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Psoriasis and other complex trait dermatoses: from loci to functional pathways

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Abstract

Driven by advances in molecular genetic technologies and statistical analysis methodologies, there have been huge strides taken in dissecting the complex genetic basis of many inflammatory dermatoses. One example is psoriasis where application of classical linkage analysis and genome wide association investigation has identified genetic loci of major and minor effect. Although most loci independently have modest genetic effect, they identify important biological pathways potentially relevant to disease pathogenesis and therapeutic intervention. In the case of psoriasis these appear to involve the epidermal barrier, NF-κB mechanisms and Th17 adaptive immune responses. The advent of next generation sequencing methods will permit a more detailed and complete map of disease genetic architecture, a key step in developing personalised medicine strategies in the clinical management of the complex inflammatory dermatoses.

Introduction

In some way or other all disease has a genetic basis. While this is obvious for Mendelian conditions including the genodermatoses (see review 1), at least in part the same holds true for all acquired diseases extending from cancer, through metabolic, degenerative and inflammatory diseases to infectious diseases. In the latter, the host's response to the pathogen, which determines the clinical phenotype and outcome, is, as exemplified by leprosy, in great part under genetic control (Vannberg *et al.*, 2011). This provides an example of how genes and environment may interact to cause disease.

In contrast to Mendelian diseases where very rare variants (mutations) have a major effect on disease phenotype, in common traits the genetic contribution is complex. In a small number of cases rare alleles with major effect and in others low frequency variants of intermediate effect may be responsible. However, in the large majority of cases common variants of small individual effect are likely to be involved. Building upon technological advances and on the wealth of information generated by the HapMap and the 1000 Genomes project (Altshuler *et al.*, 2010; The 1000 Genomes Project Consortium, 2010) huge strides have been made, in determining the genetic architecture of common, complex diseases.

Within dermatology are a group of disorders which are commonly grouped together as the 'inflammatory dermatoses'. Included under this umbrella term are diseases very frequent within the general population that are the cause of poor life quality and which, despite several therapeutic advances, retain significant unmet clinical need. To date, progress in

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unraveling fundamental biological pathways of disease has been sporadic. For these diseases, given their documented heritability, current and future genetic approaches hold much promise. Application of such methods has been outstandingly successful when applied to some of these inflammatory dermatoses of which two excellent examples are atopic dermatitis (MIM #603165) and psoriasis (MIM #177900). Intriguingly different approaches were used in each. For atopic dermatitis, a candidate gene approach based on the discovery of genetic variants in ichthyosis vulgaris, a frequently associated disease, led to the key observation that alterations in filaggrin, and thus the epidermal barrier, play a key role in pathogenesis (Palmer *et al.*, 2006). Testing the hypothesis that common variants may play a role in susceptibility to disease, several genome wide association studies (GWAS) have been performed in psoriasis. These have confirmed the primary role of the Major Histocompatibility Complex (MHC) in disease susceptibility, while identifying multiple genes of smaller effect which nevertheless provide a framework for understanding pathogenesis and explaining efficacy of several receptor targeted therapies (Ellinghaus *et al.*, 2010; Huffmeier *et al.*, 2010; Strange *et al.*, 2010; Stuart *et al.*, 2010; Sun *et al.*, 2010b). The GWAS approach has been applied to many other inflammatory dermatoses including vitiligo (MIM #193200), alopecia areata (MIM #104000) and atopic dermatitis, with varying degrees of success (Jin *et al.*, 2010a; Jin *et al.*, 2010b; Petukhova *et al.*, 2010).

This article provides a perspective on the application of genetics to the complex trait psoriasis, what information it has provided, the clinical and therapeutic implications and what it potentially means for personalized medicine. Psoriasis is used as a model for the article but clearly the principles it demonstrates are applicable to other dermatoses such as atopic dermatitis and acne vulgaris (MIM #604324).

