ORIGINAL RESEARCH

Genetic Variation along the Histamine Pathway in Children with Allergic versus Nonallergic Asthma

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Abstract

Histamine is an important mediator in the pathogenesis of asthma. Variation in genes along the histamine production, response, and degradation pathway may be important in predicting response to antihistamines. We hypothesize that differences exist among single-nucleotide polymorphisms (SNPs) in genes of the histamine pathway between children with allergic versus nonallergic asthma. Children (7–18 yr of age; $n = 202$) with asthma were classified as allergic or nonallergic based on allergy skin testing. Genotyping was performed to detect known SNPs ($n = 10$) among genes (*HDC*, *HNMT*, *ABP1*, *HRH1*, and *HRH4*) within the histamine pathway. Chi square tests and Cochran-Armitage Trend were used to identify associations between genetic variants and allergic or nonallergic asthma. Significance was determined by $P < 0.05$ and false-positive report probability. After correction for race differences in genotype were observed, *HRH1*-17 TT (6% allergic versus 0% nonallergic; $P = 0.04$), *HNMT*-464 TT (41% allergic versus 29% nonallergic; $P = 0.04$), and *HNMT*-1639 TT (30% allergic versus 20% nonallergic; $P = 0.04$) were overrepresented among children with allergic asthma. Genotype differences specifically among the African-American children were also observed: *HRH1*-17 TT (13% allergic versus 0% nonallergic; $P = 0.04$) and *HNMT*-1639 TT (23% allergic versus 3% nonallergic; $P = 0.03$) genotypes were overrepresented among African-American children with allergic asthma. Our study suggests that genetic variation within the histamine pathway may be associated with an allergic versus nonallergic asthma phenotype. Further studies are needed to determine the functional significance of identified SNPs and their impact on antihistamine response in patients with asthma and allergic disease.

Keywords: asthma; genetics; histamine

Clinical Relevance

This research highlights the potential importance of histamine in the pathogenesis of allergic asthma, especially within the understudied African-American racial group.

Asthma is a chronic inflammatory disease characterized by airway hyperresponsiveness, airflow obstruction, and variable reversibility in response to environmental exposures. According to the Centers for Disease Control and Prevention (CDC) National Asthma Surveillance Report, since 2001 the prevalence of asthma has increased by 2.9% each year from 20.3 million persons in 2001 to 25.7 million persons in 2010 (1). Asthma is also one of the most common chronic childhood diseases in developed countries; according to the 2012 National Health Interview Survey, more than 7.1 million children had an asthma diagnosis in 2011 (1).

Asthma is a complex disease for which the underlying pathophysiology is not completely understood. Several phenotypes of asthma have been identified based on underlying inflammatory mediators or triggers (2). Allergic and nonallergic asthma are common phenotypic classifications among patients with asthma. Allergic asthma is defined as asthma with allergen hypersensitivity, whereas nonallergic asthma is defined as asthma without allergen hypersensitivity. It is reported that up to 80% of patients with asthma classify as allergic asthma (3). A better understanding of the underlying pathophysiology of differing asthma phenotypes is important to improving disease evaluation and management.

Histamine (2-[4-imidazole] ethylamine) is a biogenic amine and

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Table 1. Demographic Characteristics of all Participants and among Those Classified as Allergic and Nonallergic

Demographics	Total Subjects (*n* = 202)	Subjects with Allergic Asthma (*n* = 110)	Subjects with Nonallergic Asthma (*n* = 110)	*P* Value
Age, yr (mean ± SD)	12.2 ± 3.1	12.6 ± 3.1	11.9 ± 3.2	0.80
Sex,* % (*n*)				0.03
Male	57 (115)	56 (65)	44 (50)	
Female	43 (87)	41 (36)	59 (51)	
Race,† % (*n*)				0.16
African American‡	39 (79)	23 (47)	15 (32)	
White	50 (101)	22 (44)	28 (57)	
Other	11 (22)	6 (10)	6 (12)	

