# Interleukin-6 Promoter Polymorphism at Position –174 in Giant Cell Arteritis

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*ABSTRACT.* ***Objective.*** To investigate potential associations between the -174 G/C interleukin-6 (IL-6) promoter polymorphism and susceptibility to and clinical features of giant cell arteritis (GCA), particularly in patients with or without polymyalgia rheumatica (PMR) and with or without ischemic complications.

***Methods.*** One hundred and twenty-six patients with biopsy-proven GCA who were residents in Reggio Emilia, Italy, and 112 population-based controls from the same geographic area were genotyped for IL-6 polymorphism at position -174 by molecular methods. Patients were divided in subgroups according to presence or absence of PMR and ischemic complications (visual loss, jaw claudication, cerebrovascular accidents, aortic arch syndrome).

***Results.*** Distribution of the G/C 174 genotype was similar in patients with GCA and controls. No significant associations with the IL-6 promoter polymorphism at position -174 were found when GCA patients with or without PMR or with or without ischemic complications were compared. Further, IL-6 genotypes did not significantly affect levels of C-reactive protein or other inflammatory markers at diagnosis.

***Conclusion.*** Our findings show that the 174 G/C promoter IL-6 polymorphism does not seem to be implicated in susceptibility to and clinical expression of GCA. (J Rheumatol 2005;32:2173–7)

*Key Indexing Terms:*
GIANT CELL ARTERITIS
INTERLEUKIN-6 POLYMORPHISM
POLYMYALGIA RHEUMATICA
ISCHEMIC COMPLICATIONS

An intense acute phase response characterizes the vast majority of patients with giant cell arteritis (GCA)[1,2]. Interleukin-6 (IL-6) is the chief stimulator of the production of most acute-phase proteins[3]. Increased production of IL-6 is typically found in patients with GCA, and corticosteroids (CS) rapidly reduce levels of circulating IL-6. IL-6 seems to be a sensitive indicator of disease activity in GCA and polymyalgia rheumatica (PMR)[4-9].

Some studies have shown that patients with GCA with a weaker inflammatory response have a higher risk of developing ischemic manifestations[10-14]. Specifically, Hernàndez-Rodriguez, *et al* found that IL-6 expression in temporal artery inflammatory infiltrates and circulating levels of IL-6 were significantly lower in patients with ischemic complications[15]. Therefore, patients with GCA with ischemic events appear to produce low levels of IL-6 and have a weaker systemic inflammatory reaction.

Recently, a biallelic polymorphism, localized at position -174 of the promoter region of the IL-6 gene, has been identified. This polymorphism has been reported as functionally important, since it appears to influence the transcription rate of the gene and the plasma concentrations of IL-6[16].

Our aim was to assess the role of this IL-6 polymorphism in susceptibility to and clinical expression of GCA in a population-based cohort of Italian patients.

## MATERIALS AND METHODS

*Study population*. We reviewed the computerized pathology laboratory's register, which contains information on all temporal artery biopsies performed in Reggio Emilia between 1986 and 2003. Positive specimens were reviewed by a pathologist, and 151 patients residing in the Reggio Emilia area were identified. Of these, 126 patients could be contacted, and these individuals were willing to participate in the present study.

Patients were diagnosed as having biopsy-proven GCA if the histological examination of the temporal artery biopsy (TAB) showed disruption of the internal elastic lamina with infiltration of mononuclear cells into the arterial wall with or without giant cells. TAB procedures in Reggio Emilia have been described[17,18]. TAB was routinely performed in all patients with clinical manifestations of GCA. Segments longer than 2 cm were generally obtained.

Clinical findings at diagnosis and during followup, erythrocyte sedimentation rate (ESR) at diagnosis, C-reactive protein (CRP) values at diagnosis, and initial prednisone dosage were evaluated through interviews and

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*Accepted for publication June 27, 2005.*

by reviewing medical records. Patients were divided in subgroups according to presence or absence of PMR (marked aching and stiffness bilaterally without other apparent cause in at least 2 of the 3 following regions: neck, shoulder girdle, or hip girdle) and ischemic complications (visual loss and/or jaw claudication and/or cerebrovascular accidents and/or aortic arch syndrome).

Controls were randomly recruited from lists of patients under the care of medical practitioners in the same public health service. Stratification by random number of the group by age and sex was used to approximately match controls with cases according to their age and sex distribution. At the end of this selection process, 112 controls were identified. Median age of controls was 69 years (range: 50-79 years); 27.8% of controls were men and 72.2% women.

