Rheumatology Advance Access published July 10, 2013

Review

doi:10.1093/rheumatology/ket231

Genetic component of giant cell arteritis

F. David Carmona[1], Miguel A. González-Gay[2] and Javier Martín[1]

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.

[1]Instituto de Parasitología y Biomedicina López-Neyra, CSIC, Granada and [2]Department 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

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

[a]Scandinavian descent.

Table 2 Susceptibility loci for GCA outside the HLA region identified by candidate gene studies

Year of publication	Susceptibility loci	Associated variation	Population	Cohort size (GCA/controls)	*P*-value (allele test)	OR (95% CI)[a]	Association	Replication	Reference	Gene associations with other vasculitides
2000	*TNF*	TNFa2	Northwestern Spain	62/147	0.003	2.50 (1.30, 4.80)	Global disease	No	Mattey *et al*. [46]	BD, AAV, TA [173–175]
2000	*TNF*	TNFa10	Northwestern Spain	62/147	0.02	0.30 (0.10, 0.80)	Global disease	No	Mattey *et al*. [46]	
2000	*CCL5*	rs2107538	Northwestern Spain	30/65	NS	NA	PMR	No	Makki *et al*. [88]	
2000	*ICAM1*	rs1799969	Northern Italy	56/228	0.00005	5.00 (2.20, 11.50)	Global disease (PMR)	No	Salvarani *et al*. [106]	BD [176]
2002	*IL6*	rs1800795	Northwestern Spain	62/124	0.06[b]	2.3 (NA)	PMR	No	Gonzalez-Gay *et al*. [71]	BD, TA [177, 178]
2012	*IL6*	rs7805828	Spain	82/166	0.0119	0.33 (0.13, 0.82)	Global disease	No	Enjuanes *et al*. [72]	
2012	*IL6*	rs1546762	Spain	82/166	0.037	2.04 (1.03, 4.05)	Global disease	No	Enjuanes *et al*. [72]	
2003	*NOS3*	rs1799983	Northern Italy	91/133	0.02	1.60 (1.10, 2.30)	Global disease	No	Salvarani *et al*. [127]	BD [179]
2003	*NOS3*	C-1-T[c]	Northwestern Spain	57/117	0.02	0.30 (0.10, 0.80)	Global disease	No	Amoli *et al*. [126]	
2003	*VEGF*	rs2010963	Northern Italy	92/200	0.019	1.53 (1.06, 2.21)	Global disease	Yes	Boiardi *et al*. [114]	BD [180]
2005	*VEGF*	rs2010963	Northwestern Spain	103/226	0.021	1.75 (1.08, 2.88)	VIM	Yes	Rueda *et al*. [115]	
2012	*VEGF*	rs2010963	Spain	82/166	0.0097	NA	Global disease	Yes	Enjuanes *et al*. [72]	
2012	*VEGF*	rs699946	Spain	82/166	0.0137	NA	Global disease	No	Enjuanes *et al*. [72]	
2012	*VEGF*	rs699947	Spain	82/166	0.0364	NA	Global disease	No	Enjuanes *et al*. [72]	
2004	*IFNG*	allele*3 microsatellite (intron 1)	Northwestern Spain	59/129	0.01	3.13 (1.27, 7.68)	VIM	No	Gonzalez-Gay *et al*. [50]	BD [181]
2004	*IL4*	T-T-C-A-C[d]	Northwestern Spain	82/102	0.02[e]	2.00 (1.00, 3.90)	Global disease	No	Amoli *et al*. [51]	BD [182]
2005	*NOS2A*	TAAA repeat	Northwestern Spain	103/198	0.007	1.98 (1.20, 3.27)	Global disease	No	Gonzalez-Gay *et al*. [121]	
2012	*NOS2A*	rs2779251	Spain	82/166	<0.0001	0.27 (0.14, 0.52)	Global disease	No	Enjuanes *et al*. [72]	
2005	*MCP1*	C-C[f]	Northwestern Spain	79/99	0.03[e]	2.09 (1.09, 4.02)	Global disease	No	Amoli *et al*. [85]	BD [83]
2012	*MCP1*	rs1860190	Spain	82/166	0.0347	NA	Global disease	No	Enjuanes *et al*. [72]	
2006	*IL10*	rs1800872	Northern Italy	140/200	0.0002	2.00 (1.40, 2.80)	Global disease	No	Boiardi *et al*. [57]	BD, AAV [165, 183]
2007	*IL10*	rs1800896	Northwestern Spain	103/226	0.1[g]	1.29 (0.92, 1.80)	Global disease	No	Rueda *et al*. [58]	
2006	*FCGR3A*	rs396991	Northwestern Spain	85/132	0.06[h]	NA	Global disease	No	Morgan *et al*. [148]	BD [184]
2006	*FCGR2A*	rs1801274	Northwestern Spain	85/132	0.05[i]	NA	Global disease	No	Morgan *et al*. [148]	BD [184]
2008	*MMP9*	rs2250889	Philadelphia (USA)	30/23	0.009	NA	Global disease	No	Rodríguez-Pla *et al*. [137]	
2008	*MPO*	rs2333227	Northern Italy	156/235	0.0001	2.00 (1.40, 2.90)	Global disease	No	Salvarani *et al*. [159]	
2009	*TLR4*	rs4986790	Spain	210/678	0.01	1.65 (1.08, 2.52)	Global disease	No	Palomino-Morales *et al*. [140]	BD [185]
2010	*IL18*	rs360719	Spain	212/405	0.003	1.48 (1.13, 1.95)	Global disease	No	Palomino-Morales *et al*. [76]	BD [186]
2010	*IL18*	rs1946518	Spain	212/405	0.02	1.32 (1.04, 1.69)	Global disease	No	Palomino-Morales *et al*. [76]	
2011	*IL12RB2*	rs3790567	Spain	357/574	0.039	1.25 (1.01, 1.54)	Global disease (VIM)	No	Rodriguez-Rodriguez *et al*. [101]	BD [165]
2011	*IL2/IL21*	rs6822844	Spain	272/791	0.04	1.76 (1.02, 3.04)	Jaw claudication	No	Rodriguez-Rodriguez *et al*. [97]	BD, TA [182, 178]
2012	*NLRP1*	rs8182352	Spain and Italy	685/2898	0.0026	1.20 (1.06, 1.35)	Global disease	Yes	Serrano *et al*. [164]	

