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APOC3 Promoter Polymorphisms C-482T and T-455C Are Associated with the Metabolic Syndrome[1]

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Abstract

Background—Despite the growing epidemic of the metabolic syndrome (MetS), few studies have evaluated genetic polymorphisms associated with the MetS phenotype. One candidate, APOC3, modulates lipid and lipoprotein metabolism and the promoter polymorphisms C-482T/T-455C are associated with loss of insulin downregulation.

Methods—One hundred twenty two consecutive MetS cases were matched by age, sex and race in a 1:1 case-control design to evaluate the prevalence of common polymorphisms in the following candidate genes: *APOC3*, *APOE*, *B3AR*, *FABP2*, *GNB3*, *LPL*, and PPARα and PPARγ.

Results—Compared to controls, MetS subjects exhibited a greater prevalence of *APOC3* promoter polymorphisms. Specifically, the frequency of the variant C-482T and T-455C alleles was 70.5 and 81.9% of cases compared to 43.4 and 54.1% in controls, respectively (p <0.0001). Overall, *APOC3* promoter variants were associated with a greater likelihood of MetS compared to wild type [C-482T (OR: 4.3; 95% CI: 2.2, 8.6 [p <0.0001]), T-455C (OR: 3.6; 95% CI: 2.0, 6.7 [p <0.0001])]. No material differences were identified between the other genetic variants tested and prevalence of MetS.

Conclusions—These data, therefore, suggest that the *APOC3* promoter polymorphisms C-482T and T-455C are associated with the MetS.

Keywords

Apolipoprotein C3; Metabolic syndrome; Polymorphisms; Molecular; Dyslipidemia; CHD

Introduction

In the U.S. (1), India (2) and other countries, the high prevalence of the metabolic syndrome (MetS) has gained prominence in the public health sector, owing to the increased risk of cardiovascular (CVD) complications (3-5). While environmental factors such as a lifestyle that consists of excess caloric intake and reduced energy expenditure may contribute to visceral adiposity, dyslipidemia, impaired fasting glucose and elevated blood pressure, the hallmark of MetS (6,7), the potential genetic triggers for these phenotypic alterations, are not well understood. This is a legitimate area to investigate, owing to the central role that gene–gene and gene–environment interactions play in various metabolic processes including blood

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pressure, weight control, glucose homeostasis and lipid metabolism (8). To this end, we studied common genetic polymorphisms believed to affect these metabolic parameters.

Eight common genetic polymorphisms were chosen because of prior investigations, suggesting an association with single or multiple components that characterize MetS. They include promoter polymorphisms in apolipoprotein C3 (C-482T and T-455C), associated with both dyslipidemia and insulin resistance (9). Similarly, apoE genotypic variation has been well described to influence lipid and lipoprotein metabolism (10). Moreover, the β3-adrenoreceptor is expressed in visceral fat and may mediate lipolytic activity. Indeed, a common variant, Trp64Arg, has been associated with abdominal obesity and insulin resistance (11,12). The intestinal fatty acid-binding protein (FABP2) plays a role in the intracellular transport of long-chain fatty acids and a common variation, T54, is believed to lead to enhanced affinity and intestinal incorporation of these fatty acids, resulting in elevated TG and increased BMI (13). The G protein β3 subunit (*GNB3*) plays an important role in cellular signal transduction and a common polymorphism, C825T, is associated with both essential hypertension and obesity (14). The common promoter polymorphism of lipoprotein lipase (LPL) −93G is associated with low HDL-C and elevated TG (15). The peroxisome proliferator-activated receptor (PPARα) regulates fatty acid metabolism and PPARα agonists may reduce triglycerides (TGs), improve insulin sensitivity and potentially delay the onset of diabetes mellitus (16). The intronic 7 variant (G/C) was shown to blunt the TG-lowering response of PPARα agonists (17). PPARγ plays a role in adipocyte differentiation and glucose homeostasis and a relatively common variant, Pro12Ala, has also been associated with central obesity and diabetes mellitus (18). The premise of the present investigation was, therefore, to evaluate the extent to which one or more of the aforementioned common polymorphisms may be linked with the MetS phenotype.

