The Association of HLA-class I Genes and the Extent of Atherosclerotic Plaques in Patients with Psoriatic Disease

Lihi Eder, Fatima Abji, Cheryl F. Rosen, Vinod Chandran, Richard J. Cook, and Dafna D. Gladman

ABSTRACT. ***Objective.*** To investigate the association between HLA susceptibility and disease severity markers and the extent of atherosclerosis in patients with psoriatic disease.

Methods. White patients with psoriatic arthritis (PsA) and psoriasis without PsA (PsC) were recruited. An ultrasound of the carotid arteries was performed and the size of each atherosclerotic plaque was measured. The resulting score, the total plaque area (TPA), represented the extent of atherosclerosis. HLA genotyping was performed using sequence-specific oligonucleotide probes. The association between 10 HLA susceptibility and severity markers of PsC and PsA and the severity of atherosclerosis was assessed by ordinal logistic regression models adjusted for age, sex, and cardiovascular (CV) risk factors.

Results. The study involved 411 patients (273 PsA, 138 PsC). Of them, 61.8% had at least 1 atherosclerotic plaque. HLA-B*13:02 and HLA-C*06:02 were associated with more severe atherosclerosis (age- and sex-adjusted OR 2.31, 95% CI 1.23–4.32 and OR 1.68, 95% CI 1.12–2.52, respectively). HLA-B*38:01 was associated with less severe atherosclerosis (OR 0.49, 95% CI 0.28–0.86). These associations remained statistically significant after adjusting for CV risk factors. Higher levels of erythrocyte sedimentation rate (ESR) were associated with more severe atherosclerosis (age- and sex-adjusted OR 1.33, p = 0.02). HLA-B*13:02–positive (p = 0.01) as well as HLA-C*06:02–positive (p = 0.008) patients had higher levels of ESR over time.

Conclusion. HLA-C*06:02 and B*13:02 alleles are associated with a higher burden of atherosclerosis in patients with psoriatic disease. This association may be mediated by a higher level of systemic inflammation. (J Rheumatol First Release September 1 2016; doi:10.3899/jrheum.151469)

Key Indexing Terms:
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Both psoriasis and psoriatic arthritis (PsA) have been linked to an increased risk of developing atherosclerotic cardiovascular (CV) disease[1,2,3,4]. This risk remains high after accounting for established CV risk factors, suggesting that psoriatic disease is an independent risk factor for CV events[5,6]. This concept is supported by observations that higher cumulative levels of inflammation in the joints and the skin over time are associated with abnormal levels of soluble cardiometabolic biomarkers and increased CV risk[3,7,8,9,10,11].

Atherosclerosis, the underlying process leading to CV events, is an inflammatory disorder of the arteries in which immune mechanisms interact with metabolic risk factors to initiate and propagate lesions in the vascular walls[12]. Atherosclerosis and psoriatic disease share underlying pathophysiologic mechanisms including Th1 and Th17 pathway activation and reduced T regulatory cell activity. These events result in high serum levels of proinflammatory cytokines that upregulate cell-mediated immunity and promote inflam-

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matory cell migration through the vascular endothelium, resulting in endothelial dysfunction that may lead to atherogenesis[13,14,15].

B-mode ultrasound (US) of the carotid arteries is one of the most frequently used modalities for imaging atherosclerosis. Measurements of carotid intima-media thickness (cIMT) and the extent of atherosclerotic plaques have long been regarded as methods to evaluate the burden of atherosclerosis. However, accumulating evidence questions the value of cIMT as an independent predictor of CV events[16]. In contrast, the presence and the extent of carotid atherosclerotic plaques are strongly associated with traditional CV risk factors and independently predict CV events[17,18].

