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The immunological and genetic aspects in psoriasis

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Abstract

Psoriasis is a chronic and immune-mediated inflammatory skin disorder associated with complex genetic susceptibility. Studies focused on the immunological mechanism have revealed innate and adaptive immune activation in psoriatic lesions, including large numbers of immune cells activated to produce many cytokines, chemokines, and other inflammatory molecules. Knowledge on the genetic basis of psoriasis highlights genetic susceptibility factors that play a crucial role in regulation of immunity, epidermal proliferation, and skin barrier formation. Genetic susceptibility factors affecting both the immune system and epidermis could predispose to disease. Herein, we review the current knowledge on the role of genetic and immunological factors in the development of psoriasis.

Keywords: Psoriasis; Immunity; Genetics; Pathogenesis

Review

Introduction

Psoriasis (MIM *177900) is a common, chronic, and immunologically mediated inflammatory skin disease that affects individuals at rates varying from 0.5% to 4.6% across diverse ethnic populations (Lebwohl 2003). Symptoms typically develop in early adulthood, between the age of 15 and 25 years old (Henseler and Christophers 1985), but individuals of all ages can be affected. The disease has certain distinct but overlapping clinical phenotypes, including psoriasis vulgaris, which appears in approximately 90% of all patients (Griffiths and Barker 2007), and at least 10% to 30% of patients develop arthritis (Nickoloff and Nestle 2004; Ibrahim et al. 2009). Although psoriasis is rarely life threatening, its morbidity and associated comorbidities have a severe negative impact on the quality of life of the patients and also confer a certain socioeconomic burden. Over the past few decades, substantial researches on the pathogenesis of psoriasis have been a focus in the field of cutaneous disease. However, the mechanism of psoriasis pathogenesis likely involving the complex interplay among genetic, immunological, and environmental risk factors (Nestle et al. 2009) has not been fully elucidated.

The concordance of monozygotic twins both suffering from psoriasis has been reported to approximately 70%, and the sibling recurrence risk is estimated to range between 4 and 11 (Bhalerao and Bowcock 1998). Through a conventional family-associated on genetic linkage approach, psoriasis-associated chromosomal regions have been identified. A major genetic determinant of psoriasis, designated psoriasis susceptibility 1 (*PSORS1*), resides in

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the major histocompatibility complex (MHC) on chromosome 6p21, tightly linked to *HLA-Cw6*, which is as the most frequently detected allele in psoriasis (Veal et al. 2002; Nair et al. 2006). More recently, with the development of high-throughput genotyping platforms and a comprehensive map of human haplotypes, genome-wide association studies (GWAS) have evolved into a powerful tool for investigating the genetic architecture of human complex diseases (Manolio et al. 2008). Taking advantage of GWAS, researchers have revealed many novel and/or confirmed previous genetic loci associated with disease, and ongoing studies are exploring additional genetic factors for associated with psoriasis.

The cellular features of psoriasis are epidermal hyperplasia and altered keratinocyte differentiation, but substantial evidence implicates both innate and acquired immunity in the disease pathogenesis (Gaspari 2006). The disease state is triggered by an activated cellular immune system, marked infiltration of T cells, dendritic cells (DCs), and inflammatory cytokines in psoriatic skin lesions (Bowcock and Krueger 2005). As in other immune-mediated diseases, such as rheumatoid arthritis (RA), Crohn's disease (CD), multiple sclerosis (MS), and juvenile-onset diabetes, psoriasis is regarded as a T cell-mediated autoimmune disease (Lowes et al. 2007). Therefore, it fits the definition of an autoimmune disease (Davidson and Diamond 2001). Recent progress in the understanding of both the immunological and genetic basis of the disease has provided a deep insight into the pathogenesis. In this review, we detail the recent advances in the understanding of psoriasis pathogenesis, including the information regarding immunological factors, genetic aspects, and susceptibility genes shared with other autoimmune or inflammatory diseases.

Immunological factors

Cells and molecules of immunity

Psoriasis is characterized by hyper-proliferation and aberrant differentiation of keratinocytes (KCs), vascular abnormalities, and inflammatory infiltration. The cell types in psoriatic plaques are involved in wound repair and/or are composed of the antigen-presenting cells (APCs), including T lymphocytes cells, KCs, DCs, Langerhans cells (LCs), and macrophages. The cellular innate and adaptive immune responses, especially the activation of T cells, play a dominant pathogenic role in psoriasis (Krueger 2002; Cai et al. 2012). Evidence for the central role of T lymphocytes has been found in animal models of psoriasis (Boehncke and Schon 2007), successful treatment of psoriasis patients with cyclosporine A to inhibit T cell proliferation and cytokine production (Mueller and Herrmann 1979) and specifically recruited T cell clones that permanently involve the psoriatic inflammation (Vollmer et al. 2001). A dense infiltration is composed of clusters of $CD4^+$T cells and antigen-presenting DCs in the dermis, while $CD8^+$T cells and neutrophils are predominant in the epidermis of psoriatic lesions (Lowes et al. 2007). The expression of activation markers by both $CD8^+$T and $CD4^+$T cells has been observed in psoriatic lesions, and most of the T cells can also express the memory cell antigens (Liu et al. 2007). Once the psoriatic plaques appear after T cell infiltration as the activated memory-effector T cells, cytokines, such as interleukin (IL)-2, tumor necrosis factor-α (TNF-α), and interferon γ (IFN-γ) could be generated, which stimulate an inflammatory response and change the characteristic of psoriasis (Austin et al. 1999; Friedrich et al. 2000). An interrelation exists in that, $CD4^+$T cells may provide critical inductive and helper signals, while $CD8^+$T cells are likely to be the

principal effector agents in the pathogenesis of psoriasis (Gudjonsson et al. 2004). Thus, in the epidermal compartment of psoriatic lesions, $CD8^+$T cells could be activated and proliferated after $CD4^+$T cells interact with antigen-presenting cells.

The changes in keratinocyte activation and proliferation that cause them to mature too rapidly result in psoriasis. Keratinocytes in psoriatic lesions produce an array of immune response-related proteins, such as the S100 proteins and intercellular adhesion molecule 1 (ICAM-1), CD40, and HLA-DR, which attract leukocytes. The link is that a positive feedback leads leukocytes to upregulate the S100 proteins (Bowcock and Krueger 2005).Upon activation, KCs express a plethora of cytokines, chemokines, and accessory molecules, transmitting both positive and negative signals to immune cells (Albanesi et al. 2005). KCs also produce endothelial cell mitogens such as VEGF and PDGF, leading to angiogenesis (Costa et al. 2007).

