Review

Genetic component of giant cell arteritis

F. David Carmona¹, Miguel A. González-Gay² and Javier Martín¹

Abstract

Important steps forwards have been taken during recent years towards the understanding of the genetic basis of autoimmunity. The increasing number of study cohorts is allowing better characterization of the genetic component of most autoimmune diseases. However, the molecular mechanisms leading to some less common diseases remain poorly understood. GCA, an antigen-driven systemic vasculitis affecting medium and large blood vessels of elderly people, represents one of these cases. However, although underpowered to detect low to moderate effect sizes and without replication steps, many genetic studies on this disease have been published in the past decade. These reports clearly point to genes located in the MHC region, in particular HLA-DRB1*04 alleles, and other key members of the immune and inflammatory response (including cytokines, adhesion molecules and regulators of innate immunity), as crucial players in the development and progression of GCA. Considering that no literature review has been published so far about the genetic component of this vasculitis, we aimed to summarize here the current knowledge on the genetics underlying GCA predisposition and severity.

Key words: giant cell arteritis, vasculitis, genetic component, HLA-DRB1*04, cytokines.

Introduction

GCA is a chronic autoimmune vasculitis whose major hallmark is inflammatory damage of medium-size and large blood vessels, mainly the aorta and external carotid arteries and their corresponding branches [1]. One of the most common comorbidities of GCA is PMR, which is considered to be a manifestation of this vasculitis by some authors [1]. GCA affects predominantly women, with a sex ratio around 2–3:1, and people generally >50 years of age, reaching the highest incidence rates in the eighth decade of life [2, 3].

Besides its inflammatory condition, the model depicting GCA as an antigen-driven disease was accepted long ago [4]. Cumulative data suggest that at least two separate lineages of CD4+ T cells, Th17 and Th1, are recruited at the adventitia-media border by chemoattractant processes orchestrated by dendritic cells (DCs). These T cells are subsequently activated, undergo clonal expansion and begin to release IFN-γ, which leads to the differentiation and migration of macrophages that result in the formation of multinucleated giant cells forming granulomas in the media. Finally, both T cell types and macrophages produce proinflammatory cytokines contributing to inflammation of the arterial wall and vessel occlusion [5–7].

GCA shows a complex aetiology in which both environmental and genetic factors seem to influence the development and progression of the disease. Some studies suggest that DCs may be activated by environmental infectious factors or autoantigens [8]. For example, an increase in the incidence of GCA has been correlated with epidemics of Mycoplasma pneumoniae, parvovirus B19 and Chlamydia pneumoniae in Denmark [9]. Nevertheless, there is no consistent evidence of any particular microorganism as a direct trigger factor for GCA. On the other hand, increasing knowledge points to an important genetic component as a key susceptibility factor for this vasculitis. Familial aggregation with sharing of HLA alleles is being observed from decades ago for this disease [10–18]. Many genetic studies on GCA have been performed during recent years, making this disease the best example of vasculitis in which a genetic influence has been implicated in both disease susceptibility and severity [19]. Considering that there is no extended review on the genetic background of GCA in the literature, we aimed to summarize here the described genetic associations with this vasculitis.

¹Instituto de Parasitología y Biomedicina López-Neyra, CSIC, Granada and ²Department of Rheumatology, Hospital Universitario Marqués de Valdecilla, IFIMAV, Santander, Spain.

Submitted 19 December 2012; revised version accepted 10 May 2013.

Correspondence to: Javier Martin, Instituto de Parasitología y Biomedicina López-Neyra, Consejo Superior de Investigaciones Científicas, Parque Tecnológico Ciencias de la Salud, Avenida del Conocimiento s/n, 18100-Armilla, Granada, Spain.

E-mail: martin@ipb.csic.es
HLA associations

MHC class II associations

GCA has been consistently associated with MHC class II molecules (i.e. HLA-DR3, HLA-DR4, HLA-DR5 and HLA-DRB1) in many independent studies, particularly with carriage of HLA-DRB1*04 alleles (generally with DRB1*0401, but also with DRB1*0404) [20–32]. The association of HLA-DRB1*04 with GCA has been clearly observed in different Caucasian populations, except for a cohort from northern Italy [33] (Table 1). The reason for this is unknown, although it is likely that the study was underpowered to detect an association (only 39 patients were analysed). Interestingly, carriage of the HLA-DRB1*04 allele has been associated with resistance to corticosteroid treatment [29] and with a higher risk to develop visual manifestations in GCA patients [34, 35].

There are controversial results regarding the genetic association of the HLA-DRB1 molecule with the PMR condition. Although some studies have suggested that distribution of HLA-DRB1 alleles in PMR resembles that in GCA (reviewed in [36]), a study in GCA patients from northwestern Spain evidenced a distinct pattern of MHC class II association between both conditions. In this population, GCA patients either with or without PMR were clearly associated with HLA-DRB1*0401, and more weakly with HLA-DRB1*0101 and HLA-DRB1*0102, whereas isolated PMR (without GCA) was not associated with these alleles but with HLA-DRB1*13 and DRB1*14 [24]. Absence of similarity in the HLA-DRB1 allele distribution between PMR and GCA was also observed in a French cohort, in which HLA-DR1 and HLA-DR3 alleles were more significantly represented in isolated PMR and the HLA-DR4 and HLA-DRB1*0701 alleles in GCA [37]. However, other studies suggested that the increased frequency of HLA-DR4 described in GCA patients was likely due to the association of this haplotype with PMR [22, 30].

