Genetics of psoriasis: a basis for precision medicine

Delin Ran1,2, Minglong Cai1,2 and Xuejun Zhang1,2,*

1Institute of Dermatology and Department of Dermatology of the First Affiliated Hospital, Anhui Medical University, Hefei 230032, China, and 2Key Laboratory of Dermatology, Anhui Medical University, Ministry of Education, Hefei 230032, China

*Correspondence: Xuejun Zhang, ayzxj@vip.sina.com

Abstract
Psoriasis is an inflammatory skin disease with a background of polygenic inheritance. Both environmental and genetic factors are involved in the etiology of the disease. In the last two decades, numerous studies have been conducted through linkage analysis, genome-wide association study (GWAS), and direct sequencing to explore the role of genetic variation in disease pathogenesis and progression. To date, >80 psoriasis susceptibility genes have been identified, including HLA-Cw6, IL12B, IL23R, and LCE3B/3C. Some genetic markers have been applied in disease prediction, clinical diagnosis, treatment, and new drug development, which could further explain the pathogenesis of psoriasis and promote the development of precision medicine. This review summarizes related research on genetic variation in psoriasis and explores implications of the findings in clinical application and the promotion of a personalized medicine project.

Key words: psoriasis; genetic variation; linkage analysis; genome-wide association study; precision medicine

Introduction
Psoriasis is a chronic and recurrent skin disease, which has serious negative effects on quality of life (QOL). The prevalence of psoriasis reported in different countries ranges from 0.09% to 11.43%, but in China, it is 0.47%. Current treatment can only alleviate the symptoms of psoriasis not cure them, leaving a huge burden on family and society. The etiology of the disease is unknown, but current research suggests that psoriasis is a complicated disease induced by immune and environmental factors and controlled by interactions of multiple genes. Epidemiological research has confirmed a familial genetic predisposition of psoriasis, with >20% of patients having a positive family history. Investigations have indicated that among psoriasis patients, there is higher morbidity in their first/secondary-degree relatives when compared with the general population, and the morbidity presents a downward trend with increasing parentage coefficient. Further evidence indicates that psoriasis has a genetic predisposition, with researchers having identified >80 susceptibility genes/loci. Gene function studies are under way, which could help us to better understand the pathogenesis of disease and provide new ideas for diagnosis and treatment.

Genetic epidemiology studies
Genetic epidemiology studies mainly include familial aggregation, twin studies, pedigree analysis, and susceptibility...
and heritability analysis. Psoriasis has a distinct family aggregation tendency; in Chinese patients, about 31.26% were reported to have a family history of psoriasis, which covered the entire family tree, and the heritability in first- and second-degree relatives was 67% and 47%, respectively.8 In the past two decades, familial aggregation and twin studies have revealed evident heredity in psoriasis, and it was thought that heritability could be estimated by comparing the concordance between monozygotic (MZ) and dizygotic (DZ) twins.9 However, the results of different studies were inconsistent in concordance rates, possibly because of insufficient numbers of included twins and population heterogeneity.10,11 A large-scale study of 10,725 twin pairs showed that MZ twins had higher concordance rates than DZ twins (proband-wise concordance of 0.33 and 0.17 respectively), indicating a distinct genetic predisposition for psoriasis.12

**Linkage study of psoriasis**

Early genetic research into complex diseases relied on candidate gene analysis and family-based linkage studies.13 Using genetic markers, genotyping was carried out in family members, then mathematical calculations were made to identify whether the markers were co-separated from the disease. A genetic study identified 15 psoriasis susceptibility regions, named Psoriasis Susceptibility 1–15 (PSORS1–15),14 which are suspected to be the main contributors to genetic pathogenesis of psoriasis.

**PSORS1**

Linkage analysis identified PSORS1 in psoriasis, located on the short arm of chromosome 6 within the major histocompatibility complex (MHC) region. PSORS1 has been reported to be associated with psoriasis in different races.15,16 At the PSORS1 locus, the most significant risk allele is HLA-C*06:02, which has been confirmed to have a role in pathogenesis of psoriasis as HLA-C is involved in the immune responses through presenting antigens to CD8+ T cells, the main inflammatory T cells, while migrating into the epidermis.17 Research further revealed that HLA-C*06:02 is involved in the skin autoimmune response mediated by T cells, as it can trigger an autoimmune response against melanocytes in skin through presenting autoantigen.18 HLA-C*06:02 has been found to be associated with psoriasis in different populations such as Asians and Europeans, and defines disease severity, early onset, and familial inheritance of psoriasis.19,20 In addition, this allele is also associated with psoriasis subtypes, with one study finding that HLA-C*06:02 was protective of psoriatic arthritis (PsA) compared to cutaneous psoriasis (PsC).21 Some studies suggested that the HLA-C*06:02 risk allele was associated with a younger age of psoriasis onset; however, in a recent study, after controlling for the age of psoriasis onset, no association of PsA to HLA-C*06:02 was observed.21

There are genes other than HLA-C*06:02 located in the PSORS1 region, such as CCHCR1 and CDSN. CCHCR1, coiled-coil α-helical rod protein 1, also known as pg8 (putative gene 8), HCR, or C6orf18, is located 113 kb telomeric to the HLA-C locus. This gene is highly polymorphic, including at least 12 coding variants. CCHCR1 has been confirmed as a susceptibility gene for psoriasis in several populations such as the Finnish, Indians, and Chinese, and several studies have reported that CCHCR1 is associated with early onset psoriasis, but its exact relationship with the disease pathogenesis is imprecise because of its strong linkage with HLA-Cw6.22,23 An epidemiological study showed that HLA-Cw6 and CCHCR1 had largely the same clinical associations with psoriasis.24 The pattern of expression of CCHCR1 in psoriasis was different from patterns for other hyperproliferative skin diseases, presenting a downregulation in cultured non-lesional keratinocytes when compared to normal healthy keratinocytes. This phenomenon may be explained by a hypothesis that interferon-γ (IFN-γ) might downregulate CCHCR1, allowing activated T lymphocytes to accumulate, which in turn would contribute to keratinocyte hyperproliferation.25,26

The CDSN gene is highly polymorphic and shows restricted expression toward skin. This gene encodes corneodesmosin, and in the process of keratocyte maturation, the encoded proteins undergo a succession of cleavages and are localized to human epidermis. CDSN has been associated with psoriasis, but because of the strong linkage with HLA-Cw6, it is difficult to distinguish its individual genetic effects for psoriasis.27 Identification of PSORS1 facilitated the investigation boom of genetic research into psoriasis, and subsequently PSORS2-12 were gradually identified in diverse populations.16,28,29