DCs are professional APCs involved in the regulation of the balance between immunity and immunological tolerance. Cytokine profile studies have shown that dermal DCs obtained from psoriatic lesions mediated a T cell response with high levels of IL-2 and IFN-γ (Nestle et al. 1994). Plasmacytoid DCs (PDCs) have been identified in the psoriatic skin and in uninvolved, healthy-looking psoriatic skin and were shown to be the principal IFN-α-producing cells in early and developing psoriasis (Nestle et al. 2005). Myeloid DCs, which are activated by PDCs and keratinocyte-derived cytokines, are also accumulated in the psoriatic tissues (Zaba et al. 2009) and are believed to be required for sustaining and amplifying the T cell inflammatory reaction (Chu et al. 2011). Studies have shown that DCs may be the primary cell type that drives T-helper 17 (Th17) differentiation in psoriasis through the production of IL-6 and IL-23 (Chu et al. 2011). The crucial link between DCs and the IL-23/Th17 axis has been further strengthening the suggestion that DCs obtained from psoriatic lesions could activate T cells to produce both IL-17 and IFN-γ (Zaba et al. 2009).

LCs reside in the basal and suprabasal layers of the skin and are closely associated and interact with KCs through E-cadherin (Tang et al. 1993). A role for LCs has been indicated in the pathogenesis of psoriasis (Cumberbatch et al. 2006), inducing the generation of distinct IL-22-producing Th22 cells infiltrating into the skin (Fujita et al. 2009). Macrophages can contribute to both epithelial-based and T cell-mediated pathways of inflammation in psoriasis (Clark and Kupper 2006). Macrophages interact with KCs and secrete a variety of pro-inflammatory cytokines, such as TNF-α, IFN-α/β, IL-1β, IL-6, IL-12, IL-10, and IL-18 cytokines, under various conditions (Wang et al. 2009a). Previous researches have suggested that the maintenance of psoriasiform skin inflammation critically depends on efficient recruitment and activation of macrophages with a sufficient release of TNF-α (Wang et al. 2006). As mentioned above, the cellular features of psoriasis are epidermal hyperplasia and altered keratinocyte differentiation, but mounting evidences have implicated both innate and acquired immunity in the disease progression of the disease (Nestle et al. 2009).

Several cytokines and chemokines, which induced keratinocyte proliferation, are strongly expressed in the psoriatic skin. It has been well established by many experimental studies that psoriatic inflammation mediated by T-helper 1 (Th1) cells (Uyemura et al. 1993; Schlaak et al. 1994). Characterization of cells and cytokines involved in the initiation and maintenance of psoriasis showed elevated levels of IFN-γ, TNF-α, and IL-12, but not of IL-4, IL-5, or IL-10, at both the mRNA and protein levels (Nestle et al. 1994; Schlaak

et al. 1994; Austin et al. 1999). Th17 cells, a newly appreciated T cell subset that produce IL-17 (Miossec et al. 2009) and IL-22 (Liang et al. 2006), have been implicated in psoriasis. As a potent pro-inflammatory cytokine, IL-17 may stimulate keratinocytes to produce neutrophil-attracting CXC chemokines (Nograles et al. 2008), as well as CCL20, which draws $CCR6^+$ cells into sites of inflammation (Harper et al. 2009). A mixed Th1 and Th17 inflammatory environment is found in the affected skin during the disease process (Lowes et al. 2008). IL-23, which is composed of two subunits, a unique p19 subunit and a p40 subunit shared with IL-12 (Lee et al. 2004), represents a cytokine pathway that is differentially increased in psoriatic lesions and is important in Th17 cells. IL-23 is overproduced by DCs (Lee et al. 2004) and stimulates Th17 cells within the dermis to make cytokines in psoriatic lesions. Recent studies have demonstrated that the IL-23/Th17 cell axis plays an important role in the pathogenesis of psoriasis and presents a potential therapeutic target (Di Cesare et al. 2009; Nakajima 2012). In addition to IL-23 and IL-17, IL-22 has also been reported to induce cutaneous inflammation in an experimental murine model of psoriasis and has also been shown to induce *in vitro* an inflammatory-like phenotype *in vitro* (Van Belle et al. 2012). IL-22 is a member of the IL-10 cytokine family, which is primarily secreted by Th17 cells (Trifari et al. 2009). IL-22 is remarkably over-expressed in psoriasis, most likely as a result of upregulated the levels of IL-23 and IL-6 (Boniface et al. 2007; Zheng et al. 2007). TNF-α has been identified as a promising target molecule, with the expression of TNF-α and its receptors enhanced in psoriasis (Ettehadi et al. 1994). The efficacy of TNF-α antagonists in the treatment of psoriasis suggests a central role of this factor in psoriatic plaque formation (Tobin and Kirby 2005).

In addition to T cell-derived cytokines, numerous antigen-presenting cells infiltrate the psoriatic skin and produce inflammatory cytokines. A variety of chemokines and chemokine receptors are present in psoriatic plaques. The percentages of peripheral blood $CD8^+$T cells expressing CXCR6 are higher in psoriasis patients than in healthy individuals, and CXCL16-CXCR6 interactions mediate the homing of $CD8^+$T cells to psoriatic lesion (Gunther et al. 2012). In immune-pathogenesis of psoriasis, including TARC (CCL17), MIG (CXCL9), IP10 (CXCL10), MDC (CCL22), and RANTES (CCL5), as well as CXCR2, CXCR3, CCR4, CCL27-CCR10, MIP3α (CCL20), MIP3β (CCL19), and CCR6, all involved in the inflammatory response of psoriasis (Nickoloff and Nestle 2004). Once chemokines bind to their respective receptors, they activate the cells to release of cytokines and growth factors to form a thick, erythematous scaly plaque.

Inflammation pathways

Psoriasis is a representative inflammatory skin disease, which is mediated through a cytokine network. The activated DCs and T cells are central in its pathogenesis, creating a Type 1 inflammatory pathway, which links the activation of multiple inflammatory responses, such as the release of IFN-γ, IL-23, and IL-12 into the lesions (Lew et al. 2004). This model is conceptually useful, but it accounts for only a small fraction of the pathogenesis and cannot explain the total inflammatory character of psoriatic lesions.

Previous studies have shown that the activity of the p38 mitogen-activated protein kinases (MAPKs) is increased in the psoriatic skin, supporting the potential role of these kinases in the pathogenesis of psoriasis (Funding et al. 2007). The mitogen- and stress- activated protein kinases 1(MSK1) are found to be involved in the phosphorylation of cyclic adenosine monophosphate response element-binding (CREB) protein in

keratinocytes and regulate the expression of the pro-inflammatory cytokines IL-6, IL-8, and TNF-α (Funding et al. 2006). Evidence shows that MAPK inhibitors are effective anti-inflammatory drugs that reduce the synthesis of inflammation mediators at multiple levels and block pro-inflammatory cytokine signaling (Kaminska and Swiatek-Machado 2008). It has therefore been confirmed that the pathway of the p38 MAPK/MSK1 signaling pathway may play a potential role in psoriasis by producing pro-inflammatory cytokines (Arthur and Darragh 2006).

