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Association of polymorphisms in *CASP10* and *CASP8* with FEV_1/FVC and bronchial hyperresponsiveness in ethnically diverse asthmatics

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Summary

Background—Several chromosomal regions have been identified using family-based linkage analysis to contain genes contributing to the development of asthma and allergic disorders. One of these regions, chromosome 2q32-q33, contains a gene cluster containing *CFLAR*, *CASP10* and *CASP8*. These genes regulate the extrinsic apoptosis pathway utilized by several types of immune and structural cells that have been implicated in the pathogenesis of asthma.

Objective—To assess the role of genetic variation in *CFLAR*, *CASP10* and *CASP8* in asthma and related phenotypes in individuals of diverse ethnic backgrounds.

Methods—We tested 26 single nucleotide polymorphisms (SNPs) in the *CFLAR*, *CASP10* and *CASP8* gene cluster for association with asthma and related phenotypes in African-American, non-Hispanic whites, and Hispanic case–control populations (cases, $N = 517$, controls, $N = 644$).

Results—Five *CASP10* SNPS were associated with forced expiratory volume in 1 s (FEV_1)/forced expiration volume capacity (FVC) in the African-American subjects with asthma ($P = 0.0009$–0.047). Nine SNPs, seven in *CASP10* and two in *CASP8*, were also associated with the degree of bronchial hyperresponsiveness (BHR) (as determined by PC_{20}) in race-specific analysis, predominately in the Non-Hispanic white cases. Two SNPs, rs6750157 in *CASP10* and rs1045485 in *CASP8* were modestly associated with asthma in the African-American ($P = 0.025$) and Hispanic ($P = 0.033$) populations, respectively.

Conclusion—These data suggest a role for *CASP10* as a potential modifier of the asthma phenotype, specifically with measures of airway obstruction and BHR.

Keywords

asthma; bronchial hyperresponsiveness; CASP10; chromosome 2q; FEV_1/FVC

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Introduction

Asthma is a respiratory disorder that develops due to the interaction of specific genetic variants and environmental exposures. It is characterized by bronchial inflammation, bronchial hyperresponsiveness (BHR), intermittent airway obstruction, and atopy. Analysis of airway biopsies and bronchioalveolar lavage (BAL) samples from individuals with asthma have supported the role of T helper type II (Th2) cytokines such as IL-4, IL-5, IL-9, and IL-13 [1] as well as other inflammatory cells that include mast cells, eosinophils, fibroblasts, and airway epithelial cells [2, 3]. The large number of diverse cellular elements and signaling molecules involved in asthmatic and allergic inflammation supports the value of genetic approaches to understand and dissect this complex inflammatory process.

Genetic linkage studies have previously identified chromosomal regions that contain genes involved in the development of asthma and related phenotypes [4]. One such region is chromosome 2q32-q33, where there is evidence for linkage to asthma in a Hispanic population [5], and to atopic phenotypes in Hutterite [6], German [7], and Dutch populations [8, 9]. Evidence for linkage to this same region to forced expiratory volume in 1 s (FEV_1)/forced expiration volume capacity (FVC) has also been observed in the same Dutch population [10], and a nearby region (2q36) has shown evidence for linkage with pulmonary function in families ascertained by a proband with early onset chronic obstructive pulmonary disease (COPD) [11]. Interestingly, a cluster of genes containing caspase 8 (*CASP8*), caspase 10 (*CASP10*), and CASP8 and FADD-like apoptosis regulator (*CFLAR*) falls within the LOD-1 confidence interval for the linkages with asthma in Hispanics and with total serum IgE levels, eosinophilia, and FEV_1/FVC in the Dutch. Because of the localization of multiple asthma-related phenotypes and the relevant biological function of the caspase gene cluster, additional analysis of this chromosomal segment is warranted.

