Further Genetic Evidence for Three Psoriasis-Risk Genes: ADAM33, CDKAL1, and PTPN22

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Further Genetic Evidence for Three Psoriasis-Risk Genes: ADAM33, CDKAL1, and PTPN22

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Predisposition to psoriasis is known to be affected by genetic variation in HLA-C, IL12B, and IL23R, and although other psoriasis-associated variants have been identified, incontrovertible statistical evidence for these markers has not yet been obtained. To help resolve this issue, we tested 15 single-nucleotide polymorphisms (SNPs) from 7 putative psoriasis-risk genes in 1,448 psoriasis patients and 1,385 control subjects; 3 SNPs, rs597980 in ADAM33, rs6908425 in CDKAL1 and rs3789604 in PTPN22, were significant with the same risk allele as in prior reports (one-sided \(P<0.05\), false discovery rate <0.15). These three markers were tested in a fourth sample set (599 cases and 299 controls); one marker, rs597980, replicated (one-sided \(P<0.05\)) and the other two had odds ratios with the same directionality as in the original sample sets. Mantel–Haenszel meta-analyses of all available case-control data, including those published by other groups, showed that these three markers were highly significant (rs597980: \(P=0.0057\) (2,025 cases and 1,597 controls), rs6908425: \(P=1.57 \times 10^{-5}\) (3,206 cases and 4,529 controls), and rs3789604: \(P=3.45 \times 10^{-5}\) (2,823 cases and 4,066 controls)). These data increase the likelihood that ADAM33, CDKAL1, and PTPN22 are true psoriasis-risk genes.

INTRODUCTION

Psoriasis is a common, chronic, T-cell-mediated inflammatory disease of the skin found in most ethnic groups, with a prevalence of 1.5–3% in Caucasians and 0.5–2% in Asians and Africans (Campalani and Barker, 2005). The disease is characterized by an inflammatory process and marked hyperproliferation of the epidermis, resulting in aberrant terminal differentiation of keratinocytes. Psoriasis occurs equally in men and women with \(\sim 75\%\) of patients developing disease before the age of 40 years.

Twin studies suggest that approximately two-thirds of the variation in psoriasis risk is heritable. Disease concordance in monozygotic twins (65–72%) is higher than in dizygotic twins (15–30%), and the incidence is substantially increased in family members of affected individuals (e.g., 6% for first-degree relatives) (Bowcock and Cookson, 2004). Specific genetic variants, in the form of single-nucleotide polymorphisms (SNPs) and/or haplotypes in three genes, HLA-C, IL12B, and IL23R, have been consistently associated with psoriasis risk in multiple independent sample sets (Tsunemi et al., 2002; Nair et al., 2006, 2008; Capon et al., 2007; Cargill et al., 2007; Smith et al., 2007; Liu et al., 2008), and there is increasing evidence that variants in the IL13/IL4 gene region also contribute to psoriasis risk (Chang et al., 2008; Li et al., 2008). However, the combined effects of these four loci do not fully account for the heritability of this disease.

Additional genes in inflammatory and other pathways have been implicated in the genetic etiology of psoriasis (Zhang et al., 2007; Lesueur et al., 2007b; Capon et al., 2008; Hollox et al., 2008; Liu et al., 2008; Smith et al., 2008; Wolf et al., 2008); however, further testing in large, independent sample sets is required to ascertain whether these findings represent genuine associations. Here we tested 15 markers in 7 putative-risk gene regions including ADAM33, IL15, SPATA2, CDKAL1, FLJ45139, PTPN22, and a region on chr 1q24 in up to 2,047 individuals with psoriasis and 1,684 control subjects. We provide meta-analysis evidence from up to 3,206 cases and 4,529 controls suggesting three may be true psoriasis susceptibility genes.

