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HLA and environmental interactions in sarcoidosis

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Abstract. Sarcoidosis is a systemic granulomatosis of unknown etiology despite being described over 100 years ago. While both genetic predisposition and environmental exposures have been proposed as playing a role in this disease, there have not been any systematic investigations of gene-environmental interaction in this disease. In the ACCESS dataset, detailed environmental histories and high resolution HLA class II typing were performed on 476 cases of newly diagnosed sarcoidosis and 476 matched controls from the patients' community. We evaluated gene-environmental interactions in exposures or HLA class II alleles that were present in > 5% of the population and had an odd ratio of > 1.0. Four exposures and four HLA Class II alleles met these criteria and were evaluated. Significant interaction was observed between HLA DRB1*1101 and insecticide exposure at work ($p < 0.10$) and suggestive interaction was observed between HLA DRB1*1101 and exposure to mold and musty odors and DRB1*1501 and insecticide exposure at work ($P < 0.15$). In addition, HLA DRB1*1101 and insecticide exposure at work was associated with extrapulmonary sarcoidosis, specifically cardiac sarcoidosis and hypercalcemia ($p<0.05$) and HLA DRB1*1101 and exposure to molds and musty odors was associated with pulmonary only sarcoidosis ($P < 0.05$). These studies suggest that sarcoidosis is due to an interaction of genetic predisposition and environmental exposure in at least some cases of sarcoidosis. Future studies in defined phenotypes of sarcoidosis may be necessary to define environmental and genetic associations with sarcoidosis. *(Sarcoidosis Vasc Diffuse Lung Dis 2008; 25: 125-132)*

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Introduction

Sarcoidosis is a generalized granulomatosis that predominately affects the lungs. Despite the fact that disease was first described over 100 years ago and over 200 manuscripts have been published on the etiology of sarcoidosis, no specific cause of the disease has been identified. Two major foci of investigation are that sarcoidosis is a reaction to an envi-

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ronmental exposure and/or that there is a genetic predisposition (1).

Because of the frequency of pulmonary involvement in sarcoidosis, environmental agents that might enter through the respiratory tract have been postulated as the etiologic agent in this condition (e.g.. mycobacterium (2) and pine pollen (3)). Unfortunately, no single exposure has yet been shown to be convincingly associated with a majority of sarcoidosis cases (4). Cigarette smoking, the only agent with repeatable associations with sarcoidosis, has been shown to be negatively associated with sarcoidosis (4). The inability to identify a specific etiologic agent in sarcoidosis has led to the speculation that multiple environmental agents, rather then a single one may be associated with sarcoidosis (4).

A genetic predisposition to sarcoidosis has been suggested by familial studies (5-7). Since the 1980's studies have attempted to identify HLA antigens and molecules associated with sarcoidosis (reviewed in (8)). In addition, a recent genome wide search for genes associated with sarcoidosis suggested that the HLA region was the area with the highest lod score (9). In the most comprehensive study to date, we found significant HLA associations with the DRB1 locus in patients with newly diagnosed sarcoidosis (8).

Immunopathologically, sarcoidosis appears to be mediated by CD4+ T cells, since they have been consistently found at the sites of disease activity (10).The HLA class II molecules play an important role in the ability of CD4+ T cells to respond to antigenic stimuli (11). On antigen presenting cells, HLA class II molecules bind and present antigenic peptides to immunologically competent CD4+ T lymphocytes. Thus, the HLA class II molecule is part of the protein complex to which the T lymphocyte responds. In addition, the affinity of an HLA molecule for a specific antigenic peptide has marked variability. Thus, the ability of an individuals HLA molecule to bind specific peptides may determine that individual's susceptibility to disease and/or hypersensitivity.

Because of the important role that HLA molecules play in antigen recognition, we decided to review the high resolution HLA class II typing that was performed in the ACCESS study and the detailed environmental questionnaire, to determine if we could detect gene-environmental interactions in sarcoidosis.

Methods

Study Design

Blood specimens were collected prospectively from patients and matched controls who were entered into a case control etiology study of sarcoidosis (ACCESS) (12). Between November 1996 and June 1999, 736 cases with 706 matched controls were entered into the study. HLA studies were only performed on the first 474 cases and matched controls. All cases and controls completed informed consent in accordance with a protocol approved by the Institutional Review Boards of all participating centers.

Cases

Cases of sarcoidosis were recruited prospectively within geographic regions surrounding the ten participating clinical centers between 1996 and 1999 and the criteria for entry was previously described (12). Specific phenotypes of sarcoidosis were determined with an instrument developed by the ACCESS group (13). The clinical characteristics of the study patients were reported elsewhere (14) and shown in table 1.