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-rs1799983*T. [d]SNP order: rs2070874-rs2227284-rs2227282-rs2243266-rs2243267. [e]Haplotype *P*-value. [f]SNP order: rs4586-rs13900. [g]Genotypic $P = 0.034$. [h]Dominant model: $P = 0.03$, OR = 3.09 (1.10, 8.64). [i]Recessive model: $P = 0.02$, OR = 2.10 (1.12, 3.77).

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 *TNFb3*, 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 signalling 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-DRBI*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*A/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*A/G (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 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 (rs1799983*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 metallopeptidase 9

Proteins of the MMP family are zinc-dependent enzymes with proteolitic 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 atherogenesis 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 composes 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 hemoprotein 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 a 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 a 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

1 Salvarani C, Cantini F, Boiardi L *et al*. Polymyalgia rheumatica and giant-cell arteritis. N Engl J Med 2002;347:261–71.

2 Borchers AT, Gershwin ME. Giant cell arteritis: a review of classification, pathophysiology, geoepidemiology and treatment. Autoimmun Rev 2012;11:A544–54.

3 Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ *et al*. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum 2009;61:1454–61.

4 Weyand CM, Goronzy JJ. Giant cell arteritis as an antigen-driven disease. Rheum Dis Clin North Am 1995;21:1027–39.

5 Weyand CM, Younge BR, Goronzy JJ. IFN-gamma and IL-17: the two faces of T-cell pathology in giant cell arteritis. Curr Opin Rheumatol 2011;23:43–9.

6 Cid MC, Campo E, Ercilla G *et al*. Immunohistochemical analysis of lymphoid and macrophage cell subsets and their immunologic activation markers in temporal arteritis. Influence of corticosteroid treatment. Arthritis Rheum 1989;32:884–93.

7 Andersson R, Jonsson R, Tarkowski A *et al*. T cell subsets and expression of immunological activation markers in the arterial walls of patients with giant cell arteritis. Ann Rheum Dis 1987;46:915–23.

8 Duhaut P, Bosshard S, Ducroix JP. Is giant cell arteritis an infectious disease? Biological and epidemiological evidence. Presse Med 2004;33:1403–8.

9 Elling P, Olsson AT, Elling H. Synchronous variations of the incidence of temporal arteritis and polymyalgia rheumatica in different regions of Denmark; association with epidemics of Mycoplasma pneumoniae infection. J Rheumatol 1996;23:112–9.

10 Liozon E, Ouattara B, Rhaiem K *et al*. Familial aggregation in giant cell arteritis and polymyalgia rheumatica: a comprehensive literature review including 4 new families. Clin Exp Rheumatol 2009;27:S89–94.

11 Fietta P, Manganelli P, Zanetti A *et al*. Familial giant cell arteritis and polymyalgia rheumatica: aggregation in 2 families. J Rheumatol 2002;29:1551–5.

12 Bartolome MJ, Martinez-Taboda VM, Lopez-Hoyos M *et al*. Familial aggregation of polymyalgia rheumatica and giant cell arteritis: genetic and T cell repertoire analysis. Clin Exp Rheumatol 2001;19:259–64.

13 Liang GC, Simkin PA, Hunder GG *et al*. Familial aggregation of polymyalgia rheumatica and giant cell arteritis. Arthritis Rheum 1974;17:19–24.

14 Granato JE, Abben RP, May WS. Familial association of giant cell arteritis. A case report and brief review. Arch Intern Med 1981;141:115–7.

15 Mathewson JA, Hunder GG. Giant cell arteritis in two brothers. J Rheumatol 1986;13:190–2.

16 Wernick R, Davey M, Bonafede P. Familial giant cell arteritis: report of an HLA-typed sibling pair and a review of the literature. Clin Exp Rheumatol 1994;12:63–6.

17 Gros F, Maillefert JF, Behin A, Guignier F *et al*. Giant cell arteritis with ocular complications discovered simultaneously in two sisters. Clin Rheumatol 1998;17:58–61.

18 Raptis L, Pappas G, Akritidis N. Horton's three sisters: familial clustering of temporal arteritis. Clin Rheumatol 2007;26:1997–8.

19 Ly KH, Regent A, Tamby MC *et al*. Pathogenesis of giant cell arteritis: more than just an inflammatory condition? Autoimmun Rev 2010;9:635–45.

20 Armstrong RD, Behn A, Myles A *et al*. Histocompatibility antigens in polymyalgia rheumatica and giant cell arteritis. J Rheumatol 1983;10:659–61.

21 Bignon JD, Barrier J, Soulillou JP *et al*. HLA DR4 and giant cell arteritis. Tissue Antigens 1984;24:60–2.

22 Cid MC, Ercilla G, Vilaseca J *et al*. Polymyalgia rheumatica: a syndrome associated with HLA-DR4 antigen. Arthritis Rheum 1988;31:678–82.