HLA genes are implicated in the pathogenesis of psoriasis and PsA. HLA class I genes confer the highest risk for developing psoriatic disease and are also associated with more severe disease phenotypes[19]. Within the HLA region, the largest and the most consistently reported association is with the HLA-C*06:02 allele. This allele is associated with more severe disease phenotypes, such as an earlier onset and more severe cutaneous psoriasis[20,21,22]. While HLA-C*06:02 is also associated with PsA, the strength of association is weaker compared to patients with psoriasis, which may suggest a higher penetration of HLA-C*06:02 regarding skin disease compared to the joint manifestations[23]. On the other hand, HLA-B*27, the hallmark of spondyloarthritis, is consistently associated with PsA but not with psoriasis[23,24,25,26,27]. The presence of this allele identifies a more severe PsA phenotype that includes axial involvement, an earlier onset of arthritis, and greater progression of joint damage[28,29,30]. Additional HLA markers for PsA susceptibility include HLA-B*08:01, HLA-B*38:01, and HLA-B*39:01[25,26,27,28].

Relevant to the strong link between immune response and atherosclerosis, HLA alleles have been assessed as markers for CV risk. An association was reported between the HLA-class II allele, HLA-DRB1*01, and myocardial infarction in patients with rheumatoid arthritis (RA) and in people without rheumatic conditions[29,30,31]. In our study we aimed to investigate the hypothesis that inflammation contributes significantly to CV morbidity in patients with psoriasis and PsA by assessing the association between the extent of atherosclerosis and HLA markers of disease susceptibility and severity. We hypothesized that these genes may serve as markers of systemic inflammation, thus reflecting an increased risk of developing atherosclerosis; alternatively, these molecules may play a direct role in the inflammatory process within the vessel wall, which may result in atherosclerosis progression.

MATERIALS AND METHODS

Setting. The study population included patients with psoriasis without arthritis (PsC) and patients with PsA who were enrolled in 2 large longitudinal cohorts. The University of Toronto Psoriatic Arthritis cohort was established in 1978 as part of an ongoing prospective study[32]. The majority of the patients in this cohort satisfy the ClASsification for Psoriatic ARthritis criteria (CASPAR) criteria[33]. The patients in this cohort are assessed every 6–12 months according to a standardized protocol by a rheumatologist. The Toronto psoriasis cohort was established in 2006 as part of an ongoing study to investigate risk factors for PsA in patients with psoriasis[34]. It enrolls subjects who have a diagnosis of psoriasis confirmed by a dermatologist and who have been assessed by a rheumatologist to exclude a diagnosis of PsA. The patients in this cohort are assessed annually according to the same protocol as in the PsA cohort. As of January 2010, consecutive patients from the 2 cohorts were recruited for participation in a substudy that assesses CV risk in patients with psoriatic disease. The participants in this substudy undergo a comprehensive CV risk evaluation that includes an assessment of their CV risk factors and an US of the carotid arteries. Patients with a history of carotid endarterectomy were excluded. The current analysis was limited to whites to avoid population stratification bias due to variation in the distribution of HLA alleles across ethnic groups.

CV risk factor assessment. Subjects were considered to have hypertension if they were taking antihypertensive agents or if they had a systolic blood pressure of > 140 mm Hg and/or a diastolic blood pressure of > 90 mm Hg on at least 2 visits. Height and weight were measured and body mass index (BMI) was calculated. Diabetes mellitus was defined as any of the following: a physician-confirmed history of diabetes, use of antidiabetic medications or glycosylated hemoglobin level of > 6.5%. Patients who smoked daily for > 1 year were classified as smokers. Dyslipidemia was defined as any of the following: use of lipid-lowering agents or non–high-density lipoprotein cholesterol > 4.3 mmol/l. History of CV events including myocardial infarction, angina pectoris, and stroke was recorded.

Disease activity assessment. Outcomes of disease activity included tender and swollen joint counts in 68/66 joints, respectively, and Psoriasis Area and Severity Index (PASI) and erythrocyte sedimentation rate (ESR). To capture the burden of disease activity over time, a time-adjusted arithmetic mean of all available measurements from the first visit to the clinic to the time of US assessment was calculated for these disease-related variables.

