SEX-DEPENDENT EFFECTS OF THE UCP1 −3826 A/G POLYMORPHISM ON OBESITY AND BLOOD PRESSURE

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Objective: To ascertain the association of −3826 A/G polymorphism with blood pressure and different obesity markers.

Design and subjects: A total of 96 adult participants (49 males, 47 females) were studied. Anthropometric measurements and blood pressure were taken using standardized techniques. Obesity indices of body mass index (BMI), waist hip ratio (WHR), waist height ratio (WHtR) and grand mean thickness (GMT) were computed. For genetic analysis, DNA was extracted from 50 μL blood.

Results: A statistically significant difference between various genotypes of UCP1 and BMI, GMT, systolic blood pressure, diastolic blood pressure was found among females. In GG homozygote, blood pressure showed positive and significant association with fat percentage and GMT ($P<.001$). Waist circumference, WHR, WHtR and BMI also showed positive association with blood pressure in heterozygous and homozygous GG form.

Conclusion: This study links the GG homozygous form of UCP1 with obesity and blood pressure among females only. (*Ethn Dis.* 2012;22(2):181–184)

Key Words: Uncoupling Protein 1, Blood Pressure, Obesity Markers, Adults, Polymorphism

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INTRODUCTION

Uncoupling protein 1 (UCP1) is mainly expressed in mitochondrial membrane of brown adipose tissue (BAT) which plays an important role in thermogenesis. The amount of BAT is reported to decrease in human adults but could still be responsible for 1–2% of the energy expenditure, preventing a weight gain of 1–2 kg/year.[1–3] UCP1 has been suggested as an obesity gene in humans and one study reported its association with blood pressure also.[4] Kozak et al[5] in their study have provided some clues regarding the relationship existing between respiratory uncoupling and obesity.

The relationship between obesity and hypertension is well established both in children and adults,[6] also in Indian populations.[7,8] Understanding the biological and environmental factors that control the expression of adipocyte helps in providing new strategies by which enhanced thermogenesis can be used to reduce obesity.[9]

The main aim of our study was to examine the role of −3826 A/G polymorphism in the promoter of the UCP1 gene as determinant of obesity and hypertension among adult Indian populations; such studies are lacking from the subcontinent, which is experiencing a surge of obesity and associated health problems.

METHODOLOGY

Our study was based on ninety-six subjects (49 males, 47 females; mean age with standard deviation of 44 ± 17 yrs and 48 ± 17 yrs, respectively). Adult males and females visiting yoga centres were interviewed. After explaining the purpose of the study and methodology to be used, those who volunteered were enrolled for the study. From this group, adult males and females who were having one or more symptoms of metabolic syndrome were included in our sample. All the participants were measured for height, weight, waist circumference, hip circumference and skinfold thickness, which were taken using standard techniques.[10] Body mass index (BMI), waist hip ratio (WHR), waist height ratio (WHtR) and grand mean thickness (GMT) were computed.

Blood pressure was taken by sphygmomanometer. Mean of two readings was used. Body fat was assessed by bioelectric impedance technique through Tanita Body Composition analyzer.

For genetic analyses, DNA was extracted from 50 μL blood (through single prick) by using the Qiagen DNA mini kit and genotyped the subjects for

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the −3826 G variant of UCP1 by PCR using New England Biolabs PCR kit (primer 5′-3′ CTTGGGTAGTGA-CAAAGTAT and3′-5′ CCAAAGGG-TCAGATTTCTAC were used to amplify a 470 bp DNA fragment)[11] and enzyme digestion (Bcl 1 enzyme).

Our study was conducted in accordance with the ethical standards of the institutional committee. The purpose of the study was explained to each participant and an informed written consent was obtained from all prior to beginning the study. The statistical software SPSS (Statistical Package for the Social Sciences) version 16.0 was used for data management and statistical analysis. The analysis of variance (one way ANOVA) test was used to compare means of more than two groups of participants when analysing continuous variables with normal distribution. Pearson's correlation (two-tailed) was used to evaluate the strength and direction of linear relationship between hypertension and obesity measures according to different genotypes. Gene frequency was calculated using the Hardy Weinberg law.

RESULTS

Table 1 shows mean SD and F value of obesity measures and blood pressure in accordance with different genotypes of UCP1. Among females, the GG genotype of UCP 1 showed higher mean values of fat %, GMT, WHtR and WC as compared to other two genotypes. The BMI, systolic blood pressure (SBP) and diastolic blood pressure (DBP) showed significant difference between the three genotypes in females ($P<.001$). On the contrary, GG genotype among males showed lowest mean values of all the obesity markers and blood pressure and AA genotype showed higher means. The differences between genotypes was found to be statistically significant for DBP ($P<.001$) with highest value being in AA genotype. In males, although no statistical significant effect was observed, with the exception of DBP, there was a tendency for all parameters to be related to the polymorphism in the opposite direction to that observed in females.

The gene frequency of GG genotype was 13.5%, AG 46.5% and AA was 39.9% respectively in the participants.

Among females with heterozygous genotype (AG), correlation of SBP and DBP with WC, fat %, BMI, WHtR and WHR ($P<.001$) was found to be statistically significant (Table 2). Among females in GG genotype, DBP was found to be significantly correlated with WC and WHtR ($P<.05$) only. Among males, no statistically significant association was found between obesity markers and blood pressure in any of the genotypes.

