Review
Genetic epidemiology
Giant cell arteritis and polymyalgia rheumatica
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Abstract

Giant cell arteritis (GCA) (temporal arteritis) and polymyalgia rheumatica (PMR) are common, frequently related conditions in people generally over 50 years of age. Most studies have shown an association of GCA with HLA-DRB1*04 alleles. As regards isolated PMR, however, the HLA class II genetic susceptibility varies from one population to another. Besides associations with HLA, tumor necrosis factor appears to influence susceptibility to both conditions. Genetic polymorphisms have also been considered to be important candidates as factors of susceptibility to GCA and PMR. In this regard, gene polymorphisms for ICAM-1 (intercellular adhesion molecule 1), RANTES (regulated upon activation, normal T cell expressed, and presumably secreted), and interleukin (IL)-1 receptor antagonist seem to play a role in the pathogenesis of GCA and PMR in some populations. However, additional studies are required to clarify the genetic influence on susceptibility to these conditions.

Keywords: disease susceptibility, genetic polymorphisms, giant cell arteritis, HLA-DRB1, polymyalgia rheumatica, TNF alpha

Introduction
Giant cell arteritis (GCA) (temporal arteritis) constitutes a common vasculitic syndrome in European and North American countries that affects large and middle-sized blood vessels, with a predisposition to the cranial arteries, in people generally over 50 years of age [1].

Polymyalgia rheumatica (PMR) is also a common syndrome in people over the age of 50. The symptoms are pain, aching, and morning stiffness involving the neck, the shoulder girdle, and the hip girdle, which are generally associated with an elevated erythrocyte sedimentation rate [2]. PMR and GCA are related diseases, as PMR may be the presenting manifestation of GCA and is found in up to 50% of patients with GCA [2]. However, PMR is sometimes an isolated condition unrelated to GCA. The possibility of a genetic influence on susceptibility to GCA was initially supported by reports of cases of GCA among first-degree relatives.

Human leukocyte antigens in susceptibility to GCA and PMR
Human leukocyte antigen class II genes
GCA is the best example of an association between vasculitis and genes that lie within the HLA class II region [3]. Most studies have shown an association with HLA-DRB1*04 alleles [4]. In addition, the risk of visual complications is also associated with HLA-DRB1*04 alleles [1].

bp = base pair; CC = CC-chemokine; CCR5 = CC_chemokine receptor 5; GCA = giant cell arteritis; HLA = human leukocyte antigen; ICAM = intercellular adhesion molecule; IL = interleukin; IL-1 RN = IL-1 receptor antagonist; PMR = polymyalgia rheumatica; RA = rheumatoid arthritis; RANTES = regulated upon activation, normal T cell expressed and presumably secreted; TNF = tumor necrosis factor.

Unlike PMR in the context of GCA, which is mostly associated with HLA-DRB1*04, the susceptibility to isolated PMR associated with HLA class II genes varies from one population to another [4]. Relapses of PMR, however, have been found to be significantly more common in patients who have the HLA-DRB1*04 allele, and particularly in those carrying the HLA-DRB1*0401 allele [5]. A lack of homozygosity of the shared epitope in GCA has been reported in northwestern Spain [4] and Rochester, Minnesota [6]. This finding contrasts with observations regarding rheumatoid arthritis (RA), where homozygosity of the shared epitope is generally associated with additional risk of a more severe disease. These findings suggest that the pathology seen in GCA may be due to antigenic cross-reactivity or hypersensitivity after exposure and response to an infectious agent [4]. This mechanism would be consistent with some epidemiological data and the observed seasonal variation in disease onset. However, other, unknown, predisposing factors in the elderly may be implicated in the pathogenesis of these conditions.

Role of TNF in susceptibility to GCA and PMR
Apart from HLA-class II genes, it is likely that other genetic factors may contribute to the susceptibility to these conditions, particularly those factors involved in inflammation. GCA and PMR share evidence of an inflammatory process. However, concentrations of tumor necrosis factor (TNF)-α have not been found to be elevated in either condition. In northwestern Spain, GCA and PMR are associated with different TNF microsatellite polymorphisms. GCA is strongly associated with the allele encoding the TNF-a2 microsatellite. This association is largely independent of the association of GCA with HLA class II genes. A negative association with TNF-a10 was also found. In contrast, in patients with isolated PMR, there is a positive association with TNF-b3, which is also independent of the HLA class II association with isolated PMR, and a negative association with TNF-d4 [7]. Thus, TNF and HLA associations appear to be able to influence susceptibility to these conditions independently of each other.