On the other hand, an association between HLA-DRB1*04 alleles that carry the shared epitope (SE) and GCA (but not isolated PMR) has been described [24, 32], which suggests common pathological mechanisms between GCA and RA [38]. Nevertheless, homozygosity for this sequence motif increases susceptibility to the latter, but is rare in GCA, and seems not to confer the risk of more severe disease in GCA patients. This fact suggests that GCA onset could be related to antigenic cross-reactivity or hypersensitivity to a pathogen infection [24].

MHC class I associations

Early genetic studies on GCA reported weak associations with MHC class I alleles (i.e. HLA-A*31, HLA-B*8, HLA-Cw3, HLA-Cw6) [20, 25, 39], although other studies failed to find evidence of an association with this region [30]. Recent published data also suggest that MHC class I polymorphisms may be involved in the genetic predisposition to GCA, likely by influencing the antigen presentation to T cells [40]. Specifically, HLA-B*15 has been associated with GCA in a Caucasian population from northwest Spain. Moreover, an independent signal within MHC class I polypeptide-related sequence A (MICA) gene, which encodes a stress-inducible transmembrane molecule [41], has been described as a genetic risk factor for this vasculitis [40]. Interestingly, MICA is associated with Behçet’s disease (BD) [42]. However, further studies are needed in larger and independent populations to confirm these associations.

In the following sections we will review the significant associations of non-HLA loci with GCA predisposition that have been reported thus far. These mainly include genes of the immune system, the inflammatory process and the endothelial function, which are in most cases common susceptibility genes for other vasculitides (Table 2).

Associations with genes encoding cytokines and their receptors

Tumour necrosis factor

The TNF gene, located within the MHC class III, encodes a proinflammatory cytokine involved in the regulation of immune cells. It is produced mainly by activated macrophages, but also by CD4+ T cells and NK cells [43]. It is considered one of the most important cytokines driving the inflammatory process in RA [44]. Interestingly, elevated levels of TNF have been detected in GCA patients

### Table 1 Genetic studies of HLA-DRB1*04 alleles in GCA described to date

<table>
<thead>
<tr>
<th>Year of publication</th>
<th>Location</th>
<th>HLA-DRB1*04 association</th>
<th>Cohort analysed (case/control)</th>
<th>P-value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>Rochester, Minnesota (USA)</td>
<td>Yes</td>
<td>42/63</td>
<td>0.03</td>
<td>Weyand et al. [31]</td>
</tr>
<tr>
<td>1994</td>
<td>Rochester, Minnesota (USA)</td>
<td>Yes</td>
<td>52/72</td>
<td>0.0001</td>
<td>Weyand et al. [32]</td>
</tr>
<tr>
<td>1998</td>
<td>Toulouse (France)</td>
<td>Yes</td>
<td>41/384</td>
<td>&lt;0.001</td>
<td>Rauey et al. [29]</td>
</tr>
<tr>
<td>1998</td>
<td>Montpellier (France)</td>
<td>Yes</td>
<td>42/1609</td>
<td>0.0005</td>
<td>Combe et al. [23]</td>
</tr>
<tr>
<td>1998</td>
<td>Lugo (Spain)</td>
<td>Yes</td>
<td>53/145</td>
<td>&lt;0.05</td>
<td>Dababneh et al. [24]</td>
</tr>
<tr>
<td>1999</td>
<td>Reggio Emilia (Italy)</td>
<td>No</td>
<td>39/250</td>
<td>&gt;0.05</td>
<td>Salvarani, et al. [33]</td>
</tr>
<tr>
<td>2002</td>
<td>Copenhagen (Denmark)</td>
<td>Yes</td>
<td>65/193</td>
<td>0.01</td>
<td>Jacobsen et al. [26]</td>
</tr>
<tr>
<td>2004</td>
<td>Cantabria (Spain)</td>
<td>Yes</td>
<td>44/99</td>
<td>0.04</td>
<td>Martinez-Taboda et al. [28]</td>
</tr>
</tbody>
</table>

*aScandinavian descent.*
### Table 2: Susceptibility loci for GCA outside the HLA region identified by candidate gene studies