HLA genotyping. HLA-B and HLA-C genotyping was performed from DNA extracted from peripheral blood using LabType SSO typing kits (One Lambda). HLA-B and –C are transmitted as haplotypes, which are conserved segments of chromosomes. Haplotype information was inferred using the expectation–maximization algorithm (SAS-Genetics), generating maximum likelihood estimates given a multilocus sample of HLA-C and HLA-B genotypes[35]. Analysis was limited to alleles that were reported in the literature as being associated with susceptibility and severity of psoriasis and/or PsA to minimize false-positive results due to multiple testing[21,23,25]. The following HLA-B and –C alleles and their corresponding haplotypes were assessed: B*08:01, B*27:05, B*38:01, B*39:01, C*01:02, C*02:02, C*12:03 (associated with PsA), B*13:02, B*57:01, and C*06:02 (associated with psoriasis).

Carotid US assessment. A single physician trained in vascular US performed all measurements following the study protocol, which has previously been described in detail[8]. Scans were performed with MyLab 30 and MyLab 70 XVision (Esaote) scanners with a linear LA523 7–13 MHz transducer (Esaote). The scan included detailed B-mode images of both right and left carotid arteries. All US scans were saved as video files for later reading. An atherosclerotic plaque was defined as the presence of focal wall thickening that is at least 50% greater than that of the surrounding vessel wall or as a localized intimal thickening exceeding 1 mm that protrudes into the lumen and is distinct from the adjacent boundary. Plaque area was measured as described by Spence[36]. The plane for measurement of each plaque was chosen by reviewing the video of the scan to find the largest extent of plaque as seen in the longitudinal view. The image was then frozen, and the plaque was measured by tracing around the perimeter with a cursor on the screen. The assessor then moved on to the next plaque and repeated the process until all observed plaques in the common, external, and internal carotid arteries were measured[36]. Measurement was performed using MyLab desktop software (Esaote). Reading of the US scans was performed independently

from the scanning by a single reader who was blinded to the clinical data. Total plaque area (TPA) was recorded as the sum of cross-sectional areas of all plaques in the right and left carotid arteries. Because the distribution of TPA was skewed heavily to the left, it was classified into 4 ordered categories based on tertiles of TPA in patients with plaques: (1) TPA 0 (no atherosclerosis); (2) $0 < TPA \leq 13$ mm^2 (mild atherosclerosis); (3) $13 < TPA \leq 37$ mm^2 (moderate atherosclerosis); (4) TPA > 37 mm^2 (severe atherosclerosis). A TPA of > 11.7 mm^2 for men and > 9.5 mm^2 for women was associated with a relative risk of 2.3 and 2.9, respectively, for developing MI in a large population-based study[18]. Within-observer variability of measuring TPA was assessed by measuring TPA in 20 scans at 2 separate occasions, at least 1 month apart. The intraobserver intraclass correlation coefficient for TPA was 0.94.

Statistical analysis. Baseline descriptive statistics were computed with continuous variables summarized by their means and SD. The association between each HLA allele/haplotype and the extent of atherosclerosis, as measured by TPA categories, was assessed in an ordinal logistic regression analysis. The initial model included a single HLA allele/haplotype in addition to age and sex as covariates. A total of 10 HLA alleles were assessed that were selected based on knowledge from prior literature about the genetic epidemiology of PsA. Because this was considered an exploratory analysis, we did not account for multiple testing. For those alleles/haplotypes that were found to be significantly associated with atherosclerosis in the age- and sex-adjusted model, traditional CV risk factors (hypertension, diabetes, dyslipidemia, smoking, BMI) were then added as covariates to the regression model. Backward selection procedures were used for the final multivariate regression model, keeping all variables with a $p \leq 0.10$ in the model. All models satisfied the proportional odd assumption. Because HLA-C*06:02, B*57:01, and B*13:02 are predominantly associated with psoriasis while the remaining alleles are associated with PsA, the interaction between disease status (PsA vs PsC) and these alleles was assessed to investigate whether there is a differential effect of HLA alleles across the 2 diseases. In addition, a subgroup analysis was performed to assess whether the association between HLA alleles is modified by duration of psoriasis (≤ 15 yrs and > 15 yrs). To further investigate whether the extent of inflammation was an underlying mechanism mediating the association between HLA alleles and atherosclerosis, we compared the levels of disease activity measures over time (adjusted mean levels of ESR, tender and swollen joint counts, and PASI) between carrier and noncarriers of these alleles. ESR and its interaction with sex were then added as covariates to the multivariate model to determine the extent to which it mediates the association between HLA and atherosclerosis.

