

GENETICS OF PSORIASIS SUSCEPTIBILITY AND TREATMENT RESPONSE

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Abstract

Psoriasis is a chronic, recurrent skin disease that has an unknown trigger. Recent development in understanding the disease mechanisms led to the idea that psoriasis has a genetic background on which external triggers act to develop the psoriatic lesions. This review presents the newest information regarding the genetic variants of the psoriatic patients and their influence on disease evolution and treatment response.

Rezumat

Psoriazisul este o boală dermatologică cronică, recurentă, de cauze necunoscute. Cercetări recente efectate pentru înțelegerea mecanismelor bolii au condus la ideea că prezintă un fond genetic, cu implicații cauzale externe, care determină leziunile psoriazice. Acest studiu prezintă cele mai noi informații privind variabilele genetice ale pacienților psoriazici și influența acestora asupra evoluției bolii și a răspunsului la tratament.

Keywords: psoriasis, single nucleotide polymorphism

Introduction

Psoriasis is a chronic, recurrent skin disease characterized by keratinocyte hyper-proliferation and abnormal differentiation, increased dermal angiogenesis and vasodilatation, and cutaneous inflammation. These pathological changes lead to the development of well demarcated papulo-squamous lesions that can affect any area of the body with variable extent and severity. Ethnicity greatly influences the prevalence of this condition, which varies between 0% in the Samoan population to 12% in the Kasach'ye population. Psoriasis is estimated to affect 2-3% of the Caucasian population [1]. Its aetiology is still incompletely elucidated, the disease being the result of an extremely complex interplay between a series of genetic, immunologic and environmental factors.

The familial aggregation, present in approximately one third of psoriasis cases [2] and the high concordance rate among monozygous (approximately 70%) and dizygous twins (15-20%) [3], support the existence of a genetic predisposition for the development of psoriasis, but debate continues regarding the exact mode of inheritance of the disease. Although an autosomal dominant with reduced penetrance and a recessive mode of inheritance have been hypothesised, in the majority of cases, the disease has a polygenic and

multifactorial aetiology [4]. A modern integrative perspective is that psoriasis represents, in fact, a spectrum of diseases, from the rare monogenic forms to the more frequent polygenic and multifactorial ones. This explains the striking clinical heterogeneity of the disease. The age of onset, disease severity, the presence of extra cutaneous manifestations and the response to treatment are all influenced by the genetic background.

Both innate and acquired immune mechanisms are involved in the pathogenesis of psoriasis, interfering at cellular and molecular level and the attempt to separate the two mechanisms is artificial. Figure 1 illustrates a simplified model of psoriasis pathogenesis. In genetically predisposed individuals, certain environmental factors (trauma, stress, infections, etc.) unmask a yet unknown antigen present in the *stratum corneum* that is normally not accessible to immune recognition. Epidermal antigen presenting cells (APCs) are activated by the contact with the antigen and migrate to the regional lymph nodes, where they meet and activate naïve CD4+ or CD8+ T cells. Activated T cells that express the cutaneous lymphocyte antigen (CLA) migrate to the skin. They leave the post-capillary venules and infiltrate the skin in impressive numbers. CD4+ T cells predominate within the

affected dermis, while CD8+ T cells represent the majority of the T cells that infiltrate the epidermis [5]. The great number and variety of APCs (Langerhans cells, plasmacytoid dendritic cells, myeloid dendritic cells) in psoriasis plaques are responsible for the polarization of immune cells towards a type 1 phenotype through the production of interleukin (IL) 12 [6]. Type 1 cytokines [IL2, tumour necrosis factor (TNF) alpha, interferon (IFN) gamma] are subsequently released and stimulate the local production of chemokines. A true cytokine and

chemokine cascade ensues, the result being epidermal hyper-proliferation, dermal neovascularization and cutaneous inflammation [5].

The inflammation in psoriasis is not limited to the skin. Serum levels of inflammatory biomarkers (erythrocyte sedimentation rate, fibrinogen, C reactive protein) are elevated in psoriasis patients and, although they decrease during periods of clinical amelioration of psoriatic lesions, they do not return to normal limits [7].

