

A study of IgE sensitization and skin response to histamine in Asian-Pacific American adults

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ABSTRACT

Allergic disorders and skin response to histamine have been noted to vary in different ethnicities. We investigated IgE-mediated allergic sensitization and skin response to histamine in Asian Pacific Americans (APAs), black and Hispanic Americans, and white adults. A retrospective questionnaire-based study was performed of 2222 adults presenting at a New York City allergy referral center from 1994 to 2003. Questionnaire data included sex, age, and ethnicity and personal and family history of atopic disorders. Skin-prick test (SPT) data included saline and histamine controls and response to a standardized panel of 10 aeroallergens. APA patients had a lower odds of asthma (adjusted odds ratio [aOR], 0.68; 95% confidence interval [CI], 0.52–0.89; $p = 0.005$) and/or animal allergies (aOR, 0.64; 95% CI, 0.50–0.82; $p = 0.0003$). Histamine response was not significantly different in APA (aOR, 0.90; 95% CI, 0.73–1.12; $p = 0.36$) or Hispanic Americans (aOR, 1.03; 95% CI, 0.85–1.24; $p = 0.76$), but was higher in black Americans (aOR, 2.32; 95% CI, 1.67–3.21; $p < 0.0001$). APA had higher odds of a positive SPT to trees (aOR, 1.49; 95% CI, 1.16–1.91; $p = 0.002$), grasses (aOR, 1.32; 95% CI, 1.05–1.43; $p = 0.02$), feathers (aOR, 1.65; 95% CI, 1.31–2.09; $p < 0.0001$), and cockroaches (aOR, 1.37; 95% CI, 1.10–1.62; $p = 0.005$). Moreover, APA had a higher total number of positive SPTs when compared with white patients (5.5 ± 3.2 versus 4.9 ± 3.3 ; aOR, 1.34; 95% CI, 1.10–1.62 $p = 0.004$). APA adults in our patient population had more IgE sensitizations but not an increased skin response to histamine. In contrast, black Americans had increased skin response to histamine.

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Allergic disorders, such as asthma, allergic rhinitis, and atopic dermatitis, have reportedly increased in prevalence over the last 50 years.^{1–3} The increased prevalence of these disorders has been found to differ according to ethnicity,⁴ particularly in black and Hispanic Americans.⁵ However, the nature of allergic disorders in Asian Pacific Americans (APAs) has not been reported.

In 2008, 15.5 million APAs were living in the United States, constituting 4.5% of the American population.⁶ Although previous studies have shown high rates of atopic disease in many Asian countries,^{7,8} few studies have examined the prevalence of allergic disorders in APAs in the United States. Recent studies showed increased asthma hospitalization rates^{9,10} and increased atopic diseases, including asthma,¹¹ allergic rhinitis,¹² and atopic dermatitis¹³ in APAs compared with white patients.

Allergy skin testing, particularly prick-puncture testing, is widely regarded as the most reliable screening

method for detecting immunologic evidence of IgE sensitization in patients.^{14,15} Variables such as age, seasonal variation, drug history, area of the body, and ethnicity have all been shown to influence skin test results.^{16–20} In particular, histamine wheal size has been regarded as a marker of skin reactivity to histamine²¹ and is increased with allergic sensitization²² and increasing age.²³ In particular, racial differences in skin function have been recognized, and may influence skin reactivity.^{20,24} Little is known regarding ethnic variation of allergic sensitization and histamine reactivity in IgE-mediated skin-prick testing. We hypothesized that APAs have increased reactivity to histamine and skin-prick test (SPT) positivity. In the present study, we use a retrospective study of adult patients who were treated at an allergy clinic in New York City.

