Influence of *IL17A* gene on the pathogenesis of immunoglobulin-A vasculitis

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Received on November 7, 2019; accepted in revised form on February 3, 2020.

Clin Exp Rheumatol 2020; 38 (Suppl. 124): S166-S170.

Key words: IgA, *IL17A*, vasculitis

Competing interests: none declared.

ABSTRACT

Objective. *Cytokines signalling pathway genes represent a key component of the genetic network implicated in the pathogenesis of immunoglobulin-A vasculitis (IgAV), an inflammatory vascular pathology. Interleukin (IL)17A is described as a genetic risk locus for some autoimmune diseases, such as giant cell arteritis and spondyloarthritis. Accordingly, we aimed to determine the potential influence of IL17A on the pathogenesis of IgAV.*

Methods. *Five IL17A tag polymorphisms (rs4711998, rs8193036, rs3819024, rs2275913 and rs7747909), which cover the major variability of this gene, were genotyped in 360 Caucasian patients with IgAV and 1,003 sex and ethnically matched healthy controls using TaqMan probes.*

Results. *No statistically significant differences between patients with IgAV and healthy controls were observed when each IL17A genetic variant was analysed independently. Similarly, no statistically significant differences between patients with IgAV and healthy controls were found when the five IL17A polymorphisms were evaluated combined conforming haplotypes. In addition, there were no statistically significant differences in genotype, allele and haplotype frequencies of IL17A when patients with IgAV were stratified according to the age at disease onset or to the presence/absence of gastrointestinal or renal manifestations.*

Conclusion. *Our results do not support an influence of IL17A on the pathogenesis of IgAV.*

Introduction

Immunoglobulin-A vasculitis (IgAV) is classically a childhood inflammatory small-sized blood vessel disease (1-4), although it may also develop in adults (1, 2, 4, 5). The classic clinical triad of IgAV consists of palpable purpura (involving mainly the lower extremities), joints and the gastrointestinal tract. Nevertheless, renal complications are also common in affected patients (3, 5-7). IgAV has a multifactorial aetiology in which genes play a relevant role in both the predisposition and clinical phenotype of the disease (6, 8). In this regard, cytokines signalling pathway genes represent a key component of the genetic network implicated in the pathogenesis of IgAV (6, 9-12).

Interleukin (IL)-17 encompasses a family of cytokines defined as major players in the immune response to foreign pathogens (13). Among them, IL-17A is implicated in pro-inflammatory responses and participates in the pathogenic mechanisms of autoimmune processes (14-17). With respect to this, genetic studies have provided strong evidence of the role of *IL17A* as a genetic risk *locus* for some immune-mediated diseases, such as giant cell arteritis (GCA) (18) and spondyloarthritis (19). Taken all these considerations into account, this study aimed to determine the potential influence of *IL17A* on the pathogenesis of IgAV. For this purpose, we genotyped five *IL17A* tag polymorphisms, which cover the major variability of this gene, in the largest series of Caucasian patients diagnosed with IgAV ever assessed for genetic studies.

Patients and methods

Study population

A series of 360 unrelated Spanish patients of European ancestry who fulfilled both Michel *et al*. (20) and the American College of Rheumatology

(21) classification criteria for IgAV were included in the present study. Centres involved in the recruitment of these patients included Hospital Universitario Marqués de Valdecilla (Santander), Hospital Universitario San Cecilio (Granada), Hospital Universitario Lucus Augusti (Lugo), Hospital Universitario de La Princesa (Madrid), Hospital Universitario Virgen del Rocío (Sevilla) and Hospital Universitario de Basurto (Bilbao). Information on the main clinical features of these patients is shown in Table I. For gastrointestinal (GI) manifestations, bowel angina was considered present if there was diffuse abdominal pain that worsened after meals or bowel ischaemia usually with bloody diarrhea. GI bleeding was defined as the presence of melena, haematochezia, or a positive test for occult blood in the stool. Renal manifestations were defined to be present if at least one of the following findings was observed: haematuria, proteinuria or nephrotic syndrome at any time over the clinical course of the disease and/or renal sequelae (persistent renal involvement) at last follow-up.

In addition, a set of 1,003 sex and ethnically matched healthy controls without history of cutaneous vasculitis or any other autoimmune disease, constituted by blood donors from Hospital Universitario Marqués de Valdecilla (Santander) and National DNA Bank Repository (Salamanca), was also included in this study.

All patients with IgAV and healthy controls signed an informed written consent before being included in the study. The procedures followed were in accordance with the ethical standards of the approved guidelines and regulations, according to the Declaration of Helsinki. All experimental protocols were approved by the Ethics Committees of clinical research of Cantabria for Hospital Universitario Marqués de Valdecilla, of Andalucía for Hospital Universitario San Cecilio and Hospital Universitario Virgen del Rocío, of Galicia for Hospital Universitario Lucus Augusti, of Madrid for Hospital Universitario de La Princesa and of País Vasco for Hospital Universitario de Basurto.

