# Lack of Association Between Intercellular Adhesion Molecule-1 Gene Polymorphisms and Giant Cell Arteritis

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*ABSTRACT.* ***Objective.*** Studies have shown an association between HLA-DRB1*04 and giant cell arteritis (GCA). Intercellular adhesion molecule-1 (ICAM-1) gene polymorphisms were reported to contribute susceptibility to GCA in Italian patients where susceptibility to GCA is not associated with HLA-DRB1*04 alleles. ICAM-1 is also highly expressed within inflammatory infiltrates of the blood vessels of GCA patients. To investigate the clinical implications of ICAM-1 polymorphisms in GCA, we examined their potential association and influence in the development of visual ischemic complications in a series of patients with GCA from Northwest Spain where GCA susceptibility is associated with HLA-DRB1*04.

***Methods***. Fifty-eight biopsy proven GCA and 129 ethnically matched controls were studied. Patients and controls were genotyped for ICAM-1 polymorphism at codons 241 and 469 by PCR-RFLP.

***Results***. The distribution of the alleles and genotypes for each ICAM-1 polymorphism did not show significant differences between GCA patients and controls. Although visual manifestations were significantly more likely to occur in men than women (OR 5.2, p = 0.018), allele and genotype frequencies of ICAM-1 polymorphisms in patients with GCA were not associated with development of visual complications or anemia. Visual complications in GCA were primarily associated with carriage of an HLA-DRB1*04 allele. No evidence was found for interaction between HLA-DRB1*04 and ICAM-1 polymorphism.

***Conclusion***. ICAM-1 polymorphisms are not genetic risk factors for the susceptibility and severity of GCA in Northwest Spain. (J Rheumatol 2001;28:1600–4)

*Key Indexing Terms:*
GIANT CELL (TEMPORAL) ARTERITIS INTERCELLULAR ADHESION MOLECULE-1
DISEASE SUSCEPTIBILITY HLA-DRB1 VISUAL COMPLICATIONS

Giant cell arteritis (GCA; temporal arteritis) constitutes the most frequent vasculitic syndrome in European and North American countries[1,2]. It involves large and middle size blood vessels with a predisposition to the cranial arteries in people generally over 50 years of age[1-3]. An association between GCA and genes that lie within the HLA-class II region has been reported[4] and most studies have shown an association between HLA-DRB1*04 and GCA[4-8]. Genetic polymorphisms in endothelial cell adhesion molecules have also been considered to be important candidate susceptibility factors to multifactorial diseases that have an inflammatory component. The intercellular adhesion molecule (ICAM-1) is a member of the immunoglobulin superfamily and plays an important role in endothelial cell-leukocyte interactions during inflammation[9]. Expression of ICAM-1 on endothelium is induced by inflammatory mediators that include lipopolysaccharide and cytokines such as interleukin 1, tumor necrosis factor-α, and interferon-γ.

In temporal artery biopsies from GCA patients, ICAM-1 is highly expressed in the adventitial microvessels and neovessels within inflammatory infiltrates[10], and changes in concentrations of circulating soluble ICAM-1 have been correlated with disease activity in GCA[11]. Two coding region polymorphisms have been identified for the ICAM-1: Gly (G) or Arg (R) at codon 241 (exon 4) and Lys (K) or Glu (E) at codon 469 (exon 6)[12]. Salvarani, *et al* have described a higher frequency of the allele R at codon 241 of ICAM-1 in patients with polymyalgia rheumatica (PMR) and GCA[13]. These authors reported an association between polymorphism at codon 241 and an increased risk of relapses in PMR. However, no information about the possible risk of severe ischemic complications in GCA was

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shown. Further, GCA is not associated with HLA-DRB1*04 in this particular region of Northern Italy[14]. As blindness due to ischemic complications continues to be the main matter of concern for clinicians who see elderly patients with GCA, the search for markers that may predict the risk of visual ischemic complications is an important issue. Moreover, an inverse correlation between a strong inflammatory response, defined as lower concentration of hemoglobin, and a low risk of developing cranial ischemic complications of GCA has recently been reported[15,16]. To investigate the role of ICAM-1 polymorphisms in GCA, we examined a series of unselected biopsy proven patients from the Lugo region in Northwest Spain, where GCA susceptibility is associated with HLA-DRB1*04[8].