MATERIALS AND METHODS

Setting and Study Population

The study was approved by The Institutional Review Board for human subjects of Beth Israel Medical Center (BIMC), New York, NY. All patients who presented to the Allergy Clinic at BIMC were given paper-based self-administered questionnaires as part of routine clinical practice from 1994 to 2003. The Allergy Clinic at BIMC is the major academic referral center for lower Manhattan and provides care to a very ethnically diverse population, including large numbers of Asian Americans/Pacific Islanders residing in the Chinatown

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neighborhood. The *a priori* aims of the questionnaire were to identify determinants of atopy, including ethnicity and other demographic information. However, Institutional Review Board approval was for retrospective data collection and chart review from 2003 to 2006. Exclusion criteria were aged <18 years, dermatographism, as judged by saline control response of ≥ 1.0 mm, and incomplete follow-up. No personal identifiers were used during the study. Written informed consent was obtained as part of the questionnaire. Data were collected and entered into a computerized database by an observer who was neither aware of the *a priori* hypothesis nor involved in the statistical analysis.

Questionnaire

The collected data included self-reported age; sex; ethnicity (black American, Hispanic American, APA, or white); date of visit; and personal and family history of asthma, allergic rhinitis, eczema, and food or drug allergies. The questionnaire was written in English at a third- to fourth-grade reading level. Personal assistance and/or translation were provided for patients that had difficulty filling in the questionnaire or those with a language barrier, respectively.

Skin-Prick Testing and Histamine Controls

No patients were taking oral antihistamines or corticosteroids for at least 1 week or topical antihistamines or corticosteroids for at least 72 hours before skin-prick testing. All skin tests were standardized with >20-mm spacing between specific test sites. The skin-prick testing panel included the following standardized allergens: seven Tree Mix (American beech, eastern cottonwood, red oak, river birch, shagbark hickory, white ash, and American elm), seven grass mix (Kentucky blue/June, meadow fescue, orchard, perennial ryegrass, redtop, sweet vernal, and timothy), national weed mix (cocklebur, giant ragweed, lamb's quarter, rough/redroot pigweed, and short ragweed), mold mix (*Alternaria alternata*, *Aspergillus niger*, *Bipolaris sorokiniana*, *Cladosporium sphaerospermum*, and *Penicillium chrysogenum*), dog epithelia, cat hair (*Felis catus domesticus*), dust-mite mix (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), mouse epithelia (*Mus musculus*), feather mix (chicken feathers, duck feathers, and goose feathers), and American cockroach (*Periplaneta americana*) in 1:20 w/v prick-testing concentrations (Greer Laboratories, Inc, Lenoir, NC). Normal saline was used as a negative control. Histamine dihydrochloride (10 mg/mL; Hollister Stier Allergy, Spokane, WA) was used as a positive control. All skin tests were performed *via* prick technique using one time use, disposable 25G $\frac{5}{8}$ precision glide needles (Becton Dickinson, Franklin Lakes, NJ) to the volar surface of the arm. Wheal size was evaluated 10 and 15 minutes later

and documented (mm). Previous studies have shown accurate interpretation of skin-prick testing as early as 10 minutes after placement.²⁵ Wheal size was determined by the mean cross-whealed diameter. A positive skin test was judged by wheal size of 3 mm greater than normal saline and/or being greater than or equal to histamine control. Flare size was routinely not measured because of occasional difficulty appreciating flares in skin of color and questionable reliability.²⁶

Patients were considered dermatographic by a ≥ 1.0 -mm wheal for the normal saline control or other frank evidence of immediate or delayed dermatographism.

Statistics

The baseline characteristics of those patients with atopic dermatitis and those without atopic dermatitis were reviewed. Age at presentation was found to be not normally distributed as judged by analysis of residuals. Therefore, age was encoded as an ordinal variable (≤ 20 , 20–40, 40–60, or ≥ 60) for all analyses. All tests were two-sided, and data processing and statistics were done in SAS Version 9.2 (SAS Institute, Inc., Cary, NC).

Binary logistic regression was used to determine whether personal or family history of atopic disease is associated with being APA. Logistic regression was also used to determine whether specific SPT positivity is associated with being APA.