Materials and Methods

Study Subjects

We genotyped 122 consecutive cases of the MetS identified in two lipid clinics in Baltimore, Maryland ($n = 82$) and New Delhi, India ($n = 40$). For each case, we selected a sex-, race-, and age- (±1 year) matched control. Control subjects were volunteers, hospital personnel and family members of cases who did not have the MetS. The ethnicity of the study cohort was as follows: Caucasian (57%), South Asians (33%), and African-Americans (11%). Informed consent was obtained from all participants and the study was approved by the Institutional Review Board at the University of Maryland Medical System.

Risk Factor and Biochemical Measurements

Peripheral and anthropometric measurements performed at the respective clinical facilities included blood pressure (BP), height and weight for the calculation of body mass index (BMI) and waist circumference using standard methods of measurement. Plasma samples were obtained following an overnight fast (8–12 h) and analyzed at each facility for measurements of fasting blood glucose (FBG) and lipids and lipoproteins as previously described (19). The criteria of the MetS were based on the Adult Treatment Panel of the National Cholesterol Education Program which defines MetS by the presence of any three of the following: blood pressure ≥130/85 mmHg (or treatment for hypertension), triglycerides (TGs) >150 mg/dL (1.69 mmol/L) (or treatment for hypertriglyceridemia), high-density lipoprotein cholesterol (HDL-C) <40 mg/dL (1.03 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women, fasting blood glucose ≥110 mg/dL (or treatment for diabetes mellitus) and waist circumference ≥35 (88.9 cm) and 40 (101.6 cm) inches in women and men, respectively (20). However, because of recent recommendations by the American Diabetes Association, we modified FBG levels >100 mg/dL (21). In addition, because the WHO classification for obesity (22) is used in India, we

also interchanged a high waist circumference with BMI ≥30 kg/m^2 to define obesity. We also recorded whether each participant currently smoked cigarettes daily or performed any aerobic activity as previously defined (23).

DNA Extraction and Genotyping

DNA was extracted from blood samples that had been obtained either at the All India Institute of Medical Sciences in New Delhi, India or at the University of Maryland Medical System, using the DNA Isolation Kit for Mammalian Blood (Roche Diagnostics Corp., Indianapolis, IN). All genetic analyses were performed at the University of Maryland, Veterans Affairs Medical Center in Baltimore, Maryland. Candidate genes and associated polymorphisms selected for study included those affecting triglyceride and/or HDL-C metabolism: apolipoprotein C3 [*APOC3*; C-482T /T-455C] (24), apolipoprotein E isoforms [*APOE* (E2/E3/E4)] (25), fatty acid-binding protein-2 [*FABP2*; A54T] (13) and lipoprotein lipase [*LPL* (T-93G, D9N and N291S)] (27), visceral adiposity: β3-adrenergic receptor [*B3AR*; Trp64Arg) (28), blood pressure: G protein β3 [*GNB3*; C825T] (26,29) and insulin resistance: peroxisome proliferator-activated receptor [*PPARα*; G/C intron7 polymorphism] and [*PPARγ* (Pro12Ala)] (30,31).

The primers used, annealing temperatures, DMSO usage for amplicons as indicated and restriction enzymes are outlined in Table 1. PCR conditions as previously employed (32) consisted of 20 pmol of each primer in a total volume of 50 μL containing 0.3 mmol/L each dNTP, 0.1 μg cDNA, 0.5 U of DyNAzyme EXT (MJ Scientific, Waltham, MA) in 1X buffer F-514 containing 50 mmol/L Tris-HCl [pH 9.0 at 25°C, 1.5 mmol/L Mg^{2+}, 15 mmol/L $(NH_4)_2SO_4$, and 0.1% Triton X-100 (MJ Scientific)]. PCR reaction was carried out in a Techne Genius Thermocycler (Techne Inc., Princeton, NJ), consisting of an initial denaturation step of 92°C for 5 min, followed by 35 cycles: denaturation at 92°C for 30 sec, annealing at various temperatures °C for 30 sec (see above), and extension at 72°C for 45 sec. A final extension step at 72°C for 5 min followed the last PCR cycle. Given that some of the digested products result in DNA fragments that are very close in size, all digestions are resolved on 16% polyacrylamide gels and visualized with ethidium bromide.