RESULTS

We genotyped 15 candidate markers from 7 distinct gene regions in three white, North American psoriasis case–control sample sets (sample sets 1–3) described in detail elsewhere.
Table 1. Genotyped markers

<table>
<thead>
<tr>
<th>Associated disease in prior studies</th>
<th>Publication</th>
<th>Putative risk gene/region</th>
<th>SNP ID</th>
<th>Chr</th>
<th>Position (bp)</th>
<th>SNP type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
<td>Lesueur et al. (2007b)</td>
<td>ADAM33</td>
<td>rs512625</td>
<td>20</td>
<td>3,596,378</td>
<td>Intergenic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>rs677044</td>
<td>20</td>
<td>3,597,431</td>
<td>Intergenic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>rs2280089</td>
<td>20</td>
<td>3,598,127</td>
<td>Intron</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>rs597980</td>
<td>20</td>
<td>3,599,165</td>
<td>Intron</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>rs44707</td>
<td>20</td>
<td>3,599,226</td>
<td>Intron</td>
</tr>
<tr>
<td></td>
<td>Zhang et al. (2007)</td>
<td>IL15</td>
<td>rs10519613</td>
<td>1</td>
<td>142,873,534</td>
<td>3’UTR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>g.96516</td>
<td>4</td>
<td>142,873,720</td>
<td>3’UTR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>rs1057972</td>
<td>4</td>
<td>142,873,882</td>
<td>3’UTR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>rs10833</td>
<td>4</td>
<td>142,873,997</td>
<td>3’UTR</td>
</tr>
<tr>
<td></td>
<td>Capon et al. (2008)</td>
<td>SPATA2</td>
<td>rs495337</td>
<td>20</td>
<td>47,955,737</td>
<td>Synonymous</td>
</tr>
<tr>
<td></td>
<td>Smith et al. (2008)</td>
<td>PTPN22</td>
<td>rs1217414</td>
<td>1</td>
<td>114,214,190</td>
<td>Intron</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>rs3789604</td>
<td>1</td>
<td>114,156,466</td>
<td>Synonymous</td>
</tr>
<tr>
<td>Psoriasis/Crohn’s disease</td>
<td>Wolf et al. (2008)</td>
<td>1q24</td>
<td>rs12037606</td>
<td>1</td>
<td>171,165,025</td>
<td>Intergenic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CDKAL1</td>
<td>rs6908425</td>
<td>6</td>
<td>20,836,710</td>
<td>Intron</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FLJ45139</td>
<td>rs2836754</td>
<td>21</td>
<td>39,213,610</td>
<td>Intron</td>
</tr>
</tbody>
</table>

SNP: single-nucleotide polymorphism; 3’-UTR, 3’-untranslated region.

1Positions according to genomic contig NT_011387.8 (Entrez Nucleotide) in the National Center for Biotechnology Information Genome Build 36.3.

(Cargill et al., 2007) (Table 1). These SNPs were chosen from recent candidate gene-based or genome-wide association studies; 13 markers were modestly associated with psoriasis in these previous studies whereas 2 SNPs, not significant on their own, were part of disease-associated haplotypes (Zhang et al., 2007; Lesueur et al., 2007b; Capon et al., 2008; Smith et al., 2008; Wolf et al., 2008) (for details see ‘Materials and Methods’).

Genotype distributions in our sample sets showed no consistent or pronounced violation of Hardy–Weinberg equilibrium in either cases or controls (all Hardy–Weinberg equilibrium $P > 0.01$) except for g.96516 ($P = 0.003$ in sample set 2 cases) (Supplementary Table 1). The allele frequencies of all markers were similar to previous reports except for two IL15 SNPs, rs10519613 and g.96516. SNP g.96516, the most significant marker in the Chinese case–control study (Zhang et al., 2007) with a control minor allele frequency of 23%, was rare in our white samples (minor allele frequency = 0.4%), which is consistent with findings in another white sample set (Weger et al., 2008).

