Original Report:
Obesity

Screening of Peroxisome Proliferator-Activated Receptors (PPARs) α, γ and α Gene Polymorphisms for Obesity and Metabolic Syndrome Association in the Multi-Ethnic Malaysian Population

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Objective: This study aimed to investigate the association of peroxisome proliferator-activated receptor (PPAR) genes *PPARα* L162V, *PPARγ2* C161T and *PPARδ* T294C single nucleotide polymorphisms (SNPs) with obesity and metabolic syndrome (Met-S) in a multi-ethnic population in Kampar, Malaysia.

Methods: Socio-demographic data, anthropometric and biochemical measurements (plasma lipid profile, adiponectin and interleukin-6 [IL-6] levels) were taken from 307 participants (124 males; 180 obese; 249 Met-S; 97 Malays, 85 ethnic Chinese, 55 ethnic Indians).

Results: The overall minor allele frequencies were .08, .22 and .30 for *PPAR* α L162V, γ C161T, δ T294C, respectively. All SNPs were not associated with obesity, Met-S and obesity with/without Met-S by χ^2 analysis, ethnicity-stratified and logistic regression analyses. Nevertheless, participants with V162 allele of *PPARα* had significantly higher IL-6, while those with T161 allele of *PPARγ2* had significantly lower HOMA-IR.

Conclusions: All *PPAR* SNPs were not associated with obesity and Met-S in the suburban population of Kampar, Malaysia, where only *PPARα* V162 and *PPARγ2* T161 alleles were associated with plasma IL-6 and HOMA-IR, respectively. *Ethn Dis*. 2015;25(4):383-390; doi:10.18865/ed.25.4.383

Keywords: Peroxisome Proliferator-Activated Receptors, Single Nucleotide Polymorphism, Obesity, Metabolic Syndrome, Malaysia

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Introduction

Metabolic syndrome (Met-S) is a group of risk factors including insulin resistance, central obesity, dyslipidemia and hypertension.[1] Peroxisome proliferator activated receptors (PPAR) are composed of three isotypes, PPARα, PPARδ/β and PPARγ. They are ligand-activated nuclear transcription factors that modulate the expression of an array of genes involved in regulating glucose, lipid and cholesterol metabolism.[2] Considering this, any dysregulation of these metabolic pathways caused by single nucleotide polymorphisms (SNPs) can lead to Met-S and obesity.

Three common SNPs that have been variably associated with obesity and Met-S in different populations are *PPARα* L162V, *PPARγ2* C161T and *PPARδ* T294C. *PPARα* L162V SNP (rs1800206) is identified as 484C/G transversion in exon 5, which results in a missense mutation of leucine to valine at codon 162.[3,4] *PPARγ2* C161T SNP (rs3856806) is a silent His477His polymorphism in exon 6,[5] while *PPARδ* T294C SNP (rs2016520) is located at the 5'- untranslated region (UTR) of exon 4, 87 nucleotides upstream of the start codon.[6]

Expanding the study to a relatively larger and more multi-ethnic sample population, we screened the above two SNPs and included the PPARδ T294C SNP, and also measured additional anthropometrics and biochemical variables related to obesity and Met-S.

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We previously performed a pilot study investigating the association of *PPARα* L162V and *PPARγ2* C161T SNPs with overweight among university students (majority were of the Chinese ethnicity, n = 256), and found no association.[7] Expanding the study to a relatively larger and more multi-ethnic sample population, we screened the above two SNPs and included the *PPARδ* T294C SNP, and also measured additional anthropometrics and biochemical variables related to obesity and Met-S.

