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REVIEW ARTICLE

Etiopathogenesis of Psoriasis from Genetic Perspective: An updated Review

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Abstract: Psoriasis is an organ-specific autoimmune disease characterized by the aberrant proliferation and differentiation of keratinocytes, leading to skin lesions. Abnormal immune responses mediated by T cells and dendritic cells and increased production of inflammatory cytokines have been suggested as underlying mechanisms in the pathogenesis of psoriasis. Emerging evidence suggests that there is a heritable basis for psoriatic disorders. Moreover, numerous gene variations have been associated with the disease risk, particularly those in innate and adaptive immune responses and antigen presentation pathways. Herein, this article discusses the genetic implications of psoriatic diseases' etiopathogenesis to develop novel investigative and management options.

Keywords: Genetics, immune response, autoimmunity, psoriasis, etiopathogenesis, keratinocytes.

1. INTRODUCTION

Psoriasis is a chronic, autoinflammatory disease of the skin with various morphology, severity, and disease course. According to epidemiological reports, the prevalence of psoriasis ranges from 1 to 12% among various populations [1]. Psoriasis was once regarded to be a disorder due to uncontrolled proliferation and impaired differentiation of keratinocytes. Nonetheless, it is currently believed that psoriasis is a skin-specific T-cell mediated autoimmune condition with hyperkeratosis and parakeratosis, leading to various disease manifestations [2, 3]. Moreover, induction and migration of autoreactive CD4+ and CD8+ T cells into the skin might lead to the recruitment of other inflammatory cells and the development of psoriatic-plaques [2, 4]. However, there is a growing consensus on the critical role of keratinocytes in the psoriasis pathogenesis through both initiation and perpetuation of the disease. In fact, the function of keratinocytes that finally influence the disease is contingent upon different factors, such as genetics, cell signaling, cell metabolism, antimicrobial peptides, cytokines and related receptors, non-coding RNAs, transcription factors, environmental stimuli, and epigenome [5].

Numerous investigations have suggested a strong familial component in the etiology and pathogenesis of psoriatic disease. Epidemiologic studies report that the two major types of psoriatic diseases, namely psoriatic arthritis (PsA) and psoriasis vulgaris (PsV), have a heritable basis [6]. On the other hand, shared genetic implications of psoriasis have been associated with a number of comorbidities [7]. Even though many genes have been identified to be associated with psoriasis risk, a complete comprehension of disease etiology with respect to genetic viewpoint remains inconclusive. Therefore, the purpose of the current study was to clarify the genes associated with psoriasis' etiopathogenesis.

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2. GENETIC EPIDEMIOLOGY OF PSORIASIS

Based on familial and epidemiologic twin studies, psoriasis has been regarded as a complex multigenic disorder. A cohort study that included 69,828 patients diagnosed with psoriasis enrolled in national health insurance evaluated the relative risks of psoriasis in individuals with affected relatives. That study revealed that the adjusted relative risks for individuals with an affected first-degree relative and an affected second-degree relative were 5.50 and 2.54, respectively. Consequently, a family history of psoriasis can be considered a risk factor for psoriasis [8]. In comparison to dizygotic (DZ) twins, the concordance rate of psoriasis in monozygotic (MZ) twins has commonly been established to be three times more frequent [9]. The concordance rate of psoriasis in monozygotic twins has been reported to be 90% [10]. Moreover, concordant MZ twin pairs share many similarities with regard to the age of onset, disease severity and course, and manifestation pattern compared with DZ twins [11]. A survey of 10,725 twin pairs in the Danish Twin Registry demonstrated that the concordance rate for MZ and DZ twins was 33 % *vs*. 17 %, respectively. Moreover, genetic factors were established to be accounting for only 54% of the disease risk, and environmental factors were responsible for 34% of psoriasis predisposition risk [12]. Overall, it was predicted that the heritability of psoriasis was 68 % [13]. Considering these observations, MZ twins revealed about 8-times higher psoriasis risk relative to the general population, while these DZ twins demonstrated an about 4-fold increased risk of the disease. That notwithstanding, the inheritance pattern of psoriasis remains inconclusive.