<table>
<thead>
<tr>
<th>Year of publication</th>
<th>Susceptibility loci</th>
<th>Associated variation</th>
<th>Population</th>
<th>Cohort size (GCA/controls)</th>
<th>P-value (allele test)</th>
<th>OR (95% CI)</th>
<th>Association</th>
<th>Replication</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td><strong>TNF</strong></td>
<td><strong>TNFa2</strong></td>
<td>Northwestern Spain</td>
<td>62/147</td>
<td>0.003</td>
<td>2.50 (1.30, 4.80)</td>
<td>Global disease</td>
<td>No</td>
<td>Mattey et al. [46]</td>
</tr>
<tr>
<td>2000</td>
<td><strong>TNF</strong></td>
<td><strong>TNFa10</strong></td>
<td>Northwestern Spain</td>
<td>62/147</td>
<td>0.02</td>
<td>0.30 (0.10, 0.80)</td>
<td>Global disease</td>
<td>No</td>
<td>Mattey et al. [46]</td>
</tr>
<tr>
<td>2000</td>
<td><strong>CCL5</strong></td>
<td>rs2107538</td>
<td>Northwestern Spain</td>
<td>30/65</td>
<td>NS</td>
<td>NA</td>
<td>PMR</td>
<td>No</td>
<td>Makki et al. [48]</td>
</tr>
<tr>
<td>2002</td>
<td><strong>IL6</strong></td>
<td>rs1800795</td>
<td>Northwestern Spain</td>
<td>62/124</td>
<td>0.066</td>
<td>2.3 (NA)</td>
<td>PMR</td>
<td>No</td>
<td>Salvarani et al. [106]</td>
</tr>
<tr>
<td>2012</td>
<td><strong>IL6</strong></td>
<td>rs7805828</td>
<td>Spain</td>
<td>82/166</td>
<td>0.0119</td>
<td>0.33 (0.13, 0.82)</td>
<td>Global disease</td>
<td>No</td>
<td>Enjuanes et al. [72]</td>
</tr>
<tr>
<td>2012</td>
<td><strong>IL6</strong></td>
<td>rs1546762</td>
<td>Spain</td>
<td>82/166</td>
<td>0.037</td>
<td>2.04 (1.03, 4.05)</td>
<td>Global disease</td>
<td>No</td>
<td>Enjuanes et al. [72]</td>
</tr>
<tr>
<td>2003</td>
<td><strong>NOS3</strong></td>
<td>rs1799983</td>
<td>Northern Italy</td>
<td>91/133</td>
<td>0.02</td>
<td>1.60 (1.10, 2.30)</td>
<td>Global disease</td>
<td>No</td>
<td>Salvarani et al. [127]</td>
</tr>
<tr>
<td>2003</td>
<td><strong>NOS3</strong></td>
<td>C-1-Tc</td>
<td>Northwestern Spain</td>
<td>57/117</td>
<td>0.02</td>
<td>0.30 (0.10, 0.80)</td>
<td>Global disease</td>
<td>No</td>
<td>Amoli et al. [128]</td>
</tr>
<tr>
<td>2003</td>
<td><strong>VEGF</strong></td>
<td>rs2010963</td>
<td>Northern Italy</td>
<td>92/200</td>
<td>0.019</td>
<td>1.53 (1.06, 2.21)</td>
<td>Global disease</td>
<td>Yes</td>
<td>Boiardi et al. [114]</td>
</tr>
<tr>
<td>2005</td>
<td><strong>VEGF</strong></td>
<td>rs2010963</td>
<td>Northwestern Spain</td>
<td>103/226</td>
<td>0.021</td>
<td>1.75 (1.08, 2.88)</td>
<td>VIM</td>
<td>Yes</td>
<td>Rueda et al. [115]</td>
</tr>
<tr>
<td>2012</td>
<td><strong>VEGF</strong></td>
<td>rs689946</td>
<td>Spain</td>
<td>82/166</td>
<td>0.0137</td>
<td>NA</td>
<td>Global disease</td>
<td>No</td>
<td>Enjuanes et al. [72]</td>
</tr>
<tr>
<td>2012</td>
<td><strong>VEGF</strong></td>
<td>rs689947</td>
<td>Spain</td>
<td>82/166</td>
<td>0.0364</td>
<td>NA</td>
<td>Global disease</td>
<td>No</td>
<td>Enjuanes et al. [72]</td>
</tr>
<tr>
<td>2004</td>
<td><strong>IFNG</strong></td>
<td><strong>allele*3</strong></td>
<td>Northwestern Spain</td>
<td>59/129</td>
<td>0.01</td>
<td>3.13 (1.27, 7.68)</td>
<td>VIM</td>
<td>No</td>
<td>Gonzalez-Gay et al. [50]</td>
</tr>
<tr>
<td>2004</td>
<td><strong>IL4</strong></td>
<td>T-T-C-A-C (c')\</td>
<td>Northwestern Spain</td>
<td>82/102</td>
<td>0.02</td>
<td>2.00 (1.00, 3.90)</td>
<td>Global disease</td>
<td>No</td>
<td>Amoli et al. [51]</td>
</tr>
<tr>
<td>2005</td>
