Lack of Association Between IRF5 Gene Polymorphisms and Biopsy-proven Giant Cell Arteritis

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ABSTRACT. ***Objective.*** Interferon (IFN) regulatory factors (IRF) are transcriptional mediators of IFN-induced signaling pathways and are involved in immune response. We have analyzed for the first time the association of 2 IRF5 gene variants in the susceptibility to giant cell arteritis (GCA).

Methods. Two hundred twenty patients with biopsy-proven GCA and 520 matched controls were assessed. DNA from patients and controls was obtained from peripheral blood. Samples were genotyped for the IRF5 rs2004640 and for the IRF5 CGGGG insertion/deletion polymorphism using a predesigned TaqMan allele discrimination assay and by polymerase chain reaction amplification, followed by an ABI3100 sequencer, respectively.

Results. A genotyping rate of 96% was achieved in this series of GCA patients. No significant differences were found in the genotype distribution between GCA patients and controls for both IRF5 gene variants. In this regard, similar genotype frequencies were found in GCA patients and controls. No significant differences were observed when GCA patients were stratified according to the presence of specific clinical features of the disease such as polymyalgia rheumatica or severe ischemic complications.

Conclusion. Our results showed no association of IRF5 rs2004640 and CGGGG insertion/deletion polymorphisms in the susceptibility to and clinical expression of GCA. (First Release Nov 15 2009; J Rheumatol 2010;37:136–40; doi:10.3899/jrheum.090744)

Key Indexing Terms:
GIANT CELL ARTERITIS DISEASE SUSCEPTIBILITY IRF5
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Giant cell arteritis (GCA), the most common systemic vasculitis in the elderly in Western countries[1], is a granulomatous vasculitis of large and medium-size blood vessels characterized by involvement of the aorta and especially its cranial branches[1]. GCA is an antigen-driven disease with local T cell and macrophage activation in the vessel wall, with an important role of proinflammatory cytokines[2]. Activated T cells experience clonal expansion and are stimulated to produce interferon-γ (IFN-γ). This leads to the differentiation and migration of macrophages and the formation of giant cells. IFN-γ specifically seems to play a pivotal role in the pathogenesis of GCA[2], and in the clinical expression of this vasculitis[3]. High transcription of IFN-γ messenger RNA was associated with the formation of giant cells and with the evidence of cranial ischemic symptoms in GCA patients[3]. IFN-γ may dictate the functional properties of other cell populations in the vascular infiltrates and guide the response-to-injury reaction of the artery[3].

GCA is a complex polygenic disease and a number of gene polymorphisms have been reported to be implicated in both disease susceptibility and the presence of specific clinical patterns of this vasculitis[4]. A cytosine-adenine repeat functional polymorphism in the first intron of the IFN-γ gene was associated with some clinical differences between biopsy-proven GCA and isolated polymyalgia rheumatica (PMR)[5]. This was also the case for specific clinical manifestations of GCA such as visual ischemic complications. An association was found between a 126-base pair allele

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(high IFN-γ production) and GCA patients with visual ischemic manifestations, and the inverse correlation with the 128-base pair allele (low IFN-γ producer)[5].

IFN regulatory factors (IRF) are transcriptional mediators of virus and IFN-induced signaling pathways and have been shown to be involved in antiviral defense, immune response, and cell growth regulation[6]. Among the 9 identified members of the IRF family (IRF1 to IRF9), 3 IRF (IRF3, IRF5, and IRF7) were found to function as direct transducers of virus-mediated signaling and play a crucial role in the expression of type I IFN genes[7] as well as in the chemokine gene expression. Recent findings have demonstrated that the IRF5 gene is an important genetic risk factor for the most common chronic autoimmune rheumatic diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA)[8-10].

We investigated whether the IRF5 gene is associated with susceptibility to GCA and the clinical spectrum of this vasculitis. To test this hypothesis we assessed the 5-UTR mutation represented by single-nucleotide polymorphism (SNP) rs2004640, located in the intron-exon border of exon 1B of the IRF5 gene in the human chromosome 7q32[11], which has been the most actively investigated IRF5 genetic variant in RA[10]. We also tested whether a structural 5-bp CGGGG insertion/deletion polymorphism, located in the promoter region of the IRF5 gene[9], might be associated with either susceptibility to or severity of GCA.

MATERIALS AND METHODS

Patients. A total of 220 patients diagnosed with biopsy-proven GCA between 1991 and 2007 were initially included in this study. Most of them (n = 128) were diagnosed in the Division of Rheumatology of the Hospital Xeral-Calde (Lugo, Spain). The remaining patients were diagnosed in 2 centers in Madrid (Hospital Clínico San Carlos and Hospital de la Princesa; n = 82) and Granada (Hospital Clínico San Cecílio; n = 10). A control population (n = 520) from the corresponding cities matched by age, sex, and ethnicity with GCA patients was also studied.