Mutations in *CASP10* have been shown to cause or are related to autoimmune lymphoproliferative syndrome, type II (ALPS2), a condition in which abnormal lymphocyte and dendritic cell homeostasis causes chronic, non-malignant adenopathy and splenomegaly as well as autoimmune disorders [12]. Inactivating mutations in *CASP10* have also been identified in patients with non-Hodgkin lymphoma [13]. Since mutations in the coding region of this gene have been shown to be associated with severe immune diseases, it is possible that more subtle changes in gene expression could contribute to the more complex immune abnormalities observed in asthma.

In this study, 26 single nucleotide polymorphisms (SNPs) encompassing *CASP8*, *CASP10* and *CFLAR* were identified through the dbSNP database. Additional *CASP10* SNPs in two genomic regions that are conserved between multiple species were identified through DNA sequencing. Single SNP association and haplotype analyses were performed in three ethnically diverse, well-characterized populations with asthma and related phenotypes.

Materials and methods

Population

African-American, non-Hispanic white, and Hispanic (from New Mexico) subjects with asthma were characterized using the NHLBI Collaborative Study on the Genetics of Asthma (CSGA) criteria [14]. Written informed consent for adults or written parental assent for children was obtained from all participants. This study was approved by the Institutional Review Board at Wake Forest University School of Medicine.

Clinical characteristics for each of the three populations used in this study are shown in Table 1. The case population for association studies was assembled from the original CSGA

families used for the linkage studies, the probands from CSGA trios, or recruited individually. Since the CSGA families contained affected sibling pairs (each a proband), the 'case' proband for this study was selected by choosing the sibling with the most phenotype data available. The controls were generally older than the cases, reducing the probability of undiagnosed asthma among the controls. Other characteristics were similar between the populations, with the exception of total serum IgE levels, which showed some variability. A subject was considered to have asthma if he/she met the following criteria: physician's diagnosis for asthma, demonstrated BHR or bronchodilator reversibility, and a medical history of at least two of the following symptoms: wheeze, dyspnoea, chest tightness, or cough. Subjects were considered hyperresponsive if their PC_{20} was ≤ 25 mg/mL methacholine. Because of safety concerns, in children (≤ 18 years of age) with an FEV_1 < 70% of predicted or adults with an FEV_1 < 60% of predicted, reversibility testing to an inhaled beta agonist was used to demonstrate bronchial liability, defined by an increase in FEV_1 of ≥ 15% after bronchodilator inhalation [14].

Cases and controls were characterized by a questionnaire that evaluated asthma and allergy symptoms, health care utilization, and medication use. Controls were recruited separately by public advertisement and had no history of asthma and no first-degree relatives with asthma, but did not undergo further testing. Whole blood was collected for determination of total serum IgE levels and isolation of DNA.

Sequencing and Genotyping

SNPs were selected for genotyping from dbSNP (http://www.ncbi.nlm.nih.gov/SNP) based on allele frequency and putative functional relevance. Two intronic regions of *CASP10* spanning base pairs (bp) 201 834 876–201 835 395 and 201 820 881–201 823 623 (NCBI Build 35) were highly conserved between multiple species, indicative of a potential functional element. For the detection of polymorphisms in these regions, resequencing was performed on a panel of subjects including US Non-Hispanic white, African-American, and US Hispanic cases and controls (eight cases and 16 controls from each population). Genotyping was performed using the MassARRAY SNP genotyping system according to the manufacturer's instructions (Sequenom Inc., San Diego, CA, USA).

Genetic Analysis

Tests for Hardy–Weinberg Equilibrium (HWE) were assessed using chi-square tests, as determined by SnpA-nalyzer 1.1 (http://www.fhcrc.org/labs/kruglyak/Downloads/). Pairwise marker–marker linkage disequilibrium (LD) was assessed using r^2 and plotted using Haploview [15].

Asthma was analyzed as a binary trait using logistic regression models performed using PROC LOGISTIC in SAS statistical software (SAS Institute, Cary, NC, USA). Measures of pulmonary function (FEV_1/FVC, percent of predicted FEV_1, and percent of predicted FVC) and BHR (PC_{20}) were analyzed as continuous variables, in the cases only, using linear regression models (PROC GLM). *P*-values were calculated based on a two degree-of-freedom test for genotypic association. Because race is potentially a confounding factor, interactive effects between each polymorphism and race were examined in the tests described above. If the interaction term was not significant, results are presented for the combined racial populations (for associated SNPs only). Otherwise, analyses stratified by race were performed.

