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Authors
Gupta, Rashmi
Debbaneh, Maya G
Liao, Wilson

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Genetic Epidemiology of Psoriasis

Rashmi Gupta, Ph.D.[1], **Maya G. Debbaneh, B.A.**[1,2], and **Wilson Liao, M.D.**[1]

[1]University of California, San Francisco, Department of Dermatology, San Francisco, CA

[2]University of California, Irvine, School of Medicine, Irvine, CA

Abstract

Psoriasis is a chronic, inflammatory, immune-mediated skin condition with a prevalence of 0-11.8% across the world. It is associated with a number of cardiovascular, metabolic, and autoimmune disease co-morbidities. Psoriasis is a multifactorial disorder, influenced by both genetic and environmental factors. Its genetic basis has long been established through twin studies and familial clustering. The association of psoriasis with the HLA-Cw6 allele has been shown in many studies. Recent genome-wide association studies have identified a large number of other genes associated with psoriasis. Many of these genes regulate the innate and adaptive immune system. These findings indicate that a dysregulated immune system may play a major role in the pathogenesis of psoriasis. In this article, we review the clinical and genetic epidemiology of psoriasis with a brief description of the pathogenesis of disease.

Keywords

psoriasis; genetic; prevalence; epidemiology; pathogenesis

Introduction

Psoriasis is a chronic inflammatory disease of skin characterized by well-demarcated, erythematous and thickened plaques with overlying scale. According to the National Psoriasis Foundation (NPF), it affects approximately 2.2 to 2.6% of the population of the United States. It is a disease known to negatively impact quality of life, including reduced levels of employment and income [1-3]. Every year approximately 150,000 new cases are reported in U.S. and the majority of these cases are in persons less than 30 years of age. Psoriasis is also common in other parts of the world. According to World Psoriasis Day consortium, psoriasis affects 3% of the world's population, about 125 million people. It shows a higher prevalence in people of European descent than those of African and Asian descent [4, 5].

Corresponding Author: Wilson Liao 515 Spruce Street San Francisco, CA 94118 Phone: (415) 476-8364 Fax: (415) 476-8837 LiaoWi@derm.ucsf.edu.
Contact Information:
Rashmi Gupta 2340 Sutter Street San Francisco, California 94143 Phone: 415-476-8787 GuptaR@derm.ucsf.edu
Maya G. Debbaneh 515 Spruce Street San Francisco, California 94115 Phone: 714-501-5193 maya.debbaneh@gmail.com

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It is known that psoriasis has a genetic component based on studies done in families and twins and epidemiological studies done in different populations. These studies suggest that psoriasis is a multifactorial or polygenetic disease that is influenced by both genetic and environmental factors. Linkage and association studies have found a major susceptibility locus called psoriasis susceptibility locus 1 (PSORS1), which resides in the major histocompatibility complex (MHC). Recent studies have identified 41 new psoriasis susceptibility loci [6-14]. But collectively these loci do not explain the entire genetic contribution to disease and additional loci may be present. Here, we review the genetic epidemiology of psoriasis and the susceptibility loci identified to date.

Prevalence of Psoriasis Around the World

The prevalence of psoriasis varies significantly around the world (Table I). The prevalence of psoriasis appears to be highest in Northern Europe and lowest in East Asia. Individual populations may have unusually high rates (Kazachye, Russia, 11.8%) or low rates (Andean Indians and Australian Aborigines, 0%) suggesting that genetic factors or environmental contributions such as diet may play an outsize role in these populations.

Early Onset and Late Onset Psoriasis

It has been noted in several studies that clinical differences exist between early onset psoriasis and late onset psoriasis. Henseler et al. first described early onset, or type I psoriasis, with a disease onset of less than 40 years of age. They observed that type I psoriasis was more likely to be familial, have a severe clinical course and is associated with HLA-Cw6, −B13 and −B57. Late onset, or type II psoriasis, generally occurs in those between the ages 50 to 60 and is correlated with HLA-Cw2 and −B27 [15, 16].

Similarly, a 2002 Spanish study showed that early onset psoriasis, defined as onset below 30 years of age, was more likely to be unstable, more severe, and associated with a positive family history of psoriasis. Furthermore, early onset psoriasis tended to have a greater psychosocial impact on patients and guttate-type psoriasis was associated with younger age of onset and with nail involvement. The presence of a precipitating factor was also more often observed in patients below the age of 30, most commonly an upper respiratory infection or climatic change. On the other hand, in late onset psoriasis (above 40 years old), palmoplantar psoriasis was significantly more common. Interestingly, no correlation between presence of psoriatic arthritis and age of onset was observed [17].

Psoriasis and Co-morbidities

In recent years, the link between psoriasis and several comorbidities has been established, including psoriatic arthritis (PsA), cardiovascular disease, hypertension, obesity, diabetes and Crohn's disease [18]. These are relevant in the management of psoriasis, especially in the presence of other risk factors for these conditions. Studies have also shown that patients with moderate-to-severe psoriasis, as determined by whether they are receiving systemic treatment or phototherapy, have higher incidence of myocardial infarction, independent of other risk factors [19-22]. One population-based cross-sectional study demonstrated dose response trends between psoriasis severity and cardiovascular comorbid diseases, including

myocardial infarction and peripheral vascular disease. Shared inflammatory pathways between psoriasis and atherosclerosis, including the activation of inflammatory cells and the expression of proinflammatory cytokines may link psoriasis with cardiovascular disease [23].

Studies have shown treatment with systemic agents, such as TNF-inhibitors or oral medications, decrease the incidence of myocardial infarction (MI) in patients with psoriasis [24, 25]. A retrospective study of 8845 patients showed that the 1673 patients who had received TNF inhibitor for at least two months (n = 1673) had a significantly lower risk of MI compared with the 5075 patients who had only received topical therapy (adjusted hazard ratio 0.50; 95% CI, 0.32 – 0.79) [24]. Similarly, a Danish cohort study (n = 2400) showed that patients with severe psoriasis treated with systemic biologics or methotrexate was had lower cardiovascular disease event rates compared to patients treated with other anti-psoriatic therapies [25].