All GCA patients had a positive temporal artery biopsy showing disruption of the internal elastic laminae with infiltration of mononuclear cells into the arterial wall with or without giant cells[12].

Severe ischemic complications, mainly strokes in the vertebrobasilar region, may occur after the onset of corticosteroid therapy. In this regard, strokes have been observed within the first month after GCA diagnosis[13] and visual ischemic events have also been reported to occur within the first 48–72 hours after the onset of corticosteroid therapy[14]. However, severe ischemic complications related to the disease are uncommon in corticosteroid-treated patients for at least 1 month. Because of this, to encompass the whole spectrum of clinical manifestations directly attributed to GCA, we assessed all the clinical manifestations that occurred in the time from the onset of GCA symptoms to 1 month after the onset of corticosteroid therapy.

GCA patients were considered to have PMR manifestations if they had severe bilateral ache and pain involving the neck, the shoulder, and/or the pelvic girdle, associated with morning stiffness[15]. Patients were considered to have visual ischemic complications in the context of GCA if they experienced at least 1 of the following ocular manifestations: transient visual loss including amaurosis fugax, permanent visual loss, or diplopia[16]. Severe ischemic manifestations were considered to be present if GCA patients experienced at least 1 of the following complications: visual ischemic complications, strokes and/or transient ischemic attacks, jaw claudication, or large-artery stenosis of the extremities that caused signs of occlusive manifestations[17].

There were no significant differences in the demographic and clinical features between GCA patients from Lugo and those from Madrid or Granada (data not shown).

Patients and controls were included in this study after providing written informed consent. Ethical committee approval was obtained.

IRF5 gene genotyping. DNA was obtained from peripheral blood mononuclear cells, using standard methods. The genotyping of the IRF5 G/T (rs2004640) polymorphisms was performed using a predesigned TaqMan SNP genotyping assay (Applied Biosystems, Foster City, CA, USA). Allele-specific probes were labeled with the fluorescent dyes VIC and FAM. Polymerase chain reaction (PCR) was carried out in a total reaction volume of 5 μl, containing 50 ng genomic DNA as template, 2.5 μl of TaqMan genotyping master mix, 0.25 μl of 20× assay mix, and ddH_2O up to 5 μl of final volume. The amplification protocol used was the following: initial denaturation at 95˚C for 10 min followed by 40 cycles of denaturation at 92˚C for 15 s, and annealing/extension at 60˚C for 1 min. Post-PCR, the genotype of each sample was attributed automatically by measuring the allelic-specific fluorescence on the ABI Prism 7900 sequence detection system using SDS 2.3 software for allelic discrimination (Applied Biosystems).

To determine the IRF5 5-bp indel (CGGGG indel), genotyping was performed after amplification by a fluorescent PCR primer, and the amplified fragments were analyzed using an ABI-3100 sequencer (Applied Biosystems). In all GCA patients and controls the CGGGG indel was amplified as a 100/105-bp PCR fragment. The PCR conditions consisted of an initial denaturation step at 95˚C for 5 min, 35 cycles of incubation at 95˚C for 30 s, 68˚C for 30 s and 72˚C for 30 s, with a final extension at 72˚C for 7 min. The amplified products were monitored by electrophoresis on 2% agarose gel containing ethidium bromide. Duplicate samples and negative controls were included to check the accuracy of genotyping.

Statistical analysis. We used the chi-squared test for assessment of Hardy-Weinberg equilibrium. Genotype and allele frequencies were also analyzed using the chi-squared test. OR and 95% confidence intervals (CI) were calculated according to Woolf's method using the Statcalc program (Epi Info 2002, Centers for Disease Control and Prevention, Atlanta, GA, USA). P values less than 0.05 were considered statistically significant.

Pairwise linkage disequilibrium measures were investigated, and haplotypes were constructed using the expectation- maximization algorithm implemented in the Unphased software package. The power of the study to detect an effect of a polymorphism on disease susceptibility was estimated using Quanto version 0.5 software (Department of Preventive Medicine, University of Southern California, Los Angeles, CA, USA).

RESULTS

Two hundred twenty patients with biopsy-proven GCA were enrolled. Most were women (n = 150; median age at disease diagnosis 74 yrs; range 52–93 yrs). From the onset of GCA symptoms to 1 month after the onset of corticosteroid therapy, 173 (78.6%) had headache, 103 (46.8%) experienced PMR manifestations, 88 (40.0%) jaw claudication, and 54 (24.5%) visual ischemic manifestations. In addition, 23 (10.4%) experienced irreversible vision loss, 11 (5.0%) had strokes, and 119 (54.1%) fulfilled the definitions for severe ischemic manifestations. As expected in a disease associated with high inflammatory response[16], most patients (n = 216; 98.2%) had an erythrocyte sedimentation rate > 40 mm/hour.

