

Ethnic differences in asthma and associated phenotypes: Collaborative Study on the Genetics of Asthma

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Background: In the Collaborative Study on the Genetics of Asthma, 314 families with 2584 subjects were characterized for asthma and allergy.

Objective: The purpose of this investigation was to examine clinical heterogeneity observed in asthma and allergic characteristics among 3 ethnic groups (African American, white, and Hispanic family members).

Methods: Pulmonary function parameters and asthma-associated phenotypes were compared among the ethnic groups.

Results: In comparison with the other groups, African American sibling pairs had a significantly lower baseline FEV₁ percent of predicted ($P = .0001$) and a higher rate of skin test reactivity to cockroach allergen ($P = .0001$); Hispanic sibling pairs had significantly more skin reactivity overall ($P = .001$); and white sibling pairs had significantly lower total serum IgE ($P < .05$). In addition, there were significantly more relatives with asthma among the African American families than among the white and the Hispanic families ($P = .001$).

Conclusion: Although different environmental backgrounds should be considered, these clinical differences could be due to differences in genetic susceptibility among the ethnic groups, such as those suggested by our previous genome screen. (*J Allergy Clin Immunol* 2001;108:357-62.)

Key words: Asthma, bronchial hyperresponsiveness, atopy, ethnic differences

Asthma is a phenotypically heterogeneous disorder in which complex interactions between environmental and genetic factors cause bronchial inflammation with vari-

Abbreviations used

ANCOVA: Analysis of covariance
ATS: American Thoracic Society
BHR: Bronchial hyperresponsiveness
CSGA: Collaborative Study on the Genetics of Asthma
PC₂₀ FEV₁: Methacholine provocative concentration producing a 20% decrease in FEV₁

able, reversible airway obstruction that produces characteristic clinical symptoms. Family studies have shown both an increased frequency of asthma in first-degree relatives of individuals with asthma and increased concordance rates for asthma in monozygotic twins in comparison with dizygotic twins, suggesting a significant genetic basis for asthma.¹ The interactions of environmental factors with specific genes might influence age of presentation as well as heterogeneity in clinical course and therapeutic responses.

The Collaborative Study on the Genetics of Asthma (CSGA), a multicenter study supported by the National Heart, Lung, and Blood Institute, collected 314 families (2584 subjects) from 3 US ethnic groups: whites, African Americans, and Hispanics. Sibling pairs (sib-pairs) with asthma were recruited from 6 geographic locations that included urban, suburban, and rural populations. Despite identical eligibility criteria for the selection of sib-pairs with asthma, chromosomal regions showing the strongest evidence for linkage to asthma differed among the ethnic groups.² This finding might reflect variation in allele frequencies between ethnic groups or variation in environmental exposures and clinical disease heterogeneity.

The purpose of this report is to examine clinical characteristics, levels of bronchial responsiveness, and frequencies of allergic sensitization in 3 ethnic groups recruited for genetic studies of asthma susceptibility. The overall goal of our study is to improve the understanding of the asthma phenotype with respect to the joint contributions of genotype and environment.

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METHODS

Study populations

Subjects with asthma were evaluated at 4 centers chosen to participate in the CSGA. The Johns Hopkins University (center 1) studied an urban Baltimore population and an inner-city population from Washington, DC, in collaboration with Howard University; the University of Chicago (center 2) studied Chicago inner-city and suburban families; the University of Minnesota (center 3) studied large, multigenerational families; and the University of Maryland (center 4) studied an urban Baltimore population and, in collaboration with the University of New Mexico, a Hispanic population residing in New Mexico. The Data Coordinating Center, at the Wake Forest University School of Medicine, did collection, collation, and analysis of clinical data.

African American, white, and Hispanic families, each with 2 siblings aged 6 years or older having asthma, were recruited from adult and pediatric asthma clinics at all sites. In addition, subjects were recruited at the University of Minnesota from multigenerational families who had participated in previous studies of atopy.^{3,4} In some centers, subjects were recruited by direct advertisement. Ethnicity was self-reported, and in families with mixed racial parentage (less than 10% of the study population), the race of the proband was specified as African American if at least one parent was African American and as Hispanic if at least one parent was Hispanic. All centers secured the approval of human subjects review boards. Written informed consent or, in the case of children aged 6 to 18 years, assent was obtained from all participants.

