Genetic Variations in Cytokines and Cytokine Receptors Associated with Psoriasis Found by Genome-Wide Association

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Genetic variants have long been suspected to be important in psoriasis. Recent work has suggested that *HLA-Cw6* on chromosome 6 is the risk variant in the *PSORS1* [MIM 177900] susceptibility locus that confers the greatest risk for early onset of psoriasis. Although numerous minor susceptibility loci have been identified by linkage analysis, few biologically relevant candidates have been discovered within these intervals. Recent large-scale genome-wide association studies have yielded new candidates in genes encoding cytokines with functional relevance to psoriasis. Polymorphisms within the genes encoding the IL-12 p40 subunit, *IL12B*, and one of the IL-23 receptor subunits, *IL23R*, have been replicated in US and European populations and overlap with risk of Crohn's disease. Polymorphisms within the gene encoding IL-13, a Th2 cytokine, also confer risk for psoriasis. Variants of the gene *IL15* encoding IL-15 have been identified that associate with psoriasis in a Chinese population. These discoveries pose the challenge of elucidating the role of common genetic variants in susceptibility to and manifestations of psoriasis.

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PSORIASIS IS A COMPLEX POLYGENIC DISORDER

Psoriasis is a chronic inflammatory disorder that affects 0.6–4.8% of the population worldwide (Naldi, 2004). Psoriasis has long been considered a disorder with a genetic basis, supported by familial clustering of the disease (Lomholt, 1976), increased concordance among monozygotic twins (Brandrup *et al.*, 1982) and the repeatedly confirmed association with *HLA-Cw6* (Nair *et al.*, 2006). However, only 60–65% of individuals with psoriasis carry this risk variant, and 15% of individuals without psoriasis carry *HLA-Cw6* (Gudjonsson *et al.*, 2006), lending support to the widely held belief that other common genetic variants contribute to psoriasis susceptibility. In the last decade, numerous genome-wide scans using linkage analysis on multiply affected families, have elucidated eight other replicated susceptibility loci (*PSORS2–9*) as reviewed by Capon *et al.* (2004). Follow-up sequencing and fine mapping within these susceptibility loci have, to date, yielded few candidate genes with biologic relevance to psoriasis pathophysiology.

A NEW ERA OF GENOME-WIDE ASSOCIATION

Genome-wide studies were initially performed using linkage analysis, which relies on the concept that a marker allele near a disease gene is coinherited with that disease gene within a family unless a recombination event has occurred. Marker alleles are then traced in families that have affected and unaffected individuals. With the better understanding of genomic variation of the human genome provided by the International HapMap Consortium (2005), genome-wide studies can now be performed by association rather than linkage. Association analyses compare the frequencies of the alleles of single-nucleotide polymorphisms (SNPs) between cases and controls. With the advances in high-throughput technologies, sophisticated statistical techniques, and availability of large collections of well-phenotyped patients, large genome-wide association studies (GWAS) can compare the frequencies of hundreds of thousands of SNPs in cases and controls. GWAS have, to date, been successfully used to find risk variants in large cohorts of patients with diabetes, Crohn's disease (Wellcome Trust Case Control Consortium, 2007), and many other disorders with complex inheritance. In the past 2 years, genome-wide case–control studies (Capon *et al.*, 2007; Cargill *et al.*, 2007) and two confirmation analyses (Smith *et al.*, 2007; Nair *et al.*, 2008) of psoriasis populations have yielded two candidate loci at *IL12B* and *IL23R*. These candidates offer the promise of clinical relevance as their gene products have very recently been considered to have key roles in psoriasis pathophysiology. In addition, other cytokine genes, *IL13* and *IL15*, have been identified as harboring variants that associate with psoriasis. What follows is a review of the recently discovered risk variants in genes encoding cytokines or their receptors and their potential relevance to the pathogenesis of psoriasis.