Clearly, transcription factors, such as signal transducer and activator of transcription 1 and 3 (STAT1 and STAT3) and nuclear factor-κB (NF-κB), are activated in psoriasis. Research on the transcriptional regulatory network for psoriasis shows that E2F transcription factor 1 (E2F1), jun proto-oncogene (JUN), NF-κB 1, STAT1, STAT3, and SP3 are pivotal in the transcriptome network involved in the mechanism of psoriasis (Lu et al. 2013). NF-κB is a key regulatory element in inflammatory pathways, in cellular proliferation and differentiation, and in apoptosis as well as a crucial mediator in psoriasis (Goldminz et al. 2013). In a mouse model of psoriasis, NF-κB signaling is essential for the pathogenesis and is strongly activated in psoriatic lesions (Wang et al. 2009b). Compared to the non-psoriatic skin, the samples of the psoriatic skin demonstrate elevated levels of activated, phosphorylated NF-κB (Lizzul et al. 2005). It is targeted by numerous effector cells, including keratinocytes, Th17, and DCs, which respond to extracellular stimuli consisting of TNF-α, plasmin, and TLRs (Goldminz et al. 2013). A blockade of NF-κB signaling within various target cells leads to decrease production of pro-inflammatory cytokines.

The Janus kinase (JAK)/STAT signaling pathway is well known to be involved in many cellular processes including inflammation. The JAK/STAT pathway converts cytokine signals into genomic responses that regulate proliferation and differentiation of the immune cells (Kaminska and Swiatek-Machado 2008). JAK inhibitors may be a new class of immunomodulatory agents with immunosuppressive, anti-inflammatory, and antiallergic properties. When keratinocytes from the psoriatic skin were cultured, a significant induction of the STAT1-induced transcriptional activity was stimulated with either IFN-γ or IFN-α (Hald et al. 2013).STAT3 are involved in the upregulation of keratin 17 (K17) expression induced by IL-22. Both STAT1 and STAT3 pathways are involved in the upregulation of K17 expression induced by IL-17A, and this regulation could be partially suppressed by STAT1 or STAT3 small interfering RNAs and inhibitors (Shi et al. 2011). Taken together, these cellular signaling pathways, which have been shown to be involved in the progression of psoriasis, present potential targets for new prosiasis therapies.

Genetic factors

Linkage and candidate gene association study

Although psoriasis has a multifactorial etiology, it is strongly influenced by genetic factors (Lowes et al. 2007). Compared with the general population, a higher incidence of the disease has been identified among first-degree and second-degree relatives of psoriasis. The risk of psoriasis is greater in monozygotic twins than in dizygotic twins, confirming the genetic basis of the disease (Nestle et al. 2009). Prior traditional approaches, such as family-based linkage studies and population-based candidate gene association studies, have had some success in identifying genetic risk factors. The major

locus strongly associated with psoriasis is *PSORS1* on chromosome 6p21, spanning approximately 300 kb of the MHC class I region (Veal et al. 2002). Large-scale resequencing has established *HLA-C* and its *HLA-Cw*06* allele as the most likely *PSORS1* candidate genes (Nair et al. 2006). Variants associated with the *HLA-Cw*06* allele contribute to one-third and one-half of the genetic susceptibility to psoriasis (Elder 2006) and are determinant for the development of early-onset psoriasis (Zhang et al. 2003).

In addition to *PSORS1*, linkage analyses and association studies have highlighted psoriasis loci on several other chromosomes outside of the MHC region, designated *PSORS2-PSORS10* (Bowcock and Krueger 2005; Perera et al. 2012). *PSORS2* was localized to the chromosomal region 17q25.3 in a family of European ancestry and has also been observed in a Taiwanese family with multiple psoriasis-affected members (Jordan et al. 2012). Two disease-causing *CARD14* mutations in psoriasis identified by using genomic capture and DNA sequencing suggest that the involvement of *PSORS2* is due to the mutation of this gene (Jordan et al. 2012). In the *PSORS3* locus, on chromosome 4q (Matthews et al. 1996), evidence from an association study suggests a putative association between the interferon regulatory factor 2 *(IRF2*) and psoriasis, which indicates that the *IRF2* gene as a candidate for *PSORS3* (Foerster et al. 2004). *PSORS4* is in the 1q21 region (Matthews et al. 1996), where a common deletion (*LCE3C_LCE3B-del*) in the late cornified envelope (LCE) cluster is associated with psoriasis (Coto et al. 2011). The locus, *PSORS5*, on chromosome 3q21 has been found in family-based analysis studies (Enlund et al. 1999). The cystatin A, zinc finger protein 148, and solute carrier family 12 member A8 (SLC12A8) genes are proposed as candidate genes at the psoriasis susceptibility locus *PSORS5* (Samuelsson et al. 2004; Huffmeier et al. 2005). *PSORS6*, located at 19p13 (Lee et al. 2000), has been suggested to interact with *PSORS1* (Huffmeier et al. 2009). *PSORS7* at 1p (Veal et al. 2001), *PSORS8* at 16q (Nair et al. 1997), and *PSORS9* at 4q31-34 (Yan et al. 2007; Zhang et al. 2007) are all linked to psoriasis. Although other susceptibility loci and genes have also been postulated, it is difficult to replicate the results of these studies, a result of interethnic differences and environmental variations.

Genome-wide association studies

GWAS have become an effective approach for identifying genetic variants associated with disease risk (Price et al. 2010). To date, several large GWAS for psoriasis in both the European and Asian populations have been performed (Nair et al. 2009; Zhang et al. 2009; Ellinghaus et al. 2010; Huffmeier et al. 2010; Strange et al. 2010; Stuart et al. 2010; Sun et al. 2010; Tsoi et al. 2012) to identify novel susceptibility genes and mechanisms associated with psoriasis with kinds of algorithms (Tables 1 and 2). It is worth mentioning that the most highly significant associated single nucleotide polymorphisms (SNPs) in different populations are localized in the MHC class I region, which encodes the HLA molecules *HLA-A*, *HLA-B*, and *HLA-C*. The findings of GWAS pertaining to psoriasis and psoriatic arthritis GWAS (Liu et al. 2008) demonstrate that the strongest associated SNP alleles are highly correlated with the *HLA-Cw*06*, which is consistent with the previously described involvement of the *PSORS1* region. Through in-depth analyses of the GWAS data, two additional susceptibility loci within the HLA region have been shown to confer risk of psoriasis in both Chinese and European lineages (Feng et al. 2009).