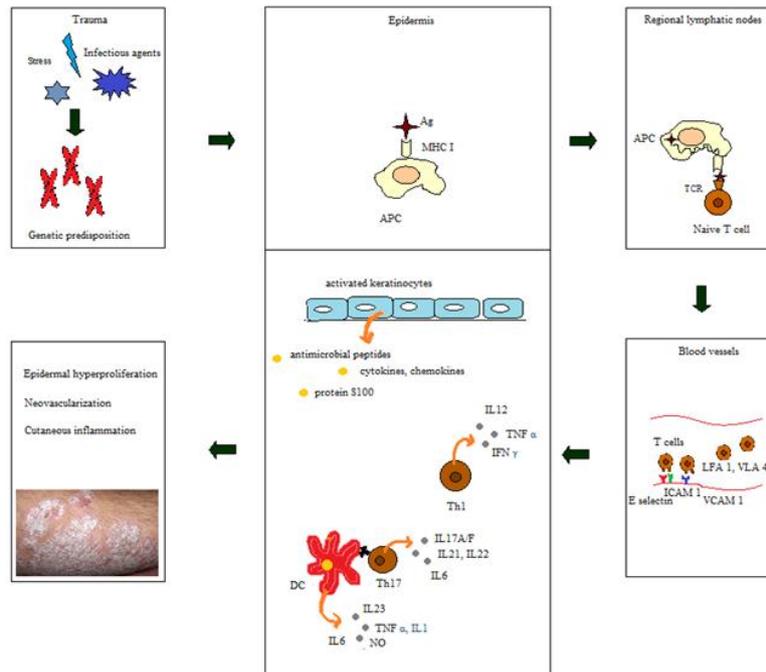


Figure 1.

Schematic representation of psoriasis pathogenesis

Legend: Ag = antigen; APC = antigen presenting cell; MHC I: major histocompatibility complex; TCR: T cell receptor; ICAM 1: intercellular adhesion molecule 1; VCAM 1: vascular cell adhesion molecule 1; LFA 1: leukocyte function associated antigen 1, VLA 4: very late antigen 4; Th: T helper; NO: nitric oxide

Until recently, attempts to classify psoriasis patients into subgroups according to their genetic background have been limited to HLA-C status, the presence of HLA-C*06:02 haplotype being associated with earlier onset (under 40 years) and more severe disease [8]. With the advances of the genotyping technology, ongoing intensive research aims to identify genotype-phenotype risk patterns that will enable early diagnosis, will help predict disease course and will influence the choice of therapeutic agents.

A series of psoriasis susceptibility loci have been identified, nine of which, designated PSORS 1–9, are strongly associated with the disease: 6p21.3 (PSORS 1), 17q24-25 (PSORS 2), 4q34 (PSORS 3), 1q21 (PSORS 4), 3q21 (PSORS 5), 19p13-q13 (PSORS 6), 1p35-p34 (PSORS 7), 16q (PSORS 8), 4q31 (PSORS 9) [4]. Some of these genes are specific to psoriasis, while others probably play a

role in the regulation of inflammatory responses and are involved in a variety of immune disorders.

PSORS 1

The most important psoriasis susceptibility locus, involved in the occurrence of up to 50% of psoriasis cases is PSORS1, a DNA block of 250 kb located in the class I major histocompatibility complex region (MHC) on chromosome 6p21.3 [9]. Nine protein-coding genes have been identified within PSORS1: human leukocyte antigen (HLA)-C, octameric transcription factor 3 (OTF3, also known as POU5F1), transcription factor 19 (TCF19 or SC1), alpha-Helix Coiled coil Rod homologue (HCR or PG8), corneodesmosin gene (CSDN, also named gene S), the gene for a small protein rich in proline (SPR 1), gene SEEK 1 and gene STG, but it is still unclear which of them are involved in the

development of psoriasis [4, 10, 11]. Only one association signal was detected within PSORS1, which implies that a single genetic determinant confers disease risk [12].