**PSORS2**

PSORS2 is located on chromosome 17q25, and mainly refers to mutation in the CARD14 gene.30 CARD14 encodes a caspase recruitment domain-containing protein CARMA2, part of the membrane-associated guanylate kinase (MAGUK) family. This protein mediates the activation of the nuclear factor kappa B (NF-κB) pathway, which plays an important role in cell activation and proliferation, and also relates to the pathophysiology of psoriasis.31 Mutation in CARD14 may result in an inflammatory response in the epidermis and aggravate the formation of psoriasis-like lesions.32 Some studies have found that CARD14 is associated with psoriasis vulgaris (PsV) and generalized pustular psoriasis (GPP), including in the Chinese Han population. A single nucleotide polymorphism (SNP) rs11652075 in this gene was reported as having susceptibility to psoriasis in several races, but not all researchers agreed with this conclusion, perhaps as a result of different sample sizes studied.30,33,34 A recent meta-analysis demonstrated an association between rs11652075 and psoriasis with strong evidence.35 Subsequent functional research is needed to further verify the role of this gene in psoriasis.
**PSORS3–PSORS15**

PSORS3 is deemed to be a significant locus for psoriasis. It is located on chromosome 4q near D4S1535, and the IRF2 gene within PSORS3 has been identified as a risk locus for psoriasis. PSORS4 is located in 1q21, and comprises the epidermal differentiation complex (EDC). The genes in the EDC (18 members in LCE gene family divided into six groups LCE1–LCE6) are mainly expressed in the upper strata of the epidermis. LCE3C-LCE3B-del was identified as a genetic risk factor for psoriasis in Caucasian and Asian populations for a possible effect in skin barrier function, but not in Tunisian families. A study among German patients found that LCE3C-LCE3B-del was only associated with PsV, not PsA. Because the CDSN gene in PSORS1 and LCE gene both express proteins in the epidermis, especially in the stratum corneum, it was hypothesized that direct protein–protein interactions between them may be internal factors for their variant association with psoriasis, but no evidence was found for direct interaction between PSORS1 and PSORS4. PSORS5 was identified early through a genome-wide scan in the Swedish population as being located in 3q21. SLC12A8 in PSORS5 has been described as having an association with PsV. Another psoriasis-associated gene in this region is CSTA (cystatin A), which encodes the skin barrier cystein protease inhibitor, a precursor of cornified cell envelope formed in the process of the keratinocyte terminal differentiation. It was closely associated with keratinocyte differentiation, and it was suggested that the association between CSTA variant and psoriasis was attributed to its linkage with HLA-Cw6, but this was later confirmed as an independent association. PSORS6 is located on chromosome 19p13. The risk factor at PSORS6 relevant to type I psoriasis (at younger age, ≤40 years) was proved to be an interaction with PSORS1. In a series of studies, PSORS6–PSORS15 were discovered and defined. Among these loci, PSORS9 was found to be unique to the Chinese Han population.

Although linkage analysis is reliable and effective in practical applications, it has obvious limitations in the study of complex diseases and is more suitable for genetic research of monogenic disease. It has good applicability to genetic variations of high pathogenicity and small quantity, but is insufficient for mutations with medium or weak effects. Moreover, linkage analysis cannot realize fine mapping, it can provide only some reference opinions for complex diseases. Fortunately, the emergence of genome-wide association study (GWAS) resolved these problems.

**Genome-wide association study**

GWAS is a strategy to find genetic variations that affect complex traits. It is based on high-throughput genotyping technology, through analysis of millions of single nucleotide polymorphisms to find relevant clinical manifestations or phenotypic traits. GWAS provides a new way to study the genetic characteristics of complex diseases, allowing detection throughout the patient's whole genome to identify mutation allele frequencies rather than selecting disease-causing genes as candidate genes. Furthermore, it helps to identify genes and pseudoautosomal regions that have not been previously discovered, and thus can provide more clues to the pathogenesis of complex diseases.

The first published GWAS study worldwide was on age-related macular degeneration, announced in the journal Science in 2005. The first GWAS for psoriasis was published in 2007, which confirmed IL12B and IL23R as risk loci among American individuals. To date, through a series of linkage studies, large-scale GWAS studies, and genome-wide meta-analyses, researchers have identified >80 susceptibility genes for psoriasis, mainly for European and Asian populations (Table 1). The first GWAS of psoriasis in a Chinese population was conducted by Zhang et al. in 2009. To add to the two known loci rs1265181 within the MHC region and rs3213094 in gene IL12B, they identified a new susceptibility rs4085613 within LCE gene on 1q21. Subsequent GWAS study confirmed that ERAP1 and ZNF816A genes were associated with early onset psoriasis in the Chinese Han population. GWAS among European populations identified a number of susceptibility loci related to genes IL28RA, RELB, TYK2, ERAP1, TRAF3IP2, NOS2, and FBXL19. Recently, one large-scale meta-analysis of GWAS was published, including data from eight independent Caucasian cohorts and 439,000 individuals. There were 16 loci that achieved genome-wide significance, related to genes FASLG, IKBKE, BRAP, MAPKAPK5, TRIM47, TRIM65, and so on. Most of the signals were enriched among enhancers in CD4+ T-helper and CD8+ cytotoxic T cells. Further functional analysis demonstrated the important role of the NF-κB cascade and interferon signaling for disease pathophysiology. Disease susceptibility risks for European and Asian populations are different as a result of heterogeneity. To search for genetic variations that are common between different populations, a trans-ethnic genome wide meta-analysis on both Chinese and European populations was conducted and identified four risk loci LOC144817, COG6, RUNX1, and TP63. Those variants were based on the elimination of population heterogeneity, which could better explain the genetic variation of the disease itself. Among the genetic variations identified, the MHC region contributed a major part in the disease's genetic pathogenesis.

In Chinese and European populations, the MHC region counts for major genetic variations of psoriasis. In this region, the greatest risk locus is HLA-C*06:02, which belongs to MHC class I molecule. HLA-C*06:02 has been confirmed as having an association with a subtype of early onset psoriasis and disease severity, and allele frequency differs both ethnically and geographically. In European and East, the HLA-C*06:02 allele has been validated with the strongest risk of psoriasis; however, in
### Table 1. Summary of susceptibility genes for psoriasis.

