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# –463 G/A myeloperoxidase promoter polymorphism in giant cell arteritis

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## ABSTRACT

**Objective:** To investigate potential associations between –463 G/A myeloperoxidase (MPO) promoter polymorphism and susceptibility to, and clinical features of giant cell arteritis (GCA).

**Methods:** A total of 156 patients with biopsy-proven GCA who were residents of Reggio Emilia, Italy, and 235 population-based controls from the same geographic area were genotyped for –463 G/A promoter polymorphism of the MPO gene by molecular methods. The patients were subgrouped according to the presence or absence of polymyalgia rheumatica and severe ischaemic complications (visual loss and/or cerebrovascular accidents).

**Results:** The distribution of the MPO-G/A genotype differed significantly between patients with GCA and the controls ( $p_{\text{corr}} = 0.003$ ). Allele G was significantly more frequent in patients with GCA than in the controls ( $p_{\text{corr}} = 0.0002$ , OR 2.0, 95% CI 1.4 to 2.9). Homozygosity for the G allele was significantly more frequent in patients with GCA than in controls ( $p_{\text{corr}} = 0.0002$ , OR 2.2, 95% CI 1.4 to 3.4). No significant associations were found when patients with GCA with and without polymyalgia rheumatica or with and without severe ischaemic complications were compared.

**Conclusions:** Our findings show that the –463 G/A promoter polymorphism of the MPO gene is associated with GCA susceptibility and support a role for MPO in the pathophysiology of GCA.

Giant cell arteritis (GCA) is a systemic vasculitis in which T cells and macrophages infiltrate the wall of medium-sized and large arteries.<sup>1</sup>

GCA is considered a T cell driven disease, in particular CD4+ T cells are thought to play a central role in inducing and maintaining the vasculitic process.<sup>1</sup> Tissue destruction in GCA largely depends on macrophage effector functions, with T cell derived cytokines controlling the activity/differentiation of such macrophages.<sup>1</sup>

Less is known about the role of early recruited phagocytes, such as monocytes and neutrophils. However, recently Foell *et al*<sup>2</sup> demonstrated that neutrophils and recently recruited monocytes may contribute to the inflammation of GCA by secretion of the proinflammatory S100 proteins S100A8, S100A9 and S100A12.

Myeloperoxidase (MPO) is a haem-containing peroxidase expressed and stored in neutrophils and monocytes.<sup>3</sup> MPO catalyses a reaction between hydrogen peroxide and chloride to generate hypochlorous acid, a potent oxidant that can cause vascular damage when released by activated cells at inflammatory sites. MPO also inactivates protease inhibitors and reduces nitric oxide (NO)

bioavailability.<sup>4</sup> Therefore MPO may play a central role in the initiation and propagation of acute and chronic vascular inflammatory diseases.

The promoter region of the MPO gene has a single G-to-A base substitution at position –463, which has been reported to be functionally important as it influences MPO expression.<sup>5–6</sup> High-expression GG genotype has been associated with an increased risk of Alzheimer's disease,<sup>7–8</sup> multiple sclerosis,<sup>9–10</sup> MPO-antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis,<sup>11</sup> while low-expression genotypes (AG and AA) have a protective role in coronary artery disease.<sup>12–14</sup> Therefore, genetically determined increased levels of MPO expression could provide a mechanism for promoting endothelial dysfunction and vessel wall damage.

The aim of this study was to examine the relationship between this MPO promoter polymorphism and the susceptibility to and clinical expression of GCA in a population-based cohort of Italian patients with biopsy-proven disease.

## PATIENTS AND METHODS

### Study population

We reviewed the computerised registry of the Pathology Laboratory at Arcispedale Santa Maria Nuova, which had stored the results of all temporal artery biopsies performed in Reggio Emilia, Italy, between 1986 and 2005. GCA-positive specimens were reviewed by a pathologist. A total of 184 patients with GCA residing in the Reggio Emilia area were identified. Their median age was 74 years (range 56–90 years). Of these, 156 patients could be contacted, all of whom were willing to participate in this study.

Patients were diagnosed as having biopsy-proven GCA if histological examination of the temporal artery biopsy specimen showed disruption of the internal elastic lamina, with infiltration of mononuclear cells into the arterial wall, with or without giant cells. Temporal artery biopsy procedures in Reggio Emilia have been described in detail elsewhere.<sup>15–16</sup> A temporal artery biopsy was routinely performed in all patients with clinical manifestations of GCA. Segments longer than 2 cm were generally obtained.