23 Combe B, Sany J, Le Quellec A *et al*. Distribution of HLA-DRB1 alleles of patients with polymyalgia rheumatica and giant cell arteritis in a Mediterranean population. J Rheumatol 1998;25:94–8.

24 Dababneh A, Gonzalez-Gay MA, Garcia-Porrua C *et al*. Giant cell arteritis and polymyalgia rheumatica can be differentiated by distinct patterns of HLA class II association. J Rheumatol 1998;25:2140–5.

25 Hansen JA, Healey LA, Wilske KR. Association between giant cell (temporal) arteritis and HLA-Cw3. Hum Immunol 1985;13:193–8.

26 Jacobsen S, Baslund B, Madsen HO *et al*. Mannose-binding lectin variant alleles and HLA-DR4 alleles are associated with giant cell arteritis. J Rheumatol 2002;29:2148–53.

27 Lowenstein MB, Bridgeford PH, Vasey FB *et al*. Increased frequency of HLA-DR3 and DR4 in polymyalgia rheumatica-giant cell arteritis. Arthritis Rheum 1983;26:925–7.

28 Martinez-Taboda VM, Bartolome MJ, Lopez-Hoyos M *et al*. HLA-DRB1 allele distribution in polymyalgia rheumatica and giant cell arteritis: influence on clinical subgroups and prognosis. Semin Arthritis Rheum 2004;34:454–64.

29 Rauzy O, Fort M, Nourhashemi F *et al*. Relation between HLA DRB1 alleles and corticosteroid resistance in giant cell arteritis. Ann Rheum Dis 1998;57:380–2.

30 Richardson JE, Gladman DD, Fam A *et al*. HLA-DR4 in giant cell arteritis: association with polymyalgia rheumatica syndrome. Arthritis Rheum 1987;30:1293–7.

31 Weyand CM, Hicok KC, Hunder GG *et al*. The HLA-DRB1 locus as a genetic component in giant cell arteritis. Mapping of a disease-linked sequence motif to the antigen binding site of the HLA-DR molecule. J Clin Invest 1992;90:2355–61.

32 Weyand CM, Hunder NN, Hicok KC *et al*. HLA-DRB1 alleles in polymyalgia rheumatica, giant cell arteritis, and rheumatoid arthritis. Arthritis Rheum 1994;37:514–20.

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.

34 Gonzalez-Gay MA, Garcia-Porrua C, Llorca J *et al*. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. Medicine 2000;79:283–92.

35 Gonzalez-Gay MA, Garcia-Porrua C, Hajeer AH *et al*. HLA-DRB1*04 may be a marker of severity in giant cell arteritis. Ann Rheum Dis 2000;59:574–5.

36 Gonzalez-Gay MA, Amoli MM, Garcia-Porrua C *et al*. Genetic markers of disease susceptibility and severity in giant cell arteritis and polymyalgia rheumatica. Semin Arthritis Rheum 2003;33:38–48.

37 Labbe P, Flipo RM, Fajardy I *et al*. [HLA DRB1 polymorphism in rhizomelic pseudo-polyarthritis and Horton disease]. Rev Med Interne 1995;16:778–81.

38 Gregersen PK. Susceptibility genes for rheumatoid arthritis—a rapidly expanding harvest. Bull NYU Hosp Jt Dis 2010;68:179–82.

39 Kemp A, Marner K, Nissen SH *et al*. HLA antigens in cases of giant cell arteritis. Acta Ophthalmol 1980;58:1000–4.

40 Gonzalez-Gay MA, Rueda B, Vilchez JR *et al*. Contribution of MHC class I region to genetic susceptibility for giant cell arteritis. Rheumatology 2007;46:431–4.

41 Bahram S, Bresnahan M, Geraghty DE *et al*. A second lineage of mammalian major histocompatibility complex class I genes. Proc Natl Acad Sci USA 1994;91:6259–63.

42 Yabuki K, Mizuki N, Ota M *et al*. Association of MICA gene and HLA-B*5101 with Behcet's disease in Greece. Invest Ophthalmol Vis Sci 1999;40:1921–6.

43 Locksley RM, Killeen N, Lenardo MJ. The TNF and TNF receptor superfamilies: integrating mammalian biology. Cell 2001;104:487–501.

44 Feldmann M, Maini SR. Role of cytokines in rheumatoid arthritis: an education in pathophysiology and therapeutics. Immunol Rev 2008;223:7–19.

45 Hernandez-Rodriguez J, Segarra M, Vilardell C *et al*. Tissue production of pro-inflammatory cytokines (IL-1beta, TNFalpha and IL-6) correlates with the intensity of the systemic inflammatory response and with corticosteroid requirements in giant-cell arteritis. Rheumatology 2004;43:294–301.

46 Mattey DL, Hajeer AH, Dababneh A *et al*. Association of giant cell arteritis and polymyalgia rheumatica with different tumor necrosis factor microsatellite polymorphisms. Arthritis Rheum 2000;43:1749–55.

47 Schoenborn JR, Wilson CB. Regulation of interferon-gamma during innate and adaptive immune responses. Adv Immunol 2007;96:41–101.

48 Weyand CM, Hicok KC, Hunder GG *et al*. Tissue cytokine patterns in patients with polymyalgia rheumatica and giant cell arteritis. Ann Intern Med 1994;121:484–91.

49 Weyand CM, Tetzlaff N, Bjornsson J *et al*. Disease patterns and tissue cytokine profiles in giant cell arteritis. Arthritis Rheum 1997;40:19–26.

50 Gonzalez-Gay MA, Hajeer AH, Dababneh A *et al*. Interferon-gamma gene microsatellite polymorphisms in patients with biopsy-proven giant cell arteritis and isolated polymyalgia rheumatica. Clin Exp Rheumatol 2004;22:S18–20.