| Region         | Gene/loci                  | Population                        | Reference                  |
|----------------|----------------------------|-----------------------------------|----------------------------|
| 1q21.3         | LCE cluster                | Chinese                           | 33,72                      |
| 1q22           | AIM2                       | Chinese                           | 72                         |
| 1q31.1         | LRRC7                      | European                          | 48                         |
| 1q31.3         | DENND1B                    | Caucasian                         | 49                         |
| 1p36.3         | MTHFR                      | Chinese                           | 72                         |
| 1p36.23        | SLC45A1, TNFRSF9           | Caucasians                        | 82                         |
| 1p36.11        | MAN1C1                     | Chinese                           | 69                         |
| 1p36.11        | RUNX3                      | Caucasians                        | 82                         |
| 1p36.11        | IL28RA                     | Chinese, European, Caucasians     | 52,56,82                   |
| 1p36.11        | ZNF683                     | Chinese                           | 72                         |
| 1p36.12        | ECE1                       | Chinese                           | 69                         |
| 1p31.3         | IL23R                      | Chinese, European, Caucasians     | 33,56,73,82                |
| 1p31.3         | C1orf141                   | Chinese                           | 72                         |
| 2q24.3         | IFIH1                      | Chinese, European                 | 50,56                      |
| 2q12.1         | IL1RL1                     | Chinese                           | 72                         |
| 2q21.2-q21.3   | MGAT5                      | Spanish                           | 53                         |
| 2p16.1         | REL                        | European, Caucasians              | 56,57,82                   |
| 2p15           | B3GNT2                     | Caucasians                        | 82                         |
| 3q13           | CASR                       | Chinese                           | 72                         |
| 3q26.2-q27     | GPR160                     | Chinese                           | 72                         |
| 3p24.3         | PLCL2                      | European                          | 48                         |
| 3q12.3         | NFKBIZ                     | European                          | 48                         |
| 3q28           | TP63                       | Chinese                           | 60                         |
| 4q24           | NFKB1                      | Chinese                           | 50                         |
| 4q35.1         | IRF2                       | European                          | 36                         |
| 5p13.1         | CARD6                      | European                          | 48                         |
| 5q33.3         | PTTG1                      | Chinese                           | 55                         |
| 5q33.3         | IL12B                      | Chinese, European, Caucasians     | 54,56,58,72,73,82          |
| 5q33.1         | TNIP1                      | Chinese, Caucasians, European     | 55,72,73,82                |
| 5q33.1         | IL13                       | Caucasians                        | 73,82                      |
| 5q33.1         | ANXA6                      | Chinese                           | 88                         |
| 5q14           | ZFYVE16                    | Chinese                           | 72                         |
| 5q15           | ERAP1                      | Chinese, European, Caucasians     | 33,50,55,56,82             |
| 5q15           | LNPEP                      | Chinese                           | 52                         |
| 6q25.4         | EXOC2, IRF4                | Caucasians                        | 82                         |
| 6q25.3         | TAGAP                      | Caucasians                        | 82                         |
| 6q23.3         | TNFAIP3                    | European, Caucasians              | 73,82                      |
| 6q21           | TRAF3IP2                   | European, Caucasians              | 56,58,82                   |
| 6p21.33        | HLA region                 | Chinese, European, Caucasians     | 51,54,56,58,73,82          |
| 6p21.33        | HCP5                       | European                          | 51                         |
| 7p14.1         | ELMO1                      | Caucasians                        | 82                         |
| 7p14.3         | CCDC129                    | Chinese                           | 72                         |
| 8q24.3         | EIF2C2                     | Chinese                           | 69                         |
| 8p23.2         | CSMD1                      | Chinese                           | 55                         |
| 9q34.13        | TSC1                       | European                          | 73                         |
| 9q31.2         | KLF4                       | Caucasian                          | 82                         |
| 9p21.1         | DDX58                      | Caucasian                          | 82                         |
| 10q22.2        | CAMK2G                     | Caucasian                          | 82                         |
| 10q22.3        | ZMIZ1                      | Caucasian                          | 82                         |
| 11q24.3        | ETS1                       | Caucasian                          | 82                         |
| 11q24.3        | ZC3H12C                    | Caucasian                          | 82                         |
| 11q13.1        | RPS6KA4, PRDX5             | Caucasian                          | 82                         |
| 11p15.4        | ZNF143                     | Chinese                           | 72                         |
| 12p13.3        | CD27-LAG3                  | Chinese                           | 50                         |

Continued
the Japanese population, HLA-C*06:02 has a low allele frequency and is almost absent. As reference panels are being built in different populations, through next generation sequencing, imputation methods, and fine-mapping analysis, researchers have identified other HLA-class I and class II risk loci independent of HLA-C*06:02, such as HLA-C*12:03, HLA-C*07:02, HLA-B*27, HLA-B*57, HLA-A*02:07, HLA-DPB1*05:01, and even some amino acids in HLA-A, HLA-B, and HLA-DQA1 genes. These loci are heterogeneous in different populations: HLA-A*02:07 shows strong associations in Chinese populations, but is very rare or even absent in Europeans, whereas HLA-B*07 shows strong associations in Caucasians but is rare in the Chinese. Some loci that showed consistency in different races, for instance, HLA-C*06:02 and HLA-B amino acid 67 were identified in both Caucasians and Chinese. In addition, research on subtypes of disease in the HLA region also found some genetic variants. HLA-B*27 was identified as specific for PsA, in spite of a lower prevalence when compared with ankylosing spondylitis. A large-scale fine-mapping study of PsV risk in the MHC region revealed that HLA-B Glu45 increased PsA susceptibility in comparison to PsC susceptibility, and alleles HLA-B*27, HLA-B*38, and HLA-B*39 all carried HLA-B Glu45.

### Post-GWAS era

Although GWAS was used to identify multiple loci associated with diseases, it revealed only a small fraction of the genetic factors associated with complex diseases, and could not cover all genetic variations. This may be because of interactions between genes as well as genes and environment, in which some low frequency and rare variations are difficult to discover. With the development of the high-throughput detection techniques, next generation sequencing, imputation methods, and whole exome sequencing were used in the study of complex diseases and more low frequency and rare variations were found. Tang conducted exome sequencing to analyze nonsynonymous single-nucleotide variants (SNVs) across the genome in a Chinese population and discovered two low frequency missense SNVs in genes IL23R and GJB2 which increased risk for psoriasis. A large exome array study containing 11,861 psoriasis patients and 28,610 controls revealed a risk locus...
rs6478108 at gene TNFSF15, and validated low-frequency (minor allele frequency < 0.01) protein-altering variants within IFIH1 and TYK2 that showed protective effect. This result highlights the functional effect of low-frequency variants in potential mechanisms of disease.\textsuperscript{67} Recently, bioinformatics has been an active hot topic in research on DNA methylation, an important component of epigenetics research and closely related to the occurrence and development of psoriasis. DNA methylation is a form of chemical modification of DNA that can alter genetic expression without altering the DNA sequence.\textsuperscript{68} Zhou\textsuperscript{69} performed DNA methylation research on psoriasis, identifying significant associations between skin-specific DNA methylation of nine disease-associated differentially methylated sites and psoriasis. Further analysis revealed that these sites were not significantly affected by genetic variations and the expression of CYP2S1, ECE1, EIF2C2, MAN1C1, and DLGAP4 was negatively correlated with DNA methylation.