HLA-C is considered the most likely candidate gene for this locus. It codes for class I MHC, which plays a key role in antigen presentation and self-tolerance. Class I MHC also stimulates response to intracellular pathogens by presenting non-self-cytoplasmic peptides to cytotoxic T lymphocytes. HLA-Cw6 allele is associated with early psoriasis onset, more severe disease and exacerbation of skin lesions secondary to streptococcal tonsillar infections [13]. Nevertheless, only 10% of HLA-Cw6 positive individuals develop psoriasis [2], and only 2/3 of psoriasis patients are HLA-Cw6 positive [10], suggesting that association with this locus reflects the causal role of a mutant allele located in the proximity of HLA-Cw6 or the co-segregation of regulatory polymorphisms with HLA-Cw6. Recent studies showed that SNPs in HLA-C promoter induce differential expression of HLA-Cw alleles [14]. Such regulatory variants would explain the fact that, in psoriatic lesions, the expression and not the function of HLA-Cw6 is altered [15, 16]. In addition, the HLA gene region harbours SNPs associated with both psoriasis and increased risk of cardiovascular disease and hyperlipidaemia [17], a finding that explains, at least partially, the elevated cardiovascular and metabolic risk of psoriasis patients. Characterization of these genes by further research could lead to the identification of subsets of psoriasis patients who are at increased risk for such comorbidities.

It is improbable that OTF3, STG, SC1, SPR1, and SEEK1 confer susceptibility to psoriasis, given the nature of their products. On the other hand, the other two genes identified within PSORS 1 interval, HCR and CDSN could be involved in the development of the disease. HCR codes for an ubiquitously expressed protein of unknown function with increased expression in the epidermis of psoriasis lesions. CDSN codes for corneodesmosin, a structural protein implicated in the adhesion process and epidemic desquamation [18]. Corneodesmosin has an increased production and decreased degradation in psoriatic epidermis [19] and has been linked to psoriasis development in several populations [20].

In an attempt to clarify the relationship between psoriasis and HLA-C, HCR, and CDSN, a series of haplotypes that comprise the three loci have been generated. These studies identified a major risk haplotype that contains HLA-C, HCR and CDSN and a minor risk haplotype that contains only HLA-C and CDSN alleles [21]. Haplotypes that contain only one of the three alleles are not associated with psoriasis [20]. The concept of multiple genes underlying a single susceptibility locus is not new

for multifactorial genetic disorders, being also encountered in type 1 diabetes mellitus [22] and multiple sclerosis [23].

Numerous psoriasis susceptibility loci outside the MHC interval have been reported but rarely reproduced in more than one population due to the high prevalence of these predisposing alleles in the general population.

PSORS 2

PSORS 2 is located on chromosome 17q, which is also the most important candidate region for psoriasis arthritis and rheumatoid arthritis susceptibility [10]. Therefore, it is not surprising that the association of psoriasis with PSORS 2 is strongest in patients with articular manifestations of disease. Within this interval, several genetic variants have been identified. The runt-related transcription factors 1 and 3 (RUNX 1 and RUNX 3) encode transcription factors involved in immune and inflammatory responses [24]. The SLC9A3R1 gene is implicated in the immune synapse, its malfunctioning probably leading to prolonged antigen presentation to the T cell receptor and sustained inflammation [25, 26]. Another possible psoriasis susceptibility allele within PSORS2 is the regulatory-associated protein of mTOR (RAPTOR), a key regulator of T lymphocyte function and growth [27].

PSORS 3

PSORS3, located on chromosome 4q, carries a series of genes that code for immunoregulatory molecules, such as interferon regulatory factor-2 (IRF-2), IL15, and toll-like receptors 2 and 3 [28]. SNPs across the IL15 gene have been shown to confer psoriasis susceptibility in the Chinese Han population [29], but not in Caucasian populations [30]. There are contradictory reports regarding the risk conferred by the polymorphisms of PSORS 3 genes, suggesting that the predisposing effect of certain alleles is masked by concomitant variation in other interacting genes.