51 Amoli MM, Gonzalez-Gay MA, Zeggini E *et al*. Epistatic interactions between HLA-DRB1 and interleukin 4, but not interferon-gamma, increase susceptibility to giant cell arteritis. J Rheumatol 2004;31:2413–7.

52 Moore KW, de Waal Malefyt R, Coffman RL *et al*. Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol 2001;19:683–765.

53 Koch W, Kastrati A, Bottiger C *et al*. Interleukin-10 and tumor necrosis factor gene polymorphisms and risk of coronary artery disease and myocardial infarction. Atherosclerosis 2001;159:137–44.

54 Hajeer AH, Lazarus M, Turner D *et al*. IL-10 gene promoter polymorphisms in rheumatoid arthritis. Scand J Rheumatol 1998;27:142–5.

55 Rood MJ, Keijsers V, van der Linden MW *et al*. Neuropsychiatric systemic lupus erythematosus is associated with imbalance in interleukin 10 promoter haplotypes. Ann Rheum Dis 1999;58:85–9.

56 Hulkkonen J, Pertovaara M, Antonen J *et al*. Genetic association between interleukin-10 promoter region polymorphisms and primary Sjogren's syndrome. Arthritis Rheum 2001;44:176–9.

57 Boiardi L, Casali B, Farnetti E *et al*. Interleukin-10 promoter polymorphisms in giant cell arteritis. Arthritis Rheum 2006;54:4011–7.

58 Rueda B, Roibas B, Martin J *et al*. Influence of interleukin 10 promoter polymorphisms in susceptibility to giant cell arteritis in northwestern Spain. J Rheumatol 2007;34:1535–9.

59 Murphy KM, Reiner SL. The lineage decisions of helper T cells. Nat Rev Immunol 2002;2:933–44.

60 Kishimoto T. Interleukin-6: from basic science to medicine–40 years in immunology. Annu Rev Immunol 2005;23:1–21.

61 Fishman D, Faulds G, Jeffery R *et al*. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest 1998;102:1369–76.

62 Schotte H, Schluter B, Rust S *et al*. Interleukin-6 promoter polymorphism (-174 G/C) in Caucasian German patients with systemic lupus erythematosus. Rheumatology 2001;40:393–400.

63 Cenit MC, Simeon CP, Vonk MC *et al*. Influence of the IL6 gene in susceptibility to systemic sclerosis. J Rheumatol 2012;71:1034–41.

64 Emonts M, Hazes MJ, Houwing-Duistermaat JJ *et al*. Polymorphisms in genes controlling inflammation and tissue repair in rheumatoid arthritis: a case control study. BMC Med Genet 2011;12:36.

65 Fife MS, Ogilvie EM, Kelberman D *et al*. Novel IL-6 haplotypes and disease association. Genes Immun 2005; 6:367–70.

66 Terry CF, Loukaci V, Green FR. Cooperative influence of genetic polymorphisms on interleukin 6 transcriptional regulation. J Biol Chem 2000;275:18138–44.

67 Pascual M, Nieto A, Mataran L *et al*. IL-6 promoter polymorphisms in rheumatoid arthritis. Genes Immun 2000;1: 338–40.

68 Dasgupta B, Panayi GS. Interleukin-6 in serum of patients with polymyalgia rheumatica and giant cell arteritis. Br J Rheumatol 1990;29:456–8.

69 Roche NE, Fulbright JW, Wagner AD *et al*. Correlation of interleukin-6 production and disease activity in polymyalgia rheumatica and giant cell arteritis. Arthritis Rheum 1993;36:1286–94.

70 Salvarani C, Casali B, Farnetti E *et al*. Interleukin-6 promoter polymorphism at position -174 in giant cell arteritis. J Rheumatol 2005;32:2173–7.

71 Gonzalez-Gay MA, Hajeer AH, Dababneh A *et al*. IL-6 promoter polymorphism at position -174 modulates the phenotypic expression of polymyalgia rheumatica in biopsy-proven giant cell arteritis. Clin Exp Rheumatol 2002;20:179–84.

72 Enjuanes A, Benavente Y, Hernandez-Rodriguez J *et al*. Association of NOS2 and potential effect of VEGF, IL6, CCL2 and IL1RN polymorphisms and haplotypes on susceptibility to GCA—a simultaneous study of 130 potentially functional SNPs in 14 candidate genes. Rheumatology 2012;51:841–51.

73 Thompson SR, Humphries SE. Interleukin-18 genetics and inflammatory disease susceptibility. Genes Immun 2007;8: 91–9.

74 Sanchez E, Palomino-Morales RJ, Ortego-Centeno N *et al*. Identification of a new putative functional IL18 gene variant through an association study in systemic lupus erythematosus. Hum Mol Genet 2009;18: 3739–48.

75 Nabili S, Bhatt P, Roberts F *et al*. Local expression of IL-18 in the temporal artery does not correlate with clinical manifestations of giant cell arteritis. Neuro-Ophthalmology 2008;32:3–6.

76 Palomino-Morales RJ, Vazquez-Rodriguez TR, Torres O *et al*. Association between IL-18 gene polymorphisms and biopsy-proven giant cell arteritis. Arthritis Res Ther 2010; 12:R51.

77 Carr MW, Roth SJ, Luther E *et al*. Monocyte chemoattractant protein 1 acts as a T-lymphocyte chemoattractant. Proc Natl Acad Sci USA 1994;91:3652–6.

78 Ellingsen T, Elling P, Olson A *et al*. Monocyte chemoattractant protein 1 (MCP-1) in temporal arteritis and polymyalgia rheumatica. Ann Rheum Dis 2000;59: 775–80.