**Action pathways of susceptibility genes**

According to the different pathways of the susceptible loci identified by linkage analysis, GWAS, next generation sequencing, imputation, and other methods, these discoveries can be classified into skin barrier function, innate immune response, and adaptive immune response.

**Skin barrier function genes**

The pathological characteristics of psoriasis are hyperkeratosis and parakeratosis in epidermis. To some extent, damage to the skin barrier function is one trigger of psoriasis. Higher genomic copy number for \(\beta\)-defensin gene DEFB4, DEFB103, and DEFB104 encoded hBD-2, hBD-3, and hBD-4, respectively. Among those genes, DEFB4 was important in promoting inflammatory response in skin lesions of psoriasis.\textsuperscript{70} Late cornified envelope (LCE) within PSORS4 acted on epidermal terminal differentiation. Perhaps during the formation of psoriatic lesions, genetic variants within LCE3 gene interrupted keratinocyte differentiation.\textsuperscript{71,72} GJB2 encodes gap junction proteins, which are known as connexins. These act to maintain the stability of keratinocyte structure, and comparing expression in PsV lesions with that in normal skin, a variant in gene GJB2 was confirmed to confer susceptibility to PsV in a Chinese population.\textsuperscript{55}

**Innate immune response**

A vital pathogenesis of psoriasis is immunological factors, of which NF-κB signaling is an important component. Numerous genes have been associated with PsV and PsA. Production of TNFAIP3 and TNIP1 genes regulates NF-κB signaling, with variants in these genes showing strong association with psoriasis.\textsuperscript{73} Mutation in CARD14/CARMA2 genes within PSORS2 can up-regulate the inflammatory product in keratinocytes which was evoked by NF-κB, and this has been associated with both psoriasis and PsA.\textsuperscript{30} Expression of FBXL19 gene was higher in psoriatic skin compared with normal skin, but its product inhibited NF-κB signaling.\textsuperscript{57} Absent expression of AIM2 (melanoma 2) gene can induce innate immune activation and further activate the formation of psoriatic lesions.\textsuperscript{72} Other genes were identified to be involved in NF-κB signaling pathway, such as UBE2L3, REL, and TYK2, which also played a role in pathogenesis of psoriasis or PsA.\textsuperscript{74–76} Interferon (IFN) signaling promotes an inflammatory response in innate immunity, with a role in the occurrence of psoriasis. Genetic variant research into psoriasis discovered several genes related to IFN signaling, such as TYK2, TAGAP, IFIH1, Dock2, SOCS1, and IFNLR1.\textsuperscript{50,58,77–80}

**Acquired immune response**

Obvious pathological features of psoriasis are abnormal activation of T cells, and infiltration and excessive proliferation of keratinocytes. Th17 cells and IL-23/IL-17 axis play a key role in formation of psoriatic lesions. Genetic variations that affect antigen presentation can disrupt the process of adaptive immunity. ERAP1 is involved in the antigen presentation of MHC class I molecules, and variants of this gene were susceptible to psoriasis patients who carried the risk allele HLA-C.\textsuperscript{56} ETS1 transcription factor acts in differentiation of thymic CD8 cell lines through enhancing the expression of Runx3. A meta-analysis of GWAS identified RUNX3 as susceptible to psoriasis, as it can regulate T cell function.\textsuperscript{81,82} A study conducted high-throughput sequencing of the entire \(\alpha\)-TCR and \(\gamma\delta\)-TCR repertoire in psoriasis. Skin samples included normal skin biopsies from healthy volunteers, non-lesional and lesional skin from psoriasis patients, with results showing a significant increase in abundance of unique \(\alpha\)- and \(\gamma\delta\)-TCR sequences in lesional skin when compared to non-lesional and normal skin. The entire T cell repertoire in psoriasis was polyclonal, and there was similar diversity to normal and non-lesional skin. In the same patient, there were many common clones of \(\alpha\)-TCR and \(\gamma\delta\)-TCR repertoire between paired non-lesional and lesional samples.\textsuperscript{83}

An important pathogenesis of psoriasis is the interleukin (IL)-23/Th17 pathway. IL-23 induces differentiation and proliferation of Th17 cells, and mature Th17 can secrete a variety of cytokines such as IL-17, IL-21, and IL-22. Th17 cytokines play an important role in many autoimmune diseases and inflammatory diseases, such as psoriasis.\textsuperscript{84} Many genes related to the Th17 pathway have been confirmed to be associated with psoriasis, such as IL-23A, IL-23R, HLA-C, TRAF3IP2, IL-12B, STAT3, and SOCS1.\textsuperscript{18,73,79,82} As one subunit of IL-23, p19 mRNA was increased in psoriasis lesional skin
compared with non-lesional skin, and the other subunit p40 which is shared by IL-12 and IL-23 was also increased in lesional skin.\textsuperscript{85} Proteins encoded by gene TRAF3IP2 are involved in the NF-κB pathway and IL-17 signaling. One GWAS study revealed a shared susceptibility of this gene in both PsV and PsA.\textsuperscript{88} STAT3 acts as a regulator in the process of Th17 differentiation and production of cytokines, such as IL-6 and IL-10, and expression of STAT3 was upregulated in psoriasis.\textsuperscript{89} SOCS1 participates in innate and adaptive immunity. It inhibits IFN signaling through interaction with kinase Tyk2, and also regulates differentiation of Th17 cells. GWAS analysis discovered susceptibility loci related to the SOCS1 gene in both psoriasis and Crohn disease, accounting for a shared genetic risk in both diseases.\textsuperscript{78,87}

**Genetic basic research promotes the progress of precision medicine**

Through the study of genetic variations, numerous susceptibility sites related to disease have been found. The combination of basic findings with disease prevention and treatment is the original intention of precision medicine and is also the requirement of personalized medicine. Some identified genetic markers have been applied in disease prediction, diagnosis, subtype distinction, drug development, and evaluation of drug efficacy or side effects.\textsuperscript{88–94}