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Abbreviations: GWAS, genome-wide association study; IBD, inflammatory bowel disease; OR, odds ratio; SNP, single-nucleotide polymorphism; TNF-α, tumor-necrosis factor-α

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IL12B VARIANTS AND PSORIASIS RISK

The first large-scale genome-wide case–control association study of psoriasis that yielded an association between psoriasis and cytokines and cytokine receptors relevant to the pathophysiology of psoriasis was reported by Cargill *et al.* (2007). This study was carried out by genotyping 467 well-characterized psoriasis patient from our registry (the Utah Psoriasis Initiative) and 500 controls for 25,215 gene-centric SNPs using a disease-phenotype pooling strategy, a method that essentially screens for associated polymorphisms while conserving DNA. Polymorphisms that associated with psoriasis were evaluated in a second sample set, and those that maintained their significance were then individually genotyped.

The screening phase of this study revealed a highly significant association of *rs3212227* (1188A>C) with psoriasis. The presence of the common (A) allele confers risk of psoriasis with an odds ratio (OR) of 1.59 in the discovery cohort (confidence interval 1.24–2.04, allelic *P*-value of 1.89×10^{-4}) and an OR of 1.81 in the replication cohort (confidence interval 1.42–2.28) (Table 1). This polymorphism, located in the 3′-untranslated region of IL12B, was first described in 2000, but early studies did not detect significant association in patient cohorts of rheumatoid arthritis, multiple sclerosis, or large granular lymphocyte leukemia with or without arthritis (Hall *et al.*, 2000). In 2002, a Japanese group reported an increased frequency of the common (A) allele of *rs3212227* in psoriasis patients but replication in an independent sample was never performed (Tsunemi *et al.*, 2002).

Further sequencing and tagSNP analysis of *IL12B* also yielded a risk SNP ~60 kb upstream of *IL12B*, *rs6887695* (*G*>*C*). Again, the common (G) allele conferred risk in the discovery and two replication cohorts. When considered together, the two *IL12B* risk SNPs (A-G) form a psoriasis-associated haplotype; individuals homozygous for the risk alleles at both SNPs have a combined OR of 1.40 ($P_{\text{combined}} = 8.11 \times 10^{-9}$) for having psoriasis.

Since publication of the Cargill paper, three other studies have confirmed the association of *IL12B* SNPs with psoriasis. Risk alleles of *rs3212227* and *rs6887695* were both shown to confer risk for psoriasis in a UK data set of early onset psoriasis (Smith *et al.*, 2007) and in a case–control and family based study performed with US and German patients (Nair *et al.*, 2008). Another study which confirmed association with *rs3212227* also identified an additional SNP upstream of *IL12B*, *rs10045431*, that was not seen in the Cargill study

Table 1. Summary of genotype frequencies, minor allele frequencies, and odds ratios for *IL12B* SNP *rs3212227*

		Genotype frequency		Minor allele frequency		Odds ratio (for common allele conferring risk) (confidence interval)
	Genotype	Patients	Controls	Patients	Controls	
Cargill	AA	0.736	0.630			
Discovery[1]	AC	0.242	0.322	0.143	0.209	1.59 (1.24–2.04)
	CC	0.021	0.047			
Cargill	AA	0.750	0.603			
Replication[1]	AC	0.226	0.348	0.137	0.223	1.81 (1.42–2.28)
	CC	0.024	0.049			
Smith UK[2]	AA	0.718	0.647			
	AC	0.256	0.316	0.154	0.194	1.33 (1.11–1.57)
	CC	0.026	0.036			
Nair US[3]	AA	0.734	0.594			
	AC	0.244	0.346	0.145	0.221	1.67 (1.45–1.92)
	CC	0.023	0.044			
Nair Kiel[3]	AA	0.730	0.651			
	AC	0.254	0.316	0.144	0.191	1.41 (1.11–1.50)
	CC	0.017	0.033			
Capon UK	AA	NA	NA			
Discovery[4]	AC	NA	NA	0.150	0.180	1.24 (0.99–1.56)
	CC	NA	NA			
Capon UK	AA	NA	NA			
Replication[4]	AC	NA	NA	0.160	0.200	1.31 (1.11–1.55)
	CC	NA	NA			

NA, not applicable.
[1]Cargill *et al.* (2007).
[2]Smith *et al.* (2007).
[3]Nair *et al.* (2008).
[4]Capon *et al.* (2007).