Additionally, psoriasis has been shown to greatly affect quality of life. It has been observed that the prevalence of anxiety, depression, bipolar disorder or delirium is higher in psoriatic patients than controls. The proportion of patients receiving antidepressants, anxiolytics or antipsychotics was higher in psoriatic patients than controls [26]. In fact, the average total yearly health care cost for psoriasis patients (US $11,369) was significantly higher than for controls ($3,427), placing a large economic burden on patients and the healthcare system.

Environmental Triggers of Psoriasis

Twin studies have suggested that psoriasis is not only influenced by genes but also by environmental factors. Known environmental triggers such as infection, stress, excess body weight, medications, cigarette smoking, excessive alcohol intake and even weather and climate can induce or exacerbate psoriasis in many patients. While several bacterial, viral and even fungal infections have been linked to psoriasis, the strongest association occurs with tonsillar *Streptoccocus pyogenes* infection, which has been linked to the development of guttate psoriasis and can persist as chronic plaque psoriasis [27]. Psychological or emotional stress is a commonly reported exacerbating factor in psoriasis [28-30]. In fact, one study showed a significant association between psoriasis and stressful life events in the year preceding diagnosis [28]. This may be due to the observation that stress promotes enhanced migration of dendritic cells to lymph nodes resulting in increased antigen-specific T cell responses [31]. Several studies have also linked increased body mass index (BMI) to increased severity of psoriasis [32-36] and it has been shown that weight loss can lead to improvement of psoriasis [37-39].

Furthermore, certain drugs are known to be inciting or exacerbating triggers of psoriasis, including beta-blockers, lithium, synthetic antimalarial drugs, NSAIDs and tetracyclines [27, 40, 41]. There is some evidence that ACE inhibitors and interferons may also contribute to psoriasis and additional medications have been reported including digoxin, clonidine, and fluoxetine, among others [40]. Even certain climates have been reported to increase the symptoms of both psoriasis and psoriatic arthritis. For example Balato et al. conducted a cross-sectional study documenting worsening of skin psoriasis in the winter, and

improvement in the summer. Similarly, the symptoms of psoriatic arthritis seemed to worsen with cold and improve with heat [42].

Genetic Inheritance of Psoriasis

The present understanding of the genetic inheritance of psoriasis is based on studies conducted in different populations around the world, in affected families and in twins.

Population-Based Studies

Initial evidence of the genetic basis of psoriasis was obtained through studies done on large populations. These studies reported higher incidence of psoriasis among relatives compared with the general population [43-45]. One of the very first such studies was performed by Lamholt et al. in 1963 on 11,000 out of the 30,000 total inhabitants of the Faroe Islands [44]. After studying psoriatic patients and their relatives, there was a much higher rate of occurrence of psoriasis observed in relatives of psoriatic patients; 91% of subjects with psoriasis had affected, first- or second-degree relatives. This study was followed by another large study conducted in Sweden, where Hellgren et al., observed that the risk of developing psoriasis was 8% to 23% in first-degree relatives of psoriasis patients [43-45].

Family-Based Studies

Psoriasis has been extensively studied in multi-generation families [46, 47] and these studies support a genetic basis for psoriasis. According to family-based studies, an offspring of two affected parents has a 50% chance of developing psoriasis; this chance decreases to 16% if only one parent is affected. Also, if a child has psoriasis and neither parent has it, there is an 8% chance for that child's sibling to develop psoriasis [45]. It is estimated that approximately one-third of psoriatic patients have a first-degree relative affected by the disease [48]. Furthermore, the heritability, which denotes the proportion of variability of a trait attributed to a genetic factor, is believed to range from 60% to 90% in psoriasis [49, 50].

Twin Studies

The genetic basis of psoriasis is supported by results of studies done in monozygotic and dizygotic twins in different parts of the world. Most of these studies report a high concordance rate in monozygotic twins (35% to 72%) in comparison to dizygotic twins (15% to 23%) [51-53]. The genetic basis of psoriasis is further established by the finding that monozygotic twins concordant for psoriasis show similarity in age of onset, body distribution, severity and course. However, none of these studies reported a 100% concordance rate, indicating the potential role of environmental factors in triggering psoriasis.

Identification of Genetic Loci

Psoriasis is regarded as a complex genetic disease involving multiple genes, some of which may interact with each other [10, 54]. In the last 30 years, many attempts have been made to identify genetic loci that confer susceptibility to psoriasis.

Linkage-Based Approaches

The earliest attempts to identify susceptibility loci in psoriasis began in the 1990s when a number of groups performed genome wide scans in families affected by psoriasis to identify psoriasis susceptibility loci [55-62]. All these studies used genetic linkage techniques to identify disease susceptibility loci.

Linkage based analyses are family based. In these studies, two marker alleles, one on each side of a susceptibility locus, are first identified. These marker alleles should be spaced on the chromosome in such a way that they are always transmitted together along with the disease allele. These studies rely on the assumption that a marker allele located near a disease gene is always transmitted along with the disease allele in a family, if there is no recombination event in that family. This approach is quite successful in genetic studies of Mendelian diseases. These diseases are generally caused by one gene and the disease allele is often a rare allele that has a substantial effect on those with the disease. However, in the case of a common and complex genetic disorder like psoriasis, linkage-based approaches are less successful. The reason for this is because in complex disease, the causative allele is often a common allele in the population with a low penetrance and mild contribution to the disease. All these factors require that a large number of samples be studied for genetic markers to obtain good statistical power. Nonetheless, studies based on the linkage approach have identified 10 loci (PSORS1 to 10) as psoriasis susceptibility regions. These susceptibility regions, detected by linkage analysis in psoriasis family, include 6p21.3 (PSORS1), 17q25 (PSORS2), 4q (PSORS3), 1q21 (PSORS4), 3q21 (PSORS5), 19p13 (PSORS6), 1p (PSORS7), 16q (PSORS8), 4q31-34 (PSORS9) and 18p11.23 [63]. However, other than PSORS1, no other major susceptibility locus has been consistently replicated by other studies.

