Eur Respir J 2011; 38: 1151–1157
DOI: 10.1183/09031936.00025011

HLA-DRB1* alleles and symptoms associated with Heerfordt's syndrome in sarcoidosis

P. Darlington*,#, L. Tallstedt¶, L. Padyukov+, I. Kockum§, K. Cederlundƒ, A. Eklund*,# and J. Grunewald*,#

ABSTRACT: Heerfordt's syndrome (HS) consists in its complete form of uveitis, parotid or salivary gland enlargement and cranial nerve palsy. The objective of the present study was to analyse if there are also links between HLA-DRB1* alleles and HS, as it is a specific phenotype of sarcoidosis.

1,000 patients with sarcoidosis, out of whom 83 had symptoms associated with HS, were included in the study together with a group of 2,000 healthy individuals from the same population, matched for sex and age. HLA-DRB1* allelic groups were determined for all individuals, and comparisons were made between different disease subgroups and between patients and healthy controls.

We found that the HLA-DRB1*04 allele was overrepresented in patients with symptoms associated with HS. 83 (8.3%) of all patients had one or more of the symptoms and 46 (55%) of them were HLA-DRB1*04 positive. 44 (55%) of the patients with ocular sarcoidosis, *i.e.* the most common symptom associated with HS, were HLA-DRB1*04 positive, compared with 35.9% of healthy controls ($p=0.0008$), and only 26.6% of the whole group of sarcoidosis patients ($p<0.0001$).

HLA-DRB1*04 seems to protect against overall sarcoidosis but appears to be a significant risk factor for ocular sarcoidosis as well as for other manifestations associated with HS.

KEYWORDS: Eyes, Heerfordt's syndrome, human leukocyte antigen, ocular sarcoidosis, sarcoidosis

Sarcoidosis is a systemic granulomatous disease of unknown aetiology. It is characterised by formation of noncaseating granulomas in the affected organs. The lungs and/or thoracic lymph nodes are engaged in >90% of all cases but almost any organ, such as the eyes, skin, heart and the nervous system can be involved [1, 2]. The course of the disease varies significantly. Many patients recover but some develop chronic disease with pulmonary fibrosis and eventually respiratory failure. The first line of treatment is oral corticosteroids. Treatment is usually initiated in patients with progressive loss of lung function, but extrapulmonary manifestations, such as involvement of the heart, eyes and nervous system, are also common indications for treatment [1].

Earlier studies have shown that there are links between certain HLA class II alleles and distinct clinical manifestations of sarcoidosis, such as the well-known association of HLA-DRB1*03 and Löfgren's syndrome (LS) [3, 4]. LS is characterised by an acute onset usually with fever, bilateral ankle arthritis and/or erythema nodosum and bilateral hilar lymphadenopathy with, in some cases, parenchymal infiltrates [5]. LS is common in Scandinavia but very rare in patients of Japanese origin in whom DRB1*0301 is virtually missing [6]. Heerfordt's syndrome (HS) is another, more unusual manifestation of sarcoidosis described in the literature. This syndrome was originally termed ''Febris uvea-parotidea subchronica'' and was described in 1909 by Heerfordt [7]. He described three patients with uveitis, parotid swelling, cranial nerve palsy and fever. In 1937, WALDENSTRÖM [8] classified it as a distinct manifestation of sarcoidosis. The complete form of HS is considered to consist of uveitis, parotid or salivary gland enlargement and cranial palsy, especially facial, and fever is also common [9].

In patients with ocular sarcoidosis, uveitis is by far the most common manifestation and sometimes co-exists with symptoms associated with HS, such as cranial nerve palsy and engagement of parotid and/or salivary glands. The incidence of eye involvement in patients with sarcoidosis varies from 5% in Finland to >70% in Japan, supporting the notion of a genetic influence on

AFFILIATIONS
*Dept of Medicine, Division of Respiratory Medicine,
¶Dept of Ophtalmology, St. Erik Eye Hospital,
+Dept of Medicine Solna, Rheumathology Unit,
§Dept of Clinical Neurosciences,
ƒDept of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet, and
#Division of Respiratory Medicine, Karolinska University Hospital, Stockholm, Sweden.