Haplotype analysis was performed using a score test developed by Schaid [16], as implemented by the haplo.stats program (http://mayoresearch.mayo.edu/mayo/research/schaid_lab/software.cfm//www.mayo.edu/statgen). Statistical differences in overall

haplotype frequencies were tested for association with all outcomes. Specific haplotype effects were examined if the test for the overall frequency distribution was significant ($P \leq 0.05$).

Results

Sequencing of the two evolutionarily conserved *CASP10* genomic regions identified 11 SNPs, two of which had a minor allele frequency (MAF) >5% in each of the sequenced populations (rs10188598 and rs13396523). These two SNPs were included in the genotyping. Allele frequencies and sequences for all of the SNPS identified can be found in Table S1 in the online data supplement.

Twenty-six SNPs were genotyped and analyzed in the African-American, non-Hispanic white and Hispanic case–control populations (Table 2). As expected, LD patterns differed between the three populations with two to three haplotype blocks calculated using the method described by Gabriel *et al*. [17] (Fig. 1).

FEV_1/FVC, a measure of airway obstruction, was associated with five SNPs in *CASP10* in African-Americans and one in Hispanics (Table 3). In both populations, the minor allele was generally associated with lower FEV_1/FVC compared with the major allele, and this trend appeared to be additive.

Associations with BHR, as measured by PC_{20}, were observed with seven SNPs in *CASP10* ($P = 0.0003–0.0024$), predominately in non-Hispanic white cases (Table 4). The phenotype trend was similar between non-Hispanic whites and Hispanics, with individuals homozygous for the major allele having higher PC_{20} values, indicating less BHR. Marginal associations ($P = 0.016–0.043$) were also observed with two SNPs in *CASP8* – one in non-Hispanic whites and one in Hispanics (Table 4). The association data for all SNPs with these two phenotypes is available in supplementary Tables S2 and S3. Only two SNPs were associated with asthma – rs6750157 in *CASP10* in African-Americans ($P = 0.025$) and rs1045485 in *CASP8* in Hispanics ($P = 0.033$) (Table S4).

Haplotypes for the entire *CASP10* locus (SNPs 7–17) were generated for each population to evaluate FEV_1/FVC and PC_{20} in the cases. In the non-Hispanic white cases, the *CASP10* haplotype GGGGCCACACG (frequency = 4%) was associated with lower PC_{20} ($P = 0.0004$). This haplotype alone contains each of the alleles associated with lower PC_{20} individually, and none of the other three haplotypes observed in cases contained any associated allele, making it unclear whether the observed association is due to the individual SNPs or the haplotype. In the African-American cases, two *CASP10* haplotypes were associated with FEV_1/FVC. The GAGGTCACACA haplotype (13%) was associated with a lower FEV_1/FVC ($P = 0.001$), and all of the alleles individually associated with the lower FEV_1/FVC were contained in this haplotype. The AGGACTATAAG haplotype (14%) was associated with a higher ratio FEV_1/FVC ($P = 0.014$), and all of the single SNP alleles associated with higher values were present on this haplotype.

Discussion

CFLAR, *CASP10*, and *CASP8* form a gene cluster in a genomic region on chromosome 2q with consistent evidence for linkage in multiple studies of asthma and related phenotypes. In the present study, 26 SNPs were selected throughout this cluster and association studies were conducted for asthma and associated phenotypes in three ethnically diverse case–control populations. The results demonstrate that both SNPs and haplotypes from this region, predominantly in *CASP10*, contribute to phenotypes that are closely associated with

asthma. The most consistent associations observed were with phenotypes associated with asthma expression instead of disease susceptibility. FEV_1/FVC, a measure of pulmonary obstruction, was associated with five SNPs in *CASP10* in the African-American population. PC_{20}, a measure of BHR, was significantly associated with *CASP10* SNPs in the non-Hispanic white population, with a trend towards a similar effect in the Hispanic population. Haplotype analysis was consistent with the single SNP analysis, but did not shed light on which SNPs may be of primary importance.