We tested association of these SNPs with psoriasis risk using the same genetic model suggested in the original report—13 SNPs at the single marker level and 2 purported haplotypes in ADAM33 and IL15. Because our individual sample sets had low power to replicate markers with a weak effect, we evaluated replication in the three sample sets combined (1,448 psoriasis patients and 1,385 control subjects). On the basis of a Mantel–Haenszel analysis, three markers replicated (one-sided $P < 0.05$): rs597980 in ADAM33, rs6908425 in CDKAL1, and rs3789604 in PTPN22 (Table 2). This is more than one would expect under the null hypothesis (13 markers tested $\times 0.05 = \sim 1$ marker), suggesting that some of these significant SNPs are likely to be genuine psoriasis markers. These three SNPs all had a false discovery rate of less than 0.15, indicating that one in six of these markers may be false positive (Table 2).

Although the ADAM33 SNP, rs597980, was significant, the three-marker ADAM33 haplotype (defined by rs512625, rs2280089, and rs535964), which showed the most significant association in the original report ($P = 0.00004$) (Lesueur et al., 2007b), was not significant in our sample sets (best haplotype $P = 0.28$, global $P = 0.34$). Similarly, we did not observe significant association of the four marker (rs10519613, g.96516, rs1057972, and rs10833) IL15 haplotype in our sample sets (best haplotype $P = 0.37$, global $P = 0.52$), even though this haplotype was associated with both psoriasis and increased IL15 transcriptional activity in the Chinese case-control study (Zhang et al., 2007).

Next, we tested the three replicated SNPs in a fourth sample set consisting of 599 psoriasis cases and 299 controls. The ADAM33 marker replicated (one-sided $P = 0.031$), and, although the other two markers were not significant in this sample set, the directionality of the odds ratios was the same as reported in the original sample sets (Table 3). A Mantel–Haenszel analysis of our four psoriasis sample sets combined, showed that all three SNPs were significant (one-sided $P < 0.05$). A meta-analysis of the CDKAL1 and PTPN22 markers in our replication sample sets plus the original case-control reports showed that both were highly significant (rs6908425: $P = 1.57 \times 10^{-5}$ and rs3789604: $P = 3.45 \times 10^{-5}$). Because the initial study of ADAM33 was family-based, we could not carry out a meta-analysis for rs597980.
Table 2. Association test of putative psoriasis risk markers in the three sample sets combined