Controls

Controls were recruited by random digit dialing (RDD) methods (12, 15, 16) from within the same geographic region as cases. Controls were matched to cases on the basis of age (within five years), gender, and self-reported race and ethnicity. Controls were excluded if they reported a history of sarcoidosis or medical conditions that made the determination of sarcoidosis uncertain (e.g., granulomatous hepatitis, idiopathic uveitis).

DNA Preparation and HLA Analsysis

Heparinized blood was collected from each case/control at the time of the interview and sent by overnight courier to the DNA Core for purification of the DNA as described previously(8). Masked samples of DNA were sent to the HLA typing laboratory for analysis of HLA Class II alleles. Locus and allele-specific amplifications of genomic DNA

Table 1. Characteristics of Study Population (n= 736)

		% of population
Matched Criteria		
Age		
	< 40 years	46%
	>=40	54%
Gender		
	Males	36%
	Females	64%
Race		
	White	53%
	Black	44%
	Other	3%
Clinical characteristics		
X-ray Stage		
	0	8.3
	1	39.7
	2	36.7
	3	9.8
	4	5.4
% predicted Vital Capacity		
	<50%	2.5
	50-69%	11.1
	70-79%	17.6
	>80%	68.8
% predicted FEV1		
	<50%	3.8
	50-69%	16.5
	70-79%	17.6
	>80%	62.2
FEV1/FVC, absolute %		
	<50%	0.8
	50-69%	13.2
	70-79%	39.0
	>80%	46.9
Organ involvement		
	Lungs	95.0
	Skin	15.9
	Lymph node	15.2
	Eye	11.8
	Liver	11.5
	Erythema nodosum	8.3
	Spleen	6.7
	Neurologic	4.6
	Parotid/Salivary	3.9
	Bone Marrow	3.9
	Calcium	3.7
	ENT	3.0
	Cardiac	2.3
	Renal	0.7
	Bone/Joint	0.5
	Muscle	0.4

were performed for DRB1-, DRB3-, DRB4-, DRB5-, DQB1- and DPB1-associated alleles as described earlier (8).

Data Collection

Data for cases and controls were collected in face-to-face interviews. Cases and controls completed the same exposure questionnaires. Interviewers were not blind to case/control status.

Questionnaire Instrument

The questionnaire was designed to identify activities and occupational agents that could plausibly cause sarcoidosis or other granulomatous diseases. Interviews followed proposed scripts. The occupational and environmental questions were embedded in larger questionnaires that also included questions regarding demographics, family history, access to health care, and scales measuring psychological variables and socioeconomic status (17), helping to blind subjects to our hypotheses. In brief, the questionnaire pertaining to occupational and environmental hypotheses consisted of 1) dichotomous questions concerning specific jobs, hobbies, and exposures both at home and at work, 2) a structured interview to obtain a detailed chronology of jobs held for at least six months, and 3) tobacco use based on the American Thoracic Society (ATS) standardized questionnaire (18).

Statistical Evaluation

ACCESS data were analyzed using matched case-control analysis methods. Analyses of categorical variables used McNemar's Test (19). Matched logistic regression analyses were performed using the methods described in Breslow and Day (20). The PHREG procedure in SAS was used to analyze these data.

A stepwise logistic regression was used to obtain the most parsimonious model that relates alleles or amino acid epitopes to sarcoidosis or environmental exposures to sarcoidosis. Some of the variables mentioned above were present in very low frequencies. The inclusion of these variables resulted in singular information matrices that destabilized the model that was being generated. The variables resulting in singularities that destabilized the model were excluded from the logistic regression. Because of the limited power to do interaction analyses in a case-control study of 474, only alleles/amino-acid residues or environmental exposures that had significant association with sarcoidosis ($p<0.05$), odds ra-

tio greater than 1.0 and were present in 5% of the control population were entered into the interaction analysis. Because the test of interaction measured whether of not the interaction of the odds ratio of the gene and environmental effects was super-multiplicative and not super-additive (a very stringent criterion), a p value of < 0.1 was considered significant and a value of < 0.15 was considered suggestive.

To address whether specific combinations of an allele and environmental exposure were associated with a clinical phenotypic of sarcoidosis, a chi-square test was performed to test whether the clinical phenotype was equally prevalent in sarcoidosis patients who had the allele and environmental exposure compared to those who did not have the allele and environmental exposure. The significance level for the p-value for these associations was set at 0.05.