Table 1 The genetic loci associated with psoriasis identified by GWAS

Chromosomal	Reported gene(s)	SNP	Context	*P* value	Odds ratio (95% CI)	Population	Ref.
1q21.3	*LCE3B*, *LCE3D*	rs6677595	Intergenic	$2.1 ? 10^{-33}$	1.26 [NR]	European	(Tsoi et al. 2012)
	LCE3D, *LCE3A*	rs4085613	Intergenic	$7 ? 10^{-30}$	1.32 [1.25 to 1.39]	Chinese	(Zhang et al. 2009)
	LCE3D	rs4112788	Intergenic	$3 ? 10^{-10}$	1.29 [1.19 to 1.40]	European	(Strange et al. 2010)
1p36.23	*SLC45A1*, *TNFRSF9*	rs11121129	Intergenic	$1.7 ? 10^{-8}$	1.13 [NR]	European	(Tsoi et al. 2012)
1p36.11	*RUNX3*	rs7536201	nearGene-5	$2.3 ? 10^{-12}$	1.13 [NR]	European	
	IL28RA	rs7552167	Intergenic	$8.5 ? 10^{-12}$	1.21 [NR]	European	
		rs4649203	Intergenic	$7 ? 10^{-8}$	1.13 [1.05 to 1.22]	European	(Strange et al. 2010)
				$3.91 ? 10^{-12}$	1.16 [NR]	Chinese	(Cheng et al. 2013)
1p31.3	*IL23R*	rs2201841	Intron	$1.75? 10^{-10}$	1.23 [NR]	European	(Elder 2009)
		rs9988642	nearGene-3	$1.1 ? 10^{-26}$	1.52 [NR]	European	(Tsoi et al. 2012)
		rs11209026	Missense	$7 ? 10^{-7}$	1.49 [1.27 to 1.74]	European	(Strange et al. 2010)
		rs2201841	Intron	$3 ? 10^{-8}$	1.13 [NR]	European	(Nair et al. 2009)
2q24.3	*IFIH1*	rs17716942	Intron	$1 ? 10^{-13}$	1.29 [1.17 to 1.43]	European	(Strange et al. 2010)
2p16.1	*FLJ16341*, *REL*	rs62149416	Intergenic	$1.8 ? 10^{-17}$	1.17 [NR]	European	(Tsoi et al. 2012)
	REL	rs702873	Intron	$4 ? 10^{-9}$	1.12 [1.04 to 1.20]	European	(Strange et al. 2010)
	NR	rs842636	Intron	$6 ? 10^{-6}$	1.15 [NR]	European	(Stuart et al. 2010)
2p15	*B3GNT2*	rs10865331	Intergenic	$4.7 ? 10^{-10}$	1.12 [NR]	European	(Tsoi et al. 2012)
5q33.3	*PTTG1*	rs2431697	Intergenic	$1.11 ? 10^{-8}$	1.20 [1.13 to 1.28]	Chinese	(Sun et al. 2010)
	IL12B	rs12188300	Intergenic	$3.2 ? 10^{-53}$	1.58 [NR]	European	(Tsoi et al. 2012)
		rs2546890	ncRNA	$1 ? 10^{-20}$	1.54 [1.32 to 1.79]	European	(Ellinghaus et al. 2010)
		rs3213094	Intron	$5 ? 10^{-11}$	1.39 [1.26 to 1.53]	European	(Strange et al. 2010)
		rs2082412	Intergenic	$2 ? 10^{-28}$	1.44 [NR]	European	(Nair et al. 2009)
		rs3213094	Intron	$3 ? 10^{-26}$	1.28 [1.23 to 1.35]	Chinese	(Zhang et al. 2009)
		rs2082412	Intergenic	$4.75? 10^{-18}$	1.42 [NR]	European	(Elder 2009)

Table 1 The genetic loci associated with psoriasis identified by GWAS *(Continued)*

5q33.1	*TNIP1/ANXA6*	rs3762999	Intergenic	$4.55 ? 10^{-18}$	1.23 [1.18 to 1.29]	Chinese	(Sun et al. 2010)
		rs999556	Intergenic	$3.83 ? 10^{-21}$	1.25 [1.20 to 1.31]	Chinese	
	TNIP1	rs17728338	Intergenic	$1.4? 10^{-13}$	1.56 [NR]	European	(Elder 2009)
		rs2233278	UTR-5	$2.2 ? 10^{-42}$	1.59 [NR]	European	(Tsoi et al. 2012)
		rs17728338	Intergenic	$1 ? 10^{-20}$	1.59 [NR]	European	(Nair et al. 2009)
	IL13, IL4	rs1295685	Intergenic	$3.4 ? 10^{-10}$	1.18 [NR]	European	(Tsoi et al. 2012)
	IL13	rs20541	Missense	$5 ? 10^{-15}$	1.27 [NR]	European	(Nair et al. 2009)
5q15	*ERAP1*	rs27432	Intron	$1.9 ? 10^{-20}$	1.2 [NR]	European	(Tsoi et al. 2012)
		rs27524	Intron	$3 ? 10^{-11}$	1.13 [1.05 to 1.22]	European	(Strange et al. 2010)
		rs151823	Intergenic	$9.32 ? 10^{-9}$	0.89 [0.85 to 0.92]	Chinese	(Sun et al. 2010)
5q15	*LNPEP*	rs2303138	Missense	$1.83 ? 10^{-13}$	1.16 [NR]	Chinese	(Cheng et al. 2013)
6q25.4	*EXOC2, IRF4*	rs9504361	Intergenic	$2.1 ? 10^{-11}$	1.12 [NR]	European	(Tsoi et al. 2012)
6q25.3	*TAGAP*	rs2451258	Intergenic	$3.4 ? 10^{-8}$	1.12 [NR]	European	
6q23.3	*TNFAIP3*	rs610604	Intron	$3.07? 10^{-10}$	1.23 [NR]	European	(Elder 2009)
		rs582757	Intron	$2.2 ? 10^{-25}$	1.23 [NR]	European	(Tsoi et al. 2012)
		rs610604	Intron	$9 ? 10^{-12}$	1.19 [NR]	European	(Nair et al. 2009)
6q21	*TRAF3IP2*	rs33980500	Missense	$4.2 ? 10^{-45}$	1.52 [NR]	European	(Tsoi et al. 2012)
		rs458017	Missense	$2 ? 10^{-16}$	1.37 [1.22 to 1.54]	European	(Strange et al. 2010)
		rs13196377	Intron	$1.39 ? 10^{-12}$	1.67 [1.45 to 1.93]	European	(Huffmeier et al. 2010)
		rs13190932	Intron	$8.56 ? 10^{-17}$	1.83 [1.59 to 2.12]	European	
		rs13210247	Missense	$1.73 ? 10^{-14}$	1.69 [1.48 to 1.94]	European	
		rs33980500	Missense	$1 ? 10^{-16}$	NR	European	(Ellinghaus et al. 2010)
		rs240993	Intron	$5 ? 10^{-20}$	1.25 [1.16 to 1.34]	European	(Strange et al. 2010)
6p21.33	*HLA-C*	rs1265181	Intergenic	$1.93 ? 10^{-208}$	22.62 [NR]	Chinese	(Zhang et al. 2009)
		rs12191877	Intergenic	$2.98? 10^{-178}$	2.87 [NR]	European	(Elder 2009)