All study subjects were white, of Italian descent, and had been resident in Italy for at least one generation. No ethnic differences were found between patients and controls. None of the study participants had a Jewish background.

The study was approved by the Ethics Committee of Reggio Emilia Hospital and informed consent was obtained from all patients or their relatives.

*DNA extraction and genotyping*. DNA was obtained from whole blood using phenol/chloroform method, according to standard procedures. We designed a new primer pair to amplify a 268 bp region of IL-6 promoter containing -174 G/C polymorphism (forward primer 5' TTC GTG CAT GAC TTC AGC TT 3' and reverse primer 5' ACT CAT GGG AAA ATC CCA CA 3'). Polymerase chain reaction (PCR) amplification was performed in a 25 ul reaction containing 100 uM of each dNTP, 20 pmol each primer, and 1 unit Taq polymerase[16]. Amplification profile was as follows: initial denaturation 95˚C for 2 min; 35 cycles of 94˚C for 30 s, 62˚C for 30 s, and 72˚C for 30 s; and final extension at 72˚C for 3 min.

We performed digestion of 10 $\mu$l PCR product using Nla III restriction endonuclease. This enzyme can reveal the presence of C or G nucleotide at -174 position after electrophoresis analysis of digested PCR products in 2% agarose gel stained with ethidium bromide (0.5 $\mu$g/ml).

*Statistical analysis*. Statistical analysis was done using SPSS statistical package (SPSS Inc., Chicago, IL, USA). Student's t test and Mann-Whitney test were computed to compare means for parametrically and non-parametrically distributed data, respectively. Frequencies of alleles and genotypes among the patients and controls were compared by chi-square test, with the values predicted by the assumption of Hardy-Weinberg equilibrium in the sample. Odds ratios (OR) were calculated together with their 95% confidence intervals (95% CI). Corrected p values (pcorr) were calculated by multiplying p by the number of alleles compared.

We performed power calculations for an unmatched case-control study and estimated relative risk using Power and Sample Size, version 2.1.31.

## RESULTS

Table 1 shows clinical and demographic characteristics of the 126 patients with GCA. Seventy-three patients had ischemic complications. Visual loss was present in 25 patients, jaw claudication in 61 patients, cerebrovascular accidents in 4 patients, and aortic arch syndrome in 4 patients.

Allele and genotype frequencies of the -174 G/C promoter polymorphism of IL-6 were not statistically different in GCA patients and controls as shown in Table 2. Distribution of the G/C 174 genotype in the GCA group and in the controls was compatible with Hardy-Weinberg distribution (chi-squared = 0.2, p = 0.9 in GCA patients; chi square = 0.06, p = 0.97 in controls). Allele C was marginally reduced in frequency in GCA patients; however the significance was lost after correction for the number of alleles tested (p = 0.04, pcorr = 0.08). Given the sample sizes (126 patients with GCA and 112 controls) and the allele frequencies of the polymorphism examined, we can exclude with 80% certainty a genetic relative risk of 0.70 at -174 G/C IL-6 promoter polymorphism.

Similarly, the distribution of genotype and carriage rate frequencies of the -174 G/C polymorphism did not differ significantly comparing patients with and without PMR (Table 3) and those with and without ischemic complications (data not shown).

Given the sample sizes (69 GCA cases without PMR and 57 GCA cases with PMR) and the allele frequencies of the polymorphism examined, we can exclude with 80% certainty a genetic relative risk of 0.64 at -174 G/C IL-6 promoter polymorphism.

Given the sample sizes (53 GCA cases without ischemic complications and 73 GCA cases with ischemic complications) and the allele frequencies of the polymorphism examined, we can exclude with 80% certainty a genetic relative risk of 1.9 at -174 G/C IL-6 promoter polymorphism.

More specifically, there was no association between the distribution of genotype and carriage rate frequencies, on one hand, and ocular and cerebrovascular ischemic events (28 patients), on the other (data not shown).

ESR and CRP values at diagnosis were significantly higher in patients without ocular and cerebrovascular ischemic events compared with those with (95 ± 30 vs 85 ± 28 mm/h, p = 0.05; and 10.5 ± 6.6 vs 6.6 ± 4.4 mg/dl, p = 0.02).

ESR, CRP, hemoglobin, and platelet values at diagnosis were stratified according to the carriage rate of the -174 G/C promoter polymorphism of IL-6. Again, no associations were found between any of the above markers and the genotype and carriage rate frequencies of the -174 G/C polymorphism (data not shown).

