Role of *IRF5* in the pathogenesis of immunoglobulin-A vasculitis

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ABSTRACT

Objective. *Interferon regulatory factor 5 (IRF5) is a major regulator of type I interferon induction and is also critical to produce pro-inflammatory cytokines. An influence of IRF5 genetic variants on the increased risk of immune-mediated diseases has been described. Accordingly, we aimed to evaluate the implication of IRF5 in the pathogenesis of Immunoglobulin-A vasculitis (IgAV), an inflammatory vascular pathology.*

Methods. *Three tag genetic variants (rs2004640, rs2070197 and rs10954213), representative of 3 different haplotype blocks within IRF5, were genotyped in 372 Caucasian patients with IgAV and 876 sex and ethnically matched healthy controls by TaqMan assays.*

Results. *No significant differences in the genotype and allele frequencies between patients with IgAV and healthy controls were observed when each IRF5 polymorphism was evaluated independently. Likewise, no significant differences between patients with IgAV and healthy controls were found when we assessed the three IRF5 polymorphisms combined, conforming haplotypes. In addition, there were no significant differences in genotype, allele and haplotype frequencies of IRF5 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 IRF5 on the pathogenesis of IgAV.*

Introduction

Immunoglobulin-A vasculitis (IgAV) is in general a benign and self-limited inflammatory vascular disease in children and a more severe condition in adults (1-5). Although IgAV typically involves the skin, joints and the gastrointestinal (GI) tract (3, 5-8), nephritis is also common in affected patients and constitutes the most feared complication of this vasculitis (1-5). IgAV has a multifactorial aetiology in which genes are crucial in the susceptibility and severity of the disease (6, 9). Outside the human leukocyte antigen region, cytokines signalling pathway genes have been proposed as a key component of the genetic network leading to IgAV (6, 10-13).

Interferon regulatory factor 5 (IRF5) is member of a family of transcription factors involved in the control of inflammatory and immune responses (14). With respect to this, IRF5 has been described as a major regulator of the type I interferon induction (15, 16). Likewise, cumulative knowledge clearly suggests that IRF5 is also a critical molecule involved in the production of pro-inflammatory cytokines, such as interleukin (IL)-6 and IL-12 (17). In addition, several genetic studies have revealed an influence of different *IRF5* polymorphisms on the increased risk of immune-mediated diseases (18-22).

Taking into account all these considerations, in the present study we aimed to determine, for the first time, the potential implication of *IRF5* in the pathogenesis of IgAV. For this purpose, we genotyped three *IRF5* polymorphisms (rs2004640, rs2070197 and rs10954213) in the largest series of Caucasian patients diagnosed with IgAV ever assessed for genetic studies. These three specific *IRF5* polymorphisms were selected considering that they were previously described as tag genetic variants, representative of three different haplotype blocks within *IRF5* (23), that define risk and protective haplotypes for the development of

Table I. Main clinical features of the 372 patients with IgAV included in the study.

	% (n)
Children (age ≤20 years)/ adults (age >20 years)	295/77
Males/females	185/187
Age at disease onset (years, median [IQR])	7 [5-19]
Duration of follow-up (years, median [IQR])	1 [1-3]
Palpable purpura and/or maculopapular rash	100 (372)
Arthralgia and/or arthritis	58.0 (216)
GI manifestations (if "a" and/or "b")	55.9 (208)
a) Bowel angina	52.9 (197)
b) GI bleeding	17.7 (66)
Renal manifestations (if any of the following characteristics)	37.6 (140)
a) Haematuria*	36.3 (135)
b) Proteinuria*	34.1 (127)
c) Nephrotic syndrome*	5.4 (20)
d) Renal sequelae (persistent renal involvement)**	7.0 (26)

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

different inflammatory diseases (18, 22, 24) and that also exhibit different functional consequences (23-25).

Patients and methods

Study population

A series of 372 unrelated Spanish patients of European ancestry who fulfilled both Michel *et al*. (26) and the American College of Rheumatology (27) 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 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 876 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.

Single nucleotide polymorphisms selection and genotyping

Three polymorphisms (rs2004640, rs2070197 and rs10954213), representative of 3 different haplotype blocks within *IRF5*, were selected in this study.

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

Patients with IgAV and healthy controls were genotyped for the three *IRF5* genetic variants mentioned above using predesigned TaqMan 5´ single-nucleotide polymorphism genotyping assays (C___9491614_20 for rs2004640, C___2691236_10 for rs2070197 and C__31283335_10 for rs10954213) 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).

Table II. Genotype and allele frequencies of *IRF5* in patients with IgAV and healthy controls.