Table 1 The genetic loci associated with psoriasis identified by GWAS *(Continued)*

		rs13191343	Intergenic	$2.32 ? 10^{-72}$	2.37 [2.16 to 2.61]	European	(Huffmeier et al. 2010)
		rs12191877	Intergenic	$4 ? 10^{-32}$	2.79 [2.35 to 3.33]	European	(Ellinghaus et al. 2010)
		rs10484554	Intergenic	$4 ? 10^{-214}$	4.66 [4.23 to 5.13]	European	(Strange et al. 2010)
		rs12191877	Intergenic	$1 ? 10^{-100}$	2.64 [NR]	European	(Nair et al. 2009)
		rs10484554	Intergenic	$2 ? 10^{-39}$	2.8 [2.40 to 3.30]	European	(Liu et al. 2008)
		rs3134792	Intergenic	$1 ? 10^{-9}$	NR	European	(Capon et al. 2008)
	HLA-B, HLA-C	rs4406273	Intergenic	$4.5 ? 10^{-723}$	4.32 [NR]	European	(Tsoi et al. 2012)
	HCP5	rs2395029	ncRNA	$2 ? 10^{-26}$	4.1 [3.10 to 5.30]	European	(Liu et al. 2008)
7p14.1	*ELMO1*	rs2700987	Intron	$4.3 ? 10^{-9}$	1.11 [NR]	European	(Tsoi et al. 2012)
8p23.2	*CSMD1*	rs7007032	Intron	$3.78 ? 10^{-8}$	1.16 [1.10 to 1.22]	Chinese	(Sun et al. 2010)
		rs10088247	Intron	$4.54 ? 10^{-9}$	1.17 [1.11 to 1.23]	Chinese	
9q34.13	*TSC1*	rs1076160	Intron	$6 ? 10^{-6}$	1.09 [NR]	European	(Nair et al. 2009)
9q31.2	*KLF4*	rs10979182	Intergenic	$2.3 ? 10^{-8}$	1.12 [NR]	European	(Tsoi et al. 2012)
9p21.1	*DDX58*	rs11795343	Intron	$8.4 ? 10^{-11}$	1.11 [NR]	European	
10q22.3	*ZMIZ1*	rs1250546	Intron	$6.8 ? 10^{-7}$	1.1 [NR]	European	
11q24.3	*ETS1*	rs3802826	Intron	$9.5 ? 10^{-10}$	1.12 [NR]	European	
	ZC3H12C	rs4561177	nearGene-5	$7.7 ? 10^{-13}$	1.14 [NR]	European	
11q13.1	*RPS6KA4, PRDX5*	rs645078	Intergenic	$2.2 ? 10^{-6}$	1.09 [NR]	European	
12q13.3	*STAT2, IL23A*	rs2066819	Intergenic	$5.4 ? 10^{-17}$	1.39 [NR]	European	
	IL23A, STAT2	rs2066808	Intron	$1 ? 10^{-9}$	1.34 [NR]	European	(Nair et al. 2009)
	IL23A	rs2066807	Missense	$1.9? 10^{-5}$	1.33 [NR]	European	(Elder 2009)
		rs2066808	Intron	$2 ? 10^{-7}$	1.49 [1.28 to 1.73]	European	(Strange et al. 2010)
12q13.2	*RPS26*	rs12580100	Intergenic	$1 ? 10^{-6}$	1.17 [NR]	European	(Stuart et al. 2010)
13q14.11	*COG6*	rs7993214	Intron	$2 ? 10^{-6}$	1.41 [1.22 to 1.61]	European	(Liu et al. 2008)
	GJB2	rs3751385	UTR-3	$8.57 ? 10^{-8}$	0.87 [0.84 to 0.91]	Chinese	(Sun et al. 2010)

Table 1 The genetic loci associated with psoriasis identified by GWAS *(Continued)*

14q13.2	*NFKBIA, PSMA6*	rs12586317	Intron	$2 ? 10^{-8}$	1.15 [NR]	European	(Stuart et al. 2010)
	NFKBIA	rs8016947	Intergenic	$2 ? 10^{-11}$	1.19 [1.11 to 1.27]	European	(Strange et al. 2010)
				$3.9 ? 10^{-10}$	1.12 [NR]	Chinese	(Li et al. 2013)
16p13.13	*PRM3, SOCS1*	rs367569	Intergenic	$4.9 ? 10^{-8}$	1.13 [NR]	European	(Tsoi et al. 2012)
16p11.2	*PRSS53, FBXL19*	rs12445568	Intergenic	$1.2 ? 10^{-16}$	1.16 [NR]	European	
	FBXL19, POL3S	rs10782001	Intron	$9 ? 10^{-10}$	1.16 [NR]	European	(Stuart et al. 2010)
17q25.3	*CARD14*	rs11652075	Missense	$3.4 ? 10^{-8}$	1.11 [NR]	European	(Tsoi et al. 2012)
17q21.2	*PTRF, STAT3, STAT5A/B*	rs963986	Intergenic	$5.3 ? 10^{-9}$	1.15 [NR]	European	
17q11.2	*NOS2*	rs28998802	Intron	$3.3 ? 10^{-16}$	1.22 [NR]	European	
		rs4795067	Intron	$4 ? 10^{-11}$	1.19 [NR]	European	(Stuart et al. 2010)
	NR	rs1975974	Intergenic	1 ? 10-7	1.17 [NR]	European	
18q22.1	*SERPINB8*	rs514315	nearGene-3	$5.92 ? 10^{-9}$	0.87 [0.83 to 0.91]	Chinese	(Sun et al. 2010)
18q21.2	*POL1, STARD6, MBD2*	rs545979	Intergenic	$3.5 ? 10^{-10}$	1.12 [NR]	European	(Tsoi et al. 2012)
19q13.41	*ZNF816A*	rs9304742	Intron	$2.11 ? 10^{-9}$	0.88 [0.84 to 0.92]	Chinese	(Sun et al. 2010)
19p13.2	*ILF3, CARM1*	rs892085	Intergenic	$3.0 ? 10^{-17}$	1.17 [NR]	European	(Tsoi et al. 2012)
	TYK2	rs34536443	Missense	$9.1 ? 10^{-31}$	1.88 [NR]	European	
		rs12720356	Missense	$4 ? 10^{-11}$	1.4 [1.23 to 1.61]	European	(Strange et al. 2010)
		rs280519	Intron	$4 ? 10^{-9}$	1.13 [1.05 to 1.21]	European	
20q13.13	*ZNF313*	rs2235617	Intron	$2 ? 10^{-6}$	1.2 [1.11 to 1.30]	European	
	RNF114	rs1056198	Intron	$1.5 ? 10^{-14}$	1.16 [NR]	European	(Tsoi et al. 2012)
	ZNF313	rs495337	Cds-synon	$1 ? 10^{-8}$	1.25 [1.12 to 1.39]	European	(Capon et al. 2008)
20q13.12	*SDC4*	rs1008953	Intergenic	$1 ? 10^{-7}$	1.14 [NR]	European	(Stuart et al. 2010)
22q11.21	*UBE2L3*	rs4821124	Intron	$3.8 ? 10^{-8}$	1.13 [NR]	European	(Tsoi et al. 2012)

NR, not reported; UTR, untranslated region; ncRNA, noncoding RNA; nearGene-5/3, a SNP close to the 5′ or 3′ end of a gene. Intergenic: a stretch of sequences located between genes.