RESULTS

A total of 411 patients with psoriatic disease (273 PsA, 138 PsC) were included in the analysis. Six patients were excluded because of poor-quality images. The mean followup time in the cohorts was 6.8 ± 7.9 years. At least 1 atherosclerotic plaque was found in 61.8% of the participants. The characteristics of the study population are presented in Table 1.

Association between HLA alleles and the extent of atherosclerosis. The distribution of HLA alleles across the TPA categories and the age- and sex-adjusted OR for each of the assessed HLA alleles is presented in Table 2. This analysis showed that HLA-B*13:02 and HLA-C*06:02 alleles and the corresponding haplotype HLA-B*13:02-C*06:02, which are psoriasis susceptibility and severity markers, are associated with more severe atherosclerosis. In contrast, HLA-B*38:01 allele and HLA-B*38:01-C*12:03 haplotype, susceptibility markers of PsA, were associated with less severe atherosclerosis. The same alleles remained significantly associated with the extent of atherosclerosis after adjusting for traditional CV risk factors in multivariate regression analysis (Table 2). When all 3 risk alleles were included in a single multivariate model, in addition to CV risk factors, only HLA-B*13:02 and B*38:01 remained significantly associated with atherosclerosis (Table 3). Therefore, it appears that the association of B*13:02 with atherosclerosis is stronger than that of C*06:02. A sensitivity analysis excluding the 26 patients with prior CV events showed similar results [OR for HLA-B*13:02 of 2.17 (95% CI 1.13–4.15) and OR for HLA-B*38:01 of 0.51 (95% CI 0.29–0.92)]. Overall, these findings suggest that the observed association between HLA alleles and atherosclerosis is independent of traditional CV risk. The interaction between disease status (PsA vs PsC) and HLA alleles was not statistically significant (B*38:01 p = 0.58; B*13:02 p = 0.94; C*06:02 p = 0.33). Therefore no subgroup analysis by disease status was conducted.

Association between HLA alleles and atherosclerosis by disease duration. To further investigate the association between the identified HLA-B and –C alleles and atherosclerosis, we performed a subgroup analysis by duration of

Table 1. Characteristics of the study population at the time of assessment (n = 411). Data are n (%) unless otherwise indicated.

Characteristics	Values
Age, yrs, mean ± SD	55.5 ± 11.5
Male	229 (55.7)
Age at psoriasis onset, yrs, mean ± SD	30 ± 15.8
Age at PsA onset, yrs, mean ± SD	38.8 ± 13.2
Cardiovascular disease*	26 (6.3)
Hypertension	192 (46.7)
Dyslipidemia	112 (27.3)
Diabetes mellitus	47 (11.5)
Smoking: ever	219 (53.3)
BMI, mean ± SD	28.8 ± 5.8
ESR**, mean ± SD	13.2 ± 9.8
Tender joint count**, mean ± SD	5 ± 6.2
Swollen joint count, mean ± SD *	1.9 ± 2.9
PASI**, mean ± SD	3.77 ± 4
HLA-B*08:01	83 (20.2)
HLA-B*13:02	39 (9.5)
HLA-B*27:05	41 (10)
HLA-B*38:01	53 (12.9)
HLA-B*39:01	20 (4.9)
HLA-B*57:01	69 (16.7)
HLA-C*01:01	29 (7.1)
HLA-C*02:02	48 (11.7)
HLA-C*06:02	130 (31.7)
HLA-C*12:03	81 (19.8)
B*08:01-C*07:01	78 (19)
B*13:02-C*06:02	38 (9.3)
B*27:05-C*02:02	27 (6.6)
B*38:01-C*12:03	52 (12.7)
B*57:01-C*06:02	65 (15.8)

* History of myocardial infarction, angina pectoris, or stroke. **Adjusted mean levels. PsA: psoriatic arthritis; BMI: body mass index; ESR: erythrocyte sedimentation rate; PASI: Psoriasis Area and Severity Index.