CORRESPONDENCE
P. Darlington
Dept of Medicine, Division of Respiratory Medicine
Södersjukhuset (Stockholm South General Hospital)
Sjukhusbacken 10
11883 Stockholm
Sweden
E-mail: pernilla.darlington@sodersjukhuset.se

Received:
Feb 09 2011
Accepted after revision:
April 18 2011
First published online:
May 12 2011

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

signs of disease presentation [10–12]. Other examples of eye involvement are lacrimal gland inflammation, optic neuritis and conjunctival granulomas. Commonly, both eyes are engaged [11]. Anterior uveitis is reported to be more common in African-Americans (70–75%) while posterior uveitis is more common in Caucasians (65–83%) [13]. In patients with sarcoidosis with anterior uveitis, treatment with topical corticosteroids is commonly sufficient, while posterior uveitis usually requires more frequent monitoring and is more difficult to treat [12].

Since HS is a distinct phenotype of sarcoidosis, and there is a strong genetic influence as suggested by sharp differences in disease phenotypes in patients with different ethnic origin, we hypothesised that there might be associations between specific HLA-DRB1* alleles and HS. The objective of the present study was therefore to analyse whether there are links between HLA-DRB1* alleles and symptoms associated with HS, such as uveitis, engagement of parotid and/or salivary glands or cranial nerve palsy, with particular focus on uveitis.

MATERIALS AND METHODS

Study subjects

A total of 1,000 HLA-typed patients were included in the study, of whom 383 were classified as having LS. All those included were consecutive patients referred to the outpatient clinic at the Division of Respiratory Medicine, Karolinska University Hospital, Solna, Sweden, but patients from the South General Hospital, Stockholm, Sweden, were also included. All patients were referred for diagnostic investigation and activity assessment to the respective outpatient clinic. The vast majority of patients were seen by one of the authors (A. Eklund), from 1994 onwards. Patients were diagnosed with sarcoidosis through typical clinical and radiographic manifestations, findings at bronchoscopy with bronchoalveolar lavage (BAL), including an elevated CD4/CD8 cell ratio, and positive biopsies, using the criteria outlined by the World Association of Sarcoidosis and other Granulomatous disorders (WASOG) [14]. All patients with ocular involvement were examined by ophthalmologists and had findings compatible with ocular sarcoidosis according to International Criteria for the Diagnosis of Ocular Sarcoidosis [11]. In total, 80 out of the 1,000 patients were found to have ocular sarcoidosis *i.e.* inflammatory activity located in the eye, secondary to the sarcoidosis disease. Only patients with symptoms originating in the eyes (such as pain, photophobia and blurred vision) were seen by an ophthalmologist, in the vast majority by one of the authors (L. Tallstedt) at the St. Erik Eye Hospital, Stockholm, Sweden. Patients with uveitis were classified according to anterior, posterior, unilateral or bilateral involvement. Ocular manifestation with only iridocyclitis without signs of posterior uveitis were defined as anterior uveitis and patients with vitreous floaters/snowballs, venous vasculitis, neovascularisation, choroidal granulomas, macular oedema, papilloedema or chororetinal peripheral lesions were classified as having posterior uveitis. Patients were judged to have involvement of the parotid and salivary glands if this was biopsy-proven and/or if there was an obvious enlargement and simultaneously co-existing findings were compatible with sarcoidosis. Patients were defined as having neurosarcoidosis according to Zajicek criteria (in this study, only patients with cranial nerve palsy and co-existing findings compatible with sarcoidosis were included) [15]. Chest radiographs were evaluated and findings staged by one of the authors (K. Cederlund), who is subspecialised in chest radiology, with a long experience of interstitial pulmonary disease. Chest radiographs were controlled at the time of diagnosis and at 2 yrs' follow-up. Chest radiographs in patients with sarcoidosis were classified into five stages: stage 0, normal; stage I, bilateral hilar lymphadenopathy; stage II, bilateral lymphadenopathy with parenchymal infiltrates; stage III, parenchymal infiltrates alone; and stage IV, fibrotic bands and volume retraction [16]. The study was approved by the regional ethical committee and all patients included gave their informed consent.