Influence of IRF5 variants in susceptibility to GCA. A geno-

typing rate of 96% was achieved in this series of GCA patients. No evidence of departure from Hardy-Weinberg equilibrium was observed in controls. The case:control ratio achieved was 1:2.5. The estimated power of this study for an estimated OR between 1.5 and 2.0 was 59%–95%, for a type I error rate of 0.05, dominant inheritance mode, and 0.0001% of population risk.

No significant differences in the genotype and allele frequencies on the IRF5 variants were observed when GCA patients from Lugo were compared with those from Madrid or Granada. Moreover, the allele and genotype distribution of the IRF5 variants was similar in controls from the 3 different regions (data not shown).

Table 1 shows the genotype and allele frequencies of the rs2004640 and insertion/deletion polymorphisms of IRF5 gene in GCA patients and controls. No significant differences in the genotype distribution between GCA patients and controls for the 2 IRF5 gene variants were observed. In this regard, a similar genotype frequency was found (Table 1).

In addition to the analyses based on a single variant, we performed haplotype estimations. Nevertheless, these IRF5 polymorphisms did not form haplotype blocks according to the method of Gabriel, *et al*[18]. Analysis of linkage disequilibrium showed a low degree of linkage disequilibrium between both IRF5 gene variants in the study population ($r^2 = 0.44$).

Influence of IRF5 gene variants in the clinical spectrum of GCA. To determine whether polymorphisms of the IRF5 gene might influence the clinical spectrum and severity of the GCA, we stratified GCA patients according to the presence/absence of PMR, visual ischemic manifestations, and severe ischemic complications of this vasculitis. However, as shown in Table 2, no significant differences for the IRF5 rs2004640 and IRF5 insertion/deletion gene variants were found.

The genotypic distribution shown in patients with or without severe ischemic complications did not differ when we excluded from this category the patients who presented only jaw claudication but not other severe ischemic complications [IRF5 rs2004640 T allele frequency 54.5% in this subgroup of GCA patients with severe ischemic complications excluding jaw claudication vs 55.0% in GCA patients without severe ischemic complications (p = 0.89, OR 0.97, 95% CI 0.66–1.43); IRF5 insertion allele frequency 57.7% in GCA patients with severe ischemic complications excluding jaw claudication vs 50.0% in GCA patients without severe ischemic complications (p = 0.11, OR 1.36, 95% CI 0.93–1.99)].

DISCUSSION

Our study constitutes the first attempt to establish the potential influence of 2 functional polymorphisms of the IRF5 gene in the susceptibility and phenotypic expression of biopsy-proven GCA. However, our data show no association between the rs2004640 and the insertion/deletion variants of the IRF5 gene with disease susceptibility or with specific features of GCA.

There is now a growing consensus among investigators on the possibility that a variety of inflammatory and autoimmune diseases might share a common genetic background. Besides regulating the IFN system, the IRF family plays an important role as regulator of the activation of immune cells[10]. In addition, IRF5 activates the transcription of proinflammatory cytokine genes, such as tumor necrosis factor, interleukin 6, and interleukin 12p40, presumably in cooperation with nuclear factor-κB[6,7].

It is known that the differential expression of IRF5 target genes conferred by IRF5 genotype may modify the immune response[10]. Several studies have emphasized the association of the IRF5 gene variants with autoimmune diseases such as SLE and RA, which are considered the prototypes of common inflammatory autoimmune rheumatic diseases[8-10].

Table 1. Genotype and allele frequencies of the rs2004640 and the insertion/deletion 5-bp CGGGG of IRF5 gene polymorphisms in GCA patients and controls.

	GCA, n = 211 (%)	Controls, n = 520 (%)	p	OR (95% CI)
IRF5 rs2004640				
GG	42 (19.9)	108 (20.8)	—	1 (reference)
GT	107 (50.7)	258 (49.6)	0.76	1.07 (0.69–1.66)
TT	62 (29.4)	154 (29.6)	0.88	1.04 (0.64–1.69)
G	191 (45.3)	474 (45.6)	—	—
T	231 (54.7)	566 (54.4)	0.91	1.01 (0.80–1.28)
IRF5* Promoter indel				
3/3	40 (19.0)	122 (23.5)	—	1 (reference)
4/3	117 (55.5)	278 (53.5)	0.24	1.28 (0.83–1.99)
4/4	54 (25.6)	120 (23.1)	0.19	1.37 (0.83–2.28)
3	197 (46.7)	522 (50.2)	—	—
4	225 (53.3)	518 (49.8)	0.22	1.15 (0.91–1.45)

* The alleles for the promoter indel are 3 or 4 CGGGG units.