Manual of operations and technician training

A detailed manual of operations was compiled to ensure uniformity of pulmonary function testing, allergy skin testing, and bronchial challenge testing across centers. This manual incorporated established guidelines, such as the American Thoracic Society (ATS) criteria for spirometry,⁵ and standardized protocols for allergy skin tests, bronchial challenge testing, and the administration of a detailed questionnaire. Study coordinators and pulmonary function technicians from each center participated in a centralized training session before the study began.

Sampling strategy and definition of asthma (eligibility criteria)

A hierarchical sampling strategy was used to identify and recruit families in which there was asthma.^{2,6} This process began with the identification of the asthma probands on the basis of a strict definition of asthma. To qualify as probands, 2 siblings were each required to have 2 of 3 symptoms commonly associated with asthma—cough, wheeze, and shortness of breath—as well as a history or physician diagnosis consistent with asthma. Individuals were excluded if they had any of the following: (1) a birth weight <2 kg; (2) congenital or acquired cardiac or pulmonary disease; (3) a possible conflicting diagnosis, such as chronic obstructive pulmonary disease, chronic bronchitis, or emphysema; (4) tuberculosis or any other active pulmonary infections; (5) severe cardiac disease; (6) systemic vasculitis involving the lungs; (7) isolated occupational asthma, or (7) a 3-pack-year or greater history of cigarette and/or equivalent tobacco use at any time in the past. A family was also excluded if both parents of the sib-pair had asthma. Bronchodilators were withheld for 12 hours before the spirometry, but no other changes in asthma medications were required—eg, no attempt was made to ask potential probands to stop using inhaled corticosteroids. Histories of current medication usage were recorded.

If baseline FEV₁ was ≥70% of predicted, (60% of predicted at the University of Maryland), a methacholine bronchial challenge was performed. Through use of a standardized protocol⁷ (initial

methacholine concentrations being modified for children and for all subjects with potentially high levels of bronchial responsiveness), bronchial diluent control (saline + phenol + citric acid buffer) was administered; this was followed by increasing concentrations of methacholine up to 25 mg/mL until either the highest concentration was administered or there was a ≥20% decline in FEV₁. The methacholine provocative concentration producing a 20% decrease in FEV₁ (PC₂₀ FEV₁) was determined by interpolation of the dose-response curve as the concentration of methacholine at which there was a 20% fall in FEV₁. For the probands whose FEV₁ was <70% of predicted (60% of predicted at the University of Maryland), bronchodilator reversibility testing was performed. Albuterol (0.5 mL of 0.5% solution in 3 mL of saline) was administered to children by means of a nebulizer, and albuterol (2 to 4 puffs) was administered by means of a metered dose inhaler to adults. Individuals with either a PC₂₀ FEV₁ of ≤25 mg/mL or ≥15% reversibility met the eligibility criteria for enrollment into the study.

Clinical studies in probands and family members

Once a proband sib-pair met the eligibility criteria, family members were studied. All available first-degree relatives of the proband underwent baseline spirometry and bronchodilator reversibility or bronchial challenge testing through use of the same protocols that were used with the probands. A modified ATS respiratory health questionnaire⁶ that included additional questions about the presence of intermittent asthmatic or allergic symptoms was administered. The ATS questionnaire was further modified for use in all individuals under 18 years of age, and mothers usually answered questions for children under 12 years of age.⁸ Nonproband family members over 65 years of age and those with histories of cardiac disease did not undergo bronchial challenge.

The probands, as well as all other members of their families, underwent allergy skin testing to 14 common environmental allergens belonging to 5 groups, as follows: mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), mold (*Alternaria alternata*, *Cladosporium herbarum*, and *Aspergillus fumigatus*), animal dander (*Felis domesticus* [cat] and *Canis familiaris* [dog]), insects (*Blattella germanica* [German cockroach] and *Periplaneta americana* [American cockroach]), and pollens (*Lolium perenne* [rye grass], *Ambrosia artemisiifolia* [short ragweed], *Artemisia vulgaris* [common mugwort], *Quercus alba* [white oak], *Betula verrucosa* [silver birch]). For the Hispanic families in New Mexico, 3 additional allergens that are common to that area (mountain cedar, Russian thistle, and Bermuda grass) were used. Glycerol-saline and histamine controls were used as negative and positive controls. All antigens were supplied from a single commercial source (ALK Labs, Copenhagen, Denmark) to assure uniformity of skin testing between study sites. Skin test results were considered positive if the mean wheal diameter was 3 mm greater than that of the negative control. Antihistamines were withheld for an appropriate time period before skin testing, depending on the duration of action of the specific agent.