Histamine wheal cross-diameter was not normally distributed with considerable left skew as judged by analysis of residuals and Kolmogorov-Smirnov testing. Therefore, standard parametric techniques, *e.g.*, mean and SD, were not used. Instead, wheal size was treated as a categorical variable with scale. Therefore, analysis of wheal size as a categorical variable was presented. Ordinal logistic regression was used to determine whether histamine control response is associated with being APA. This approach was preferred over selecting an arbitrary threshold for strong histamine response and performing binary logistic regression. Because there were few subjects with histamine responses of 0, 1, 5, or 6 mm, these numbers were collapsed into ≤ 2 -, 3-, and ≥ 4 -mm groupings. This allowed for parsimonious statistical models with accurate estimates. Ordinal logistic regression was also used to determine whether histamine control response is associated with the number of positive SPTs. Adjusted odds ratios (aOR) were calculated by including sex, age, season of visit, and personal history of atopic disorders, as appropriate. Linear interactions between covariates were tested, but were excluded from final models if not significant ($p > 0.05$).

A two-sided value of $p < 0.05$ was taken to indicate statistical significance for all estimates. However, the

Table 1 Characteristics of the patients

Variable No. (%)	Asian Pacific (n = 422)	Black American (n = 151)	Hispanic (n = 535)	White (n = 1114)	p Value*
Female sex	279 (67.7)	111 (73.5)	770 (69.1)	381 (71.2)	0.46
Age (yr)					<0.0001
18–40	325 (77.2)	104 (68.9)	321 (60.0)	694 (62.3)	
40–60	78 (18.5)	36 (23.8)	166 (31.0)	36 (23.8)	
≥60	18 (4.3)	11 (7.3)	48 (9.0)	11 (7.3)	
Season of visit [†]					0.03
Winter	101 (24.1)	45 (29.8)	137 (25.6)	277 (24.9)	
Spring	227 (54.1)	64 (42.4)	234 (43.7)	508 (45.6)	
Summer	44 (10.5)	19 (12.6)	82 (15.3)	176 (15.8)	
Autumn	48 (11.4)	23 (15.2)	153 (13.7)	82 (15.3)	

* χ^2 tests were used for all variables.

multiple dependent tests performed in this study increased the risk of falsely rejecting the null hypothesis.

RESULTS

Population Characteristics

Two thousand four hundred forty patients were selected for the study; 41 were excluded due to dermatographism. Of the 2399 subjects, 2222 were adults, 1640 were women, 467 were APA, 165 were black American, 595 were Hispanic American, and 1171 were white. Median $\pm$ interquartile age at presentation was 33.0 $\pm$ 17.0 years.

APA patients were similar to patients of other ethnicity with respect to gender ($p = 0.46$), but were significantly younger ($p < 0.0001$; Table 1). In addition, APA patients presented more frequently during the spring season ($p = 0.03$; Table 1).

Personal and Family History of Atopic Disease

APA patients were found to have a significantly lower odds of asthma (aOR, 0.68; 95% CI, 0.52–0.89; $p = 0.005$) and/or animal allergies (aOR, 0.64; 95% CI, 0.50–0.82; $p = 0.0003$; Table 2). Moreover, APA patients had a significantly lower odds of a family history of asthma (aOR, 0.52; 95% CI, 0.40–0.68; $p < 0.0001$), drug allergies (aOR, 0.45; 95% CI, 0.30–0.67; $p = 0.0001$), or animal allergies (aOR, 0.64; 95% CI, 0.49–0.85; $p = 0.002$; Table 2).

Histamine Response

The majority of subjects had histamine responses ≥ 3 mm (84.1%). Sex and current age were not significantly associated with histamine response ($p = 0.17$ – 0.97 ; Table 3).

Histamine response was significantly smaller with age 40–59 and ≥ 60 years compared with 18–40 years (ordinal logistic regression, 40–60; OR, 0.80; 95% CI,

0.66–0.97; $p = 0.006$; ≥ 60 , OR, 0.73; 95% CI, 0.55–0.96; $p = 0.02$) and during summer (OR, 0.68; 95% CI, 0.52–0.89; $p = 0.006$) and fall seasons (OR, 0.73; 95% CI, 0.55–0.96; $p = 0.02$) when compared with winter. Interestingly, histamine response was significantly higher in patients with personal history of allergic rhinitis (aOR, 1.26; 95% CI, 1.06–1.50; $p = 0.008$) but lower with personal history of food allergy (aOR, 0.82; 95% CI, 0.62–0.99; $p = 0.04$; Table 3).