Psoriasis as a complex trait dermatosis

Background

For the past 200 years psoriasis has been defined primarily by its clinical appearance. The spectrum of what are now considered to be psoriatic diseases demonstrates marked heterogeneity in clinical morphology (e.g plaques or pustules), distribution and disease severity, such that it remains unclear to what extent these represent different manifestations of the same inflammatory process, or distinct disease entities. Even within the apparently more homogenous subgroup of psoriasis vulgaris (chronic plaque psoriasis), heterogeneity has been demonstrated between disease of early onset (before 40 years of age) and later onset disease (Henseler and Christophers, 1985), and further subdivisions seem probable (Griffiths et al., 2007). The phenotype of psoriasis vulgaris has long been recognized to pass from one generation to the next but, with rare exceptions, without a Mendelian pattern of inheritance. The heritability of this form of psoriasis has been confirmed in twin studies, from which it can be estimated that about 80% of its phenotypic variance can be attributed to genetics (Brandrup et al., 1982). However, there are few data concerning the extent to which the phenotype, including for instance the presence of psoriatic arthritis or disease severity, breed true in pedigrees. Although precipitants such as infection are well established, the role of other environmental factors in determining disease susceptibility is less clear.

Linkage studies and the identification of PSORS1

The familial recurrence of psoriasis being well established, the disease has long been considered a complex genetic trait, resulting from gene-gene and gene-environment interactions (Nestle et al., 2009). As methods for linkage analysis of multifactorial conditions were developed in the early 1990s, several genome-wide scans were undertaken, with a view to pursuing the search for psoriasis susceptibility genes by means of positional

cloning. These studies provided very robust evidence for the presence of a disease susceptibility locus (named *PSORS1*) lying within the MHC, on chromosome 6p21.3 (Capon et al., 2002). Of note, the pathogenic involvement of the MHC was consistent with the results of previous serological studies, which had repeatedly identified an association between psoriasis and the HLA-Cw6 allele (Mallon et al., 1999; Tiilikainen et al., 1980).

Outside of the MHC, genome-wide linkage scans generated conflicting results (Capon et al., 2004b) and even the joint analysis of multiple family resources failed to validate any of the susceptibility regions that had emerged from these studies (The International Psoriasis Genetics Consortium, 2003). This phenomenon was by no means unique to psoriasis, as the poor performance of genome-wide linkage scans was plaguing the analysis of most complex traits. In fact, it eventually became apparent that linkage studies lacked the statistical power to detect common susceptibility loci with small phenotypic effects (Risch, 2000).

The search for the PSORS1 susceptibility gene

As linkage studies demonstrated that *PSORS1* was the major genetic determinant for psoriasis susceptibility (Nair et al., 1997; Trembath et al., 1997), several attempts were made to define a minimal disease interval and to identify the gene underlying the linkage signal. A linkage disequilibrium (LD) based fine mapping approach was undertaken by different groups, who analyzed dense microsatellite maps across the *PSORS1* locus, searching for markers that showed association as well as linkage with the disease (Nair et al., 2000; Veal et al., 2002). These efforts led to the identification of a 250 kb critical interval, which spanned part of the MHC class I region and included nine genes (Capon et al., 2002). Among these, *HLA-C* (human leukocyte antigen C), *CCHCR1* (coiled-coil alpha-helical rod protein 1) and *CDSN* (corneodesmosin) rapidly emerged as attractive candidate genes, based on their function and on the presence of disease associated alleles within their coding sequence.

HLA-C plays a fundamental role in immune responses as it encodes a class I MHC molecule involved in the process of antigen presentation to $CD8^+$ T lymphocytes (Falk et al., 1993). Highly significant association between psoriasis and the HLA-Cw6 allele had been reported in a wide range of populations, leading some researchers to propose that HLA-Cw6 might be the causal disease susceptibility allele at the *PSORS1* locus (Capon et al., 2002). *CCHCR1* encodes a protein of unknown function, which is over-expressed in the skin lesions of psoriatic patients (Asumalahti et al., 2000). Genetic studies identified an intragenic haplotype, which consisted of four non-synonymous substitutions and was associated with psoriasis susceptibility across multiple populations (Asumalahti et al., 2002). Transcriptome profiling of transgenic mice carrying the risk *CCHCR1* haplotype revealed changes in the expression of genes involved in keratinocyte terminal differentiation, suggesting that variation at this locus has functional consequences that are relevant to the pathogenesis of psoriasis (Elomaa et al., 2004).