Methods

Study Population, Questionnaire and Clinical Measurements

Based on the population of 88,638 in Kampar (Department of Statistics Malaysia, 2010),[8] a minimum sample size of 288 had to be recruited, assuming a margin of error of 5%, CI 95% and response distribution of at least 25% (Raosoft® Sample Size Calculator Software, Raosoft Inc, USA). A total of 307 participants was recruited (age range: 21-80; mean age 53.3 ± 14.2 years; 124 males, 183 females; 127 non-obese, 180 obese; 58 non-Met-S, 249 Met-S; 97 Malays, 85 Chinese, 55 Indians) from patients who attended the Kampar Health Clinic from June to December 2011. Patrons of the clinic who had fasted overnight to have their blood drawn were recruited by convenience sampling. The exclusion criteria included medical conditions such as hyperthyroidism, pituitary diseases, chronic liver/renal diseases, acute infection hematologic diseases, pregnancy, patients undergoing dialysis, body builders or highly trained athletes, people with a fever or swelling and patients with osteoporosis. Clinical and anthropometric measurements were taken as described in our previous study.[9] The BMI cutoff point for obesity was ≥ 25 kg/m^2.[10] The presence of Met-S was based on having three of five criteria set by the US National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) for Asians, according to Tan et al[1]: waist circumference ≥ 90 cm for males and ≥ 80 cm for females; high triglyceride (TG) level with ≥ 1.7 mmol/L (150 mg/dL) or specific treatment for this lipid abnormality, low HDL-C level with < 1.03 mmol/L (40 mg/dL) for males and < 1.29 mmol/L (50 mg/dL) for females or specific treatment for this lipid abnormality; high systolic blood pressure (SBP)/diastolic blood pressure (DBP) of ≥ 130/85 mm Hg; and high fasting blood glucose (FBG) of ≥ 5.6 mmol/L (100 mg/dL); or previously diagnosed type 2 diabetes.

Overnight fasting blood samples of participants were collected under routine phlebotomy by professional nurses. Our study was registered under the National Medical Research Registry (NMRR-09-826-4266) and the protocol was approved by the Medical Research and Ethnics Committee, Ministry of Health Malaysia. All participants in this study signed informed consent forms and all samples were taken in accordance with the Declaration of Helsinki (revised in Seoul, 2008).

Clinical Biochemistry

The fasting plasma concentration of total cholesterol (TC), HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), triglycerides (TG) and total cholesterol/HDL cholesterol ratio (TC/HDL-C) were measured via an outsourced service (Pathology and Clinical Laboratory (M) Sdn. Bhd.). Fasting blood glucose concentration of the subjects was determined using One Touch® Ultra-Easy blood glucose monitoring system (LifeScan, Inc. USA). Fasting plasma insulin, adiponectin and interleukin-6 (IL-6) levels were measured using commercial ELISA kits (Cortez Diagnostics Inc., USA or R&D Systems, USA). Insulin resistance was calculated via homeostatic model assessment (HOMA-IR), where the product of fasting glucose (mmol/L) and fasting insulin (μU/mL) was divided by 22.5.[11]

Genotyping

Genomic DNA of the participants was extracted from the leukocytes using the Genomic DNA Mini Kit (Blood/Cultured Cell) (Geneaid, USA). The genotyping of *PPARα* L162V, *PPARγ2* C161T and *PPARδ* T294C SNPs was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), as described in our previous study[7] and Miao et al.[12] The annealing temperatures for *PPARα* L162V, *PPARγ2* C161T and *PPARδ* T294C were 55°C, 56°C and 60°C, respectively and their respective PCR products were digested with 3U of restriction enzymes *BglI* (New England Biolabs, USA) and *PmlI* (Thermo Scientific, USA) at 37°C, or *BslI* (Thermo Scientific, USA) at 55°C. All PCR reactions were carried out on the MJ Mini™ Personal Thermal Cycler (Biorad, US). Gels were then stained with ethidium bromide and visualized under UV light after electrophoresis. Three genotypes from each SNP were verified by direct DNA sequenc-

Table 1. *PPAR*α L162V, *PPAR*γ2 C161T and *PPAR*δ T294C allele distribution according to demographic and anthropometric-clinical classes

