

HLA-DR polymorphism in allergic bronchopulmonary aspergillosis

Yolande Aron, MS,^a Thierry Bienvenu, MD, PhD,^b Dominique Hubert, MD,^c Daniel Dusser, MD,^c Josette Dall'Ava, MD,^d and Barbara S. Polla, MD^a Paris, France

The fungus *Aspergillus* genus causes a spectrum of diseases, among which is allergic bronchopulmonary

Abbreviations used

ABPA: Allergic bronchopulmonary aspergillosis

CF: Cystic fibrosis

CFTR: Cystic fibrosis transmembrane conductance regulator

From ^aLaboratoire de Physiologie Respiratoire, ^bLaboratoire de Biochimie et Génétique Moléculaire, ^cService de Pneumologie, APHP, and ^dService de Physiologie, Explorations Fonctionnelles, APHP, Groupe Hospitalier et universitaire Cochin-Port Royal, Université Paris V, Paris.

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Reprint requests: Yolande Aron, MS, Laboratoire de Physiologie Respiratoire, UFR, Cochin Port-Royal, Université Paris V, 24 rue du Faubourg Saint-Jacques, 75679 Paris cedex 14, France.

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aspergillosis (ABPA). In ABPA, *Aspergillus* species colonizes the bronchi without invading the tissue, and the hypersensitivity reactions to *Aspergillus* antigens cause the pathologic manifestations (ie, recurrent wheezing and evanescent infiltrates on chest radiography). ABPA occurs in approximately 1% to 2% of asthmatic subjects and 7% to 10% of patients with cystic fibrosis (CF). Furthermore, IgE antibodies to *Aspergillus* develop in 25% of patients

TABLE I. DR4 and DR7 allelic distribution in 16 patients with ABPA compared with control subjects and patients with allergy and CF

DRB1 alleles	Control subjects (n = 39)		Patients with ABPA (n = 16)			Patients with allergy (n = 56)			Patients with CF (n = 98)		
	No.	%	No.	%	P value	No.	%	P value	No.	%	P value
DR4	1	2.5	6	37.5	<2.10 ⁻³	22	39.2	<4.10 ⁻⁵	23	23.5	<4.10 ⁻³
DR7	0	0	5	31.2	<2.10 ⁻³	12	21.4	<5.10 ⁻³	26	26.5	<4.10 ⁻⁴

with asthma and 60% of patients with CF. The immune response to *Aspergillus* species antigens, whether in allergy, asthma, or ABPA, is characterized by a T_{H2} CD4⁺ T-cell response and specific IgE production, as is the response to allergens in atopy. We previously reported an association between atopy and allergic asthma on the one hand and HLA-DR4 and HLA-DR7 alleles on the other.¹ We also found a strong association between the same DR4 and DR7 alleles and CF in an adult population with CF.² Furthermore, Chauhan et al^{3,4} found that DR2 or DR5 molecules were the main restriction elements for Asp f 1 antigen presentation and that these alleles were elevated among patients with ABPA.

Here we analyzed the HLA-DR allelic distribution in 16 patients with ABPA and compared this group with previously studied atopic-allergic and CF populations without ABPA for the following susceptibility *DRB1* alleles: DR2, DR4, DR5, and DR7. We also investigated, in this group of patients with ABPA, the possibility of CF mutations.⁵ Our results suggest genetic overlap of HLA polymorphism in the 3 diseases studied: ABPA, allergy, and CF.

