The presence of both *HLA-DRB1*04:01* and *HLA-B*15:01* increases the susceptibility to cranial and extracranial giant cell arteritis

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ABSTRACT

Objective. *To determine if patients with the predominant extracranial large-vessel vasculitis (LVV) pattern of giant cell arteritis (GCA) have a distinctive HLA-B association, different from that reported in biopsy-proven cranial GCA patients. In a further step we assessed if the combination of HLA-B and HLA-DRB1 alleles confers an increased risk for GCA susceptibility, both for the cranial and extracranial LVV phenotypes.*

Methods. *A total of 184 patients with biopsy-proven cranial GCA, 105 with LVV-GCA and 486 healthy controls were included in our study. We compared HLA-B phenotype frequencies between the three groups.*

Results. *HLA-B*15 phenotype was significantly increased in patients with classic cranial GCA compared to controls (14.7% vs. 5.8%, respectively; p<0.01; OR [95% CI]=2.81 [1.54-5.11]). It was mainly due to the HLA-B*15:01 allele (12.5% vs. 4.0%, respectively; p<0.01; OR [95% CI]=3.51 [1.77-6.99]) and remained statistically significant after Bonferroni correction. Similar HLA-B*15 association was observed in patients with the LVV-GCA (11.4% vs. 5.8%, p=0.04, OR [95% CI]=2.11 [1.04-4.30]). This association was also mainly due to the HLA-B*15:01 allele (10.5% vs. 4.0%, respectively; p=0.0054; OR [95% CI]=2.88 [1.19-6.59]). Noteworthy, the presence of HLA-B*15:01 together with HLA-DRB1*04:01 led to an increased risk of developing both cranial and extracranial LVV-GCA.*

Conclusion. *Susceptibility to GCA is strongly related to the HLA region, regardless of the clinical phenotype of expression of the disease.*

Introduction

Giant cell arteritis (GCA) is a systemic vasculitis characterised by the involvement of medium and large vessels in individuals over 50 years (1). Classically, GCA was described as a vasculitis with a predilection for the affection of cranial arteries, presenting with cranial ischaemic manifestations such as headache, jaw claudication or visual ischaemic manifestations (2, 3). However, in the recent years the use of imaging techniques has allowed to identify a different subset of GCA patients with predominant extracranial involvement (4-7). These patients with the predominant extracranial large-vessel vasculitis (LVV) pattern of GCA are usually younger than those with the classic cranial phenotype and they often present as a glucocorticoid-resistant polymyalgia rheumatica or as patients with fever or constitutional syndrome of unknown origin (7-10).

Genetic factors seem to play an important role in the pathogenesis of GCA (11). This vasculitis follows a polygenic inheritance pattern, mostly associated with HLA class II genes (12-15). However, it remains unknown whether a different genetic susceptibility and/or cytokine profile expression may explain the different clinical phenotypes of GCA. In a first attempt to determine if genetic differences between classic-cranial GCA and LVV-GCA existed, we performed a comparative analysis of *HLA-DRB1** phenotype frequencies between both subgroups. In this study, we could not find any differences as both cranial and extracranial-LVV-GCA shared a strong association with *HLA-DRB1*04*, in particular with *HLA-DRB1*04:01* (16).

Besides the strong association of GCA with HLA class II genes, there is evidence that class I region is also involved in the genetic susceptibility to cranial GCA. In this regard, association with *HLA-B*15* was observed in a cohort of patients with biopsy-proven GCA (17). This implication of HLA class I genes in the susceptibility to cranial GCA was further confirmed in large-scale studies (13, 14).