Total serum IgE levels were determined through use of microplate total IgE assays performed by a central laboratory (Access Immunoassay System, Sanofi Pasteur Diagnostics). Serum samples were collected from each subject, and aliquots were frozen at -20°C and shipped to central laboratories. DNA was extracted from whole blood by standard methods at the individual centers and stored for subsequent testing.

Data analysis and statistical methods

Comparisons of continuous variables between sites and ethnic groups were performed through use of nested analysis of covariance (ANCOVA) techniques, with sib-pairs nested within families and

TABLE I. Clinical characteristics of CSGA probands (N = 628 siblings from matched pairs)

Characteristic	African American (N = 256)	White (N = 292)	Hispanic (N = 80)	P value
Mean (SD) age at examination (y)	13.3 (6.6)	19.5 (12.8)	11.0 (3.7)	.0001
Mean (SD) age at first symptom (y)	4.6 (4.4)	6.8 (8.2)	4.0 (3.1)	.0001
Male (%)	54.3	52.7	56.3	.8167
Mean (SD) FEV ₁ % predicted	84.9 (17.2)	88.7 (16.7)	95.6 (16.1)	.0001
Mean (SD) FEV ₁ /FVC	0.83 (0.10)	0.80 (0.09)	0.81 (0.08)	.0094 (.1080*)
Mean (SD) PC ₂₀ FEV ₁	3.58 (5.05)	4.17 (5.75)	4.87 (5.94)	.3695
Mean (SD, n) reversibility FEV ₁ (%)	28.4 (14.4, 72)	33.2 (23.7, 31)	42.8 (19.9, 6)	.1105
Mean (SD) no. of positive skin test results	3.6 (3.7)	4.0 (3.4)	7.2 (4.9)	.0001
≥1 positive skin test (%)	74.5	79.4	86.3	.1607
≥3 positive skin tests (%)	50.6	59.9	78.8	.0006
Median IgE (IU/mL)	335.4	175.2	357.3	.0005
Mean (SD) log IgE	2.40 (0.68)	2.24 (0.69)	2.49 (0.63)	.0361
IgE >100 IU/mL (%)	74.3	67.4	78.7	.1133

Comparisons of continuous variables between sites and ethnic groups were performed through use of nested ANCOVA techniques, with sib-pairs nested within families and families nested within sites. For site and ethnic group comparisons of categorical variables, generalized estimating equation methods were used to account for the nesting of sib-pairs within families and families within sites.

For a point of reference, total IgE levels over 100 to 120 IU/mL and FEV₁/FVC ratios below 75% are considered clinically significant.

*P value from age-adjusted analysis.

families nested within sites.⁹ Because IgE values were highly skewed, comparisons were performed both through use of nonparametric statistics based on ranks and after log transformation of the original IgE values. Age adjustment of these comparisons was performed through use of age at examination as a continuous covariate in the nested ANCOVA models. For site and ethnic group comparisons of categorical variables, such as a positive skin test result, generalized estimating equation methods were used to account for the nesting of sib-pairs within families and families within sites.¹⁰ As in comparisons of continuous variables, age adjustment was performed with age used as a continuous covariate in these models.

Because not all ethnic groups were enrolled by every clinical site (African Americans were enrolled at centers 1, 2, and 4, whites at all 4 centers, and Hispanics only at center 4), it was possible that comparisons evaluating ethnic differences could be confounded by potential site differences. To address this, a 2-step approach was used. First, comparisons were carried out between ethnic groups on the whole data set, not adjusted for center. Second, center-adjusted comparisons between African Americans and whites were performed within the 3 centers (1, 2, and 4) that enrolled participants from each of these ethnic groups. Interactions between center and ethnic group were explored within this subsample. Findings in the second analysis that were qualitatively different from findings in the initial analysis are reported.