Airway obstruction is related to increased airway responsiveness in asthma [18]. In addition, increased airway responsiveness is related to longitudinal decline in pulmonary function [19]. Therefore it is not surprising that we observed association with measurements of these specific phenotypes simultaneously. Our measure of airway obstruction in this population, FEV_1/FVC, was associated with SNPs in *CASP10* in the African-American population. The lack of association in the non-Hispanic white and Hispanic groups is most likely due to the lower MAF of 4% in these populations compared with 30% in the African-American group. Replication of these SNPs in larger populations will be helpful in evaluating the significance of this finding.

For PC_{20}, significant association was observed predominately with *CASP10* SNPs in the non-Hispanic white population. A similar trend was also observed in the Hispanic population (carriers of the minor allele have lower PC_{20} values), but the same SNPs were not significantly associated. This is probably due to the smaller number of Hispanic cases, and therefore less power in this population. This trend was much more difficult to detect in the African-American population, which may be a reflection of the ascertainment of cases in this population. To be classified as a 'case,' individuals were required to be hyperresponsive ($PC_{20} \leq 25$ mg/mL methacholine) or show 15% reversibility of FEV_1 post-bronchodilator. Individuals with baseline FEV_1 values ≤70% (children under 18 years of age) or ≤60% (over 18 years of age) were not tested for BHR but were included based on reversibility data only. More African-American cases (26.2%) were included based on reversibility compared with non-Hispanic whites (5.6%) and Hispanics (8.6%). Thus, fewer African-Americans were available for the PC_{20} analysis.

With a few exceptions, the same SNPs associated with FEV_1/FVC in African-Americans were associated with PC_{20} in the non-Hispanic White population, indicating the importance of these SNPs in the expression of asthma. These SNPs were in LD with each other, limiting our ability to determine which single SNPs or combinations may have potential function effects. Only one of the associated SNPs codes for an amino acid change (rs1045485 in *CASP8*), and there were no coding polymorphisms in *CASP10* associated with either FEV_1/FVC or PC_{20}. All other associated SNPs were located in introns or upstream of the first exon. Bioinformatic analysis reveals that all of these SNPs alter the consensus-binding site of a transcription factor, and inappropriate regulation of this gene may alter its expression (data not shown). Also, one of the SNPs from the sequencing in the conserved regions (rs13396523) was associated with both FEV_1/FVC and PC_{20}. Further tests will be required to elucidate if any of these SNPs cause changes in transcription factor binding or regulation of this gene. It is also possible that associations may be due to another variation in LD with the associated alleles, which would also contribute to the different associations in each ethnic group.

Because of the variable LD between racial groups, we did not provide a formal adjustment for multiple comparisons. However, using a simple Bonferroni correction and adjusting for 26 independent tests (i.e. 26 SNPs), the adjusted *P*-value would be 0.0019. Two SNPs remain significant for FEV_1/FVC in the African-American group and five SNPs remain significant for PC_{20} in the non-Hispanic white group for this adjusted *P*-value.