PSORS1

PSORS1 region is one of the most extensively studied regions in psoriasis. This region is approximately 300kb and immediately telomeric to the gene coding for HLA-B. Association of PSORS1 to psoriasis has been replicated in a number of studies. According to various reports, PSORS1 accounts for 35% to 50% of the heritability of the disease [58, 60]. In addition to *HLA-B* and *HLA-C*, it contains around nine other genes [60, 64]. It has been very difficult to identify the actual causative gene(s) due to extensive linkage disequilibrium (LD) in the region. In 2006, Nair et al. used ancestral haplotype mapping and DNA sequencing to map the PSORS1 region in 678 affected families [65]. Their results suggested *HLA-C* as the causative gene and normal *HLA-Cw6* allele as the susceptibility allele in PSORS1 region. These findings are consistent with previous serological findings in which an association between the *HLA-Cw6* allele and psoriasis was observed [66, 67]. The role of *HLA-C* in psoriasis has been replicated by many groups and has also been confirmed in a study done in Chinese Han patients using fine linkage mapping [68]. A recent study involving 1,727 psoriasis cases and 3,581 controls has shown that additional HLA alleles such as B*38:01, A*02:01, B*39:01, B*27:05, B*08:01, B*14:02, B*55:01, and *B*57:01* independently contribute to the PSORS1 signal in individuals of European descent [69].

Association Studies

Linkage studies are not well suited for studying common complex diseases such as psoriasis. For such diseases, association studies are more powerful than linkage studies. Association studies are population-based studies in which the association between a disease allele and a particular disease trait is studied in both a case and control population. Association studies rely on studying a large number of markers within or around a candidate gene or region. However, association studies are technologically challenging, as they require a large number of genetic markers to completely scan the genome [70]. Thus, association studies were not feasible in the past. With the advent of genome-wide single nucleotide polymorphism (SNP) microarrays and the completion of HapMap project, it became possible to comprehensively scan the genome. In the last 5 years, 12 genome-wide association studies (GWAS) have been performed on psoriasis [71, 72, 12, 13, 73]. These studies report 41 genetic loci associated with psoriasis (Table II).

There are several interesting findings of these GWAS. First, these studies confirm the previous major finding that psoriasis is associated with the *HLA-C* locus. Additionally, these studies report that many disease alleles are relatively common in the population, with a minor allele frequency (MAF) greater than 5%. Also, several of the loci observed to be associated with psoriasis in these studies have also been reported to be associated with other autoimmune diseases. Finally, these studies indicate a significant association between psoriasis and genes involved in specific inflammatory pathways, including NF-kB and IL23-Th17.

Rare Variants

Although GWAS studies conducted in recent years have contributed greatly to our present understanding of the genetic variants associated with psoriasis, our catalogue of genetic susceptibility factors is still incomplete. This is because GWAS studies are based on the Common Disease Common Variant (CDCV) hypothesis, which states that genetic variants predisposing to common diseases are common variants in a population. GWAS studies, which do not examine rare variants (MAF<5%), do not explicitly capture the contribution of rare variants to disease susceptibility. In recent years, a number of studies have looked at the role of these rare variants in psoriasis. These studies have analyzed a number of genetic loci, including *IL36RN/IL1F5*, *CARD14* and *IFIH1* and have observed more rare variants in cases than in controls [74, 75]. In another study of rare variants, Li et al. observed that rare variants in *IFIH1* were associated with decreased risk of psoriasis [76].

Psoriasis is an immune-mediated disorder

Most of the current research indicates that psoriasis is caused by dysregulation of the immune system, with a number of cytokines involved in the pathogenesis of psoriasis. As already mentioned, GWAS studies have identified a number of genetic loci associated with psoriasis. Several of these loci belong to various immunological pathways, indicating a role of these pathways in the pathogenesis of psoriasis. Some of these pathways are discussed below:

HLA-Cw6 and Psoriasis

As already stated, *HLA-Cw6* is one of the most studied alleles in psoriasis. In a study conducted on 201 psoriasis patients and 77 healthy controls in Sweden, it was observed that 67% of the patients were positive for one or two copies of the allele, while only 12% of the controls were positive [77]. Similar percentages have been observed in other studies [78]. The *HLA-Cw6* allele has also been associated with early age of onset and more severe disease [79]. It has also been reported that patients homozygous for this allele have a higher disease risk (2.5 times) than the patients who are heterozygous for this allele [78]. In addition, guttate-type psoriasis, which is characterized by appearance of small red scaly lesions, is mostly observed in *HLA-Cw6* positive patients [79, 80]. All these facts indicate a strong association of *HLA-Cw6* with psoriasis. In spite of all these associations, the actual function of *HLA-Cw6* in psoriasis is not known, although many mechanisms have been proposed. According to one theory, *HLA-Cw6* might exert its effect via both the innate and adaptive immune systems. It has been proposed that *HLA-Cw6* may regulate the adaptive immune response by presenting antigens to T cells. In addition, *HLA-Cw6* can regulate the innate immune response by interacting with a class of receptors known as killer immunoglobulin like receptors (KIR), which are expressed on natural killer and natural killer T cells. This interaction can either activate or inhibit NK cells, depending upon the type of KIR receptor. NK and NKT cells serve as a bridge between innate and adaptive immunity and can play an important role in the pathogenesis of psoriasis. It may be possible that the presence of the HLA-Cw6 allele, may affect the expression and/or activity of HLA-C leading to abnormal innate or adaptive immune responses, resulting in psoriasis.