HLA class I genes also play an important role in the genetic susceptibility of Takayasu's arteritis (TAK) (14, 18). LVV-GCA, as well as TAK, usually affects individuals who are younger than patients with the classic cranial pattern of GCA, and are characterised by the affection of larger arteries that may lead to the development of stenosis, aneurysms and aortic dissection (19, 20). Since TAK and classic cranial GCA differ in HLA association, we aimed to determine if patients with LVV-GCA have a distinctive *HLA-B* association, different from that reported in biopsy-proven cranial GCA patients. In a further step we assessed if the combination of *HLA-B* and *HLA-DRB1* alleles confers an increased risk for GCA susceptibility, either for the cranial and extracranial LVV phenotypes.

Methods

Patients and controls

A total of 184 patients with biopsy-proven cranial GCA, 105 with LVV-GCA and 486 healthy controls were included in our study. All patients and controls were Spanish of European ancestry. They were recruited in ten collaborative centres: Hospital Universitario Marqués de Valdecilla (Santander, Spain), Hospital Universitario de Basurto (Bilbao, Spain), Hospital de León (León, Spain), Hospital Universitario de La Princesa (Madrid, Spain), Hospital Universitario y Politécnico La Fe (Valencia, Spain), Hospital Universitario Virgen del Rocío (Sevilla, Spain), Hospital Universitario de Pontevedra (Pontevedra, Spain), Hospital Universitario Lucus Augusti (Lugo, Spain) Hospital Universitario San Cecilio (Granada, Spain) and Hospital San Agustín (Avilés, Spain).

The study was approved by the Ethics Committee of clinical research of Cantabria for Hospital Universitario Marqués de Valdecilla as well as by the remaining participant centres mentioned above. All subjects provided informed written consent before being enrolled in the study. The procedures followed were in accordance with the ethical standards of the approved guidelines and regulations, according to the Declaration of Helsinki.

Patients with classic cranial phenotype of GCA

A set of 184 patients with the cranial phenotype of GCA were included in our study. GCA diagnosis was based on the American College of Rheumatology (ACR) 1990 classification criteria (21). In addition, the diagnosis of GCA was confirmed in all patients by a positive temporal artery biopsy showing the typical histopathologic findings of this vasculitis. Noteworthy, none of them presented clinical symptoms suggesting peripheral arterial involvement.

Patients with extracranial LVV-GCA phenotype

A cohort of 105 ethnically matched patients with the extracranial LVV-GCA phenotype were also included in our study. LVV-GCA diagnosis was established by experienced rheumatologists based on confirmatory imaging techniques, such as 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT), angiographic magnetic resonance (MRI-A) and/or computed tomography angiography (CT-A).

For the purpose of the present study, in an attempt to assess a well-defined LVV-GCA group of patients who were clinically different from the former ones of cranial GCA, patients with LVV-GCA who presented cranial GCA symptoms were excluded from the analysis (Table I). Patients with other underlying inflammatory conditions, infections or neoplastic diseases that could present with LVV involvement were also excluded.

Healthy controls

A total of 486 ethnically matched unaffected control subjects, without history of vasculitis or any other autoimmune disease, constituted by blood donors from Hospital Universitario Marqués de Valdecilla (Santander, Spain) and National DNA Bank Repository (Salamanca, Spain), were also included in this study.

HLA-B genotyping

High-molecular-weight genomic DNA was extracted from whole blood using the Maxwell 16 Blood DNA Purification Kit (Promega Biotech Ibérica, S.L., Spain) according to the manufacturer's instructions. All DNA samples were stored at -20°C until the HLA analysis. DNA-based *HLA-B* typing was performed using the Luminex 100 system (Luminex, Austin, TX, USA) and the Lifecodes HLA typing Kits, and analysed by using the MatchIT software (Gen-Probe Inc., San Diego, CA, USA) following the manufacturer's instructions. *HLA-DRB1* typing was performed as previously reported (15).