Table I. Main clinical features of the 360 patients with IgAV included in the study.

	% (n)
Children (age ≤20 years)/ adults (age >20 years)	285/75
Males/ females	181/179
Age at disease onset (years, median [IQR])	7 [5-16]
Duration of follow-up (years, median [IQR])	1 [1-3]
Palpable purpura and/or maculopapular rash	100 (360)
Arthralgia and/or arthritis	60.0 (216)
GI manifestations (if "a" and/or "b")	57.2 (206)
a) Bowel angina	54.4 (196)
b) GI bleeding	18.0 (65)
Renal manifestations (if any of the following characteristics)	39.4 (142)
a) Haematuria*	37.8 (136)
b) Proteinuria*	35.8 (129)
c) Nephrotic syndrome*	6.1 (22)
d) Renal sequelae (persistent renal involvement)**	7.2 (26)

IgAV: IgA vasculitis; IQR: interquartile range; GI: gastrointestinal.
*At any time over the clinical course of the disease.
**At last follow-up.

Single nucleotide polymorphisms selection and genotyping

Five polymorphisms within *IL17A* gene (rs4711998, rs8193036, rs3819024, rs2275913 and rs7747909), which tag over 86% of the variability of this *locus* as described elsewhere (18), were selected in this study.

Genomic deoxyribonucleic acid from all the individuals included in the study was extracted from peripheral blood using standard procedures.

Patients with IgAV and healthy controls were genotyped for the five *IL17A* genetic variants mentioned above using predesigned TaqMan 5' single-nucleotide polymorphism genotyping assays (C___1799586_20, C___1799585_10, C__11545877_10, C__15879983_10 and C__29315993_10) in a QuantStudio™ 7 Flex Real-Time polymerase chain reaction system, according to the conditions recommended by the manufacturer (Applied Biosystems, Foster City, CA, USA).

Negative controls and duplicate samples were included to check the accuracy of the genotyping.

Statistical analyses

All genotype data were checked for deviation from Hardy-Weinberg equilibrium (HWE) by chi-square test.

Differences in *IL17A* frequencies were evaluated between patients with IgAV and healthy controls as well as patients with IgAV stratified according to specific clinical characteristics of the disease (age at disease onset or presence/absence of GI or renal manifestations). First, each *IL17A* polymorphism was analysed independently. Both genotype and allele frequencies were calculated and compared between the groups mentioned above by chi-square test. Strength of association was estimated using odds ratios (OR) and 95% confidence intervals (CI).

Subsequently, *IL17A* genetic variants were analysed combined conforming haplotypes using the Haploview v. 4.2 software. Haplotype frequencies were calculated and compared between the groups mentioned above by chi-square exact test. Strength of association was estimated by OR and 95% CI. *P*-values lower than 0.05 were considered as statistically significant.

All analyses were performed with STATA statistical software 12/SE (Stata Corp., College Station, TX, USA).

Results

The genotyping success rate was greater than 99%.

No evidence of departure from HWE was observed at the 5% significance level. Genotype and allele frequencies of the five *IL17A* polymorphisms evaluated were similar to those reported for populations of European origin in the 1000 Genomes Project (http://www.internationalgenome.org/).

Table II. Genotype and allele frequencies of *IL17A* in patients with IgAV and healthy controls.

Polymorphism	Change 1/2	Samples Set	Genotypes, % (n) 1/1	1/2	2/2	Alleles, % (n) 1	2
rs4711998	G/A	IgAV patients	53.3 (192)	39.2 (141)	7.5 (27)	72.9 (525)	27.1 (195)
		Healthy controls	52.7 (529)	41.2 (413)	6.1 (61)	73.3 (1471)	26.7 (535)
rs8193036	T/C	IgAV patients	56.1 (202)	39.2 (141)	4.7 (17)	75.7 (545)	24.3 (175)
		Healthy controls	60.3 (605)	35.2 (353)	4.5 (45)	77.9 (1563)	22.1 (443)
rs3819024	A/G	IgAV patients	43.9 (158)	43.3 (156)	12.8 (46)	65.6 (472)	34.4 (248)
		Healthy controls	45.6 (457)	44.6 (447)	9.9 (99)	67.8 (1361)	32.2 (645)
rs2275913	G/A	IgAV patients	44.7 (161)	42.8 (154)	12.5 (45)	66.1 (476)	33.9 (244)
		Healthy controls	44.8 (449)	44.2 (443)	11.1 (111)	66.8 (1341)	33.2 (665)
rs7747909	G/A	IgAV patients	53.6 (193)	39.7 (143)	6.7 (24)	73.5 (529)	26.5 (191)
		Healthy controls	53.0 (532)	39.4 (395)	7.6 (76)	72.7 (1459)	27.3 (547)

All the allele frequencies did not show significant differences between patients with IgAV and healthy controls.
IgAV: IgA vasculitis.