3. FINDINGS OF GENOME-WIDE INVESTIGATIONS

To date, nine genome-wide linkage studies have been accomplished in PsV and discerned ten loci, from *PSORS1* to *PSORS10*, and the *PSORS1* gene at chromosome 6p21.3. These loci demonstrated the most robust and most consistent association [14]. On the other hand, only one genome-wide linkage study has been performed in PsA and demonstrated significant linkage of variants found on chromosome 16q [15].

In the meantime, genome-wide association studies (GWAS) have shown the implications of multiple genes in psoriasis [16-18]. The candidate genes with genome-wide significance belong to the functional pathways of skin barrier genes, innate immunity-related genes with the particular importance of nuclear factor-kappa B (NF-kB) and interferon (IFN) signaling, and adaptive immunity-related genes with involvement of CD8+ T and CD4+ T lymphocytes (T helper or Th), especially Th17 signaling. Furthermore, several genes have been found in the major histocompatibility complex (MHC) region on chromosome 6.

4. PSORIASIS AND MHC GENES

Genetic loci in the MHC region, located on the short arm of chromosome 6, have repetitively been the most relevant genetic susceptibility region in psoriatic disease. Epidemiological estimations established that the MHC region is responsible for one-third of the overall genetic contribution of psoriasis. The significant genetic association of psoriasis, namely *PSORS1*, was first found in the MHC I region, in which human leukocyte antigen (HLA)-Cw6 was considered the *PSORS1* risk variant [19]. Later, with the advent of new techniques in molecular studies, the association between *HLA-Cw0602* and PsA [20, 21], *HLA-C*0602* allele with guttate psoriasis, type 1 psoriasis, koebner phenomenon, and psoriasis improvement during pregnancy were recognized [22]. The *HLA-C*0602* allele has been associated with the late onset of arthritis in PsA patients. Moreover, this variant has negatively been associated with psoriatic nail disease [23]. Recent GWAS of the Japanese population revealed the PsV risk of *HLA-C*0602*. However, its impact was relatively small (0.4%) in comparison to other populations because of rare allele frequency in Japanese controls. A recent study indicated that the treatment response was lower in the HLA-Cw6 positive psoriasis patients [24]. Fine-mapping of HLA variants in association with PsV demonstrated that *HLA-A*0207*, which corresponds to the cysteine residue at HLA-A amino acid position 99 (HLA-A Cys99), had the most significant association with PsV risk in the Japanese population. In addition, the stepwise conditional analysis resulted in the identification of an independent PsV risk of HLA-DQβ1 Asp57 [25].

Reports show that PsA has specifically been associated with the *HLA-B*27* allele, despite the greater importance of this allele in ankylosing spondylitis (AS) [26]. PsA patients show a 20% frequency of *HLA-B*27*, while the prevalence of *HLA-B*27* is 70% to 90% in AS. The *HLA-B*27* allele has also been associated with subphenotypes of psoriasis, such as axial involvement, articular damage, and dactylitis [27]. As a result, HLA-B*27 positive psoriatic patients might develop more severe manifestations of the disease. On the other side, *HLA-B* 38*, *HLA-B*08*, and *HLA-B*39* are the most continuously reported *HLA-B* alleles specific to PsA [26, 28]. An extensive fine-mapping survey of psoriatic disease was done with respect to the MHC region, employing 9247 affected patients comprising 3038 PsA cases, 3098 cutaneous psoriasis cases, and 3111 cases with undefined classification and 13,589 control subjects with European ethnicity. This investigation identified that the *HLA-B*27* allele was remarkable in distinguishing between psoriasis arthritis and cutaneous psoriasis [29]. Moreover, a refined analysis disclosed that the HLA-B antigen with glutamine in position 45 emerged as the strongest PsA risk. This polymorphic site is found within the binding groove of the HLA-B molecule on the cell surface and can modulate the binding circumstance of a peptide to the HLA-B. It is noteworthy that all PsA associated alleles, including *HLA-B*27*, *HLA-B*38*, and *HLA-B*39,* encode proteins that contain glutamine at position 45 [29].

5. PSORIASIS AND NON-MHC GENES

Other than MHC loci, numerous gene association studies have been conducted with findings of non-MHC gene's involvement in PsA. *MICA* locus is regarded as the most crucial non-HLA gene located within the MHC region and is found in the proximity of the HLA-B locus. In a Spanish cohort, the *MICA*002* trinucleotide repeat polymorphism was associated with PsA independent of *MICB*, *TNF*, or *HLA-Cw6* [30]. Nonetheless, the large fine-mapping study described earlier did not show any association of *MIC* alleles with PsA susceptibility [29].