PSORS 4

Psoriasis is also strongly associated with polymorphisms in the epidermal differentiation complex (EDC) region of PSORS4, which lies on chromosome 1q21 [31]. EDC harbours numerous genes essential for epidermal maturation, among which are the late cornified envelope (LCE) genes [32]. The expression of LCE3B and LCE3C is significantly increased in psoriasis [33].

PSORS 5

Chromosome 3q21 contains a psoriasis susceptibility locus, designated PSORS 5. Within this region, alleles of three SNPs showed significant association

with psoriasis. SLC12A8 gene that encodes a member of the solute carrier family 12 proteins is believed to be the gene that increases the risk of psoriasis [34].

PSORS 6

Another psoriasis susceptibility locus on chromosome 19p13 is positioned near fucosyltransferase 2 (FUT 2) gene that regulates the expression of Lewis human blood group of antigens. This locus also predisposes to Crohn disease [35].

PSORS 7

Chromosome 1p harbours PSORS 7 locus [36]. Variants mapping to IL23 receptor (IL23R) gene located in this region are strongly associated with psoriasis [37]. Another non-MHC predisposing allele is IL12B gene on chromosome 5q that codes for the p40 subunit of IL23 and IL12 [37, 38]. The IL23 levels are increased in psoriasis skin lesions. Moreover, psoriasis plaques can be induced by injection of IL23 into mouse skin [39]. IL23 promotes survival and expansion of T helper (Th) 17 lymphocytes that protect epithelia against fungal and bacterial infections [40]. Th 17 cells are also implicated in autoimmunity and altered IL23 expression could cause uncontrolled, chronic immune responses that target epithelial cells [41]. The evidence of the key role of IL12 and IL23 in the pathogenesis of psoriasis lead to the development of ustekinumab, a human monoclonal antibody with proven efficacy in this dermatosis [42, 43].

PSORS 8

A susceptibility variant for psoriasis and psoriatic arthritis maps to chromosome 16q [44].

PSORS 9

Multiple GWAS, carried out in both Caucasian and Chinese populations point to chromosome 4q31 as the site of psoriasis susceptibility genes, albeit with weak effects [45].

Pharmacogenetics, a complex topic in the management of psoriatic patients

While the susceptibility alleles of most Mendelian diseases are rare in the general population, such genes involved in multifactorial disorders are frequently encountered and have modest individual contributions to the development of the disease. Therefore, they are difficult to identify by linkage studies, tests of association being much more appropriate in this setting [46]. The major sources of genetic variations are single nucleotide polymorphisms (SNPs), copy number variations (CNVs),

which are larger DNA segments that vary in copy number, and copy-neutral loss of heterozygosity (LOH). Genome-wide association studies (GWAS) have recently become feasible owing to HapMap, which provided millions of genetic markers in the form of SNPs [47]. Efforts are made to determine the set of SNPs that best predict disease susceptibility, in order to clarify psoriasis pathogenesis and to anticipate the effect of medication on gene expression and disease course.

A series of psoriasis GWASs have been performed [48]. All confirmed the previously described strong association with SNPs in the vicinity of the HLA-C region and identified new psoriasis susceptibility loci based on association signals in genes that code for cytokines, chemokines and their receptors, growth factors, transcription factors, etc.

Even if psoriasis is considered to be an incurable disease, proposed therapies managed to control it. Immunosuppressive drugs, such as methotrexate and cyclosporine, and the latest biologic agents that specifically block the TNF alpha system or target interleukins (IL-12/IL-23) are the main systemic treatments for severe psoriasis.

The patient's response to therapy is variable and no accurate predictors are currently available. It is becoming increasingly clear that patients might be genetically predisposed to benefit or not from certain medication and that treatment should be individualized according to the particular genotype. Furthermore, adverse effects of such therapies are not neglectable as they can also be anticipated and potentially avoided by the identification of relevant predisposing genetic variants. Therefore, pharmacogenetics remains a complex topic aimed to identify not only the genetic predictors to drug response but also their efficacy and toxicity.