DISCUSSION

Genetic factors involved in the modulation of energy intake and the determination of energy expenditure have been receiving increasing attention. It is thought that the genetic component of obesity is dependent upon a large number of genes.[12,13]

In our study, females of GG genotype had significantly higher BMI as compared to those of AA and AG genotypes. GG genotypes also had higher fat percentage and GMT as compared to AA and AG genotypes, however the difference was statistically nonsignificant. Various studies showed association of GG homozygote of UCP1 with higher body weight gain. UCP1 gene variant has been shown to be associated with high weight gain in morbidly obese Caucasian subjects.[14] It was reported by Fumeren et al[15] that if obese individuals followed a low calorie diet, the same polymorphism was associated with lower body weight loss. Adaptive adrenergic thermogenesis in humans represents brown adipose tissue activity, the absence of which may contribute to middle-age obesity.[16] According to Nagai et al[17] children with GG allele genotype of the UCP1 gene may easily become obese as a consequence of abundant fat intake over a long period of time. On the contrary, studies like SOS cohort,[18] reported no

Table 1. Mean SD and F value of obesity measures and blood pressure among different genotypes of UCP1 genes

	Females				Males			
	AA (*n*=15)	AG (*n*=25)	GG (*n*=07)	F	AA (*n*=15)	AG (*n*=28)	GG (*n*=06)	F
Body mass index, kg/m^2	26 ± 5	29 ± 7	35 ± 8	4.5[b]	31 ± 8	28 ± 5	26 ± 6	2.4
Fat, %	34 ± 10	37 ± 9	40 ± 3	1.0	28 ± 7	25 ± 7	23 ± 3	1.6
Grand mean thickness, mm	21 ± 6	21 ± 6	25 ± 4	1.7	18 ± 7	18 ± 7	15 ± 6	.5
Waist hip ratio	.8 ± .1	.8 ± .0	.8 ± .1	.1	.9 ± .0	.9 ± .0	.9 ± .1	2.5
Waist height ratio	.5 ± .1	.5 ± .1	.6 ± .1	.5	.5 ± .1	.5 ± .1	.5 ± .1	.9
Waist circumference, cm	86 ± 12	87 ± 13	89 ± 7	.2	94 ± 15	93 ± 10	85 ± 6	1.3
Systolic blood pressure, mm Hg	122 ± 13	129 ± 13	143 ± 7	6.8[b]	134 ± 10	132 ± 12	127 ± 8	.7
Diastolic blood pressure, mm Hg	80 ± 7	81 ± 9	90 ± 9	3.1[a]	88 ± 6	84 ± 8	75 ± 6	8.4[b]

[a] $P<.05$.
[b] $P<.01$.

Table 2. Correlation of blood pressure and obesity markers among males and females in variants of UCP1

	Females						Males					
	AA Genotype		AG Genotype		GG Genotype		AA Genotype		AG Genotype		GG Genotype	
Obesity markers	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Body mass index	.3	.4	.7[b]	.6[b]	.1	.7	−.3	−.1	.3	−.1	.4	−.4
Fat, %	.4	.6	.7[b]	.6[b]	.1	.4	.1	−.1	.3	.1	.3	0.0
Grand mean thickness	.4	.5	.1	.1	.1	.6	−.1	.1	.05	−.03	.3	.3
Waist hip ratio	.3	.05	.5[b]	.5[b]	.6	−.1	.1	−.3	.2	.2	−.5	−.9
Waist height ratio	.5	.5	.8[b]	.7[b]	.3	.8[a]	−.02	−.1	.3	.1	.2	−.8
Waist circumference	.5	.5	.7[b]	.6[b]	.3	.8[a]	−.1	−.1	.2	−.1	.04	−.6

[a]$P<.05$.
[b]$P<.01$.
SBP, systolic blood pressure; DBP, diastolic blood pressure.

Strong association of fat percentage and GMT with blood pressure in polymorphic form of UCP1 was also found in our GG genotype females but not among males.

association of UCP1 gene with obesity related phenotypes.

The obesity-hypertension syndrome may have distribution of fat as one of its important determinants, with a predominantly central distribution being particularly threatening, as is the association of hypertension with obesity. Strong association of fat percentage and GMT with blood pressure in polymorphic form of UCP1 was also found in our GG genotype females but not among males. Kotani et al[4] suggested that the GG genotype may be associated with the presence of hypertension in Japanese males.

Weight loss is the cornerstone in the management of the obesity-hypertension syndrome.[19] Genotypic expressions may play an imperative role in it. Our participants with the GG homozygote had greater central obesity as depicted in WC, WHR, WHtR, and the risk of hypertension was also higher among these females. The polymorphic form of UCP1 was found to be associated with blood pressure among Korean females.[20] Kotani et al[4] suggested that the GG genotype may be associated with the presence of hypertension in Japanese older males whereas in our study such association was seen among females but not among males. Hypertension and obesity are complex processes that involve environmental and genetic factors (eg, ethnic differences, age, sex, nutrition). It is not clear whether it is individual gene contributions to the obesity-hypertension syndrome, or the combination of different environmental variants. Besides the debate, UCP1 showed a strong link between hypertension and obesity phenotypes, so it may be considered an excellent candidate for cardiovascular disease.

We found an association of high blood pressure with obesity measures in AG genotype as was reported by Nakano et al also.[21] Of concern, our results for adult Indian males were contrary to previous studies. Further investigation is needed to find the more apparent depiction of uncoupling protein in different sexes. The expression of UCP1 variants in different sociocultural and ethnic contexts may partially answer this; also additional data and DNA sequencing could be more explicit in explaining this discrepancy.

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AUTHOR CONTRIBUTIONS

Design and concept of study: Dhall, Chaturvedi, Rai, Kapoor
Acquisition of data: Dhall
Data analysis and interpretation: Dhall, Chaturvedi, Rai, Kapoor
Manuscript draft: Dhall, Kapoor
Statistical expertise: Dhall
Acquisition of funding: Kapoor
Administrative: Chaturvedi, Rai, Kapoor
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