	Change		Genotypes, % (n)			Alleles, % (n)	
Polymorphism	1/2	Samples Set	1/1	1/2	2/2	1	2
rs2004640	T/G	IgAV patients	29.3 (109)	47.8 (178)	22.8 (85)	53.2 (396)	46.8 (348)
		Healthy controls	29.3 (257)	50.5 (442)	20.2 (177)	54.6 (956)	45.4 (796)
rs2070197	T/C	IgAV patients	82.3 (306)	16.4 (61)	1.3 (5)	90.5 (673)	9.5 (71)
		Healthy controls	82.3 (721)	17.1 (150)	0.6 (5)	90.9 (1592)	9.1 (160)
rs10954213	A/G	IgAV patients	37.9 (141)	46.2 (172)	15.9 (59)	61.0 (454)	39.0 (290)
		Healthy controls	38.2 (335)	49.0 (429)	12.8 (112)	62.7 (1099)	37.3 (653)

IgAV: IgA vasculitis.
All the genotype and allele frequencies did not show statistically significant differences ($p \geq 0.05$).

Table III. Haplotype analysis of *IRF5* between patients with IgAV and healthy controls.

Haplotypes			*p*	OR (95% CI)
rs2004640	rs2070197	rs10954213		
T	T	A	-	Ref.
G	T	G	0.37	1.09 (0.89-1.35)
G	T	A	0.77	1.04 (0.77-1.39)
T	C	A	0.78	1.06 (0.67-1.67)
T	T	G	0.75	1.07 (0.68-1.66)

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

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).

Differences in *IRF5* frequencies were evaluated between patients with IgAV and healthy controls as well as between 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, comparisons were performed considering all polymorphisms 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, we carried out the allelic combination analysis for the three *IRF5* genetic variants studied. Haplotype frequencies were calculated by the Haploview v4.2 software and then, compared between the groups mentioned above by chi-square exact test. Strength of association was estimated by OR and 95% CI. *p*-values less 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 rs2004640, rs2070197 and rs10954213 genotypes distribution was in HWE. The genotyping success was greater than 99% for the three *IRF5* polymorphisms assessed.

Genotype and allele frequencies of the three *IRF5* polymorphisms evaluated in the study were similar to those reported for populations of European origin in the 1000 Genomes Project (http://www.internationalgenome.org/).

Differences in IRF5 frequencies between patients with IgAV and controls

Firstly, we compared genotype, allele and haplotype frequencies of *IRF5* between patients with IgAV and healthy controls.

Table II describes the distribution of *IRF5* polymorphisms (considering the 3 genetic variants independently) in patients with IgAV and healthy controls. As shown in Table II, no statistically significant differences were observed in the genotype and allele frequencies of each *IRF5* polymorphism between IgAV patients and healthy controls ($p \geq 0.05$). The haplotype analysis of *IRF5* did not yield additional informa-

Table IV. Genotype and allele frequencies of *IRF5* 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=295)	No (n=77)	Yes (n=208)	No (n=164)	Yes (n=140)	No (n=232)
rs2004640						
TT	28.8 (85)	31.2 (24)	31.7 (66)	26.2 (43)	32.9 (46)	27.2 (63)
TG	47.1 (139)	50.6 (39)	45.7 (95)	50.6 (83)	45.7 (64)	49.1 (114)
GG	24.1 (71)	18.2 (14)	22.6 (47)	23.2 (38)	21.4 (30)	23.7 (55)
T	52.4 (309)	56.5 (87)	54.6 (227)	51.5 (169)	55.7 (156)	51.7 (240)
G	47.6 (281)	43.5 (67)	45.4 (189)	48.5 (159)	44.3 (124)	48.3 (224)
rs2070197						
TT	83.4 (246)	77.9 (60)	81.3 (169)	83.5 (137)	80.7 (113)	83.2 (193)
TC	14.9 (44)	22.1 (17)	17.3 (36)	15.2 (25)	17.1 (24)	15.9 (37)
CC	1.7 (5)	0	1.4 (3)	1.2 (2)	2.1 (3)	0.9 (2)
T	90.8 536)	89.0 (137)	89.9 (374)	91.2 (299)	89.3 (250)	91.2 (423)
C	9.2 (54)	11.0 (17)	10.1 (42)	8.8 (29)	10.7 (30)	8.8 (41)
rs10954213						
AA	37.6 (111)	39.0 (30)	41.8 (87)	32.9 (54)	40.7 (57)	36.2 (84)
AG	44.4 (131)	53.2 (41)	42.8 (89)	50.6 (83)	45.7 (64)	46.6 (108)
GG	18.0 (53)	7.8 (6)	15.4 (32)	16.5 (27)	13.6 (19)	17.2 (40)
A	59.8 (353)	65.6 (101)	63.2 (263)	58.2 (191)	63.6 (178)	59.5 (276)
G	40.2 (237)	34.4 (53)	36.8 (153)	41.8 (137)	36.4 (102)	40.5 (188)

IgAV: IgA vasculitis; GI: gastrointestinal.
All the genotype and allele frequencies did not show statistically significant differences ($p \geq 0.05$).

tion, since haplotypes frequencies were similar between patients with IgAV and healthy controls (Table III).