One of the most immunosuppressive drug, *methotrexate*, is the gold standard treatment for moderate to severe psoriasis and psoriatic arthritis due to its mechanism of action that inhibits T cell activation, down regulates B cells and inhibits the binding of interleukin 1beta to its receptor [49]. In addition, it is involved in purine synthesis inhibiting DNA synthesis and cell replication. One of the most important studies [50] highlighted the link between SNPs and genes involved in methotrexate uptake, ABCC1 and ABCG2 [50]. The toxicity of this drug, hepatotoxicity and gastrointestinal toxicity in particular, [51] was associated with the presence of five SNPs in ABCC1 and a decreased amount of folate carrier 1 gene (RFC1) [52]. However, there is no link between genes that code the enzymes involved in Methotrexate's metabolism such as 5-aminoimidazole-4-carboxamide ribonucleotide transformylase (ATIC), folypolyglutamate synthase (FPGS) and gamma-glutamyl hydrolase (GGH) [52].

Compared with the efficacy of *cyclosporin*, Methotrexate has a more complex clearance according to the study of Sandhu *et al.* [53], but, on the other hand, Heydendael *et al.* [54] revealed no differences in efficacy of the two drugs. [54] However, the combination between the methotrexate and cyclosporin is indicated in the treatment of moderate to severe psoriasis mostly because cyclosporine is a macrolide with a strong immunosuppressant action that neutralizes the immune response of T cells, thus decreasing the activity of genes coding for IL 2 and related cytokines [55]. Up to date, no study managed to point out clear aspects of pharmacogenetic of cyclosporin.

It is well known that TNF alpha is a key cytokine in the pathogenesis of psoriasis (Figure 1). The development of biological therapies marked out several perspective of treatment in psoriasis. To date, five biologic agents are recommended as a treatment for psoriasis: three of them target TNF alpha pathway (infliximab, etanercept, adalimumab), ustekinumab aims for IL-12 and IL-23 while alefacept targets T cells [56].

For instance, Infliximab is a recombinant DNA derived chimeric human-mouse IgG antibody that is recommended in many autoimmune diseases such as psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease and ulcerative colitis, because of its mechanism of action against TNF- α . It inhibits the biological activity of TNF- α by neutralizing the binding of TNF- α with its receptors. [57] Tejasvi T. *et al.* [58] revealed a link between the response to anti-TNF alpha therapy and SNP in the TNF gene promoter region 1031-rs1799964.

Unlike infliximab, adalimumab, another TNF- α blocker, is a fully human monoclonal antibody usually recommended in mild to severe forms of psoriasis, significantly improving the patients' quality of life [59]. Another biologic agent involved in psoriasis treatment is etanercept, a human fusion protein from recombining DNA aimed to bind, not only to TNF alpha, but also beta. Even if HLA (human leucocyte antigen)-C, KIR (killer immunoglobulin receptor) and VDR (vitamin D receptor) are involved in the pharmacogenetics of Etanercept and Adalimumab, Kyan *et al.* [60] demonstrated that they do not predict treatment response, therefore more research needs to be conducted for clarification.

Another efficient biologic agent is ustekinumab, a human monoclonal antibody that binds p40 subunit of both IL-12 and IL-23, suppressing immune-mediated inflammatory response in psoriasis. [61] Even if GWAS have emphasized that IL23R, IL23A, IL12B genes are critical to pathogenesis of psoriasis, this drug didn't demonstrate its efficiency for all patients.

To complete the biologic scheme for psoriasis, alefacept is a dimeric fusion protein, part of the extracellular membrane CD2 on T cells. It has a double mechanism of action, firstly by blocking the interaction between leukocyte and the costimulatory molecule LFA-3, inhibiting the activation of CD4 and CD8 T cells and, secondly, by inducing apoptosis of activated memory T cells *in vitro*, CD45RO, thereby decreasing the proliferation of keratinocytes [62, 63]. Nevertheless, personalized medicine needs further studies to establish individual genes profiles that respond to individual therapeutic management.