There are many induced factors for psoriasis, with unhealthy living habits being one of the triggers. Yin\textsuperscript{88} identified interactions between alcohol use and TNIP1/ANXA6, cigarette smoking and CSMD1, respectively. The study conclusion highlighted the importance of gene–environment interactions in the pathogenesis of psoriasis. Mutations of IL36RN (encoding the IL-36 receptor antagonist) were a demonstrated risk for GPP. A new study revealed a more severe manifestation in the earlier age of onset IL36RN-positive individuals, and in the IL36RN-positive individuals, the prevalence of PsV showed a significant reduction, implying that this locus could be a genetic distinguishing marker for PsV and GPP.\textsuperscript{95} HLA-Cw6 is well known as the most significant risk for psoriasis, and has been confirmed as the distinguishing marker for psoriasis type I (early onset < 40 years) and type II (late-onset ≥ 40 years).\textsuperscript{94} In the Turkish population, HLA-Cw6, HLA-B57, and HLA-DRB1*07 alleles were more significant in patients with type I psoriasis when compared with type II psoriasis, so those alleles could be regarded as distinguishing markers of two subtypes.\textsuperscript{96} Pharmacogenomic studies found that compared to HLA-Cw6-negative patients, HLA-Cw6-positive patients showed evident improvement in response to methotrexate and also showed fewer adverse events.\textsuperscript{90} Ye\textsuperscript{97} carried on research in Chinese PsV patients, with all patients being treated with methotrexate. Patients who achieved PASI75 after 12 weeks were considered to be effective, but any with lower than PASI75 were ineffective. Using whole exon high-throughput sequencing in the initial phase and MassARRAY method in verification stage, three SNPs were found: rs216195T > C, rs1050301G > A, and rs2285421T > C, related, respectively, to genes SMG6, IMMT, and UPK1A that showed association with the responders. These three SNPs could be used as predictors for the efficacy of methotrexate in treatment of PsV. Vasilopoulos\textsuperscript{91} conducted a study in 84 psoriasis patients who were treated with cyclosporine; 62% of individuals showed response to medicine and 38% were non-responders. SNP 3435T in gene ABCB1 was statistically significantly associated with negative response, and regarded as a predictive indicator of drug efficacy among psoriasis patients. A recent study confirmed that there were high binding affinities of multiple 9-mer peptides to the HLA-C*06:02 molecule. The peptides were derived from cathelicidin 37(LL-37), which was reported as a T cell autoantigen in psoriasis. According to this clue, a peptide with high binding affinity for HLA-C*06:02 and low affinity for TCRs could be designed in the future to act as a prophylactic agent specialized for HLA-C*06:02-positive people without psoriasis.\textsuperscript{98}

As the IL-23/IL-17 axis has been identified as a vital trigger in formation of psoriasis, there is great development in biologics targeted to block Th17 axis, such as ustekinumab, ixekizumab, and secukinumab.\textsuperscript{99,100} Some related studies have reported more effective and safer management of psoriasis, especially in PsA.\textsuperscript{101,102} Secukinumab is a fully human monoclonal antibody against IL-17A, approved by the American FDA for treatment of moderate to severe plaque psoriasis and PsA. It can inhibit the radiographic progression of PsA, but its therapeutic effect was not as satisfactory in PsA as it was in plaque psoriasis.\textsuperscript{103,104} Clinical study indicated that compared to TNF-α inhibitors, IL-17A inhibitors were more effective in treatment of plaque psoriasis and TNF-α inhibitors were superior for PsA.\textsuperscript{105} Ustekinumab is a fully human monoclonal antibody targeting IL-12 and IL-23. It inhibits both proinflammatory cytokines by binding to the common p40 subunit of IL-12 and IL-23 and preventing them from binding to the receptor IL-12 p10 on the cell surface. It is licensed for treatment of psoriasis and PsA.\textsuperscript{106} However, in treatment of moderate-to-severe psoriasis, ustekinumab was inferior to secukinumab in drug safety.\textsuperscript{107} Risankizumab is a humanized IgG1 monoclonal antibody against the p19 subunit of IL-23. On treatment, around 90% of psoriasis patients achieved a PASI75 by week 12, a good curative effect. A phase II clinical trial was carried out to compare the therapeutic effects of risankizumab and ustekinumab. Using the standard dosage of each drug, 77% of patients achieved PASI90 at week 12 in the risankizumab group compared with 40% for the ustekinumab group.\textsuperscript{108,109} Pharmacogenetic study of biological agents in the treatment of psoriasis was carried out in a Greek population, with results showing that rs10484554 in gene HLA-C was associated
with a good response to anti-TNF-α agents, other than ustekinumab, and related loci in gene ERAP1 showed association with good response to anti-IL-12/23 therapy.60 A series of relevant pharmacogenomic research revealed the meaningful role of genetic markers in practical applications.14 Such findings can help doctors to select appropriate treatment protocols according to individual genetic characteristics, aiming to maximize drug effectiveness and reduce the incidence of adverse reactions, in accordance with the original purpose of precision medicine and also the future requirements of medical science.

Conclusions

To date, genetic studies have identified >80 susceptibility loci for psoriasis and provided mechanistic insights into its pathogenesis. Related gene function research is also in full swing. With development of next generation sequencing technology, more accurate and reliable genetic markers have been identified, and development of target biological agents is progressing rapidly, with novel agents in the development phase or at clinical trial stage. These findings provide guidance for the pathogenesis, prevention, and effective treatment of diseases, and lay a solid foundation for research into precision medicine.

Acknowledgements

This study was supported financially by the National Natural Science Foundation of China (grant number: 81320108016).

Conflict of interest statement

None declared.