Alleles	Ethnicity			Sex		Obesity		Met-S		Obese with Met-S	
	Malay *n* (%)	Chinese *n* (%)	Indian *n* (%)	Male *n* (%)	Female *n* (%)	Non-obese *n* (%)	Obese *n* (%)	Absent *n* (%)	Present *n* (%)	Absent *n* (%)	Present *n* (%)
PPARα L162V											
L162	181 (93.3)	284 (91.6)	101 (91.8)	225 (9.7)	341 (93.2)	234 (92.1)	332 (92.2)	105 (9.5)	461 (92.6)	32 (94.1)	300 (92.0)
V162	13 (6.7)	26 (8.4)	9 (8.2)	23 (9.3)	25 (6.8)	20 (7.9)	28 (7.8)	11 (9.5)	37 (7.4)	2 (5.9)	26 (8.0)
χ2; *P*		.50; .78		1.23; .27		.002; .964		.550; .458		NP	
PPARγ C161T											
C161	154 (79.4)	226 (72.9)	96 (87.3)	186 (75.0)	290 (79.2)	193 (76.0)	283 (78.6)	84 (72.4)	392 (78.7)	25 (73.5)	258 (79.1)
T161	40 (2.6)	84 (27.1)	14 (12.7)	62 (25.0)	76 (2.8)	61 (24.0)	77 (21.4)	32 (27.6)	106 (21.3)	9 (26.5)	68 (2.9)
χ2; *P*		1.18; .01[a]		1.52; .22		.590; .443		2.144; .143		.577; .448	
PPARδ T294C											
T294	133 (68.6)	212 (68.4)	86 (78.2)	166 (66.9)	265 (72.4)	174 (68.5)	257 (71.4)	80 (69.0)	351 (7.5)	23 (67.6)	234 (71.8)
C294	61 (31.4)	98 (31.6)	24 (21.8)	82 (33.1)	101 (27.6)	80 (31.5)	103 (28.6)	36 (31.0)	147 (29.5)	11 (32.4)	92 (28.2)
χ2; *P*		4.09; .13		2.11; .15		.592; .441		.103; .748		.257; .612	

NP, χ^2 test not performed due presence of cell having the count of less than 5, χ^2 and *P* by Pearson's χ^2 test
a. *P* significant at <.05.

ing of PCR products (First BASE Laboratories Sdn. Bhd., Malaysia).

Statistical Analysis

SPSS statistics software was used to analyze the data of the study. Allelic frequencies for each SNP 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) or adjusted means ± standard error of the mean (SEM) and as frequency for categorical variables. The normality of distributions of continuous variables was tested with the Kolmogorov-Smirnov test and variables that were not distributed normally were log-transformed prior to statistical analysis. Genotype and allele frequencies of the SNPs with respect to BMI status, sex, and ethnicity were assessed for association using χ^2 test while univariate analysis of variance using General Linear model (adjusted for age and ethnicity) was performed for continuous variables. Logistic regression analysis (enter method) was performed with adjustment for age, gender and ethnicity to evaluate the association between obesity, metabolic syndrome and obese with/without metabolic syndrome with the three SNPs. A *P* of <.05 was considered statistically significant.

Results

The distribution of all the *PPAR*α L162V, *PPARγ2* C161T and *PPAR*δ T294C alleles according to ethnicities and sex is shown in Table 1, which did not deviate from the Hardy-Weinberg equilibrium. The overall minor allele frequencies (MAFs) for *PPAR*α L162V, *PPARγ2* C161T and *PPAR*δ T294C SNPs were .08, .22 and .30, respectively. *PPAR*α V162 allele was the least common allele due to the absence of subjects carrying *PPAR*α V162V genotype. According to Malay/Chinese/Indian ethnicities, their MAFs were .07/.08/.08; .21/.27/.13; .31/.32/.22, respectively, where only the allele distribution of *PPARγ2* C161T was significantly associated with ethnicity – MAF of Indians being significantly lower. The allele distribution of all the SNPs was also not significantly different between the sexes (Table 1).

Participants were then catego-

Table 2. Logistic regression analysis for the association of *PPARα* L162V, *PPARγ2* C161T and *PPARδ* T294C genotypes/alleles with anthropometric-clinical classes[a]

Genotypes and allele	Obesity			Met-S			Obese with Met-S		
	OR	*P*[b]	95% CI	OR	*P*[b]	95% CI	OR	*P*[b]	95% CI
PPARα L162V									
L162V	.977	.942	.519, 1.838	.944	.897	.396, 2.250	1.732	.507	.342, 8.774
V162	1.021	.945	. 559, 1.867	.950	.903	.417, 2.163	1.647	.530	.348, 7.804
PPARγ2 C161T									
C161T/T161T	.783	.303	.491, 1.248	.625	.165	.322, 1.214	.775	.638	.269, 2.239
T161	.845	.391	.574, 1.243	.693	.178	.407, 1.182	.764	.534	.327 , 1.785
PPARδ T294C									
T294C/C294C	.714	.155	.448, 1.136	1.109	.761	.571, 2.153	1.120	.834	.387, 3.244
C294	.850	.369	.596, 1.211	1.008	.976	.607, 1.672	.910	.816	.409, 2.022