RESULTS

A total of 2584 individuals from 314 families were evaluated during the 3-year period of active recruitment (1993-1996). The mean family size was 8.2; centers 1, 2, and 4 predominantly studied small nuclear families (mean size = 6.5), and center 3 studied 22 large, multigenerational families (mean family size, 32.3). The sample was 46% white, 41% African American, and 13% Hispanic.

Clinical characteristics

The 314 affected sib-pairs who met the diagnostic criteria for asthma were classified as probands (Table I). African American and Hispanic subjects were younger than white subjects at the time of recruitment and at the

time of reported first symptoms of asthma. The age at first asthma symptoms was 5.0 ± 5.3 years for centers 1, 2, and 4; it was 12.4 ± 13.3 years at center 3. There were no differences in sex distribution among the ethnic groups, but 59% of the 441 subjects under 18 years of age were male; this compared with 41% of the 143 individuals 18 years of age or older ($P < .001$).

Pulmonary function

The mean FEV₁ percent of predicted ranged from $84.8\% \pm 19.5\%$ to $88.7\% \pm 16.9\%$, and the ratio of FEV₁ to forced vital capacity (FVC) ranged from $0.77 \pm .09$ to $0.83 \pm .09$. After adjustment for age differences, the FEV₁/FVC ratio was not significantly different among centers ($P = .37$). However, as shown in Table I, African Americans had lower baseline FEV₁ values than whites and Hispanics despite race correction. This was also found to be the case when the analysis focused on the 3 sites that enrolled both whites and African Americans. The FEV₁/FVC ratio was significantly different between ethnic groups ($P = .0094$); however, after adjustment for age, this difference was no longer significant ($P = .11$). There were no differences among the ethnic groups with respect to mean PC₂₀ FEV₁ methacholine for the 519 individuals who underwent bronchial responsiveness testing ($P = .37$) or with respect to mean percent change in FEV₁ for the 109 subjects who underwent bronchodilator testing.

Allergy evaluation

The results of allergy skin tests and IgE determination are summarized in Table I. The mean number of positive allergy test results was different between ethnic groups ($P = .0001$), Hispanics having a higher number of positive test results as well as more individuals with ≥ 3 positive skin test results. In comparison with whites, African Americans and Hispanics had higher IgE levels when

TABLE II. Clinical characteristics of probands on the basis of skin test reactivity

Characteristic	No. of positive skin tests		P value
	0 (N = 134)	≥1 (N = 484)	
Mean (SD) age at examination (y)	13.2 (10.2)	16.6 (10.2)	.0072
Mean (SD) age at first symptom (y)	5.0 (6.2)	5.7 (6.6)	.5074
Male (%)	50.0	55.0	.3013
Mean (SD) FEV ₁ % predicted	88.0 (17.8)	88.1 (17.0)	.7544
Mean (SD) FEV ₁ /FVC	0.85 (0.09)	0.81 (0.09)	.0001 (.0018*)
Mean (SD) PC ₂₀ FEV ₁	5.90 (6.61)	3.57 (5.09)	.0033
Mean (SD, n) reversibility FEV ₁ (%)	27.8 (15.3, 28)	31.9 (18.9, 79)	.2325
Mean (SD) no. of positive skin test results	—	5.4 (3.6)	—
≥3 positive skin tests (%)	—	74.8	—
Median IgE (IU/mL)	43.6	354.7	.0001
Mean (SD) log IgE	1.73 (0.75)	2.51 (0.56)	.0001
IgE >100 IU/mL (%)	32.3	82.8	.0001

Comparisons of continuous variables between sites and ethnic groups were performed through use of nested ANCOVA techniques, with sib-pairs nested within families and families nested within sites. For site and ethnic group comparisons of categorical variables, generalized estimating equation methods were used to account for the nesting of sib-pairs within families and families within sites. Ten individuals had missing skin test results.

FVC, Forced vital capacity.

*Age-adjusted P value.