References

1. Moradi M, Renzf C, Brodzsky V, et al. Health status and quality of life in patients with psoriasis: an Iranian cross-sectional survey. Arch Iran Med 2015;18(3):153–9. doi:10151805/AIM.004.
2. Danielson K, Olsen AO, Wilsgaard T, et al. Is the prevalence of psoriasis increasing? A 30-year follow-up of a population-based cohort. Br J Dermatol 2013;168(6):1303–10. doi:10.1111/bjd.12230.
3. Ding X, Wang T, Shen Y, et al. Prevalence of psoriasis in China: a population-based study in six cities. Eur J Dermatol 2012;22(5):563–7. doi:10.1684/ejd.2012.1802.
4. Yin X, Wineinger NE, Cheng H, et al. Common variants explain a large fraction of the variability in the liability to psoriasis in a Han Chinese population. BMC Genomics 2014;15:87. doi:10.1186/1471-2164-15-87.
5. Mohd Affandi A, Khan I, Ngah Saaya N. Epidemiology and clinical features of adult patients with psoriasis in Malaysia: 10-year review from the Malaysian Psoriasis Registry (2007–2016). Dermatol Res Pract 2018;2018:4371471. doi:10.1155/2018/4371471. eCollection 2018.
6. Harden JL, Krueger JG, Bowcock AM. The immunogenetics of psoriasis: a comprehensive review. J Autoimmun 2015;64:66–73. doi:10.1016/j.jaut.2015.07.008.
7. Capon F. The genetic basis of psoriasis. Int J Mol Sci 2017;18(12). doi:10.3390/ijms18122526.
8. Zhang X, Wang H, Te-Shao H, et al. The genetic epidemiology of psoriasis vulgaris in Chinese Han. Int J Dermatol 2002;41(10):663–9. doi:10.1046/j.1365-4362.2002.01596.x.
9. Generali E, Ceribelli A, Stazi MA, et al. Lessons learned from twins in autoimmune and chronic inflammatory diseases. J Autoimmune 2017;83:51–61. doi:10.1016/j.jaut.2017.04.005.
10. Duffy DL, Spelman LS, Martin NG. Psoriasis in Australian twins. J Am Acad Dermatol 1993;29(3):428–34. doi:10.1016/0190-9622(93)70206-9.
11. Grijbovski AM, Olsen AO, Magnus P, et al. Psoriasis in Norwegian twins: contribution of genetic and environmental effects. J Eur Acad Dermatol Venereol 2007;21(10):1337–43. doi:10.1111/j.1468-3083.2007.02268.x.
12. Lonnberg AS, Skov L, Skyttea T, et al. Heritability of psoriasis in a large twin sample. Br J Dermatol 2013;169(2):412–6. doi:10.1111/bjd.12375.
13. Ricano-Ponce I, Wijmenga C. Mapping of immune-mediated disease genes. Annu Rev Genomics Hum Genet 2013;14:325–53. doi:10.1146/annurev-genom-091212-153450.
14. Singh S, Pradhan D, Puri P, et al. Genomic alterations driving psoriasis pathogenesis. Gene 2019;683:61–71. doi:10.1016/j. gene.2018.09.042.
15. Nair RP, Henseler T, Jenisch S, et al. Evidence for two psoriasis susceptibility loci (HLA and 17q) and two novel candidate regions (16q and 20p) by genome-wide scan. Hum Mol Genet 1997;6(8):1349–56. doi:10.1093/hmg/6.8.1349.
16. Zhang XJ, He PP, Wang ZX, et al. Evidence for a major psoriasis susceptibility locus at 6p21 (PSORS1) and a novel candidate region at 4q31 by genome-wide scan in Chinese hans. J Invest Dermatol 2002;119(6):1361–6. doi:10.1046/j.1523-1747.2002.17612.x.
17. Austin LM, Coven TR, Bhardwaj N, et al. Intraepidermal lymphocytes in psoriatic lesions are activated GMP-17 (TIA-1) + CD8 + CD3 + CTLs as determined by phenotypic analysis. J Cutan Pathol 1998;25(2):79–88. doi:10.1111/j.1600-0560.1998.tb01694.x.
18. Prinz JC. Melanocytes: target cells of an HLA-C*06:02–restricted autoimmune response in psoriasis. J Invest Dermatol 2017;137(10):2053–8. doi:10.1016/j.jid.2017.05.023.
19. Lenz TL, Deutsch AJ, Han B, et al. Widespread non-additive and interaction effects within HLA loci modulate the risk of autoimmune diseases. Nat Genet 2015;47(9):1085–90. doi:10.1038/ng.3379.
20. Chandra A, Lahiri A, Senapati S, et al. Increased risk of psoriasis due to combined effect of HLA-Cw6 and LCE3 risk alleles in Indian population. Sci Rep 2016;6:24059. doi:10.1038/srep24059.
21. Bowes J, Ashcroft J, Dand N, et al. Cross-phenotype association mapping of the MHC identifies genetic variants that differentiate psoriatic arthritis from psoriasis. Am Rheum Dis 2017;76(10):1774–9. doi:10.1136/annrheumdis-2017-211414.
22. Chang YT, Shiao YM, Chin PJ, et al. Genetic polymorphisms of the HCR gene and a genomic segment in close proximity to HLA-C are associated with patients with psoriasis in Taiwan. Br J Dermatol 2004;150(6):1104–11. doi:10.1111/j.1365-2133.2004.05972.x.
23. Gandhi G, Buttar BS, Albert L, et al. Psoriasis-associated genetic polymorphism in North Indian population in the CCHCR1 gene and in a genomic segment flanking the HLA-C
28. Enlund F, Kainu K, Onkamo P, et al. Clinical associations of the risk alleles of HLA-Cw6 and CCHCR1*VVCC in psoriasis. Acta Derm Venereol 2007;87(2):127–34. doi:10.2340/00015555-0184.

25. Suomela S, Elomaa O, Asumalathi K, et al. HCR, a candidate gene for psoriasis, is expressed differently in psoriasis and other hyperproliferative skin disorders and is downregulated by interferon-gamma in keratinocytes. J Invest Dermatol 2003;121(6):1360–4. doi:10.1046/j.1523-1747.2003.12642.x.

26. Tialla I, Suomela S, Hoohtanen J, et al. The CCHCR1 (HCR) gene is relevant for skin steiodogenesis and downregulated in cultured psoriatic keratinocytes. J Mol Med (Berl) 2007;85(6):589–601. doi:10.1007/s00109-006-0155-0.

27. Capon F, Toal IK, Evans JC, et al. Haplotype analysis of distinctly related populations implicates corneodesmosin in psoriasis susceptibility. J Med Genet 2003;40(6):447–52. doi:10.1136/jmg.40.6.447.

28. Enlund F, Samuelsson L, Enerback C, et al. CARD14 gene misregionation, and to 17q, but not to 4q. Hum Hered 1999;49(1):2–8. doi:10.1159/000022832.

29. International Psoriasis Genetics Consortium. The International Psoriasis Genetics Study: assessing linkage to 14 candidate susceptibility loci in a cohort of 942 affected sib pairs. Am J Hum Genet 2003;73(2):430–7. doi:10.1086/377159.

30. Jordan CT, Cao L, Roberson ED, et al. PSORS2 is due to mutations in CARD14. Am J Hum Genet 2012;90(5):784–95. doi:10.1016/j.ajhg.2012.03.012.

31. Jiang C, Lin X. Regulation of NF-kappaB by the CARD proproteins. Immunol Rev 2012;246(1):141–53. doi:10.1111/j.1600-065x.2012.01110.x.

32. Gaffney SL. Structure and signalling in the IL-17 receptor family. Nat Rev Immunol 2009;9(8):556–67. doi:10.1038/nri2586.

33. Tang H, Jin X, Li Y, et al. A large-scale screen for coding variants predisposing to psoriasis. Nat Genet 2014;46(1):45–50. doi:10.1038/ng.2827.

34. Qin P, Zhang Q, Chen M, et al. Variant analysis of CARD14 in a Chinese Han population with psoriasis vulgaris and generalized pustular psoriasis. J Invest Dermatol 2014;134(12):2994–6. doi:10.1038/jid.2014.269.

35. Shi G, Li SJ, Wang TT, et al. The common CARD14 gene missense polymorphism rs11652075 (c.C2458T/p.Arg820Trp) is associated with psoriasis: a meta-analysis. Genet Mol Res 2016;15(3). doi:10.4238/gmr.15038357.