APOC3

Following PCR amplification using the primers listed above, amplicon size is 155 bp. Digestion with MspI (−482) results in no digest of the “T” allele, resulting in a single band of 155 bp. The homozygous “C” allele is indicated by complete digestion into two bands of 108 and 47 bp. Digestion with BseGI (−455) results in either no digest (single band of 155 bp) for the “C” allele, whereas complete digestion gives two bansds of 81 and 74 bp, which indicates the “T” allele. Heterozygous results for C/T at −482 are indicated by three bands of 155, 108, and 47 bp, and at −455, by three bands of 155, 81, and 74 bp. Fragments are resolved on a 16% acrylamide gel.

ApoE

Amplification yields an amplicon of 174 bp. Upon digestion with HhaI, E2 is indicated with two bands, 91 and 83 bp. E3 is indicated with three bands, 91, 48, and 35 bp. E4 is indicated with four bands, 72, 48, 35, and 19 bp.

B3-AR

PCR amplification yields an amplicon of 210 bp. The common Trp64 allele is indicated after digest with MvaI by five bands, only three of which are visible on the gel, 97, 61, and 31 bp. The rare allele Arg64 is indicated by two visible bands, 158 and 31 bp.

FABP2

PCR amplification yields an amplicon of 180 bp. Undigested fragment (180 bp) indicates the Thr allele at amino acid 54. The digested amplicon identifies the Ala54 amino acid with two fragments of 99 and 81 bp.

GNB3

PCR amplification yields an amplicon of 267 bp. Undigested fragment (267 bp) indicates the "825T" allele, whereas the digested amplicon of two fragments (152 and 115 bp) indicates the "825C" allele. The "T" variant is associated with the occurrence of splice variants.

LPL Promoter –93

PCR amplification yields an amplicon of 380 bp. The common "T" allele is indicated after digest with ApaI by two bands, 260 and 120 bp. The rarer "G" allele is indicated by three bands, 143, 120, and 117 bp.

PPARα

PCR amplification yields an amplicon of 266 bp. Digest with TaqI yields two fragments (216 and 50 bp) and identifies a polymorphic site, a G to C change in intron 7.

PPARγ

PCR amplification yields an amplicon of 268 bp. A proline allele is indicated by an absence of digest (single band 268 bp). The alanine allele is indicated by two bands: one of 224 bp and the other of 44 bp.

Statistical Analysis

Using a 1:1 case control study design, the sample size calculations were estimated in the Caucasian group based on the assumption of minor allele frequency (MAF) (0.28) (32), disease prevalence of MetS (0.25) (1) and odds ratio (3.5) that would provide 80% power to detect an association in 60 cases at an $\alpha = 0.05$.

Results are presented as mean ± SD for continuous variables. Student's *t*-test (two-tailed) was used to compare the mean differences in demographic, anthropometric and biochemical parameters. The association between genetic polymorphisms and the prevalence of MetS was assessed using chi-square tests. Odds ratio was determined by comparing each polymorphism (heterozygous, homozygous) to wild type and the 95% confidence intervals were calculated using the PHREG procedure (33) that was matched for age and sex and enabled by SAS statistical software, version 8.0 (SAS Institute, Inc., Cary, NC). Levels of significance were defined as $p < 0.05$.

Results

The descriptive data for cases and controls is shown in Table 2. As expected, MetS cases were characterized by higher BMI, waist circumference, blood pressure, FBG, TG and lower HDL-C compared to controls ($p < 0.0001$). Both active cigarette smoking and aerobic activity were rare (<10%) in both groups and were therefore not included in further analysis.

The prevalence of each of the MetS components for the study population is shown in Table 3. Compared to wild type, the variant APOC3 promoters (C-482T, T-455C) were associated with a higher frequency of dyslipidemia and borderline elevations in blood pressure. In contrast, similar trends were not observed with the other polymorphisms studied.

The genotype frequency of the candidate gene polymorphisms in MetS cases and respective controls are shown in Table 4. Compared to wild type, the *APOC3* promoter variants, C-482T (70.5 vs. 43.4%) and T-455C (81.9 vs. 54.1%) were significantly more common in cases compared to controls ($p < 0.0001$). In contrast, there were no differences between cases and controls in genotype frequency of other potential MetS candidate polymorphisms studied (e.g., *APOE* (3/4,2/3,2/4,4/4) *B3AR* (Trp64Arg), *FABP2* (Ala54Thr), *GNB3* 825 (C/T, T/T), *LPL* (−93G), *PPARα* (intron 7 G/C, C/C) *and PPARγ* (Pro12Ala). All genetic polymorphisms studied were in Hardy-Weinberg equilibrium.

