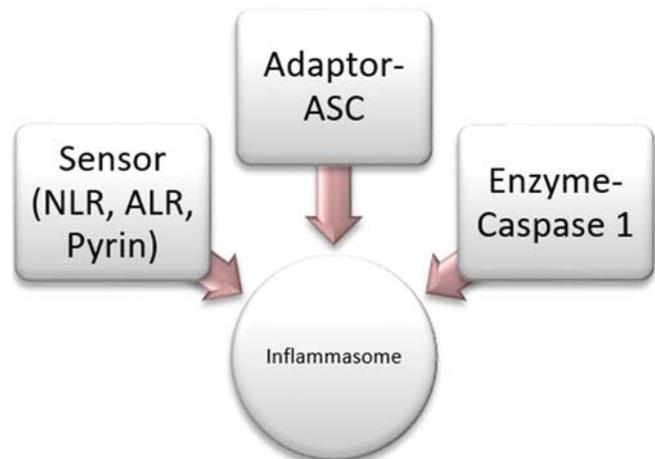
An inflammasome (Fig. 1) consists of an inflammasome sensor molecule—which is a pattern recognition receptor (PRR)—an adaptor protein ASC, and caspase-1 [41]. There are three types of inflammasome sensors:

- nucleotide-binding domain–like receptors (NLRs),
- absent in melanoma 2–like receptors (ALR-AIM2), and
- pyrin.

Besides a PRR (NLR, ALR, or pyrin) and an enzymatic component (caspase-1), most inflammasomes also use an adaptor molecule known as ASC (apoptosis-associated speck-like protein containing a caspase activation and recruitment domain) [40]. ASC consists of two death-fold domains, one pyrin domain, and one caspase activation and recruitment domain (CARD) [41]. With the help of a CARD, ASC is responsible for the aggregation of monomers of procaspase-1.

### Mechanism of action

Depending on the stimuli, inflammasomes detect either PAMPs or DAMPs in the cytosol (Fig. 2). This



**Figure 2:** The components of an inflammasome.

triggers the respective inflammasome sensors and leads to the assembly of the PRRs. Proteolytic cleavage of dormant procaspase-1 into active caspase-1 takes place, which results in the conversion of cytokine precursors pro-IL-1 $\beta$  and pro-IL-18 into mature and biologically active IL-1 $\beta$  and IL-18, respectively [42]. Pyroptosis, a form of programmed pro-inflammatory cell death distinct from apoptosis, also manifests itself in inflammasome activation [43].

### What are the different types of inflammasomes?

Inflammasomes are identified by the PRR linked and, to date, 6 types are known to form these immune protein complexes: NLRP1, NLRP3, NLRC4, NLRP12, pyrin, and AIM2 [44]. Other members of the NLR and PYHIN family include NLRP6, NLRP7, and IFI16 [45]. Several studies have focused on NLRP1 and NLRP3 as mediators of inflammation, which are under investigation for their possible role in autoimmune and auto-inflammatory diseases [46-48].

### Diseases caused by NLRP1 mutations

An NLRP1 inflammasome is triggered by muramyl dipeptide (MDP) and anthrax lethal toxin (mouse NLRP1b) [49]. Several NLRP1 gene polymorphisms have been associated with an increased risk of autoimmune disorders and vitiligo.

A study [50] carried out in Jordanian Arab patients revealed two SNPs in the NLRP1 gene to be especially correlated with generalized vitiligo and, marginally, several other SNPs in the NLRP1 region. Another study [51], using association analysis, identified DNA sequence variants in the NLRP1 region to be associated with a risk of vitiligo and several autoimmune and autoinflammatory diseases. Sequence variants in the NLRP1 gene were

found to be in association with Addison's autoimmune disease, type-1 diabetes, rheumatoid arthritis, and systemic lupus erythematosus [52]. Another study [53], conducted to find an association between polymorphisms in the NLRP1 gene and autoimmune thyroid disease, produced promising results. A study [54] in southern Brazil also showed an association between NLRP1-gene polymorphisms and systemic lupus erythematosus, while the same study failed to find any association between NLRP3 and SLE. Single-nucleotide polymorphisms (SNPs) in the NLRP1 and NLRP3 genes are also associated with inflammatory bowel diseases, rheumatoid arthritis, and juvenile idiopathic arthritis [55-58].

#### *Diseases caused by NLRP3 mutations*

Several infectious and endogenous ligands have been known to trigger NLRP3 and this is thought to be involved in the pathogenesis of several autoinflammatory diseases, including arthritis, gout, diabetes, obesity, and Alzheimer's disease [46,48,59]. The triggers include pathogen-derived ligands such as microbial cell wall components, nucleic acids, and pore-forming toxins; environmental crystalline pollutants such as silica, asbestos, and alum; and endogenous danger signals such as ATP, serum amyloid A, and uric acid crystals [40]. Because of the diversity in its activators, NLRP3 is very much distinct from the other inflammasomes and makes the possibility of direct interaction with each activator unlikely. NLRP3 inflammasomes, hence, may either interact with another common activator downstream of these triggers or respond to cellular stress stemming from infection or tissue damage [40].