*Increased frequency of those with allergic asthma compared with those with nonallergic asthma among male subjects.
†No difference in allergic versus nonallergic asthma among all racial groups combined.
‡Increased frequency of allergic asthma among African-American subjects compared with white subjects.

a known mediator in the pathogenesis of allergic rhinitis and asthma (4, 5). In the lungs, histamine receptor activation results in bronchospasm and airway obstruction. Plasma histamine levels have been found to correlate with asthma severity (6, 7), and histamine receptor activation results in increased vascular permeability, mucus production, and contraction of airway smooth muscle cells (8–11). Furthermore, targeting histamine as a therapeutic treatment has shown benefit among some patients with asthma. In one study, H1 antihistamines reduced respiratory symptoms and the need for rescue medications in children with allergic asthma (12). In another study, the use of antihistamines in atopic children and children considered high-risk for atopy appeared to prevent the onset of asthma when compared with placebo (13, 14). These data suggest that histamine plays an important role in disease pathogenesis of asthma and the therapeutic response to asthma treatments, especially among targeted phenotypes such as allergic asthma. Therefore, more research in this area is needed.

Histamine synthesis begins with the α-decarboxylation of L-histidine by the enzyme histadine decarboxylase (HDC) (5, 15), and the amine exerts its effects by activating histamine receptors (HR1, HR2, HR3, and HR4) on various cells throughout the body. Histamine is degraded by two major enzymes, histamine N-methyltransferase (HNMT) and diamine oxidase, for subsequent removal from the body (5, 9). Genetic variation has been observed among the genes coding for the proteins responsible for histamine production, response, and degradation (*HDC*, *HRH1*, *HRH2*, *HRH3*, *HRH4*, *HNMT*, and *ABP1*) (5). For example, one single-nucleotide polymorphism (SNP), HNMT 314 C/T, has been widely investigated in relation to asthma and allergic disease (16–21). This polymorphism results in an amino acid change (Ala138Val) and decreased enzyme activity (22). Three other SNPs have also been investigated within the pathway that also result in differences in enzyme function (ABP1 47 C/T, ABP1 995 C/T, and ABP1 4107 C/G). Although the functional significance of many identified SNPs within the pathway is unknown, several studies have been conducted to explore potential associations between histamine-related genes and asthma and allergic disease, but these studies have yielded mixed results (5, 15–26). However, previous studies have often been conducted among undefined asthma phenotypes and typically only included SNPs within single genes. In addition, we have previously reported that *HRH1* was more highly expressed in buccal tissue from those with asthma compared with those without asthma (27). Therefore, it is plausible that variation among genes involved in histamine production, response, and/or degradation may influence the disposition and effect of the amine within the body and effect disease pathophysiology. Identification of genetic variants related to the pharmacology of histamine may also be important to guide therapeutic treatments for histamine-related asthma phenotypes. Consequently, we conducted a pilot investigation to identify differences in genetic variants along the histamine production, response, and degradation pathway between children with allergic and nonallergic asthma.

Materials and Methods

Study Population

All study participants were enrolled in an Institutional Review Board–approved protocol after obtaining parental permission and, when appropriate (i.e., age ⩾7 yr), child assent. Convenience sampling was used for this clinic-based case-control study. Children with asthma were enrolled from Allergy, Asthma, and Immunology outpatient clinics at Children's Mercy in Kansas City, MO. Asthma was defined by ⩾12% post-bronchodilator reversibility in FEV_1 or by an allergy/asthma specialist diagnosis based on clinical symptoms in children unable to perform spirometry. Children were classified as allergic asthma based on at least one positive skin prick test (mean wheal/flare diameter ⩾ mean diameter of the positive histamine control) to at least one seasonal or perennial allergen. Subjects