All 1,000 patients were characterised by age, sex, HLA-type, treatment/no treatment, resolving/nonresolving disease and LS/non-LS (table 1). Nonresolving disease was defined as disease duration >2 yrs with remaining signs of active disease as evaluated by the chest radiographic findings, recurrent uveitis and other disease parameters (*i.e.* fatigue, cough and fever). Patients were in general followed at the outpatient clinic for $\geqslant$2 yrs and longer if signs of active disease. Symptoms associated with HS were defined as uveitis, engagement of parotid and/or salivary glands and cranial nerve palsy. Patients with uveitis and one of the other symptoms were regarded having an incomplete form of HS and patients with all three symptoms to have the complete form. The control group consisted of healthy individuals from the same population, 1,138 females and 862 males, and were matched for the distribution of age and sex with the patients.

TABLE 1 Clinical characteristics in patients with ocular sarcoidosis, all sarcoidosis patients and healthy controls

	Ocular sarcoidosis	All patients with sarcoidosis	Healthy controls
Subjects n	80	1000	2000
Sex			
Males	40	570	1138
Females	40	430	862
Age yrs	37 (19–75)	38 (9–78)	42 (15–73)
Radiographic stage			
0	13	61	
I	40	484	
II	21	323	
III	6	104	
IV	0	28	
Never-smoker	38	553	
Ever-smoker	40	433	
Unknown	2	14	
Löfgren	10#	383	
Non-Löfgren	70#	617	
Resolving	6#	409	
Nonresolving	64#	493	
Unknown	10	98	

Data are presented as n or median (range). #: $p<0.0001$ compared with patients without ocular sarcoidosis. For definition of the radiographic stage, see the Materials and Methods section.

HLA typing

Genomic DNA was extracted from whole blood samples and HLA-DRB1* allelic groups were determined (table 2) for every patient using the PCR-sequence-specific primers (SSP) technique (Olerup SSP DR Low Resolution Kit; Olerup SSP AB, Saltsjöbaden, Sweden) [17]. For the controls, the majority were HLA-typed using PCR-SSP but some of the HLA-DRB1* alleles were determined with restriction length polymorphism [18, 19].

Statistical analysis

Data were analysed by the Chi-squared test or, in the case of small numbers, by Fisher's exact test. Statistical analyses were performed with Graph Pad Prism 4.03 (Graphpad Software Inc., San Diego, CA, USA). When comparing different allele frequencies, $p<0.003$ was regarded significant (after Bonferroni correction for the number of alleles (n=13), *i.e.* dividing 0.05 with 13 = 0.003). Otherwise $p<0.05$ was regarded significant.

RESULTS

Among all 1,000 HLA-typed sarcoidosis patients, 80 (8%) were found to have eye involvement and, out of these 80, 72 (90%) had uveitis, 19 (2%) were found to have engagement of parotid or salivary glands and facial nerve palsy occurred in 11 (1%) (fig. 1). Uveitis, involvement of parotid or salivary glands and cranial nerve palsy are three different symptoms known to be associated with HS, and simultaneous presence of all symptoms represents the complete form of this syndrome. The majority of patients with ocular engagement had uveitis, often bilateral and usually a prolonged disease course. In the patients with involvement of parotid and salivary glands, they were bilateral in eight cases and unilateral in nine cases (unknown in two cases). In all cases, the salivary gland enlargement gradually subsided. The cranial nerve palsy was unilateral and transient in all 11 cases. In patients with symptoms associated with HS, the diagnosis was verified with biopsy in the majority of patients and most of them were taken from parotid and salivary glands, peripheral lymph nodes, skin lesions, lungs and, in rare cases, also from the eyes. The remaining patients had, with the exception of the extrapulmonary manifestations, typical chest radiograph findings, LS, high CD4/CD8 ratio in BAL fluid and/or a elevated serum ACE level. 13 patients had radiological stage 0 and eight of these patients had the diagnose confirmed *via* biopsy taken from peripheral lymph nodes, skin biopsies or parotid glands. The other five were patients that met the criteria; they had typical ocular findings as judged by an experienced ophthalmologist and laboratory tests supporting the diagnosis.

Out of all patients (n=1,000), 83 (8.3%) had uveitis and/or engagement of parotid or salivary glands and/or cranial palsy and 46 (55%) of them were HLA-DRB1*04 positive. 40 (55%) of the patients with uveitis were HLA-DRB1*04 positive, 10 (53%) of the patients with involvement of parotid and salivary glands and 8 (73%) of the patients with cranial nerve palsy also carried the same allele. Out of the 83 patients with at least one of the symptoms associated with HS, there were 16 (19%) patients who had two or three of the symptoms, 10 (62.5%) were HLA-DRB1*04 positive (figs 2a and b). Among the 80 patients with ocular sarcoidosis, eight patients had no uveitis and were therefore not counted as having symptoms associated with HS. Several of these patients had conjuctival granulomas. These eight patients were included, however, in the whole group of patients with ocular sarcoidosis (*i.e.* inflammatory activity located in the eye, secondary to the sarcoidosis disease). Four of these patients (50%) were HLA-DRB1*04 positive.