Differences in IRF5 frequencies between patients with IgAV stratified according to age at disease onset

Given that IgAV is generally a self-limited pathology in children and a more severe condition in adults, we also assessed if potential differences in *IRF5* frequencies could exist in IgAV patients stratified according to the age at disease onset.

However, as shown in Table IV, no differences in genotype and allele frequencies of each *IRF5* genetic variant were detected when children (age ≤20 years) were compared to adults (age >20 years). Similarly, haplotype frequencies of *IRF5* did not significantly differ when patients with IgAV were stratified according to the age at disease onset (Supplementary Table S1).

Differences in IRF5 frequencies between patients with IgAV stratified according to the presence / absence of GI or renal manifestations

Genotype, allele and haplotype frequencies of *IRF5* were also examined in patients with IgAV stratified according to the presence/absence of GI or renal manifestations.

No statistically significant differences in *IRF5* genotype, allele and haplotype frequencies were disclosed when patients with IgAV who developed GI manifestations were compared to those who did not exhibit these complications (Table IV and Suppl. Table S2). This was also the case when patients with IgAV were stratified according to the presence/absence of renal manifestations (Table IV and Suppl. Table S3).

Discussion

Inflammatory diseases are pathologies characterised by common pathogenic traits and a genetic overlap between them (28-30). In this regard, several studies have emphasised the role of *IRF5* as a risk *locus* for numerous rheumatic conditions (18-22), suggesting that this gene may be acting as a potential inductor of the immune response (31).

Based on these considerations, we evaluated whether *IRF5* was also implicated in the pathogenesis of IgAV, an inflammatory leucocytoclastic vasculitis involving small blood vessels. For that purpose, we analysed three tag polymorphisms, representative of three different haplotype blocks within *IRF5* (23), that define risk and protective haplotypes for the development of different inflammatory diseases (18, 22, 24) in the largest series of patients with IgAV ever assessed for genetic studies. These three genetic variants also exhibit different functional consequences such as alteration of a consensus splice donor site allowing expression of an alternative exon 1, creation of an early polyadenylation site that leads to a shorter isoform and alteration of the protein stability (23-25). Our results showed no influence of *IRF5* on the susceptibility to IgAV when we studied each of the polymorphisms separately. Moreover, when we analysed all the genetic variants together conforming haplotypes, our results revealed a lack of association between *IRF5* and IgAV susceptibility. Since previous studies disclosed that some gene polymorphisms were associated with an increased risk of nephritis or GI disease in IgAV (10-12, 32), we also aimed to determine if *IRF5* genetic variants might account for increased risk of nephritis or GI complications. However, data from the study of our cohort do not support a role of *IRF5* polymorphisms (assessed independently or combined conforming haplotypes) in the phenotype expression of IgAV, indicating that this gene does not represent a risk factor for the severity of the disease.

We previously assessed the potential association of *IRF5* polymorphisms in the susceptibility to and clinical expression of giant cell arteritis (33), another primary systemic vasculitis that, unlike IgAV, involves large- and medium-sized blood vessels. However, in keeping with the results found in IgAV, no association of *IRF5* polymorphisms with giant cell arteritis was detected in a well-characterised cohort of Caucasian patients in whom the diagnosis of giant cell arteritis was confirmed by a positive biopsy of the temporal artery (33). Similarly, no association between *IRF5* and Behçet's disease, a condition affecting blood vessels of all sizes and types, was disclosed (34, 35). In contrast, a potential influence of *IRF5* on the genetic predisposition to anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis was found (36-38). Consequently, and despite the lack of implication of *IRF5* in the pathogenesis of IgAV, further studies are required to determine the potential effect of this gene in those vasculitides no evaluated so far.

IRF5 is a direct transducer of virus-mediated signalling and plays a crucial role in the expression of type I IFN genes (39, 40). The lack of implication of *IRF5* in the pathogenesis of IgAV is in keeping with previous reports that failed to detect a significant association between genes related to the IFN pathway and IgAV (41-43), supporting the fact that this vasculitis may be an independent IFN signature disease. Accordingly, and based on the results derived from our study, the use of inhibitors of the IFN pathway may not have a beneficial effect in patients with IgAV and that drug development focusing on the blockade of other immunological pathways may be more effective for the treatment of IgAV. Since the pathogenic mechanism of IgAV is mainly due to IgA dominant immune deposits (1), suggesting that this vasculitis is predominantly a B-cell mediated disease, it could be plausible to think that drugs blocking the B-cell signalling pathway may have a beneficial effect in the treatment of IgAV.

In summary, our results do not support an influence of *IRF5* on the pathogenesis of IgAV.

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