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Short Communication

SHORT COMMUNICATION

Genetics of psoriasis: a basis for precision medicine

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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).[1] The prevalence of psoriasis reported in different countries ranges from 0.09% to 11.43%,[2] but in China, it is 0.47%.[3] 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.[4] Epidemiological research has confirmed a familial genetic predisposition of psoriasis, with >20% of patients having a positive family history.[5] 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.[4] Further evidence indicates that psoriasis has a genetic predisposition,[6] 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.[7]

Genetic epidemiology studies

Genetic epidemiology studies mainly include familial aggregation, twin studies, pedigree analysis, and susceptibility

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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 secondary-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 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.[36] *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.[37–39] 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*.[40] *PSORS5* was identified early through a genome-wide scan in the Swedish population as being located in 3q21.[41] *SLC12A8* in *PSORS5* has been described as having an association with PsV.[42] 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 is 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.[43] *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*.[44] 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.[16]

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.[45] The first GWAS for psoriasis was published in 2007,[46] 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[47–53] (Table 1). The first GWAS of psoriasis in a Chinese population was conducted by Zhang *et al.*[54] 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.[55] GWAS among European populations identified a number of susceptibility loci related to genes *IL28RA*, *RELB*, *TYK2*, *ERAP1*, *TRAF3IP2*, *NOS2*, and *FBXL19*.[56–58] 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.[59] 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*.[60] 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, European	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*	Caucasians	82
9p21.1	*DDX58*	Caucasians	82
10q22.2	*CAMK2G*	Caucasians	82
10q22.3	*ZMIZ1*	Caucasians	82
11q24.3	*ETS1*	Caucasians	82
11q24.3	*ZC3H12C*	Caucasians	82
11q13.1	*RPS6KA4, PRDX5*	Caucasians	82
	AP5B1	Chinese	72
11p15.4	*ZNF143*	Chinese	72
12p13.3	*CD27-LAG3*	Chinese	50

Continued

Table 1. Continued

Region	Gene/loci	Population	Reference
12q13.3	*STAT2, IL23A*	European, Caucasians	73,82
12q13.2	*RPS26*	European	57
13q14.11	*COG6*	European, Chinese	51,60
13q14.11	*GJB2*	Chinese	33,55
13q14.12	*LOC144817*	Chinese	60
14q13.2	*NFKBIA*	Chinese, European	56,57,72
14q23.2	*SYNE2*	Chinese	72
14q32.13	*CLMN*	Caucasian	94
16p13.13	*PRM3, SOCS1*	Caucasians	82
16p11.2	*FBXL19*	Caucasians	57,82
17q25.3	*CARD14*	Caucasians	82
17q21.2	*PTRF, STAT3, STAT5A/B*	Caucasians	82
17q11.2	*NOS2*	Caucasians	57,82
17q11.2	*NR*	European	57
17q12	*CCL4L*	Caucasian	94
17q12	*IKZF3*	Chinese	50
17q25.3	*TMC6*	Chinese	72
18q22.1	*SERPINB8*	Chinese	55
18q21.2	*POL1, STARD6, MBD2*	Caucasians	82
19q13.41	*ZNF816A*	Chinese	33,55
19p13.2	*ILF3,CARM1*	Caucasians	82
19q13.2	*CYP2S1*	Chinese	69
19p13.2	*TYK2*	European, Caucasians	56,82
20q11.23	*DLGAP4*	Chinese	69
20q13.13	*ZNF313*	Chinese, European, Caucasians	50,56,82
20q13.12	*SDC4*	European	57
21q22.11	*IFNGR2*	Chinese	72
21q22.11	*SON*	Chinese	72
21q22.12	*RUNX1*	Chinese	60
22q11.21	*UBE2L3*	Caucasians	82

the Japanese population, *HLA-C*06:02* has a low allele frequency and is almost absent.[19,61,62] 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*,[61] such as *HLA-C*12:03*, *HLA-C*07:02*, *HLA-C*07:04*, *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.[63,64] 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.[60] 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,[65] 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.[61]

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.[66] 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[33] 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.[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.[68] Zhou[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 β-defensin gene *DEFB* posed a significant risk of psoriasis. In the family of *DEFB* genes, *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.[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.[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.[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.[73] Mutation in *CARD14/CARMA2* genes within *PSORS2* can upregulate the inflammatory product in keratinocytes which was evoked by NF-κB, and this has been associated with both psoriasis and PsA.[30] Expression of *FBXL19* gene was higher in psoriatic skin compared with normal skin, but its product inhibited NF-κB signaling.[57] Absent expression of *AIM2* (melanoma 2) gene can induce innate immune activation and further activate the formation of psoriatic lesions.[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.[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*.[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*.[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.[81,82] A study conducted high-throughput sequencing of the entire αβ-TCR and γδ-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 β- and γ-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 αβ-TCR and γδ-TCR repertoire between paired non-lesional and lesional samples.[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.[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*.[18,73,78,82] 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.[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.[58] *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.[86] *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.[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 distinguish, drug development, and evaluation of drug efficacy or side effects.[88–94]

There are many induced factors for psoriasis, with unhealthy living habits being one of the triggers. Yin[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.[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).[94] In the Turkish population, *HLA-Cw6*, *HLA-B*57*, 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.[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.[90] Ye[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[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.[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.[99,100] Some related studies have reported more effective and safer management of psoriasis, especially in PsA.[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.[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.[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 β1 on the cell surface. It is licensed for treatment of psoriasis and PsA;[106] however, in treatment of moderate-to-severe psoriasis, ustekinumab was inferior to secukinumab in drug safety.[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.[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.[92] 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.

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Conflict of interest statement

None declared.

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