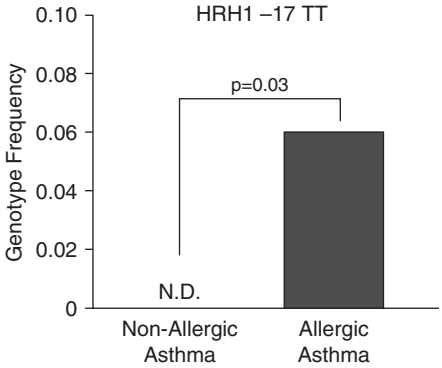

Figure 1. Differences observed in the *HRH1*-17 TT genotype between allergic and nonallergic asthma phenotype. The frequency of the *HRH1*-17 variant TT genotype between allergic and nonallergic children differed; the homozygous variant genotype was not present in the nonallergic groups (0.06 allergic versus 0 nonallergic children; $P = 0.03$). N.D. indicates that the genotype was not detected in that group.

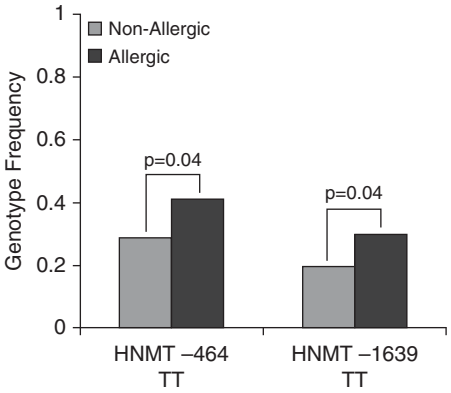

Figure 2. Differences observed in *HNMT*-464 and *HNMT*-1639 genotype frequencies between participants with allergic versus nonallergic asthma. The *HNMT*-464 homozygous variant TT and *HNMT*-1639 TT genotype frequencies differed between children with allergic and nonallergic asthma: *HNMT*-464 TT genotype 0.41 allergic versus 0.29 nonallergic, $P = 0.04$ (after adjustment for race, $P = 0.03$); *HNMT*-1639 TT genotype 0.3 allergic versus 0.2 nonallergic after adjustment for race, $P = 0.04$.

with nonallergic asthma were defined as children with negative skin prick test to regional seasonal and perennial allergens in the past year.

DNA Extraction and Genotyping

Five milliliters of blood was collected into a glass tube containing acid citrate dextrose or calcium EDTA anticoagulant, mixed by repeated inversion, and either stored for up to 7 days at 4°C or immediately frozen at −80°C. Genomic DNA was extracted from blood using the Illustra Blood Genomic Prep Mini Spin Kit (GE Healthcare, Piscataway, NJ). Genotyping assays were performed on genomic DNA (12–16 ng) using commercially available TaqMan assays to detect the following SNPs of interest: rs1049793 (*ABP1* 47 C/T), rs10156191 (*ABP1* 4107 C/G), rs1049742 (*ABP1* 995 C/T), rs17740607 (*HDC* 92 C/T), rs901865 (*HRH1*-17 C/T), rs11665084 (*HRH4* 413 C/T), rs6430764 (*HNMT*-1639 C/T), rs2071048 (*HNMT* 464 C/T), rs1050900 (*HNMT* 3′UTR A/T), and rs11558538 (*HNMT* 314 C/T) (Applied Biosystems, Foster City, CA) and using a KAPA Probe Fast quantitative PCR master mix (Kapa Biosystems, Boston, MA) according to the manufacturer's recommendations. SNPs were chosen based on their potential functional significance and previously investigated variants (*see* Table E1 in the online supplement) as well as those with an expected minor allele frequency ⩾2% within our expected participant population (5, 18, 22, 28). All samples were performed in duplicate to rule out random error.

