Association of *UCP1* -3826A/G and *UCP3* -55C/T Gene Polymorphisms with Obesity and Its Related Traits among Multi-ethnic Malaysians

Kah-Hui Lee, BSc; Voon-Yun Chai, BSc; Sathia S. Kanachamy, BSc; Yee-How Say, PhD

Objective: Our study investigated the association of *UCP1* -3826A/G and *UCP3* -55C/T single nucleotide polymorphisms (SNPs) with obesity and its related traits among multi-ethnic Malaysians.

Participants: A total of 447 (225 males; 46 Malays, 339 ethnic Chinese, 62 ethnic Indians; 111 obese) participated.

Methods: Demographic and anthropometric data were collected, and genotyping was performed by polymerase chain reaction-restriction fragment length polymorphism.

Results: The minor allele frequencies (MAFs) for *UCP1* according to Malay/Chinese/Indian ethnicities were .61/.55/.52 and .32/.55/.38, respectively. *UCP3* genotype and allele distribution was significantly associated with ethnicity and waist-to-hip ratio (WHR), but among non-obese and Chinese participants only, respectively, after stratified analysis. Chinese participants with T allele had significantly lesser risk to be centrally obese [odds ratio =.69 (CI =.48, 1.00; *P*=.04)], and also had significantly lower WHR compared to those with C allele. The *UCP1* or *UCP3* SNPs were not associated with obesity/BMI and total body fat (TBF), but combinatory genotype analysis revealed that those having the AA and CC genotype for the former and latter SNPs had significantly highest BMI and TBF compared to other genotype combinations.

Conclusions: *UCP3* -55C/T SNP was associated with central obesity among Malaysian participants of Chinese descent. Combinatory genotype analysis showed that BMI and TBF were significantly different among *UCP1* -3826A/G and *UCP3* -55C/T genotype combinations, suggesting the existence of a gene interaction between *UCP1* and *UCP3* in influencing obesity and adiposity. (*Ethn Dis.* 2015;25[1]:65–71)

Key Words: Uncoupling Protein 1, Uncoupling Protein 3, Single Nucleotide Polymorphism, Obesity, Malaysia

From Department of Biomedical Science, Faculty of Science, Universiti Tunku Abdul Rahman (UTAR) Perak Campus, Kampar, Perak, Malaysia. (KHL, VYC, SSK, YHS)

Address correspondence to Yee-How Say, PhD; Department of Biomedical Science; Faculty of Science; Universiti Tunku Abdul Rahman (UTAR) Perak Campus; Jalan Universiti; Bandar Barat; 31900 Kampar, Perak, Malaysia; +605-4688888 ext. 4505; +605-4661676 (f); sayyh@utar.edu.my

Introduction

The prevalence of obesity is rising at an alarming rate worldwide including Malaysia, where the latest global meta-analysis reported the combined prevalence of overweight and obesity at 43.8% and 48.6% among men and women aged >20 years, respectively.[1] Obesity is a multifactorial disorder that involves an interplay between genetic and environmental factors, causing an imbalance between energy intake and expenditure.[2] There are more than 120 candidate genes that have been linked with obesity-related phenotypes,[3] and uncoupling proteins (UCPs) genes are a family of them.

Uncoupling proteins, with approximately 32 kDa mitochondrial transporters present in the inner membrane of mitochondria, play an important role in allowing protons to reenter the mitochondria without using energy, thus, energy is released by heat.[4] Three distinct UCPs namely UCP1, UCP2 and UCP3 have been identified. UCP1, an integral component of the mitochondrial inner membrane solely expressed in brown adipose tissues, plays a role in increasing thermogenesis that contributes to energy expenditure in humans.[5] On the other hand, UCP3 is predominantly found in skeletal muscles, and plays a role in energy homeostasis and substrate oxidation.[6]

The relationship between UCP loci and susceptibility to obesity and its related traits has been investigated in a number of human genetic studies and particular attention has been focused on the -3826A/G (rs1800592) polymorphism in the promoter region of *UCP1* gene and the -55C/T (rs1800849) polymorphism in the promoter region of *UCP3* gene.[7] The results of these studies are inconsistent, with some of them demonstrating associations between one or both of these polymorphisms with obesity and related traits such as type 2 diabetes, while others failed to detect any association.[8–10]

Therefore, our study aimed to determine the association of *UCP1* -3826A/G and *UCP3* -55C/T SNPs with obesity (assessed by BMI), overall adiposity (assessed by total body fat percentage – [TBF]) and central adiposity (assessed by waist-to-hip ratio [WHR]) in a representative sample of the multi-ethnic Malaysian population.