36. Matthews D, Fry L, Fowles A, et al. Evidence that a locus for familial psoriasis maps to chromosome 4q. Nat Genet 1996;14(2):231–3. doi:10.1038/ng1096-231.

37. de Cid R, Riveira-Munoz E, Zeeuwen PL, et al. Deletion of the late cornified envelope LCE3B and LCE3C genes as a susceptibility factor for psoriasis. Nat Genet 2009;41(2):211–5. doi:10.1038/ng.313.

38. Li M, Wu Y, Chen G, et al. Deletion of the late cornified envelope genes LCE3C and LCE3B is associated with psoriasis in a Chinese population. J Invest Dermatol 2011;131(8):1639–43. doi:10.1038/jid.2011.86.

39. Ammar M, Bouchlaka-Souissi C, Soumaya K, et al. Failure to find evidence for deletion of LCE3C and LCE3B genes at PSORS4 contributing to psoriasis susceptibility in Tunisian families. Pathol Biol (Paris) 2014;62(1):34–7. doi:10.1016/j.patbi.2013.10.003.

40. Bergboer JS, Dulak MG, van Vlijmen-Willems IM, et al. Analysis of protein-protein interaction between late cornified envelope proteins and corneodesmosin. Exp Dermatol 2014;23(10):769–71. doi:10.1111/exd.12524.

41. Enlund F, Samuelsson L, Enerback C, et al. Psoriasis susceptibility locus in chromosome region 3q21 identified in patients from southwest Sweden. Eur J Hum Genet 1999;7(7):783–90. doi:10.1038/sj.ejhg.5200365.

42. Huffmeier U, Laszcz J, Traupe H, et al. Systematic linkage disequilibrium analysis of SLC12A8 at PSORS5 confirms a role in susceptibility to psoriasis vulgaris. J Invest Dermatol 2005;125(5):906–12. doi:10.1038/jid.2005.23847.x.

43. Vasiliopoulos Y, Walters K, Cork MJ, et al. Association anaanalysis of the skin barrier gene cystatin A at the PSORS5 locus in psoriatic patients: evidence for interaction between PSORS1 and PSORS5. Eur J Hum Genet 2008;16(8):1002–9. doi:10.1038/ejhg.2008.40.

44. Huffmeier U, Laszcz J, Becker T, et al. Characterisation of psoriasis susceptibility locus 6 (PSORS6) in patients with early onset psoriasis and evidence for interaction with PSORS1. J Med Genet 2009;46(11):736–44. doi:10.1136/jmg.2008.065029.

45. Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration. Science 2005;308(5720):385–9. doi:10.1126/science.1109557.

46. Cargill M, Schrodi SJ, Chang M, et al. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. Am J Hum Genet 2007;80(2):273–90. doi:10.1086/510515.

47. Stuart PE, Nair RP, Tsai LC, et al. Genome-wide association analysis of psoriatic arthritis and cutaneous psoriasis reveals differences in their genetic architecture. Am J Hum Genet 1999;65(4):816–36. doi:10.1093/ajhg/65.4.816.

48. Tsai LC, Spain SL, Ellingham E, et al. Enhanced meta-analysis and replication studies identify five new psoriasis susceptibility loci. Nat Commun 2015;6:7001. doi:10.1038/ncomms8001.

49. Bowes J, Budu-Aggrey A, Huffmeier U, et al. Dense genotyping of immune-related susceptibility loci reveals new insights into the genetics of psoriatic arthritis. Nat Commun 2015;6:6046. doi:10.1038/ncomms7046.

50. Sheng Y, Jin X, Xu J, et al. Sequencing-based approach identified three new susceptibility loci for psoriasis. Nat Commun 2015;4:4331. doi:10.1038/ncomms5331.

51. Liu Y, Helms C, Liao W, et al. A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. PLoS Genet 2008;4(3):e1000041. doi:10.1371/journal. pgen.1000041.

52. Cheng H, Li Y, Zuo XB, et al. Identification of a missense variant in LNPEP that confers psoriasis risk. J Invest Dermatol 2014;134(2):359–65. doi:10.1038/jid.2013.317.

53. Aterido A, Julia A, Ferrandiz C, et al. Genome-wide pathway analysis identifies genetic pathways associated with psoriasis. J Invest Dermatol 2016;136(3):593–602. doi:10.1016/j.jid.2015.11.026.

54. Zhang RX, Huang W, Yang S, et al. Psoriasis genome-wide association study identifies susceptibility variants within LCE gene cluster at 1q21. Nat Genet 2009;41(2):205–10. doi:10.1038/ng.310.

55. Sun LD, Cheng H, Wang ZX, et al. Association analyses identify six new psoriasis susceptibility loci in the Chinese population. Nat Genet 2010;42(11):1005–9. doi:10.1038/ng.690.
65. Haroon M, Winchester R, Giles JT, et al. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nat Genet 2010;42(1):985–90. doi:10.1038/ng.694.

57. Stuart PE, Nair RP, Manabe Y, et al. Genetic Analysis of Psoriasis Consortium & the Wellcome Trust Case Control Consortium, Strange A, et al. A genome-wide association study identifies new psoriasis susceptibility loci. Nat Genet 2010;42(11):991–5. doi:10.1038/ng.689.

56. Genetic Analysis of Psoriasis Consortium & the Wellcome Trust Case Control Consortium, Strange A, et al. A genome-wide association study identifies new psoriasis susceptibility loci. Nat Genet 2010;42(11):991–5. doi:10.1038/ng.689.

58. Ellinghaus E, Ellinghaus D, Stuart PE, et al. Large scale meta-analysis characterizes genetic architecture for common psoriasis associated variants. Nat Commun 2017;8:15382. doi:10.1038/ncomms15382.

60. Yin X, Low HQ, Wang L, et al. Genome-wide meta-analysis identifies multiple novel associations and ethnic heterogeneity of psoriasis susceptibility. Nat Commun 2015;6:6916. doi:10.1038/ncomms7916.

61. Okada Y, Han B, Tsoi LC, et al. Fine mapping major histocompatibility complex associations in psoriasis and its clinical subtypes. Am J Hum Genet 2014;95(2):162–72. doi:10.1016/j.ajhg.2014.07.002.

62. Mabuchi T, Ota T, Manabe Y, et al. HLA-C*12:02 is a susceptibility factor in late-onset type of psoriasis in Japanese. J Dermatol Sci 2014;72(2):157–64. doi:10.1016/j.jdermsci.2014.07.002.

63. FitzGerald O, Haroon M, Giles JT, et al. Combined analysis identifies a psoriasis susceptibility locus identified by a previously known association study. J Invest Dermatol 2017;137(3):550–6. doi:10.1016/j.jid.2016.11.007.