To study the possibility of an independent association between each genetic polymorphism and likelihood of the MetS, the odds ratio was calculated using the case/ control-defined PHREG method (Table 5). The presence of either C-482T or T-455C conferred a 4-fold increased likelihood of MetS compared to wild-type. There were no significant differences between the other genetic polymorphisms studied and prevalence of MetS.

Because subjects of African descent represented a small proportion of the study cohort and in view of the potential concern related to selection of mixed ethnicities, we performed another analysis evaluating the APOC3 C-482T and MetS comparing Asian-Indians to Caucasians only (Table 6). These data did not reveal material differences between these ethnicities and MetS in association with the *APOC3* promoter polymorphism.

Discussion

The most important finding in the present study is that the *APOC3* promoter polymorphisms C-482T and T-455C are associated with MetS, even after controlling for age, race and gender. As such, it represents the first study to our knowledge that distinguishes *APOC3* promoter polymorphisms, among the other polymorphisms studied, as being associated with MetS. We are aware of only one other published study that specifically evaluated *APOC3* promoter polymorphisms and prevalence of MetS (34). Of 180 South Asians evaluated, a higher prevalence of MetS was identified with *FABP2* Thr-54 and *APOC3* C-482T or T-455C in controls ($n = 70$) rather than diabetic cases ($n = 110$). However, limitations of the former study included the lack of 1:1 case-control design resulting in a disproportionate lower percentage of male cases compared to controls (54 vs. 40%) and associated differences in anthropometric and biochemical parameters. Other studies evaluating *APOC3* promoter polymorphisms have also disclosed differences between ethnicities with C-482T genotype correlating with elevated TG in South Asians and Caucasians and higher fasting glucose levels among African descendants (35). In contrast to previous reports, each case was matched by age, gender and ethnicity in our study. Overall, South Asians evidenced a greater likelihood of variant alleles in the *APOC3* promoter (75.7%) compared to Caucasians (35.5%) as previously observed (32). However, this difference was less discernible in Caucasians with MetS because the vast majority (66.2%) also evidenced *APOC3* promoter (e.g., −482, −455) variation.

The relationship between *APOC3* promoter polymorphisms and predisposition to MetS underscores the intricate relationship between insulin, APOC3 and LPL. That is, insulin interacts with an insulin response element (IRE) contained within the *APOC3* promoter region to downregulate *APOC3* expression. However, with variation in the *APOC3* promoter, this effect is suppressed (9) and that may lead to enhanced *APOC3*-mediated inhibition of LPL, resulting in dyslipidemia and abnormal glucose homeostasis (36,37). In addition to *APOC3* promoter polymorphisms, APOC3 levels have also been shown to correlate positively with MetS and CHD risk (38,39).

From a clinical standpoint, variation in APOC3 promoter polymorphisms may also result in greater atherothrombotic potential than wild type. For example, −455T homozygotes were

found to have greater increases in LDL-C following saturated fat consumption (40). However, while other APOC3 polymorphisms (e.g., Sst-1) when combined with LPL variants have been associated with alteration in serum TG and HDL-C (41), they have not necessarily been associated with increased prevalence of coronary heart disease (42). This underscores the variable phenotypic impact of genetic polymorphisms as reflected by their potential interactions with other genes and environmental triggers.

That several polymorphisms evaluated in the present study failed to be associated with MetS has also been recently corroborated in other studies. Specifically, lack of a relationship between MetS or some of its components has been identified with polymorphisms in FABP2 (43), GNB3 (44,45), PPARα (46) and PPARγ (47). In contrast, *APOC3* promoter polymorphisms affect multiple metabolic parameters (e.g., insulin sensitivity, HDL-C and TG) that in turn may have resulted in a higher prevalence of MetS.

There are several limitations associated with the present study. They include the inability to determine the rate of developing MetS based on genotype. Moreover, although attempts were made to control for age, race, and gender by matching, it is recognized that they may be insufficient to control for the fact that disease prevalence and environmental influences may be different among different ethnicities. Finally, the selection of single nucleotide polymorphisms was not comprehensive with respect to the genes studied and as a consequence, the negative results do not rule out potential involvement of that corresponding gene.