<td><strong>NOS2A</strong></td>
<td>TAA-A repeat</td>
<td>Northwestern Spain</td>
<td>103/198</td>
<td>0.007</td>
<td>1.98 (1.20, 3.27)</td>
<td>No</td>
<td>Gonzalez-Gay et al. [121]</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td><strong>NOS3</strong></td>
<td>rs2779251</td>
<td>Spain</td>
<td>82/166</td>
<td>-0.0001</td>
<td>0.27 (0.14, 0.52)</td>
<td>Global disease</td>
<td>No</td>
<td>Enjuanes et al. [72]</td>
</tr>
<tr>
<td>2005</td>
<td><strong>MCP1</strong></td>
<td>C-1-Tc</td>
<td>Northwestern Spain</td>
<td>79/99</td>
<td>0.03</td>
<td>2.09 (1.09, 4.02)</td>
<td>Global disease</td>
<td>No</td>
<td>Amoli et al. [85]</td>
</tr>
<tr>
<td>2012</td>
<td><strong>MCP1</strong></td>
<td>rs1800872</td>
<td>Northern Italy</td>
<td>140/200</td>
<td>0.0002</td>
<td>2.00 (1.40, 2.80)</td>
<td>Global disease</td>
<td>No</td>
<td>Boiardi et al. [57]</td>
</tr>
<tr>
<td>2012</td>
<td><strong>IL10</strong></td>
<td>rs1800866</td>
<td>Northwestern Spain</td>
<td>103/226</td>
<td>0.11</td>
<td>1.29 (0.92, 1.80)</td>
<td>Global disease</td>
<td>No</td>
<td>Rueda et al. [58]</td>
</tr>
<tr>
<td>2006</td>
<td><strong>FCGR3A</strong></td>
<td>rs396991</td>
<td>Northwestern Spain</td>
<td>85/132</td>
<td>0.03</td>
<td>NA</td>
<td>Global disease</td>
<td>No</td>
<td>Morgan et al. [148]</td>
</tr>
<tr>
<td>2006</td>
<td><strong>FCGR2A</strong></td>
<td>rs121724</td>
<td>Northwestern Spain</td>
<td>85/132</td>
<td>0.03</td>
<td>NA</td>
<td>Global disease</td>
<td>No</td>
<td>Morgan et al. [148]</td>
</tr>
<tr>
<td>2008</td>
<td><strong>MMP9</strong></td>
<td>rs250889</td>
<td>Philadelphia (USA)</td>
<td>30/23</td>
<td>0.009</td>
<td>NA</td>
<td>Global disease</td>
<td>No</td>
<td>Rodriguez-Pila et al. [137]</td>
</tr>
<tr>
<td>2008</td>
<td><strong>MPO</strong></td>
<td>rs233327</td>
<td>Northern Italy</td>
<td>156/235</td>
<td>0.0001</td>
<td>2.00 (1.40, 2.90)</td>
<td>Global disease</td>
<td>No</td>
<td>Salvarani et al. [159]</td>
</tr>
<tr>
<td>2009</td>
<td><strong>TLR4</strong></td>
<td>rs4986790</td>
<td>Spain</td>
<td>21/678</td>
<td>0.01</td>
<td>1.65 (1.08, 2.52)</td>
<td>Global disease</td>
<td>No</td>
<td>Palomino-Morales et al. [140]</td>
</tr>
<tr>
<td>2010</td>
<td><strong>IL18</strong></td>
<td>rs207084</td>
<td>Northwestern Spain</td>
<td>21/405</td>
<td>0.003</td>
<td>1.48 (1.13, 1.95)</td>
<td>Global disease</td>
<td>No</td>
<td>Palomino-Morales et al. [76]</td>
</tr>
<tr>
<td>2010</td>
<td><strong>IL18</strong></td>
<td>rs1946518</td>
<td>Spain</td>
<td>21/405</td>
<td>0.02</td>
<td>1.32 (1.04, 1.69)</td>
<td>Global disease</td>
<td>No</td>
<td>Palomino-Morales et al. [76]</td>
</tr>
<tr>
<td>2011</td>
<td><strong>IL12RB2</strong></td>
<td>rs3790567</td>
<td>Spain and Italy</td>
<td>37/574</td>
<td>0.039</td>
<td>1.25 (1.01, 1.54)</td>
<td>Global disease</td>
<td>No</td>
<td>Rodriguez-Rodriguez et al. [101]</td>
</tr>
<tr>
<td>2011</td>
<td><strong>IL2/IL21</strong></td>
<td>rs6822844</td>
<td>Spain</td>
<td>272/791</td>
<td>0.04</td>
<td>1.76 (2.06, 3.04)</td>
<td>Jaw claudication</td>
<td>No</td>
<td>Rodriguez-Rodriguez et al. [97]</td>
</tr>
<tr>
<td>2012</td>
<td><strong>NLRP1</strong></td>
<td>rs1812352</td>
<td>Spain and Italy</td>
<td>685/298</td>
<td>0.0026</td>
<td>1.20 (1.06, 1.35)</td>
<td>Global disease</td>
<td>Yes</td>
<td>Serrano et al. [164]</td>
</tr>
</tbody>
</table>