Influence of genetic polymorphisms in the susceptibility to GCA and PMR
ICAM-1 biallelic polymorphisms
Genetic polymorphisms in endothelial-cell adhesion molecules have also been considered to be important candidate susceptibility factors for GCA and PMR. The intercellular adhesion molecule (ICAM-1) is a member of the immunoglobulin-like superfamily group of adhesion molecules and is a ligand for β_2 integrins present on leukocytes. It plays an important role in interactions between endothelial cells and leukocytes during inflammation. Expression of ICAM-1 on vascular endothelial cells can be significantly increased in the presence of mediators, which include lipopolysaccharide and cytokines such as interleukin-1 (IL-1), TNFα, and interferon-γ. In biopsies of temporal arteries

from GCA patients, ICAM-1 is highly expressed in the adventitial microvessels and neovessels within inflammatory infiltrates [8], and changes in concentrations of circulating soluble ICAM-1 have been correlated with disease activity in GCA [9]. Two polymorphisms of the coding region have been identified for ICAM-1: G or R at codon 241 (exon 4) and K or E at codon 469 (exon 6) [10]. In Italian patients with PMR and GCA, a higher frequency of the allele R at codon 241 of ICAM-1 has recently been reported [11]. In these patients, an association between polymorphism at codon 241 and an increased risk of relapses in PMR was also observed. However, unlike the findings in most series, GCA was not associated with HLA-DRB1*04 in that particular region of northern Italy. In northwestern Spain, in contrast, where susceptibility to GCA has been associated with HLA-DRB1*04 [4], no evidence was found of an interaction between HLA-DRB1*04 and polymorphisms of ICAM-1. Thus, in that particular region, ICAM-1 polymorphisms are not genetic risk factors affecting the susceptibility and severity of GCA [12].

Polymorphism in the human RANTES gene promoter
The cytokine RANTES is a potent chemotactic factor for monocytes, CD45RO+ memory T cells, basophils, eosinophils, and mast cells. Increased serum levels of this CC chemokine have been found in untreated PMR [13]. Hajeer *et al* have recently reported a novel polymorphism (G or A) in the human RANTES gene promoter at position −403 [14]. Because of this finding, an analysis of the polymorphism at this position was performed in patients with isolated PMR and with biopsy-proven GCA unassociated with PMR. The frequency of allele A was significantly higher in patients with PMR − but not in patients with GCA − than in controls [15]. This observation suggests that the presence of the RANTES allele A at position −403 may make a person susceptible to the development of PMR.

CCR5 polymorphism
RANTES is secreted by T lymphocytes, platelets, and synovial fibroblasts. After interaction with the CC chemokine receptor 5 (CCR5), it activates memory T cells and monocytes, which are the predominant cells in the synovial tissue of patients with PMR [16]. The chemokine receptor CCR5 is encoded by the CMKBR5 gene located on the p21.3 region of human chromosome 3, and is the major coreceptor for the macrophage-tropic strains of HIV-1. A 32-nucleotide deletion (Δ32) in one or both alleles of the CCR5 gene has been observed [17,18]. This 32-bp deletion within the coding region results in a frame shift, because of which this gene variant yields a protein product − a nonfunctional receptor − that is biologically inactive [17,18]. In patients homozygous for CCR5Δ32, the concentration of RANTES secreted by their lymphocytes is 5−10 times that found in patients homozygous for CCR5 [19]. Chemokines are suggested to be critical for establishment of inflammatory processes in autoimmune

diseases such as RA. In a series of 673 patients with RA, none had the homozygous CCR5Δ32 genotype, compared with a frequency of 0.009 in a group of 815 controls [20]. However, two other studies have not confirmed the association of CCR5 with RA [21,22]. To assess whether this 32-bp deletion might play a role in PMR, Salvarani *et al* examined the CCR5 genotype in 88 patients with PMR in whom RA was excluded, and in 87 controls [23]. Those workers found that the allele and genotype frequencies of CCR5Δ32 in patients with PMR and healthy controls did not differ significantly. They also found that the 32-bp deletion from the CCR5 receptor was not associated with any particular feature of the disease or with a different frequency of relapses. Thus, the 32-bp deletion of the CCR5 receptor does not seem to be implicated in the pathogenesis of PMR.

Influence of the IL-1 receptor antagonist gene
The IL-1 receptor antagonist (IL-1 RN) gene is located on chromosome 2, in close proximity to the IL-1A and IL-1B genes. Several polymorphic sites have been described for this gene, including a variable number of 86-base-pair tandem repeats within its second intron [24]. Allele 2 of this polymorphism was associated with increased production of IL-1 RN by monocytes and with higher plasma concentrations. It has also been associated with severity of the disease in systemic lupus erythematosus, ulcerative colitis, and alopecia areata. Boiardi and colleagues recently reported a significant association between susceptibility to PMR and the IL-1 RN*2 allele, particularly in the homozygous state [25]. However, they found no associations between IL-1 RN biallelic gene polymorphism and relapses of the disease or duration of corticosteroid therapy.

Conclusion
Although a genetic influence in the pathogenesis of GCA and PMR does exist, additional studies in different populations are required to clarify the pathogenesis of these common and frequently associated conditions. Moreover, it will be clinically useful to search for genetic markers that may predict the severity of disease in both conditions.

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