Letters to the Editor

Interleukin-4 receptor α polymorphisms in primary Sjögren’s syndrome

Sirs.

The interleukin-4 receptor α chain gene (IL-4RA) is a polymorphic gene which has been associated with susceptibility for the development of atopy, asthma and autoimmune diseases (1, 2). The IL-4RA chain binds IL-4 with high affinity, leading to dimerization with another protein to form either a type I or type II receptor (3). While the type I receptor is only expressed on hematopoietic cells, expression of the type II IL-4RA, which also binds to IL-13, has been reported in non-hematopoietic cells (e.g. epithelia) (4).

Sjögren’s syndrome (SS) is a systemic autoimmune disease that mainly affects the exocrine glands (autoimmune epithelitis) (5), and an enhanced sensitivity of the glandular epithelium to IL-4 might play an etiopathogenic role in primary SS. We investigated 48 consecutive patients (47 women and 1 man; mean age 56 years; range 23 to 77 years) attending our Department. All patients were white and fulfilled 4 or more of the new classification criteria for SS recently proposed by the American-European Consensus Group (6). As controls, 98 ethnically matched healthy blood donor volunteers were recruited from the Blood Bank of our hospital.

Polymerase chain reaction (PCR) amplification was performed on a Perkin Elmer 2400 thermal cycler (Applied Biosystems, Foster City, CA), using the Expand High Fidelity PCR System (Roche Diagnostics, Mannheim, Germany) and combinations of intronic and exonic primers for IL-4RA(7). No significant differences were found in the genotype analysis, haplotype frequency or haplotype carrier rate in patients with primary SS compared with healthy controls. Homozygous ECSSQV was the more frequent genotype found in our patients (63%), followed by ECSSQV/ARSPRV (19%). Most patients (98%) carried the ECSSQV haplotype. Systemic involvement (defined as cutaneous vasculitis, peripheral neuropathy, renal and/or pulmonary involvement) was more frequent in the ECSSQV/ECSSQV carriers, although the difference did not reach statistical significance. ARSPRV carriers showed a similar prevalence of extra-glandular disease compared with non-carriers, but a higher prevalence of parotid gland enlargement (50% vs 16%, p = 0.036). Overall, ARSPRV carriers showed a tendency for a higher prevalence of positive immunologic markers, especially a positive RF (60% vs 29%, p = 0.13) (Table I).

The clinical significance of the IL-4RA haplotypes and its correlation with the epidemiologic, clinical and immunologic features of primary SS has been little studied. No associations with clinical or immunologic SS features were described by Lester et al. (8), although a protective effect of the R551 allele was found for Raynaud’s phenomenon, while Youn et al. (9) did not analyse the correlation with clinical or immunologic SS features. In this study, we found no significant differences in the gender and age at SS onset, nor in the main extra-glandular, analytical and immunological features in SS patients carrying the ARSPRV haplotype compared to controls. Nevertheless, a higher frequency of parotid gland enlargement was observed, as well as a tendency to a higher frequency of positive immunological markers (mainly RF). We may hypothesize that in primary SS, a disease considered to be an “autoimmune epithelitis” (3), an enhanced sensitivity of the glandular epithelium to IL4/IL13 might induce, on the one hand, a specific recruitment of T-cells (with a posterior B-cell stimulation) and on the other hand an inflammatory process that finally produces an enlargement of the parotid glands. In fact, recent studies have described that IL-4 mRNA is expressed at a high frequency in cultured lymphocytes from the salivary glands of SS patients (10).

In conclusion, the distribution of IL-4RA genotypes and haplotypes in patients with primary SS compared with healthy controls were found to be similar in our study, although we found some statistical associations. ARSPRV carriers presented a higher frequency of parotid gland enlargement and a tendency for a higher prevalence of positive immunological parameters. These two features probably are a result of local inflammation and B-cell activation, respectively, and might reflect an enhanced sensitivity to IL-4/IL-13 in ARSPRV carriers.

Table I. Frequency of the main epidemiologic, clinical, hematologic and immunologic SS features according to the presence of the ARSPRVhaplotype.

<table>
<thead>
<tr>
<th>ARSPRV carriers</th>
<th>Non-ARSPRV carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 10</td>
<td>n = 38</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Age onset (years), mean ± SD</td>
<td>45.6 ± 11.1</td>
</tr>
<tr>
<td>Parotidomegaly</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Systemic disease</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Hypergammoglobulinemia (&gt; 4 g/L)</td>
<td>29 (22%)</td>
</tr>
<tr>
<td>ESR &gt; 50 mm/hour</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Anti-Ro/La antibodies</td>
<td>5 (50%)</td>
</tr>
</tbody>
</table>

*p = 0.036; **p = 0.13

Systemic disease: presence of cutaneous vasculitis, peripheral neuropathy, pulmonary and/or renal involvement; ESR: erythrocyte sedimentation rate.

M. R AMOS-CASALS, MD, PhD
J. FONT, MD, PhD
P. BRITO-ZERON, MD
O. TREJO, MD, PhD

M. GARCÍA-CARRASCO, MD, PhD
F. LOZANO, MD, PhD

Departments of Autoimmune Diseases and Immunology, Hospital Clinic, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Facultad de Medicina, Universitat de Barcelona, Barcelona, Spain.

Address correspondence to: Manuel Ramos-Casals, MD, Servi de Malalties Autoinmunes, Hospital Clinic, C/Villarroel, 170, 08036– Barcelona, Spain. E-mail: mramos@clinic.ub.es

References


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