NF-kB signaling

Various GWAS studies on psoriasis have indicated association with genes, whose products are involved in NF-kB signaling pathway. NF-kB is a transcription factor that plays an important role in the inflammatory response. In resting cells, it remains localized in the cytoplasm by binding to inhibitors of kB (IkB). In response to stimulation, it gets activated and translocates to the nucleus where it binds to DNA and initiates transcription. Its activation is initiated by a signal-induced ubiquitination and degradation of IkB by IkB kinase (IKK). GWAS studies done in psoriasis identified five genes associated with NF-kB signaling: *TNFAIP3, TNIP1* (TNFAIP3 interacting protein 1), *TRAF3IP2, REL*, and *NFKBIA* [8, 72, 9-12, 81]. The products of *TNFAIP3* and *TNIP1*, A20 and ABIN1, respectively interact with each other and participate in negative regulation of the NF-kB pathway. *NFKBIA* codes for the inhibitory protein, IkBa and *TRAF3IP2* codes a protein involved in regulating responses to cytokines by members of the Rel/NF-kB transcription factor family. All these associations indicate that a dysregulated NF-kB pathway might play important role in psoriasis. Recently, Huffmeier et al. performed functional studies on the coding variant TRAF3IP2 p.Asp10Asn (rs33980500), which was the most significantly associated SNP in their study, observing that this variant showed reduced binding to TRAF6, a protein that plays important role in NF-kB activation [72].

IL23/Th17 pathway

IL23 is a heterodimer cytokine consisting of two subunits (IL12p40 and IL23p19). GWAS studies in psoriasis have found three genetic markers that map to components of IL23 ligand-receptor complex [82, 9]—IL12B, IL23A and IL23R. The important role of IL23 signaling in the pathogenesis of psoriasis is suggested by elevated mRNA expression of IL23p19 and IL12p40 in lesional skin compared with non-lesional skin in psoriasis patients [83, 84]. Clinical studies have also shown that reduction in the level of IL23 by cyclosporine, ultraviolet (UV) therapy or biological agents lead to improvement in psoriasis [85]. It has also been shown that blocking IL-12 and IL-23 by using a monoclonal antibody targeting the p40 subunit, has a positive effect on psoriasis lesions [86-88]. DiMegelio et al. performed functional studies on a non-synonymous G to A SNP (rs11209026) in the IL23R gene [89], which was previously shown to confer protection against psoriasis in many GWAS findings [55, 9]. They generated Th17 cells from healthy individuals heterozygous for the protective allele and showed that there was impairment in IL-17A production in response to IL23 in these cells. They further found that AA homozygous individuals were almost unresponsive to IL23 induction [90].

IL23 also plays a role in expansion and survival of a recently discovered subset of T cells, referred to as Th17 cells [91, 92]. These cells produce proinflammatory cytokines, IL-17A, IL-17F, IL-22 and IL-26. These cytokines can cause hyperproliferation of keratinocytes and lead to production of more cytokines, chemokines and antimicrobial peptides. All these factors may further enhance the inflammation. A great emphasis has recently being given to the role of Th17 pathway in pathology of psoriasis [93, 94]. It has also been observed that the number of Th17 cells and IL-17 producing innate cells are increased in blood as well as skin of psoriasis patients [95-97]. Similarly, mRNA level of IL17A is increased in psoriasis lesions in comparison to non-lesional skin [98]. In an interesting study conducted in transgenic mice, it was observed that IL-17A deficient mice showed partial attenuation of psoriatic lesions, which were further attenuated by anti-IL-12/23p40 Ab treatment [99]. All these studies indicate an important role of IL-23/Th17 pathway in psoriasis. These studies also indicate that modulating the IL-23 and/or IL-17A could have a therapeutic effect on psoriasis.

Pathogenesis of Psoriasis

It is currently believed that both the adaptive and innate immune systems play important roles in pathogenesis of psoriasis. The various cell types observed within psoriatic lesions include keratinocytes (KC), dendritic cells (DC), monocytes, macrophages and T and B lymphocytes [100-103]. The involvement of T cells with psoriasis has been supported by many studies. These studies report that suppressing T cells, either through use of cyclosporine, a T cell immunosuppressant [104] or other biologics, e.g. anti-CD4 antibodies [105] lead to improvement in psoriasis lesions. Psoriatic lesions have different subsets of T cells, including T helper 1 cells (Th1), cytotoxic T cells (Tc) and Th17 cells. The crucial role of T cells in psoriasis is further established by a report indicating that different kinds of T cells are present in different anatomic sites of the lesional skin—Th1 and Th17 cells are predominantly found in upper dermis [97] whereas Tc cells are mostly present in the

epidermis. The key effector cells of the innate immune response involved in the pathogenesis of psoriasis include macrophages, KCs, DCs, mast cells, neutrophils, natural killer (NK) cells and natural killer T (NKT) cells [106]. Various studies indicate that number of these cells is increased in psoriatic skin lesions [107-110]. Various innate cytokines such as IL-12, IFN-γ, IL-17, Il-23, IL-6, IL-8, and TNF-α play an important role in the pathogenesis of psoriasis by recruiting pro-inflammatory cells to psoriasis lesions. It has also been suggested that, signaling by pathogen recognition receptors such as TLR3, −4, −7 and −9 may lead to the development of an inflammatory environment in which autoantigen-specific T cells become activated. This may further promote development of psoriasis.