The clinical findings at diagnosis and during follow-up, the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values at diagnosis, as well as the initial prednisone dosage, were ascertained through interviews with the patients and by reviewing the patients' medical records. Patients were subgrouped according to the presence or absence of polymyalgia rheumatica

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(PMR) (marked aching and early morning stiffness bilaterally, without other apparent cause, in at least two of the three following regions: neck, shoulder girdle or hip girdle) and the presence or absence of severe ischaemic complications (vision loss and/or cerebrovascular accidents).

Severe ischaemic complications were attributed to GCA if they occurred within the time between the onset of GCA symptoms and 2 weeks after GCA diagnosis. Severe ischaemic complications developing later were considered GCA-related only when associated with at least one of the other GCA signs/symptoms and elevation of ESR and/or CRP.

Controls were randomly recruited from the lists of patients who were under the care of the medical practitioners of the same public health service. Control patients had no evidence of GCA and/or PMR. Stratification by the random-number method according to age and sex was used to approximately match the controls with the patients according to their age and sex distribution. At the end of this selection process, 235 control subjects were identified. The median age of the controls was 69 years (range 50–80 years).

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

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

### DNA extraction and genotyping

DNA was extracted from peripheral blood leucocytes using phenol/chloroform method, according to standard procedures. Polymorphisms were detected by using restriction fragment length polymorphism–polymerase chain reaction analysis as described by London *et al.*<sup>17</sup> A 350 bp DNA fragment was amplified using forward primer MPOF (5'-CGG TAT AGG CAC ACA ATG GTG AG) and reverse primer MPOR (5'-GCA ATG GTT CAA GCGATT CTT C).

Polymerase chain reaction amplification was performed in 25 µl reaction containing 100 µM of each dNTP, 20 pmol each primer, 1 unit Taq polymerase. 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, 72°C for 30 s
- ▶ final extension at 72°C for 3 min.

Polymerase chain reaction products were digested with the restriction enzyme *AclI*. This enzyme can reveal the presence of A or G nucleotide at –463 position. Electrophoresis analysis of digested polymerase chain reaction products were performed in 2% agarose gel stained with ethidium bromide (0.5 µg/ml) to show patterns for the three genotypes: 169, 120 and 61 bp fragments for the homozygous wild type (–463GG); 289, 169, 120 and 61 bp fragments for the heterozygous type (–463AG); and 289 and 61 bp fragments for the homozygous mutant type.

### 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. The frequencies of the alleles and genotypes among the case patients and control group were compared by  $\chi^2$  test. Odds ratios (OR) were calculated together with their 95% confidence

intervals (95% CI). Corrected p values ( $p_{\text{corr}}$ ) were calculated by multiplying p by the number of the alleles compared.

We performed power calculation for an unmatched case–control study and estimated relative risk using Power and Sample Size calculation version 2.1.31 software.

### RESULTS

Table 1 shows the clinical and demographic characteristics of the 156 patients with GCA. Permanent partial or total visual loss and/or cerebrovascular accidents were diagnosed in 34 patients. Anterior ischaemic optic neuropathy was seen in 24 patients, and central retinal artery occlusion in six patients. Four patients had a vertebrobasilar stroke. Giant cells were observed in the biopsy specimens in 107 patients (68.6%).

The allele and genotype frequencies of the –463GA MPO promoter polymorphism in patients with GCA and in the control group are shown in table 2. The distribution of the MPO-G/A genotype differed significantly between patients with GCA and the controls ( $p = 0.001$ ,  $p_{\text{corr}} = 0.003$ ). The distribution of the genotype in the MPO-G/A polymorphism indicated that the differences in allele distribution were related to a higher frequency of the GG genotype in patients with GCA as compared with the controls, whereas the AA genotype was less frequent in patients with GCA.

Allele G was significantly more frequent in patients with GCA than in the controls ( $p = 0.0001$ ,  $p_{\text{corr}} = 0.0002$ , OR 2.0, 95% CI 1.4 to 2.9). Homozygosity for the G allele was significantly more frequent in patients with GCA than in controls ( $p = 0.0001$ ,  $p_{\text{corr}} = 0.0002$ , OR 2.2, 95% CI 1.4 to 3.4).

Given the sample size (156 patients with GCA and 235 controls) and allele frequencies of the polymorphism examined, we can conclude at the level of 80% of statistical power that there is a genetic relative risk of 1.56 at –463 G/A MPO promoter polymorphism.