HLA-DRB1*04 was present in 266 (26.6%) of all 1,000 patients compared with 718 (35.9%) in healthy controls ($p<0.0001$). The HLA-DRB1*04 allele was strongly connected to the HLA-DQB1*03 allele (data not shown). Among the 266 HLA-DRB1*04-positive patients, 46 (17%) had uveitis and/or engagement of parotid and salivary glands and/or cranial nerve palsy. Among the 734 HLA-DRB1*04-negative patients, these combinations occurred in only 37 (5%) patients ($p<0.0001$). Thus,

TABLE 2 Carrier frequency of HLA-DRB1 alleles

	Control subjects	All patients with sarcoidosis	Ocular sarcoidosis
Subjects n	2000	1000	80
***01**	22.3	12.7#	7.5¶
***03**	22.7	37.9#	18.8
***04**	35.9	26.6#	55.0¶
***07**	15.9	11.4¶	10.0
***08**	8.4	8.9	10.0
***09**	3.4	2.5	1.2
***10**	1.1	1.7	1.2
***11**	12.5	12.4	5.0
***12**	4.2	5.2	5.0
***13**	26.6	26.3	20.0
***14**	4.1	8.5#	7.5
***15**	27.6	33.1¶	36.3
***16**	1.5	0.7	1.2

Data are presented as %, unless otherwise stated. #: $p<0.0001$ compared with healthy controls; ¶: p-value <0.003 compared with healthy controls.

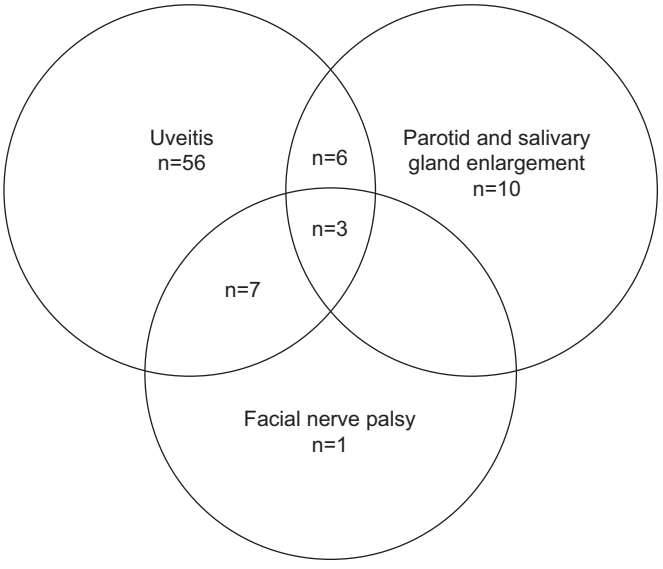

FIGURE 1. Patients with uveitis, parotid and salivary gland enlargement and facial nerve palsy. As shown, some of the patients had two or three symptoms.