Statistical Analysis

Concordance with Hardy-Weinberg equilibrium was confirmed for each SNP using available online software (29). Haplotype information was inferred using PHASE 15 software (30). Statistical analyses were performed using SAS 9.2 (SAS, Cary, NC). Chi-square tests and Student's *t* test were used to compare demographics between allergic and nonallergic asthma groups. Chi-square tests were used to compare frequency distributions of genotype, allele, and haplotype in subjects with asthma with and without allergic sensitization. Cochran-Armitage Trend was used to test for associations between genotype frequency among allergic and nonallergic asthma. For genotype, we further performed dominant analysis (comparing homozygous wild-type + heterozygous versus non–wild-type homozygous genotypes) and recessive analysis (comparing homozygous non–wild-type + heterozygous genotype versus wild-type homozygous genotype)

Table 2. Comparison of Allele Frequencies among Studied Histamine-Related Genes between Children with Allergic versus Nonallergic Asthma

SNP (Major/Minor Allele)	Allele	Subjects with Allergic Asthma		Subjects with Nonallergic Asthma		*P* Value*
		n	%	*n*	%	
HDC 92 C/T	C	14	7	21	10	0.2
rs17740607	T	188	93	181	90	
HRH1-17 C/T	C	155	77	170	84	0.06
rs901865	T	47	23	32	16	
HRH4 413 C/T	C	193	96	189	94	0.4
rs11665085	T	9	4	13	6	
HNMT-1639 C/T	C	90	45	103	51	0.2
rs 6430764	T	112	55	99	49	
HNMT-464 C/T	C	69	34	88	44	0.04†
rs2071048	T	133	66	114	56	
HNMT 314 C/T	C	187	93	183	91	0.5
rs11558538	T	15	7	19	9	
HNMT 3′UTR A/T	A	160	79	153	76	0.4
rs1050900	T	42	21	49	24	
ABP1 47 C/T	C	121	60	135	67	0.1
rs10156191	T	81	40	67	33	
ABP1 995 C/T	C	181	90	183	91	0.7
rs1049742	T	21	10	19	9	
ABP1 4107 C/G	C	117	58	121	60	0.7
rs1049793	G	85	42	81	40	

Definition of abbreviation: SNP, single-nucleotide polymorphism.
*P values represent χ^2/Fisher's exact P values for comparison of allele frequency between allergic and nonallergic asthma.
†P value from the Cochran-Mantel Haenszel controlling for race effect.

using Fisher's exact test. We performed the Cochran-Mantel-Haenszel test to compare frequencies of genotype, allele, and haplotype between allergic and nonallergic subjects, adjusted by observed confounders. Significance was determined by $P < 0.05$. Statistical significance was also determined using the False Positive Report Probability (FPRP) (31). FPRP is the probability of no true association between a genetic variant and disease given a statistically significant finding.

As a secondary exploratory analysis, we further evaluated genotype frequency according to the subgroup stratifications of race.

Results

A total of 202 children, 7 to 18 years of age, were included in this preliminary study. Participant demographics are shown in Table 1. Allergic asthma was more common among male subjects ($P = 0.03$). African-American children also tended to have allergic asthma rather than nonallergic asthma when compared with white children ($P = 0.04$). There were no differences in age between the two asthma phenotypes.

Allele and Genotype Results

We observed differences in genotype frequency for 3 of the 10 SNPs evaluated between subjects with allergic and nonallergic asthma. The *HRH1*-17 variant TT genotype was more frequent among those with allergic asthma compared with nonallergic asthma (0.06 allergic versus 0 nonallergic; $P = 0.03$) (Figure 1). After adjusting for race, this finding was no longer significant. However, the recessive model analysis for *HRH1*-17 (TT versus CC + CT) demonstrated modest association between the genotype and allergic asthma ($P = 0.01$; after adjustment for race, $P = 0.04$). The *HNMT*-464 homozygous variant TT genotype was also overrepresented among those with allergic asthma compared with nonallergic asthma (0.41 allergic versus 0.29 nonallergic; $P = 0.04$, and $P = 0.03$ after adjustment for race) (Figure 2). The *HNMT*-464 T allele was also more frequent among the allergic than among the nonallergic group (0.66 allergic versus 0.56 nonallergic after adjustment for race; $P = 0.04$). Finally, the homozygous variant *HNMT*-1639 genotype (TT) was also more common among subjects with allergic asthma than among subjects with nonallergic asthma (TT = 0.3 allergic versus TT = 0.2 nonallergic; $P = 0.04$ after adjustment for race; $P = 0.02$ for recessive model analysis after race adjustment)