**Table 1** Demographic and clinical features of the 156 patients with biopsy proven giant cell arteritis\*

Males (%)/females (%)	31/156 (19.9)/125/156 (80.1)
Age at onset of disease, years, mean (SD)	74 (7)
Headache	125/156 (80.1%)
Abnormalities of temporal arteries†	104/155 (67.1%)
Scalp tenderness	61/153 (39.9%)
Jaw claudication	76/156 (48.7%)
Visual manifestations	46/156 (29.5%)
Visual loss	31/156 (19.9%)
Severe ischaemic complications‡	34/156 (21.8%)
Systemic symptoms and/or signs§	116/156 (74.4%)
Polymyalgia rheumatica	71/156 (45.5%)
Duration of therapy months, mean (SD)	19 (15)
Duration of follow-up months, mean (SD)	25 (19)
ESR at diagnosis mm/h, mean (SD)	90 (30)
CRP at diagnosis mg/dl, mean (SD)	9.2 (6.4)

\*Except where indicated otherwise, values are the number (%) of patients.

†Artery tenderness and/or decreased or absent temporal artery pulsation.

‡Severe ischaemic complications comprised visual loss and/or cerebrovascular accidents.

§Presence of at least one of the following: asthenia, anorexia, weight loss of at least 4 kg or fever.

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

**Table 2** Frequencies of alleles, genotypes and carriage rates of myeloperoxidase polymorphism in patients with GCA and controls\*

	Patients with GCA (156)	Controls (235)	p Value†	OR (95% CI)
Allele				
G	266/312 (85.3)	350/470 (74.5)		
A	46/312 (14.7)	120/470 (25.5)	0.0001	2.0 (1.4 to 2.9)
Genotypes				
G/G	112/156 (71.8)	126/235 (53.6)		
G/A	42/156 (26.9)	98/235 (41.7)	0.001	
A/A	2/156 (1.3)	11/235 (4.7)		
Carriage rate				
G/G	112/156 (71.8)	126/235 (53.6)		
A/A+G/A	44/156 (28.2)	109/235 (46.4)	0.0001	2.2 (1.4 to 3.4)
G/G+G/A	154/156 (98.7)	224/235 (95.3)	0.085	3.8 (0.8 to 17.3)
A/A	2/156 (1.3)	11/235 (4.7)		

\*Values are the number/total number examined (%).

†The corrected p values for each significant difference are 0.0002, 0.003 and 0.0002. GCA, giant cell arteritis.

As a number of studies have shown that the influence of MPO-G/A polymorphism could be gender-specific, we compared the influence of MPO genotype in GCA men and women. No influence of gender was observed (data not shown). We confirmed that in both GCA men and women GG genotype was significantly associated with GCA.

The association between the -463GA MPO polymorphism and the clinical features of GCA was evaluated by comparing the 71 patients with GCA who had PMR with the 85 patients who did not have PMR. Given the sample size (71 patients with PMR and 85 without) and allele frequencies of the polymorphism examined, we can conclude at the level of 80% of statistical power that there is a genetic relative risk of 1.19 at -463 G/A MPO promoter polymorphism.

We also compared the 34 patients with GCA who had severe ischaemic complication (visual loss and/or cerebrovascular accidents) with the 122 patients who did not have ischaemic complications. No significant associations were found (data not shown). Given the sample size (34 patients with severe ischaemic complications and 122 without) and allele frequencies of the polymorphism examined, we can conclude at the level of 80% of statistical power that there is a genetic relative risk of 1.78 at -463 G/A MPO promoter polymorphism.

No significant associations with -463GA MPO polymorphism were found comparing the 107 patients who had giant cells in the biopsy specimens with the 49 who did not (data not shown).

## DISCUSSION

Cellular immune responses involving dendritic cells, T lymphocytes and effector tissue macrophages are thought to result in vascular inflammatory injury in GCA. The contribution of phagocytes, such as monocytes and neutrophils to vessel wall damage in GCA has been poorly evaluated, although they are among the first cells to invade the inflammatory sites.<sup>1</sup>

In this regard, G n reau *et al*<sup>18</sup> detected elevated circulating plasma levels of neutrophil elastase in patients with active disease, although this enzyme was not detected at immunohistochemistry within the temporal artery wall.

By contrast, neutrophils have extensively been studied in ANCA-associated vasculitides where they play a central role in determining vascular damage.<sup>19 20</sup> However, Foell *et al*<sup>2</sup> recently demonstrated that early recruited monocytes expressing the S100A8/S100A9 complex, a member of the proinflammatory

S100 protein family (a marker of early phagocyte activation),<sup>21</sup> were abundant in the adventitia and media of affected arteries of patients with GCA, while neutrophils positive for both S100A8/S100A9 and S100A12 were found almost exclusively in and around the vasa vasorum.

The specific presence of neutrophils around vasa vasorum in GCA lesions has been confirmed by Esteban *et al*<sup>22</sup> by immunodetection of neutrophil elastase.