(Capon *et al.*, 2007). In all three studies, the common allele is more frequent in individuals with psoriasis (the minor allele is protective). A summary of the genotype and allele frequencies for *rs3212227* (with ORs performed in the context of the common allele conferring ''risk'') from these studies is presented in Table 1, which illustrates a modest, yet consistent, effect of this common variant.

IL23R VARIANTS AND PSORIASIS RISK

The discovery of the association of *IL12B* with psoriasis prompted a thorough search of other risk variants within the IL-12/23 receptor–ligand pathway that associate with psoriasis. This led to the discovery of and report by Cargill *et al.* of two psoriasis-associated polymorphisms within the gene encoding one subunit of the IL-23 receptor, *IL23R*. Genotyping and haplotype analysis of SNPs within *IL23R* yielded two additional SNPs, rs*7530511* and *rs11209026* that also conferred risk of psoriasis. Of note, the *rs11209026* polymorphism is a nonsynonymous SNP that results in an Arg to Gln substitution (Arg381Gln, or Q381R) that had recently been found to associate risk of Crohn's disease (Duerr *et al.*, 2006). Both *rs7530511* and *rs11209026* have been replicated in the aforementioned UK (Smith *et al.*, 2007) and US and German populations (Nair *et al.*, 2008) and *rs11209026* was also significant in the Capon study. A summary of the genotype and allele frequencies for *rs11209026* (with ORs performed in the context of the minor allele conferring protection) is presented in Table 2, which again demonstrates a consistently modest effect.

ROLE OF IL-12 AND IL-23 IN PSORIASIS

In recent years the roles of cytokines IL-12 and IL-23 in psoriasis have become increasingly more clear (Fitch *et al.*, 2007). IL-23 and IL-12 are heterodimeric members of the IL-12 cytokine family. They are structurally related in that they share the p40 subunit; IL-12 is formed by the p40 and p35 subunits; IL-23 is formed by the p19 and p40 subunits. IL-12 is known to promote the differentiation of naïve T cells (Th0) into Th1 lymphocytes, which in turn produce IFN-γ and IL-2. Until recently the ''Th1'' paradigm was considered central to the development of psoriasis. However, mounting evidence suggests that IL-23 may have a more critical role than IL-12 in the development of psoriasis. Both p40 and p19 mRNA levels are increased in lesional psoriatic skin, whereas p35 is not (Lee *et al.*, 2004). In the presence of IL-6 and transforming growth factor-β, Th0 cells can differentiate into a population

Table 2. Summary of genotype frequencies, minor allele frequencies, and odds ratios for IL23R SNP *rs11209026*

		Genotype frequency		Minor allele frequency		
Study population	Genotype	Patients	Controls	Patients	Controls	Odds ratio (for minor allele conferring protection) (confidence interval)
Cargill	GG	NA	NA			
Discovery[1]	GA	NA	NA	0.044	0.060	0.73 (0.406–1.299)
	AA	NA	NA			
Cargill	GG	NA	NA			
Replication[1]	GA	NA	NA	0.051	0.077	0.64 (0.360–1.077)
	AA	NA	NA			
Smith UK[2]	GG	0.926	0.883			
	GA	0.074	0.117	0.037	0.060	0.62 (0.446–0.848)
	AA	0.000	0.000			
Nair US[3]	GG	0.894	0.867			
	GA	0.103	0.129	0.053	0.066	0.78 (0.573–1.070)
	AA	0.003	0.004			
Nair Kiel[3]	GG	0.914	0.856			
	GA	0.086	0.137	0.043	0.072	0.56 (0.318–0.986)
	AA	0.000	0.006			
Capon UK	GG	NA	NA			
Discovery[4]	GA	NA	NA	0.022	0.072	0.29 (0.158–0.545)
	AA	NA	NA			
Capon UK	GG	NA	NA			
Replication[4]	GA	NA	NA	0.045	0.069	0.63 (0.430–0.925)
	AA	NA	NA			

