Lack of association between *IL6* gene and Henoch-Schönlein purpura

Sirs,

Henoch-Schönlein purpura (HSP), the most common type of primary small-sized blood vessel leukocytoclastic vasculitis, is characterised by infiltration of the small blood vessels with polymorphonuclear leukocytes and presence of leukocytoclasia. IgA dominant immune deposits in the walls of the small vessels and in the renal glomeruli are also characteristic features of this vasculitis (1). Skin, joint, gastrointestinal tract and kidney involvement may be affected in patients with HSP (2). Although the etiology of HSP remains unknown, environmental factors and a susceptible genetic background have been associated with HSP (3).

Interleukin-6 (IL-6) is a pleiotropic cytokine produced by different cells. Dysregulated IL-6 production plays a crucial role in human autoimmune and inflammatory processes. IL-6 is likely to be released from vascular endothelial cells, thus initiating and propagating the inflammatory response. Once inflammatory mechanisms are activated, IL-6 facilitates autoinimmune phenomena and amplifies acute inflammation. IL-6 stimulates the production of acute phase proteins and induces leukocytosis, fever and angiogenesis (4).

In this study, we assessed, for first time, the implication of several *IL6* gene polymorphisms in the largest series of patients with HSP ever included in a genetic study. We genotyped 3 polymorphisms located within the *IL6* gene (rs2069827, rs1800795 and rs2069840), that tag over 80% of the variability of this locus, by predesigned TaqMan allelic discrimination assays (Applied Biosystems, Foster City, California, USA) in 285 Spanish patients with cutaneous vasculitis who fulfilled the American College of Rheumatology and the Michel et al. (5, 6) classification criteria. Most patients were children (239 [84%]; aged ≤20 years) and 51% males. All of them had palpable purpura, 59% gastrointestinal manifestations (bowel angina and/or gastrointestinal bleeding) and 38% renal manifestations (haematuria, proteinuria, nephrotic syndrome with/without renal sequelae). A set of 877, sex, and ethnically matched controls constituted by blood donors from National DNA Bank Repository, without history of vasculitis or autoimmune diseases were also assessed. Subject’s written consent was obtained and the purpose of the work was approved by the Spanish Ethics Committees. Genotyping success was >98%, and rs2069827, rs1800795 and rs2069840 genotype distribution in controls was in Hardy-Weinberg equilibrium. The study had >80% of power to detect genotypic OR>1.4. No significant differences in the genotypic and allelic frequencies between HSP patients and controls were observed when the rs2069827, rs1800795 and rs2069840 polymorphisms were analysed independently (Table I) or combined conforming haplotypes (data not shown). Since HSP is a more severe condition in adults (7), we also assessed potential differences between HSP patients according to the age of onset. However, no statistically significant differences were found. Moreover, there were no differences when patients were stratified according to the presence/absence of nephritis or gastrointestinal manifestations (data not shown).

A former study on a small series of patients did not disclose association of the *IL6* promoter rs1800795 polymorphism with HSP (8). Since *IL6* gene is mainly regulated at the transcriptional level (9), in this study we assessed a larger population and studied additional polymorphisms to establish the actual role of the *IL6* gene in HSP pathogenesis. However, our results do not support any association between the rs2069827, rs1800795 and rs2069840 polymorphisms and HSP, which is in accordance with recent studies performed in other autoimmune diseases (10).

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Table I. Genotype and allele frequencies for *IL6*-tagging single nucleotide polymorphisms in HSP patients and controls.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Change</th>
<th>Sample set</th>
<th>Genotype, n. (%)</th>
<th>Allele test</th>
<th>1/2</th>
<th>p</th>
<th>OR [95% CI]*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1/1</td>
<td>1/2</td>
<td>2/2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs2069827</td>
<td>G/T</td>
<td>HSP patients</td>
<td>285 (81.8)</td>
<td>50 (17.2)</td>
<td>2 (0.7)</td>
<td>0.19</td>
<td>1.26 [0.90-1.74]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls</td>
<td>877 (85.4)</td>
<td>120 (13.7)</td>
<td>8 (0.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1800795</td>
<td>G/C</td>
<td>HSP patients</td>
<td>285 (83.7)</td>
<td>126 (44.2)</td>
<td>35 (12.3)</td>
<td>0.87</td>
<td>1.01 [0.83-1.23]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls</td>
<td>877 (85.4)</td>
<td>393 (45.8)</td>
<td>102 (11.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs2069840</td>
<td>C/G</td>
<td>HSP patients</td>
<td>285 (83.6)</td>
<td>139 (48.8)</td>
<td>41 (14.4)</td>
<td>0.16</td>
<td>1.15 [0.94-1.39]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls</td>
<td>877 (84.5)</td>
<td>403 (46.0)</td>
<td>110 (12.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HSP: Henoch-Schönlein purpura; SNP: single nucleotide polymorphism; n: number of patients; OR [95% CI]: Odds Ratio with 95% Confidence Interval.

*For the minor allele.

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R. López-Mejías, PhD*
B. Sevilla Pérez, MD*
F. Genre, PhD*
S. Castañeda, MD, PhD
N. Ortego-Centeno, MD, PhD
J.A. Miranda-Filloy, MD
J. Llorca, MD, PhD
J. Martín, MD, PhD
R. Blanco, MD, PhD**
M.A. González-Gay, MD, PhD**

Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, Rheumatology Division, Hospital Universitario Marqués de Valdecilla, IFIMAV, Santander, Spain; 2 Department of Medicine Hospital Universitario San Cecilio, Granada, Spain; 3 Rheumatology Department, Hospital Universitario la Princesa, IIS-Princesa, Madrid, Spain; 4 Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IFIMAV, Santander, Spain; 5 Instituto de Parasitología y Biomedicina López-Neyra, C.S.I.C., Granada, Spain; 6 Division of Rheumatology, Hospital Universitario Lucus Augusti, Lugo, Spain.

**R. López-Mejías, B. Sevilla Pérez and F. Genre made an equal contribution.
**M.A. González-Gay and R. Blanco shared senior authorship in this study.

Address correspondence to: Dr Miguel A. González-Gay, Hospital Universitario Marqués de Valdecilla, IFIMAV, Avenida de Valdecilla, s/n, 39008 Santander, Spain.

E-mail: miguelggay@hotmail.com

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*Letters to the Editors*