<table>
<thead>
<tr>
<th>Gene/region</th>
<th>SNP</th>
<th>Minor allele</th>
<th>Major allele</th>
<th>Case allele frequency</th>
<th>Control allele frequency</th>
<th>OR (95% CI)</th>
<th>Allelic P</th>
<th>FDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAM33</td>
<td>rs512625&lt;sup&gt;3&lt;/sup&gt;</td>
<td>A</td>
<td>G</td>
<td>0.298</td>
<td>0.310</td>
<td>0.94 (0.84–1.06)</td>
<td>0.176</td>
<td>0.286</td>
</tr>
<tr>
<td>ADAM33</td>
<td>rs677044</td>
<td>G</td>
<td>A</td>
<td>0.213</td>
<td>0.211</td>
<td>1.01 (0.89–1.14)</td>
<td>0.572</td>
<td>0.620</td>
</tr>
<tr>
<td>ADAM33</td>
<td>rs597980</td>
<td>A</td>
<td>G</td>
<td>0.475</td>
<td>0.450</td>
<td>1.10 (0.99–1.22)</td>
<td>0.030</td>
<td>0.136</td>
</tr>
<tr>
<td>ADAM33</td>
<td>rs444707</td>
<td>G</td>
<td>T</td>
<td>0.389</td>
<td>0.409</td>
<td>0.92 (0.82–1.02)</td>
<td>0.068</td>
<td>0.176</td>
</tr>
<tr>
<td>IL15</td>
<td>rs10519613</td>
<td>A</td>
<td>C</td>
<td>0.096</td>
<td>0.093</td>
<td>1.03 (0.86–1.23)</td>
<td>0.366</td>
<td>0.433</td>
</tr>
<tr>
<td>IL15</td>
<td>g.96516</td>
<td>T</td>
<td>A</td>
<td>0.0014</td>
<td>0.004</td>
<td>0.34 (0.11–1.09)</td>
<td>0.058</td>
<td>0.176</td>
</tr>
<tr>
<td>IL15</td>
<td>rs1057972</td>
<td>T</td>
<td>A</td>
<td>0.472</td>
<td>0.476</td>
<td>0.98 (0.88–1.09)</td>
<td>0.626</td>
<td>0.626</td>
</tr>
<tr>
<td>SPATA2</td>
<td>rs495337</td>
<td>A</td>
<td>G</td>
<td>0.388</td>
<td>0.393</td>
<td>0.97 (0.88–1.09)</td>
<td>0.354</td>
<td>0.433</td>
</tr>
<tr>
<td>q24</td>
<td>rs12037606</td>
<td>A</td>
<td>G</td>
<td>0.420</td>
<td>0.406</td>
<td>1.05 (0.95–1.17)</td>
<td>0.155</td>
<td>0.286</td>
</tr>
<tr>
<td>CDKAL1</td>
<td>rs6908425</td>
<td>T</td>
<td>C</td>
<td>0.200</td>
<td>0.220</td>
<td>0.88 (0.77–1.00)</td>
<td>0.031</td>
<td>0.136</td>
</tr>
<tr>
<td>FLJ45139</td>
<td>rs2836754</td>
<td>T</td>
<td>C</td>
<td>0.383</td>
<td>0.368</td>
<td>1.06 (0.95–1.18)</td>
<td>0.123</td>
<td>0.265</td>
</tr>
<tr>
<td>PTPN22</td>
<td>rs1217414</td>
<td>A</td>
<td>G</td>
<td>0.276</td>
<td>0.266</td>
<td>1.03 (0.93–1.18)</td>
<td>0.204</td>
<td>0.295</td>
</tr>
<tr>
<td>PTPN22</td>
<td>rs3798904</td>
<td>G</td>
<td>T</td>
<td>0.184</td>
<td>0.208</td>
<td>0.86 (0.75–0.98)</td>
<td>0.013</td>
<td>0.136</td>
</tr>
</tbody>
</table>

SNP, single-nucleotide polymorphism; FDR, false discovery rate.
Markers with P<0.05 in boldface.
<sup>1</sup>One-sided, based on previous studies except for g.96516 whose allele frequencies were markedly different between the White and Asian populations.
<sup>2</sup>False discovery rate.
<sup>3</sup>rs512625 was recently reported to be significant in another case-control study (Siroux et al., 2008). A meta-analysis of this marker in our three sample sets and that of Siroux et al. showed that this SNP was not significant (Mantel-Haenszel P<sub>combined</sub>=0.27, OR<sub>combined</sub>=0.94 (95% CI: 0.85–1.05), Breslow-Day test for OR homogeneity P=0.99).

DISCUSSION

These results suggest that variants in three distinct genes may be associated with psoriasis risk. Although evidence of replication for individual SNPs in our combined sample sets was modest (one-sided P=0.0057–0.015), the overall observation is significant in the context of our study design—these three markers had false discovery rates <0.15 suggesting at least two may be considered true positives. Furthermore, two of the three markers were highly significant in a meta-analysis of all sample sets combined (P=1.57×10<sup>-5</sup> and 3.45×10<sup>-5</sup>). The observed effect sizes for the three variants, however, were modest, with odds ratios all less than 1.25. This is typical of other recently identified genetic variants that make incremental contributions to disease risk in common, complex disorders (Wellcome Trust Case Control Consortium, 2007; Barrett et al., 2007; Gregersen et al., 2004; Gregersen et al., 2006). It should be noted, however, that the PTPN22 variant associated with psoriasis risk is different from the major variant (R620W missense SNP) associated with rheumatoid arthritis and other diseases; previous studies have shown that R620W is not significantly associated with psoriasis in our sample sets (unpublished results) or other sample sets (Criswell et al., 2005; Nistor et al., 2005; Huffmeier et al., 2006). These findings are consistent with evidence suggesting variants in noncoding regions of the PTPN22 gene region are involved in psoriasis (Huffmeier et al., 2006).