VIM: visual ischaemic manifestation; NS: non-significant; NA: not available; AAV: ANCA-associated vasculitis; TA: Takayasu’s arteritis. $^a$Odds ratio for the minor allele. $^b$P-value of the analysis of the CC genotype in GCA patients with PMR vs those with isolated GCA = 0.02. $^c$Haplotype: rs2070744-C-VNTR 1 in intron 4-rs179983-T. $^d$SNP order: rs207084-rs222784-rs222782-rs2243266-rs2243267. $^e$Haplotype P-value. $^f$SNP order: rs4586-rs13900. $^g$Genotypic P = 0.03. $^h$Dominant model: P = 0.03, OR = 3.09 (1.10, 8.64). $^i$Recessive model: P = 0.02, OR = 2.10 (1.10, 3.77).

Downloaded from https://academic.oup.com/rheumatology/article-abstract/53/1/6/1778960 by guest on 04 February 2019
with a strong systemic inflammatory response, and a high production of this cytokine was associated with longer corticosteroid requirements for these patients [45].

A study by Mattey et al. [46] evidenced differential TNF microsatellite associations for GCA and PMR. TNFa2 was strongly associated with isolated GCA (without PMR), and this association was independent of those for HLA-DRB1*0401 and HLA-DRB1*0101. On the other hand, the analysis of patients with isolated PMR showed a statistically significant association with TNFd3, also independent of the described HLA associations HLA-DRB1*13 and HLA-DR1*14. The authors also observed that the frequency of the microsatellite TNFa10 was significantly decreased in GCA patients without PMR manifestations compared with those showing PMR or with isolated PMR, supporting the idea of the different genetic background underlying both pathological conditions.

**IFN-γ**

IFN-γ is a key cytokine in the immune system involved in the innate and adaptive immunity against intracellular pathogens and tumour control. It is produced predominantly by NK cells and CD4+ and CD8+ T cells, being the signature cytokine of the Th1 response. Genetic variation and misregulation of gene expression for this cytokine have been associated with a wide spectrum of chronic inflammatory and autoimmune diseases [47].

High expression of IFNG is directly related to the pathogenic mechanisms affecting the arterial walls in GCA patients [48, 49]. In this regard, GCA is considered a typical Th1 disease, and IFN-γ-producing CD4+ T cells have been described as one of the dominant cell populations in the arterial infiltrates. It has been observed that IFN-γ is released in the vasculitic lesions even after months of corticosteroid therapy [5].

Interestingly, allele*3 of the microsatellite dinucleotide (CA) repeat within the first intron of the IFNG gene was associated with visual ischaemic manifestations in GCA patients [50]. However, no association with the global disease was observed in a subsequent study in which three different tag single-nucleotide polymorphisms (SNPs) of the IFNG locus were analysed, suggesting that IFNG functional variants may influence disease severity rather than susceptibility [51].

**IL-10**

IL-10 is an anti-inflammatory Th2 cytokine produced mainly by monocytes, but also by T cells, with pleiotropic effects in the immune system. It is involved in the down-regulation of genes encoding Th1 cytokines like IFNG, and it also promotes B cell survival, proliferation and antibody production. IL-10 is also involved in the repression of NF-κB activity and in the regulation of the JAK-STAT signaling pathway [52].

Different functionally relevant IL10 genetic variants have been tested for association with GCA predisposition, including SNPs located at positions −1082 (rs1800896* A/G), −592 (rs1800872* A/C) and −819 (rs1800871* C/T) of the IL10 promoter region. These three variants were associated with an increased risk of developing cardiovascular conditions [53], as well as different rheumatic diseases such as RA [54], SLE [55] and SS [56], among others. Two independent studies in Italian and Spanish populations indicated that variation of the IL10 promoter region is involved in the genetic susceptibility to GCA [57, 58]. However, different association signals were observed when the allelic frequencies between cases and controls were compared in each study. The IL10 rs1800872 polymorphism was associated with GCA risk in the Italian population [57], whereas in the Spanish study the associated variant was IL10 rs1800896 [58]. In any case, the haplotype containing the minor alleles of the three promoter SNPs (rs1800896*G-rs1800871*T-rs1800872*A) was strongly associated in both studies (P < 0.0001). The discrepancy in the results of the allele tests could be due to a lack of statistical power. Further studies in additional populations may help to narrow the IL10 association with GCA.

**IL-4**

The IL-4 gene (IL4) encodes a cytokine that acts reciprocally with IFN-γ, inducing the Th2 immune response and regulating a number of T cell functions in the humoral and adaptive immunity. Both proteins modulate the Th1/Th2 balance [59].

Different IL4 genetic variants showed evidence of an association with a predisposition to develop GCA, and these associations substantially increased their statistical significance when the HLA-DRB1*04 status was considered, suggesting a possible interaction between both loci [51].

**IL-6**

IL-6 is a cytokine with a pleiotropic effect in both the innate and adaptive immunity that may exert both proinflammatory and anti-inflammatory functions. It is released by many different cell types, including lymphocytes, monocytes, fibroblasts and endothelial cells, under inflammatory conditions [60]. A promoter polymorphism at the position −174 (rs1800795* G/C) of this gene has been shown to influence IL-6 levels, and dysregulated IL6 expression has been implicated in the development of clinical phenotypes in a number of autoimmune diseases such as systemic-onset JCA, SSc, SLE and RA [61–67].

Studies on GCA evidenced a correlation between plasma IL-6 concentrations and clinical symptoms in GCA patients [68, 69]. Two independent studies performed in Italy and Spain did not report evidence of an association between the promoter polymorphism rs1800795 and predisposition to GCA [70, 71], although the study on the Spanish population suggested that this polymorphism may be related to PMR development in GCA patients, especially in those not carrying HLA-DRB1*04 alleles [71]. However, a recent report on an independent Spanish cohort identified two different IL6 genetic variants associated with GCA (rs1546762, located in the promoter region, and rs7805828, located upstream of the 3’ end of the gene) [72].
IL-18

IL-18, also known as IFN-γ-inducing factor, is a proinflammatory cytokine produced by macrophages and other immune cells that induces T-helper 1 differentiation and has cytotoxic T cell functions. This cytokine plays an important role in chronic inflammation and has also been related to different autoimmune diseases [73]. A significant increase in the relative expression of IL18 mRNA in individuals carrying the IL18 rs360719*C allele in peripheral blood cells [74] has been observed, and increased IL18 expression levels were detected in temporal artery biopsies of GCA patients [75]. Interestingly, the previous SNP and IL18 rs1946518*G/T have been recently associated with GCA susceptibility [76].