NA, not applicable.
[1]Cargill *et al.* (2007).
[2]Smith *et al.* (2007).
[3]Nair *et al.* (2008).
[4]Capon *et al.* (2007).

of mature T cells distinct from Th1 and Th2, known as Th17 cells. Th17 cells uniquely express the IL-23 receptor, made up of two subunits, IL23R and IL12Rβ1. In the presence of IL-23, Th17 cells produce Th17 cytokines, including IL-17A, IL-17F, IL-6, tumor-necrosis factor (TNF)-α, and IL-22, which drive downstream events that sustain psoriatic plaques. Recent data also suggest that etanercept, a TNF-α, receptor–Ig fusion protein, may inhibit Th17 cytokine production by dendritic cells within the first 2 weeks of therapy, whereas Th1-mediated IFN-γ production diminishes much later, supporting a more upstream role of the Th17 cytokines (Zaba *et al.*, 2007). Last, neutralization of p40 with a human mAb leads to marked clinical improvement of psoriasis plaques, further implicating IL-23 and IL-12 as having an important role in psoriasis (Kauffman *et al.*, 2004; Krueger *et al.*, 2007). To date, the risk variants in *IL12B* and *IL23R* have not been directly linked to the expression of IL-12, IL-23, or other key cytokines playing a role in psoriasis. Figure 1 summarizes the chromosomal location of the risk SNPs at *IL12B* and *IL23R*, the subunits that may be affected by these variants, and the Th1 and Th17 cytokines that could be modulated by altered expression of IL-12 or IL-23.

IL23R VARIANTS AND INFLAMMATORY BOWEL DISEASE

Polymorphisms in *IL23R* have also been found to associate with risk of inflammatory bowel disease (IBD) and have been replicated in multiple studies. The same SNP that associates with psoriasis, *rs11209026*, was reported initially in a Crohn's disease case–control study (Duerr *et al.*, 2006). Interestingly, this study did not identify the association of Crohn's disease with the *IL12B* risk variants. The *rs11209026* polymorphism and others in *IL23R* have subsequently been seen in the Wellcome Trust Case–Control Consortium (2007) GWAS of 14,000 cases and 3,000 controls, and numerous other GWAS of adult Crohn's disease (Libioulle *et al.*, 2007; Parkes *et al.*, 2007; Raelson *et al.*, 2007; Rioux *et al.*, 2007), UC (Buning *et al.*, 2007), and pediatric IBD (Baldassano *et al.*, 2007; Van Limbergen *et al.*, 2007).

Like psoriasis, IBD is considered an immune-mediated multifactorial and polygenic disorder. These two conditions frequently overlap. Patients with Crohn's disease have a fivefold risk of developing psoriasis (Lee *et al.*, 1990) and anti-TNF-α therapies have efficacy in both disorders. Crohn's disease was considered primarily a Th1-mediated disorder until the Th17 pathway emerged, and IL-23, not IL-12, was shown to mediate colitis following intestinal bacterial infection in a mouse model (Hue *et al.*, 2006; Uhlig *et al.*, 2006). Furthermore, a mAb to IL-23p19 has been shown to treat and prevent chronic colitis in a mouse model of IBD (Elson *et al.*, 2007). Although risk variants within *IL23R* have an unknown impact on the causation of IBD, a recent study has demonstrated that carriers of the *IL23R* risk variants have significantly higher serum levels of the Th17 cytokine, IL-22, and greater disease activity scores than the *IL23R* protective variant carriers (Schmechel *et al.*, 2008). Thus, more than just circumstantial evidence is emerging to link genetic variation to pathogenesis.