Interpretation of our negative results for the other putative psoriasis-risk variants should take into account various factors such as the overall sample size, marker effect sizes, the allele frequencies of the tested markers, and the possibility of genetic heterogeneity. Our three combined sample sets (1,448 cases and 1,385 controls) have >80% power to replicate allelic association for a marker with a >0.20 control allele frequency, as is the case for 11 out of the 13 markers tested here, and an odds ratio of 1.2. However, our three combined sample sets have less than 50% power to replicate markers with odds ratio of 1.1 or less, regardless of marker allele frequency. Not surprisingly, all three significant markers identified in this study had odds ratio ≥1.1 in our sample sets.
In conclusion, our data suggest that three genes, ADAM33, CDKAL1, and PTPN22, in addition to HLA-C, IL12B, IL23R, and IL13/IL4, may be psoriasis-risk factors. Given the modest effect sizes, further replication, followed by a meta-analysis, is required to confirm or refute these hypotheses and detailed fine mapping is required to pinpoint the causal variants. In addition, although we did not observe significant association of the other tested markers with psoriasis, we cannot rule out their involvement in the genetics of the disease, due to the modest power of our sample sets to detect small effect sizes. An unequivocal identification of unreported genetic risk factors should further our understanding of the underlying disease mechanism, provide fresh leads to drug discovery, and identify potential pharmacogenomic markers.

**MATERIALS AND METHODS**

**Marker selection**

The primary goal of this study was to replicate 15 genetic variants recently reported to be associated with psoriasis risk (see Table 1 for the complete list of SNPs).

**ADAM33.** Having confirmed the presence of a psoriasis susceptibility locus on chromosome 20p13 in a linkage study (Lesueur et al., 2007a), Lesueur et al. (2007b) fine mapped a 17 Mb region using a family-based association study and identified ADAM33 as the putative psoriasis-risk gene. Five of the tested SNPs reached significance ($P = 0.01–0.04$) and testing combinations of SNPs revealed a three-SNP haplotype that was highly significant ($P = 0.0009$). Although these findings were not replicated in a second smaller family-based sample set (all $P > 0.05$) (Lesueur et al., 2007b), a recent French study replicated association of one ADAM33 SNP, rs512625, with psoriasis (Siroux et al., 2008).

**IL15.** Employing a candidate gene approach, Zhang et al. (2007) tested 12 SNPs in the IL15 gene, which lies within the PSORS9 locus on chromosome 4q31.2–q32.1, in a Chinese case-control sample set (632 psoriasis patients/485 control subjects). Four markers were significant ($P < 0.05$), with a reported 3'-untranslated region (UTR) SNP (g.96516A→T) showing the strongest association ($P_{	ext{correction}} = 0.00006$). Two haplotypes containing the minor T allele of g.96516 were highly correlated with disease susceptibility and...
increased \( \text{IL15} \) transcriptional activity. \( \text{IL15} \), a proinflammatory cytokine affecting T-cell activation and proliferation, is involved in regulation of inflammatory events in several diseases including psoriasis (McInnes and Gracie, 2004). In addition, targeting the \( \text{IL15} \) protein was efficacious in alleviating psoriasis pathology in an animal model (Villadsen et al., 2003).

**SPATA2.** In a genome-wide association study testing 408,000 SNPs, Capon et al. (2008) identified strong association of a reported SNP, rs495337, with psoriasis risk (\( P = 1.4 \times 10^{-7} \), 2,679 cases and 2,215 controls). rs495337 maps to the SPATA2 transcript and is in perfect linkage disequilibrium with several SNPs in the adjacent ZNF313 gene. On the basis of the association of rs495337 with ZNF313 expression and a potential role for ZNF313 in regulating T-cell activation, ZNF313 was proposed as a risk factor for psoriasis.