Table 2. The association between HLA alleles and atherosclerosis – distribution of alleles across the TPA categories and results of the age- and sex-adjusted ordinal logistic regression model (n = 411).

Variable	Age- and Sex-adjusted Model		Fully-adjusted Model*	
	OR (95% CI)	p	OR (95% CI)	p
B*08:01	1.24 (0.78–1.97)	0.35		
B*13:02	**2.31 (1.23–4.32)**	**0.009**	**2.22 (1.18–4.17)**	**0.01**
B*27:05	1.03 (0.55–1.91)	0.93		
B*38:01	**0.49 (0.28–0.86)**	**0.01**	**0.49 (0.27–0.86)**	**0.01**
B*39:01	0.93 (0.39–2.17)	0.86		
B*57:01	1.22 (0.74–2.01)	0.43		
C*01:02	1.92 (0.93–3.97)	0.08		
C*02:02	1.03 (0.57–1.84)	0.93		
C*06:02	**1.68 (1.12–2.52)**	**0.01**	**1.63 (1.08–2.45)**	**0.02**
C*12:03	0.68 (0.43–1.09)	0.11		
B*08:01-C*07:01	1.21 (0.76–1.94)	0.43		
B*13:02-C*06:02	**2.49 (1.32–4.72)**	**0.005**	**2.19 (1.15–4.18)**	**0.017**
B*27:05-C*02:02	0.97 (0.45–2.08)	0.93		
B*38:01-C*12:03	**0.45 (0.26–0.80)**	**0.006**	**0.46 (0.25–0.84)**	**0.01**
B*57:01-C*06:02	1.18 (0.71–1.97)	0.52		

*Adjusted for age, sex, diabetes, hypertension, body mass index, smoking, and dyslipidemia. Significant data are in bold face. TPA: total plaque area.

Table 3. The association between HLA alleles and TPA category by ordinal logistic regression analysis adjusted for age, sex, and cardiovascular risk factors (age, sex, diabetes, hypertension, BMI, smoking, dyslipidemia).

Variable	OR (95% CI)	p
B*13:02	2.26 (1.19–4.31)	0.01
B*38:01	0.51 (0.29–0.91)	0.02
Age	1.10 (1.08–1.12)	< 0.0001
Female	0.45 (0.31–0.68)	< 0.0001
Smoker ever	1.56 (1.07–2.29)	0.02
Diabetes	2.16 (1.16–4.07)	0.02
Dyslipidemia	1.50 (0.95–2.34)	0.08

Noncontributing variables were removed (p < 0.10). TPA: total plaque area; BMI: body mass index.

Table 4. The association between HLA alleles and TPA category by duration of psoriasis*.

Variables	≤ 15 Years, n = 113		> 15 Years, n = 281	
	OR (95% CI)	p	OR (95% CI)	p
B*13:02	1.07 (0.29–3.87)	0.92	2.98 (1.34–6.64)	0.007
B*06:02	0.80 (0.32–2.04)	0.63	2.30 (1.38–3.81)	0.001
B*38:01	1.09 (0.33–3.61)	0.88	0.34 (0.16–0.70)	0.003

*Adjusted for age, sex, diabetes, hypertension, smoking, BMI, and dyslipidemia.

psoriasis (≤ 15 yrs, > 15 yrs). The association between HLA-B*13:02, C*06:02, and B*38:01 and atherosclerosis burden was statistically significant and the effect size was much higher in patients with long duration of psoriasis. The results are shown in Table 4.