The killer-cell immunoglobulin-like receptors (KIR), which are found on natural killer (NK) cells, are not encoded by the MHC region but have interactions with HLA class I molecules [31]. A highly polygenic and polymorphic region on chromosome 19q13 encodes KIR that has been associated with the risk of several autoimmune disorders [32-35]. Studies showed that KIR2DS2 was more prevalent in PsA patients in comparison to healthy controls. Moreover, when KIR2DS2 was coupled with HLA-C ligands, it increased the PsA risk more than before. Additionally, the KIR2DS2 allele increased the PsA risk compared to PsV patients [36].

5.1. Association of Psoriasis with Skin-related Gene

There is a hyperplasia of skin keratinocytes in psoriasis that may be due to the function of cytokines released by immune cells. Epidermal keratinocytes have also been implicated to have a role in the initiation of psoriasis. GWAS, copy number variation (CNV), and functional studies have revealed significant associations of psoriatic diseases with genes coding defensin, *late cornified envelope* (*LCE*) genes, and connexin. β-Defensins function by providing a chemical barrier through small antimicrobial peptides that exert a broad spectrum of antimicrobial activities in epithelium lyre [37]. Studies show that the *DEFB4* gene CNV increased the relative risk of psoriasis [38]. The hBD-2 protein, encoded by the DEFB4 gene, is stimulated in the skin of psoriatic patients during the inflammatory response and psoriatic keratinocytes are then modulated to produce and secrete large amounts of β-defensins in response to Th1 or Th17-related mediators [39]. *LCE* gene encodes cornified envelope proteins required for epidermal cell differentiation. A CNV evaluation genome-wide study discerned a significant association of *PSORS4* locus, carrying *LCE3B* and *LCE3C* genes, with increased PsV proneness in several populations [40]. Furthermore, GWAS, followed by targeted candidate gene studies, validated the associations of LCE3 genes with psoriasis risk in several study populations [41, 42]. Additionally, epistasis has also been identified between *HLA-Cw6* and *LCE3C_LCE3B-del* genes [43].

Connexin expression is commonly observed in the periphery of keratinocytes within psoriatic plaques, but normal healthy skin does not express it [44]. Connexin mediated adenosine triphosphate released by keratinocytes causes epidermal proliferation and differentiation, specifically observed in psoriasis [45]. GJB2 gene encodes the connexin 26 protein, and a GWAS identified a variant in this gene as a PsV risk locus [46].

5.2. Psoriasis Association with Innate Immunity-related Genes

The components of the innate immune response include physical epithelial barriers and their antimicrobial agents, phagocytes like macrophages and neutrophils, dendritic cells [DCs], NK cells, and plasma proteins like complement components. NF-κB is considered the critical intracellular signaling molecule of the innate response that acts as a transcription factor in several immune cells. NF-κB mediates the transcription of numerous genes, which underlie the manifestations and pathogenesis of several inflammatory disorders like PsV and PsA. Genome-wide significant genes in psoriasis that produce proteins by interaction with NF-κB and affect the signaling process within the immune cell are *TNIP1*, *TNFAIP3*, *NFKBIA*, *REL*, *NOS2*, *FBXL19*, *CARD14*, *CARM1*, *UBE2L3*, and *TYK2* (Table **1**) [16-18, 46-52]. Several GWAS studies have implicated the involvement of *TNIP1* in the susceptibility to autoimmune diseases like PsV and rheumatoid arthritis (RA) [53]. The protein encoded by *TNF-a–inducible protein 3* (*TNFAIP3*) gene is vital in the inhibition of NF-κB signaling. *TNFAIP3* gene polymorphisms have been associated with predisposition to several autoimmune disorders such as psoriasis, systemic lupus erythematosus (SLE), systemic sclerosis [SSc], celiac disease, and RA [14]. A large meta-analysis evaluating the polymorphisms of the *TNFAIP3* gene disclosed several SNPs associations with psoriasis, particularly the rs582757. Further analyses indicated *TNFAIP3* psoriasis risk haplotypes, proposing complex genetic interactions of this region [54]. GWAS of the Japanese population also indicated an association of TNFAIP3-interacting protein 1 (TNIP1) with PsV risk [25].