Table 2 The algorithms of psoriasis GWAS

Chromosomal	Reported gene(s)	SNP	Algorithms	Ref.
1q21.3	*LCE3B*, *LCE3D*	rs6677595	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
	LCE3D, *LCE3A*	rs4085613	Plink 1.02, PCA, Cochran-Armtiage trend test, Cochran-Mantel-Hanezel stratification analysis	(Zhang et al. 2009)
	LCE3D	rs4112788	SNPTEST, R, IMPUTE2, PHASE, logistic regression	(Strange et al. 2010)
1p36.23	*SLC45A1*, *TNFRSF9*	rs11121129	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
1p36.11	*RUNX3*	rs7536201		
	IL28RA	rs7552167		
		rs4649203	SNPTEST, R, IMPUTE2, PHASE, logistic regression	(Strange et al. 2010)
			PCA, PLINK 1.07, R, EIGENSTRAT, Cochran-Armitage trend test	(Cheng et al. 2013)
1p31.3	*IL23R*	rs2201841	X^2 statistic, logistic regression , MACH	(Nair et al. 2009)
		rs9988642	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
		rs11209026	SNPTEST, R, IMPUTE2, PHASE, logistic regression	(Strange et al. 2010)
2q24.3	*IFIH1*	rs17716942	SNPTEST, R, IMPUTE2, PHASE, logistic regression	(Strange et al. 2010)
2p16.1	*FLJ16341*, *REL*	rs62149416	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
	REL	rs702873	SNPTEST, R, IMPUTE2, PHASE, logistic regression	(Strange et al. 2010)
	NR	rs842636	MACH version 1.0, Meta-analysis	(Stuart et al. 2010)
2p15	*B3GNT2*	rs10865331	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
5q33.3	*PTTG1*	rs2431697	R, PCA, Cochran-Armitage trend test, Heterogeneity tests	(Sun et al. 2010)
	IL12B	rs12188300	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
		rs2546890	MACH v.1.0.16, MACH2DAT, gPLINK v2.049, CopyCaller v1.0, METAL	(Ellinghaus et al. 2010)
		rs3213094	SNPTEST, R, IMPUTE2, PHASE, logistic regression	(Strange et al. 2010)
		rs2082412	X^2 statistic, logistic regression , MACH	(Nair et al. 2009)
		rs3213094	Plink 1.02, PCA, Cochran-Armtiage trend test, Cochran-Mantel-Hanezel stratification analysis	(Zhang et al. 2009)
5q33.1	*TNIP1/ANXA6*	rs3762999	R, PCA, Cochran-Armitage trend test, Heterogeneity tests	(Sun et al. 2010)
		rs999556		
	TNIP1	rs17728338	X^2 statistic, logistic regression , MACH	(Nair et al. 2009)
		rs2233278	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
	IL13, *IL4*	rs1295685	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
	IL13	rs20541	X^2 statistic, logistic regression , MACH	(Nair et al. 2009)
5q15	*ERAP1*	rs27432	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
		rs27524	SNPTEST, R, IMPUTE2, PHASE, logistic regression	(Strange et al. 2010)
		rs151823	R, PCA, Cochran-Armitage trend test, Heterogeneity tests	(Sun et al. 2010)
5q15	*LNPEP*	rs2303138	PCA, PLINK 1.07, R, EIGENSTRAT, Cochran-Armitage trend	(Cheng et al. 2013)
6q25.4	*EXOC2*, *IRF4*	rs9504361	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)

Table 2 The algorithms of psoriasis GWAS *(Continued)*

6q25.3	*TAGAP*	rs2451258		
6q23.3	*TNFAIP3*	rs582757	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
		rs610604	X^2 statistic, logistic regression , MACH	(Nair et al. 2009)
6q21	*TRAF3IP2*	rs33980500	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
		rs458017	SNPTEST, R, IMPUTE2, PHASE, logistic regression	(Strange et al. 2010)
		rs13196377	birdseed-v2 algorithm, MACH1, X^2 test, Cochran-Mantel-Haenszel tests, PHASE	(Huffmeier et al. 2010)
		rs13190932		
		rs13210247		
		rs33980500	MACH v.1.0.16, MACH2DAT, gPLINK v2.049, CopyCaller v1.0, METAL	(Ellinghaus et al. 2010)
		rs240993	SNPTEST, R, IMPUTE2, PHASE, logistic regression	(Strange et al. 2010)
6p21.33	*HLA-C*	rs1265181	Plink 1.02, PCA, Cochran-Armtiage trend test, Cochran-Mantel-Hanezel stratification analysis	(Zhang et al. 2009)
		rs13191343	birdseed-v2 algorithm, MACH1, Chi-Square test, Cochran-Mantel-Haenszel tests, PHASE	(Huffmeier et al. 2010)
		rs12191877	MACH v.1.0.16, MACH2DAT, gPLINK v2.049, CopyCaller v1.0, METAL	(Ellinghaus et al. 2010)
		rs10484554	SNPTEST, R, IMPUTE2, PHASE, logistic regression	(Strange et al. 2010)
		rs12191877	X^2 statistic, logistic regression , MACH	(Nair et al. 2009)
		rs10484554	STRUCTURE, EIGENSTRAT, Cochran-Armitage Test, R, Haploview 3.2	(Liu et al. 2008)
		rs3134792	Haploview software, Fisher's exact test, PLINK, I^2 statistic	(Capon et al. 2008)
	HLA-B, *HLA-C*	rs4406273	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
	HCP5	rs2395029	STRUCTURE, EIGENSTRAT, Cochran-Armitage Test, R, Haploview 3.2	(Liu et al. 2008)
7p14.1	*ELMO1*	rs2700987	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
8p23.2	*CSMD1*	rs7007032	R, PCA, Cochran-Armitage trend test, Heterogeneity tests	(Sun et al. 2010)
		rs10088247		
9q34.13	*TSC1*	rs1076160	X^2 statistic, logistic regression , MACH	(Nair et al. 2009)
9q31.2	*KLF4*	rs10979182	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
9p21.1	*DDX58*	rs11795343		
10q22.3	*ZMIZ1*	rs1250546		
11q24.3	*ETS1*	rs3802826		
	ZC3H12C	rs4561177		
11q13.1	*RPS6KA4*, *PRDX5*	rs645078		
12q13.3	*STAT2*, *IL23A*	rs2066819	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
	IL23A, *STAT2*	rs2066808	X^2 statistic, logistic regression , MACH	(Nair et al. 2009)
			SNPTEST, R, IMPUTE2, PHASE, logistic regression	(Strange et al. 2010)
12q13.2	*RPS26*	rs12580100	Imputation(MACH software version 1.0), Meta-analysis	(Stuart et al. 2010)
13q14.11	*COG6*	rs7993214	STRUCTURE, EIGENSTRAT, Cochran-Armitage Test, R, Haploview 3.2	(Liu et al. 2008)
	GJB2	rs3751385	R, PCA, Cochran-Armitage trend test, Heterogeneity tests	(Sun et al. 2010)