Results

HLA Results

The results of the analysis of the HLA Class II typing that was done in the ACCESS study have been reported in detail elsewhere (8). For the HLA DRB1 locus, 53 different alleles and 60 amino acid residue polymorphisms were identified. 10 of these alleles and 14 amino acid residues had a univariable p < 0.10. For the HLA DQB1 locus, 19 different alleles and 51 amino acid residues were identified and 2 alleles and 7 amino acid residues had a univariable p < 0.10. For the HLA DPB1 locus, 41 different alleles and 33 different amino acid residues were identified and only 1 allele and 3 amino acid residues had a univariable p < 0.10. The presence of a DRB3 or DRB4 allele had a univariable p < 0.10 and only the presence of the DRB3*0101 allele among the 4 DRB3 alleles identified was associated with a univariable p < 0.10. To determine independent candidate HLA Class II alleles or amino acid residues that might interact with specific environmental exposures, a logistic regression was performed (Tab. 2). Only 4 HLA Class II alleles or amino acid residues were identified that were significantly associated with sarcoidosis (p < 0.05), present in 5% of the control population, and had an odds ratio of greater than 1.0.

Environmental Questionnaire Results

The detailed results of the environmental questionnaire in ACCESS have been reported elsewhere (4). Because those results were performed for the cohort of 706 cases and controls, the analysis was repeated in the 474 cases and controls for which HLA typing was available. Of the 702 variables that were screened, at the 0.1 level, 57 were significant in whites, 59 in blacks, 50 in males and 73 in females. The results of the logistic regression (Table 3) in this subgroup were similar to the results of the logistic regression in the entire cohort. Only four environmental exposures were significantly associated with sarcoidosis (p < 0.05), present in 5% of the controls and had odds ratios greater than 1.0.

Interaction of Environmental Exposures and HLA Class II Alleles or Amino acid Residues

The four HLA Class II alleles or amino acid residues and the four environmental exposures

Table 2. Forward Logistic Regression Analysis of the Association of HLA DRB1, DRB3, DQB1, and DPB1 Alleles and Amino Acid Residues and Sarcoidosis

HLA Allele or AA residue	% Cases	% Controls	Odds Ratio (95% CI*)	P Value
Associated with Sarcoidosis				
DRB1*1101	22.36	13.08	2.68 (1.78-4.03)	< 0.001
DRB1*0402	3.80	1.69	4.59 (1.76-12.0)	0.002
DRB1*1201	8.02	4.43	2.62 (1.38-4.95)	0.003
DRB1*1501	21.52	14.13	1.84 (1.22-2.77)	0.004
DRB3*0101	33.12	26.58	1.60 (1.16-2.20)	0.004
DPB1-V^{76}	51.27	48.73	1.56 (1.14-2.12)	0.005
DRB1*1401	7.59	4.64	2.29 (1.21-4.34)	0.011
Associated with Controls				
DRB1-H^{13}	17	23	0.32 (0.12-0.87)	0.026

* CI = confidence interval
Alleles in bold were utilized in the gene-environmental interaction

Table 3. Backward Logistic Regression Analysis of the Association of Environmental Exposures and Sarcoidosis

Environmental Exposure	% Cases	% Controls	Odds Ratio (95% CI*)	P Value
Associated with Sarcoidosis				
Insecticide, occup - ever	22.57	15.19	1.82 (1.29-2.57)	0.001
ia1.7.2 industrial organic dusts	5.06	2.11	3.50 (1.67-7.33)	0.001
Job teaching middle school or high school - ever	9.07	6.33	1.98 (1.22-3.20)	0.006
Exposure to musty odors - ever	35.44	29.96	1.49 (1.11-1.99)	0.008
Job in animal lab	0.84	0.21	32.79 (2.37-453.50)	0.009
Job as rubber factory worker - ever	1.27	0.21	14.57 (1.47-144.66)	0.022
Used humidifier – in the reference period	43.88	35.44	1.36 (1.04-1.77)	0.024
52 Building mat and hardware	1.69	0.63	3.23 (1.10-9.52)	0.033
Associated with Controls				
Smoke cigarettes now	7.81	30.80	0.13 (0.08-0.20)	<0.001
Exposure to child care - ref	49.16	58.44	0.57 (0.44-0.75)	<0.001
Job as DP/typist/programmer - eve	32.28	37.13	0.57 (0.44-0.75	<0.001
Exposure to hot tubs -ref	31.43	34.39	0.65 (0.49-0.86)	0.003
Feathers/down - ever	71.52	76.16	0.66 (0.49-0.89)	0.007
83 Social services	10.97	15.40	0.59 (0.39-0.87)	0.009
Exposure as hosp vol - ever	7.38	8.86	0.55 (0.34-0.88)	0.013
Fish (tank > 10 gal) - ever	28.06	37.13	0.72 (0.55-0.94)	0.014
oa1.1 metal dust / metal fume ass	10.55	13.92	0.61 (0.40-0.91)	0.017
Cats - ref	25.11	33.97	0.73 (0.54-0.98)	0.036