Recently, polymorphisms in several genes including adiponectin (I164T) (48), tyrosine phosphatase (49) and the interleukin-6 promoter (50) have been reported to be associated with MetS. The present study supports a potential role for the LPL inhibitor, *APOC3*, in promoting this syndrome as well. Further investigation evaluating the impact of these genetic polymorphisms may advance screening efforts aimed at preventing the clinical expression of MetS and its potential adverse cardiovascular consequences (51).

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Table 1

Primers, restriction enzymes and selected conditions for polymorphism screening

	Primer	Annealing temperature (° C)	DMSO	RE
ApoC3-5′	GGGAGGGGCTGTGAGAGCTC	55	Y-3 μL	MspI
ApoC3-3′	CCAAGCCCTGAACACAGCCT			
ApoC3-5′	GGGAGGGGCTGTGAGAGCTC	55	Y-3 μL	BseGI
ApoC3-3′	CCAAGCCCTGAACACAGCCT			
ApoE-S	TCCAAGGAGCTGCAGGCGGCGCA	65	Y-4 μL	HhaI
ApoE-AS	ACAGAATTCGCCCCGGCCTGGTACACTGCCA			
B3-AR-S	CGCCCAATACCGCCAACAC	57.5	*N*	MvaI
B3-AR-AS	CCACCAGGAGTCCCATCACC			
FABP2-S	CACTTCCTATGGGATTTGACT	55	*N*	HhaI
FABP2-AS	TTGGGTAGAAAAATCAAGAATG			
GNB3-825-S	TGACCCACTTGCCACCCGTGC	57.5	*N*	BseDI
GNB3-825-AS	GCAGCAGCCAGGGCTGGC			
LPL-S	GCCTCGAGGCCGATCAAATGTAATTTAACAGC	55	*N*	ApaI
LPL-AS	TACGGAAGCTTGGGAATCGAGTCTGACAC			
PPARalphaInt7-S	ACAATCACTCCTTAAATATGGTGG	55	*N*	TaqI
PPARalphaInt7-AS	AAGTAGGGACAGACAGGACCAGTA			
PPARgamma-S	GCCAATTCAAGCCCAGTC	57.5	*N*	Bsh1236I
PPARgamma-AS	GATATGTTTGCAGACAGAGTGTATCGTGAAGGAATCGCTTTCCG			

Y indicates that DMSO was added to the reaction and the corresponding amount.

N indicates that no DMSO was added to the reaction.

Table 2

Descriptive data for MetS cases and matched controls

	Cases (*n* = 122)	Controls (*n* = 122)
Age (years)	54.5 (13.1)	54.5 (13.3)
Gender (% male)	69%	69%
Ethnicity		
Caucasian	56.6%	56.6%
South Asian	32.7%	32.7%
African	10.7%	10.7%
BMI (kg/m^2)	29.9 (5.5)	25.5 (4.4)*
Waist (inches)	37.0 (3.6)	33.8 (3.6)*
SBP (mmHg)	139.6 (16.9)	125.6 (17.8)*
DBP (mmHg)	85.8 (10.0)	78.8 (9.0)*
FBG (mg/dL)	122.8 (51.0)	98.2 (25.5)*
TC (mg/dL)	225.9 (57.3)	216.0 (59.4)
LDL-C (mg/dL)	128.6 (45.6)	127.6 (46.4)
TG (mg/dL)	306.1 (287.4)	172.0 (185.8)*
HDL-C (mg/dL)	38.5 (10.2)	53.4 (22.9)*

Data are expressed as mean ± SD. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, fasting triglyceride; HDL-C, high-density lipoprotein cholesterol.

* p <0.0001 between cases and controls.