Burden of atherosclerosis associated with higher levels of ESR over time. Systemic inflammation has been associated with increased CV morbidity in patients with and without rheumatic conditions[37,38,39]. In our study, higher mean levels of ESR were associated with more severe atherosclerosis [age- and sex-adjusted OR for being in a higher TPA category for ESR (10-unit increase) 1.33, 95% CI 1.04–1.70, p = 0.02]. The probability of having severe atherosclerosis (being in the highest TPA category vs having no plaques) as a function of ESR level is shown in Figure 1.

Inflammation as a potential mediator of the association between HLA alleles and atherosclerosis. We then assessed the hypothesis that the observed association between HLA alleles and atherosclerosis is mediated at least partially by systemic inflammation and by a higher burden of disease activity over time. The levels of disease activity outcomes were compared in carriers and noncarriers of the identified risk alleles and haplotypes. The adjusted mean levels of ESR were higher in patients who were carriers of HLA-B*13:02 and HLA-C*06:02, but not in carriers of HLA-B*38:01 (Figure 2). The remaining outcomes of disease activity were similar in carriers and noncarriers of these alleles (data not shown). The inclusion of ESR and the interaction of sex and ESR as covariates in the multiple regression model resulted in an attenuation of the association between HLA-B*13:02 (OR 1.94, 95% CI 0.86–4.38, p = 0.11) or HLA-C*06:02 (OR 1.40, 95% CI 0.83–2.37, p = 0.20) and atherosclerosis, suggesting that this association was mediated in part by the level of systemic inflammation.

DISCUSSION

Evidence from studies of patients with psoriasis or PsA suggests that the CV risk is elevated in these patients. However, few studies examined the independent role of systemic inflammation versus traditional CV risk factors as

