
Interleukin 1 beta (*IL1β*) rs16944 genetic variant as a genetic marker of severe renal manifestations and renal sequelae in Henoch-Schönlein purpura

R. López-Mejías¹, F. Genre¹, S. Remuzgo-Martínez¹, B. Sevilla Pérez², S. Castañeda³, J. Llorca⁴, N. Ortego-Centeno², B. Ubilla¹, V. Mijares¹, T. Pina¹, V. Calvo-Río¹, J.A. Miranda-Fillooy⁵, A. Navas Parejo⁶, D. de Argila⁷, J. Sánchez-Pérez⁷, E. Rubio⁸, M.L. Luque⁸, J.M. Blanco-Madrigal⁹, E. Galíndez-Aguirregoikoa⁹, J. Martín¹⁰, R. Blanco¹, M.A. González-Gay^{1,11,12}

Raquel López-Mejías, PhD*
Fernanda Genre, PhD*
Sara Remuzgo-Martínez, PhD*
Belén Sevilla Pérez, MD
Santos Castañeda, MD, PhD
Javier Llorca, MD, PhD
Norberto Ortego-Centeno, MD, PhD
Begoña Ubilla, BSc
Verónica Mijares, BSc
Trinitario Pina, MD, PhD
Vanessa Calvo-Río, MD, PhD
José A. Miranda-Fillooy, MD, PhD
Antonio Navas Parejo, MD
Diego de Argila, MD
Javier Sánchez-Pérez, MD
Ester Rubio, MD
Manuel León Luque, MD
Juan María Blanco-Madrigal, MD
Eva Galíndez-Aguirregoikoa, MD
Javier Martín, MD, PhD
Ricardo Blanco, MD, PhD**
Miguel A. González-Gay, MD, PhD**

*These authors contributed equally.

**M.A. Gonzalez-Gay and R. Blanco shared senior authorship in this study.

Authors' affiliations on page S-87.

Please address correspondence to:

Dr Miguel A. González-Gay,
Epidemiology, Genetics and Atherosclerosis
Research Group on Systemic Inflammatory
Diseases, IDIVAL, University of Cantabria,
Santander, Spain.

E-mail: miguelaggay@hotmail.com.

Received on October 28, 2015; accepted in
revised form on January 18, 2016.

Clin Exp Rheumatol 2016; 34 (Suppl. 97):
S84-S88.

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EXPERIMENTAL RHEUMATOLOGY 2016.

Key words: Henoch-Schönlein
purpura, *IL1*, rs16944, vasculitis

Funding: This study was supported by
a grant from "Fondo de Investigaciones
Sanitarias" PI12/00193 (Spain). F. Genre
is a recipient of a Sara Borrell postdoctoral
fellowship from the Instituto de Salud Carlos
III at the Spanish Ministry of Health (Spain)
(CD15/00095). B. Ubilla is supported by
funds from the RETICS Program (RIER)
(RD12/009/0013).

Competing interests: none declared.

ABSTRACT

Objective. Data from a small series suggested that the Interleukin 1 beta (*IL1β*) rs16944 polymorphism may be associated with severe renal involvement and persistent renal damage (renal sequelae) in Henoch-Schönlein purpura (HSP). To confirm this association, we assessed the largest cohort of Caucasian HSP patients ever considered for genetic studies.

Methods. 338 Spanish HSP patients and 635 sex and ethnically matched controls were recruited in this study. All patients were required to have had at least 6 months' follow-up. Patients and controls were genotyped for *IL1β* rs16944 by TaqMan genotyping assay.

Results. No differences between *IL1β* rs16944 genotype or allele frequencies were found either in the case/control study or when HSP patients were stratified according to the age at disease onset, presence of nephritis or gastrointestinal manifestations. Nevertheless, 4 (25%) of the 16 HSP patients who developed severe renal manifestations carried the TT genotype versus 29 (9%) of 322 who did not develop this complication ($p=0.01$, $OR=5.48$, 95% $CI: 1.01-28.10$). Accordingly, patients carrying the mutant T allele had an increased risk of developing severe nephropathy ($p=0.016$, $OR=2.35$, 95% $CI: 1.09-5.07$). Additionally, a significant increase of the TT genotype was observed in patients with persistent renal damage when compared with those patients without this complication (25% versus 8.6%, respectively; $p=0.0035$, $OR=4.90$, 95% $CI: 1.26-18.51$). Moreover, renal sequelae were more common in patients carrying the

mutant T allele ($p=0.0076$, $OR=2.20$, 95% $CI: 1.17-4.14$).