Our study aimed to determine the association of UCP1 *-3826A/G and* UCP3 *-55C/T SNPs with obesity, overall adiposity and central adiposity in a representative sample of the multi-ethnic Malaysian population.*

Methods

Participants

Convenience sampling was conducted from Oct–Dec 2008 and Feb–

Table 1. Baseline characteristics of the participants

Variables	Males ($n = 225$)			Female ($n = 222$)		
	Non-obese Mean Age: 22.42 ± 6.80	Obese Mean Age: 23.61 ± 7.61	*P*	Non-obese Mean Age: 22.06 ± 4.79	Obese Mean Age: 30.57 ± 12.76	*P*
n (%)	158 (70.2)	67 (29.8)		178 (80.2)	44 (19.8)	
SBP, mm Hg	123.89 ± 16.04	130.21 ± 14.00	< .001[a]	115.35 ± 16.07	124.60 ± 17.03	< .001[a]
DBP, mm Hg	75.88 ± 9.00	80.32 ± 9.65	< .001[a]	68.53 ± 7.82	76.28 ± 10.20	< .001[a]
PR, bpm	81.09 ± 12.34	79.97 ± 13.47	.44	84.02 ± 13.00	82.28 ± 12.24	.36
BMI	21.12 ± 2.30	29.12 ± 4.04	< .001[a]	20.09 ± 2.37	29.30 ± 3.87	< .001[a]
WHR	.82 ± .05	.90 ± .07	< .001[a]	.75 ± .06	.87 ± .06	< .001[a]
TBF, %	14.45 ± 5.17	31.82 ± 9.15	< .001[a]	18.94 ± 5.48	39.70 ± 9.51	< .001[a]

Data are mean ± SD unless specified otherwise.
BMI, body mass index; WHR, waist-to-hip ratio; TBF, total body fat; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate.
[a] *P* significant at < .05, *P* by Mann-Whitney *U* test.

Apr 2009, among 447 unrelated participants (225 males, 222 females; 46 Malays, 339 ethnic Chinese, 62 ethnic Indians; 336 non-obese, 111 obese), comprising staff and students of Universiti Tunku Abdul Rahman (UTAR) and Kolej Tunku Abdul Rahman (KTAR) at Setapak, Kuala Lumpur. Oversampling of Chinese was due to the inevitable fact that these two institutions are historically predominantly Chinese. The ethnicities of the participants were self-identified. Our study received ethical approval from the UTAR Scientific and Ethical Review Committee (SERC), all participants signed informed consents, and the study was conducted in accordance with the Declaration of Helsinki (amended in Seoul, 2008).

Anthropometric Measurements and Blood Pressures

Anthropometric measurements and blood pressures, namely systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, waist circumference (WC), hip circumference (HC), WHR, weight, height, BMI and TBF were measured as described in our previous study.[11] The cut-off points for obesity, overall adiposity (TBF) and central adiposity (WHR) were BMI ≥ 25 kg/m^2,[12] 20% (males) or 30% (females)[13] and .90 (males) or .85 (females),[14] respectively.

DNA Extraction and Genotyping

DNA extraction from mouthwash samples was carried out as described previously.[15] *UCP1* -3826A/G and *UCP3* -55C/T SNPs were analyzed by PCR using primers, reagents and conditions adopted from previous studies.[16,17] Genotyping for *UCP1* -3826A/G and *UCP3* -55C/T SNPs was performed by digesting PCR products with *Bcl*I and *Sma*I restriction enzymes (Thermo Scientific, MA, USA) at 55°C and 25°C, respectively, for ≥5 hours. All PCR reactions were carried out on the Eppendorf Mastercycler® Thermal Cycler, electrophoresed on agarose gels, stained with ethidium bromide and visualized under UV light.

Statistical Analysis

Statistical power calculation was performed using Quanto version 1.2.4, with these parameters: outcome, disease; design, matched case control; hypothesis, gene only; significance, .05, 2 sided; mode of inheritance, recessive; allele frequency (Malay/Chinese Indian), .61/.55/.52 and .32/.55/.38 for *UCP1* and *UCP3*, respectively; population risk (based on the obesity prevalence of Malay/Chinese Indian), .522/.189/.371; genetic effect, 2. With the case-control pairs sample size of 46/339/62 for Malay/Chinese Indian, a statistical power of more than 90% was achieved among Chinese participants, whereas the maximum statistical power among Malays and Indians was only 40%.