Differences in IL17A frequencies between patients with IgAV and controls

Firstly, we compared genotype, allele and haplotype frequencies of *IL17A* between patients with IgAV and healthy controls.

As shown in Table II, no statistically significant differences in the genotype and allele frequencies of each *IL17A* polymorphism were disclosed when patients with IgAV were compared to healthy controls. The haplotype analysis of *IL17A* did not yield additional information, since haplotypes frequencies were similar between patients with IgAV and healthy controls (Table III).

Table III. Haplotype analysis of *IL17A* between patients with IgAV and healthy controls.

Haplotypes					*p*	OR [95% CI]
rs4711998	rs8193036	rs3819024	rs2275913	rs7747909		
G	T	A	G	G	-	Ref.
G	T	G	A	A	0.58	1.09 [0.77-1.54]
A	T	A	G	G	0.97	0.99 [0.68-1.42]
A	C	G	A	A	0.96	0.99 [0.66-1.47]
A	T	G	A	A	0.90	1.02 [0.68-1.51]

IgAV: IgA vasculitis; OR: odds ratio; CI: confidence interval.

Differences in IL17A frequencies between patients with IgAV stratified according to the age at disease onset

Since IgAV is generally a benign and self-limited pathology in children and a more severe condition in adults, leading in some cases to chronic kidney disease, we analysed potential differences in the genotype, allele and haplotype frequencies of *IL17A* between patients with IgAV stratified according to the age at disease onset.

However, no genotype or allele differences of each *IL17A* genetic variant were detected when children (age ≤20 years) were compared to adults (age >20 years) (Table IV). Similarly, haplotype frequencies of IL17A did not significantly differ when patients with IgAV were stratified according to the age at disease onset (Supplementary Table S1).

Differences in IL17A frequencies between patients with IgAV stratified according to the presence/absence of GI or renal manifestations

We also examined whether genotype, allele and haplotype frequencies of *IL17A* differed between patients with IgAV stratified according to the presence/absence of GI or renal manifestations.

No statistically significant differences in genotype, allele and haplotype frequencies of *IL17A* between patients with IgAV with or without GI manifestations were found (Table IV and Supplementary Table 2). This was also the case when patients with IgAV who developed renal manifestations were compared to those who did not exhibit these complications (Table IV and Suppl. Table S3).

Discussion

Accumulating evidence clearly suggests that a common genetic component may underlie different autoimmune diseases. *IL17A* is described as a genetic risk *locus* for GCA (18) and spondyloarthritis (19), raising the question of whether this gene may be also implicated in the pathogenic mechanisms of other immune-mediated diseases.

Taking into account these considerations, we evaluated the potential implication of *IL17A* on the pathogenesis of IgAV, an inflammatory leukocytoclastic vasculitis in whose aetiology cytokines signalling pathway genes may be considered as an essential component (6, 9-12). For that purpose, we evaluated five tag *IL17A* polymorphisms that allow us to perform combination analyses, often helping to uncover hidden signals, in the largest series of Caucasian patients with IgAV ever assessed for genetic studies. Our results showed no influence of *IL17A* genetic variants (evaluated independently or combined conforming haplotypes) on the susceptibility to IgAV. Furthermore, no specific association of *IL17A* polymorphisms (assessed independently or combined conforming haplotypes) with clinical features of IgAV was observed in our study, indicating that this gene does not represent a risk factor for the severity of the disease. To the best of our knowledge, only a study performed by Xu *et al*. has evaluated the role of *IL17A* in the

Table IV. Genotype and allele frequencies of *IL17A* in patients with IgAV stratified according to the age at disease onset or the presence/absence of GI or renal manifestations.