On the same line, S100A8/S100A9 and S100A12 serum concentrations were significantly higher in patient with GCA than in healthy controls, suggesting that they are secreted by activated phagocytes during the inflammatory process in GCA. The release of the S100 proteins at the vasa vasorum in the adventitia may be crucial for the initiation and perpetuation of inflammatory lesions in GCA by upregulating proinflammatory cytokines, inducing adhesion molecule expression on endothelial cells, and regulating transendothelial migration of phagocytes and leucocytes.<sup>21 23</sup>

Myeloperoxidase is a haem-containing peroxidase expressed and stored in neutrophils and monocytes and secreted upon cell activation.<sup>3</sup> The presence of activated neutrophils at sites of vascular inflammation in GCA<sup>3</sup> suggests that MPO may play a part in determining vascular damage, not only in ANCA-associated vasculitis, but also in GCA. Furthermore, also some macrophage subsets expressing MPO could contribute to vascular damage.<sup>24</sup> Emerging evidence suggests that enhanced MPO activity may be an important risk factor for vascular disease. MPO is expressed in human atherosclerotic plaques and displays potent pro-atherogenic properties by inducing foam cell formation, endothelial dysfunction and plaque rupture.<sup>25</sup> Neutrophils have been demonstrated to release MPO into the coronary circulation, leading to elevated MPO plasma levels in patients with unstable angina and acute myocardial infarction.<sup>26 27</sup> Given its proinflammatory properties, MPO may contribute directly to the damage to the arterial wall in GCA. For example, MPO has been shown to activate metalloproteinase and catalytically consume endothelium-derived NO by reducing its bioavailability and impairing its vasodilatory and anti-inflammatory functions.<sup>25</sup>

Metalloproteinases are expressed in tissue-infiltrating inflammatory cells in GCA and have been implicated in arterial wall injury via digestion of the elastic lamina.<sup>28</sup> Endothelial dysfunction evaluated by endothelium-dependent vasodilation occurs in patients with GCA at the time of diagnosis.<sup>29</sup> Significant differences in endothelial nitric oxide synthase haplotype frequencies between Spanish patients with GCA and controls support a potential role for these polymorphisms in the susceptibility to GCA.<sup>30</sup> In this regard, a recent study from our group showed that the Asp298 polymorphism of the endothelial nitric oxide synthase gene was associated with GCA, supporting the view that genetic factors may be involved in the risk of developing GCA.<sup>31</sup>

A functional promoter polymorphism has been identified in the promoter region of the MPO gene, consisting of a G to A substitution. The -463 G/A polymorphism is situated within an Alu-encoded hormone response element and determines a SP1 site in the G allele promoter, and an oestrogen receptor  $\alpha$  binding site in the A promoter. The GG genotype is associated with a two- to threefold higher expression of MPO messenger RNA and protein expression compared with GA/AA genotypes.<sup>5 6</sup> Individuals with the GA/AA genotypes have been identified as having a reduced risk for coronary artery disease.<sup>12 13</sup> Recently, Asselbergs *et al*<sup>14</sup> confirmed these results showing that subjects with homozygous G/G genotype have an



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increased risk of developing cardiovascular events. The GG genotype was also found to be associated with an increased risk of MPO-ANCA-associated vasculitis in women, but not in men.<sup>11</sup>

We studied the -463 G/A polymorphism in Italian patients with GCA and found an association between this polymorphism and the susceptibility to develop GCA. The significance of this association is further strengthened by the evidence of a consistent susceptibility among individuals homozygous for the G allele. Differently from Reynolds *et al*<sup>11</sup> findings in MPO-ANCA associated vasculitis, no influence of gender was observed in patients with GCA, the GG genotype being associated with GCA in both men and women. Therefore, in GCA as in MPO-ANCA-associated vasculitis a genetically determined up-regulation of MPO expression may predispose to the development of vasculitis.

A second aim of this study was to determine whether this MPO polymorphism might be associated with the presence of severe ischaemic complications (vision loss and/or cerebrovascular accidents) or with PMR. However, when patients with and without these manifestations were compared, no associations were found.

Taken together, our findings suggest that subjects homozygous for the allele G have an increased risk of developing GCA related to a genetically determined higher MPO expression. Although this finding requires further confirmation in other populations, it is potentially important because it implies that MPO are involved in the pathophysiology of GCA. Neutrophils, despite their apparent insignificance in GCA, have been shown to have a strategic localisation in and around the vasa vasorum,<sup>2</sup> which supports an important, although incompletely studied, role for them and MPO in determining wall vessel lesions in GCA. Further studies are required both to replicate our findings in other populations and to better investigate the role of neutrophils and MPO in the inflammatory events leading to vascular injury in GCA.

**Competing interests:** None.

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