The IBM SPSS Statistics software was used to analyze the data of the study. Allelic frequencies were estimated by gene counting and the distribution of genotypes was tested for Hardy-Weinberg equilibrium using the chi-square (χ^2) test. Data for continuous variables were presented as means ± standard deviations (SD). The normality of distributions of continuous variables was tested with the Kolmogorov-Smirnov test. Categorical data were compared for significant association by Pearson's χ^2 test in both overall and stratified analysis based on BMI status and ethnicity. The means of anthropometric measurements and blood pressures were compared using non-parametric Mann-Whitney *U* test (between 2 variables) or Kruskal-Wallis test (between > 2 variables). Logistic regression analysis (enter method) was performed to calculate the odds ratio for central obesity (WHR) for *UCP3* -55C/T genotypes and alleles. A $P<.05$ was considered statistically significant.

RESULTS

Table 1 shows the baseline characteristics of the participants. The ratio of males to females was almost equal, but there were more obese males compared

Table 2. Association of *UCP1* -3826A/G and *UCP3* -55C/T genotype and allele distribution with demographic and anthropometric categories

		Genotype			Allele	
Variables	**SNP**	**1/1**	**1/2**	**2/2**	**1**	**2**
Sex						
Male	*UCP1* -3826A/G	38 (16.9)	124 (55.1)	63 (28.0)	200 (44.4)	250 (55.6)
	UCP3 -55C/T	65 (28.9)	102 (45.3)	58 (25.8)	232 (51.6)	218 (48.4)
Female	*UCP1* -3826A/G	35 (15.8)	131 (59.0)	56 (25.2)	201 (45.3)	243 (54.7)
	UCP3 -55C/T	50 (22.5)	112 (50.5)	60 (27.0)	212 (47.7)	232 (52.3)
χ^2, *P*			.71, .70; 2.44, .30		.06, .80; 1.30, .26	
Ethnicity						
Malay	*UCP1* -3826A/G	5 (10.9)	26 (56.5)	15 (32.6)	36 (39.1)	56 (60.9)
	UCP3 -55C/T	21 (45.7)	21 (45.7)	4 (8.7)	63 (68.5)	29 (31.5)
Chinese	*UCP1* -3826A/G	54 (15.9)	197 (58.1)	88 (26.0)	305 (45.0)	373 (55.0)
	UCP3 -55C/T	70 (20.6)	164 (48.4)	105 (31.0)	304 (44.8)	374 (55.2)
Indian	*UCP1* -3826A/G	14 (22.6)	32 (51.6)	16 (25.8)	60 (48.4)	64 (51.6)
	UCP3 -55C/T	24 (38.7)	29 (46.8)	9 (14.5)	77 (62.1)	47 (37.9)
χ^2, *P*			3.44, .49; 26.10, < .001[a]		1.85, .40; 27.01, < .001[a]	
BMI category						
Non-obese	*UCP1* -3826A/G	48 (14.3)	197 (58.6)	91 (27.1)	293 (43.6)	379 (56.4)
	UCP3 -55C/T	79 (23.5)	164 (48.8)	93 (27.7)	322 (47.9)	350 (52.1)
Obese	*UCP1* -3826A/G	25 (22.5)	58 (52.3)	28 (25.2)	108 (48.6)	114 (51.4)
	UCP3 -55C/T	36 (32.4)	50 (45.0)	25 (22.5)	122 (55.0)	100 (45.0)
χ^2, *P*			4.17, .12; 3.67, .16		1.72, .19; 3.31, .07	
WHR category						
Normal	*UCP1* -3826A/G	52 (16.5)	183 (57.9)	81 (25.6)	287 (45.4)	345 (54.6)
	UCP3 -55C/T	71 (22.5)	151 (47.8)	94 (29.7)	293 (46.4)	339 (53.6)
High	*UCP1* -3826A/G	20 (15.4)	72 (55.4)	38 (29.2)	114 (43.5)	148 (56.5)
	UCP3 -55C/T	43 (33.1)	63 (48.5)	24 (18.5)	151 (57.6)	111 (42.4)
χ^2, *P*			.62, .74; 8.50, .01[a]		.27, .60; 9.42, .002[a]	
TBF category						
Normal	*UCP1* -3826A/G	58 (15.6)	216 (58.1)	98 (26.3)	332 (44.6)	412 (55.4)
	UCP3 -55C/T	90 (24.2)	181 (48.7)	101 (27.2)	361 (48.5)	383 (51.5)
High	*UCP1* -3826A/G	15 (20.0)	39 (52.0)	21 (28.0)	69 (46.0)	81 (54.0)
	UCP3 -55C/T	25 (33.3)	33 (44.0)	17 (22.7)	83 (55.3)	67 (44.7)
χ^2, *P*			1.21, .55; 2.79, .25		.10, .76; 2.32, .13	