Statistical analysis

HLA-B phenotype frequencies were calculated by direct counting. Comparisons between *HLA-B* phenotype of patients with classic cranial GCA and healthy controls, patients with extracranial LVV-GCA and healthy controls, and patients with classic cranial GCA and those with the extracranial LVV-GCA pattern were performed. The strength of association was estimated using odds ratios (OR) and 95% confidence intervals (CI). Levels of significance were determined using contingency tables and either chi-square test or Fisher's exact test (expected values <5). Results were subjected to Bonferroni adjustment for multiple comparisons. After the adjustment, a value of $P_{BNF} < 0.05$ was considered statistically significant.

All analyses were performed with Stata statistical software v. 12/SE (StataCorp., College Station, TX, USA).

Results

HLA-B phenotype frequencies were compared between patients with the classic cranial GCA pattern and healthy controls (Table II). Noteworthy, the frequency of the *HLA-B*15* phenotype

Table I. Main clinical features of patients with classic cranial GCA and LVV-GCA pattern.

	Classic cranial GCA pattern n=184	LVV-GCA pattern n=105	*p*
Age at diagnosis, years (mean ± SD)	74.0 ± 10.4	67.5 ± 9.8	<0.01
Women, n (%)	122 (66.3%)	76 (72.4%)	0.24
Positive TAB, n (%)	184 (100%)	3/37 (8.1%)	<0.01
Headache, n (%)	144 (78.3%)	0 (0%)	<0.01
Abnormal temporal artery on physical examination, n (%)	109 (59.2%)	0 (0%)	<0.01
Jaw claudication, n (%)	72 (39.1%)	0 (0%)	<0.01
Polymyalgia rheumatica, n (%)	74 (40.2%)	86 (81.9%)	<0.01
Visual manifestations, n (%)	47 (25.5%)	0 (0%)	<0.01
Permanent visual loss, n (%)	21 (11.4%)	0 (0%)	<0.01
Peripheral arteriopathy, n (%)	0 (0%)	12 (11.4%)	<0.01
Stroke, n (%)	8 (4.4%)	0 (0%)	0.05
ESR >40 mm/1st h. at diagnosis, n (%)	181 (98.4%)	84 (80.0%)	<0.01

ESR: erythrocyte sedimentation rate; GCA: giant cell arteritis; LVV: large-vessel vasculitis; SD: standard deviation; TAB: temporal artery biopsy.

Table II. HLA-B frequencies in patients with a classic cranial GCA pattern, LVV-GCA pattern and healthy controls.

HLA-B		Classic cranial GCA pattern (n=184)	LVV-GCA pattern (n=105)	Healthy controls (n=486)
HLA-B*07	07:02	13.6 (25)	18.1 (19)	13.8 (67)
	07:05	0	0	2.1 (10)
HLA-B*08	08:01	17.4 (32)	13.3 (14)	9.7 (47)
HLA-B*13	13:02	7.1 (13)	1.9 (2)	3.3 (16)
HLA-B*14	14:01	5.4 (10)	2.9 (3)	3.5 (17)
	14:02	15.2 (28)	10.5 (11)	10.5 (51)
HLA-B*15	15:01	12.5 (23)a	10.5 (11)	4.0 (19)a
	15:03	0.5 (1)	0	1.0 (5)
	15:17	1.6 (3)	1.0 (1)	0.8 (4)
HLA-B*18	18:01	10.9 (20)	9.5 (10)	17.3 (84)
HLA-B*27	27:05	6.0 (11)	10.5 (11)	5.1 (25)
HLA-B*35	35:01	8.7 (16)	8.6 (9)	7.8 (38)
	35:02	1.1 (2)	0	4.1 (20)
	35:03	4.9 (9)	3.8 (4)	4.3 (21)
	35:08	1.6 (3)	0	4.5 (22)
HLA-B*37	37:01	1.6 (3)	1.0 (1)	2.1 (10)
HLA-B*38	38:01	4.3 (8)	4.8 (5)	8.6 (42)
HLA-B*39	39:01	3.8 (7)	1.9 (2)	2.3 (11)
	39:06	1.1 (2)	1.0 (1)	2.1 (10)
HLA-B*40	40:01	5.4 (10)	10.5 (11)	4.1 (20)
	40:02	1.1 (2)	1.9 (2)	1.4 (7)
HLA-B*41	41:01	0	1.0 (1)	3.3 (16)
	41:02	0	1.0 (1)	0.6 (3)
HLA-B*44	44:02	13.6 (25)	13.3 (14)	13.4 (65)
	44:03	14.1 (26)	15.2 (16)	12.1 (59)
HLA-B*45	45:01	1.1 (2)	3.8 (4)	3.1 (15)
HLA-B*49	49:01	4.3 (8)	5.7 (6)	7.0 (34)
HLA-B*50	50:01	7.1 (13)	7.6 (8)	3.9 (19)
HLA-B*51	51:01	16.8 (31)	11.4 (12)	12.8 (62)
HLA-B*52	52:01	2.2 (4)	1.9 (2)	3.1 (15)
HLA-B*53	53:01	3.2 (6)	5.7 (6)	2.3 (11)
HLA-B*55	55:01	1.6 (3)	1.9 (2)	2.5 (12)
HLA-B*57	57:01	6.5 (12)	9.5 (10)	5.1 (25)
HLA-B*58	58:01	1.1 (2)	2.9 (3)	2.1 (10)