64. Zhou F, Cao H, Zuo X, et al. Genome-wide association study identifies a psoriasis susceptibility locus at TRAF3IP2. Nat Genet 2010;42(11):991–5. doi:10.1038/ng.689.

65. Haroon M, Winchester R, Giles JT, et al. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nat Genet 2010;42(1):985–90. doi:10.1038/ng.694.

66. Ellinghaus E, Ellinghaus D, Stuart PE, et al. Genome-wide association study identifies a psoriasis susceptibility locus at TRAF3IP2. Nat Genet 2010;42(11):991–5. doi:10.1038/ng.689.

67. Dand N, Mucha S, Tsoi LC, et al. Exome-wide association study reveals association of psoriasis with IL-23 and NF-kappaB pathways. Nat Genet 2009;41(2):199–204. doi:10.1038/ng.311.

68. Hwang ST, Nijsten T, Elder JT. Recent highlights in psoriasis research. J Invest Dermatol 2017;137(3):550–6. doi:10.1016/j.jid.2016.11.007.

69. Zhou F, Wang W, Shen C, et al. Association of the late cornified envelope-3 genes with psoriasis and psoriatic arthritis: a systematic review. J Genet Genomics 2015;42(2):49–56. doi:10.1016/j.jgg.2015.01.001.

70. Chang X, Gao J, Yin X, et al. Association of the late cornified envelope-3 genes with psoriasis and psoriatic arthritis: a systematic review. J Genet Genomics 2015;42(2):49–56. doi:10.1016/j.jgg.2015.01.001.
affect risk of psoriasis. J Dermatol Sci 2013;70(2):94–8. doi:10.1016/j.jdermsci.2013.02.006.
89. O’Rielly DD, Rahman P. Genetics of susceptibility and treatment response in psoriatic arthritis. Nat Rev Rheumatol 2011; 7(12):718–22. doi:10.1038/nrrheum.2011.169.
90. West J, Ogston S, Berg J, et al. HLA-Cw6-positive patients with psoriasis show improved response to methotrexate treatment. Clin Exp Dermatol 2017;42(6):651–5. doi:10.1111/ced.13100.
91. Vasilopoulos Y, Sarri C, Zafrriou E, et al. A pharmacogenetic study of ABCB1 polymorphisms and cyclosporine treatment response in patients with psoriasis in the Greek population. Pharmacogenomics J 2014;14(6):523–5. doi:10.1038/tpj.2014.23.
92. Masouri S, Stefanaki I, Nritsos G, et al. A pharmacogenetic study of psoriasis risk variants in a Greek population and prediction of responses to anti-TNF-alpha and anti-IL-12/23 agents. Mol Diagn Ther 2016;20(3):221–5. doi:10.1007/s40291-016-0198-z.
93. Anbunathan H, Bowcock AM. The molecular revolution in cutaneous biology: the era of genome-wide association studies and statistical, big data, and computational topics. J Invest Dermatol 2017;137(5):e113–e8. doi:10.1016/j.jid.2016.03.047.
94. Prieto-Perez R, Solano-Lopez G, Cabaleiro T, et al. Polymorphisms associated with age at onset in patients with moderate-to-severe plaque psoriasis. J Immunol Res 2015;2015:101879. doi:10.1155/2015/101879.
95. Hussain S, Berki DM, Choon SE, et al. IL36RN mutations define a severe autoinflammatory phenotype of generalized pustular psoriasis. J Allergy Clin Immunol 2015;135(4):1067–70.e9. doi:10.1016/j.jaci.2014.09.043.
96. Atasoy M, Pirim I, BayrakOF, et al. Association of HLA class I and class II alleles with psoriasis vulgaris in Turkish population. Influence of type I and II psoriasis. Saudi Med J 2006; 27(3):373–6.
97. Kuang YH, Lu Y, Yan KK, et al. Genetic polymorphism predicting methotrexate efficacy in Chinese patients with psoriasis vulgaris. J Dermatol Sci 2019;93(1):8–13. doi:10.1016/j.jdermsci.2018.06.009.
98. Mabuchi T, Hirayama N. Binding affinity and interaction of LL-37 with HLA-Cw06:02 in psoriasis. J Invest Dermatol 2016; 136(9):1901–3. doi:10.1016/j.jid.2016.04.033.
99. Boutet MA, Nerviani A, Gallo Afflitto G, et al. Role of the IL-23/IL-17 axis in psoriasis and psoriatic arthritis: the clinical importance of its divergence in skin and joints. Int J Mol Sci 2018;19(2). doi:10.3390/ijms19020530.
100. Baker KF, Isaacs JD. Novel therapies for immune-mediated inflammatory diseases: What can we learn from their use in rheumatoid arthritis, spondyloarthritides, systemic lupus erythematosus, psoriasis, Crohn’s disease and ulcerative colitis? Ann Rheum Dis 2018;77(2):175–87. doi:10.1136/annrheumdis-2017-211555.
101. Fragoulis GE, Siebert S, McInnes IB. Therapeutic targeting of IL-17 and IL-23 cytokines in immune-mediated diseases. Ann Rev Med 2016;67:337–53. doi:10.1146/annurev-med-051916-021940.
102. Robert M, Miossec P. IL-17 in rheumatoid arthritis and precision medicine: from synovitis expression to circulating bioactive levels. Front Med (Lausanne) 2018;5:364. doi:10.3389/fmed.2018.00364.
103. Torres T, Balato A, Conrad C, et al. Secukinumab drug survival in patients with psoriasis: a multicenter, real-world, retrospective study. J Am Acad Dermatol 2019. doi:10.1016/j.jaad.2019.02.033.
104. Gisondi P, Geat D, Idoloai L, et al. Relapse of psoriatic arthritis in patients with active psoriasis swapped from TNF-alpha to IL-17A inhibitor. Br J Dermatol 2019. doi:10.1111/bjd.17837.
105. Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet 2015;386(9993):541–51. doi:10.1016/S0140-6736(15)01625-8.
106. Johnsson HJ, McInnes IB. Interleukin-12 and interleukin-23 inhibition in psoriatic arthritis. Clin Exp Rheumatol 2015;33(5 Suppl 93):S115–8.
107. Blauvelt A, Reich K, Tsai TF, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: results from the CLEAR study. J Am Acad Dermatol 2017;76(1):60–9. e9. doi:10.1016/j.jaad.2016.08.008.
108. Papp KA, Blauvelt A, Bukhale M, et al. Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis. N Engl J Med 2017;376(16):1551–60. doi:10.1056/NEJMoa1607017.
109. Chan TC, Hawkes JE, Krueger JG. Interleukin 23 in the skin: role in psoriasis pathogenesis and selective interleukin 23 blockade as treatment. Ther Adv Chronic Dis 2018;9(5): 111–9. doi:10.1177/2040622318759282.