METHODS

The study involved 16 European-born unrelated white adults who met the following criteria: history of asthma, recurrent pulmonary infiltrates and/or radiographic evidence of central bronchiectasis, positive immediate epicutaneous skin test response to *Aspergillus* allergens elevated total serum IgE level of 1000 IU/mL or greater, positive serum precipitins to *Aspergillus* species, and peripheral blood eosinophilia. Thirty-nine selected subjects without allergy who were previously described in detail¹ were used as control subjects. Fifty-six allergic patients and 98 patients with CF who were previously typed and described in detail^{1,2} were used to establish a comparison with the patients with ABPA. DNA samples were typed for HLA class II DRB1 alleles by using the PCR-RFLP method, as previously described.¹ Genomic DNA samples were screened for 31 CF transmembrane conductance regulator (CFTR) mutations, which account for 80% of mutations in patients with CF in France, by using the oligonucleotide ligation assay (Perkin Elmer Applied Biosystem, Foster City, Calif). Statistical analysis was performed by using the χ^2 test. For *P* values, the Fischer exact test was used, and the level of significance was set at .05.

RESULTS AND DISCUSSION

Table I shows the associations among ABPA, allergy, CF, and the DR4 and DR7 alleles. In a random French population of 158 subjects, DR4 and DR7 allelic distributions were 12.6% and 13.9%, respectively.¹ These alleles were significantly increased in our 3 patient populations compared with selected control subjects without atopy and major diseases.¹ Association of DR7 was high-

est in patients with ABPA (31.2%) compared with patients with allergy (21.4%) and CF (26.5%), whereas DR4 was highest in the allergy group (39.2%).

As reported by Chauhan et al,⁴ we also found that DR5 was elevated when comparing patients with ABPA with a random population (43.5% vs 13.3%). However, this elevation was below the level of significance when using the χ^2 test (not shown), and Chauhan et al,^{3,4} considering the number of subjects studied, used the Fisher exact test. Furthermore, because DRB1 alleles are involved in several diseases, the negative selection of our control group for atopy-allergy might also explain the contrasting results of the current study.

Finally, we found, a posteriori, a CFTR mutation in 4 of 14 patients with ABPA (1 R1162X, 1 N1303K, and 2 Δ F508 mutations), which is in agreement with the findings of Weiner Miller et al.⁵ The percentage of CFTR mutations among our population with ABPA was thus 28% versus 4% in the random population.

We conclude that DR4 and DR7 alleles are strongly associated with ABPA, as they are with allergy and CF. These results suggest that these 3 distinct but overlapping diseases have a common genetic background. In the case of CF, the DR7 allele was correlated with an elevation in total IgE, as well as with an increase in the frequency of colonization with *Pseudomonas aeruginosa*.² Elevated IgE levels, which are found in the 3 diseases considered here, might be a consequence of their common genetic polymorphism. It is also possible, according to our results in patients with CF, that DR7 generally facilitates the colonization of bronchi by pathogens, whether *P aeruginosa* in CF or *Aspergillus* in ABPA.

REFERENCES

1. Aron Y, Desmazes-Dufeu N, Matran R, Polla BS, Dusser D, Lockhart A, et al. Evidence of a strong positive association between atopy and the HLA class II alleles DR4 and DR7. *Clin Exp Allergy* 1996;26:821-8.
2. Aron Y, Polla BS, Bienvenu T, Dall'Ava J, Dusser D, Hubert D. HLA class II polymorphism in cystic fibrosis: a possible modifier of pulmonary phenotype. *Am J Respir Crit Care Med* 1999;159:1464-8.
3. Chauhan B, Knutsen AP, Hutcheson PS, Slavov RG, Bellone CJ. T cell subsets, epitope mapping, and HLA-restriction in patients with allergic bronchopulmonary aspergillosis. *J Clin Invest* 1996;97:2324-31.
4. Chauhan B, Santiago L, Kirschmann DA, Hauptfeld V, Knutsen AP, Hutcheson PS, et al. The association of HLA-DR alleles and T cell activation with allergic bronchopulmonary aspergillosis. *J Immunol* 1997;159:4072-6.
5. Weiner Miller P, Hamosh A, Macek M, Greenberger PA, MacLean J, Walden SM, et al. Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations in allergic bronchopulmonary aspergillosis. *Am J Hum Genet* 1996;59:45-51.