## MATERIALS AND METHODS

The study group comprised patients diagnosed with biopsy proven GCA (n = 58) in the Department of Medicine of Hospital Xeral-Calde and ethnically matched controls (n = 129) from the area surrounding Lugo, in Galicia, Spain. The mean age ± standard deviation of the GCA patients was 73.7 ± 6.7 years, while that of controls was 57.6 ± 17.1 years. Hospital Xeral-Calde is the only referral center for a mixed urban and rural population of almost 250,000 people living in the Lugo region of Northwest Spain. The main characteristics of the Lugo population have been reported[17,18]. Briefly, the population is relatively static, has its own regional language, and patients are considered to be of Celtic descent[8].

Patients were included in the study if they had a positive temporal artery biopsy showing infiltration of mononuclear cells into the arterial wall with or without giant cells. Visual ischemic complications were considered to be present if patients had at least one of the following: (1) permanent visual loss (partial or complete permanent visual loss related to GCA despite any possible improvement related to corticosteroid therapy), (2) amaurosis fugax (transient visual loss that was followed by complete recovery or normal vision), or (3) diplopia (related to palsy of extrinsic ocular muscles). Patients with biopsy proven GCA were considered to have an associated diagnosis of PMR if they also had marked aching and stiffness bilaterally without other apparent cause in at least 2 of 3 regions: neck, shoulder girdle, and pelvic girdle[17,18]. As reported[15], anemia in this elderly population was defined by hemoglobin values < 11 g/dl.

*Molecular analysis of ICAM-1*. The first amino acid polymorphism consisted of a substitution of arginine (R) for glycine (G) at codon 241. This bi-allelic polymorphism was examined as follows: we designed a novel polymerase chain reaction (PCR) assay to detect the single nucleotide polymorphism. The single base change G to A at codon 241 does not introduce or abolish a restriction site. To overcome this we mutated the forward primer by one base pair (G or T) to introduce the restriction site for the enzyme *Bsr*GI.

Forward 5′ CCG TGG TCT GTT CCC TG**T** AC3′

Reverse 5′ GAA GGA GTC GTT GCC ATA GG 3′

*Bsr*GI digested the PCR product only when the mutant A allele was present, yielding DNA fragments of 90 and 20 base pairs.

A total of 100 ng genomic DNA was amplified in a 25 $\mu$l PCR reaction containing 1 × $NH_4$ buffer (Bioline, London, UK), 2.5 mM $MgCl_2$, 0.2 mM dNTPs (Bioline), 5 pmol of each primer, 0.5 U Taq polymerase (Bioline), and 1 mM Betaine (Sigma, Poole, UK). The DNA was denatured at 95°C for 2 min followed by 35 cycles of: 95°C for 45 s, 50°C for 45 s, 72°C for 45 s. The final extension was at 72°C for 2 min. The presence of product (110 base pairs) was verified on a 2% agarose gel stained with ethidium bromide. PCR products were digested with *Bsr*GI in a 15 $\mu$l final volume. This contained 7 $\mu$l of PCR product, 1 × NE buffer, 1 × bovine serum albumin, and 5 U *Bsr*GI. The digest was incubated overnight at 37°C and the products of the digest were then visualized on a 3% agarose gel stained with ethidium bromide.