In summary, we report associations with SNPs in *CASP10* with measurements of airway obstruction (FEV_1/FVC) and BHR (PC_{20}). Because of the strong LD between these SNPs, it is unclear which specific SNPs or haplotypes are ultimately important, or if they all play a particular role. Additional replication studies and functional evaluation of *CASP10* and its contribution to apoptosis in immune or airway cells are required to further understand the mechanisms responsible for the persistent inflammation, injury, and remodelling characteristic of asthma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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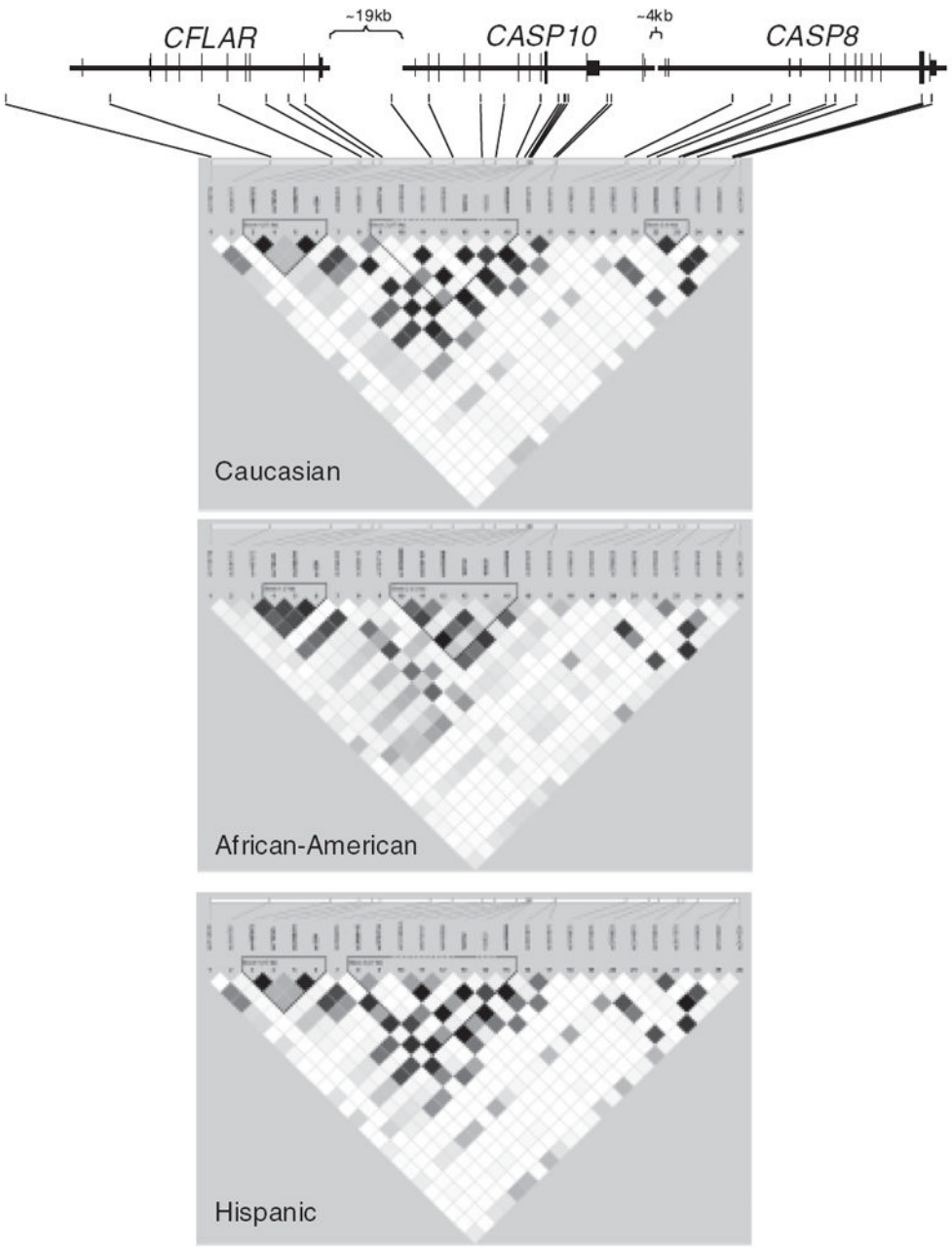

Fig. 1.

Linkage disequilibrium (LD) pattern of *CFLAR*, *CASP10* and *CASP8* in non-Hispanic white (top), African-American (middle), and Hispanic (bottom) populations generated by HaploView [15]. LD is represented by r^2 values, with black boxes indicating an r^2 value ≥0.90. Haplotype blocks were defined by the Confidence Interval algorithm [17].