Monocyte chemotactic protein-1

Monocyte chemotactic protein-1 (MCP-1), also known as chemokine (C-C motif) ligand 2 (CCL2), is a member of the CC subfamily of chemokines that recruits monocytes and T cells to the sites of inflammation in acute inflammatory conditions, although it can also be involved in chronic inflammation [77]. The fact that this chemokine has been detected in the majority of mononuclear cells, some smooth muscle cells and giant cells of arterial biopsies samples from GCA patients suggests that it may play a role in the monocytic infiltration of the artery wall leading to the vascular damage in this vasculitis [78]. In addition, an increased MCP1 expression was observed in patients with GCA and other autoimmune diseases, including RA and atherosclerosis [78–80].

Different MCP1 gene polymorphisms were associated with the clinical severity of different autoimmune diseases as well as with coronary artery complications [81–84]. Regarding GCA, significant differences in the frequency of a haplotype (composed of three SNPs located in intron 1, exon 2 and the 3’UTR region of the gene) were observed between northwestern Spanish patients and controls [85]. In addition, evidence of an association between the MCP1 SNP rs1860190*A/T and GCA in an independent Spanish population has been also reported [72].

Chemokine (C-C motif) ligand 5

The chemokine (C-C motif) ligand 5 gene (CCL5), also known as regulated and normal T cell expressed and secreted (RANTES), encodes a potent chemotactic factor for monocytes, T cells, basophils, eosinophils and mast cells [86].

Increased serum levels of this chemokine were reported in untreated PMR patients. Interestingly, corticosteroid therapy seemed to normalize its production [87]. A study on GCA patients from northwest Spain was performed to investigate the possible implication of a promoter polymorphism at position –403 (rs2107538*G/A). Although no statistically significant differences in the allele frequencies were observed when GCA cases were compared against controls, an association with the isolated PMR condition was shown [88].

IL-2/IL-21

IL-21 controls a wide range of immune processes through both positive and negative regulatory effects on lymphoid and myeloid target cells [89]. IL-2 is also essential for the correct function of the immune system and represents a key factor for T cell activation and immune function [90]. A SNP located between the both loci, rs6822844*G/T, has been associated with several autoimmune diseases [91–95]. It is unclear whether this signal reflects specific associations with IL2 or IL21, probably due to the extensive linkage disequilibrium in this region [96]. Its possible implication in GCA was studied in a Spanish cohort. Although no effect on the susceptibility to the global disease was observed, a higher frequency of the rs6822844 minor allele among patients with severe ischaemic complications than those without them was observed. When the analysis was carried out specifically in patients with jaw claudication, statistical significance was reached, suggesting that the IL2/IL21 genomic region may contribute to phenotypic expression of the disease [97].

IL-12 receptor beta 2

IL-12 receptor beta 2 (IL12RB2) is a subunit of the IL-12 receptor whose expression is regulated by IFN-γ. It plays an important role in Th1 and Th17 cell differentiation and is thought to contribute to the inflammatory response [98, 99]. Considering that these two cell types are central players in GCA pathophysiology [100], a study in a Spanish cohort was performed to evaluate whether this gene may represent a genetic risk factor for GCA. A significant association between the IL12RB2 polymorphism rs3790567*AV/G and GCA susceptibility was observed, particularly with the subgroup of patients showing visual ischaemic complications, which suggests a potential collaborative effect of both Th1 and Th17 cells in the development of these manifestations [101].

Associations with molecules involved in the endothelial function

Intercellular adhesion molecule 1

Intercellular adhesion molecule 1 (ICAM-1) is a member of the immunoglobulin superfamily that encodes a cell surface glycoprotein with an important role in the interactions between immune and endothelial cells during the inflammation process [102, 103]. ICAM-1 serum levels were correlated with disease activity in GCA patients, and elevated expression of this molecule was also detected in shoulder synovial membrane of active PMR as well as in the inflammatory infiltrates of the temporal artery in GCA, which suggests that this protein may be a relevant component of the inflammatory processes of these conditions [104, 105]. A non-synonymous SNP located at exon 4, rs1799969*AV (G241R), was associated with GCA and PMR predisposition and with an increased risk of relapse/recurrence in PMR patients in an Italian cohort [106]. However, this finding was not replicated in a subsequent study performed in a Spanish population [107].
Vascular endothelial growth factor

VEGF is a key proangiogenic mediator that induces adhesion molecules on endothelial cells during inflammation, orchestrating vasculogenesis [108]. Angiogenesis has been proposed as one of the main mechanisms influencing the progression of GCA by playing a dual role, compensating for ischaemia on the one hand and acting as a proinflammatory factor on the other [109, 110]. Interestingly, increased levels of circulating VEGF have been detected in PMR patients [111], and recent evidence suggests that these high soluble VEGF concentrations may be related to optic nerve ischaemia in GCA patients [112].

