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Increased frequency of HLA-B44 in recurrent sinopulmonary infections (RESPI)

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Abstract To test whether MHC alleles associated with common variable immune deficiency (CVID) might also be over-represented in patients with normal serum immunoglobulin levels who suffer with recurrent sinopulmonary infections (RESPI), we identified 62 consecutive RESPI patients and compared their HLA-B and HLA-DR antigen frequencies to those of 60 consecutive patients with CVID, 1627 Alabama Caucasian bone marrow donors, and 997,230 published US Caucasians. Either HLA-B44, -B8, -DR3(17), or -DR7 was present in 74% of the RESPI and 85% of the CVID patients. HLA-B44 prevalence in particular proved identical between RESPI and CVID. When compared to US Caucasians, the increased prevalence of the four HLA alleles proved significant at $P < 0.0001$, $P < 0.0001$, $P = 0.0005$, and $P = 0.02$, respectively. When compared to Alabama Caucasians, only the increased prevalence of HLA-B44 achieved statistical significance ($P = 0.0001$). Inheritance of HLA-B44 may yield susceptibility to recurrent sinopulmonary infection even in the presence of normal serum immunoglobulin levels.

Introduction

In 2002, there were more than 9 million patients suffering with chronic bronchitis and more than 30 million with chronic rhinosinusitis in the United States [1,2]. These types of chronic respiratory infections are common in smokers and patients with primary immune deficiencies [3]. For other patients, the factors that predispose to recurrent sinopulmonary infections (RESPI) remain unclear.

Genetic susceptibility to IgA deficiency (IgAD) and CVID has been linked to two loci within the major histocompatibility complex (MHC) on chromosome 6 [4–7]. Patients with these diagnoses can be positioned within a spectrum of immune deficiency progressing from isolated IgAD to panhypogammaglobulinemia [8]. Within our Adult Primary Immunodeficiency Clinic in the Southeastern US, the majority of our IgAD/CVID patients have inherited part or

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Table 1 Patient demographics

	RESPI group	CVID group	*P* value
Sample size (*n*)	62	60	
Ethnicity			
Caucasian	98%	92%	0.11
African American	1.6%	3.3%	0.62
Hispanic	0%	5%	0.12
Sex			
Male	16%	54%	<0.0001
Female	84%	47%	<0.0001
Mean age at presentation			
Sinusitis	20.9 + 2 (89%)	16.5 + 2 (75%)	0.16
Bronchitis	18.1 + 3 (61%)	17.6 + 2 (75%)	0.89
Pneumonia	21.8 + 3 (56%)	23.9 + 3 (60%)	0.62
Bronchiectasis	45 + 10 (8%)	27.2 + 4 (22%)	0.14
Mean serum immunoglobulin			
IgM (*n*)	124.5 ± 9 (61)	25.7 ± 3 (57)	<0.0001
IgA (*n*)	198.4 ± 13 (62)	21.3 ± 4 (58)	<0.0001
IgG (*n*)	914.5 ± 31 (62)	251.5 ± 18 (60)	<0.0001
IgG1 (*n*)	530 ± 22 (58)	256.1 ± 38 (20)	<0.0001
IgG2 (*n*)	308 ± 16 (58)	87.2 ± 28 (20)	<0.0001
IgG3 (*n*)	48 ± 4 (58)	46 ± 12 (19)	0.88
IgG4 (*n*)	25 ± 3 (58)	8.13 ± 3 (19)	0.0004
IgE (*n*)	50 ± 16 (51)	14.3 ± 5 (24)	<0.04

all of two extended MHC haplotypes: HLA-B8-DR3(17) and HLA-B44-DR7 [7].

In addition to IgAD/CVID, we see a large number of non-smoking adults with RESPI where we have been unable to identify a host defense deficit that would account for their infections. This population includes first or second degree relatives of CVID patients who, like their affected relatives, suffer with recurrent sinopulmonary infections but express normal serum levels of IgM, IgG, and IgA. This unexplained observation impelled us to test whether the MHC alleles linked to CVID might also be overexpressed in normogammaglobulinemic patients with a history of recurrent sinopulmonary infections.

Methods

Patient selection

We identified 62 consecutive patients with unexplained RESPI and normal serum immunoglobulin levels who were referred during the period of 2001 through 2004 inclusive to the UAB Adult Primary Immunodeficiency Clinic (Table 1, Fig. 1). Of these, five (8%) were first-degree relatives of CVID patients. Excluded were patients with a >20-pack year smoking history, patients who reported treatment with intravenous gammaglobulin, and patients exposed to oral corticosteroids or other known immunosuppressive agents. Serum IgM levels ranged between 31 and 357 mg/dl, IgG between 600 and 1590 mg/dl, and IgA between 60 and 482mg/dl (Fig. 2). For both RESPI and CVID, a detailed clinical history was collected in person by the senior author. This included the first occurrence of sinusitis, bronchitis, and pneumonia by self-report. This group was compared to 60 consecutive clinic patients with CVID, which included 56 patients from a previous study [7].

MHC haplotyping

Human leukocyte antigen (HLA)-B and -DR alleles were typed by PCR using LABType SSO PCR-SSO (Thermalcycler; Luminex Corporation, Austin, TX) at low resolution. Antigen

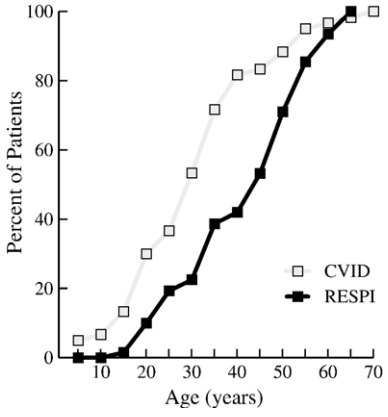

Figure 1 Cumulative distribution of the age at the time of disease recognition. RESPI patients exhibit a pattern of age-associated disease onset that is similar to that observed in CVID (Table 1) but on average recognition is delayed by one decade (41 + 2 versus 30+ 2 years, respectively; $P < 0.0001$).