CDSN codes for a keratinocyte structural protein that is involved in the process of skin desquamation, which is typically altered in psoriasis (Guerrin et al., 1998). Association between *CDSN* coding polymorphisms and psoriasis susceptibility were reported in several populations of European and Asian descent (Capon et al., 2003; Hui et al., 2002). Functional studies demonstrated that one disease associated variant affected the stability of *CDSN* mRNA (Capon et al., 2004a) and possibly accounted for the gene over-expression in patient skin lesions (Allen et al., 2001).

Despite these efforts at characterizing and validating disease association, the interpretation of genetic studies was constantly confounded by the conservation of linkage disequilibrium across *PSORS1*. With highly significant associations observed at all three gene loci, the

identification of the causal disease susceptibility allele proved to be an extremely challenging task (Capon et al., 2002). In an attempt to overcome this difficulty, the entire *PSORS1* region was sequenced in individuals bearing different *HLA-C* alleles, with a view to identifying Single Nucleotide Polymorphisms (SNPs) that were unique to the *PSORS1* risk haplotype. The results of these experiments suggested that *HLA-C* was the most likely *PSORS1* candidate gene (Nair et al., 2006).

Genome-wide association studies

Although theoretical calculations have long established that association studies are ideally suited to the identification loci of small genetic effect (Risch, 2000), the implementation of GWAS has only become achievable in the last five years, thanks to our improved understanding of human genetic variation and to technological advances in high-throughput genotyping (Frazer et al., 2007; The International HapMap Consortium, 2005). Since the Wellcome Trust Case Control Consortium carried out a landmark study of seven common conditions (The Wellcome Trust Case-Control Consortium, 2007), GWAS have become the instrument of choice in the analysis of complex traits. Whenever these studies have been applied to the analysis of adequately powered and carefully phenotyped datasets, they have been successful, leading to the identification of hundreds of disease susceptibility regions. The field of psoriasis genetics has embraced these advances and nine GWAS have been carried out in the last few years (Capon *et al.*, 2008; Cargill *et al.*, 2007; Ellinghaus *et al.*, 2010; Huffmeier *et al.*, 2010; Nair *et al.*, 2009; Strange *et al.*, 2010; Stuart *et al.*, 2010; Sun *et al.*, 2010b; Zhang *et al.*, 2009). These studies have included increasingly large sample sizes, reflecting a trend documented for most common and complex traits. At the same time, the design of these experiments has remained fundamentally unchanged, with the typical GWAS consisting of the analysis of 500,000-1,000,000 SNPs in a discovery dataset, followed by the validation of the most significant findings in an independently ascertained resource (Figure 1). This approach has proved to be extremely robust and has allowed the identification of 22 novel psoriasis susceptibility regions. Although these disease associated intervals tend to encompass several transcripts, most regions include at least one immune related gene. Remarkably, the proteins encoded by these positional candidate genes appear to contribute to a small number of signalling pathways (Table 1, Figure 2). Thus, the elevated statistical significance of the *HLA-C* association highlights the fundamental importance of antigen presentation in psoriasis. This notion is reinforced by the identification of disease susceptibility alleles within the *ERAP1* (endoplasmic reticulum amino-peptidase 1) gene, which encodes a peptidase contributing to the generation of class I MHC ligands (York et al., 2002). Of note, a genetic interaction between *HLA-C* and *ERAP1* has been documented, whereby *ERAP1* variants confer disease susceptibility only in individuals carrying the *HLA-C* risk allele (Strange et al., 2010). Given the small number of known interactions between complex disease loci, this is a remarkable observation, which emphasizes the significance of HLA-Cw6 restricted responses in psoriasis. At the same time, the associations at the *IL12B* (interleukin 12B), *IL23A (*interleukin 23A*), IL23R* (interleukin 23 receptor) and *TRAF3IP2* (TRAF3 interacting protein 2) loci underscore the pathogenic involvement of the IL-23/IL-17 axis. Likewise, the presence of susceptibility alleles within the *IFIH1 (*interferon induced with helicase C domain 1), *RNF114* (ring finger protein 114), *IL28RA* (interleukin 28 receptor alpha) and *TYK2* (tyrosine kinase 2) gene regions highlight a hitherto unsuspected role for the disruption of innate antiviral responses. Finally, the pathogenic impact of NF-κB signalling dysregulation is illustrated by the associations observed at the *REL* (v-rel viral oncogene homologue), *NFKBIA* (NF-κB inhibitor alpha), *TNFAIP3* (tumor necrosis factor alpha induced protein 3) and *TNIP1* (TNFAIP3 interacting protein 1) genes. Of note, key genes from all the above pathways have also been implicated in other immune-mediated conditions (Table 2), suggesting a genetic basis for the well documented occurrence of systemic co-morbidities in psoriasis