Table 3. Comparison of Genotype Frequencies among Studied Histamine-Related Single Nucleotide Polymorphisms in Children with Allergic versus Nonallergic Asthma

SNP	Genotype	Subjects with Allergic Asthma		Subjects with Nonallergic Asthma		*P* Value*
		n	%	*n*	%	
HDC 92 C/T	CC	1	1	1	1	0.4
rs17740607	CT	12	12	19	19	
	CC	88	87	81	80	
HRH1-17 C/T	CC	60	59	69	68	0.03
rs901865	CT	35	35	32	32	
	TT	6	6	0	0	
HRH4 413 C/T	CC	92	91	89	88	0.5
rs11665085	CT	9	9	11	11	
	TT	0	0	1	1	
HNMT-1639 C/T	CC	19	19	22	22	0.04†
rs 6430764	CT	52	51	59	58	0.44‡
	TT	30	30	20	20	
HNMT-464 C/T	CC	9	9	16	16	0.04†
rs2071048	CT	51	50	56	55	0.40‡
	TT	41	41	29	29	
HNMT 314 C/T	CC	87	86	83	82	0.7
rs11558538	CT	13	13	17	17	
	TT	1	1	1	1	
HNMT 3′UTR A/T	AA	64	63	55	54	0.3
rs1050900	AT	35	32	43	43	
	TT	5	5	3	3	
ABP1 47 C/T	CC	37	37	44	44	0.3
rs10156191	CT	47	46	47	47	
	TT	17	17	10	10	
ABP1 995 C/T	CC	81	80	84	83	0.7
rs1049742	CT	19	19	15	15	
	TT	1	1	2	2	
ABP1 4107 C/G	CC	33	33	40	40	0.3
rs1049793	CG	51	50	41	40	
	GG	17	17	20	20	

For definition of abbreviation, *see* Table 2.
*P value is from the χ^2/Fisher's exact test.
†P value from the Cochran-Mantel Haenszel controlling for race effect.
‡Genotype associations with asthma phenotype demonstrated false-positive report probability values <0.5, which is considered noteworthy for our study type per Wacholder and colleagues (31).

Table 4. *P* Values from Chi Square Test

SNP (Major/Minor Allele)	Minor Allele/Genotype Frequency		*P* Value (Allele/Genotype)
	White	African American	
HDC 92 C/T rs17740607	0.86/0.74	0.98/0.98	<0.01*
HRH1-17 C/T rs901865	0.14/0	0.27/0.08	<0.01*
HRH4 413 C/T rs11665085	0.08/ND	0.03/ND	0.03/ND
HNMT-1639 C/T rs 6430764	0.57/0.31	0.43/0.15	0.01/0.02
HNMT 314 C/T rs11558538	0.13/0.02	0.01/ND	<0.01*
HNMT 3′UTR A/T rs1050900	0.27/ND	0.18/ND	0.04/ND
ABP1 47 C/T rs10156191	0.29/0.10	0.46/0.18	<0.01*
ABP1 4107 C/G rs1049793	0.29/0.12	0.52/0.27	<0.01*

Definition of abbreviations: ND, no difference in genotype frequency between white and African-American subjects; SNP, single-nucleotide polymorphism.
**P* values for allele and genotype comparisons between white and African-American subjects are both <0.01.

(Figure 2). There were no significant differences observed for allele or genotype for the other SNPs evaluated (Tables 2 and 3).

To prevent false-positive discoveries and to adjust for multiple testing, we calculated the FPRP for significant SNPs identified in Table 4 (31). According to Wacholder and colleagues (31), we consider our study as a small initial study and chose a FPRP value <0.5 to be noteworthy. Assuming a prior probability of association of 0.4 and an odds ratio of true association of 2, the FPRP for *HNMT 1639* C/T rs6430764 was 0.11 and for *HNMT 464* C/T rs2071048 was 0.09. These results are supportive of an association of genetic variants in *HNMT* with allergic asthma.