Multiple predisposing SNPs have been detected in the TNF alpha gene, especially in its promoter region [64]. TNF alpha 238A/G and TNF α 308A/G variants are associated with increased risk of psoriasis [65]. In addition, TNF alpha promoter SNPs 857T/C, 1031C/T, and 863A/C predispose to psoriasis and psoriatic arthritis [66], probably by altering TNF alpha expression. The presence of TNF alpha 857C allele has also been shown to confer positive response to anti TNF alpha agent, etanercept [67].

Two other genetic signals are represented by TNF alpha-induced protein 3 (TNFAIP3) and TNFAIP3-interacting protein 1 (TNIP 1) [68]. Together, the products of these genes are induced in inflammatory states and function as negative regulators of the immune response triggered by TNF-alpha and natural factor (NF)- κ B activation, limiting T cells activation [69]. Interestingly, different polymorphisms of TNFAIP3 gene predispose to different immune diseases (lupus erythematosus, rheumatoid arthritis, psoriasis) [70-72]. Of note, in animal studies TNFAIP3 also increases coronary artery disease [73], an important comorbidity of psoriasis. The expression of TNFAIP3 is increased in mild psoriasis, but is negatively correlated with psoriasis severity [66]. In the absence of TNFAIP3 expression upregulation that is probably due to TNFAIP3 polymorphism or the methylation of TNFAIP3 promoter [74], the inflammatory reaction is not restricted, leading to severe skin disease. Lower TNFAIP3 expression is also influenced by several SNPs (two intronic SNPs: rs610604 and rs5029930, and a SNP of a regulatory region located near TNFAIP3 gene) [75, 76]. Given its important role in psoriasis pathogenesis, TNFAIP3 represents an attractive target for future therapeutic agents. Moreover, recent studies showed that polymorphisms in TNFAIP3 influence the response of psoriasis lesions to anti-TNF alpha agents. Carriers of the G allele of SNP rs610604 of the TNFAIP3 gene, especially homozygous carriers and its haplotype with the T allele of SNP rs2230926, better respond to anti-TNF alpha therapy than non-carriers [77]. These studies pave the way for further research that aims to identify a set of SNPs that could be routinely typed in

psoriasis patients and used as predictors of the response to various treatments. Such information that would guide the medical approach of psoriasis patients and help choose the optimal treatment for each patient is of great medical and economic importance considering the significant side effects of immunosuppressive therapies and the high costs of biologic treatment.

Recent GWAS have found associations between psoriasis and polymorphisms of IL13 and IL4 genes, located on chromosome 5q31.1, in the vicinity of TNFAIP3 and TNIP1 genes. Although the expression of IL13 and IL4 is increased in allergic reactions but low in psoriasis [56], IL4 treatment was shown to ameliorate psoriasis lesions [78]. RAD50 gene is located in the close proximity of IL13 and IL4 genes, in a block of linkage disequilibrium. Therefore, a functional variant could influence the effects of all these genes [79]. Psoriasis is by definition a Th1 disease and genetic defects in this region could modulate the Th1/Th2 balance towards a Th1 phenotype.

IL6 is also involved in the pathogenesis of psoriasis. High levels of this proinflammatory cytokine were found in endothelial cells, macrophages, dendritic cells and Th17 lymphocytes present in psoriasis lesions [80]. It was hypothesized that IL6 diminishes the suppressive activity of regulatory T cells, favouring T cell expansion [80]. IL6 gene polymorphism 174 C/C was shown to confer susceptibility to psoriasis [81]. Tocilizumab is a humanized monoclonal antibody against the IL6 receptor approved for the treatment of moderate to severe rheumatoid arthritis non responsive to disease-modifying antirheumatic drugs and TNF alpha blockers and systemic juvenile idiopathic arthritis. In Japan, Castleman's disease represents another indication of tocilizumab treatment. It has also been successfully used in refractory psoriatic arthritis [82], and in persistent palmoplantar pustular psoriasis induced by anti-TNF alpha therapy is administered for rheumatoid arthritis [83].