Parentheses indicate percentage within the same demographic/anthropometric categories.

BMI, body mass index; WHR, waist-to-hip ratio; TBF, total body fat; 1/1, Homozygous wild-type AA (*UCP1* -3826A/G) or CC (*UCP3* -55C/T); 1/2, Heterozygous AG (*UCP1* -3826A/G) or CT (*UCP3* -55C/T); 2/2, Homozygous variant GG (*UCP1* -3826A/G) or TT (*UCP3* -55C/T); 1, Wild-type allele A (*UCP1* -3826A/G) or C (*UCP3* -55C/T); 2, Variant allele G (*UCP1* -3826A/G) or T (*UCP3* -55C/T).

[a] *P* significant at < .05, *P* by Pearson's chi-square test.

to obese females. Except for pulse rate, all measurements were significantly higher in obese participants, regardless of sex.

Table 2 shows the genotype and allele distribution, which did not deviate from the Hardy-Weinberg equilibrium, categorized under different demographic and anthropometric categories. The overall minor allele frequencies (MAFs) for *UCP1* -3826A/G and *UCP3* -55C/T SNPs were quite similar at .55 and .50, respectively, while according to Malay/Chinese/Indian, their MAFs were .61/.55/.52 and .32/.55/.38, respectively. Therefore, the genotype and allele distributions of *UCP3* -55C/T were significantly associated with ethnicity with the MAF of Chinese being significantly higher. Meanwhile, MAFs for non-obese/obese for *UCP1* and *UCP3* SNPs were .56/.52 and .52/.45, respectively. As these MAFs were quite similar, there was no association of these two SNPs with obesity (based on BMI category). The genotype and allele distribution of *UCP3* -55C/T SNP was significantly associated with central adiposity (based on WHR category) but not sex and TBF category, while *UCP1* -3826A/G was not associated with all the demographic and anthropometric categories. Note: The MAFs are derived from the frequency (*n*) of the alleles and therefore not reflected in the table. Also, the association significance are based on the *P* values.

Since the distribution of *UCP3* -55C/T genotype and allele was significantly associated with ethnicity and WHR, we performed a stratified analysis according to BMI status and

Table 3. Stratified analysis of *UCP3* -55C/T SNP genotype and allele distributions based on BMI category and ethnicity