Carriers of a functional genetic variant located at position -634 of the VEGF promoter region (rs2010963*G/C), which has been reported to affect gene expression and circulating protein levels [113], were associated with susceptibility to GCA in Italians [114]. In a subsequent study in a Spanish cohort, a specific association of this VEGF variant with the presence of severe ischaemic manifestations in GCA patients was observed [115], and very recently the above and three other VEGF genetic variants (rs1885657*C/T, rs699946*A/G and rs699947*A/C) were reported to confer genetic risk to develop this vasculitis [72].

Endothelial nitric oxide synthases 2 and 3

Nitric oxide synthases (NOSs) are a family of enzymes that produce nitric oxide (NO), which is involved in a wide variety of biological processes. NO has been described as a key mediator of the Th1/Th2 balance in autoimmunity, and increased NO levels correlate with disease activity in different rheumatic disorders such as RA [116]. Three different genes encode NOSs in humans, i.e. the neuronal (NOS1), the cytokine-inducible (NOS2A) and the endothelial (NOS3) [117]. The second one encodes a key molecule in the immune system that is involved in the release of NO during the immune response. Different inflammatory mediators regulate the activation of NOS2A, and its encoding protein, known as inducible NOS (iNOS), is only present in the tissues after cytokine induction [118]. It has been observed that macrophages express NOS2A in GCA [119] and the production of NO by iNOS may have an important role in limiting the inflammatory reaction [120].

Regarding NOS2A, a TAAA repeat polymorphism within the NOS2A promoter region was associated with GCA in a cohort from northwest Spain [121]. In addition, recent evidence has confirmed that genetic variation within this locus may also be crucial in GCA predisposition, since another NOS2A promoter variant, rs2779251*A/G, showed a strongly significant protective effect for GCA [72].

On the other hand, NOS3, which is also known as constitutive NOS (cNOS) or endothelial NOS (eNOS), is expressed constitutively by the endothelial cells lining the vasculature [122]. This basal endothelial NO production is necessary for regulating local vasodilatation and for avoiding platelet and immune cell aggregation and adhesion, since NO selectively reduces endothelial expression of adhesion molecules and proinflammatory cytokines [123–125].

Consequently, it is possible that malfunction of the NO system could be involved in the vascular damage of GCA. Indeed, studies on Italian and Spanish populations confirmed NOS3 as a GCA susceptibility gene [126, 127]. In the first one, a non-synonymous SNP in exon 7 (rs1799833*T/G, Glu298Asp) showed a clear association with the disease [127], whereas the study on the Spanish cohort showed a haplotype association including this genetic variant, a variable number tandem repeat polymorphism in intron 4 and a promoter SNP at position -786 (rs2070744*T/C) [126]. Hence, although further studies are needed to confirm it, it is possible that these susceptibility variants may be influencing the disease phenotype by generating oxidative stress.

Matrix metalloproteinase 9

Proteins of the MMP family are zinc-dependent enzymes with proteolytic activity on the extracellular matrix that are involved in many physiological and pathological processes [128]. MMP9 encodes a key protein in the proteolytic systems that break the basement membrane, allowing the progression of immune cells towards the artery walls during inflammation. It plays an important role in tissue remodelling processes associated with atherosclerosis and plaque rupture [129]. An elevated expression of MMP9 has been detected in GCA lesions [130–133], and this metalloproteinase has been correlated with the progression of inflammatory infiltrates and vessel destruction and repair in GCA [134].

A functional SNP at position –1562 within the MMP9 promoter region (rs3918242*C/T) that leads to an increase of promoter activity has been associated with atherosclerosis and aortic aneurysms [135, 136]. A study in a small cohort of Caucasian American GCA patients did not find evidence of an association with this polymorphism. However, statistically significant differences between the allele frequencies of GCA cases and controls were found for another non-synonymous coding MMP9 variant (rs2250889*C/G) [137].

Associations with genes of innate immunity

Toll-like receptor 4

The Toll-like receptor (TLR) family comprises a group of transmembrane proteins expressed by various cell types, including immune cells that play a pivotal role in pathogen recognition and activation of the innate immunity. These molecules recognize pathogen-associated molecular patterns (PAMPs) and promote inflammation [138]. One member of this family is TLR-4, which has been implicated in signal transduction events induced by lipopolysaccharide (LPS) from Gram-negative bacteria, but also structures from fungal and mycobacterial pathogens and endogenous ligands [139].
A significant association between the non-synonymous TLR4 polymorphism rs4986790*A/G (Asp299Gly) and GCA in a good-sized Spanish cohort suggested that this gene may play an important role in GCA pathophysiology [140]. Interestingly, this TLR4 variant showed an additive effect with IL18 polymorphisms on GCA susceptibility [76]. Although this association was not confirmed in two subsequent studies on independent Caucasian populations [141, 142], a trend of association was evident when the three studies were meta-analysed (P = 0.082, OR = 1.46, 95% CI 0.95, 2.25) [143]. A recently published meta-analysis and systematic review of different vasculopathies (including GCA, BD and Henoch-Schönlein purpura) indicated that this variant may represent a real genetic risk factor for vasculitis in general and GCA in particular [144].