79 Nelken NA, Coughlin SR, Gordon D *et al*. Monocyte chemoattractant protein-1 in human atheromatous plaques. J Clin Invest 1991;88:1121–7.

80 Koch AE, Kunkel SL, Harlow LA *et al*. Enhanced production of monocyte chemoattractant protein-1 in rheumatoid arthritis. J Clin Invest 1992;90:772–9.

81 Kim HL, Lee DS, Yang SH *et al*. The polymorphism of monocyte chemoattractant protein-1 is associated with the renal disease of SLE. Am J Kidney Dis 2002;40: 1146–52.

82 Kim MP, Wahl LM, Yanek LR *et al*. A monocyte chemoattractant protein-1 gene polymorphism is associated with occult ischemia in a high-risk asymptomatic population. Atherosclerosis 2007;193:366–72.

83 Kim SK, Jang WC, Ahn YC *et al*. Promoter -2518 single nucleotide polymorphism of monocyte chemoattractant protein-1 is associated with clinical severity in Behcet's disease. Inflamm Res 2012;61:541–5.

84 Aguilar F, Gonzalez-Escribano MF, Sanchez-Roman J *et al*. MCP-1 promoter polymorphism in Spanish patients with systemic lupus erythematosus. Tissue Antigens 2001;58:335–8.

85 Amoli MM, Salway F, Zeggini E *et al*. MCP-1 gene haplotype association in biopsy proven giant cell arteritis. J Rheumatol 2005;32:507–10.

86 Bacon KB, Premack BA, Gardner P *et al*. Activation of dual T cell signaling pathways by the chemokine RANTES. Science 1995;269:1727–30.

87 Pulsatelli L, Meliconi R, Boiardi L *et al*. Elevated serum concentrations of the chemokine RANTES in patients with polymyalgia rheumatica. Clin Exp Rheumatol 1998; 16:263–8.

88 Makki RF, al Sharif F, Gonzalez-Gay MA *et al*. RANTES gene polymorphism in polymyalgia rheumatica, giant cell arteritis and rheumatoid arthritis. Clin Exp Rheumatol 2000;18:391–3.

89 Leonard WJ, Spolski R. Interleukin-21: a modulator of lymphoid proliferation, apoptosis and differentiation. Nat Rev Immunol 2005;5:688–98.

90 Ma A, Koka R, Burkett P. Diverse functions of IL-2, IL-15, and IL-7 in lymphoid homeostasis. Annu Rev Immunol 2006;24:657–79.

91 Diaz-Gallo LM, Simeon CP, Broen JC *et al*. Implication of IL-2/IL-21 region in systemic sclerosis genetic susceptibility. Ann Rheum Dis 2012 (in press).

92 van Heel DA, Franke L, Hunt KA *et al*. A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21. Nat Genet 2007;39:827–9.

93 Festen EA, Goyette P, Scott R *et al*. Genetic variants in the region harbouring IL2/IL21 associated with ulcerative colitis. Gut 2009;58:799–804.

94 Zhernakova A, Alizadeh BZ, Bevova M *et al*. Novel association in chromosome 4q27 region with rheumatoid arthritis and confirmation of type 1 diabetes point to a general risk locus for autoimmune diseases. Am J Hum Genet 2007;81:1284–8.

95 Maiti AK, Kim-Howard X, Viswanathan P *et al*. Confirmation of an association between rs6822844 at the IL2-IL21 region and multiple autoimmune

diseases: evidence of a general susceptibility locus. Arthritis Rheum 2010;62:323–9.

96 Hollis-Moffatt JE, Chen-Xu M, Topless R *et al*. Only one independent genetic association with rheumatoid arthritis within the KIAA1109-TENR-IL2-IL21 locus in Caucasian sample sets: confirmation of association of rs6822844 with rheumatoid arthritis at a genome-wide level of significance. Arthritis Res Ther 2010;12:R116.

97 Rodriguez-Rodriguez L, Castaneda S, Vazquez-Rodriguez TR *et al*. Role of the rs6822844 gene polymorphism at the IL2-IL21 region in biopsy-proven giant cell arteritis. Clin Exp Rheumatol 2011;29:S12–6.

98 Presky DH, Yang H, Minetti LJ *et al*. A functional interleukin 12 receptor complex is composed of two beta-type cytokine receptor subunits. Proc Natl Acad Sci USA 1996;93:14002–7.

99 Koch MA, Thomas KR, Perdue NR *et al*. T-bet(+) Treg cells undergo abortive Th1 cell differentiation due to impaired expression of IL-12 receptor beta2. Immunity 2012;37:501–10.

100 Deng J, Younge BR, Olshen RA *et al*. Th17 and Th1 T-cell responses in giant cell arteritis. Circulation 2010; 121:906–15.

101 Rodriguez-Rodriguez L, Carmona FD, Castaneda S *et al*. Role of rs1343151 IL23R and rs3790567 IL12RB2 polymorphisms in biopsy-proven giant cell arteritis. J Rheumatol 2011;38:889–92.

102 Dustin ML, Rothlein R, Bhan AK *et al*. Induction by IL 1 and interferon-gamma: tissue distribution, biochemistry, and function of a natural adherence molecule (ICAM-1). J Immunol 1986;137:245–54.

103 Springer TA. Traffic signals for lymphocyte recirculation and leukocyte emigration: the multistep paradigm. Cell 1994;76:301–14.

104 Cid MC, Cebrian M, Font C *et al*. Cell adhesion molecules in the development of inflammatory infiltrates in giant cell arteritis: inflammation-induced angiogenesis as the preferential site of leukocyte-endothelial cell interactions. Arthritis Rheum 2000;43:184–94.