Table 1

Characteristics of case–control populations

	African-American		Non-Hispanic white		Hispanic	
	Cases (*n* = 168)	**Controls (*n* = 269)**	**Cases (*n* = 233)**	**Controls (*n* = 245)**	**Cases (*n* = 116)**	**Controls (*n* = 130)**
Age, mean±SD	22.3±12.7	32.5±11.3	23.9±13.1	32.7±11.0	17.4±11.7	36.8±12.3
% Male	45.8	44.6	39.5	39.8	46.5	32.3
IgE, IU/mL (geo. mean)	204.2±4.1	66.1±4.4	138.0±4.6	15.5±6.8	223.9±4.7	32.4±4.9
FEV_1, % predicted (SD)*	75.5 (20.6)	ND	82.6 (16.4)	ND	95.2 (15.9)	ND
Mean FEV_1/FVC	0.7±0.1	ND	0.8±0.1	ND	0.8±0.1	ND
Mean PC_{20}, mg/mL	3.5±5.1	ND	3.6±5.8	ND	3.9±5.9	ND

*Percent predicted FEV_1 values for African-Americans are race-adjusted [14].

ND, not determined.

Table 2

Single nucleotide polymorphisms (SNPs) and minor allele frequencies in each population

				African-American		Non-Hispanic whites		Hispanic	
Gene	**SNP ID**	**SNP #**	**Reference Allele**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
CFLAR	rs2110728 C/T	1	T	0.34	0.36	0.18	0.18	0.14	0.17
	rs2041767 C/T	2	T	0.08*	0.07	0.00	0.00	0.01	0.00
	rs4487072 C/T	3	T	0.42	0.37	0.21	0.20	0.16	0.17
	rs719125 C/A	4	A	0.43	0.39	0.21	0.20	0.17	0.17
	rs2268791 C/G	5	G	0.49	0.46	0.48	0.50	0.38	0.41
	rs1594 C/T	6	T	0.50	0.45	0.49	0.49	0.36	0.39
CASP10	rs2098355 A/G	7	G	0.25*	0.22*	0.05	0.03	0.05	0.03
	rs3900115 G/A	8	A	0.50	0.40	0.48	0.48	0.37	0.42
	rs3731714 G/A	9	A	0.05	0.05	0.31	0.28	0.19	0.23
	rs10166093 A/G	10	G	0.29	0.31	0.04	0.03	0.05	0.03
	rs6750157 C/T	11	T	0.19	0.22*	0.00	0.00	0.02	0.01
	rs6435068 T/C	12	C	0.33	0.34	0.04	0.03	0.04	0.03
	rs10188598 A/G	13	G	0.20	0.15	0.50	0.47	0.33	0.39
	rs13396523 T/C	14	C	0.28	0.31*	0.04	0.03	0.05	0.03
	rs6435069 A/G	15	G	0.32	0.33	0.47	0.49	0.62	0.57
	rs3851975 A/C	16	C	0.30	0.32*	0.05	0.03	0.04	0.02
	rs3851976 A/G	17	G	0.20	0.20	0.05	0.04*	0.05	0.04
CASP8	rs3769825 T/C	18	C	0.36	0.34	0.46	0.45*	0.42	0.45
	rs3754935T/G	19	G	0.23	0.22	0.08	0.06	0.06	0.03
	rs3769823 C/T	20	T	0.38	0.39	0.32	0.35*	0.41	0.47
	rs2349070 C/A	21	A	0.18	0.22	0.26	0.28	0.42	0.45
	rs3754934 G/T	22	T	0.23	0.20	0.07	0.06	0.05	0.03
	rs3817578 G/A	23	A	0.19	0.22	0.06	0.06	0.05	0.03
	rs1045485 G/C	24	C	0.06	0.07	0.11	0.13	0.08	0.03
	rs1045487 G/A	25	A	0.22	0.21	0.06	0.05	0.04	0.03
	rs2141331 C/T	26	T	0.17	0.21	0.27	0.30	0.44	0.46

* Indicates deviation from expected values of Hardy–Weinberg equilibrium ($P<0.05$).

ND, not determined.