Mechanism of Disease

GWAS studies and functional studies indicate that a dysregulated immune system might be responsible for psoriasis inflammation. However, the exact mechanism of the events that lead to psoriasis is not entirely known. Various models have been proposed regarding the mechanism of disease. According to one common model (Figure 1), psoriasis occurs as a result of an interaction between genetic factors of the host and environmental triggers [2, 111, 112]. In the presence of an environmental trigger, keratinocytes become stressed and release antimicrobial peptide, LL-37, which may complex with self-DNA and thus act as an activator of pDCs through TLR9 [113]. Upon activation, pDCs release IFN-α, which activates dermal DCs. Dermal DCs enter lymph nodes and induce T cell differentiation into Th1, Th17 and Tc cells. These effector cells recirculate and migrate into skin tissues. Here, they release a number of proinflammatory cytokines responsible for causing the disease. Others have also speculated that LL-37 can complex with self RNA and that this complex can activate mDCs through TLR8 [114]. mDCs in turn can produce large amounts of TNF-α and IL-6. As mDCs can also produce IL-23 in psoriasis [83], IL23 can activate Th17 cells, which can produce effector cytokines that further cause inflammation.

Future Studies of Psoriasis

To identify additional psoriasis susceptibility variants, a number of genetic studies are currently underway. Meta-analyses of genome-wide association studies are being conducted to identify novel common variants. Exome sequencing, exome genotyping chip, and whole genome sequencing studies of psoriasis are being used to identify novel rare variants. Functional studies will be needed to address how genetic polymorphisms relate to disease mechanism. Epidemiologic studies that link genotype to clinical outcomes in psoriasis will ultimately facilitate the practice of personalized medicine.

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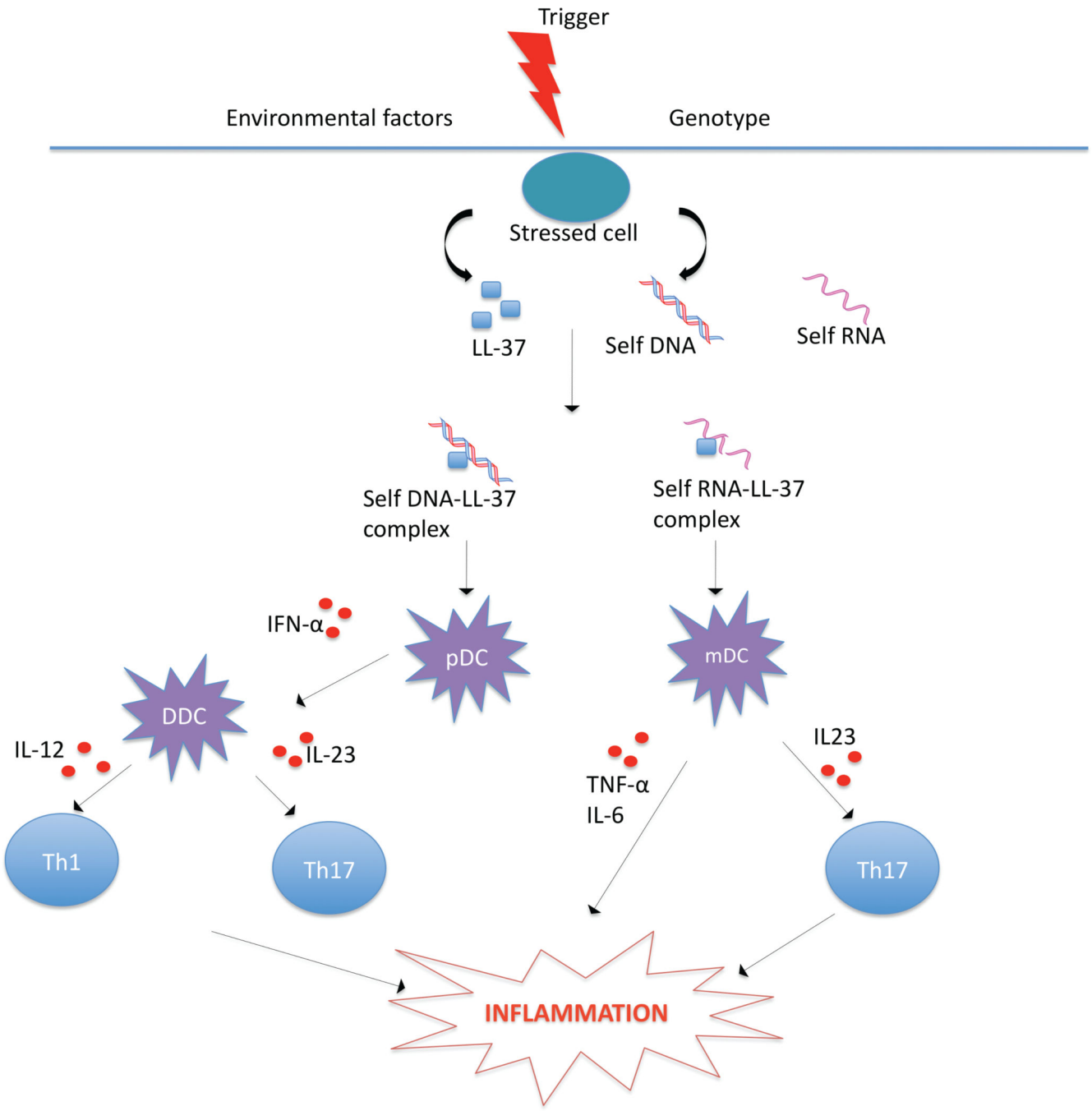

Figure 1.