Conclusion. Our results support that the *IL1β* rs16944 polymorphism may be a potential marker of severe renal manifestations and renal sequelae in HSP.

Introduction

Henoch-Schönlein purpura (HSP), recently renamed Immunoglobulin-A (IgA) vasculitis (1), is a complex polygenic disease (2, 3). Although the causes of this vasculitis are largely unknown, epidemiologic studies have implicated both environmental and socio-economical factors in HSP pathogenesis (2, 3). Furthermore, as suggested immunogenetic and familial case clusters studies, a genetic predisposition to HSP appears to influence the development and progression of this condition (3). However, the genetic background related to HSP has not been elucidated yet, since only a few studies have been carried out to address this issue (4-12). Replication studies for any novel genetic association are crucial, mainly if it has been described in a small sample size of individuals. Consequently, during the last year, much effort has been done to validate previous potential HSP susceptibility results in a well-powered cohort of HSP patients. In this regard, a recent human leukocyte antigen (HLA) typing analysis, performed in the largest series of Caucasian HSP patients ever recruited for genetic studies, has confirmed the previously suggested susceptibility effect of *HLA-DRB1*01* to HSP (13). Even more, this study has identified *HLA-DRB1*0103* as the main susceptibility HSP allele (13). In addition, an association between

*HLA-B*41:02* and HSP susceptibility, irrespective of *HLA-DRB1* status, has been disclosed in this large cohort of Caucasian HSP patients (14).

In line with the above, cytokine pathway genes have been shown to represent a key component of the genetic network associated with immune-mediated pathologies and, specifically, polymorphisms located in those genes have been related to phenotype expression of HSP, in particular to the risk of nephritis (6-7). In this respect, a former study performed by Amoli *et al.* assessed the potential influence of the interleukin 1 β (*IL1 β*) rs16944 genetic variant (*IL1 β* promoter gene polymorphism that induces the -511 C/T change) in the HSP incidence and also its possible implication in HSP severe systemic complications in Caucasians (6). Interestingly, although no association between *IL1 β* rs16944 and HSP susceptibility was disclosed, an influence of this genetic variant in HSP severity and outcome, in terms of severe nephritis and persistent renal damage (renal sequelae), was suggested (6). However, this study was performed in a small cohort of only 49 HSP Caucasian patients and it has not been validated yet.

Taken together all these considerations, this study aimed at investigating whether the *IL1 β* rs16944 polymorphism is actually involved in HSP pathogenesis, mainly in the risk of severe renal involvement and renal sequelae, in patients with HSP. For this purpose, we took advantage of the largest series of Caucasian HSP patients with this vasculitis ever assessed for genetic studies.

Patients and methods

Patients and Study Protocol

A set of 338 Spanish patients with cutaneous vasculitis who fulfilled the Michel *et al.* (15) classification criteria for HSP were included in the present study. According to them, they were classified as having HSP if they fulfilled 3 or more of the following characteristics: palpable purpura, bowel angina, gastrointestinal bleeding, macroscopic or microscopic haematuria, age at disease onset ≤ 20 years, and no

previous history of medications prior to the onset of the disease. Also, all patients included in this series were required to fulfill the American College of Rheumatology classification criteria for HSP (16). Blood samples were obtained from patients recruited from Hospital Universitario Lucus Augusti (Lugo), Hospital Universitario Marqués de Valdecilla (Santander), Hospital Universitario La Princesa (Madrid), Hospital Universitario San Cecilio (Granada), Hospital Universitario Virgen del Rocío (Sevilla) and Hospital Universitario de Basurto (Bilbao). Information on the main clinical features of the whole series of 338 HSP Spanish patients recruited in this study is shown in Table I. Renal manifestations was defined if haematuria (≥ 5 red blood cells/hpf) with or without proteinuria (>300 mg/24 h) was present at any time over the course of the disease; severe renal manifestations if nephrotic (1 g/day/m² body surface area or >3.5 g/day proteinuria with plasma albumin <25 g/l, with or without oedema) and/or nephritic (*i.e.* haematuria with at least 2 of the following: hypertension, raised plasma urea or creatinine, and oliguria) syndrome was present at the onset or during the clinical course of the disease; and persistent renal damage (renal sequelae) was considered to be present if a patient had any of the renal complications described above at last follow-up (at least 6 months' follow-up).