HLA: human leukocyte antigen; GCA: giant cell arteritis; LVV: large-vessel vasculitis.
Values are presented as percentages (number of individuals).
Results that remained statistically significant after Bonferroni adjustment are highlighted in bold: a $p<0.01$, OR=3.51 [95% CI: 1.77-6.99], PBNF <0.01.

was significantly increased in patients with cranial GCA compared to controls (14.7% *vs*. 5.8%, respectively; $p<0.01$; OR [95% CI] =2.81 [1.54–5.11]). This association was mainly due to the *HLA-B*15:01* allele (12.5% *vs*. 4.0%, respectively; $p<0.01$; OR [95% CI] =3.51 [1.77–6.99]) and remained statistically significant after Bonferroni correction ($P_{BNF}<0.01$) (Table II).

Regarding the LVV-GCA phenotype, similar *HLA-B* differences to those mentioned above for the cranial pattern were observed when LVV-GCA patients were compared to controls (Table II). This was especially true for *HLA-B*15*, which was significantly increased in these patients with extracranial LVV-GCA compared to healthy controls (11.4% *vs*. 5.8%, $p=0.04$, OR [95% CI] =2.11 [1.04–4.30]). This association was also mainly due to the *HLA-B*15:01* allele (10.5% *vs*. 4.0%, respectively; $p=0.0054$; OR [95% CI] =2.88 [1.19–6.59]) (Table II). These results remained significant after excluding the three patients with extracranial LVV-GCA who had a positive TAB.

When cranial and extracranial LVV-GCA groups were compared, no significant differences in terms of the *HLA-B* phenotype association were observed (Table II).

Noteworthy, the presence of *HLA-B*15:01* together with *HLA-DRB1* 04:01* led to an increased risk of developing both cranial GCA and extracranial LVV-GCA (Table III).

Discussion

Our study constitutes the first attempt to determine whether there is a different HLA class I susceptibility pattern in GCA patients who present the cranial and the extracranial LVV phenotype. However, we found no *HLA-B* differences between these two subsets of patients. In this regard, a similar association with *HLA-B*15*, mainly due to *HLA-B*15:01,* was observed in patients with GCA, regardless of the clinical phenotype. Furthermore, we found that the presence of both *HLA-B*15:01* and *HLA-DRB1*04:01* has an effect increasing the risk of developing both cranial and extracranial LVV-GCA.

A former study that included 98 biopsy-

Table III. *HLA-B*15:01* and *HLA-DRB1*04:01* are associated with increased susceptibility to classic cranial GCA and LVV-GCA.