* CI = confidence interval
Exposures in bold were utilized in the gene-environmental interaction

identified above were studied to determine whether or not they were positively associated with sarcoidosis. The presence of HLA DRB1*1101 and a history of insecticide exposure at work significantly ($p < 0.10$) interacted (Fig. 1A) with the combined genetic and exposure variable, resulting in an odds ratio of 5.82. HLA DRB1*1101 (Fig. 1C) also had a suggestive interaction with exposure to molds or musty odors ($p = 0.135$). Interestingly, occupational insecticide exposure (Figure 1B) also had a suggestive interaction with HLA DRB1*1501 ($p = 0.124$).

Phenotype of disease identified by gene-environmental interactions

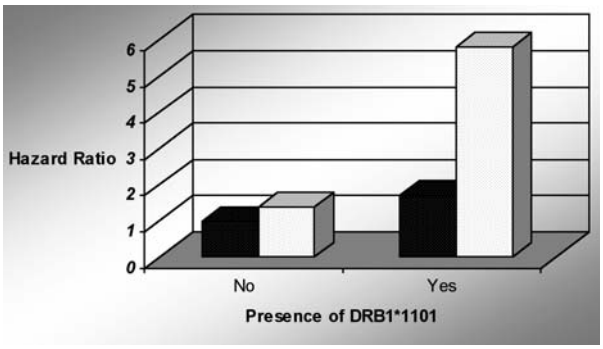
Having identified gene-environmental combinations that appeared to interact in the predisposition for sarcoidosis, we asked if these gene-environmental combinations would identify a specific phenotype of newly diagnosed sarcoidosis. This analysis yielded an occupational insecticide exposure and DRB1*1101 association with extrapulmonary sarcoidosis, specifically cardiac sarcoidosis and hypercalcemia (Tab. 3). However, DRB1*1101 and exposure to molds or musty odors was associated with pulmonary only sarcoidosis. No specific phenotype of sarcoidosis was associated with DRB1*1501 and occupational exposure to insecticides.

Discussion

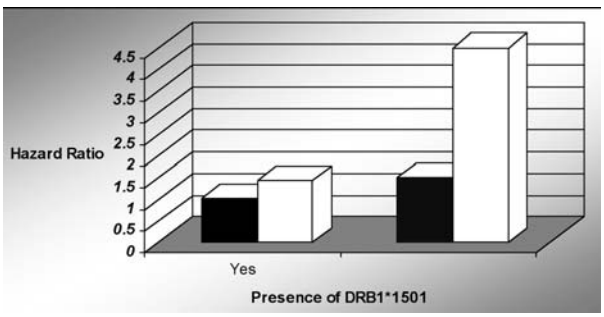
While it has been postulated for many years that sarcoidosis is caused by an environmental exposure in a genetically predisposed host, this is the first study to investigate gene-environmental interactions in sarcoidosis. Our findings suggest a role for a gene-environmental interaction in either etiologic or phenotypic expression of sarcoidosis. We found that gene-environmental combinations not only increased the risk for sarcoidosis but also increased the risk for specific phenotypes of sarcoidosis. This observation may explain the difficulty there has been in identifying causative agents in sarcoidosis. Unless populations with similar genetic predispositions are studied, similar environmental exposures may not be identified.

In this study only a limited number of genetic polymorphisms and environmental exposures were identified. Because only 474 case-control pairs were studied, this investigation had limited power to detect gene-environmental interactions of genetic polymorphisms or environmental exposures of low

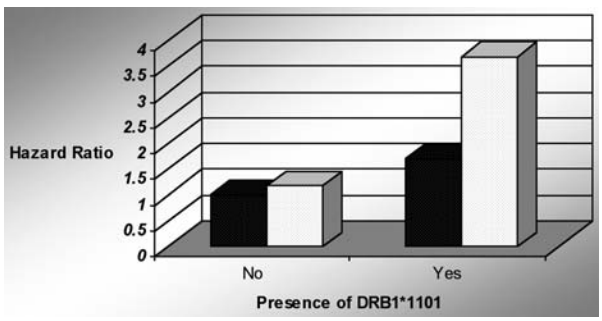
frequencies. In addition, the test for interaction determines if the product of the odds ratio of the genetic effect and the environmental effect is less than the odds ratio of the interaction effect. Statistical tests to determine if the sum of the odds ratio of the separate effects is less than the odds ratio of the interaction effect are not well developed. We compensated for this very stringent criterion by using p values that would not normally be considered significant (i.e. $p < 0.10$). Clearly, the observations in this study will have to be replicated.