Secondary Analysis between Racial Groups

Analysis by race. Genetic differences relative to race were observed among several SNPs (Table 4).

Analysis of allele and genotype frequencies in subjects with allergic versus nonallergic asthma within racial subgroups. Recognizing that disease phenotype and pathophysiology differ between races, we performed further exploratory analyses to evaluate allele and genotype frequencies within the specified racial groups of "African American" and "white" by allergic and nonallergic asthma phenotype. Similar to results in the entire cohort, African-American subjects with allergic asthma more commonly possessed the variant homozygous genotype for *HRH1*-17 (TT = 0.13) than those with nonallergic asthma (TT = 0; $P = 0.04$ and $P = 0.04$ from recessive genotype model analysis) (Figure 3A). The *HNMT*-1639 TT genotype was also more frequent among African-American subjects with allergic asthma than nonallergic asthma (TT = 0.23 allergic asthma versus TT = 0.03 nonallergic asthma; $P = 0.03$ and $P = 0.02$ for recessive genotype model analysis) (Figure 3A). Finally, we observed an increased frequency of one SNP, *ABP1 4107* C/G, among white children with nonallergic asthma. The *ABP1 4107* GG genotype was more frequent among the nonallergic children than among the allergic children (0.18 nonallergic versus 0.05 allergic; $P = 0.04$ for both genotype and recessive model genotype analyses) (Figure 3B).

Haplotype Results

Fifteen different haplotypes were observed in our cohort that differed among white and African-American subjects (Tables 5 and 6). There was no association between asthma phenotype and haplotype for any of the observed haplotypes within the entire cohort or within stratified racial groups.

Discussion

Histamine-related genes may be important in the pathogenesis of asthma. We observed an association between genetic variants of two genes within the histamine pathway, *HRH1* and *HNMT*, and the allergic asthma phenotype in our cohort of children. We also observed novel, and potentially important, associations between histamine gene variants, race, and asthma phenotype. Here we report that *HRH1*-17 TT and *HNMT*-1639 TT genotypes were associated with the allergic asthma phenotype among African-American children and that the *ABP* 4107 GG genotype was associated with nonallergic asthma among white children. This is the first study to our knowledge to describe a relationship between histamine pathway genes and allergic asthma among a phenotypically well-defined cohort. Our study provides more evidence that histamine indeed plays a significant role in asthma pathogenesis, especially within the allergic asthma phenotype. Previous investigations have yielded mixed results regarding the relationship between histamine-related genes and asthma (16, 18–21, 23–26, 32). We believe that our study underscores the importance of conducting asthma-related genetic studies within cohorts of well-defined asthma phenotypes and also among diverse racial and ethnic groups. African Americans, who bear significant morbidity and mortality associated with asthma, are a particularly understudied racial group among genetic studies of asthma (33). Previous studies of histamine pathway genes have included very low numbers of African Americans or none at all (16, 18–21, 23–26, 32).

Genome-wide association studies have been conducted to determine differences in genetic makeup between allergic and nonallergic asthma. One large, genome-wide association study identified SNPs associated with atopic asthma (34), and a genetic risk score based on these identified SNPs was developed that further confirmed an association between these gene variants and asthma (35). However, none of the histamine-related SNPs was identified to be associated with asthma (atopic or nonatopic) in these two studies. In contrast to our study, the genetic association study by Moffat and colleagues (34) evaluated atopy with total IgE levels versus positive skin prick testing, which we