Potential mechanism of initiation of psoriasis. Certain infections or skin injuries can act as trigger and stimulate keratinocytes (shown here as stressed cell) to release antimicrobial peptide, LL-37. LL-37, can in turn complex with self-DNA. This complex can then activate plasmacytoid DCs (pDCs) and stimulate them to release IFN-α, which activates dermal DCs (DDC). DDCs can induce T cell differentiation into Th1, Th17 and Tc cells by entering into lymph nodes. LL-37 can also complex with self-RNA and activate myeloid DCs (mDCs). mDCs in turn can produce large amounts of inflammatory cytokines, TNF-α and IL-6.

mDCs can also produce IL-23 and thus activate Th17 cells, which can produce effector cytokines that further cause inflammation. Adapted from Nestle et al., 2009 and Nograles et al., 2010 [2, 174].

Table I

Prevalence of psoriasis in various parts of the world.

Location	Prevalence (%)
North America	
Caribbean Islands	6.0 [115],*
Canada	4.7 [5]
United States	4.6 [5]
African Americans	0.7 [5] – 1.3 [116]
Caucasians	2.5 [116]
Andean Indians	0 [115],**
Mexico	3.0 [115]
Nicaragua	0.2 – 0.9 [115]
Guatemala	0.7 [115]
Honduras	0.7 [115]
South America	
Paraguay	4.2 [115]
Venezuela	2.0 [115]
Brazil	1.3 [115]
Europe	
Germany	2.0 [117] – 6.5 [115]
Ireland	5.5 [115]
Scotland	0.73 [117] – 4.8 [115]
Spain	1.0 [118] – 3.7 [115]
Italy	2.9 [117]
Denmark	2.84 [117]
Faroe Island	2.8 [5]
Sweden	2.0 [117] – 2.3 [115]
Norway	1.4 [5],[119] – 2.0 [115]
United Kingdom	1.5 [116] – 1.87 [117]
Yugoslavia	1.58 [117]
Croatia	1.55 [5]
Asia	
Kazachye, Russia	11.8 [115]
Malaysia	4.0 – 5.5 [115]
Kuwait	3.1 [115]
Egypt	3.0 [115]
Former USSR	2.0 [115]
India	0.5 – 1.5 [115]
China	0.2 – 1.5 [115],***

Location	Prevalence (%)
Japan	0.29 – 1.18 [115]
Africa	
South Africa	4.0 – 5.0 [115]
Kenya	3.5 [115]
Tanzania	3.0 [115]
Uganda	2.8 [115]
Nigeria	0.08 – 0.4 [115]
Angola	0.4 [115]
Mali	0.05 [115]
Australia	
White Australians	2.6 [115]
Australian Aborigines	0 [115]

* The Caribbean population includes African descendants, East Indians and Caucasians

** This reflects similar findings reported in Native Alaskan, Canadian and American populations of the United States.

*** It is suggested that the lower frequency of HLA-Cw6 in the Chinese population may contribute a lower rate of psoriasis

Table II

Genes	Description	Function	Chr	Odds Ratio	Overlap with autoimmune diseases	Ethnicity	References
HLA-B, HLA-C	Human Leucocyte antigen	Correspond to MHC class I, present antigens to immune cells.	6p21.33	4.32	AS[120] MS[121, 122] CD[123]	European, Chinese	Trembath et al., 1997[60], Nair et al., 1997[58]; Nair et al., 2006[65], Fan et al., 2008[68], Popa et al., 2011[124]
TYK2	Tyrosine Kinase 2	Associates with the cytoplasmic domain of type I and type II cytokine receptors and phosphorylates receptor subunit thus promoting cytokine signals.	19p13.2	1.88	T1D[125, 126] CD[127] IBD[123]	European	Strange et al., 2010[10]
TNIP1	TNAIP3-interacting protein	Regulation of nuclear factor kappa-B activation	5q32-q33.1	1.59	SLE[128, 129] SS[130] IBD[123]	European, Chinese	Nair et al., 2009[9], Sun et al., 2010[12]; Strange et al., 2010[10], Chen et al., 2011[69]
IL12B	p40 subunit of IL-12/23	IL12 promotes activation of T and NK cells, enhances lytic activity of killer cells and stimulates resting PBMCs to produce IFN-g. IL23 plays important roles in innate and adaptive immunity.	5q31.1-q33.1	1.58	AS[120] CD[127, 131-133] IBD[123] MS[122, 134] UC[135]	European, Chinese	Tsuenemi et al., 2002[136], Nair et al., 2009[9]
IL23R	IL23 receptor subunit	The subunit pairs with the receptor molecule IL12RB1/IL12Rbeta1 to make receptor for IL23A signaling.	1p31.3	1.52	AS[120, 137] CD[131, 132, 138-144, 127] IBD[123, 145, 146] UC[135, 14, 147, 148] Behcet's disease [149, 150]	European	Cargill et al., 2007[11], Nair et al., 2009[9]
TRAF3IP2	TRAF3-interacting protein 2	Involved in regulating responses to cytokines by members of the Rel/NF-kB transcription factor family.	6q21	1.52	IBD [123]	European, Pakistani	Ellinghaus et al., 2010[8], Shaiq et al., 2013[81]
STAT2, IL23A	Signal transducer and activator of transcription 2/ p19 subunit of IL23	STAT family members act as transcription activators. /IL23 can activate the transcription activator STAT4, and stimulate the production of interferon-gamma (IFNG)	12q13.2	1.39	Not known	European	Chen et al., 2011[69], Nair et al., 2009[9], Strange et al., 2010[10]
KCNH7, IFIH1	Potassium voltage-gated channel subfamily H member 7/IFN induced helicase	Regulating neurotransmitter release, heart rate, insulin secretion, neuronal excitability, epithelial electrolyte transport, smooth muscle contraction, and cell	2q24	1.27	IBD[123] T1D[151, 152, 126]	European	Strange et al., 2010[10], Li et al., 2010[76]