IgE was expressed as median ($P = .0005$) or $\log_{10}$ ($P = .036$). When affected probands were compared on the basis of whether they had no or ≥ 1 positive skin test result, there were no differences in age of onset of asthma or in sex (Table II). However, mean FEV₁/FVC ($P = .0001$) and mean PC₂₀ FEV₁ methacholine ($P = .003$) were lower in probands with positive skin test results, indicating a greater degree of airway obstruction and nonspecific airway responsiveness in this group. These differences were preserved across ethnic groups in all parameters except PC₂₀ FEV₁ between the allergic and nonallergic whites ($P = .14$) and Hispanics ($P = .34$). Differences between allergic and nonallergic probands with respect to IgE levels and mean numbers of reported triggers of asthma symptoms are summarized in Table II.

Among the 484 probands with 1 or more positive skin tests, specific allergen responsiveness varied among ethnic groups (Table III). The greatest difference was for cockroach allergen, only 17% of whites exhibiting a positive reaction in comparison with 46% of Hispanics and 53% of African Americans. Hispanics, all of whom were at the New Mexico site, had higher reactivity to pollens and to *Alternaria* and the other molds. After adjustment for site differences, African Americans continued to have higher reactivity to cockroach than whites ($P = .001$); however, no significant differences in skin reactivity were noted for pollens and mold. After ethnic group was adjusted for, center differences were found for *Alternaria* ($P = .01$) and pollen ($P = .001$) but not for cockroach ($P = .92$).

Asthma in other family members

Asthma in other family members was determined through use of the proband eligibility criteria. Of the 1645 nonproband subjects, 475 (28.9%) met the criteria for asthma; this included 37.4% of other siblings, 32.5% of mothers, 18.6% of fathers, and 26.8% of other relatives. Although high, these percentages might underestimate the presence of asthma, because no subject with a >3-pack-

year history of smoking was given an asthma diagnosis and no attempt was made to distinguish a separate group of "smoking-confounded asthma" cases in this analysis. Table IV illustrates the ethnic differences observed in the other affected family members identified as meeting criteria for asthma. African American families had higher numbers of affected other siblings, mothers, and other relatives (but not fathers) than did whites and the Hispanics. Because of significant ethnic and site differences in allergy test results in the 628 probands, specific allergen test results were analyzed for the 475 other affected family members who had at least 1 positive test. Consistent differences were observed for specific reactivity to cockroach, which is greatest in all African Americans.

DISCUSSION

Asthma is a disorder characterized by airway inflammation, reversible airflow obstruction, and bronchial hyperresponsiveness (BHR) to a variety of allergic and other environmental stimuli. A genetic component for asthma has been suggested from a variety of family and epidemiologic studies.¹ Genome-wide searches and candidate gene approaches have identified many genes and regions that potentially influence asthma susceptibility or asthma severity.^{2,11-18} The CSGA has studied 2584 individuals from 314 well-characterized families who are likely to have susceptibility genes for asthma. The diversity introduced by multiple sites and varied asthma family structures did not compromise the ability to obtain a group of individuals who met specific criteria for a diagnosis of asthma that was based on a combination of BHR or reversibility and symptoms. Nevertheless, these asthma probands differed in age, ethnicity, and patterns of allergic responsiveness. A genome screen for asthma susceptibility alleles provided evidence for linkage to multiple chromosomal regions; some differed in the 3 ethnic groups.² It is possible that these results are due to clinical disease heterogeneity.

TABLE III. Skin test reactivities of probands with at least 1 positive skin test

	African American (N = 187)	White (N = 228)	Hispanic (N = 69)	P value
Mean (SD) no. of positive skin tests	4.8 (3.5)	5.0 (3.0)	8.4 (4.1)	.0001
≥3 positive skin tests (%)	67.9	75.4	91.3	.0010
Positive cat skin test result (%)	50.3	61.0	55.1	.1218
Positive mite skin test result (%)	53.5	62.7	55.1	.1997
Positive cockroach skin test result (%)	52.9	17.1	46.4	.0001
Positive <i>Alternaria</i> skin test result	28.3	25.4	46.4	.0224
Positive pollen skin test result (%)	59.9	71.1	97.1	.0001
Positive mold skin test result	40.6	32.9	53.6	.0239
Mean (SD) log IgE level	2.60 (0.50)	2.39 (0.60)	2.64 (0.49)	.0004
Median IgE IU/mL	434.1	258.0	430.2	.0054

Comparisons of continuous variables (log IgE) between sites and ethnic groups were performed through use of nested ANCOVA techniques, with sib-pairs nested within families and families nested within sites. For site and ethnic group comparisons of categorical variables, generalized estimating equation methods were used to account for the nesting of sib-pairs within families and families within sites.