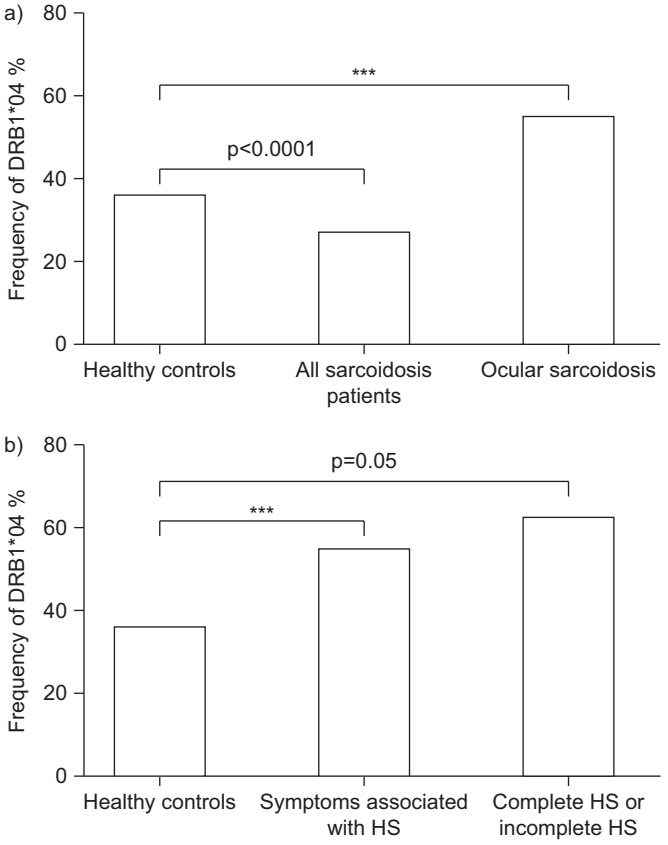

FIGURE 2. a) Frequency of HLA DRB1*04 in healthy controls (n=2,000), all sarcoidosis patients (n=1,000) and patients with ocular sarcoidosis (n=80). b) Frequency of HLA DRB1*04 in healthy controls (n=2,000), in patients with symptoms associated with Heerfordt's syndrome (HS; uveitis, parotid and/or salivary gland enlargement and cranial nerve palsy)(n=83), and in patients with incomplete HS (n=16), *i.e.* simultaneous occurrence of at least two of the three symptoms or all three of them (complete HS). p-values show a comparison with healthy controls.***: p<0.001.

there was a 3.4 times increased risk for having HS-associated manifestations in HLA-DRB1*04-positive patients. 21 (2.1%) of the whole group of sarcoidosis patients were homozygous for HLA-DRB1*04 and seven (33%) of them had eye disease; in two cases this was concomitant with facial palsy. Patients homozygous for HLA-DRB1*04 therefore had a 6.6 times increased risk for HS-associated symptoms (fig. 3). 33 (75%) out of the 44 HLA-DRB1*04-positive patients with ocular sarcoidosis were subtyped, and 28 (85%) of them carried the HLA-DRB1*0401 allele (fig. 4).

In patients with ocular sarcoidosis, other extrapulmonary manifestations were common, as 32 patients (40%) had at least one other manifestation (*e.g.* skin lesions, cranial nerve palsy and hypercalcaemia).

LS was less common in patients with ocular sarcoidosis (p<0.0001) compared with patients without. The HLA-DRB1*03 allele significantly associated with this syndrome was also less common among patients with eye involvement compared with patients without (p=0.0002). The HLA-DRB1*03 allele was also less common among patients with the incomplete

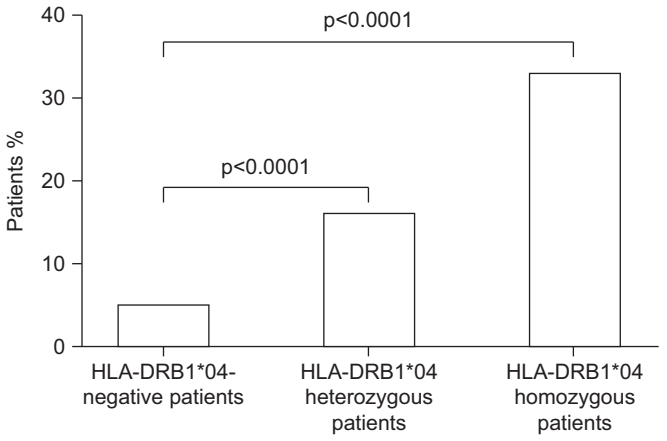

FIGURE 3. Frequency of patients with symptoms associated with Heerfordt's syndrome (uveitis, parotid and/or salivary gland enlargement and cranial nerve palsy) among HLA-DRB1*04 negative (n=734), HLA-DRB1*04 heterozygous (n=245) and HLA-DRB1*04 homozygous patients (n=21). The p-value of the frequency is in comparison with HLA-DRB1*04-negative patients.

or complete form of HS, where only two (12.5%) had the allele. In addition, the frequency of HLA-DRB1*01 was significantly lower among patients ocular sarcoidosis compared with healthy controls, and also seemed to be protective against contracting overall sarcoidosis (table 2).

Most of the patients with ocular engagement had uveitis (n=72). Among 68 patients for whom we had access to more detailed information, 36 (53%) had posterior uveitis, and the uveitis was bilateral in 45 (66%) (table 3). The localisation of uveitis did not differ significantly between the HLA-DRB1*04-positive and -negative patients.