Table 2 The algorithms of psoriasis GWAS *(Continued)*

14q13.2	*NFKBIA*, *PSMA6*	rs12586317	Imputation(MACH software version 1.0), Meta-analysis	(Stuart et al. 2010)
	NFKBIA	rs8016947	SNPTEST, R, IMPUTE2, PHASE, logistic regression	(Strange et al. 2010)
			Cochran Armitage trend test, Cochran Mantel Haenszel stratification analysis, PLINK 1.07, R 15.1	(Li et al. 2013)
16p13.13	*PRM3*, *SOCS1*	rs367569	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
16p11.2	*PRSS53*, *FBXL19*	rs12445568		
	FBXL19,POL3S	rs10782001	Imputation(MACH software version 1.0), Meta-analysis	(Stuart et al. 2010)
17q25.3	*CARD14*	rs11652075	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
17q21.2	*PTRF*, *STAT3*, *STAT5A/B*	rs963986		
17q11.2	*NOS2*	rs28998802		
		rs4795067	Imputation(MACH software version 1.0), Meta-analysis	(Stuart et al. 2010)
	NR	rs1975974		
18q22.1	*SERPINB8*	rs514315	R, PCA, Cochran-Armitage trend test, Heterogeneity tests	(Sun et al. 2010)
18q21.2	*POL1*, *STARD6*, *MBD2*	rs545979	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
19q13.41	*ZNF816A*	rs9304742	R, PCA, Cochran-Armitage trend test, Heterogeneity tests	(Sun et al. 2010)
19p13.2	*ILF3,CARM1*	rs892085	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
	TYK2	rs34536443		
		rs12720356	SNPTEST, R, IMPUTE2, PHASE, logistic regression	(Strange et al. 2010)
		rs280519		
20q13.13	*ZNF313*	rs2235617		
	RNF114	rs1056198	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)
	ZNF313	rs495337	Haploview software, Fisher's exact test, PLINK, I^2 statistic	(Capon et al. 2008)
20q13.12	*SDC4*	rs1008953	Imputation(MACH software version 1.0), Meta-analysis	(Stuart et al. 2010)
22q11.21	*UBE2L3*	rs4821124	PLINK, minimac, IMPUTE2, PCA	(Tsoi et al. 2012)

PCA, principal-component analysis.

The GWAS of psoriasis patients have implicated several other susceptibility genes that are involved in various biological processes, including the IL-23/Th17 pathway (Ellinghaus et al. 2010; Huffmeier et al. 2010; Nair et al. 2009; Strange et al. 2010), NF-κB signaling (Nair et al. 2009; Strange et al. 2010; Stuart et al. 2010), epidermal cell differentiation (de Cid et al. 2009; Sun et al. 2010; Zhang et al. 2009), MHC class I processing (Strange et al. 2010; Sun et al. 2010), the ubiquitin pathway (Capon et al. 2008; Sun et al. 2010), and Th2-type response (Nair et al. 2009) as well as genes with yet unknown functions. As mentioned above, the functional role of IL-23-induced and Th17 cell-mediated chronic inflammation is highlighted in the immune-pathogenesis of psoriasis. In GWAS findings of both European and Chinese populations, different SNP alleles associated with psoriasis in and upstream of the *IL12B* gene and the *IL23R* gene have been identified, confirming the role of the IL-23/Th17 axis in psoriasis pathogenesis (Cargill et al. 2007; Nair et al. 2009; Zhang et al. 2009). *IL12B* (encoding the p40

subunit of IL-23 and IL-12) and *IL23A* (encoding the p19 subunit of IL-23) are heterodimerize to form IL-23. The IL-23/Th17 pathway signaling could promote cellular immune responses by strengthening of a subset of IL-17-expressing T cells (Bettelli et al. 2007) or dysregulation of expression ultimately resulting in psoriasis.

Several mediators of the NF-κB signaling pathways are linked to psoriasis (Goldminz et al. 2013). As revealed by GWAS, *TNFAIP3* (TNF-α-induced protein 3) and *TNIP1* (TNFAIP3-interacting protein 1), the gene products of which modulate this pathway show a strong association with the disease (Elder 2009; Nair et al. 2009). Genetic variants in the *TRAF3IP2* (TRAF3-interacting protein 2),which encodes a protein involved in IL-17 signaling, are implicated in psoriasis susceptibility (Ellinghaus et al. 2010; Huffmeier et al. 2010). *TRAF3IP2* interacts with tumor necrosis factor receptor-associated factor (TRAF) proteins and either I-B kinase or mitogen-activated protein kinase to activate either NF-κB or Jun kinase (Ellinghaus et al. 2010). Encoding endoplasmic reticulum aminopeptidase 1 (*ERAP1*), located in 5q15 associated region, which encodes an amino peptidase regulatory factor for the quality of peptides bound to MHC class I molecules, is implicated in psoriasis in both European and Chinese populations (Strange et al. 2010; Sun et al. 2010). Compelling evidence shows that it exits the interaction between the *HLA-C* and *ERAP1* loci in the psoriasis pathogenesis process. *ERAP1* variants could influence psoriasis susceptibility in individuals who carry the *HLA-C* risk allele (Strange et al. 2010).Variants of the gene encoding zinc-finger protein 313 (*ZNF313*) are also associated with psoriasis as well (Capon et al. 2008). *ZNF313* has a similar role of as the ubiquitin ligase of *TRAC-1* to regulate T cell activation. The present data also provide evidences that skin barrier function plays a role in psoriasis susceptibility. A deletion polymorphism of two genes (*LCE3C* and *LCE3B*) is associated with psoriasis in different populations (de Cid et al. 2009; Zhang et al. 2009). The *LCE* genes encode the stratum corneum proteins of the cornified envelope, which is important in epidermal terminal differentiation (Mischke et al. 1996). Genetic susceptibility variant(s) within the *LCE* genes may influence the development of psoriasis by interrupting the terminal differentiation of keratinocytes. Collectively, the genetic determinants could lead to dysregulation of innate and adaptive immunity and to epidermal barrier dysfunction in disease process.