CARD11 gene rs4722404 SNP was revealed to elevate the risk of early-onset PsV [55]. Furthermore, the *CARD14* gene rs11652075 polymorphism was associated with clinical manifestations of PsV patients [56]. However, evaluation of seven tag SNPs in the CARMA3/CARD10 gene in 355 patients with PsV and 213 control subjects disclosed no significant association of these SNPs with the disease risk [57].

On the other hand, several genes reached genome-wide significance in psoriasis and encoded proteins that interplay with the IFN signaling pathway. These genes are *IFIH1*, *IFNLR1/IL-28RA*, *ELMO1*, *SOCS1*, *DDX58*, *RNF114*, and *TYK2* (Table **1**) [16-18, 46-52].

IFIH1 is involved in inhibiting a transduction cascade that stimulates the production of several cytokines, including interferons. An initial cohort of 1980 PsA cases and 5913 controls identified a rare coding allele in *IFIH1* gene rs35667974 SNP to protect PsA [58]. *ELMO1* encodes a protein, which is involved in Toll-like receptor (TLR)-mediated IFN-α stimulation by plasmacytoid dendritic cells (pDCs) [59]. *IL-28 receptor, alpha subunit* [*IL-28RA*] gene participates in IFN type III signaling pathway [60]. *Suppressor of cytokine signaling 1* (*SOCS1*) is a member of the suppressor of cytokine signaling family proteins that are involved in the repression of downstream signaling of INF-γ. SOCS1 also interacts with TYK2 during cytokine signaling [61]. IFN-γ induces the *DDX58* gene, encoding the RIG-I receptor, and modulates the production of IFN-α and INF-γ [62]. A ubiquitin-binding protein is encoded by the *RNF114* gene that promotes the production of IFN-α *via* perturbating the RIG-I/MDA5 signaling pathway [63]. TNIP1, REL, TYK2, and FBXL19 have reached genome-wide significance in PsA [14]. Given the findings of these investigations, an indispensable role of NF-κB and IFN signaling in the etiopathogenesis of psoriasis is suggested.

5.3. Psoriasis Association with Adaptive Immunity-related Genes

It has conventionally been a consensus that psoriasis was an autoimmune condition with the involvement of autoreactive

Table 1. List of the genes associated with the psoriasis susceptibility.

Biological Pathway/ Gene	Chromosome	Biological Pathway/ Gene	Chromosome
Skin Barrier Function		**Antigen Presentation Pathway**	
GJB2	13q11-q12	*TNFRSF9*	1p36
DEFB4	8p23.1	*B3GNT2*	2p15
KLF4	9q31	*RUNX3*	1p36
LCE3B/LCE3C	1q21.3	*TAGAP*	6p25.3
Innate Immune Response		*HLA-B/C*	6p21.3
Interferon Signaling		*IRF4*	6p25-p23
IFNLR1/IL-28RA	1p36.11	*ERAP1*	5q15
IFIH1	2q24	*MBD2*	18q21
ELMO1	7p14.1	*ETS1*	11q23.3
DDX58	9p12	**Th1 Signaling Pathway**	
SOCS1	16p13.13	*IL-12B*	5q31.1-q33.1
TYK2	19p13.2	*STAT5A/B*	17q21.31
RNF114	20q13.13	*ZC3H12C*	11q22.3
NF-κB Signaling		*ILF3*	19p13.2
TNIP1	5q32-q33.1	*TYK2*	19p13.2
REL	2p13-p12	**Th17 Signaling Pathway**	
TNFAIP3	6q23	*IL-23R*	1p31.3
CARM1	19p13.2	*IL-1RN*	2q14.2
FBXL19	16p11.2	*IL-17RD*	3p14.3
NOS2	17q11.2-q12	*TRAF3IP2*	6q21
CARD14	17q25	*IRF4*	6p25-p23
NFKBIA	14q13	*ETS1*	11q23.3
TYK2	19p13.2	*IL-2/IL-21*	4q27
UBE2L3	22q11.21	*STAT3*	17q21.31

T cells with recognition of skin or synovial antigens presented through DCs or macrophages [64]. In patients with psoriasis in the skin and joints, the inflammatory condition is characterized by the infiltration of activated T cells into the organs [65]. Psoriasis has traditionally been considered as Th1 mediated disease. However, IL-17-producing Th17 cells have been implicated as a critical contributing cell to the pathogenesis of psoriasis [66]. It seems more adaptive immunity-related genes might be involved in psoriasis pathogenesis that needs further investigations with the advent of new techniques of evaluation.