## DISCUSSION

A variety of diseases including Alzheimer's disease, cardiovascular disease, cancer, diabetes, osteoporosis, sepsis, and systemic-onset juvenile chronic arthritis[19-26] have been associated with -174 G/C promoter polymorphism of IL-6. In our study, we did not detect an association between -174 G/C promoter polymorphism of IL-6 and GCA. The lack of association between GCA and this IL-6 polymorphism is consistent with previous observations by Gonzalez-Gay, *et al*[27]. However, when patients with GCA were stratified according to the presence of PMR, they showed a significantly increased frequency of the CC genotype in GCA patients with PMR when compared with GCA patients without PMR. Interestingly, when GCA patients were stratified according to HLA-DRB1*04 status, the increased frequency of allele C in the entire group of GCA patients with PMR compared with patients with GCA without PMR appeared to

*Table 1*. Demographic and clinical features of the 126 patients with biopsy proven giant cell arteritis. Values expressed as percentages unless otherwise stated.

| | |
|---|---|
| Sex, male/female | 21.4/78.6 |
| Age at onset of disease, yrs, mean ± SD | 73 ± 7 |
| Headache | 82.5 |
| Abnormalities of temporal arteries* | 66.4 |
| Scalp tenderness | 44.7 |
| Jaw claudication | 48.4 |
| Visual manifestations | 29.4 |
| Visual loss | 19.8 |
| Ischemic complications** | 57.9 |
| Systemic symptoms and/or signs† | 80.2 |
| Polymyalgia rheumatica | 45.2 |
| Duration of therapy, mo, mean ± SD | 21 ± 15 |
| Duration of followup, mo, mean ± SD | 26 ± 21 |
| ESR at diagnosis, mm/h, mean ± SD | 97 ± 27 |
| CRP at diagnosis, mg/dl, mean ± SD‡ | 11 ± 6 |
| Hemoglobin at diagnosis, g/dl, mean ± SD | 11 ± 1 |
| Platelets, × $10^9$/l, mean ± SD | 397 ± 116 |

* Artery tenderness and/or decreased or absent temporal artery pulse. ** Ischemic complications: visual loss and/or jaw claudication and/or cerebrovascular accidents and/or aortic arch syndrome. † Fever, anorexia, and weight loss. ‡ CRP normal values < 0.5 mg/dl.

*Table 2*. Frequencies of alleles, genotypes, and carriage rates of IL-6 promoter polymorphism at position –174 in patients with GCA and controls.

| Variable | Controls n = 112 (%) | GCA n = 126 (%) | p | OR (95% CI) |
|---|---|---|---|---|
| Alleles | | | | |
| C | 83/224 (37.1) | 71/252 (28.2) | 0.04 (pcorr 0.08) | 0.7 (0.5–1.0) |
| G | 141/224 (62.9) | 181/252 (71.8) | | |
| Genotypes | | | | |
| CC | 16/112 (14.3) | 9/126 (7.1) | | |
| CG | 51/112 (45.5) | 53/126 (42.1) | NS | |
| GG | 45/112 (40.2) | 64/126 (50.8) | | |
| Carriage rate | | | | |
| CC + CG | 67/112 (59.8) | 62/126 (49.2) | NS | 0.7 (0.4–1.1) |
| GG | 45/112 (40.2) | 64/126 (50.8) | | |
| CG + GG | 96/112 (85.7) | 117/126 (92.6) | NS | 2.2 (0.9–5.1) |
| CC | 16/112 (14.3) | 9/126 (7.1) | | |

OR: odds ratio; CI: confidence interval; NS: not significant.

*Table 3*. Frequencies of alleles, genotypes, and carriage rates of IL-6 promoter polymorphism at position –174 in patients with GCA with and without PMR.