**CDKAL1, FLJ45139, and chr 1q24.** Given that psoriasis and Crohn’s disease share a common genetic etiology (Duerr et al., 2006; Cargill et al., 2007), Wolt et al. (2008) tested in their psoriasis sample set (1,256 cases/2,938 controls) 15 Crohn’s disease-associated SNPs and reported that three may be involved in psoriasis (rs12035082 in 1q24, \( P = 0.009 \); rs2836754 in FLJ45139 on 21q22.2, \( P = 0.002 \); and rs6908425 in CDKAL1 on 6p22.3, \( P = 0.00015 \)). We tested rs2836754 and rs6908425 and rs12035082 (\( r^2 = 1 \), in the CEU samples; www.hapmap.org).

**PTPN22.** Smith and colleagues recently tested whether variants in PTPN22, a widely recognized risk factor for retinoic acid (Begovich et al., 2004) and several other autoimmune diseases (Bottini et al., 2004; Criswell et al., 2005), were also associated with psoriasis (Smith et al., 2008). Although the retinoic acid-associated rs2476601 (R620W) SNP was not significant in their psoriasis sample set, agreeing with other reports (Criswell et al., 2005; Nistor et al., 2005; Huffmeier et al., 2006), they found that two other SNPs, rs1217414 and rs3789604, were significantly associated with early onset disease (\( P = 0.003 \) and 0.0002, respectively; 647 cases vs 566 controls).

**Clinical samples**

Three white, North American psoriasis sample sets, totaling 1,448 individuals with dermatologist-confirmed psoriasis (cases) and 1,385 normal subjects (controls), have been described in detail elsewhere (Cargill et al., 2007). Briefly, sample set 1, obtained from the University of Utah, consisted of 467 cases and 460 controls. Sample set 2, obtained from the Genomics Collaborative Division of SeraCare Life Sciences, consisted of 498 cases and 498 controls. Sample set 3 consisted of 483 cases and 427 control subjects; 293 of the cases and 292 of the controls were provided by Genomics Collaborative; BioCollections Worldwide provided the rest. All individuals were 18 years or older at the enrollment.

The fourth case-control sample set included 599 unrelated Caucasian patients of European descent recruited from outpatient clinics at the University of California, San Francisco and Washington University, St. Louis, MO. All subjects filled out a clinical questionnaire and received a skin examination by a dermatologist, who confirmed the diagnosis of plaque psoriasis. Controls (\( n = 299 \)) were unrelated white individuals of European descent recruited in San Francisco, who had no history of psoriasis, autoimmune disease, or cancer.

Clinical research was conducted according to the Declaration of Helsinki Principles. All protocols were approved by national and/or local institutional review boards and informed written consent was obtained from all subjects.

**Genotyping**

Genotyping of SNPs in sample sets 1–3 was carried out by allele-specific real-time PCR, with accuracy > 99% (Chang et al., 2008). For sample set 4, rs597980 (ADAM33) and rs6908425 (CDKAL1) were genotyped by TaqMan, (Applied Biosystems, Foster City, CA, USA) and rs3789604 (PTPN22) by sequencing.

**Statistical analysis**

Hardy-Weinberg equilibrium testing was performed using the exact test of Weir (Weir, 1996). Allelic association of SNPs with psoriasis risk was determined by the \( \chi^2 \)-test in individual sample sets and by meta-analysis using fixed effects of Mantel-Haenszel methods. Haplotypes were inferred from the genotypic data, and haplotype frequencies estimated and tested for association with disease status using a score test with haplotypes coded in an additive fashion (Schaid et al., 2002). Power of replication was estimated using the PS:Power and Sample Size Calculation Program (http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize). False discovery rate (Benjamini and Hockberg, 1995), was estimated using one-sided \( P \)-values obtained in the combined sample sets.

**CONFLICT OF INTEREST**

Authors with affiliations to Celera have personal financial interest in the company.

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**SUPPLEMENTARY MATERIAL**

Table S1. Genotype counts of the 13 markers in Tables 2 and 3.

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