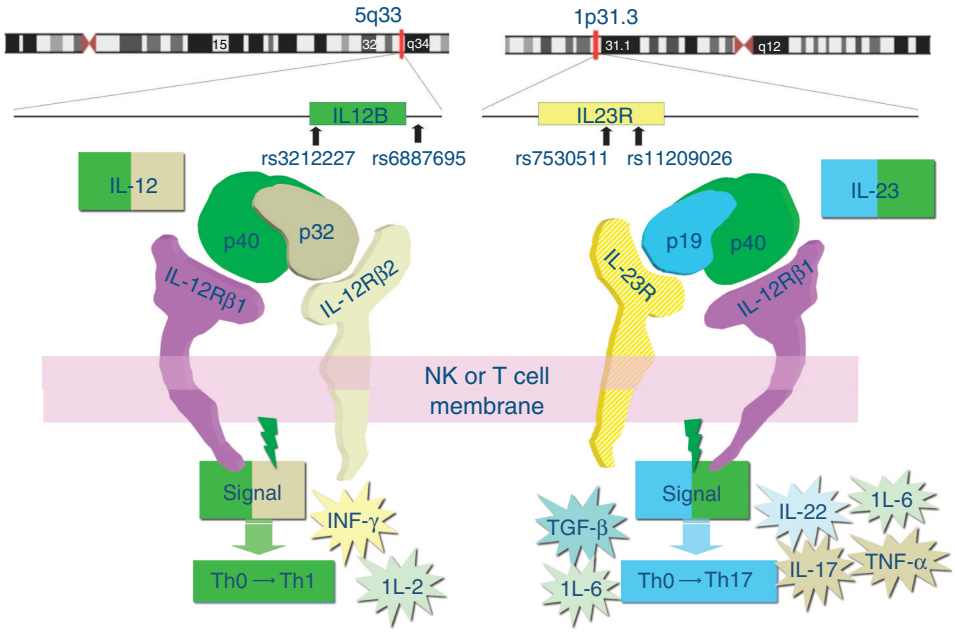

Figure 1. IL12B and IL23R SNPs. The *IL12B* SNPs that associate with psoriasis include *rs3212227*, which resides within the 3′-UTR region of IL12B, and *rs6887695*, which is ~60 kb upstream of IL12B, on chromosome 5q33. The *IL23R* SNPs that associate with psoriasis include *rs11209026* and *rs7530511* on chromosome 1p31.3. *IL12B* encodes p40, the subunit shared by both IL-12 and IL-23. *IL23R* encodes one of the two IL-23 receptor subunits. When bound to its cell-surface receptors, IL-12 promotes the differentiation of naïve Th0 cells into Th1 cells, which in turn produce IFNγ and IL-2. In the setting of IL-6 and TGF-β, IL-23 promotes the differentiation of naïve Th0 cells into Th17 cells, which secrete IL-17A, IL-17F, IL-6, TNF-α, and IL-22. The role of the *IL12B* and *IL23R* polymorphisms in the expression of IL-12, the IL-23 receptor, and their impact on psoriasis pathophysiology remains unknown (adapted courtesy of Centocor, 2008).

IL13 AND PSORIASIS RISK

Another gene of interest that appeared in the preliminary results of the Cargill genome-wide scan was *IL13*, the gene that codes for IL-13 that resides within the chromosome 5q31 cytokine cluster. IL-13, like IL-4 and IL-10, is secreted by Th2 cells, propagating the allergic inflammatory response seen in asthma, allergy, helminthic responses, and atopic dermatitis. Given its immunoregulatory role, the same multitiered approach used to identify *IL12B* and *IL23R* was used to identify association of psoriasis with three SNPs in *IL13*: *rs1800925*, *rs20541*, and *rs848* (Chang *et al.*, 2008). Like the *IL12B* and *IL23R* SNPs, the common alleles confer a modest degree of risk, with the risk haplotype CCG conferring the most risk with a combined OR of 1.27 ($P_{combined} = 1.88 \times 10^{-4}$).