Genes	Description	Function	Chr	Odds Ratio	Overlap with autoimmune diseases	Ethnicity	References
	C domain 1	volume. / Sensing viral infection and activation of a cascade of antiviral responses including the induction of type I interferons and proinflammatory cytokines.					
LCE3B, LCE3D	Late Cornified envelope	Encodes for stratum corneum proteins of cornified envelope. Barrier skin function	1q21.3	1.26	Not known	Chinese, European	de Cid R, et al 2009[6], Zhang et al., 2009[14], Chen et al., 2011[69], Xu et al 2011[153]
TNFAIP3	Tumor Necrosis factor-□ induced protein 3	A zinc finger protein and ubiquitin-editing enzyme; inhibits NF-kappa B activation as well as TNF-mediated apoptosis.	6q23.3	1.23	RA[154, 155] CeD[156] IBD[123] RA[156] SLE[157, 129, 128]	European, Chinese	Nair et al., 2009[9], Sun et al., 2010[12]
NOS2	Nitric Oxide synthase 2	Inducible by a combination of lipopolysaccharide and certain cytokines; Nitric oxide acts as a biologic mediator in several processes, including neurotransmission and antimicrobial and antitumoral activities.	17q11.1	1.22	CD[123]	European, Pakistani	Shaiq et al., 2013[81], Stuart et al., 2010[11]
IL28RA	Interleukin 28 receptor, alpha subunit	Common receptor of IFN-l1, -l2 and -l3. These IFNs have antiviral, antitumor & immunomodulatory effects	1p36.11	1.21	Not known	European	Strange et al., 2010 [10]
ERAP1	Endoplasmic reticulum aminopeptidase 1	Involved in trimming HLA class I-binding precursors so that they can be presented on MHC class I molecules.	5q15	1.2	AS[137, 120] Behcet's disease[158] IBD[123]	European, Chinese	Strange et al., 2010[10], Sun et al., 2010[12]
IL13, IL4	IL-13, -4	Modulate humoral immune response mediated by Th2 cells	5q31.1	1.18	IBD[123]	European, Pakistani	Nair et al., 2009[9], Shaiq et al., 2013[81]
FLJ16341, REL	V-rel reticuloendotheliosis viral oncogene homolog	Function not yet known/ c-Rel, a transcription factor that is a member of the Rel/NFKB family	2p16	1.17	RA[159, 160] CeD[156] IBD[123] UC [148] CD [127]	European	Strange et al., 2010[10]

Genes	Description	Function	Chr	Odds Ratio	Overlap with autoimmune diseases	Ethnicity	References
ILF3, CARM1	Interleukin enhancer binding factor 3, coactivator-associated arginine methyltransferase 1	Double-stranded RNA (dsRNA) binding protein that complexes with other proteins, dsRNAs, small noncoding RNAs, and mRNAs to regulate gene expression and stabilize mRNAs. / Involved in signal transduction, metabolism of nascent pre-RNA, and transcriptional activation	19p13.2	1.17	Not known	European	Tsoi et al., 2012[13]
NFKBIA	Nuclear factor of kappa light polypeptide gene enhancer in B cells, alpha	Inhibits NF-kappa-B signaling	14q13.2	1.16	Not known	European	Strange et al., 2010[10], Ellinghaus et a., 2010[8], Stuart et al.,2010[11]
PRSS53, FBXL19	Serine Protease 53, F-box and leucine-rich repeat protein 19	Function not known/ Encodes a member of the Skp1-Cullin-F-box family of E3 ubiquitin ligase, which binds to the transmembrane receptor ST2L and regulates its ubiquitination and degradation. This protein has been linked to the regulation of pulmonary inflammation and psoriasis.	16p11.2	1.16	Not known	European	Stuart et al., 2010[11]
RNF114	Ring finger protein 114	Ubiquitination, regulation of immune response, IFN signaling	20q13.13	1.16	Not known	European	Capon et al., 2008[161], Stuart et al., 2010[11]
PTRF, STAT3, STAT5A/B	polymerase I and transcript release factor, Signal transducer and activator of transcription 3, 5A, 5B	Regulation rRNA transcription/ Encodes for a member of the STAT protein family. In response to cytokines and growth factors, STAT family members act as transcription activators	17q21.2	1.15	CD[127, 162, 131] MS[122, 134, 163] IBD[123]	European	Tsoi et al., 2012[13]
ZC3H12C	zinc finger CCCH-type containing 12C	Encoded protein may function as RNase and regulate the levels of target RNA species	11q22.3	1.14	Not known	European	Tsoi et al., 2012[13]
PRM3, SOCS1	protamine 3, suppressor of cytokine signaling 1	Compacts sperm DNA into a highly condensed, stable and inactive complex/Cytokine-inducible negative regulators of cytokine signaling, the protein functions downstream of cytokine	16p13.3	1.13	T1D[164] CeD[156] CD and psoriasis[7] IBD[123]	European	Tsoi et al., 2012[13]