58 of the patients with ocular sarcoidosis were followed by chest radiograph at onset of disease and 2 yrs later. After 2 yrs, chest radiograph showed enlarged lymph nodes and/or infiltrates in 49 (84.5%) out of 58 patients (fig. 5). In 70 patients with ocular engagement, where there was information available regarding disease course, only six had a resolving disease and four of these had LS. As shown in figure 6a, there was no obvious difference between HLA-DRB1*04-negative and HLA-DRB1*04-positive

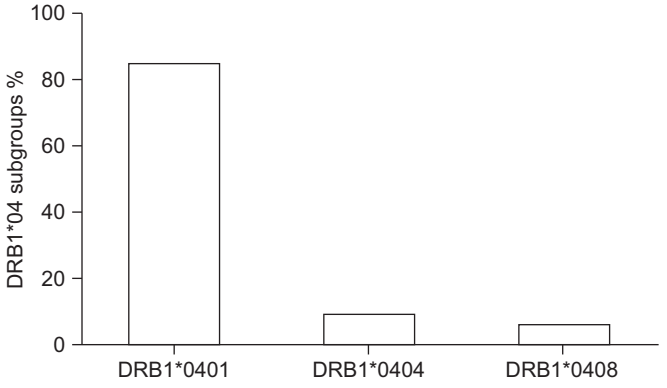

FIGURE 4. HLA subtyping of DRB1*04-positive patients with ocular sarcoidosis (n=33). Results are presented as the percentage of patients belonging to each subgroup. DRB1*0401: n=28; DRB1*0404: n=3; DRB1*0408: n=2.

TABLE 3 Characterisation and localisation of uveitis in anterior/posterior and uni-/bilateral in HLA-DRB1*04-positive and -negative sarcoidosis patients

Uveitis	All patients[#]		HLA-DRB1*04 positive[¶]		HLA-DRB1*04 negative[+]	
	Unilateral	Bilateral	Unilateral	Bilateral	Unilateral	Bilateral
Anterior	19	28	17	36	22	19
Posterior	15	38	17	30	12	47

Data are presented as %. Note that out of 72 patients with ocular symptoms compatible with Heerfordt's syndrome (*i.e.* uveitis), there was information about 68 as to whether it was posterior or anterior. [#]: n=68; [¶]: n=36; [+]: n=32.

patients with ocular sarcoidosis with regard to disease progression. Among HLA-DRB1*04-positive patients without ocular engagement (n=202), 101 (50%) had a resolving disease (fig. 6b) compared with only five (12.5%) with ocular disease ($p<0.0001$).

DISCUSSION

Complete HS consists of bilateral uveitis, parotid or salivary gland swelling and cranial nerve palsy. The complete form of the syndrome is rare, as also described by SCADDING [9]. Among our 1,000 patients, only three showed the complete syndrome. In accordance with Scadding's modification of HS, we divided the patients into incomplete or complete forms of HS. We also added patients with only uveitis and patients without uveitis but with the other two manifestations, and described them as having symptoms associated with HS. Fever is described as common in HS but we chose to exclude this parameter, as information about the body temperature was usually lacking. Christian Heerfordt, who originally described the syndrome, did not include pulmonary engagement as a part of the syndrome [7]. In our study, 67 (81%) of the patients with HS-associated symptoms had thoracic involvement. The patients with cranial nerve palsy and parotid or salivary glands were few. It is, however, interesting that 10 out of 11 patients with cranial nerve palsy also had uveitis and this strong connection strengthens the indication that this is a syndrome. Half of the patients with parotid and salivary gland enlargement did not have ocular engagement and six out of 10 were HLA-DRB1*04 positive. This also indicates that the connection to HLA-DRB1*04 is not only driven by the uveitis. The high frequency of HLA-DRB1*04 in these patients seems to be a possible genetic link, which could explain why these symptoms known to be part of HS occur simultaneously. Out of the patients with ocular inflammatory manifestations other than uveitis, half of them were HLA-DRB1*04 positive.