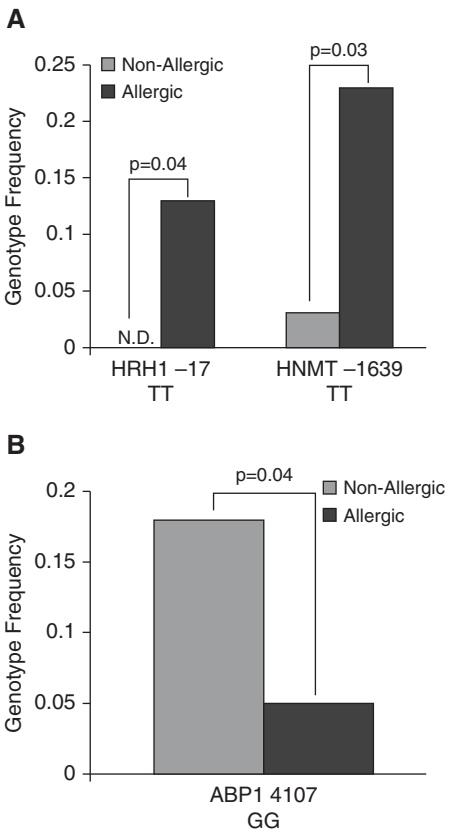

Figure 3. Differences in genotype frequencies relative to asthma phenotype among stratified African-American and white children. (*A*) African-American subjects with allergic asthma more commonly possessed the variant homozygous genotype for *HRH1*-17 (TT = 0.13) than those with nonallergic asthma (TT = 0) ($P = 0.04$; $P = 0.04$ from recessive genotype model analysis). The *HNMT*-1639 TT genotype was more frequent among African-American subjects with allergic asthma than nonallergic asthma (TT = 0.23 allergic asthma versus TT = 0.03 nonallergic asthma; $P = 0.03$ and $P = 0.02$ for recessive genotype model analysis). N.D. indicates that the genotype was not detected in that group. (*B*) In white children the *ABP1* 4107 GG genotype frequency differed between allergic and nonallergic participants (0.18 nonallergic versus 0.05 allergic; $P = 0.04$ for both genotype and recessive model genotype analyses).

used in this study. In addition, the cohorts in these studies differed from ours because they included primarily participants of European descent. We identified 4 of the 10 SNPs that we evaluated among the GABRIEL Consortium genome-wide association study and found that none of the four SNPs was associated with asthma compared with control subjects in this large cohort comprised largely of European participants. Our results presented here suggest that perhaps histamine-related genes are more important among some racial groups than others. Therefore, it is essential that relationships between genetics and disease are identified among diverse populations so as to provide medical knowledge that will lead to improved diagnostic and therapeutic treatments among differing racial and ethnic groups.

In contrast to our findings, Sasaki and colleagues (18) did not observe an association between *HRH1*-17 C/T (or *HRH2* 543 G/A and *HNMT* 314 C/T) and allergic asthma in 100 Japanese children. The lack of an association between *HRH1*-17 C/T SNP and allergic asthma in their study may have been due to a poorly defined allergic asthma phenotype because they used only an elevated IgE level as a criterion for allergic asthma. Differences in the racial makeup of their study must also be considered because previously identified SNPs were not detected in their cohort, likely due to differences in the racial makeup between their cohort and previously studied groups as well as our cohort. In our study, the *HRH1*-17 variant T allele was more common among African-American children than among white children and was also more common among African-American subjects with allergic asthma compared with those with nonallergic asthma. Our findings suggest that the *HRH1*-17 SNP may be of particular importance in the pathogenesis of allergic asthma, especially among the African-American population.

Several conflicting studies, predominantly conducted in cohorts of white subjects, exist regarding the relationship between the commonly investigated *HNMT* 314 C/T SNP and asthma (20, 21, 26). In our study, we did not find an association between *HNMT* 314 and asthma phenotype. However, we did find two novel associations between *HNMT* SNPs, *HNMT*-464 and *HNMT*-1639, and allergic asthma. The *HNMT*-1639 SNP was also specifically relevant within the African-American cohort in relation to asthma phenotype. Although the functional relevance of these noncoding SNPs is currently unclear, our findings suggest that further investigations should include these variants because they may be linked with SNPs that result in protein changes or, given their position relative to the *HNMT* gene, may affect levels of expression. Investigation of single SNPs may not adequately predict disease association and may also lead to conflicting results among studies. Future studies should include haplotype investigations among the histamine-related genes to more clearly elucidate the role of these genes in disease.