Variables	Genotype			Allele	
	CC	CT	TT	C	T
			Non-obese		
Ethnicity					
Malay	11 (50.0)	9 (40.9)	2 (9.1)	31 (70.5)	13 (29.5)
Chinese	52 (18.9)	134 (48.7)	89 (32.4)	238 (43.3)	312 (56.7)
Indian	16 (41.0)	21 (53.8)	2 (5.1)	53 (67.9)	25 (32.1)
χ^2; *P*		26.71, < .001[a]		26.25, <.001[a]	
			Obese		
Ethnicity					
Malay	10 (41.7)	12 (50.0)	2 (8.3)	32 (66.7)	16 (33.3)
Chinese	18 (28.1)	30 (46.9)	16 (25.0)	66 (51.6)	62 (48.4)
Indian	8 (34.8)	8 (34.8)	7 (30.4)	24 (52.2)	22 (47.8)
χ^2; *P*		4.71, .32		3.40, .18	
			Malay		
BMI category					
Non-obese	11 (50.0)	9 (40.9)	2 (9.1)	31 (70.5)	13 (29.5)
Obese	10 (41.7)	12 (50.0)	2 (8.3)	32 (66.7)	16 (33.3)
χ^2; *P*		NP		.15, .70	
WHR category					
Normal	8 (40.0)	9 (45.0)	3 (15.0)	25 (62.5)	15 (37.5)
High	13 (50.0)	12 (46.2)	1 (3.8)	38 (73.1)	14 (26.9)
χ^2; *P*		NP		1.17, .28	
TBF category					
Normal	13 (50.0)	10 (38.5)	3 (11.5)	36 (69.2)	16 (30.8)
High	8 (40.0)	11 (55.0)	1 (5.0)	27 (67.5)	13 (32.5)
χ^2; *P*		NP		.03, .86	
			Chinese		
BMI category					
Non-obese	52 (18.9)	134 (48.7)	89 (32.4)	238 (43.3)	312 (56.7)
Obese	18 (28.1)	30 (46.9)	16 (25.0)	66 (51.6)	62 (48.4)
χ^2; *P*		3.08, .21		2.89, .09	
WHR category					
Normal	51 (19.2)	125 (47.2)	89 (33.6)	227 (42.8)	303 (57.2)
High	19 (25.7)	39 (52.7)	16 (21.6)	77 (52.0)	71 (48.0)
χ^2; *P*		4.20, .12		3.96, .04[a]	
TBF category					
Normal	58 (19.5)	145 (48.8)	94 (31.6)	261 (43.9)	333 (56.1)
High	12 (28.6)	19 (45.2)	11 (26.2)	43 (51.2)	41 (48.8)
χ^2; *P*		1.91, .39		1.56, .21	
			Indian		
BMI category					
Non-obese	16 (41.0)	21 (53.8)	2 (5.1)	53 (68.8)	24 (31.2)
Obese	8 (34.8)	8 (34.6)	7 (30.4)	25 (53.2)	22 (46.8)
χ^2; *P*		NP		3.06, .08	
WHR category					
Normal	12 (38.7)	17 (54.8)	2 (6.5)	41 (53.2)	36 (46.8)
High	12 (38.7)	12 (38.7)	7 (22.6)	21 (44.7)	26 (55.3)
χ^2; *P*		NP		.86, .36	
TBF category					
Normal	19 (38.8)	26 (53.1)	4 (8.2)	64 (83.1)	13 (16.9)

ethnicity. As shown in Table 3, the genotype and allele distribution of *UCP3* -55C/T was significantly different among ethnicities in non-obese group only. Also, *UCP3* -55C/T allele was associated with the WHR category only among Chinese participants. This indicates that Chinese ethnicity had the main effect in associating central adiposity with *UCP3* -55C/T SNP and hence, analyses involving only Chinese were conducted.

Since *UCP3* -55C/T allele was associated with WHR, a logistic regression analysis to estimate the risk of being centrally obese by having different *UCP3* -55C/T genotypes and alleles was performed. Chinese participants with T allele were significantly less likely to be centrally obese (Odds Ratio = .69 [CI =.48, 1.00; *P*=.04]). Those with TT genotype also had half the chance to be centrally obese, albeit not statistically significant (Odds Ratio = .48 [CI =.23, 1.02; *P*=.06]) (data not shown). Indeed, comparison of means of anthropometric measurements and blood pressures also showed similar result, where participants carrying CC genotype or C allele had significantly higher WHR (Table 4). However, all other measurements were not significantly different among *UCP3* -55C/T genotypes and alleles (Table 4).

When participants were grouped based on wild-type/variant combinations of *UCP1* and *UCP3* genotypes and alleles, WHR was still significantly different among the allele combinations, where those having both A allele of *UCP1* and C allele of *UCP3* had significantly highest WHR (Table 5). Interestingly, participants with *UCP1* AA genotype and *UCP3* CC genotype had significantly highest BMI and TBF, but not WHR (Table 5).

DISCUSSION

For *UCP1* -3826A/G, we found that the majority of the Malaysian partici-

Table 3. Continued

Variables	Genotype			Allele	
	CC	CT	TT	C	T
High	5 (38.5)	3 (23.1)	5 (38.5)	34 (72.3)	13 (27.7)
χ^2; *P*		NP		2.05, .15	

Parentheses indicate percentage within the same demographic/anthropometric categories.
NP, Chi-Square Test not performed due presence of cell having the count of less than 5.
[a] *P* significant at < .05, *P* by Pearson's Chi-square test.

pants had AG genotype, followed by AA and GG, while the overall MAF was .50, similar to the Chinese Han[18] and Japanese[19] populations. In contrast, a recent meta-analysis showed that the MAF for this SNP was lower in European Caucasian populations, ranging from .18–.31.[8] As for *UCP3* -55C/T, the MAF for ethnic Chinese (.55) was significantly higher than Malays (.32) and Indians (.38). In contrast, other Asian populations showed the range of .29–.32 among Japanese[20] and .28–.21 among Han Chinese.[21] The reason for the higher MAF compared to other Asian populations is currently unknown, and further genotyping of a larger sample size is needed to confirm this high MAF.