The second amino acid polymorphism consisted of a substitution of lysine (K) for glutamic acid (E) at codon 469. For K/E 469 polymorphism analysis we used the following primers for amplification of the region:

Forward 5′-AGG ATG GCA CTT TCC CAC T-3′

Reverse 5′-GGC TCA CTC ACA GAG CAC AT-3′

The PCR was carried out in a volume of 25 $\mu$l containing 100 ng of genomic DNA, 10 × KCl buffer (Bioline), 3.5 mM $MgCl_2$, 0.2 mM dNTPs (Bioline), 5 pmol of each primer and 1 unit of Taq DNA polymerase (Bioline), and 4 mM Betaine (Sigma). The DNA was denatured at 95°C for 5 min, and temperature cycling was set at 95°C for 45 s, 56°C for 45 s, and 72°C for 45 s, followed by a final extension at 72°C for 2 min. Analysis of the PCR product was performed by enzyme digestion using *Bsr*UI (New England Biolab, Hitchin, UK), which cuts product from the E469 allele and yields 2 fragments of 106 bp and 34 bp for homozygous EE allele but does not cut the K469 and yields one fragment of 140 bp for homozygous KK allele. The digestion was incubated overnight at 37°C and the products were then visualized on a 3% agarose gel stained with ethidium bromide.

*HLA typing*. DNA was extracted from anticoagulated blood collected in EDTA using a phenol-chloroform extraction method. HLA-DRB1 phenotype data from most patients in in this study have been described[8,16,19]. They were determined using a semiautomated commercial reverse dot blot method, INNO-LiPA (Abbott Laboratories, Maidenhead, UK), following manufacturer's instructions. Reaction patterns were interpreted using INNO-LiPA software. HLA-DR4 subtypes were identified using either single strand conformational polymorphism following amplification with specific primers or the INNO-LiPA technology[8].

*Statistical analysis*. The strength of association between GCA and alleles or genotypes of ICAM-1 was estimated using odds ratios (OR) and 95% confidence intervals (CI). Levels of significance were determined using contingency tables by either chi-square or Fisher exact analysis. The same methods were used to examine the strength of association between GCA subgroups (with visual manifestations or anemia) and ICAM-1 polymorphisms. Logistic regression analyses were also used to correct for age and sex. All analyses were carried out using the Number Cruncher Statistical Package for Windows (NCSS v6.0.4) or the PEPI software package (v2.0) for epidemiologic analysis.

## RESULTS

*Clinical characteristics of patients with GCA*. All 58 GCA patients included in this study had a positive temporal artery biopsy. Twenty-seven of the 58 patients also had PMR. Fourteen had ischemic visual complications and 20 presented at the time of diagnosis with hemoglobin values < 11 g/dl.

*Allele and genotype frequencies of ICAM-1 polymorphisms at codons 241 and 469*. The frequencies of alleles and genotypes for each ICAM-1 polymorphism in the whole group of patients with GCA and in GCA with or without associated PMR were compared to those of controls. No significant differences in frequency were found between the different disease groups and controls (Table 1).

*Patients with visual manifestations*. The distribution of alleles and genotypes for each ICAM-1 polymorphism in GCA patients with visual manifestations was compared to that of GCA patients without visual complications. Again, no significant differences were found (Table 2). Of note, visual manifestations were significantly more likely to occur

*Table 1*. Allele and genotype frequencies of ICAM-1 polymorphisms at codons 241 and 469 in Spanish controls and patients with GCA*.

| | Control | GCA+PMR– | GCA+PMR+ | All GCA |
|---|---|---|---|---|
| Codon 241 | (2N = 258) | (2N = 62) | (2N = 54) | (2N = 116) |
| Alleles | | | | |
| R | 8.1 | 9.8 | 11.1 | 10.3 |
| G | 91.9 | 90.2 | 88.9 | 89.7 |
| Genotypes | (N = 129) | (N = 31) | (N = 27) | (N = 58) |
| RR | 1.5 | 0.0 | 0.0 | 0.0 |
| GG | 85.3 | 80.6 | 77.8 | 79.3 |
| RG | 13.2 | 19.4 | 22.2 | 20.7 |
| Codon 469 | (2N = 234) | (2N = 60) | (2N = 54) | (2N = 114) |
| Alleles | | | | |
| K | 52.6 | 46.7 | 40.7 | 43.9 |
| E | 47.4 | 53.3 | 59.3 | 56.1 |
| Genotypes | (N = 117) | (N = 30) | (N = 27) | (N = 57) |
| KK | 23.9 | 16.7 | 11.1 | 14.0 |
| EE | 18.8 | 23.3 | 29.6 | 26.3 |
| KE | 57.3 | 60.0 | 59.3 | 59.6 |

*No significant differences were found.