(Griffiths and Barker, 2007). Taken together, these results demonstrate the impact of GWAS on our understanding of disease processes. Although the individual genetic determinants identified by these studies confer modest increases in disease risk (with odds ratios typically ranging between 1.1 and 1.5), they collectively identify a small number of key pathogenic pathways that could be usefully targeted with novel therapeutic agents.

The post-GWAS era

Despite the remarkable success of GWAS, a significant proportion of psoriasis heritability remains unaccounted for. This phenomenon, which has been documented across most complex diseases (Maher, 2008), may be due to the lack of statistical power of the GWAS that have been carried out so far. In this context, the ongoing meta-analysis of three large studies (Ellinghaus et al., 2010; Strange et al., 2010; Stuart et al., 2010) is expected to uncover novel genetic determinants for the disease. At the same time, it is generally recognised that the current genotyping platforms present a number of limitations, which will affect the outcome of GWASs, regardless of the size of the examined sample. First of all, genotyping chips only include a fraction of the SNPs that have been annotated for the human genome. Thus, the effect size of the causal susceptibility SNPs that are not represented on current platforms can only be estimated, on the basis of the data that is available for their genotyped proxies. To address this issue, the Immunochip Consortium has recently developed a custom genotyping platform, which includes ~200,000 SNPs spanning more than 150 regions associated with immune-mediated conditions. The use of the Immunochip for the analysis of large case-control datasets is expected to identify the causal susceptibility alleles for most of the above loci, thus facilitating the interpretation of GWAS findings for conditions such as psoriasis, rheumatoid arthritis or Crohn's disease (Cortes and Brown, 2011).

Another limitation of GWAS is the under-representation of rare variants (generally defined as SNPs occurring at a frequency of less than 5%) on genotyping chips. This is of some importance, as studies carried out in other complex diseases have demonstrated that rare susceptibility alleles can play a role in the pathogenesis of common conditions (Nejentsev et al., 2009). The high-throughput mutational analyses that are required for the identification of these rare alleles are now becoming a realistic prospect, thanks to the development of next-generation sequencing (NGS) technologies. These techniques generate vast amounts of sequence information, which require the set up of complex bioinformatic pipelines and carefully designed follow-up protocols. Despite this difficulty, NGS has already had a dramatic impact on the discovery of rare Mendelian mutations (Teer and Mullikin, 2010) and is showing great promise as tool for the identification of genes underlying severe forms of skin inflammation (Onoufriadis et al., 2011; Marrakchi et al., 2011). Thus, the next few years are expected to witness significant progress in the characterization of rare sequence variants and in the understanding of their pathogenic role.

Finally, GWASs based on the analysis of bi-allelic SNPs have very limited power for the detection of complex copy number variants (CNV). In fact, the only multi-allelic CNV to be associated with psoriasis is a β-defensin cluster polymorphism (Hollox et al., 2008), which was identified in a candidate gene study. As CNV are expected to have significant phenotypic effects (Estivill and Armengol, 2007), *ad-hoc* genotyping platforms will have to be developed, in order to fully explore their pathogenic potential.