Polymorphism	Children (age ≤20 years)		GI manifestations		Renal manifestations	
	Yes (n=285)	No (n=75)	Yes (n=206)	No (n=154)	Yes (n=142)	No (n=218)
rs4711998						
GG	53.7 (153)	52.0 (39)	54.4 (112)	51.9 (80)	56.3 (80)	51.4 (112)
GA	40.0 (114)	36.0 (27)	37.9 (78)	40.9 (63)	33.1 (47)	43.1 (94)
AA	6.3 (18)	12.0 (9)	7.8 (16)	7.1 (11)	10.6 (15)	5.5 (12)
G	73.7 (420)	70.0 (105)	73.3 (302)	72.4 (223)	72.9 (207)	72.9 (318)
A	26.3 (150)	30.0 (45)	26.7 (110)	27.6 (85)	27.1 (77)	27.1 (118)
rs8193036						
TT	57.2 (163)	52.0 (39)	56.3 (116)	55.8 (86)	59.2 (84)	54.1 (118)
TC	38.2 (109)	42.7 (32)	39.8 (82)	38.3 (59)	35.2 (50)	41.7 (91)
CC	4.6 (13)	5.3 (4)	3.9 (8)	5.8 (9)	5.6 (8)	4.1 (9)
T	76.3 (435)	73.3 (110)	76.2 (314)	75.0 (231)	76.8 (218)	75.0 (327)
C	23.7 (135)	26.7 (40)	23.8 (98)	25.0 (77)	23.2 (66)	25.0 (109)
rs3819024						
AA	43.2 (123)	46.7 (35)	47.6 (98)	39.0 (60)	45.1 (64)	43.1 (94)
AG	43.2 (123)	44.0 (33)	41.3 (85)	46.1 (71)	44.4 (63)	42.7 (93)
GG	13.7 (39)	9.3 (7)	11.2 (23)	14.9 (23)	10.6 (15)	14.2 (31)
A	64.7 (369)	68.7 (103)	68.2 (281)	62.0 (191)	67.3 (191)	64.4 (281)
G	35.3 (201)	31.3 (47)	31.8 (131)	38.0 (117)	32.7 (93)	35.6 (155)
rs2275913						
GG	44.9 (128)	44.0 (33)	48.5 (100)	39.6 (61)	46.5 (66)	43.6 (95)
GA	41.1 (117)	49.3 (37)	40.3 (83)	46.1 (71)	41.5 (59)	43.6 (95)
AA	14.0 (40)	6.7 (5)	11.2 (23)	14.3 (22)	12.0 (17)	12.8 (28)
G	65.4 (373)	68.7 (103)	68.7 (283)	62.7 (193)	67.3 (191)	65.4 (285)
A	34.6 (197)	31.3 (47)	31.3 (129)	37.3 (115)	32.7 (93)	34.6 (151)
rs7747909						
GG	53.3 (152)	54.7 (41)	57.3 (118)	48.7 (75)	54.2 (77)	53.2 (116)
GA	38.9 (111)	42.7 (32)	37.4 (77)	42.9 (66)	40.8 (58)	39.0 (85)
AA	7.7 (22)	2.7 (2)	5.3 (11)	8.4 (13)	4.9 (7)	7.8 (17)
G	72.8 (415)	76.0 (114)	76.0 (313)	70.1 (216)	74.6 (212)	72.7 (317)
A	27.2 (155)	24.0 (36)	24.0 (99)	29.9 (92)	25.4 (72)	27.3 (119)

IgAV: IgA vasculitis; GI: gastrointestinal.

inflammatory process of IgAV in Asians (22). An effect of *IL17A* rs2275913 polymorphism on the susceptibility to this vasculitis was disclosed when 148 patients with IgAV from China were compared to 202 healthy controls (22). The apparent discrepancies observed between our results and those obtained by Xu *et al*. may be explained by genetic variability in populations of different ethnicity.

The results derived from our study are of potential clinical relevance. On the one hand, vasculitides constitute a heterogeneous group of autoimmune diseases that often have overlapping clinical and pathological manifestations (23). Nevertheless, differences among them in molecular terms have been proposed (24). Our data support this hypothesis since no influence of *IL17A* on the pathogenesis of IgAV in Caucasians was observed, unlike GCA (18). In addition, given that inhibitors of IL-17A seem to have preventative and/or therapeutic efficacy in patients with a wide range of autoimmune diseases (such as psoriasis, ankylosing spondylitis, and psoriatic arthritis (25, 26)), the lack of association between *IL17A* and the pathogenesis of IgAV suggests that inhibitors of IL-17A may not have a beneficial effect in Caucasian patients with this vasculitis.

In summary, our results do not support an influence of *IL17A* on the pathogenesis of IgAV.

Acknowledgements

We are indebted to the patients and healthy controls for their essential collaboration to this study. We also thank the National DNA Bank Repository (Salamanca, Spain) for supplying part of the control samples.

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Funding

This study was supported by European Union FEDER funds and "Fondo de Investigaciones Sanitarias" (grant PI18/00042) from 'Instituto de Salud Carlos III' (ISCIII, Health Ministry, Spain). RL-M is a recipient of a Miguel Servet type I programme fellowship from the ISCIII, co-funded by the European Social Fund (ESF, 'Investing in your future') (grant CP16/00033). S. R.-M. is supported by funds of the RETICS Program (RD16/0012/0009) (ISCIII, co-funded by the European Regional Development Fund (ERDF)). V.P.-C. is supported by a pre-doctoral grant from IDIVAL (PREVAL 18/01). V.M. is supported by funds of a Miguel Servet type I programme (grant CP16/00033) (ISCIII, co-funded by ESF). L.L.-G. is supported by funds of PI18/00042 (ISCIII, co-funded by ERDF).

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