Extrapituitary prolactin promoter polymorphism in Czech patients with systemic lupus erythematosus and rheumatoid arthritis

Markéta Fojtíková, Marie Černá, Pavlína Čejková, Šárka Růžičková, Ctibor Dostál


Prolactin (PRL) and its production by lymphocytes have been suggested to play a distinct role in the pathogenesis of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). PRL acts as a cytokine and influences the maturation and differentiation of immune cells. Extrapituitary PRL synthesis is regulated by an alternative promoter, which contains a single-nucleotide polymorphism (SNP) at the region −1149 G/T. Higher PRL mRNA expression is associated with the G allele in lymphocytes. High frequency of the G allele was described in patients with SLE, but was not confirmed in other work. We investigated −1149 G/T SNP in 156 patients with SLE and 173 patients with RA, and in 123 healthy individuals (control group). Patients with SLE consisted of 134 (85.9%) women and 22 (14.1%) men, with a mean age of 43.4 years. SLE diagnosis was determined using the American College of Rheumatology classification criteria. Patients with RA consisted of: 132 (76.3%) women and 41 (23.7%) men, with a mean age of 57.4 years; all fulfilled the RA diagnostic criteria. The control group consisted of 40 (32.5%) women and 83 (67.5%) men, with a mean age of 38.7 years. The study was approved by the ethics committee of The Third Medical Faculty, Charles University, Prague, Czech Republic.

The PCR—RFLP (restriction fragment length polymorphism) method was used for −1149 G/T SNP detection. During PCR, the 137 base pairs (bp) region of the PRL extrapituitary promoter was amplified by using the following primers: forward 5′-GCAGGTCAAGATAACCTGGA and reverse 5′-CATCTCAGAGTTGAATTTATTCTCTT. For RFLP, ApoI restriction endonucleasis was used. The genotypes identified were TT homozygote characterised by 120 and 17 bp, GG homozygote characterised by 85, 35 and 17 bp, and GT heterozygote characterised by 120, 85 and 35 bp + 17 bp DNA.

Abbreviations: PRL, prolactin; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SNP, single-nucleotide polymorphism

Table 1 Occurrence of genotype and allele frequencies of −1149 G/T single-nucleotide polymorphism of the extrapituitary prolactin promoter in Czech patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis and controls, and in patients with SLE according to specific organ involvement

<table>
<thead>
<tr>
<th>Subject groups</th>
<th>−1149 G/T SNP of the extrapituitary prolactin promoter</th>
<th>Allele frequency</th>
<th>Genotype</th>
<th>G</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of cases</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>SLE</td>
<td>156</td>
<td>34.60</td>
<td>44.90</td>
<td>20.50</td>
<td>0.57</td>
</tr>
<tr>
<td>Specific organ involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal With</td>
<td>63</td>
<td>31.10</td>
<td>52.40</td>
<td>17.50</td>
<td>0.56</td>
</tr>
<tr>
<td>Without</td>
<td>93</td>
<td>37.60</td>
<td>39.80</td>
<td>22.60</td>
<td>0.57</td>
</tr>
<tr>
<td>Neuropsychiatric With</td>
<td>33</td>
<td>30.30</td>
<td>51.50</td>
<td>18.20</td>
<td>0.56</td>
</tr>
<tr>
<td>Without</td>
<td>123</td>
<td>35.80</td>
<td>41.30</td>
<td>21.10</td>
<td>0.57</td>
</tr>
<tr>
<td>Cardiac With</td>
<td>35</td>
<td>36.40</td>
<td>45.70</td>
<td>18.90</td>
<td>0.59</td>
</tr>
<tr>
<td>Without</td>
<td>121</td>
<td>36.40</td>
<td>46.60</td>
<td>17.00</td>
<td>0.59</td>
</tr>
<tr>
<td>Pulmonary With</td>
<td>25</td>
<td>32.00</td>
<td>48.00</td>
<td>20.00</td>
<td>0.56</td>
</tr>
<tr>
<td>Without</td>
<td>131</td>
<td>35.10</td>
<td>43.30</td>
<td>21.60</td>
<td>0.57</td>
</tr>
<tr>
<td>Articular With</td>
<td>117</td>
<td>41.00</td>
<td>43.60</td>
<td>15.40</td>
<td>0.63</td>
</tr>
<tr>
<td>Without</td>
<td>39</td>
<td>15.40</td>
<td>48.70</td>
<td>35.90</td>
<td>0.40</td>
</tr>
<tr>
<td>Dermal With</td>
<td>94</td>
<td>36.20</td>
<td>45.70</td>
<td>18.10</td>
<td>0.59</td>
</tr>
<tr>
<td>Without</td>
<td>62</td>
<td>32.30</td>
<td>43.50</td>
<td>24.20</td>
<td>0.54</td>
</tr>
<tr>
<td>RA</td>
<td>173</td>
<td>32.40</td>
<td>56.10</td>
<td>11.50</td>
<td>0.60</td>
</tr>
<tr>
<td>Controls</td>
<td>123</td>
<td>39.80</td>
<td>41.50</td>
<td>18.70</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Pc: P corrected values; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SNP, single-nucleotide polymorphism.
Pc values were calculated by the χ2 test from 2×2 contingency tables of the separate genotype occurrence or allele frequency of (1) each patient with SLE and control group (Pc1), (2) presence or absence for the clinical feature (Pc2) and (3) each patient with RA and control group (Pc3). Bonferroni correction for multiple comparisons was used.

*OR 1.82, 95% CI 1.14 to 2.94.
**OR 2.56, 95% CI 1.51 to 4.33.
***OR 0.39, 95% CI 0.23 to 0.6.
after 3 months of etanercept treatment, superficial layer vascu-
larisation of synovial tissue was reduced by 22% compared with the placebo (P=0.0001).

There was no difference in genotype and allele frequencies in the SLE group compared with healthy Czech individuals (table 1). Our results support previous Italian findings, but differ from the UK report.7 However, with respect to the specific organ manifestation of SLE (table 1), we detected an association between the G allele and articular involvement (Pc = 0.0086, OR 2.56, 95% CI 1.51 to 4.33). Based on age when SLE was diagnosed, we observed a GG genotype frequency of 44.8% in the 21–40 years subgroup compared with 13.8% and 24.0% in the <20 years and >40 years subgroup, respectively (Pc = 0.023, OR 2.94, 95% CI 1.43 to 5.96). Additionally, we correlated the presence of alleles and genotypes of the 1149 G/T SNP with antibodies against antinuclear antibody, double-stranded DNA, Sm, RNP, Ro and La, but no connection was found (data not shown).

Significantly higher heterozygote GT genotype was detected in the RA group compared with the controls (Pc = 0.039, OR 1.82, 95% CI 1.14 to 2.94). We observed no differences in homozygote genotypes or in allele frequencies between patients with RA and controls (table 1). Across the groups, no gender differences in genotype distribution or allele frequencies were identified (data not shown).

In conclusion, the presence of the G allele and GG genotype of the PRL extrapituitary promoter—1149 G/T SNP is associated with certain clinical features of SLE. The GT genotype is a predisposing genetic factor for RA. Further investigation on this is required.

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