Other dermatoses and inflammatory skin disorders

As mentioned in Introduction, there are multiple other complex trait dermatoses and one would anticipate that the application of the techniques detailed above would likely provide great insights into disease pathophysiology. Two examples of recent progress are

generalized vitiligo (Jin et al., 2010a; Jin et al., 2010b) and alopecia areata (Petukhova et al., 2010). In both examples GWAS were performed and interestingly, as in the case of psoriasis, revealed evidence for the involvement both of genes involved in target cell / tissue biology and genes involved in the immune response. In the case of alopecia areata, GWAS revealed strongest association for SNPs within the MHC (max p value = 1.38×10^{-35}), while genome wide significance was achieved for genes involved in both innate (for example; *ULBP6,* UL16 binding protein) and adaptive (for example; *CTLA4,* cytotoxic T-lymphocyte-associated protein 4) immunity. Direct evidence for involvement of genes within the hair follicle was also observed (Petukhova et al., 2010). These results underpin the concept of a genetic basis for organ specific autoimmune disease.

The other important complex trait dermatosis, to which genetics have provided crucial insights into relevant functional pathways, is atopic dermatitis (AD). Unlike psoriasis, GWAS have to date been somewhat disappointing. However, the critical finding in AD of the association of loss of function mutations in filaggrin (Palmer et al., 2006) was discovered through a candidate gene approach following the clinical observation of the coexistence of AD with ichthyosis vulgaris, an autosomal semi-dominant disease (Brown and McLean, 2009). When this observation is taken together with candidate loci and genes observed in at least two genome-wide linkage studies, yet again the concept of a genetic aetiology involving target organ (epidermis) and immunological genes surfaces.

Conclusions

The rate of discovery of potential psoriasis genes in the past five years has been astonishing. The national and international collaborations necessary to assemble thousands of accurately-phenotyped individuals and for large-scale genotyping have fundamentally changed the research environment. However, identifying associated SNPs is only the first step in the process of gaining a better understanding of the nature of these diseases and of translation of this information into clinical applications. Identified loci require fine mapping and the functional effects of risk variants on, for instance, gene transcription, RNA splicing, or protein function need to be determined.

The impact on the management of psoriasis of translating genetic information into the clinic is potentially enormous. Currently, too small a proportion of the heritability of the disease is accounted for by known loci for genotyping to contribute to the diagnosis of psoriasis, but it can be anticipated that rare genetic mutations of major effect will be identified in severe psoriasis phenotypes that may be useful in sub-classifying psoriatic diseases and in disease classification. As the genetic architecture of psoriasis is more fully understood, investigation of gene–environment interactions may suggest interventions that prevent or modify the natural history of psoriasis.

The most immediate consequence of a greater understanding of the genetic basis of psoriasis may be in the design of new drugs, and the selection and monitoring of individual treatments. Susceptibility loci may prove to be useful therapeutic targets. In this respect, the high efficacy of monoclonal antibodies targeting the IL-23 / IL17 axis in psoriasis is encouraging, given the only modest odds ratios (1.5) of risk SNPs at *IL23R*. The genetic heterogeneity of psoriasis that is already known is currently being explored as a means of informing selection of currently available treatments, by carrying out pharmacogenetic studies alongside large psoriasis treatment registers. As more selective targeted treatments emerge, the likelihood of a differential responsiveness to treatment between patients depending on their genotype will increase and identification of genetic variants that influence the response to drug will be used in drug selection and dosing for the individual patient.

It is only a matter of time before genetic advances contribute to the clinical management of many dermatoses through the development of diagnostic and prognostic markers and identification of biological pathways relevant to therapeutic intervention.