SNPs within the promoter and 5'-untranslated regions of the vascular endothelial growth factor (VEGF) gene, located on chromosome 6p21.3, are also associated with psoriasis risk [84]. This is not surprising, considering VEGF is not only a major angiogenic mediator in psoriasis, but also a key inflammatory cytokine [85]. The functional significance of VEGF polymorphisms is still controversial, but clarifying their role could lead to the use of anti-VEGF therapies in psoriasis. A series of VEGF antagonists are approved for the treatment of wet macular degeneration, macular oedema and various cancers. Amelioration of psoriasis lesions was observed upon administration of monoclonal antibodies that target VEGF (bevacizumab) and VEGF receptors (VEGFR), decoy anti-VEGF receptors and VEGF

receptor tyrosine kinase inhibitors (sunitinib, sorafenib) in neoplastic patients, encouraging research regarding the benefits of these therapeutic agents in psoriasis [86]. Valpha, a recently developed chimeric decoy receptor that simultaneously blocks VEGF and TNF alpha showed promising results in psoriasis [87].

Other genetic signals have been detected, such as the ZNF313 gene on chromosome 20q13 [88], SNPs in the proximity of protein tyrosine phosphatase nonreceptor type 22 (PTPN22) gene on chromosome 1p13.3-13.1 [89], and in the CDK5 regulatory subunit associated protein 1-like 1 (CDKAL1) region [90].

ZNF313 gene codes for an E3 ubiquitin ligase that is expressed in CD4+ T lymphocytes, dendritic cells and skin cells, but also in testis, pancreas, kidney and spleen cells [88]. E3 ligases are involved in protein ubiquitinylation, a process implicated in immunoregulation [91]. TRAC-1, a member of the same family of RING domain E3 ubiquitin ligases as ZNF313 is a known positive regulator of T cell activation [92].

The product of PTPN22, the cytoplasmic lymphoid specific phosphatase (Lyp) is only expressed in hematopoietic cells, especially neutrophils and natural killer cells [93]. It inhibits T cell activation by inhibiting T cell receptor signalling [94]. The PTPN22 loss of function variants could, therefore, lead to enhanced immune responses. Interestingly, gain of function variants have also been linked to the development of multiple autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes, systemic sclerosis, autoimmune thyroiditis and others probably through inhibition of regulatory T cell activity [95]. Gain of function SNPs of the PTPN22 gene have been shown to predispose to psoriasis, the association being stronger in patients who also suffer from psoriatic arthritis [96].

The protein encoded by CDKAL1 gene is a member of the methyltransferase family. It is expressed in immune cells, particularly CD4+ and CD19+ lymphocytes, but not in epidermal cells [97]. Quaranta *et al.* showed that CDKAL1 expression is markedly downregulated following immune cells activation by proliferating signals [98]. Although its function in immune mediated diseases is not clear, SNPs in CDKAL1 gene confer susceptibility not only to psoriasis, but also to Crohn's disease and type 2 diabetes [90, 97].

Conclusions

All data illustrated the polygenic nature of psoriasis. It is the result of the polymorphism of multiple genes and an extremely complex network of regulatory genetic variants. It is probable that certain major genes are involved in the altered

immune regulation that characterizes the disease, while other polymorphisms explain the variability of clinical features and disease course. Along with the increasing number of psoriasis susceptibility loci that are being identified, arises the challenge of distinguishing the functional ones and turning them into therapeutic targets.

Despite the development of new promising therapeutic agents, more than 20% of psoriasis patients do not respond to biologic therapy [98]. Therefore, by assessing particular genetic markers which are predictive of response to treatment is essential to a stratified approach and an optimal individualized treatment.

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