We also identified one SNP, *ABP1* 4107 C/G, that was related to asthma phenotype among white children. This SNP, along with another variant (*ABP1* 47 C/T), has been shown to result in altered diamine oxidase enzyme activity (4, 23). In addition, Maintz and colleagues (32) observed that the *ABP1* 47 T allele was associated with "histamine intolerance," defined as headache and flushing when consuming histamine-rich substances. These findings suggest that variants within *ABP1* may be related to the function of diamine oxidase activity, which may be clinically important in disease phenotypes that involve histamine (e.g., allergic asthma). Previous studies including white subjects have not

Table 5. Observed *ABP1* Haplotypes and Frequencies among the Entire Cohort

Haplotype	*ABP1* 47 C/T	*ABP1* 995 C/T	*ABP1* 4107 C/G	% (*n*)*	Racial Differences†
1	C	C	G	18 (73)	Both
2	C	C	G	45 (182)	Both
3	C	T	T	0.5 (1)	White
4	T	C	G	13 (54)	Both
5	T	C	C	14 (55)	Both
6	T	T	T	9 (38)	Both
7	T	T	G	0.5 (1)	Other

*Number of haplotypes observed.
†Describes whether haplotype is present only in African-American subjects, only in white subjects, both, or other racial group.

Table 6. Observed *HNMT* Haplotypes and Frequencies among the Entire Cohort

Haplotype	*HNMT*-1639 C/T	*HNMT*-464 C/T	*HNMT* 314 C/T	*HNMT* 3′UTR A/T	% (*n*)*	Racial Differences†
1	T	T	C	A	49 (197)	Both
2	T	T	C	T	3 (11)	Both
3	T	T	T	T	1 (3)	White
4	C	T	C	A	6 (23)	African American
5	C	T	C	T	3 (13)	Both
6	C	C	C	A	23 (93)	Both
7	C	C	C	T	8 (33)	Both
8	C	C	T	T	7 (31)	Both

*Number of haplotypes observed.
†Describes whether haplotype is present only in African-American subjects, only in white subjects, or both.

reported an association between *ABP1* genetic variation and asthma (20, 21).

The most significant limitations of our study were the small sample size and the limited sample size for analyses conducted among racial groups. Racial heterogeneity among our cohort is a limitation, and further studies should focus on larger, racially homogeneous populations given the known differences in inheritance and linkage disequilibrium between racial groups. We believe that our findings among the African-American participants deserve more investigation given the differences in genotype frequency observed between the allergic and nonallergic groups in this racial group. We also recognize that SNPs identified to be associated with allergic asthma are in noncoding regions and therefore may only be "tagging" SNPs for other gene regions that may have functional significance. However, we believe that gene regions that may affect gene expression should also be explored. Further work is needed to determine the potential functional significance of these SNPs and to identify other more functionally relevant SNPs that may be in linkage.

We believe that our findings are important in further understanding the pathophysiology of asthma among different patient populations. With validation, this information may be useful in using genotype in predicting therapeutic response to antihistamines for the treatment of asthma because those with altered histamine production, degradation, or receptor function may respond differently to antihistamines. Future studies are needed to confirm our results in a larger cohort of participants with allergic asthma, specifically focusing on potentially relevant and understudied subgroups (e.g., African-American subjects). In addition, further studies are required to determine the functional significance of identified SNPs and their impact on disease phenotype as well as the inclusion of other potentially important histamine-related genes (*HRH2* and *HRH3*) and haplotypes. Our study supports revisiting the role of histamine in asthma and the role of antihistamine treatment for those with well-defined asthma phenotypes. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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