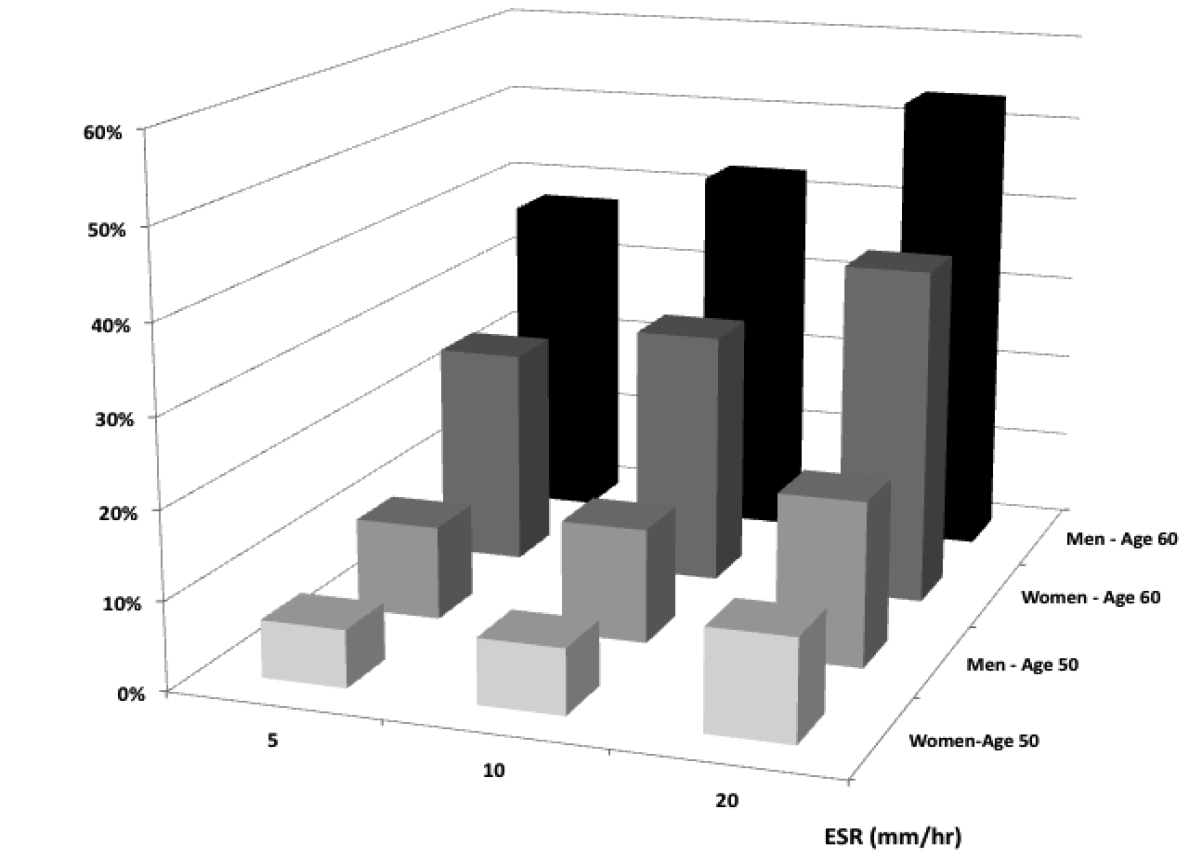

Figure 1. Predicted probability for having severe atherosclerosis (being in the highest TPA category vs having no plaques) as a function of age, sex, and mean levels of ESR over time. TPA: total plaque area; ESR: erythrocyte sedimentation rate.

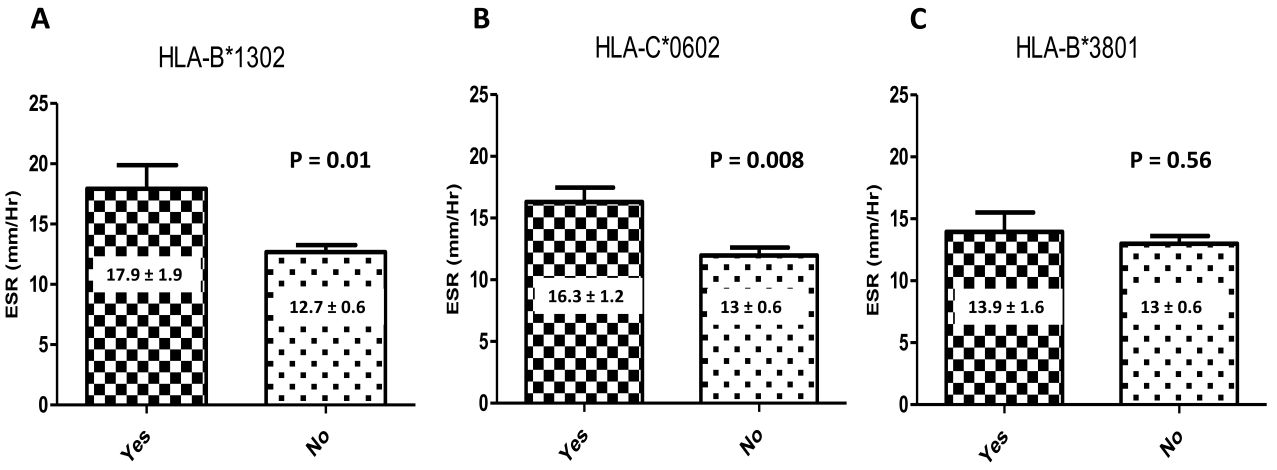

Figure 2. Mean levels of erythrocyte sedimentation rate (ESR; mm/h) in carriers and noncarriers of HLA-B*13:02 (A), HLA-C*06:02 (B), and HLA-B*38:01 (C).

underlying mechanisms for CV events in these patients. We found that certain HLA susceptibility and severity genetic markers of psoriatic disease are associated with a higher burden of atherosclerosis. Our findings also suggest that this association may be mediated, at least in part, by the extent and duration of systemic inflammation, as indicated by elevated levels of ESR and by the stronger effect size in patients with longstanding disease.

