The PRO2268 Gene as a Novel Susceptibility Locus for Vitiligo

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Vitiligo is a complex depigmentary disorder characterised by the appearance of white patches as a result of the destruction of melanocytes in the skin and hair (1). Several loci, including AIS1 (1p31) and AIS14 (4q13-q21), have been shown to confer susceptibility to the disease (2–3). However, the genetic factors involved in vitiligo are yet to be clarified. The PRO2268 gene has been mapped, by analysis of a cDNA clone (FLB8424) from human foetal liver, to the 12q14 chromosomal region, which harbours the genes encoding interferon-gamma (IFN-γ), interleukin (IL)-26 and IL-22. Of note, the IFN-γ/IL26-IL22 gene cluster is associated with autoimmune diseases including rheumatoid arthritis and type 1 diabetes (4–6). Although the PRO2268 protein (AF119871) has as yet unknown functions, a putative role for the PRO2268 gene is suggested based on our unpublished observation (data not shown), by its significantly higher expression in controls (67%) (OR = 5.67, 95% CI 2.59–12.37; p = 0.000013). As part of our ongoing research into the impact of susceptibility genetic variants on the risk of vitiligo, we selected the rs10784680 single nucleotide polymorphism (SNP) within the PRO2268 gene as a candidate in our analysis.

RESULTS AND DISCUSSION

Data analysis revealed that the frequency of the rs10784680 G allele was significantly higher in vitiligo patients (96%) than in controls (83.5%) (OR = 4.74, 95% CI 2.22–10.10; p = 0.000055) (Table I). Accordingly, the rs10784680 GG genotype was significantly more frequent in vitiligo patients (92%) than in controls (67%) (OR = 5.67, 95% CI 2.59–12.37; p = 0.000013). Notably, none of the test subjects carried the rs10784680 AA genotype. However, this observation is in accordance with the available data in the GenBank database, the rs10784680 AA genotype being reportedly absent in Hapmap-CEU, a referent population of European ancestry.

When we analysed the vitiligo patients according to their clinical subgroups, no significant differences in rs10784680 SNP allele frequency were observed when comparing patients on the basis of age at onset (> 20 years vs. ≤ 20 years; p = 0.26), sex (male vs. female; p = 1), family history (familial vs. sporadic; p = 1) or disease activity (active vs. stable vitiligo; p = 0.11) (data not shown). Furthermore, no significant differences in allele

### Table I. Allele and genotype frequencies for the rs10784680 single nucleotide polymorphism in vitiligo patients and control subjects

<table>
<thead>
<tr>
<th>Allele</th>
<th>Control (n=388)</th>
<th>Vitiligo (n=389)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>64 (16.5)</td>
<td>8 (4.0)</td>
<td>1 (ref.)</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>324 (83.5)</td>
<td>192 (96.0)</td>
<td>4.74 (2.22–10.10)</td>
<td>0.000055</td>
</tr>
<tr>
<td>Total</td>
<td>388 (100.0)</td>
<td>200 (100.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG</td>
<td>64 (33.0)</td>
<td>8 (8.0)</td>
<td>1 (ref.)</td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>130 (67.0)</td>
<td>192 (92.0)</td>
<td>5.66 (2.59–12.37)</td>
<td>0.000013</td>
</tr>
<tr>
<td>Total</td>
<td>194 (100.0)</td>
<td>100 (100.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR: odds ratio; CI: confidence interval.
distribution were detected between vitiligo patients with autoimmune and other diseases and patients with no co-morbidity ($p = 0.70$ and $p = 0.63$, respectively) (data not shown). In addition, further analysis of our patients according to clinical subtype revealed that the frequency of the rs10784680 G allele was significant higher in the vitiligo vulgaris subgroup than in the control group ($OR = 4.48$, 95% CI 2.01–10.01; $p = 0.00024$). It should be noted that stratifying patients according to clinical groups diminished the power to detect associations.

In conclusion, to our knowledge the present study is the first to address the possible influence of the PRO2268 gene on the risk of vitiligo. Although the function of the PRO2268 protein remains unknown, it is of particular interest to note that the PRO2268 gene lies adjacent to a region containing the IFN-$\gamma$-IL26-IL22 gene cluster, whose gene products play key roles in immune signalling. For this region in particular, extensive re-sequencing, further genotyping and targeted functional studies are essential in order to identify the gene(s) that play causal roles in vitiligo. It should be noted that we cannot exclude the possibility that new susceptibility variants of the PRO2268 gene may be discovered, or that the PRO2268 gene may play important roles in other skin disorders.

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REFERENCES