A set of 635, sex and ethnically matched controls without history of cutaneous vasculitis or any other autoimmune disease constituted by blood donors from National DNA Bank Repository (Salamanca, Spain), was also included in the study.

A subject's written consent was obtained according to the declaration of Helsinki, and the study was approved by the Ethics Committees of Galicia for Hospital Universitario Lucus Augusti (Lugo), of Cantabria for Hospital Universitario Marqués de Valdecilla (Santander), of Madrid for Hospital Universitario La Princesa (Madrid), of Andalucía for Hospital Universitario San Cecilio (Granada) and Hospital Universitario Virgen del Rocío (Se-

villa), and of País Vasco for Hospital Universitario de Basurto (Bilbao).

Genotyping

Genomic deoxyribonucleic acid (DNA) was extracted from peripheral blood mononuclear cells using standard methods. The *IL1 β* rs16944 (C__1839943_10) polymorphism was genotyped by TaqMan single nucleotide polymorphism (SNP) genotyping assays in a 7900 HT Real-Time polymerase chain reaction (PCR) system, according to the conditions recommended by the manufacturer (Applied Biosystem, Foster City, CA, USA). Negative controls and duplicate samples were included to check the accuracy of genotyping.

Statistical analysis

All genotypes data were checked for deviation from Hardy-Weinberg equilibrium (HWE) using <http://ihg.gsf.de/cgi-bin/hw/hwa1.pl>. Both allelic and genotypic frequencies were calculated and compared by χ^2 or Fisher tests when necessary (expected values below 5). Strength of associations were estimated using odds ratios (OR) and 95% confidence intervals (CI). All analyses were performed with STATA statistical software 12/SE (Stata Corp., College Station, TX, USA).

Results

No divergence from Hardy-Weinberg equilibrium was observed either in controls or HSP cases. The genotyping success was greater than 99%.

First, we conducted a case/control association study. Accordingly, and as shown in Table II, no statistically significant differences in the genotype and allele frequencies of the *IL1 β* rs16944 polymorphism between the whole group of HSP and controls were observed.

In a further step, to examine whether the *IL1 β* rs16944 genetic variant might influence the clinical manifestations of the disease, HSP patients were stratified according to the age at disease onset, presence of nephritis or gastrointestinal manifestations. However, no statistically significant differences in the *IL1 β* rs16944 genotype and allele fre-

Table I. Main clinical features of a series of 338 Spanish patients with HSP.

Main characteristics	% (n/N)
Children (age ≤20 years)/ adults (age >20 years)	278/60
Male/ female	173/165
Age at the onset of the disease (years, median [IQR])	7 [5-17]
Duration of follow-up (years, median [IQR])	1.5 [1-4]
Palpable purpura and/or maculopapular rash	100 (338/338)
Arthralgia and/or arthritis	56.2 (190/338)
Gastrointestinal manifestations (if any of the following characteristics)	53.2 (180/338)
a) Bowel angina	51.8 (175/338)
b) Gastrointestinal bleeding	16.5 (56/338)
Renal manifestations (if any of the following characteristics)	35.5 (120/338)
a) Haematuria	34.6 (117/338)
b) Proteinuria	32.8 (111/338)
Severe renal manifestations (if any of the following characteristics)	4.7 (16/338)
a) Nephrotic syndrome	4.1 (14/338)
b) Nephritic syndrome	1.8 (6/338)
Persistent renal damage (renal sequelae)*	7.1 (24/338)

HSP: Henoch-Schönlein purpura; IQR: interquartile range. *At the end of the study (at least 6 months' follow-up).