Common genetic factors in autoimmune or inflammatory diseases

To evaluate the relationship between psoriasis and autoimmune disease, the findings of one retrospective study suggest that psoriasis patients are more likely to be diagnosed with an autoimmune disease than individuals without psoriasis (Wu et al. 2012). Common autoimmune or inflammatory (immune-mediated) diseases, such as RA, CD, MS, celiac disease (CeD), inflammatory bowel disease (IBD), ankylosing spondylitis (AS), and systemic lupus erythematosus (SLE), are highly prevalent in psoriasis patients. Psoriasis and psoriatic arthritis (PsA) are interrelated disorders that share pathophysiological mechanisms. The occurrence of psoriasis in conjunction with chronic inflammatory arthritis is range from 10% to 30% of individuals with the disease.

Many confirmed and nominally associated psoriasis susceptibility loci show a high level of overlap with the associated loci of other autoimmune diseases. This marked overlap of autoimmune disease susceptibility loci may occur when the same variants contribute to multiple diseases or when different variants in the same gene confer

susceptibility to various autoimmune diseases. Typically, psoriasis is concomitant with autoimmune and inflammatory diseases (Makredes et al. 2009), sharing many susceptibility genes between them (Table 3). Several associated genes are also implicated in other immune-mediated disorders, notably CD (Ellinghaus et al. 2012), offering insights into the postulated shared pathogenesis of CD and PS. In addition to psoriasis, *IL23R* is associated with IBD, PsA, and MS (Duerr et al. 2006; Begovich et al. 2007; Liu et al. 2008), highlighting the functional role of the IL-23/Th17 axis in immune-mediated inflammatory and autoimmune processes. Furthermore, many genes involved in the NF-κB pathway, such as *TNFAIP3* and *NFKB1A*, are also linked to risk for other autoimmune diseases (Fung et al. 2009; Han et al. 2009; Bowes et al. 2010; Li et al. 2013). Although *HLA-C* remains the strongest susceptibility candidate gene in psoriasis, evidences for an interaction between *HLA-C* and other autoimmune diseases have been confirmed by GWAS (Raychaudhuri et al. 2012). These and other regions of genetic association shared with autoimmune diseases indicate that psoriasis may have similar immune mechanism and pathogenic pathways. However, common susceptibility genes among different phenotypes suggest that genetic variation may influence the entire pathways to increase the risk for multiple diseases.

Next-generation sequencing

Our understanding of the genetic basis of psoriasis has been rapidly advanced by GWAS approach. More than 40 robust susceptibility loci have been identified and confirmed to be associated with psoriasis using this technique. However, most of the

Table 3 Susceptibility genes in risk loci shared by autoimmune or inflammatory diseases

Region	Reported gene (s)	Biological annotations	Autoimmune and inflammatory diseases overlap
1p31.3	*IL23R*	IL-23/Th17 axis	PsV, AS, BD, CD, LE, UC
1p36.11	*RUNX3*	CD8+ T lymphocyte differentiation	PsV, CD, AS, CeD
2q24.2	*IFIH1*	Interferon signaling pathway	PsV, T1D, vitiligo
2p16.1	*REL*	Rel/NF-κB family	PsV, PA, CD, RA, CeD, IBD
5q33.3	*IL12B*	Th1 cell differentiation	PsV, CD, IBD, MS, PA, UC,
5q33.1	*TNIP1*	NF-κB pathway	PsV, IBD, SS, SLE, myasthenia gravis
5q31.1	*IL13*	Th2 cell differentiation	PsV, IBD, asthma, AD
5q15	*ERAP1*	MHC class I processing	PsV, AS, BD
6q23.3	*TNFAIP3*	NF-κB pathway	PsV, CeD, SLE, IBD, RA
6q21	*TRAF3IP2*	NF-κB pathway; IL-23/Th17 axis	PsV, IBD, PA
6p21.33	*HLA-C*	MHC class I processing	PsV, CD, PA, CRD, SJS-TEN, vitiligo
10q22.3	*ZMIZ1*	Inhibitor of activated STAT	PsV, MS, CD, vitiligo, CeD, IBD,
11q24.3	*ETS1*	Regulation of Th17 and B cells	PsV, SLE, CD, RA
16p13.13	*SOCS1*	IL-7RA/IL-7 pathway	PsV, MS, T1D
19p13.2	*TYK2*	IL-23/Th17 signaling	PsV, MS, T1D, CD
22q11.21	*UBE2L3*	Ubiquitin-conjugating enzyme	PsV, SLE, IBD, CeD, RA

(Using NHGR1 GWAS catalog data, http://www.genome.gov/gwastudies/). PsV, psoriasis vulgaris; PsA, psoriatic arthritis; AD, atopic dermatitis; IBD, inflammatory bowel disease; AS, ankylosing spondylitis; BD, Behcet's disease; CD, Crohn's disease; CeD, celiac disease; LE, leprosy; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, systemic sclerosis; T1D, type I diabetes; UC, ulcerative colitis; SJS-TEN, Stevens-Johnson syndrome and toxic epidermal necrolysis.

identified risk variants are expected to be tagged as SNPs, and the functional coding variants of these susceptibility genes, particularly those that are of low frequency and rare, are largely refractory to the interrogation by GWAS. Therefore, such variants have not been systematically investigated. With the development of technologies for next-generation sequencing (NGS) technologies, such as exome sequencing analysis, the systematic investigation of coding variants is possibly. Recently, a large-scale sequencing analysis of functional coding variants was performed to investigate the contribution of functional coding variants to the genetic susceptibility of psoriasis in a Han Chinese population, identifying seven common and low-frequency nonsynonymous variants within known psoriasis susceptibility genes, including *IL23R*, *GJB2, LCE3D*, *ERAP1*, *CARD14*, and *ZNF816A*, that are associated with psoriasis risk (Tang et al. 2013).

Conclusions

The pathogenesis of psoriasis involves a complicated interaction between genetic and immunological and environmental components. During recent years, there have been great advances and tremendous achievements in immunity and genetic research on psoriasis that have contributed to the understanding of the mechanism of psoriasis. It is clear that Th1, Th17, and Th22 cells, which interact with each other, mediate the immunity response in disease development. Recent GWAS have identified a variety of genetic components involving both the immune system and the epidermis that affect psoriasis pathogenesis. Several genetic factors and pathways shared with autoimmune and inflammatory (immune-mediated) diseases highlight a common mechanism in different diseases. However, a substantial proportion of the involved genetic factors have yet to be identified, and it is difficult to clarify how these genetic factors and pathways intersect and contribute to inflammation, proliferation, and altered differentiation in psoriasis. Fine mapping and resequencing efforts, together with extensive functional studies, are required to detect all potential causal variants for the susceptibility to psoriasis. Recent advances in next-generation sequencing technologies will enable the increased understanding of the pathogenetic mechanisms and will position a number of confirmed genes or pathways as potential targets for future therapeutic intervention.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
XJZ conceived of the review and participated in its design and coordination. LDS designed the review, drafted the manuscript, and gave the final approval of the version to be published. Both authors read and approved the final manuscript.

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