Histamine response was not significantly associated with APA (aOR, 0.90; 95% CI, 0.73–1.12; $p = 0.36$) or Hispanic American (aOR, 1.03; 95% CI, 0.85–1.24; $p = 0.76$), but was significantly related to black American extraction (aOR, 2.32; 95% CI, 1.67–3.21; $p < 0.0001$), when compared with white patients (Table 3).

Histamine response was significantly related to the number of positive SPTs (ordinal logistic regression, aOR, 1.10; 95% CI, 1.07–1.13; $p < 0.0001$), even when statistically adjusting for ethnicity, sex, age, and season of testing. No significant linear interactions were found between any of the covariates ($p > 0.05$).

Skin Prick Tests

APA patients had significantly higher odds of positive SPTs to trees (logistic regression, aOR, 1.49; 95% CI, 1.16–1.91; $p = 0.002$), grasses (aOR, 1.32; 95% CI, 1.05–1.43; $p = 0.02$), feathers (aOR, 1.65; 95% CI, 1.31–2.09; $p < 0.0001$), and cockroaches (aOR, 1.37; 95% CI, 1.10–1.62; $p = 0.005$; Table 4). In addition, APA patients had a significantly greater number of positive SPTs when compared with other ethnic groups (median $\pm$ interquartile range, 6 $\pm$ 5 versus 5 $\pm$ 6, respectively; ordinal logistic regression, aOR, 1.34; 95% CI, 1.10–1.62; $p = 0.004$; Table 4).

Table 2 Association of personal and family history of atopic disease with Asian Pacific ancestry

Variable	Asian Pacific (n = 422)*	Other (n = 1800)*	aOR (95% CI)	p Value#
Personal atopic history—no. (%)				
Hayfever	245 (61.9)	1095 (60.9)	1.02 (0.81–1.28)	0.89
Asthma	81 (20.5)	495 (27.5)	0.68 (0.50–0.89)	0.005
Eczema	194 (49.1)	813 (45.2)	1.17 (0.93–1.46)	0.18
Food allergy	117 (29.9)	503 (27.9)	1.10 (0.87–1.42)	0.40
Drug allergy	87 (22.1)	505 (28.1)	0.80 (0.61–1.04)	0.10
Animal allergy	111 (28.2)	669 (37.2)	0.64 (0.50–0.82)	0.0003
Familial atopic history—no. (%)				
Hayfever	163 (42.6)	754 (41.9)	0.99 (0.79–1.24)	0.92
Asthma	84 (22.1)	623 (34.6)	0.52 (0.40–0.68)	<0.0001
Eczema	103 (27.0)	503 (28.0)	0.91 (0.71–1.18)	0.47
Food allergy	61 (16.0)	366 (20.3)	0.74 (0.55–1.00)	0.05
Drug allergy	29 (7.7)	290 (16.1)	0.45 (0.30–0.67)	0.0001
Animal allergy	75 (19.7)	476 (26.4)	0.64 (0.49–0.85)	0.002

*N.B. missing data were excluded from statistical analysis. The percentages presented are determined from nonmissing data included in statistical analysis.

#Binary logistic regression was used for all categorical variables with personal and familial atopic history modeled as the binary dependent variables with Asian ancestry modeled as an independent variable, including season of visit, sex and age as an ordinal covariate (18–40, 40–60, ≥ 60 years).

aOR = adjusted odds ratio.

DISCUSSION

The present study shows an association between APA ancestry and altered atopic disease distribution and SPT responses. We found that (1) APAs from our patient population had significantly lower odds of asthma or animal allergies; (2) histamine control response was significantly greater in black American patients but not in APA patients; and (3) APA patients had significantly higher odds of a positive SPT to trees, grasses, feathers, and cockroach.

The present study suggests that there is a subset of Asian Americans with lower rates of asthma and atopic disease. Previous studies found increased prevalence of asthma and allergic rhinitis in APAs^{11,12} and, similarly, increased morbidity, hospitalization, and health care use from atopic diseases.^{9,10,13} There are a number of environmental factors that affect histamine reactivity and atopic disease, such as cigarette smoking²¹ and socioeconomic status.⁵ The different atopic profile observed in different subsets of Asian Americans is likely based on a complex interaction between genetics and environmental factors. Further investigation of these complex interactions is warranted in this minority group.