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Abbreviations

GWAS	Genome-Wide Association Scans
MHC	Major Histocompatibility Complex
SNPs	Single Nucleotide Polymorphisms
NGS	Next-Generation Sequencing
CNV	Copy Number Variation
AD	Atopic Dermatitis

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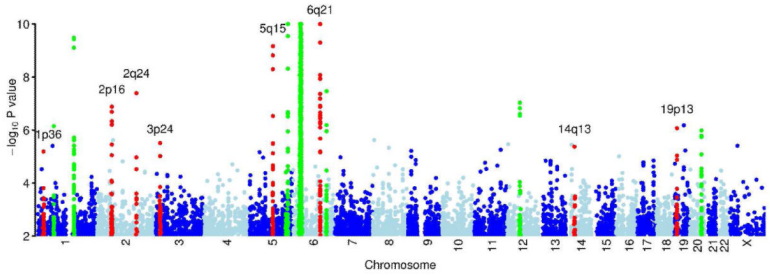

Figure 1.

An example of a Manhattan plot summarising the association results generated by a GWAS. SNPs are plotted according to their chromosomal location and each dot represents the *P* value (plotted as $-\log_{10}$ P) associated with a single marker. Green dots refer to susceptibility regions that were known at the onset of the study, with the *PSORS1* signal (which generated a $P < 10^{-200}$, but is cut here at $P = 10^{-10}$) on chromosome 6 dominating the genetic landscape. Red dots highlight novel susceptibility loci. Reproduced from Strange et al, *Nat Genet* 2010 42:985-90.

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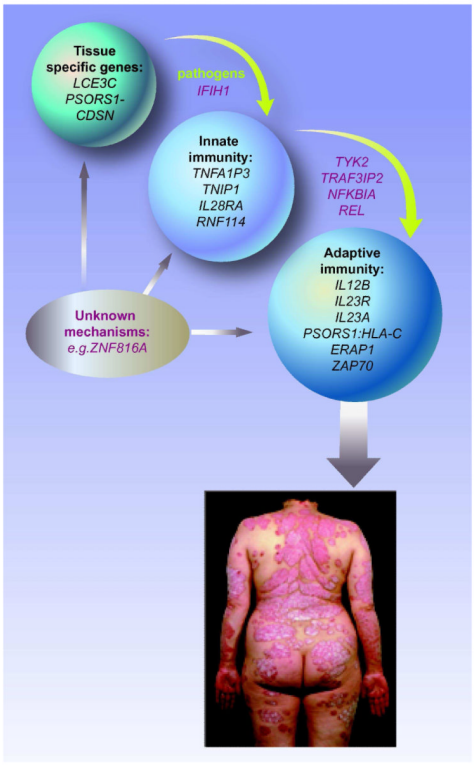

Figure 2.
Genetic studies suggest an integrated model for the pathogenesis of psoriasis. Alterations in skin barrier and immune genes determine abnormal responses to external agents (e.g. viruses detected by IFIH1), resulting in chronic skin inflammation.

Table 1

Genes associated with psoriasis susceptibility[1]