105 Coll-Vinent B, Vilardell C, Font C *et al*. Circulating soluble adhesion molecules in patients with giant cell arteritis. Correlation between soluble intercellular adhesion molecule-1 (sICAM-1) concentrations and disease activity. Ann Rheum Dis 1999;58:189–92.

106 Salvarani C, Casali B, Boiardi L *et al*. Intercellular adhesion molecule 1 gene polymorphisms in polymyalgia rheumatica/giant cell arteritis: association with disease risk and severity. J Rheumatol 2000;27:1215–21.

107 Amoli MM, Shelley E, Mattey DL *et al*. Lack of association between intercellular adhesion molecule-1 gene polymorphisms and giant cell arteritis. J Rheumatol 2001;28:1600–4.

108 Neufeld G, Cohen T, Gengrinovitch S *et al*. Vascular endothelial growth factor (VEGF) and its receptors. FASEB J 1999;13:9–22.

109 Cid MC, Hernandez-Rodriguez J, Esteban MJ *et al*. Tissue and serum angiogenic activity is associated with low prevalence of ischemic complications in patients with giant-cell arteritis. Circulation 2002;106: 1664–71.

110 Kaiser M, Younge B, Bjornsson J *et al*. Formation of new vasa vasorum in vasculitis. Production of angiogenic cytokines by multinucleated giant cells. Am J Pathol 1999;155:765–74.

111 Meliconi R, Pulsatelli L, Dolzani P *et al*. Vascular endothelial growth factor production in polymyalgia rheumatica. Arthritis Rheum 2000;43:2472–80.

112 Baldini M, Maugeri N, Ramirez GA *et al*. Selective up-regulation of the soluble pattern-recognition receptor pentraxin 3 and of vascular endothelial growth factor in giant cell arteritis: relevance for recent optic nerve ischemia. Arthritis Rheum 2012;64:854–65.

113 Lambrechts D, Storkebaum E, Morimoto M *et al*. VEGF is a modifier of amyotrophic lateral sclerosis in mice and humans and protects motoneurons against ischemic death. Nat Genet 2003;34:383–94.

114 Boiardi L, Casali B, Nicoli D *et al*. Vascular endothelial growth factor gene polymorphisms in giant cell arteritis. J Rheumatol 2003;30:2160–4.

115 Rueda B, Lopez-Nevot MA, Lopez-Diaz MJ *et al*. A functional variant of vascular endothelial growth factor is associated with severe ischemic complications in giant cell arteritis. J Rheumatol 2005;32:1737–41.

116 Yki-Jarvinen H, Bergholm R, Leirisalo-Repo M. Increased inflammatory activity parallels increased basal nitric oxide production and blunted response to nitric oxide in vivo in rheumatoid arthritis. Ann Rheum Dis 2003;62:630–4.

117 Knowles RG, Moncada S. Nitric oxide synthases in mammals. Biochem J 1994;298(Pt 2):249–58.

118 Bogdan C. Nitric oxide and the immune response. Nat Immunol 2001;2:907–16.

119 Rittner HL, Kaiser M, Brack A *et al*. Tissue-destructive macrophages in giant cell arteritis. Circ Res 1999;84: 1050–8.

120 Kobayashi Y. The regulatory role of nitric oxide in proinflammatory cytokine expression during the induction and resolution of inflammation. J Leukoc Biol 2010; 88:1157–62.

121 Gonzalez-Gay MA, Oliver J, Sanchez E *et al*. Association of a functional inducible nitric oxide synthase promoter variant with susceptibility to biopsy-proven giant cell arteritis. J Rheumatol 2005;32:2178–82.

122 Moncada S. Nitric oxide in the vasculature: physiology and pathophysiology. Ann N Y Acad Sci 1997;811:60–7; discussion 67–9.

123 Radomski MW, Palmer RM, Moncada S. Endogenous nitric oxide inhibits human platelet adhesion to vascular endothelium. Lancet 1987;2:1057–8.

124 Kubes P, Suzuki M, Granger DN. Nitric oxide: an endogenous modulator of leukocyte adhesion. Proc Natl Acad Sci USA 1991;88:4651–5.

125 De Caterina R, Libby P, Peng HB *et al*. Nitric oxide decreases cytokine-induced endothelial activation. Nitric oxide selectively reduces endothelial expression of adhesion molecules and proinflammatory cytokines. J Clin Invest 1995;96:60–8.

126 Amoli MM, Garcia-Porrua C, Llorca J *et al*. Endothelial nitric oxide synthase haplotype associations in biopsy-proven giant cell arteritis. J Rheumatol 2003;30:2019–22.

127 Salvarani C, Casali B, Nicoli D *et al*. Endothelial nitric oxide synthase gene polymorphisms in giant cell arteritis. Arthritis Rheum 2003;48:3219–23.

128 Galis ZS, Khatri JJ. Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly. Circ Res 2002;90:251–62.

129 de Nooijer R, Verkleij CJ, von der Thusen JH *et al*. Lesional overexpression of matrix metalloproteinase-9 promotes intraplaque hemorrhage in advanced lesions but not at earlier stages of atherogenesis. Arterioscler Thromb Vasc Biol 2006;26:340–6.

130 Sorbi D, French DL, Nuovo GJ *et al*. Elevated levels of 92-kd type IV collagenase (matrix metalloproteinase 9) in giant cell arteritis. Arthritis Rheum 1996;39: 1747–53.

131 Nikkari ST, Hoyhtya M, Isola J *et al*. Macrophages contain 92-kd gelatinase (MMP-9) at the site of degenerated internal elastic lamina in temporal arteritis. Am J Pathol 1996;149:1427–33.