quencies were detected between HSP in children (age ≤20 years) and adults (age >20 years) (Table II). Likewise, *IL1β* rs16944 genotype and allele frequencies did not differ when HSP patients were stratified by the presence of renal or gastrointestinal manifestations (Table II). Nevertheless, 4 (25%) of the 16 HSP patients who developed severe renal manifestations during the course of the disease carried the TT genotype versus 29 (9%) of 322 who did not develop this complication ($p=0.01$, OR=5.48, 95% CI: 1.01-28.10) (Table III). In accordance with that, HSP patients carrying the mutant T allele had an increased risk of developing severe nephropathy during the course of the disease ($p=0.016$, OR=2.35, 95% CI: 1.09-5.07) (Table III). Additionally, a statistically significant increase of TT

genotype was observed in HSP patients with persistent renal damage at last follow-up when compared with those HSP patients without this complication (25% versus 8.6%, respectively; $p=0.0035$, OR=4.90, 95% CI: (1.26-18.51)) (Table III). Moreover, renal sequelae were more commonly observed in HSP patients carrying the mutant T allele ($p=0.0076$, OR=2.20, 95% CI: (1.17-4.14)) (Table III).

Discussion

HSP is generally considered a benign and self-limited disorder (17). However, renal involvement may be a serious complications and the major cause of long-term morbidity and mortality in patients with this vasculitis (18-19). In this respect, cytokine pathway genes have been shown to represent a key

component of the genetic network associated with the risk of nephritis in HSP (6-7).

IL-1β is a proinflammatory pleiotropic cytokine that possesses the ability to stimulate the expression of genes associated with immune response and to increase the expression on endothelial adhesion molecules (20) playing a key role in the pathogenesis of inflammatory diseases (21). Accordingly, high IL-1β expression has been observed in the skin biopsy specimens of patients with HSP (22). Furthermore, high IL-1β serum concentration was also observed in HSP patients with nephritis (23). Regarding genetic studies, a potential association between *IL1β* rs16944 and HSP severity and outcome was suggested (6). Interestingly, this polymorphism seems to influence IL-1β production and it has been related to several diseases (24). However, in the former study (6), a potential false positive association could not be excluded due to the small size of the series of HSP patients analysed. Because of that, we have performed a genetic study to establish whether *IL1β* rs16944 is actually involved in HSP pathogenesis, in particular in the risk of severe renal involvement and persistent renal damage. For this purpose we took advantage of the largest series of HSP Caucasian patients ever considered for genetic studies. Interestingly, our findings revealed a genetic association between the *IL1β* rs16944 TT genotype and both severe renal involvement and persistent renal damage in HSP Caucasian patients. Our positive results were found in a

Table II. Frequency of *IL1β* rs16944 in controls and HSP patients stratified according to the age at disease onset and the presence/absence of renal and GI manifestations.

SNP	Controls (n=635)	HSP (n=338)	Children (age ≤20 years)		HSP with renal manifestations ^a		HSP with GI manifestations ^b	
			Yes (n=278)	No (n=60)	Yes (n=120)	No (n=218)	Yes (n=180)	No (n=158)
<i>IL1β</i> rs16944								
CC	280 (44.1)	163 (48.2)	125 (44.9)	27 (45.0)	62 (51.7)	101 (46.3)	90 (50.0)	79 (50.0)
CT	281 (44.3)	142 (42.0)	111 (39.9)	24 (40.0)	45 (37.5)	97 (44.5)	71 (39.5)	62 (39.2)
TT	74 (11.7)	33 (9.8)	42 (15.2)	9 (15.0)	13 (10.8)	20 (9.2)	19 (10.5)	17 (10.8)
C	841 (66.2)	468 (69.2)	361 (64.9)	78 (65.0)	169 (70.4)	299 (68.6)	251 (69.7)	220 (69.6)
T	429 (33.8)	208 (30.8)	195 (35.1)	42 (35.0)	71 (29.6)	137 (31.4)	109 (30.3)	96 (30.4)

Results are shown as n (%). HSP: Henoch-Schönlein purpura; GI: gastrointestinal; SNP: single nucleotide polymorphism.