The role of IL-13 in psoriasis is yet to be elucidated. IL-13 and the closely related cytokine, IL-4, bind to and send signals through receptors composed of combinations of four receptor subunits, IL-4Rα1, IL-13Rα1, IL-13Rα2, and a common γ chain. Although IL-13 and IL-4 could not be detected in the skin of psoriasis or healthy controls by RT–PCR or immunohistochemical techniques in two different studies (Van der Ploeg *et al.*, 1997; Cancino-Diaz *et al.*, 2002), both IL-13Rα1 and IL-4Rα1 mRNA have been shown to be overexpressed in lesional and nonlesional skin (Cancino-Diaz *et al.*, 2002). When added to primary keratinocyte cultures, IL-13 has been shown to increase IL-6 (Derocq *et al.*, 1994; Wongpiyabovorn *et al.*, 2003), an important cytokine in the early development of Th17 cells. Although still speculative at this time, IL-13 be important in the dysregulation of the innate and adaptive immune response that leads to psoriasis.

IL15 AND PSORIASIS RISK

IL-15 is also a cytokine of interest in both the pathogenesis and genetic susceptibility of psoriasis, as recently reviewed (Elder, 2007). IL-15 and its receptor IL-15Rα are expressed by keratinocytes (McInnes and Gracie, 2004), and IL-15 is known to be overexpressed in lesional psoriatic epidermis (Ruckert *et al.*, 2000). IL-15 upregulates many proinflammatory cytokines, including TNF-α, IFN-γ, macrophage inflammatory protein-1α and -1β, IL-1β, and IL-10 (Fehniger and Caligiuri, 2001), and activates human neutrophils (Girard *et al.*, 1996). IL-15 also stimulates production of IL-17 by T lymphocytes (Hoeve *et al.*, 2006). Furthermore, antibodies targeting IL-15 bound to its receptor led to reduction of psoriasiform lesions on a xenograft mouse model (Villadsen *et al.*, 2003).

IL15 resides on chromosome 4q28–31, within the PSORS9 psoriasis susceptibility locus found originally by linkage analysis (Zhang *et al.*, 2002; Sagoo *et al.*, 2004). A recent case–control analysis of SNPs in the region identified a highly significant association of four *IL15* SNPs, the most significant being g.96516A→T in the 3′-untranslated region region, with an $OR_{genotypic}$ of 1.86 ($P = 4 \times 10^{-7}$) (Zhang *et al.*, 2007). Further investigation of transcriptional activity using a luciferase reporter assay suggested that the risk haplotypes were associated with higher expression activity, lending support to a functional role of these risk variants.

MULTILOCUS MODELS OF GENETIC SUSCEPTIBILITY

A great deal of interest now lies in determining if these risk variants interact or synergize to increase psoriasis susceptibility. Nair *et al.* (2008) were unable to detect evidence of epistasis between HLA-Cw6 and the risk variants in *IL12B* and *IL23R* in a two-locus logistic regression model, but asserted that the term ''epistasis'' is not well defined biologically or statistically. We also have demonstrated lack of any additive or synergistic effect in logistic regression and case–control analyses (Tables 3–5). Table 3 shows the case–control analysis with HLA-Cw*0602 in our population (OR 4.0) (Table 3). The logistic regression analysis, shown in Table 4, reveals a higher OR for individuals carrying both Cw*0602 and the IL12B AA (risk) genotype (OR = 6.17), but did not reveal any evidence of interaction ($\chi^2 = 1.0$, $P = 0.32$ when compared to those carrying neither risk allele), suggesting that the effects of HLA-Cw6 and *IL12B* are independent. Analysis of HLA-Cw*0602+ cases and controls show that the additional presence of the *IL12B* risk genotype does not significantly increase risk of psoriasis (OR = 1.23, $P = 0.49$) (Table 5). However, in HLA-Cw*0602− cases and controls, presence of the minor allele does is associated with reduced risk, suggesting that the minor allele of *rs3212227* may confer additional protection. We conclude that presence of HLA-Cw*0602 still confers the highest risk of psoriasis, and the effects of the *IL12*, *IL23R*, and *IL13* polymorphisms are quite modest as would be expected for a common disease variant (Bodmer and Bonilla, 2008). To date, there are no statistical or biological models that suggest epistasis, but analyses of risk between the highest- and lowest-risk genotype classes in both the Chang and Nair studies suggest that obtaining a multilocus genotype may have prognostic utility in the future (Chang *et al.*, 2008; Nair *et al.*, 2008). Discovering epistatic interactions in large data sets will present a significant challenge, given the