132 Tomita T, Imakawa K. Matrix metalloproteinases and tissue inhibitors of metalloproteinases in giant cell arteritis: an immunocytochemical study. Pathology 1998; 30:40–50.

133 Rodriguez-Pla A, Bosch-Gil JA, Rossello-Urgell J *et al*. Metalloproteinase-2 and -9 in giant cell arteritis: involvement in vascular remodeling. Circulation 2005;112: 264–9.

134 Segarra M, Garcia-Martinez A, Sanchez M *et al*. Gelatinase expression and proteolytic activity in giant-cell arteritis. Ann Rheum Dis 2007;66:1429–35.

135 Zhang B, Ye S, Herrmann SM *et al*. Functional polymorphism in the regulatory region of gelatinase B gene in relation to severity of coronary atherosclerosis. Circulation 1999;99:1788–94.

136 Jones GT, Phillips VL, Harris EL *et al*. Functional matrix metalloproteinase-9 polymorphism (C-1562T) associated with abdominal aortic aneurysm. J Vasc Surg 2003;38:1363–7.

137 Rodriguez-Pla A, Beaty TH, Savino PJ *et al*. Association of a nonsynonymous single-nucleotide polymorphism of matrix metalloproteinase 9 with giant cell arteritis. Arthritis Rheum 2008;58:1849–53.

138 Medzhitov R, Preston-Hurlburt P, Janeway CA Jr. A human homologue of the Drosophila Toll protein signals activation of adaptive immunity. Nature 1997; 388:394–7.

139 Ferwerda B, McCall MB, Verheijen K *et al*. Functional consequences of Toll-like receptor 4 polymorphisms. Mol Med 2008;14:346–52.

140 Palomino-Morales R, Torres O, Vazquez-Rodriguez TR *et al*. Association between toll-like receptor 4 gene polymorphism and biopsy-proven giant cell arteritis. J Rheumatol 2009;36:1501–6.

141 Alvarez-Rodriguez L, Lopez-Hoyos M, Beares I *et al*. Lack of association between Toll-like receptor 4 gene polymorphisms and giant cell arteritis. Rheumatology 2011;50:1562–8.

142 Boiardi L, Casali B, Farnetti E *et al*. Toll-like receptor 4 (TLR4) gene polymorphisms in giant cell arteritis. Clin Exp Rheumatol 2009;27:S40–4.

143 Alvarez-Rodriguez L, Munoz Cacho P, Lopez-Hoyos M *et al*. Toll-like receptor 4 gene polymorphism and giant cell arteritis susceptibility: a cumulative meta-analysis. Autoimmun Rev 2011;10:790–2.

144 Song GG, Choi SJ, Ji JD *et al*. Toll-like receptor polymorphisms and vasculitis susceptibility: meta-analysis and systematic review. Mol Biol Rep 2013;40: 1315–23.

145 Weyand CM, Ma-Krupa W, Pryshchep O *et al*. Vascular dendritic cells in giant cell arteritis. Ann N Y Acad Sci 2005;1062:195–208.

146 Arbour NC, Lorenz E, Schutte BC *et al*. TLR4 mutations are associated with endotoxin hyporesponsiveness in humans. Nat Genet 2000;25:187–91.

147 Takai T. Roles of Fc receptors in autoimmunity. Nat Rev Immunol 2002;2:580–92.

148 Morgan AW, Robinson JI, Barrett JH *et al*. Association of FCGR2A and FCGR2A-FCGR3A haplotypes with susceptibility to giant cell arteritis. Arthritis Res Ther 2006;8: R109.

149 Klebanoff SJ. Oxygen metabolism and the toxic properties of phagocytes. Ann Intern Med 1980;93:480–9.

150 Klebanoff SJ. Myeloperoxidase: friend and foe. J Leukoc Biol 2005;77:598–625.

151 Nambi V. The use of myeloperoxidase as a risk marker for atherosclerosis. Curr Atheroscler Rep 2005;7: 127–31.

152 Zhang R, Brennan ML, Fu X *et al*. Association between myeloperoxidase levels and risk of coronary artery disease. JAMA 2001;286:2136–42.

153 Choi HK, Liu S, Merkel PA *et al*. Diagnostic performance of antineutrophil cytoplasmic antibody tests for idiopathic vasculitides: metaanalysis with a focus on anti-myeloperoxidase antibodies. J Rheumatol 2001;28: 1584–90.

154 Nikpoor B, Turecki G, Fournier C *et al*. A functional myeloperoxidase polymorphic variant is associated with coronary artery disease in French-Canadians. Am Heart J 2001;142:336–9.

155 Pecoits-Filho R, Stenvinkel P, Marchlewska A *et al*. A functional variant of the myeloperoxidase gene is associated with cardiovascular disease in end-stage renal disease patients. Kidney Int Suppl 2003;84: S172–6.

156 Asselbergs FW, Reynolds WF, Cohen-Tervaert JW *et al*. Myeloperoxidase polymorphism related to cardiovascular events in coronary artery disease. Am J Med 2004; 116:429–30.

157 Piedrafita FJ, Molander RB, Vansant G *et al*. An Alu element in the myeloperoxidase promoter contains a composite SP1-thyroid hormone-retinoic acid response element. J Biol Chem 1996;271:14412–20.

158 Vansant G, Reynolds WF. The consensus sequence of a major Alu subfamily contains a functional retinoic acid response element. Proc Natl Acad Sci USA 1995;92: 8229–33.

159 Salvarani C, Casali B, Farnetti E *et al*. -463 G/A myeloperoxidase promoter polymorphism in giant cell arteritis. Ann Rheum Dis 2008;67:485–8.