The mechanism by which HLA alleles may promote the development of atherosclerosis is not clear. Previous studies

in RA have found an association between HLA-DRB1 susceptibility alleles (the shared epitopes) and increased CV risk[31,40]. These alleles are associated with more severe RA and extraarticular manifestations; therefore, it was hypothesized that the worse RA-related outcomes and inflammatory burden promote accelerated atherosclerosis and CV events. Similarly, we found that HLA-C*06:02, the strongest genetic marker for psoriasis, is associated with more severe atherosclerosis, although the HLA-B*13:02 allele, which is in strong linkage disequilibrium with HLA-C*06:02, was found to have a stronger association with atherosclerotic burden. HLA-C*06:02 is associated with earlier onset and familial psoriasis and with more severe skin disease, although no association was found with severe outcomes in PsA[20,21,22,41]. In our study, carriers of HLA-C*06:02 and HLA-B*13:02 had higher levels of inflammatory markers during the course of their disease. In line with these findings, we recently reported an association between elevated ESR levels and clinical CV events in patients with PsA[9]. Others have found an association between serum biomarkers of cardiometabolic abnormalities and the extent of disease activity in the skin and joints in patients with psoriatic disease[10,11]. Overall, these data support the hypothesis that the exposure to an increased level of inflammation for prolonged periods is associated with accelerated atherosclerosis in patients with psoriatic disease, while effective suppression of inflammation may improve CV outcomes in these patients.

An alternative hypothesis that may explain our results can be considered. It is unclear whether HLA alleles play a direct role in promoting atherogenesis within the vessel wall. The expression of HLA-DR molecules by vascular endothelial cells and lipid-laden foam cells within the atherosclerotic plaque has been demonstrated[42]. It has been suggested that antigens, such as oxidized low-density lipoproteins and other autoantigens presented by HLA molecules, trigger an immune response by CD4+ T cells within the vessel wall, resulting in an inflammatory cascade that promotes atherogenesis[12]. Interestingly, CD8+ T cells that interact with MHC-class I molecules are as frequent as CD4+ T cells in the atherosclerotic plaques[43,44]. However, unlike MHC-class II molecules, the role of MHC-class I and their potential effect on atherogenesis have not been thoroughly investigated. To support the hypothesis that MHC class I molecules play a direct role in atherogenesis, it is expected that HLA alleles will be associated with CV morbidity in the general population. Unfortunately, our study did not include a control group of people without psoriatic disease. However, a metaanalysis of 5 genome-wide association studies in coronary artery disease identified a susceptibility variant within the MHC region, between HCG27 and HLA-C loci[45]. Because of the close proximity of genes within this region, determination of the actual causative gene is challenging.

We also found that the HLA-B*38:01 allele was associated with less severe atherosclerosis. This allele has been associated with a higher risk of developing PsA, but not with a severe disease phenotype[23]. In our study we did not find an association between HLA-B*38:01 and measures of disease activity or inflammation. We also did not find any association between this allele and CV risk factors. Therefore, the inverse association between HLA-B*38:01 allele and atherosclerosis in our study remains unexplained.

Our study has several limitations including the lack of controls without psoriatic disease, which prevented us from assessing the role of HLA-class I alleles in atherogenesis in the general population, as discussed above. In addition, the MHC region contains many genes that are relevant to immune responses and inflammation. Because these genes are tightly linked and tend to be transmitted as haplotypes, it is possible that the causal gene affecting atherosclerosis is in linkage disequilibrium with the identified HLA alleles.

Our study has several strengths. This is, to the best of our knowledge, the first study to assess the direct association between genetic markers of psoriatic disease and the extent of atherosclerosis. We used our relatively large cohorts of well-phenotyped patients with psoriasis and PsA. We were able to use information about the extent of inflammation and disease activity in these patients that was collected longitudinally during the course of their disease to explore links between the genetic data and the atherosclerosis.

We found an association between HLA risk alleles for psoriatic disease and the extent of atherosclerosis in these patients. The association between HLA-C*06:02-HLA-B*13:02 alleles/haplotype and atherosclerosis may be mediated by increased levels of systemic inflammation over time and is more pronounced in patients with longstanding psoriasis. These findings support the independent role of inflammation in the pathogenesis of CV morbidity in patients with psoriatic disease.

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