Table 3

Genotype–phenotype prevalence of MetS components in the study cohort

		n	Obese	IFG	HTN	High TG	Low HDL
APOC3							
Wild type	−482 C/C	105	30%	35%	29%	44%	39%
	−482 C/T, T/T	139	41%	44%	46%*	71%*	59%*
Wild type	−455 T/T	77	29%	35%	30%	42%	35%
	−455 T/C, C/C	166	39%	42%	42%	67%*	58%*
Apo E							
Wild type	3/3	137	33%	40%	36%	63%	51%
	3/4, 2/3, 2/4, 4/4	88	40%	41%	39%	57%	50%
B3AR							
Wild type	Trp64	181	32%	37%	37%	55%	49%
	Trp64Arg	41	37%	44%	44%	61%	56%
FABP2							
Wild type	Ala54	127	43%	35%	37%	62%	51%
	Ala54Thr	104	30%	43%	42%	56%	48%
GNB3							
Wild type	825 C/C	132	35%	41%	39%	58%	44%
	825 C/T, T/T	108	39%	40%	38%	59%	56%
LPL							
Wild type	−93 T/T	208	35%	39%	36%	60%	50%
	−93 T/G, G/G	23	52%	61%	61%*	62%	61%
PPARα							
Wild type	Intron 7 G/G	96	44%	38%	30%	56%	54%
	G/C, C/C	58	38%	45%	43%	57%	53%
PPARγ							
Wild type	Pro12	184	33%	37%	39%	55%	50%
	Pro12Ala	32	28%	41%	31%	59%	50%

Obese, ≥30 kg/m^2 or waist circumference ≥35 (88.9 cm) and 40 (101.6 cm) inches in women and men; IFG, impaired fasting glucose (>100 mg/dL); HTN, hypertension, BP ≥130/85; high TG ≥150 mg/dL and low HDL-C (<40 mg/dL in men and <50 mg/dL in women).

*p <0.05.

Table 4

Genotype frequencies of candidate gene polymorphisms in MetS cases and controls

		MetS		
		Cases (*n* = 122)	**Controls (*n* = 122)**	***p* value**
APOC3				
Wild type	−482 C/C	29.5%	56.6%	<0.0001
	−482 C/T	46.7%	39.3%	
	−482 T/T	23.8%	4.1%	
Wild type	−455 T/T	18.0%	45.9%	<0.0001
	−455 T/C	50.8%	47.5%	
	−455 C/C	31.1%	6.6%	
Apo E				
Wild type	3/3	62.2%	60.3%	ns
	3/4	25.2%	29.3%	
	2/3, 2/4 or 4/4	12.6%	10.3%	
B3AR				
Wild type	Trp64	81.5%	81.6%	ns
	Trp64Arg	17.6%	17.6%	
FABP2				
Wild type	Ala54	53.3%	56.8%	ns
	Ala54Thr	39.2%	33.3%	
	Thr54	7.5%	9.9%	
GNB3				
Wild type	825 C/C	47.1%	42.9%	ns
	825 C/T	39.7%	43.7%	
	825 T/T	13.2%	13.4%	
LPL				
Wild type	−93 T/T	87.4%	92.9%	ns
	−93 T/G or G/G	12.6%	7.1%	
PPARα				
Wild type	intron 7 G/G	63.8%	60.8%	ns
	G/C or C/C	36.3%	39.2%	
PPARγ				
Wild type	Pro12	82.2%	87.8%	ns
	Pro12Ala (P/A or A/A)	15.8%	12.2%	

ns, not significant.

Table 5

Odds ratios and 95% confidence intervals for genetic polymorphisms and metabolic syndrome

Polymorphism	OR	95% CI	*p* value
APOC3			
−482 C/T or T/T vs. C/C	4.30	2.2, 8.6	<0.0001
−455 T/C or C/C vs. T/T	3.62	2.0, 6.7	<0.0001
C-482T & T-455C vs. wild type	4.00	1.9, 8.3	<0.0001
Apo E			
3/4, 2/3, 2/4 & 4/4 vs. 3/3	1.04	0.6, 1.8	ns
B3AR			
Trp64Arg vs. wild type	1.07	0.5, 2.1	ns
FABP2			
Thr54 vs. wild type	1.16	0.7, 2.0	ns
GnB3			
825 C/T or T/T vs. wild type	0.88	0.5, 1.4	ns
PPARα			
intron 7 G/C or C/C vs. wild type	1.00	0.5, 2.1	ns
PPARγ			
Pro12Ala (P/A or A/A) vs. wild type	1.75	0.7, 4.2	ns

ns, not significant.

Table 6

Odds ratio and 95% confidence interval for *APOC3* C-482T and associated with the MetS in Caucasians (n = 138) and Asian Indians (n = 80)

APOC3	**Ethnicity**	**OR**	**95% CI**	***p* value**
C-482T vs. wild type	Caucasian	3.9	1.7, 8.9	0.002
	Asian Indian	4.7	1.3, 16.2	0.02
	Combined	4.1	2.1, 8.2	<0.0001