Gene* (location)	Protein function	Pathway	References
IL23R (1p31)	IL-23 receptor subunit	IL-23 signalling	(Capon et al., 2008; Cargill et al., 2007; Ellinghaus et al., 2010; Nair et al., 2009; Strange et al., 2010)
IL28RA (1p36)	IL-29 receptor subunit.	IFN signalling	(Strange et al., 2010)
LCE3B/3C/3D (1q21)	Keratinocyte structural protein	Skin barrier function	(de Cid et al., 2009; Ellinghaus et al., 2010; Zhang et al., 2009)
REL (2p16)	NF-κB subunit	NF-κB signalling	(Strange et al., 2010)
IFIH1/ MDA5 (2q24)	Innate antiviral receptor	IFN signalling	(Strange et al., 2010)
ERAP1 (5q15)	Amino peptidase processing MHC class I ligands	Antigen presentation	(Strange et al., 2010; Sun et al., 2010a)
IL4,IL13 (5q31)	Th2 cytokines	IL-4/IL-13 signalling	(Nair et al., 2009)
IL12B (5q33)	Subunit shared by the IL-12 and IL-23 cytokines	IL-23 signalling	(Cargill et al., 2007; Ellinghaus et al., 2010; Nair et al., 2009; Zhang et al., 2009) (Huffmeier et al.,2010) **
TNIP1 (5q33)	Inhibitor of TNF-induced NF-κB activation	NF-κB signalling	(Nair et al., 2009; Strange et al., 2010; Sun et al., 2010a)
PTTG1 (5q33)	Anaphase promoting complex substrate	Cell cycle control/DNA repair	(Sun et al., 2010a)
HLA-C (6p21)	MHC class I antigen	Antigen presentation	(Capon et al., 2008; Ellinghaus et al., 2010; Nair et al., 2009; Strange et al., 2010; Zhang et al., 2009)
TRAF3IP2 (6q21)	Adaptor mediating IL-17 induced NF-kB activation	IL-17/NF-□B signalling	(Ellinghaus et al., 2010; Strange et al., 2010) (Huffmeier et al., 2010) **
TNFAIP3 (6q23)	Inhibitor of TNF-induced NF-κB activation	NF-κB signalling	(Nair et al., 2009; Strange et al., 2010)
CSMD1 (8p23)	Tumour suppressor gene	Unknown	(Sun et al., 2010a)
IL23A (12q13)	IL-23 subunit	IL-23 signalling	(Nair et al., 2009; Strange et al., 2010)
GJB2 (13q11)	Gap junction protein	Electrolyte transport	(Sun et al., 2010a)
NFKBIA (14q13)	Inhibitor of NF-κB activation	NF-κB signalling	(Strange et al., 2010; Stuart et al., 2010)
FBXL19 (16p11)	Putative inhibitor of NF-κB activation	NF-κB signalling	(Stuart et al., 2010)

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Gene* (location)	Protein function	Pathway	References
NOS2 (17q11)	Induced nitric oxide synthase	Innate antibacterial response	(Stuart et al., 2010)
SERPINB8 (18q21)	Serine protease inhibitor	Unknown	(Sun et al., 2010a)
TYK2 (19p13)	Tyrosine kinase associated with cytokine receptors	IL-23 and IFN signalling	(Strange et al., 2010)
ZNF816A (19q13)	Zinc Finger Protein	Unknown	(Sun et al., 2010a)
ZNF313/RNF114 (20q13)	E3 ubiquitin ligase	IFN signalling	(Capon et al., 2008; Nair et al., 2009; Strange et al., 2010; Stuart et al., 2010)

[1] All the loci included in the Table showed genome-wide significant association ($P < 5 \times 10^{-8}$) with psoriasis, in at least one GWAS.

* Gene of interest found in the disease-associated susceptibility interval;

** Psoriatic arthritis GWAS.

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Table 2

Pleiotropic disease susceptibility genes associated with psoriasis

Gene	Other Associated Diseases	References
IL23R	Crohn's disease Ankylosing spondylitis	(Burton et al., 2007; Duerr et al., 2006)
REL	Rheumatoid arthritis Celiac disease Crohn's disease	(Franke et al., 2010; Gregersen et al., 2009; Trynka et al., 2009)
IFIH1	Type I diabetes	(Nejentsev et al., 2009; Smyth et al., 2006)
ERAP1	Ankylosing spondylitis	(Burton et al., 2007)
CDKAL1	Crohn's disease Type 2 diabetes	(Barrett et al., 2008; Quaranta et al., 2009; Zeggini et al., 2007)
IL12B	Crohn's disease Ulcerative colitis	(Fisher et al., 2008; Parkes et al., 2007)
PTTG1	Systemic lupus erythematosus	(Han et al., 2009)
TNIP1	Systemic lupus erythematosus	(Gateva et al., 2009)
TNFAIP3	Rheumatoid arthritis Systemic lupus erythematosus Celiac disease	(Graham et al., 2008; Musone et al., 2008; Plenge et al., 2007; Thomson et al., 2007; Trynka et al., 2009)
TYK2	Type I diabetes Multiple sclerosis Systemic lupus erythematosus Crohn's disease	(Australia and New Zealand Multiple Sclerosis Genetics Consortium (ANZgene), 2009; Franke et al., 2010; Sigurdsson et al., 2005; Wallace et al., 2010)