5.3.1. Antigen Presentation Pathway Genes

Genetic variations can cause impaired or dysregulated antigen presentation procedures, leading to inappropriate cell targeting and attacking by the effector cells, thereby contributing to psoriasis pathogenesis.

Several genetic variations found by GWASs, have been identified in loci with functional involvement in antigen presentation pathways that increase psoriasis predisposition are *ERAP1*, *MBD2*, *RUNX3*, *TNFRSF9*, *IRF4*, *ETS1*, *TAGAP*, *B3GNT2*, and *HLA-B/C* (Table **1**) [16-18, 46-52]. The involvement of HLA molecules has already been described. Differentiation and development of CD8+ T cells are mediated by several genes like MBD2, TNFRSF9, and RUNX3 [67-69]. Furthermore, proteins encoded by B3GNT2, IRF4, TAGAP, and ETS1 participate in the activation and differentiation of CD8+ T cells [70, 71].

ERAP1 encodes a protein, an aminopeptidase involved in trimming HLA class I-binding peptides in the endoplasmic reticulum to make them pertinent for presentation, which interplays with the HLA-C molecule, highlighting the impression of *ERAP1* in different steps of antigen presentation [72]. In PsA, GWASs have identified variations only in

HLA-B/C loci. Considering these observations into account, it appears that genes with involvement in suitable antigen presentation play a role in psoriasis pathogenesis due to the autoimmune nature of the disease and the involvement of T cells.

5.3.2. Th1 Signaling Pathway Genes

A bulk of evidence has indicated the importance of the Th1 signaling pathway in the pathogenesis of psoriasis. Several factors such as TNF-α, IFN-α, IFN-λ, IL-6, and IL-1β stimulate the myeloid dendritic cells [mDCs] to secrete IL-12, leading to the differentiation of Th1 cells [73]. Genetic variations in the molecules involved in the Th1 signaling pathway may lead to perturbations in Th1 differentiation, contributing to psoriasis pathogenesis. GWASs have identified a number of genetic susceptibility loci to psoriasis involved in various aspects of the Th1 signaling pathway, including *IL12B*, *ZC3H12C*, *STAT5A*, *STAT5B*, *ILF3*, and *TYK2* (Table **1**). IL-12 ligation to the IL-12 receptor causes activation of a series of downstream molecules like Tyk2, encoded by the *TYK2* gene, that directly binds to IL-12Rβ1 and is involved in the IL-12 signaling pathway [74]. The product of the *ZC3H12C* gene retes macrophage activation [75]. *STAT5A* and *STAT5B* genes encode proteins of the STAT family. STAT4 is a transcription factor that participates in the signaling of the IL-2 cytokines family, such as IL-2, IL-7, IL-15, and IL-21 [76]. *ILF3* gene encodes a double-stranded RNA-binding protein, a nuclear factor of activated T cells (NFAT) subunit, a transcription factor necessary for IL-2 expression in T cells [77]. Currently, only the *IL12B* gene has been recognized as a Th1 signaling pathway-related gene at a genome-wide level of significance in patients with PsA. However, future investigations might concentrate further on the genes with an essential role in the Th1 signaling pathway to disclose a vivid role of these genes in psoriasis pathogenesis.

5.3.3. Th17 Signaling Pathway Genes

It has been identified that the Th17 signaling pathway, mediated through the IL-23/IL-17 axis, plays an essential role in the pathogenesis of psoriasis disease. Th17 cells produce IL-17, which mediates a pro-inflammatory response by triggering the production of inflammatory cytokines and angiogenic factors [75]. IL-17 promotes the differentiation of naive T cells to the Th17 lineage [66]. The Th17-IL-17 pathway interacts with TNF-α and NF-κB and participates in the innate immune response [78-81]. This way, IL-17 demonstrates a synergistic function along with TNF-α. Both IL-23 and IL-17 cytokines cause activation of the NF-κB pathway [82], thus playing a role in psoriasis pathogenesis. Evaluation of clinical trials shows that biologics targeting IL-23 or IL-17 are clinically more beneficial than IL-12/IL-23 and TNF inhibitors in the treatment of psoriasis, suggesting that IL23/IL17 axis is critical in the pathogenesis of the disease [83].