A. HLA DRB1*1101 and occupational insecticide exposure



B. HLA DRB1*1501 and occupational insecticide exposure



C. HLA DRB1*1101 and exposure to molds or musty odors

Fig. 1. The interaction of specific HLA Class II alleles and environmental exposures are illustrated. The hazard ratio is on the Y axis. The presence or absence of the specific HLA allele is indicated on the X axis. The presence of the environmental exposure is indicated by the white columns and the absence of the exposure by the black columns. A. HLA DRB1*1101 and occupational insecticide exposure ($p = 0.074$). B. HLA DRB1*1501 and occupational insecticide exposure ($p = 0.124$). C. HLA DRB1*1101 and exposure to molds or musty odors ($p = 0.135$).

We also determined if the interactions were associated with a specific phenotype of sarcoidosis at presentation. Two of the three interactions were associated with specific phenotypes of sarcoidosis. This finding suggests that the interactions found in this investigation might be real. Future studies can be designed to test the hypothesis that DRB1*1101 and exposure to molds and musty odors is associated with pulmonary only sarcoidosis and that DRB1*1101 and occupational exposure to insecticides are related to cardiac sarcoidosis and hypercalcemia in sarcoidosis.

Insecticides have been associated with sarcoidosis in two previous studies (4, 21), however, this is the first study to associate insecticide exposure to cardiac sarcodosis or hypercalcemia in sarcoidosis. Insecticides and pesticides have been associated with diabetes, asthma, pancreatic cancer and leukemia in a cohort of Australian workers (22) In addition, agent orange has been associated with dysregulation of B and T cell function in Vietnam Korean War Veterans (23). Finally, pesticides have been associated with contact dermatitis (24) and multiple chemical sensitivities (25). Thus, a detailed investigation of the role of pesticides in sarcoidosis, particularly those with cardiac involvement or hypercalcemia might be warranted. However, despite the high odds ratios observed in the gene-environmental interaction with hypercalcemia (3.6) and cardiac sarcoidosis (4.8), the interaction only accounted for 4 of 22 cases of hypercalcemia and 3 of 13 cases of cardiac sarcoidosis in this sample.

The association of molds and musty odors with pulmonary only sarcoidosis is not surprising since molds have been associated with hypersensitivity pneumonitis (26). Over 58% of individuals who had both DRB1*1101 and exposure to molds or musty odors had evidence of pulmonary only sarcoidosis, while only 38% of individuals with one or none of the risk factors had evidence of pulmonary only disease. In the ACCESS population this gene environmental exposure was associated with 24 out of 173 (~14%) cases of pulmonary only sarcoidosis. Further studies are needed to confirm this association and define the possible molds involved.

Table 4.

Form of Disease	Gene-Environment Combination	Absence of gene or environmental exposure	Presence of gene and environmental exposure	Odds Ratio	P Value
Extrapulmonary (except skin)	Insec. & DRB1*1101	44.1% (196/444)	63.3% (19/30)	2.2	0.04
Hypercalcemia	Insec. & DRB1*1101	4.1% (18/444)	13.3% (4/30)	3.6	0.02
Cardiac	Insec. & DRB1*1101	2.3% (10/444)	10.0% (3/30)	4.8	0.02
Pulmonary Only	Musty Odors & DRB1*1101	34.4% (149/433)	58.5% (24/41)	2.7	0.02

These findings have several important implications for our understanding of sarcoidosis. First, the data suggest that sarcoidosis is probably not a specific disease due to a single etiologic agent but is a syndrome caused by many agents. Specific manifestations of sarcoidosis may be determined by environmental exposures that occur in genetically predisposed individuals. Future studies that seek to determine environmental causes of sarcoidosis should focus on phenotypic subtypes of sarcoidosis (e.g. pulmonary only disease or cardiac sarcoidosis). The strong association of Scandinavians with DR3 and Lofgren's Syndrome (27) suggest that a detailed environmental investigation of these individuals would be fruitful. In addition, in the ACCESS study, when a cases only analysis of environmental exposures was performed, associations were found with pulmonary only sarcoidosis that were not found in the initial analysis (28) (i.e. wood burning stoves). Because of the rarity of most forms of extrapulmonary sarcoidosis, multicenter collaborative studies will be necessary.

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