| Variable | With PMR n = 57 (%) | Without PMR n = 69 (%) | p | OR (95% CI) |
|---|---|---|---|---|
| Alleles | | | | |
| C | 32/114 (28.1) | 39/138 (28.3) | NS | 1.0 (0.6–1.7) |
| G | 82/114 (72.9) | 99/138 (71.7) | | |
| Genotypes | | | | |
| CC | 3/57 (5.3) | 6/69 (8.7) | | |
| CG | 26/57 (45.6) | 27/69 (39.1) | NS | |
| GG | 28/57 (49.1) | 36/69 (52.2) | | |
| Carriage rate | | | | |
| CC + CG | 29/57 (50.9) | 33/69 (47.8) | NS | 1.1 (0.6–2.3) |
| GG | 28/57 (49.1) | 36/69 (52.2) | | |
| CG + GG | 54/57 (94.7) | 63/69 (91.3) | NS | 1.7 (0.4–7.2) |
| CC | 3/57 (5.3) | 6/69 (8.7) | | |

be mainly due to the subgroup of HLA-DRB1*04 negative patients[27]. This association of the -174 IL-6 polymorphism with development of PMR in patients with biopsy-proven GCA but not in patients with isolated PMR from Northwest Spain can perhaps in part be explained by isolated PMR and PMR in the context of GCA having different genetic etiologies. Another possibility may be that in oligogenic conditions such as GCA, complex gene-gene interactions between HLA-DRB1 and IL-6 regulatory region polymorphism may contribute to disease expression.

In contrast, we were unable to find any differences in terms of IL-6 polymorphism between patients with GCA associated with PMR and those with isolated GCA. In a previous study we provided evidence that the 174 G/C promoter IL-6 polymorphism was not implicated in susceptibility to isolated PMR[28].

Our study and the study by Gonzalez-Gay, *et al*[27] are the only published investigations of the role of the 174 G/C promoter IL-6 polymorphism in patients with GCA and/or PMR. The study designs are similar in that both are population-based. Furthermore, the clinical spectrum of GCA in these 2 Southern European regions is similar[17]. Moreover, although regional differences in this polymorphism have been reported, with the -174 allele being more common in Northern than in Southern Europe[29], the genotypic distribution is similar in the Lugo and Reggio Emilia populations. At the same time, GCA susceptibility in Lugo and Reggio Emilia populations may be partially linked to different immunogenetic markers since GCA in Lugo[30], but not in Reggio Emilia[31], is associated with HLA-DRB1*04 allele. Similarly, different non-HLA alleles may be associated with GCA in these populations[32,33]. Thus allelic heterogeneity existing between these ethnic groups and possibly modulation by other genetic or environmental factors that vary between the populations studied may contribute to explain the discordant results of the 2 studies. However, the discrepancies observed might also be due to the different samples: our study included 126 GCA patients while Gonzalez-Gay, *et al* studied a mixture of GCA and PMR patients, with 62 patients having GCA with or without PMR. Sample size is a recognized crucial factor in genetic association studies. Therefore, in order to conclusively settle the question whether there is a significant association between 174 G/C promoter IL-6 polymorphism and GCA, further adequately-sized studies in various populations are required.

Although studies investigating the role of the -174 G/C promoter polymorphism in regulating plasma IL-6 concentrations *in vivo* have produced conflicting results[16,19–21,29,34,35], there is a growing body of evidence suggesting that the -174C allele is associated with higher circulating IL-6 levels. In particular, this allele was found to be associated with elevated circulating IL-6 levels in patients with abdominal aortic aneurysms[34]. In patients homozygous for the -174 C allele, plasma concentrations of IL-6 induced by coronary artery bypass grafting were significantly higher 6 hours after surgery[35]. Therefore, it may be possible that this polymorphism exerts its greatest effect on IL-6 production in an acute phase reaction. We previously reported an association between CC genotype and persistently elevated levels of IL-6 in Italian patients with isolated PMR[28]. These patients had a higher risk of developing relapses/recurrences. A significant effect of this genotype on IL-6 levels was also observed in the controls since CC homozygotes had higher IL-6 levels than the carriers of the allele G. Theoretically, a genetically modulated pattern of IL-6 production could also affect the risk of developing ischemic complications in patients with GCA. However, we have been unable to find any association between -174 G/C promoter polymorphism of IL-6 and ischemic manifestations in GCA.

Although serum levels of IL-6 in this cohort were not available, we evaluated acute phase markers at diagnosis stratified according to the carriage rate of the -174 G/C polymorphism of IL-6. IL-6 is the chief stimulator of the production of most acute-phase proteins, in particular CRP[3]. However, IL-6 genotypes did not significantly affect levels of CRP or other inflammatory markers at diagnosis.

In conclusion, our findings show that the 174 G/C promoter IL-6 polymorphism does not seem to be implicated in the susceptibility to or clinical expression of GCA. In particular, we did not observe a genetic influence of this polymorphism on the development of PMR features or of ischemic complications in GCA. However, due to the limited power of the study, multicenter collaborations to recruit an adequate number of patients are required in order to confirm our data.

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