Classic cranial GCA patients+					
*HLA-B*15:01*	*HLA-DRB1*04:01*	Classic cranial GCA % (n)	Healthy controls % (n)	*p*	OR [95% CI]
-	-	73.4 (135)	91.4 (444)	-	Ref.
+	-	5.4 (10)	3.3 (16)	0.08	2.06 [0.81-4.94]
-	+	14.1 (26)	4.7 (23)	<0.001	3.72 [1.96-7.04]
+	+	7.1 (13)	0.6 (3)	<0.001	14.25 [3.82-78.67]
LVV-GCA patients+					
*HLA-B*15:01*	*HLA-DRB1*04:01*	LVV-GCA % (n)	Healthy controls % (n)	*p*	OR [95% CI]
-	-	75.2 (79)	91.4 (444)	-	Ref.
+	-	6.7 (7)	3.3 (16)	0.05	2.46 [0.98-6.17]
-	+	14.3 (15)	4.7 (23)	<0.001	3.67 [1.69-7.69]
+	+	3.8 (4)	0.6 (3)	0.002	7.49 [1.23-51.81]
All GCA patients+					
*HLA-B*15:01*	*HLA-DRB1*04:01*	All GCA % (n)	Healthy controls % (n)	***p***	OR [95% CI]
-	-	74.0 (214)	91.4 (444)	-	Ref.
+	-	5.9 (17)	3.3 (16)	0.02	2.20 [1.02-4.76]
-	+	14.2 (41)	4.7 (23)	<0.001	3.70 [2.10-6.62]
+	+	5.9 (17)	0.6 (3)	<0.001	11.76 [3.34-63.06]

HLA: human leukocyte antigen; GCA: giant cell arteritis; LVV: large-vessel vasculitis; OR: odds ratio, CI: confidence interval.

proven GCA patients with the classic cranial pattern of the disease showed an association of this vasculitis with HLA-B genes, in particular with *HLA-B*15:01* (16). The present study that included 184 biopsy-proven GCA patients confirmed this *HLA-B*15:01* association with cranial GCA. Herein, we also show that a similar association with *HLA-B*15:01* is present in patients with the extracranial LVV-GCA phenotype.

As recently described for *HLA-DRB1* association (15), we could not find any differences in HLA class I genetic predisposition between patients with the extracranial LVV-GCA and the classic cranial GCA pattern. These findings indicate that susceptibility to GCA is strongly related to the HLA region, regardless of the clinical phenotype of expression of the disease.

Different patterns of inflammation might account for the different clinical expression of GCA. Overexpression of the Th1 inflammatory pathway and interferon-gamma (INFγ) seems to exist in patients with classic ischaemic manifestations of GCA. In contrast, the development of PMR and systemic inflammatory symptoms has been linked to the Th-17 inflammatory pathway and related cytokines, such as IL6 (22). In this regard, we found in previous studies that IFNγ functional polymorphisms were associated with an increased risk of visual ischaemic manifestations (23). In addition, a potential implication of VEGF gene polymorphisms in the development of severe ischaemic manifestations of GCA was observed (24,25). Interestingly, the frequency of the IL-6-174 allele C was statistically increased in GCA patients who had also PMR manifestations compared with GCA not associated with PMR (26). Therefore, a mayor influence of genes associated with the Th1 inflammatory response may exist in patients with the classic cranial pattern of GCA whereas Th17 pathway and IL6 related genes may be more closely correlated with the extracranial LVV-GCA phenotype. More studies on these distinct inflammatory pathways are needed to better explain the different phenotype expression of GCA.

In conclusion, no differences regarding HLA-B genetic susceptibility seem to exist between patients with the classic cranial GCA and the extracranial LVV-GCA pattern. However, the presence of *HLA-B*15:01* together with *HLA-DRB1*04:01* increases the susceptibility to both cranial and LVV-GCA. Further investigation is underway to determine if specific genetic pathways may explain the different phenotype expression of the disease.

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