Transforming growth factor (TGF)-β, IL-6, IL-1β, and IL-23 promote IL-17 production and Th17 cell differentiation, eventuating in psoriatic manifestations. There is an increased TGF-β1 expression in the epidermis and the serum of patients with psoriasis [84]. Furthermore, studies indicated that TGF-β1 serum level correlates with the disease severity in psoriatic patients [85, 86]. Nonetheless, TGF-β1 genetic variations have not been observed to be associated with psoriasis predisposition. IL-6 plays a role in the Th17 differentiation and mediates inflammation in the IL-23-induced skin [87]. IL-6 signaling, *via* STAT3, results in the expression of IL-23 receptor and triggering of IL-17A and IL-17F production [88]. While no study evaluated the role of *IL6* gene variations in PsA, the IL-6 rs1800795 SNP was associated with decreased PsV risk [89].

IL-1β and IL-23 are required for the differentiation of Th17 cells [90, 91]. Given the increased IL-1 family members in psoriatic skin, it appears that IL-1 might be involved in the disease pathogenesis [92]. GWASs have not reported the association of *IL1B* with psoriasis [44, 45]. In contrast, a significant association of *IL-1RN* was reported in purely cutaneous psoriasis that affected the severity of nail involvement and cutaneous symptoms [93]. Moreover, the *IL1* locus, which once was identified as a susceptibility region for PsA [94, 95], could not be confirmed in further investigations [18, 49, 50].

IL-23 is a pro-inflammatory cytokine that binds to IL-23R and IL-12Rβ1 and causes the proliferation and sustenance of Th17 cells [96-98]. IL-23 plays an essential role in psoriasis pathogenesis, highlighted through increased serum and skin levels of IL-23 [99, 100] and upregulation of IL-23 in monocytes from patients with psoriasis [101]. GWASs have disclosed that genetic variations located within IL-23A, IL-23R, IL-12β, TYK2, SOCS1, STAT3, and ETS1 were associated with susceptibility to psoriasis [16-18, 46-52]. *IL-23A*, *IL-23R*, and *IL-12β* are directly involved in the induction of IL-23 receptor, while *TYK2*, *SOCS1*, *STAT3*, and *ETS1* participate in the downstream signaling pathway of *IL-23R* [97, 102]. Tyk2 binds to IL-12Rβ1 and is vital for IL-23 signaling and, therefore, Th17 differentiation [74]. SOCS1 and STAT3 are needed for Th17 differentiation [103, 104]. Ets1 is a negative regulator of Th17 differentiation [105].

IL-17 binds to IL-17RA and IL-17RC [106, 107], which in turn causes the activation of DCs, macrophages, endothelial cells, chondrocytes, fibroblasts, and osteoblasts, eventuating in a pro-inflammatory setting [108, 109]. Studies have highlighted that IL-17 and its receptor IL-17R are increased in synovial fluid and skin of patients with psoriasis, supporting the role of IL-17 in the disease pathogenesis [110-113]. On the other side, GWASs have reported the association of genes involved in the Th17 interactions and functions, such as *TRAF3 interacting protein 2* (*TRAF3IP2*), *KLF4*, and *interferon regulatory factor 4* (*IRF4*). During the inflammatory responses by Th17, TRAF3IP2 is needed [80]. Studies show that rs33980500 SNP in the *TRAF3IP2 gene* was associated with PsA risk [47].