^a If haematuria with or without proteinuria was present at the onset or during the clinical course of the disease.

^b If bowel angina and/or gastrointestinal bleeding was present at the onset or during the clinical course of the disease.

Table III. Frequency of *IL1β* rs16944 in HSP patients with and without severe renal manifestations and persistent renal damage.

SNP	HSP with severe renal manifestations ^a		HSP with persistent renal damage ^b	
	Yes (n=16)	No (n=322)	Yes (n=24)	No (n=314)
<i>IL1β</i> rs16944				
CC	4 (25.0)	159 (49.4)	7 (29.1)	156 (49.7)
CT	8 (50.0)	134 (41.6)	11 (45.8)	131 (41.7)
TT	4 (25.0) ^c	29 (9.0) ^c	6 (25) ^c	27 (8.6) ^c
C	16 (50.0)	452 (70.2)	25 (52.0)	443 (70.5)
T	16 (50.0) ^d	192 (29.8) ^d	23 (48.0) ^f	185 (29.5) ^f

Results are shown as n (%).

HSP: Henoch-Schönlein purpura; SNP: single nucleotide polymorphism.

^aIf nephrotic and/or nephritic syndrome was present during the clinical course of the disease. ^bIf any renal complication was present at the end of the study (at least 6 months' follow-up). ^c*p*=0.01; OR=5.48 (95% CI: 1.01-28.10). ^d*p*=0.016; OR=2.35 (95% CI: 1.09-5.07). ^e*p*=0.0035; OR=4.90 (95% CI: 1.26-18.51). ^f*p*=0.0076; OR=2.20 (95% CI: 1.17-4.14).

small group of HSP patients and, therefore, the reliability of this finding could be considered somehow low. Nevertheless, it is important to highlight that our report may be considered as a genetic replication study whose results are in keeping with those previously described by Amoli *et al.* and further evidence that *IL1β* rs16944 may actually be a potential genetic marker of severe and persistent renal damage in HSP Caucasian patients.

In accordance with our findings, *IL1β* polymorphisms have been related to different types of primary systemic vasculitis (suggesting the relevant role of this cytokine in the pathogenesis of these conditions). In accordance with that, *IL1β* rs16944 was involved in Takayasu (a large-sized blood vessel vasculitis) disease predisposition in the Mexican population (25). Additionally, *IL1β* polymorphisms increase the susceptibility to Behçet's disease in different populations (26-27).

The results obtained in the present study provide additional evidence for the potential role that genetic factors may play in the pathogenesis of HSP. Furthermore, they may have potential clinical implication as they may help to better identify HSP individuals at risk for severe renal involvement and persistent renal damage.

In conclusion, our results support that the *IL1β* rs16944 polymorphism may be a potential marker of severe renal manifestations and renal sequelae in HSP.

Acknowledgements

We wish to thank all the patients with HSP and controls who participated to make this study possible.

We want to specially thank Patricia Fuentevilla Rodríguez, Virginia Portilla González, María Del Camino Villa Llamazares and María Eugenia Cuadrado Mantecón for their technical assistance.

Authors' affiliations

¹Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, IDIVAL, Santander, Spain;

²Medicine Department, Hospital Universitario San Cecilio, Granada, Spain;

³Rheumatology Department, Hospital Universitario La Princesa, IIS-Princesa, Madrid, Spain;

⁴Epidemiology and Computational Biology Department, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain;

⁵Division of Rheumatology, Hospital Universitario Lucus Augusti, Lugo, Spain;

⁶Nephrology Department, Hospital Universitario San Cecilio, Granada, Spain;

⁷Dermatology Department, Hospital Universitario La Princesa, IIS-Princesa, Madrid, Spain;

⁸Rheumatology Department, Hospital Universitario Virgen del Rocío, Sevilla, Spain;

⁹Rheumatology Department, Hospital Universitario de Basurto, Bilbao, Spain;

¹⁰Institute of Parasitology and Biomedicine López-Neyra, CSIC, Granada, Spain;

¹¹School of Medicine, University of Cantabria, Santander, Spain;

¹²Cardiovascular Pathophysiology and

Genomics Research Unit, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

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