Table 2. Association between the rs2004640 or insertion/deletion 5-bp CGGGG IRF5 genotypes and typical disease features in GCA patients.

	With, n (%)	Without, n (%)	p	OR (95% CI)
IRF5 rs2004640				
PMR				
GG	22 (22.0)	20 (18.0)	—	1 (reference)
GT	47 (47.0)	60 (54.1)	0.35	0.71 (0.33–1.55)
TT	31 (31.0)	31 (27.9)	0.81	0.91 (0.39–2.14)
G	91 (45.5)	100 (45.0)	—	—
T	109 (54.5)	122 (55.0)	0.92	0.98 (0.66–1.47)
Visual manifestations				
GG	13 (25.5)	29 (18.1)	—	1 (reference)
GT	22 (43.1)	85 (53.1)	0.17	0.58 (0.24–1.39)
TT	16 (31.4)	46 (28.8)	0.56	0.78 (0.30–2.02)
G	48 (47.1)	143 (44.7)	—	—
T	54 (52.9)	177 (55.3)	0.67	(0.91 (0.57–1.46)
Severe ischemic manifestations				
GG	22 (19.3)	20 (20.6)	—	1 (reference)
GT	59 (51.8)	48 (49.5)	0.76	1.12 (0.51–2.43)
TT	33 (28.9)	29 (29.9)	0.93	1.03 (0.44–2.44)
G	103 (45.2)	88 (45.4)	—	—
T	125 (54.8)	106 (54.6)	0.96	1.01 (0.67–1.51)
IRF5* promoter indel				
PMR				
3/3	20 (20.2)	20 (17.9)	—	1 (reference)
4/3	52 (52.5)	65 (58.0)	0.54	0.80 (0.37–1.74)
4/4	27 (27.3)	27 (24.1)	1.00	1.00 (0.41–2.46)
3	92 (46.5)	105 (46.9)	—	—
4	106 (53.5)	119 (53.1)	0.93	1.02 (0.68–1.52)
Visual manifestations				
3/3	9 (17.3)	31 (19.5)	—	1 (reference)
4/3	27 (51.9)	90 (56.6)	0.94	1.03 (0.41–2.67)
4/4	16 (30.8)	38 (23.9)	0.44	1.45 (0.51–4.15)
3	45 (43.3)	152 (47.8)	—	—
4	59 (56.7)	166 (52.2)	0.42	1.20 (0.75–1.92)
Severe ischemic manifestations				
3/3	18 (15.8)	22 (22.7)	—	1 (reference)
4/3	64 (56.1)	53 (54.6)	0.29	1.48 (0.68–3.23)
4/4	32 (28.1)	22 (22.7)	0.17	1.78 (0.72–4.42)
3	100 (43.9)	97 (50.0)	—	—
4	128 (56.1)	97 (50.0)	0.20	1.28 (0.86–1.92)

* The alleles for the promoter indel are 3 or 4 CGGGG units. PMR: polymyalgia rheumatica.

In assessing a metaanalysis on the potential association of the IRF5 rs2004640 within the promoter region of IRF5 gene with RA, Han, *et al* emphasized a protective effect of the allele G of this SNP in the susceptibility to RA[10]. Similarly to RA, an association with HLA-DRB1*04 alleles was observed in patients with GCA[4]. However, the immune-mediated mechanisms characterized by granulomatous infiltrates leading to vasculitic damage in GCA are different from those observed in RA[2,3]. This may explain the lack of association of the IRF5 rs2004640 with GCA.

As observed for the IRF5 rs2004640 SNP, the insertion/deletion polymorphism located in the promoter region of the IRF5 gene, associated with susceptibility to typical autoimmune rheumatic diseases like SLE[9], was not found to play a role in either susceptibility to or specific features of GCA.

The reasons for these negative associations are unknown. However, the lack of association of these IRF5 gene variants with susceptibility to GCA is in keeping with previous reports that failed to observe a significant association between disease susceptibility and other genes involved in the IFN pathways[5,19,20]. Nevertheless, further investigation in other populations is needed to fully exclude a role of these 2 IRF5 gene variants in susceptibility to GCA. Moreover, we cannot exclude that other polymorphisms located within the IRF5 locus might account for susceptibility to GCA.

Our results do not indicate a major contribution of the IRF5 rs2004640 and the IRF5 insertion/deletion polymor-

phisms in the susceptibility to or clinical manifestations of GCA.

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