TABLE IV. Asthma diagnosis in family members of probands

Group	Percent of probands meeting CSGA criteria (MC/NMC)				P value
	Total	African American	White	Hispanic	
Other siblings	37.4 (129/345)	45.0 (58/124)	31.0 (57/184)	37.8 (14/37)	.0001
Fathers	18.6 (43/231)	19.7 (15/76)	19.2 (23/120)	14.3 (5/35)	.4969
Mothers	32.5 (94/289)	40.2 (47/117)	28.8 (38/132)	22.5 (9/40)	.0053
Other relatives	26.8 (209/780)	41.9 (49/117)	23.8 (152/639)	33.3 (8/24)	.0001
Totals	28.9	38.9	25.1	26.5	.0001

MC, Number of probands who met the CSGA criteria for asthma; NMC, number of probands who did not meet the CSGA criteria for asthma.

In this report, we describe differences in baseline pulmonary function, specific allergy skin test responses, and numbers of other family members meeting criteria for asthma in these ethnic groups. Ethnicity-specific effects in asthma prevalence and severity have been reported from many centers and from sites as diverse as Boston,¹⁹⁻²¹ Chicago,²² and South Africa.²¹ Socioeconomic factors and differences in environmental exposures are thought to be major determinants of these clinical differences.²³⁻²⁵ However, different frequencies of polymorphisms in asthma susceptibility genes in each of the ethnic groups might also influence the observed asthma phenotypes.

Data obtained in this study support the established clinical finding of a strong association between asthma and atopy.^{26,27} Atopy was not included in the definition of asthma in this study, yet evidence for atopy based on ≥1 positive skin test was found in more than 75% of probands and in a similar proportion of other family members with asthma. Differences in specific allergen responsiveness varied by center, reactivity to pollens and *Alternaria* showing the most striking intersite differences and likely reflecting differences in the patterns of environmental allergen exposures.

Allergen responsiveness to cockroach varied most significantly by ethnic group, even after adjustment for site differences. Numerous reports have linked cockroach hypersensitivity and asthma.²⁸⁻³⁰ In fact, Sarpong et al³¹ suggested that African American ethnicity might be an independent risk factor for cockroach exposure in asthmatic children, and Togias et al³² speculated that genetic factors might contribute to the higher sensitization to

cockroach antigen among African Americans in inner-city environments. The striking ethnic group differences in reactivity to cockroach antigen observed in our populations are probably most strongly related to environmental exposure. However, age at initial exposure and variation in the pattern of exposure might influence the “early programming of immune response”; genetic factors³³ could also be important. Furthermore, early sensitization to specific antigens might enhance the effects of susceptibility loci in the 3 ethnic groups, thereby enhancing the differences because of gene-environment interactions among these groups.

A large number of other relatives of the asthma probands met the criteria for asthma, a finding that supports familial aggregation of this disease. When the number of relatives of probands with both asthma symptoms and BHR were evaluated, only 8% did not have a prior physician’s diagnosis, suggesting that a relatively small degree of underdiagnosis was present in these asthma families. These data revealed significant ethnic differences in the frequency of asthma among other relatives, African American families having a higher proportion of other family members affected with asthma. This might reflect early exposures to allergen, but it could also suggest the contribution of specific alleles with different frequencies or variable penetrances among the ethnic groups. Across all ethnic groups, mothers of probands had asthma more frequently than any other relatives except other siblings. This finding would support the observation from family studies that maternal asthma and/or allergy is a risk factor for the development of asthma in a child.^{34,35}

Asthma is a common disease caused by the interaction of genetic and environmental factors. Dissecting the individual genetic contribution to allergy and asthma is complex and will require studies in different ethnic groups and populations. Characterization of the asthmatic and allergic phenotypes provides important information on clinical heterogeneity in this disease and is therefore central to our understanding of the genetic basis of asthma. Once specific genes have been characterized, genotype-phenotype correlations should elucidate the basis for some of the clinical patterns observed in asthma.

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