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

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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 autoimmune 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).

Acknowledgements

We wish to thank all the patients with HSP who participated to make this study possible. We want to specially thank Begoña Ubilla, Rodrigo Ochoa, Patricia Fuentevilla Rodríguez, María Del Camino Villa Llamazares and María Eugenia Cuadrado Mantecón for their technical assistance.

Funding: this study was supported by a grant from "Fondo de Investigaciones Sanitarias" PI12/00193 (Spain). R. López-Mejías is a recipient of a Sara Borrell postdoctoral fellowship from the Instituto de Salud Carlos III at the Spanish Ministry of Health (Spain). F. Genre is supported by funds from the RETICS Programme (RIER) (RD12/0009/0013).

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Competing interests: none declared.

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

	Change			Genotype, n. (%)			Allele test	
SNP	1/2	Sample set	n.	1/1	1/2	2/2	*p*	OR [95% CI]*
rs2069827	G/T	HSP patients	285	233 (81.8)	50 (17.2)	2 (0.7)	0.19	1.26 [0.90-1.74]
		Controls	877	749 (85.4)	120 (13.7)	8 (0.9)		
rs1800795	G/C	HSP patients	285	124 (43.5)	126 (44.2)	35 (12.3)	0.87	1.01 [0.83-1.23]
		Controls	877	382 (43.6)	393 (44.8)	102 (11.6)		
rs2069840	C/G	HSP patients	285	105 (36.8)	139 (48.8)	41 (14.4)	0.16	1.15 [0.94-1.39]
		Controls	877	364 (41.5)	403 (46.0)	110 (12.5)		

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.

N Engl J Med 2013; 368: 2402-14.
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