*Table 2*. Allele and genotype frequencies of ICAM-1 polymorphisms at codons 241 and 469 in Spanish patients with visual manifestations.

| | Visual Manifestations | | | |
|---|---|---|---|---|
| | With | Without | OR (95% CI) | p |
| Codon 241 | n = 14 | n = 44 | | |
| Alleles | | | | |
| R | 7.1 | 11.4 | 0.6 (0.1–3.2) | 0.5 |
| G | 92.9 | 88.6 | 1.7 (0.3–11.8) | 0.5 |
| Genotypes | | | | |
| RR | 0.0 | 0.0 | — | — |
| GG | 85.7 | 77.3 | 1.7 (0.3–13.6) | 0.5 |
| RG | 14.3 | 22.7 | 0.6 (0.1–3.4) | 0.5 |
| Codon 469 | n = 13 | n = 44 | | |
| Alleles | | | | |
| K | 50.0 | 42.0 | 1.4 (0.5–3.6) | 0.5 |
| E | 50.0 | 58.0 | 0.7 (0.3–1.9) | 0.5 |
| Genotypes | | | | |
| KK | 15.4 | 13.6 | 1.2 (0.1–7.9) | 0.9 |
| EE | 15.4 | 29.5 | 0.4 (0.1–2.6) | 0.3 |
| KE | 69.2 | 56.8 | 1.7 (0.4–7.9) | 0.4 |

in men than women (OR 5.2, p = 0.018), after correction for age.

*Allele and genotype frequencies of ICAM-1 polymorphisms in GCA patients with anemia*. The distribution of alleles and genotypes for each ICAM-1 polymorphism in GCA patients with hemoglobin values < 11 g/dl was compared to that of GCA patients with hemoglobin values ≥ 11 g/dl. No significant differences were observed (Table 3). A weak negative association between anemia and visual manifestations (OR 0.2, p = 0.052) was found, possibly because the number of patients examined in this study was lower than in a previous report[16]. In addition, anemia was weakly associated with female patients (p = 0.051) after correction for age.

*Table 3*. Allele and genotype frequencies of ICAM-1 polymorphisms at codons 241 and 469 in Spanish GCA patients with anemia.

| | Anemia | | | |
|---|---|---|---|---|
| | With | Without | OR (95% CI) | p |
| Codon 241 | n = 20 | n = 38 | | |
| Alleles | | | | |
| R | 7.5 | 11.8 | 0.8 (0.2–3.7) | 0.8 |
| G | 92.5 | 88.2 | 1.7 (0.4–8.3) | 0.5 |
| Genotypes | | | | |
| RR | 0.0 | 0.0 | — | — |
| GG | 85.0 | 76.3 | 1.8 (0.4–9.6) | 0.4 |
| RG | 15.0 | 23.7 | 0.6 (0.1–2.8) | 0.4 |
| Codon 469 | n = 20 | n = 37 | | |
| Alleles | | | | |
| K | 42.5 | 44.6 | 0.9 (0.4–2.1) | 0.8 |
| E | 57.5 | 55.4 | 1.1 (0.5–2.6) | 0.8 |
| Genotypes | | | | |
| KK | 5.0 | 13.6 | 0.2 (0.01–2.1) | 0.2 |
| EE | 20.0 | 29.7 | 0.6 (0.1–2.5) | 0.4 |
| KE | 75.0 | 51.4 | 2.8 (0.8–11.3) | 0.08 |

*Ischemic visual complications in GCA*. Visual complications in GCA were primarily associated with carriage of an HLA-DRB1*04 allele. There was a significantly higher frequency of HLA-DRB1*04 in the patients who had visual manifestations compared to those that did not (10 of 25 vs 4 of 33; p = 0.01, OR 4.8, 95% CI 1.3–18.0). This was significant after correction for age and sex by logistic regression analysis (p = 0.03).