Genetic risk for psoriasis might be encoded at long-range interacting (LRI) enhancers that regulate IL17 pathway genes from a distance. Two LRI enhancer sites have been identified that regulate IL17RA and TRAF3IP2. The TRAF3IP2 regulator localizes to the TRAF3IP2 antisense promoter, implying a feedback regulation. Both LRI sites have been associated with psoriasis in a novel Scottish psoriasis cohort, and the TRAF3IP2-LRI at rs71562294 has been replicated in the Wellcome Trust Case Control Consor-

tium (WTCCC) cohort [114]. *KLF4* is involved in the regulation of IL-17A production through binding to its promoter [115]. Moreover, IRF4 is a transcription factor that modulates the activity IL-17A promoter [116]. To date, GWASs have not established an association of the IL-17 gene with psoriatic diseases [16-18, 46-52]. In a familial study of PsV, it was observed that *IL-17RD* gene rs12495640 SNP was associated with the disease susceptibility [117]. This gene belongs to the IL-17 receptor family and provides direct evidence of IL-17/IL-17R genetic variants in psoriasis pathogenesis. Nonetheless, genetic variants of IL-17A and IL17-RA did not impress the PsA risk in patients of northern Italian [118].

IL-22 is a newly identified cytokine of Th17 cells and plays a role in the differentiation of keratinocytes [119]. The effect of IL-22 on keratinocytes was highlighted through overexpression of IL-22 receptor (IL-22R) in the epidermis of psoriatic skin compared to that of normal skin [120]. Studies revealed that upregulation of IL-22, along with IL-12B and IFN-γ in the psoriatic skin, is involved in the initiation and sustenance of the disease [121]. A GWAS identified the IL-22 association with psoriasis in the Japanese [122]. Moreover, the copy number of the IL-22 gene demonstrated association with the clinicopathological symptoms of the patients with psoriasis. The more the copy number, the more the chance of nail manifestations in these patients [119].

IL-21 binds to IL-21R, which continues through activation of the JAK-STAT signaling pathway [123], leading to overproduction of IL-17 and overexpression of IL-23R [124, 125]. There is evidence suggesting the involvement of IL-21 in the pathogenesis of psoriasis. Studies show that IL-21 is enhanced, both at transcriptional and translational levels, in the lesional skin of patients in comparison to non-lesional skin of patients [126]. Furthermore, serum IL-21 levels demonstrated an increase in psoriatic patients and correlated with the Psoriasis Area Severity Index (PASI) score of the patients [127]. While GWASs have supported the association of IL-2/IL-21 genes with psoriasis, rs6822844 and rs2069778 were strongly associated with the disease [128]. Genetic variations of only two genes in the Th17 signaling pathway, namely *IL12B* and *TRAF3IP2*, have obtained genome-wide significance in PsA patients [47, 51]. Nonetheless, candidate gene evaluations indicate the remarkable association of STAT3, IL-23A, and IL-23R with psoriatic disorders [129-131]. In addition, *Janus kinase [JAK] 1* gene rs310241 and *JAK3* gene rs3008 were associated with psoriasis risk [132].

It seems that a small number of psoriatic patients and heterogeneity of the clinical manifestations in these patients have been the major issues in front of prosperous identification of genetic susceptibility loci involved in the pathogenesis of psoriasis.

CONCLUSION AND FUTURE DIRECTIONS

Here, we have reviewed the recent findings of several genetic factors in psoriasis patients. It has been reported that psoriasis susceptibility shows strong associations with a specific allele of the HLA-C gene in the MHC Class I locus. Nonetheless, there have been several conflicting reports in different populations, which refers to a difficulty in devising unique therapeutics for treating or managing the disease. The current line of knowledge implicates that psoriasis is a complex, multigenic, and multifactorial disease. Novel approaches are underway to dissect the exact pathogenesis of the disease concerning genetic predisposing loci or the related functions. A systematic study on the biological pathways, pathogenicity, and interaction networks of differently expressed genes in psoriasis revealed that internal and external stimuli might trigger immuno-inflammatory responses to develop psoriasis. Additionally, pathways related to infectious diseases and cancers were discerned as relevant to disease pathogenesis through functional analysis. From the gene pathogenicity viewpoint, five essential genes were reported in psoriasis, including PPARD, GATA3, TIMP3, WNT5A, and PTTG1 [133]. These state-of-the-art methods might open new horizons and shed further light on the understanding of psoriasis pathogenesis. It appears that the integration of genetic and environmental risk factors data regarding the immunological network might contribute to paving the way toward clear apprehension of etiopathogenesis of complex and multifactorial disorders like psoriasis.

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