We found an overrepresentation of HLA-DRB1*04, particularly HLA-DRB1*0401, in patients with the HS-associated manifestations uveitis, parotid and salivary glands, as well as cranial nerve palsy. In this as well as in some previous studies, HLA-DRB1*04 was otherwise shown to be protective against sarcoidosis [20, 21]. There are other studies that support our findings of a genetic association to symptoms associated with HS. For example, associations between HLA-DRB1*0401 and

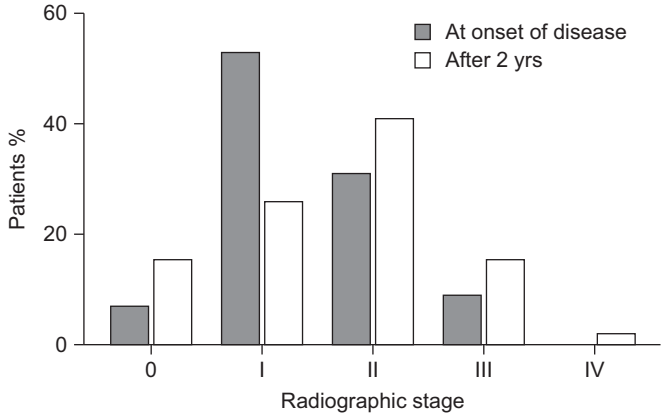

FIGURE 5. 58 patients with ocular sarcoidosis and their radiographic stage at onset of disease and 2 yrs after diagnosis. Results are presented as percentage of patients who belong to radiographic stages 0–IV, respectively.

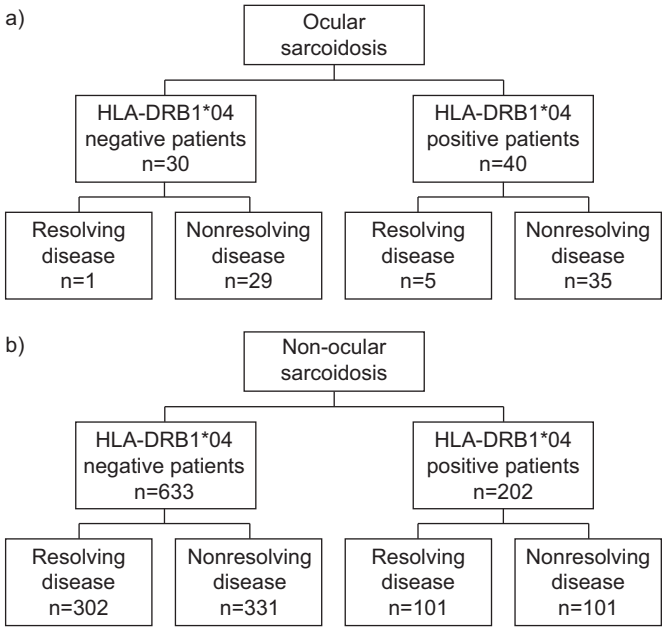

FIGURE 6. a) 70 patients with ocular sarcoidosis, where there was information available regarding resolving or nonresolving disease. The patients are divided into HLA-DRB1*04 positive and negative, respectively. The numbers of patients with resolving and nonresolving disease are given. b) Corresponding data on outcome of the disease in 202 HLA-DRB1*04 positive and 633 HLA-DRB1*04 negative patients without ocular involvement. There was a significant difference in outcome depending on whether they had ocular or nonocular sarcoidosis ($p<0.0001$).

ocular sarcoidosis have been suggested, but in significantly smaller patient cohorts and where patients of different ethnic origins were included [22, 23]. Correlations between HLA-DRB1*0401 and involvement of parotid and salivary glands were noted in a study by ROSSMAN *et al.* [22]; however, the correlation was significant only for African-Americans and not for Caucasians. In a more recent study by SATO *et al.* [23], a link between DRB1*0803 and neurosarcoidosis was reported in Japanese patients as well as between DRB1*0401/DQB1*0301 and uveitis in a UK population. Previous studies have also shown genetic associations for uveitis in sarcoidosis with the HSP70/Hom rs2075800 G allele in patients from the UK and with the CTLA-4 gene polymorphism in patients from Japan [24, 25]. There are also studies about genetic similarities between inflammatory bowel disease and sarcoidosis, both of which are associated with an increased risk for uveitis [26, 27]. One possible explanation of the genetic linkage with a specific HLA-allele is cross-reactivity, for example, there are proteins in the eye that resemble the antigen that the immune system initially reacted against. According to this theory, HLA-DRB1*04 allows an adequate antigen presentation of eye-derived proteins. Patients who are homozygous for HLA-DRB1*04 may have a more efficient antigen presentation, leading to an inflammatory reaction.