Our study is consistent with previous studies that found that the *UCP1* -3826A/G SNP was not associated with BMI and obesity in both Asian and Caucasian populations like the Chinese,[18] Japanese,[22] and Swedish[23] populations. However, a study on Japanese participants showed that children with GG genotype were more obese compared to those with AA and AG genotypes,[19] while this SNP was associated with early obesity onset among Belgians.[24] Numerous studies on the association between *UCP3* -55C/T SNP and overweight/obesity risk have generated mixed results also, where lack of association was found among Pima Indians,[25] Japanese[26] and Danish,[17] while positive association was found among French.[27] Nevertheless, two recent meta-analyses concluded that these two SNP are not associated with any change in BMI irrespective of the inheritance model or after stratification by ethnicity.[9,10]

Our study is consistent with previous studies that found that the UCP1 *-3826A/G SNP was not associated with BMI and obesity in both Asian and Caucasian populations like the Chinese,[18] Japanese,[22] and Swedish[23] populations.*

As BMI is just one phenotype of obesity, there is the possibility that *UCP1* -3826A/G and *UCP3* -55C/T SNPs could have different effects in other phenotypes, such as TBF, WHR, subcutaneous fat and visceral fat. Indeed, the *UCP3* -55C/T SNP was associated with central adiposity, but only among Chinese. Chinese with C allele had a lower risk of having higher central adiposity, and CC genotype carriers had 5.1% higher WHR compared to TT genotype. Similarly, Korean children carrying the CC genotype had significantly higher WC compared

Table 4. Means of anthropometric measurements and blood pressures for different genotypes and alleles of *UCP3* -55C/T SNP among Chinese participants

Variables	Genotype			Allele	
	CC	CT	TT	C	T
BMI	22.87 ± 4.59	21.92 ± 4.29	21.62 ± 4.04	22.36 ± 4.44	21.75 ± 4.14
P		.23		.132	
WHR	.82 ± .08	.80 ± .07	.78 ± .08	.81 ± .08	.79 ± .08
P		.001[a]		< .001[a]	
TBF, %	21.11 ± 10.63	19.68 ± 9.30	19.11 ± 9.02	20.34 ± 9.92	19.36 ± 9.12
P		.49		.23	
SBP, mm Hg	120.02 ± 19.98	118.50 ± 14.45	129.41 ± 18.28	119.20 ± 17.17	126.62 ± 17.21
P		.74		.44	
DBP, mm Hg	73.40 ± 11.05	73.44 ± 9.50	74.19 ± 9.27	73.42 ± 10.21	73.86 ± 9.36
P		.59		.39	
PR, bpm	79.93 ± 11.21	83.43 ± 12.51	81.31 ± 10.93	81.82 ± 12.02	82.24 ± 11.66
P		.08		.52	

Data are mean ± SD unless specified otherwise.
BMI, body mass index; WHR, waist-to-hip ratio; TBF, total body fat; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate.
[a] *P* significant at < .05, *P* by Kruskal-Wallis or Mann-Whitney *U* test.

Table 5. Means of anthropometric measurements and blood pressures for the genotype and allele combinations of *UCP1* -3826A/G and *UCP3* -55C/T SNPs among Chinese participants