Clinical Relevance

The prick-puncture skin test is the most widely accepted diagnostic tool for *in vivo* IgE-mediated allergic responses in the United States, and the histamine control is clearly an integral part of skin test validity.

Clarification of the accuracy of the histamine control in skin-prick-puncture testing in APAs is invaluable in the correct diagnosis of allergic disorders.

The results of the present study confirm prior reports of increased histamine response in black American patients.⁵ In the present study, we controlled for age, sex, season of testing, and personal history of atopic disorders in all statistical models and excluded any dermatographic patients.

Potential Mechanisms

The present study found that large numbers of positive skin tests, indicating atopy, were associated with larger histamine responses. The mechanism of this relationship is not well defined. Previous studies *in vivo* and *in vitro* found that interleukin-4 and IgE induce expression of the high-affinity Fc-epsilon Receptor I (FcERI) on mast cells,^{27–29} suggesting that IgE and related pathways influence mast cells and perhaps decrease histamine release.

Methodological Issues

This study has several strengths, including being well powered with a large APA population (*post hoc* power calculated to be 98.9% for an OR of 1.2), excluding dermatographic patients, and controlling for age, sex, and other confounding factors in the statistical models. The data were collected using a uniform questionnaire to all subjects, although data collection was performed retrospectively. Limitations include poten-

Table 3 Association of histamine skin response with Asian ancestry

Variable No. (%)	Histamine Response (mm)			OR (95% CI)	p Value [#]
	≤2* (n =354)	3* (n =1335)	≥ 4* (n =532)		
Female sex	240 (68.8)	949 (71.3)	352 (66.3)	0.90 (0.75–1.07)	0.24
Age (yr)					
18–39	230 (65.0)	827 (62.0)	387 (72.7)	1.00	—
40–59	97 (27.4)	393 (29.4)	122 (22.9)	0.80 (0.66–0.97)	0.02
≥60	27 (7.6)	115 (8.6)	23 (4.3)	0.66 (0.48–0.90)	0.01
Season					
Winter	79 (22.4)	329 (24.6)	152 (28.6)	1.00	—
Spring	158 (44.8)	623 (46.7)	252 (47.4)	0.88 (0.72–1.08)	0.22
Summer	57 (16.2)	204 (15.3)	60 (11.3)	0.68 (0.52–0.89)	0.006
Fall	59 (16.7)	179 (13.4)	68 (12.8)	0.73 (0.55–0.96)	0.02
Personal atopic history					
Hayfever	201 (57.9)	792 (60.0)	348 (66.2)	1.26 (1.06–1.50)	0.008
Asthma	92 (26.4)	341 (25.8)	143 (27.2)	1.04 (0.86–1.25)	0.71
Eczema	171 (49.1)	590 (44.6)	246 (46.9)	0.97 (0.82–1.15)	0.71
Food allergy	114 (32.9)	369 (27.9)	136 (26.0)	0.82 (0.62–0.99)	0.04
Drug allergy	93 (26.8)	374 (28.3)	125 (23.8)	0.88 (0.73–1.07)	0.19
Animal allergy	123 (35.5)	453 (34.3)	204 (38.9)	1.13 (0.95–1.34)	0.18
Ethnicity [§]					
Asian Pacific	75 (21.2)	245 (18.4)	100 (18.8)	0.90 (0.73–1.12)	0.36
Black American	22 (6.2)	60 (4.5)	69 (13.0)	2.32 (1.67–3.21)	<0.0001
Hispanic	87 (24.6)	325 (24.3)	123 (23.2)	1.03 (0.85–1.24)	0.76
White	170 (48.0)	705 (52.8)	239 (45.0)	1.00	—

*N.B. missing data were excluded from statistical analysis. The percentages presented are determined from nonmissing data included in each statistical analysis.

[#]Ordinal logistic regression for all models where histamine response was modeled as ≤2, 2–4, and ≥4 mm.