However, the exact pathological mechanism in which this TLR4 non-synonymous change may be implicated remains unclear. DCs localized at the adventitia-media border of medium-sized arteries are crucial in the initiation of GCA [145]. It has been shown that the TLR4 rs4986790*A/G polymorphism affects the extracellular protein domain, which interrupts TLR-4-mediated LPS signalling, thus influencing the inflammatory process [146]. Considering that triggering of TLR-4 by LPS promotes DC activation, it is likely that this protein promotes the induction of the inflammatory process in GCA [145].

Fc-γ receptors

Fc receptors are cell-surface proteins of the immunoglobulin superfamily that are located in the membrane of some immune cells, such as B cells, NK cells, macrophages, neutrophils and mast cells. Those that bind immunoglobulin G (IgG) antibodies or IgG-containing immune complexes are known as Fc-γ receptors (FcγRs) and are crucial for inducing phagocytosis of opsonized pathogens or infected cells. They are also involved in the release of cytokines, including TNF [147]. Different polymorphisms of the FCGR genes FCGR2A, FCGR3A, FCGR3B and FCGR2B were analysed in a case-control study of a small Spanish cohort. The authors described significant associations with GCA for FCGR2A rs1801274*G homozygosity (FCGR2A-131RR) and carriage of FCGR3A rs396991*T (FCGR3A-158F). Additionally, the haplotype rs1801274*G-rs396991*T (FCGR2A 131R-FCGR3A 158F) was associated with an almost 3-fold increased GCA risk [148].

Myeloperoxidase

MPO is a haemoprotein that is abundantly expressed in neutrophils and monocytes and secreted during their activation [149]. MPO is a very important molecule in the neutrophil function. It catalyses chloride ion oxidation to hypochlorous acid, which is an antimicrobial agent with potent proinflammatory properties that can cause vascular damage. Moreover, this protein causes oxidative modification of low-density lipoprotein to a high uptake form that is considered to be involved in atherogenesis [150]. Indeed, there is evidence suggesting that increased serum MPO levels may represent a risk marker for atherosclerosis and coronary artery disease [151, 152]. In addition, some autoantibodies, such as ANCA, are directed against MPO in vasculitides [153]. Moreover, previous data suggest that genotypes related to low MPO gene expression have a protective role in coronary artery disease [154–156]. The MPO promoter polymorphism rs2333227*G/A, which affects MPO expression [157, 158], was associated with GCA predisposition [159]. Taken together, it is likely that MPO represents a key component in vascular inflammatory diseases, providing a mechanism to endothelial dysfunction and vessel wall damage.

NLR family pyrin domain containing 1

The inflammasome-related protein NLRP1 is a cytoplasmic protein that stimulates innate immunity by detecting endogenous microbial products and metabolic stress. NLRP1 is involved in the assembly of the inflammasome that activates caspases 1 and 5, required for processing and activation of proinflammatory cytokines [160]. Different studies have reported the involvement of NLRP1 in the pathophysiology of several autoimmune/inflammatory disorders, being considered a common risk factor in autoimmunity [161–163]. Very recently, a well-powered case-control study in which data from a Spanish and an Italian population were meta-analysed identified NLRP1 as a novel GCA genetic risk factor, indicating that the inflammasome may be relevant in the pathophysiology of this disease [164].

Conclusions and perspectives

The reduced sample size and lack of replication in independent cohorts other than Spanish and Italian populations have made the identification of consistent genetic association signals in GCA difficult. More powered studies are necessary to definitively confirm the existing associations and to identify novel genetic risk factors. Despite this, there is clear evidence pointing to an important genetic background that influences both predisposition and manifestation of the clinical features of this vasculitis [19].

The fact that the current knowledge on the genetic basis of GCA is consistent with its phenotypic expression indicates that the investigation on this vasculitis is moving in the right direction. Use of the new technologies available for genetic studies, i.e. genome-wide association studies (GWASs) and deep sequencing, among others, will help to unravel the genetic component of this disease, as it has in other related diseases like BD [165–167] or ANCA-associated vasculitis [168]. Platforms such as the Immunochip custom SNP array [169] have allowed the identification of novel genetic factors of different autoimmune diseases for which GWAS data were already available, i.e. celiac disease, primary biliary cirrhosis and RA [170–172], and could also represent an interesting tool to elucidate the genetic network underlying GCA.
Rheumatology key messages
- GCA susceptibility loci include HLA-DRB1 alleles and genes encoding immune system and endothelial molecules.
- As most GCA studies are underpowered, collaborative efforts are required to fully unravel GCA genetics.
- The use of large-scale approaches may allow better characterization of GCA genetics.

Acknowledgements
F.D.C. was supported by Consejo Superior de Investigaciones Científicas (CSIC) through the programme JAE-DOC.

Disclosure statement: The authors have declared no conflicts of interest.

References
F. David Carmona et al.


33 Salvarani C, Boiardi L, Mantovani V et al. HLA-DRB1, DQA1, and DQB1 alleles associated with giant cell arteritis in northern Italy. J Rheumatol 1999;26:2395–9.