Combinations	*n*	BMI	WHR	TBF, %	SBP, mm Hg	DBP, mm Hg	PR, bpm
AA/CC	17	26.17 ± 5.27	.85 ± .10	28.70 ± 10.47	116.47 ± 16.01	72.03 ± 11.48	76.53 ± 10.65
AA/TT	13	22.11 ± 3.01	.79 ± .06	20.30 ± 6.73	196.77 ± 12.33	73.92 ± 6.32	74.92 ± 9.01
GG/CC	16	22.05 ± 3.77	.80 ± .07	20.28 ± 10.85	116.91 ± 18.30	71.69 ± 11.55	81.97 ± 11.43
GG/TT	32	22.38 ± 4.47	.78 ± .09	20.42 ± 10.39	120.89 ± 19.37	73.97 ± 11.57	82.68 ± 13.66
P		.01[a]	.05	.02[a]	.57	.62	.25
A/C	195	22.63 ± 4.84	.81 ± .08	21. 02 ± 10.39	118.60 ± 16.44	73.02 ± 9.79	81.50 ± 12.51
A/T	110	21.61 ± 4.18	.78 ± .07	19.28 ± 8.97	137.12 ± 17.88	73.66 ± 8.09	80.47 ± 10.16
G/C	109	21.87 ± 3.58	.80 ± .07	19.12 ± 8.94	120.27 ± 18.43	74.13 ± 10.93	82.38 ± 11.12
G/T	264	21.81± 4.13	.79 ± .07	19.39 ± 9.20	119.41 ± 15.73	73.95 ± 9.85	82.98 ± 12.18
P		.40	.003[a]	.26	.85	.81	.27

Data are mean ± SD unless specified otherwise.
BMI, body mass index; WHR, waist-to-hip ratio; TBF, total body fat; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate.
[a] *P* significant at < .05, *P* by Kruskal-Wallis test.

to other genotypes.[28] In contrast, T allele was associated with increased WHR in female South Indians[29] and Germans.[30] This indicates that *UCP3* -55C/T SNP TT genotype and T allele may have a different protective effect against central obesity, depending on ethnic population, age and sex. However, this could also be a spurious positive result, due to the oversampling of Chinese participants and the low statistical power for association analysis among Malays and Indians. Meanwhile for TBF, no association was found with this SNP, similar to a previous study.[17]

The lack of association of a single SNP of *UCP1* -3826A/G or *UCP3* -55C/T with obesity traits may indicate that these two SNPs did not have the effect alone, but might be in synergy with each other in affecting obesity traits. Therefore, a combinatory genotype and allele analysis was performed, and we found that participants with both *UCP1* A allele and *UCP3* C allele had highest WHR. This indicates the dominant effect of the latter allele since the former allele alone did not have any effect on WHR. It is also interesting to note that participants with *UCP1* AA and *UCP3* CC genotypes had highest BMI and TBF. This indicates that these two genotypes might not have any effect on BMI and TBF when they are alone, but will only exert the effect in synergy.

The *UCP3*-55C/T SNP is located 55 bp upstream of the most commonly used transcription initiation site of skeletal muscle,[31] and thus it appears to be functional. Also, the location of this SNP at 6 bp from the TATA box and 4 bp downstream of a putative peroxisome proliferator-activated receptor (PPAR) responsive element,[32] indicates that it could modify PPARγ responsiveness of the *UCP3* gene in modulating lipid metabolism and insulin sensitivity.[33] In male Pima Indians, participants with T allele had significantly higher UCP3 mRNA expression than those with CC genotype.[25] Further studies are still needed to elucidate the functional effects of this SNP on UCP3 expression.

Limitations of our study include small sample size, limiting statistical power and generalization to the overall Malaysian population. The case-control design in our study also does not allow for a causality conclusion to be made. Also as only two SNPs of *UCP1* and *UCP3* were evaluated, it is unclear whether another common *UCP1* SNP -866G/A (rs659366) or SNPs in other UCP families might have association with obesity instead.

In conclusion, *UCP3* -55C/T SNP was associated with central obesity (high WHR) among Malaysian participants of the Chinese descent, where participants with T allele had significantly 30% lesser risk of becoming centrally obese, as they had 2.5% lesser WHR compared to those with C allele. This SNP had a dominant effect over *UCP1* -3826A/G SNP, as the significance remained the same when a combinatory allele analysis was performed. While in combinatory genotype analysis, BMI and TBF were significantly different among genotype combinations, suggesting the existence of a gene interaction between *UCP1* and *UCP3* in influencing obesity and adiposity.

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AUTHOR CONTRIBUTIONS

Design and concept of study: Say
Acquisition of data: Lee, Chai, Kanachamy, Say
Data analysis and interpretation: Lee, Chai, Kanachamy, Say
Manuscript draft: Say
Statistical expertise: Lee, Chai, Kanachamy, Say
Acquisition of funding: Say
Administrative: Lee, Chai, Kanachamy, Say
Supervision: Say