[#]Adjusted ORs were calculated including sex, age, season of testing, and personal atopic history as fixed covariates in the model.

OR = odds ratio.

tial reporting and recall bias being a questionnaire-based study and potential language barrier to understanding the questionnaire. These issues were addressed by writing the questionnaire at a third- to fourth-grade reading level and providing assistance and/or translational services to improve the accuracy of responses. This study used the classification of Asian Pacific Islanders, but did not distinguish between various subgroups on the questionnaire, *e.g.*, Chinese or Japanese ancestry. Future studies are warranted to determine if there are differences of specific subgroups within Asian Pacific Islanders. Because this was not a clinical practice-based study, there was a lack of information regarding the age of onset, severity, and treatments of atopic disorders. Additional studies of the effects of ethnicity on skin responses to histamine and IgE-mediated allergic sensitization should also consider the impact of duration and severity of atopic disorders. Allergen-specific IgE levels were not collected in this study to confirm positive SPTs. This is because skin-prick

testing is more reliable, cost-effective, and has a faster time to completion than radioallergosorbent testing.^{14,15} An interesting study has recently been published showing altered histamine reactivity with certain medications.³⁰ Although no patients in the study were taking anti-H₁- or H₂-histamine blockers or oral corticosteroids, they may have been taking other medications that were previously unknown to interfere with histamine reactivity. Finally, this was a single-site study from a referral-based allergy clinic. Subjects who present to this clinic are therefore more likely to be atopic than the general population. Moreover, there may be unique local environmental and socioeconomic factors that influence atopy and perhaps histamine reactivity. Nevertheless, the large sample size across all ethnic groups in our patient population is likely reflective of other inner city populations presenting to an allergist. Future population-based studies are warranted to verify the observed differences of SPT positivity in Asian Pacific Islanders.

Table 4 Association of skin-prick test positivity with Asian Pacific American ancestry

Skin-Prick Test Positivity No. (%)	Asian Pacific (n = 422)*	Other (n = 1800)*	aOR (95% CI)	p Value#
Tree	309 (73.9)	1154 (64.2)	1.49 (1.16–1.91)	0.002
Grass	259 (62.3)	978 (54.3)	1.32 (1.05–1.43)	0.02
Weed	292 (70.0)	1137 (63.2)	1.27 (0.99–1.61)	0.05
Mold	208 (50.0)	883 (49.1)	0.99 (0.79–1.23)	0.90
Dog	141 (33.7)	591 (32.8)	0.97 (0.77–1.23)	0.80
Cat	236 (56.5)	932 (51.8)	1.10 (0.88–1.37)	0.42
Dust mite	317 (75.8)	1280 (71.1)	1.21 (0.94–1.56)	0.15
Mice	143 (34.2)	566 (31.4)	1.10 (0.88–1.39)	0.40
Feather	147 (35.2)	444 (24.7)	1.65 (1.31–2.09)	<0.0001
Cockroach	249 (60.1)	915 (50.8)	1.37 (1.10–1.71)	0.005
No. of positive skin prick tests—median $\pm$ interquartile range	6 $\pm$ 5	5 $\pm$ 6	1.34 (1.10–1.62)	0.004§

*N.B. missing data were excluded from statistical analysis. The percentages presented are determined from nonmissing data included in each statistical analysis.

#Logistic regression was used for all categorical variables with skin-prick test positivity as the binary dependent variables with Asian ancestry modeled as an independent binary variable, including sex, age as an ordinal covariate (18–39, 40–59, ≥ 60 yr), season of testing, and histamine control.

§Ordinal logistic regression was used with number of positive skin-prick tests encoded as an ordinal variable (0, 1–3, 4–6, 7–9, >9), and Asian ancestry modeled as an independent binary variable, including sex, age as an ordinal covariate (18–39, 40–59, ≥ 60 yr), season of testing, and histamine control.

aOR = adjusted odds ratio.

CONCLUSIONS

In our patient population, APAs were more likely to have multiple IgE sensitizations but not increased skin response to histamine. This study supports the validity of histamine controls for skin-prick testing in APAs. Moreover, it confirms a significant association between skin response to histamine, ethnicity, and multiple IgE sensitizations.

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