Genes	Description	Function	Chr	Odds Ratio	Overlap with autoimmune diseases	Ethnicity	References
		receptors, and takes part in a negative feedback loop to attenuate cytokine signaling.					
RUNX3	runt-related transcription factor 3	Transcription factor; plays a role in generation of CD8+ T cells	1p36.11	1.13	AS[120] CeD[156] CD [162]	European	Tsoi et al., 2012[13]
SLC45A1, TNFRSF9	solute carrier family 45, member 1, tumor necrosis factor receptor superfamily, member 9	May mediate glucose uptake along the pH gradient / Encodes for a member of the TNF-receptor superfamily, induces proliferation in peripheral monocytes, enhance T cell apoptosis induced by TCR/CD3 triggered activation, and regulate CD28 co-stimulation to promote Th1 cell responses	1p36.23	1.13	CeD[156] IBD[123] UC[135]	European	Tsoi et al., 2012[13]
UBE2L3	ubiquitin-conjugating enzyme E2L 3	This enzyme is demonstrated to participate in the ubiquitination of p53, c-Fos, and the NF-kB precursor p105 in vitro	22q11.21	1.13	SLE[129, 128, 165] IBD[123] CeD and RA[166] CeD[156]	European	Tsoi et al., 2012[13]
B3GNT2	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 2	Encodes a member of the beta-1,3-N-acetylglucosaminyltransferase family.	2p15	1.12	AS[137], RA[63]	European	Tsoi et al., 2012[13]
ETS1	v-ets erythroblastosis virus E26 oncogene homolog 1	Encodes a transcription factor activated downstream of the Ras-mitogen-activated protein kinase (MAPK) pathway, involved in the homeostatis of squamous epithelia, CD8 T-cell differentiation, negative regulator of Th17 differentiation	11q24.3	1.12	CeD[156] SLE[128], [167] [129] RA[63]	European	Tsoi et al., 2012[13]
EXOC2, IRF4	exocyst complex component 2/interferon regulatory factor 4	Polarized targeting of exocytic vesicles to specific docking sites on the plasma membrane/Regulation of interferons in response to infection by virus, and in the regulation of interferon-inducible genes.	6p25.3	1.12	CeD[156]	European	Tsoi et al., 2012[13]
KLF4	Kruppel-like factor 4	Required for establishing the barrier function of the skin and for postnatal maturation and maintenance of the	9q31.2	1.12	Not known	European	Tsoi et al., 2012[13]

Genes	Description	Function	Chr	Odds Ratio	Overlap with autoimmune diseases	Ethnicity	References
		ocular surface. Involved in the differentiation of epithelial cells and may also function in skeletal and kidney development.					
POLI, STARD6, MBD2	StAR-related lipid transfer (START) domain containing 6, methyl-CpG binding domain 2	DNA repair / Lipid transfer/ may function as a mediator of the biological consequences of the methylation signal, plays a role in generation of memory CD8+ T cells	18q21.2	1.12	Not known	European	Tsoi et al., 2012[13]
TAGAP	T-cell activation RhoGTPase activating protein	Important roles during T-cell activation (Chang et al., 2005)	6q25.3	1.12	CeD[168, 156, 123, 127] CD and CeD[169] MS[134, 122]	European	Tsoi et al., 2012[13]
CARD14	caspase recruitment domain family, member 14	Cellular adhesion, signal transduction and cell polarity control, interacts with BCL10, a protein known to function as a positive regulator of cell apoptosis and NF-kB activation	18q21.2	1.11	Not known	European	Tsoi et al., 2012[13], Jordan et al., 2012[74]
DDX58	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58	Involved in viral double-stranded dsRNA recognition and the regulation of immune response.	9p21.1	1.11	Not known	European	Tsoi et al., 2012[13]
ELMO1	engulfment and cell motility 1	Phagocytosis and cell migration, required for TLR-7 and -9 mediated IFN-α induction by pDCs.	7p14.2-7p14.1	1.11	CeD[156] CeD and RA[166] Type 2 diabetes nephropathy[170]	European	Tsoi et al., 2012[13]
ZMIZ1	zinc finger, MIZ-type containing 1	Encodes a member of the PIAS (protein inhibitor of activated STAT) family of proteins. The encoded protein regulates the activity of various transcription factors, including the androgen receptor, Smad3/4, and p53.	10q22.2	1.1	CeD[156] CD[127] CD and psoriasis[7] IBD [171] MS[122, 134, 121]	European	Ellinghaus et al., 2012[172], Tsoi et al., 2012[13]
RPS6KA4, PRDX5	ribosomal protein S6 kinase, peroxiredoxin 5	Encodes a member of the RSK (ribosomal S6 kinase) family of serine/threonine kinases, phosphorylates various substrates, including CREB1 and c-fos/An antioxidant protective role in	11q13.1	1.09	CD[127]	European	Ellinghaus et al., 2012[172], Tsoi et al., 2012[13]

Genes	Description	Function	Chr	Odds Ratio	Overlap with autoimmune diseases	Ethnicity	References
		different tissues under normal conditions and during inflammatory processes					
PTTG1	Pituitary tumor transforming gene 1	Control of mitosis, cell transformation, DNA repair and gene regulation	5q33.3	1.20*	SLE[165]	Chinese	Sun et al., 2010[12]
CSMD1	CUB and Sushi multiple domains 1	Potential tumor suppressor	8p23.2	1.17*	MS[173]	Chinese	Sun et al., 2010[12]
ZNF816A	Zinc finger protein 816A	May be involved in transcription regulation	19q13.41	0.88*	Not known	Chinese, European	Sun et al., 2010[12]
GJB2	gap junction protein, beta 2	Cell-to-cell channels that facilitate the transfer of ions and small molecules between cells.	13q12.11	0.87*	Not known	Chinese, European	Sun et al., 2010[12]
SERPINB8	Serpin peptidase inhibitor clase B member 8	High molecular weight serine proteinase inhibitors (serpins), regulate a diverse set of intracellular and extracellular processes such as complement activation, fibrinolysis, coagulation, cellular differentiation, tumor suppression, apoptosis, and cell migration.	18q21.3	0.87*	Not known	Chinese	Sun et al., 2010[12]

Odds Ratios are shown for most significant SNP within 500kb (3Mb for MHC region) of the previously published SNP is shown (Tsoi et al., 2012). AS – Ankylosing Spondylitis, MS – Multiple Sclerosis, IBD – Inflammatory Bowel Disease, UC – Ulcerative Colitis, SLE – Systemic Lupus Erythematosus, RA – Rheumatoid Arthritis, CeD – Celiac Disease, CD- Crohn's Disease, T1D - Type 1 Diabetes, SS – Systemic Sclerosis

*Odds ratio based on GWAS combined with replication 1 and 2 (Sun et al., 2010)