We investigated whether there was any evidence for interaction between HLA-DRB1*04 and ICAM-1 polymorphisms. In HLA-DRB1*04 positive patients, no significant differences in ICAM-1 allele or genotype frequencies were found between those with or without ischemic visual complications (data not shown). Further, there were no differences in ICAM-1 polymorphisms between HLA-DRB1*04 positive and negative patients with visual manifestations.

## DISCUSSION

ICAM-1 polymorphisms have been investigated in complex oligogenic diseases where diverse genetic and environmental factors are implicated in the development of an inflammatory response. In inflammatory bowel disease no significant differences between all patients and controls in both polymorphisms were found; however, when stratified by ANCA status, patients with ulcerative colitis who were antibody negative had a significantly increased frequency of allele R241 compared with antibody positive patients[20]. In patients with multiple sclerosis ICAM-1 also plays an important role in the cascade of adhesion events in the homing of inflammatory cells to the central nervous system. In these patients a significantly higher frequency of the exon 6 homozygote K469 genotype was found compared to controls[21] and it was independent of the effects attributed to

HLA-DR2 allele[21]. In renal transplant recipients allograft failure was associated with R at codon 241 and a more rapid failure of the allograft in the presence of E at codon 469 was observed[22].

ICAM-1 gene polymorphisms have also been implicated in the pathogenesis of some systemic vasculitides. For example, in Behçet's disease (BD), an association with ICAM-1 gene polymorphisms has recently been reported[23]. Verity, *et al* described a higher frequency of the ICAM-1 exon 6 E469 allele in patients compared to controls, and a decreased frequency of K469 homozygosity in patients with this vasculitis[23]. However, ICAM-1 polymorphisms were not identified to be risk factors for visual manifestations among patient with BD.

Our analysis of 58 biopsy proven patients with GCA from Northwest Spain indicated that ICAM-1 polymorphisms at codon 241 or codon 469 are not associated with a higher risk of GCA. These findings are in contrast to those of Salvarani, *et al*, who observed that the R allele at codon 241 was more common in GCA, with or without PMR, than in healthy controls. They also described that the association between HLA class II and ICAM-1 allele R241 was only maintained in HLA-DR1 negative and rheumatoid shared epitope negative patients. No such association was found in our Spanish patients. Although Salvarini, *et al* also found an association between ICAM-1 R241 and severity of isolated PMR (considered as an increased risk of relapses), no association between visual manifestations of GCA and ICAM-1 polymorphisms was observed in their series. Similarly, we found that ICAM-1 polymorphisms at codon 241 and 469 were not associated with a higher risk of visual complication, inflammatory response, or lower hemoglobin value.

Unlike patients from Northern Italy, biopsy proven GCA from Northwest Spain is associated with HLA-DRB1*04[8,16]. This is especially true in those cases with ischemic visual manifestations[16]. The absence of association between ICAM-1 gene polymorphisms and biopsy proven GCA in our unselected series of patients from Northwest Spain suggests that, at least for populations where GCA is associated with HLA-DRB1*04, ICAM-1 polymorphisms cannot be used as markers for disease incidence and severity. One possible criticism of our study would be that the age of the patients with GCA was greater than that of controls. It could be argued that the GCA patient population might be biased toward certain polymorphisms that are functionally relevant in the immune response. However, since we found no difference in the frequency of ICAM-1 polymorphisms between the GCA patients and controls it is unlikely that age had any influence on the frequency of these polymorphisms.

Although ICAM-1 polymorphisms may act as genetic risk factors for the development and severity of some inflammatory diseases in specific populations, this does not appear to be the case in HLA-DRB1*04 positive patients with GCA.

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