Table 3. Psoriasis cases and controls with (+) or without (−) Cw*0602

	Cw*0602+	Cw*0602−	OR (CI)
Cases	209	288	4.01 (2.93–5.48)
Controls	69	381	

Table 4. Logistic regression in psoriasis cases and controls for presence (+) or absence (−) of HLA-Cw*0602 and IL12B *rs3212227* risk genotype AA

Cw*0602	*rs3212227* AA	OR (CI)	*P*-value
−	−	1.0 (reference)	
−	+	1.74 (1.25–2.44)	0.001
+	−	5.01 (2.85–8.82)	<0.0001
+	+	6.17 (4.01–9.49)	<0.0001

Table 5. Cw*0602 in psoriasis cases and controls with HLA-Cw*0602, with or without IL12B *rs3212227*-risk genotype AA

	Cw*0602 +/ *rs3212227* AA	Cw*0602 +/*rs3212227* AC or CC	OR (CI)
Cases	150	57	1.23 (0.68–2.22)
Controls	47	22	

computational complexity of analyzing all possible combinations of SNPs, and some authors have suggested that examining protein–protein interaction will facilitate gene interaction discoveries (Pattin and Moore, 2008).

PERSPECTIVE

The identification of genetic variations in or near genes encoding cytokines and cytokine receptors with functional relevance to psoriasis pathogenesis provides compelling evidence that GWA is a powerful tool in finding common genetic variants. Replication of the risk variants in different populations with very similar ORs also supports the validity of the association. These findings also harmonize with previous assertions by psoriasis genetics researchers that several psoriasis genes exist and are scattered throughout the genome, and that some of these genes may be involved in a variety of other inflammatory or immune-mediated diseases other than psoriasis (Tarlow *et al.*, 1997; Elder *et al.*, 2001). It is quite possible that many more common variants exist and contribute to psoriasis risk. For this reason, collaborative efforts to pool larger cohorts of cases such as Genetics Association Information Network (Manolio *et al.*, 2007), which will yield genotypes on over 400,000 SNPs in ~1,400 cases and ~1,400 controls, are underway. Meta-analyses and replication efforts with additional patient cohorts are expected to yield important new variants with modest relative risk that have been missed in studies with smaller sample sizes.

Although GWAS have improved our ability to identify new genetic variants that associate with psoriasis, other technologies will be likely be needed to find other important variants missed by GWAS. Although large studies such as Genetics Association Information Network have increasingly dense SNP platforms, GWAS will not be useful in finding individually rare variants that may be associated with much higher risks of disease, with particular relevance to psoriasis in the familial setting. Genome-wide association also does not allow for assessment of genomic copy number, although the latest platforms now include specific copy number variant probes. Copy number variation in the 8p23.1 β-defensin cluster was recently associated with risk of psoriasis, but this locus was not identified on previous GWAS (Hollox *et al.*, 2008).

Ultimately, it will be necessary to translate the information gained from the study of genetic susceptibility to psoriasis to the pathogenesis of psoriasis. Genome-wide studies will likely provide a large number of candidates that will need to be tested for their functional relevance and for their potential genetic interactions. Studies are needed to link the presence of cytokine polymorphisms with molecular events, such as variations in transcription and translation, in patients with psoriasis and other immune-mediated disorders. It is our hope that risk variants can be linked to disease expression, such as development of psoriatic arthritis or response to therapy, providing useful prognostic information in the clinic.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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