In our study, the uveitis was often bilateral and posterior and no significant differences were found between the HLA-DRB1*04-positive and -negative patients. The presence of the HLA-DRB1*03 allele, previously shown to be associated with a good prognosis in Scandinavian patients [4, 28], was significantly reduced in patients with ocular sarcoidosis. However, in all patients, the frequency of the allele was higher compared with healthy controls and it seemed to be associated with an increased risk of contracting sarcoidosis. HLA-DRB1*01, which was previously found to strongly protect against non-LS [21], was also found to protect against eye involvement (table 2).

80 (8.0%) patients were found to have ocular sarcoidosis and this prevalence is low compared with several other studies, probably for several reasons. One explanation may be our relatively strict criteria for the patients diagnosed with ocular sarcoidosis. Only patients with obvious symptoms were examined for eye involvement. For example, patients with conjunctivitis sicca were excluded in our study but included in others [29, 30]. 70 patients were followed for 2 yrs, and among these we found no significant difference in outcome between the HLA-DRB1*04-positive or -negative patients. In comparison with patients without ocular sarcoidosis, patients with eye involvement had a significantly poorer prognosis with higher frequency of nonresolving disease. Therefore, ocular engagement seems to be of greater prognostic importance than HLA type. This is in contrast to patients with LS, in whom the HLA type (HLA-DRB1*03) could be a prognostic marker [2, 4]. Ethnicity is also likely to have an impact on the prevalence of ocular sarcoidosis; for example, it is known that in Japan the incidence is considerably higher than in Scandinavia [10]. Most of the patients with ocular sarcoidosis in our study had nonresolving disease, which sharply differs from the Japanese sarcoidosis patients in whom ocular engagement is often associated with a good prognosis [31]. In a study by PIETINALHO *et al.* [32], where Finnish and Japanese patients with sarcoidosis were compared, ocular sarcoidosis was found in more than half of the Japanese patients compared with 5% in the Finnish cohort. The majority of the Japanese patients had a normal chest radiograph after 2 yrs [32].

The vast majority of the patients were from one single centre, and likely to be representative of the general population as these patients are normally investigated at a respiratory department rather than in an outpatient clinic. However, a possible bias against mild forms of sarcoidosis could not be ruled out. Patients with one episode of uveitis might not always be investigated for sarcoidosis and patients with only cranial nerve palsy are probably not routinely investigated with chest radiograph.

In conclusion, we set out to analyse associations between HLA-DRB1* alleles and symptoms linked to HS in a large well-characterised, homogenous Scandinavian sarcoidosis population, and we specifically investigated ocular involvement. The results of our study show that there is a significant correlation between HLA-DRB1*04 and symptoms linked to HS. However, in sharp contrast to LS, where a genetic association is also known, HS has a prolonged disease course. Therefore, it seems reasonable to suggest that HLA-DRB1*04-positive patients should be closely monitored for particularly uveitis, but also parotid or salivary gland enlargement and cranial nerve palsy. Involvement of one of these organs also calls for increased awareness of possible nonresolving disease and a more intensive follow-up.

SUPPORT STATEMENT

This study was supported by The Swedish Heart–Lung Foundation, The King Oscar II Jubilee Foundation, the Swedish Research Council, Torsten and Ragnar Söderberg's Foundation, and Karolinska Institutet. Support was also given through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and the Karolinska Institutet. None of the funding sources had any influence on the production of this manuscript.

STATEMENT OF INTEREST

None declared.

ACKNOWLEDGEMENTS

The authors would like to thank H. Blomquist, B. Engvall, B. Dahlberg, M. Dahl, G. De Forest, A. Roos (all from the Dept of Medicine Solna, Respiratory Medicine Unit, Karolinska Institutet and the Division of Respiratory Medicine, Karolinska University Hospital, Stockholm, Sweden) and B. Hedquist (Eye Clinic, Södersjukhuset, Stockholm, Sweden) for their assistance. The Swedish Childhood diabetes study, Diabetes Incidence Study in Sweden and Epidemiological Investigation of Multiple Sclerosis (EIMS) and EIRA study group are acknowledged for sharing HLA genotypes from their controls.

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