NLRP3 inflammasomes have been associated with hereditary autoinflammatory syndromes—Cryopyrin-Associated Periodic Syndromes (CAPS)—which include:

- a) familial cold autoinflammatory syndrome (FCAS),
- b) Muckle–Wells syndrome (MWS), and
- c) neonatal-onset multisystem inflammatory disease (NOMID).

In order of increasing severity, FCAS, MWS, and NOMID/CINCA represent the mildest, intermediate, and most severe diseases, respectively [60]. Together, they constitute a spectrum of diseases characterized by skin rashes and episodes of fever. Other clinical features include joint and ocular symptoms, amyloidosis, and, in the case of NOMID/CINCA, severe neurological complications [61].

Abnormal NLRP inflammasome activity has also been observed in diseases such as gout, pseudo-

gout, silicosis, and asbestosis. Genetic mutation may not be the cause for these diseases as much as chronic exposure to inflammasome triggers such as MSU (causing gout), calcium pyrophosphate dihydrate (CPPD; responsible for pseudo-gout), and inflammation-inducing dust [62]. In one study [63] conducted in a pediatric population in northeastern Brazil, two SNPs in the NLRP3 gene were found to have a predilection for type-1 diabetes and celiac disease. Another study [64] indicated that NLRP3 rs10754558 C/G polymorphism was associated with susceptibility to SLE and with autoimmune and inflammatory diseases in Latin Americans.

#### *Role in psoriasis*

The relationship of the NLRP3 inflammasome with psoriasis has been investigated for its association with pro-inflammatory cytokines IL-1 $\beta$  and IL-18, which play a key role in many inflammatory diseases, including psoriasis [65]. In skin lesions of psoriasis patients, IL-1 $\beta$  has been shown to be substantially increased, and effective treatment of psoriasis to lead to a significant decrease in epidermal IL-1 $\beta$  expression, suggesting that the IL-1 subfamily plays a role in the pathogenesis of psoriasis [40]. In psoriatic skin lesions, caspase-1 and caspase-5 have been found to be elevated, leading to IL-1 $\beta$  production aided by NLRP1 and NLRP3 inflammasomes, with or without ASC, and these further prove the role of inflammasomes in psoriasis [66].

Several gene polymorphisms that have been linked with psoriasis include IL23A, IL23R, STAT3, RUNX3, and TYK2. All these genes are associated with the Th17 immune response, thus establishing the importance and role of Th17 immune response in the pathogenesis of psoriasis [67]. Moreover, a link is observed between the Th17 and IL-1 $\beta$  pathways. IL-1 $\beta$  is important for the IL-23-dependent development of Th17 cells and stimulates cytokine maturation and production in these cells [68].

In a mouse model of imiquimod-induced psoriasis, there was increased expression of the transcriptional factors pNF-kB and pSTAT-3 and the proinflammatory cytokines IL-6, IL-1 $\beta$ , and TNF- $\alpha$  I in the skin lesions. Treatment with an inflammasome blocker caused reduced expression of pNF-kB, pSTAT-3, IL-6, and TNF- $\alpha$  [69]. These results demonstrate that NLRP3 inflammasomes play an important role in psoriatic inflammation and that their blockade might present

a promising, novel therapeutic approach to improving psoriatic lesions.

Polymorphisms of NLRP1, NLRP3, and CARD8 were associated with susceptibility to psoriasis [68,70]. In one study conducted in Sweden [70] on 741 psoriatic patients, inflammasomes and their components were reported to play a role in the defective innate immune response and chronic inflammation of psoriasis. The NLRP3 rs10733113G genotype showed a significant *p* value of 0.015. Another study [71], conducted on a Chinese Han population of 540 patients, showed its significant association with genetic polymorphisms in the NLRP3 gene. Two SNPs, rs3806265 (*p* = 0.0451; OR = 0.791; 95% CI = 0.627–0.998) and rs10754557 (*p* = 0.0344; OR = 1.277; 95% CI = 0.987–1.652), exhibited strong association with psoriasis vulgaris.

However, a study [72] conducted in Denmark on 480 patients assessed 53 SNPs in 37 candidate genes and showed no significant association of psoriasis, cutaneous psoriasis, or psoriatic arthritis with NLRP1 or NLRP3 gene polymorphisms.

## CONCLUSION

The pathogenesis of psoriasis is complex and can be ascribed to factors such as genetics, immunology, and environmental triggers. An imbalance between innate and adaptive immunity may be responsible for the cascade of inflammatory events observed in psoriasis. As per the available literature, the importance of inflammasomes as part of innate immunity in the pathogenesis of psoriasis, while controversial, cannot be denied. The NLRP genes that regulate inflammasomes may, in fact, have a bigger role than what is known today, and this can help in the future development of various novel therapeutic measures to control psoriatic flares. With further large-scale studies and research, more light can be shed on the perplexing pathogenesis of psoriasis and the possible role that inflammasomes play in it.

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