Table 3

Single nucleotide polymorphisms (SNPs) associated with forced expiratory volume in 1 s (FEV_1)/forced expiration volume capacity (FVC) in *CASP10*

				African-American			Non-Hispanic white			Hispanic		
Gene	**SNP ID**	**SNP No.**	**Geno**	***N***	**Mean (FEV_1/FVC)**	***P*-value**	***N***	**Mean (FEV_1/FVC)**	***P*-value**	***N***	**Mean (FEV_1/FVC)**	***P*-value**
CASP10	rs10166093	10	AA	77	0.77	0.0033	179	0.75	NS	85	0.81	NS
			AG	55	0.71		18	0.74		9	0.75	
			GG	11	0.65							
	rs6750157	11	CC	97	0.76	0.0009	195	0.75	NS	93	0.81	NS
			CT	47	0.70		1	0.76		3	0.77	
			TT	3	0.55							
	rs6435068	12	TT	68	0.77	0.026	176	0.76	NS	83	0.81	NS
			CT	60	0.72		17	0.75		7	0.78	
			CC	15	0.69							
	rs13396523	14	TT	79	0.77	0.0014	180	0.75	NS	82	0.81	NS
			CT	56	0.71		17	0.74		9	0.75	
			CC	11	0.65							
	rs6435069*	15	AA	64	0.73	0.047	51	0.76	NS	13	0.80	NS
			AG	63	0.73		104	0.76		46	0.80	
			GG	17	0.81		41	0.73		36	0.81	
	rs3851975	16	AA	71	0.76	NS	175	0.75	NS	90	0.81	NS
			AC	60	0.71		18	0.74		8	0.75	
			CC	10	0.69							
	rs3851976	17	AA	99	0.74	NS	181	0.75	NS	86	0.81	0.0038
			AG	39	0.75		15	0.74		11	0.73	
			GG	6	0.67		1	0.85				

*Significant for race×gene interaction ($P<0.05$).

NS, not significant.

Table 4

Single nucleotide polymorphisms (SNPs) associated with PC_{20} in *CASP10* and *CASP8*

				African-American			Non-Hispanic white			Hispanic		
Gene	**SNP ID**	**SNP #**	**Genotypes**	***N***	**Mean PC20**	***P*-value**	***N***	**Mean PC20**	***P*-value**	***N***	**Mean PC20**	***P*-value**
CASP10	rs2098355*	7	AA	56	3.18	NS	183	3.87	0.0011	87	4.27	NS
			AG	44	3.87		18	1.24		10	2.32	
			GG	11	3.05							
	rs3731714	9	GG	109	3.73	NS	99	3.12	NS	66	3.53	0.013
			GA	9	2.90		89	4.51		32	5.21	
			AA				22	2.05		2	4.07	
	rs10166093*	10	AA	58	3.60	NS	193	3.84	0.0005	89	4.25	NS
			AG	50	3.75		19	0.88		9	2.33	
			GG	9	3.05							
	rs6435068*	12	TT	52	3.10	NS	191	3.99	0.0004	87	4.13	NS
			TC	52	4.25		19	0.88		8	1.88	
			CC	12	2.56							
	Rs13396523*	14	TT	61	3.59	NS	194	3.81	0.0003	86	4.14	NS
			TC	51	3.68		18	0.83		9	2.33	
			CC	9	3.05							
	rs3851975*	16	AA	54	2.93	NS	189	3.92	0.0006	94	4.14	NS
			AC	52	4.81		19	0.88		8	2.58	
			CC	9	2.54							
	rs3851976*	17	AA	77	3.02	NS	196	3.85	0.0024	92	4.11	NS
			AG	37	4.66		16	0.89		9	2.33	
			GG	4	6.70		1	0.33				
CASP8	rs3769825	18	TT	41	3.98	NS	40	2.00	0.016	34	3.52	NS
			CT	60	3.38		100	4.12		48	4.35	
			CC	10	5.24		63	3.80		19	3.39	
	rs1045485	24	GG	106	3.75	0.043	172	3.25	NS	88	4.02	NS
			GC	14	1.58		37	5.08		15	3.78	
			CC				4	1.99				

* Significant for race×gene interaction (P<0.05).

NS, not significant.