160 Tschopp J, Martinon F, Burns K. NALPs: a novel protein family involved in inflammation. Nat Rev Mol Cell Biol 2003;4:95–104.

161 Pontillo A, Vendramin A, Catamo E *et al*. The missense variation Q705K in CIAS1/NALP3/NLRP3 gene and an NLRP1 haplotype are associated with celiac disease. Am J Gastroenterol 2011;106:539–44.

162 Dieude P, Guedj M, Wipff J *et al*. NLRP1 influences the systemic sclerosis phenotype: a new clue for the contribution of innate immunity in systemic sclerosis-related fibrosing alveolitis pathogenesis. Ann Rheum Dis 2011; 70:668–74.

163 Magitta NF, Boe Wolff AS, Johansson S *et al*. A coding polymorphism in NALP1 confers risk for autoimmune Addison's disease and type 1 diabetes. Genes Immun 2009;10:120–4.

164 Serrano A, Carmona FD, Castañeda S *et al*. Evidence of association of the NLRP1 gene with giant cell arteritis. Ann Rheum Dis 2013;72:628–30.

165 Remmers EF, Cosan F, Kirino Y *et al*. Genome-wide association study identifies variants in the MHC class I, IL10, and IL23R-IL12RB2 regions associated with Behcet's disease. Nat Genet 2010;42: 698–702.

166 Mizuki N, Meguro A, Ota M *et al*. Genome-wide association studies identify IL23R-IL12RB2 and IL10 as Behcet's disease susceptibility loci. Nat Genet 2010;42: 703–6.

167 Kirino Y, Bertsias G, Ishigatsubo Y *et al*. Genome-wide association analysis identifies new susceptibility loci for Behcet's disease and epistasis between HLA-B*51 and ERAP1. Nat Genet 2013;45:202–7.

168 Lyons PA, Rayner TF, Trivedi S *et al*. Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med 2012;367:214–23.

169 Cortes A, Brown MA. Promise and pitfalls of the Immunochip. Arthritis Res Ther 2011;13:101.

170 Trynka G, Hunt KA, Bockett NA *et al*. Dense genotyping identifies and localizes multiple common and rare variant association signals in celiac disease. Nat Genet 2011;43: 1193–201.

171 Liu JZ, Almarri MA, Gaffney DJ *et al*. Dense fine-mapping study identifies new susceptibility loci for primary biliary cirrhosis. Nat Genet 2012;44:1137–41.

172 Eyre S, Bowes J, Diogo D *et al*. High-density genetic mapping identifies new susceptibility loci for rheumatoid arthritis. Nat Genet 2012;44:1336–40.

173 Touma Z, Farra C, Hamdan A *et al*. TNF polymorphisms in patients with Behcet disease: a meta-analysis. Arch Med Res 2010;41:142–6.

174 Spriewald BM, Witzke O, Wassmuth R *et al*. Distinct tumour necrosis factor alpha, interferon gamma, interleukin 10, and cytotoxic T cell antigen 4 gene polymorphisms in disease occurrence and end stage renal disease in Wegener's granulomatosis. Ann Rheum Dis 2005;64:457–61.

175 Lv N, Dang A, Zhu X *et al*. The role of tumor necrosis factor-alpha promoter genetic variation in Takayasu arteritis susceptibility and medical treatment. J Rheumatol 2011;38:2602–7.

176 Ben Dhifallah I, Karray EF, Sassi F *et al*. Intercellular adhesion molecule 1 K469E gene polymorphism is associated with presence of skin lesions in Tunisian Behcet's disease patients. Tissue Antigens 2010;75: 74–8.

177 Chang HK, Jang WC, Park SB *et al*. Association between interleukin 6 gene polymorphisms and Behcet's disease in Korean people. Ann Rheum Dis 2005;64: 339–40.

178 Saruhan-Direskeneli G, Bicakcigil M, Yilmaz V *et al*. Interleukin (IL)-12, IL-2, and IL-6 gene polymorphisms in Takayasu's arteritis from Turkey. Hum Immunol 2006;67: 735–40.

179 Salvarani C, Boiardi L, Casali B *et al*. Endothelial nitric oxide synthase gene polymorphisms in Behcet's disease. J Rheumatol 2002;29:535–40.

180 Salvarani C, Boiardi L, Casali B *et al*. Vascular endothelial growth factor gene polymorphisms in Behcet's disease. J Rheumatol 2004;31:1785–9.

181 Alayli G, Aydin F, Coban AY *et al*. T helper 1 type cytokines polymorphisms: association with susceptibility to Behcet's disease. Clin Rheumatol 2007;26: 1299–305.

182 Shahram F, Nikoopour E, Rezaei N *et al*. Association of interleukin-2, interleukin-4 and transforming growth factor-beta gene polymorphisms with Behcet's disease. Clin Exp Rheumatol 2011;29:S28–31.

183 Zhou Y, Giscombe R, Huang D *et al*. Novel genetic association of Wegener's granulomatosis with the interleukin 10 gene. J Rheumatol 2002;29:317–20.

184 Aksu K, Kitapcioglu G, Keser G *et al*. FcgammaRIIa, IIIa and IIIb gene polymorphisms in Behcet's disease: do they have any clinical implications? Clin Exp Rheumatol 2008;26:S77–83.

185 Meguro A, Ota M, Katsuyama Y *et al*. Association of the Toll-like receptor 4 gene polymorphisms with Behcet's disease. Ann Rheum Dis 2008;67:725–7.

186 Htoon J, Nadig A, Hughes T *et al*. IL18 polymorphism is associated with Behcet's disease but not lupus in patients from Turkey. J Rheumatol 2011;38:962–3.