OR, odds ratio; CI, confidence interval
a. The wild-type genotypes and alleles were set as reference or OR 1.0. Genotypes for *PPARγ2* and *PPARδ* were combined for analysis.
b. Adjusted for age, sex and ethnicity.

rized based on obesity, Met-S and obese with Met-S status (Table 2), and when analyzed for their association with *PPARα* L162V, *PPARγ2* C161T and *PPARδ* T294C SNPs, no association was found. When stratified analysis was performed according to ethnicities, similar absence of association was also found within each ethnicity (data not shown). Logistic regression analysis also revealed that participants with the mutant alleles for the three *PPAR* SNPs did not have a significantly higher odds ratio to develop obesity, Met-S or obesity with Met-S (data not shown). Similar for anthropometric and clinical measurements, their means were not significantly different among the alleles of the three *PPAR* SNPs, except for IL-6 and HOMA-IR, where they were significantly higher in subjects with *PPARα* V162 allele and *PPARγ2* C161 allele, respectively (Table 3). Furthermore, when the three *PPAR* SNPs were analyzed together, subjects with all the homozygous wild-type genotypes did not have significantly different anthropometric and clinical measurements compared to those without (Table 4).

Discussion

The *PPARα* V162V genotype was found to be absent in our study, consistent with our previous study[7] and previous studies among Caucasians[13] and African Americans,[14] while the V162 allele was found to be absent among African Senegalese.[15] Meanwhile, despite having similar demographics with Malaysia, Chan et al[16] reported lower MAFs for this SNP - .005/.004/.02 in Singaporean Malays/Chinese/Indians. In contrast, a much higher MAF of .13 was reported by Gu et al[17] among the Chinese Han population. Meanwhile, in Caucasian populations, MAF ranged from .06 to .08.[13,18-21] In agreement with our current and previous findings,[7] *PPARα* L162V SNP was not associated with obesity in the Chinese Han,[17] Brazilians[22] and Caucasians.[4,23-25] Furthermore, a study conducted by Robitaille et al[23] reported no association of this SNP with Met-S among Caucasian men, consistent with our current finding. The current study which also found that the lipid profile, glucose metabolism parameters and adiponectin levels were not affected by *PPARα* L162V SNP, is further supported by some studies,[4,18,22,24,26,27] but not others.[13,19]

For *PPARγ2* C161T SNPs, difference in the prevalence of MAF between ethnicities was noted in our current and previous[7] studies, with Indians showing significant lower MAF than Chinese. The MAF of Malaysian Indians was found to be similar with South Indians[28] and Caucasians.[5] Meanwhile, the Han Chinese from other countries portrayed similar MAF with us, for example the MAF of .25 in Taiwan[29] and .21 in Beijing[30] populations. Similar with our study, this SNP was previously found to have no significant association with obesity[28-35] and Met-S[5,28-30,36] in various populations, while others found positive association with obesity[37,38] and Met-S.[39,40] As with *PPARα* L162V, this SNP was

Table 3. Means of anthropometric and clinical measurements according *PPARα* L162V, *PPARγ*2 C161T and *PPARδ* T294C alleles[a]

Variables	*PPARα* L162V			*PPARγ*2 C161T			*PPARδ* T294C		
	L162 M:F = 1:.66 Mean age = 53.40 ± 14.00	V162 M:F = 1:.92 Mean age = 52.08 ± 15.89	*P*	C161 M:F = 1:.64 Mean age = 53.38 ± 14.02	T161 M:F = 1:.82 Mean age = 53.03 ± 14.64	*P*	T294 M:F = 1:.63 Mean age = 53.70 ± 14.16	C294 M:F = 1:.81 Mean age = 52.36 ± 14.14	*P*
Weight[a], kg	67.33 ± .60	68.07 ± 2.05	.796	67.67 ± .65	66.38 ± 1.21	.363	67.32 ± .68	67.54 ± 1.05	.781
BMI[a], kg/m^2	26.87 ± .23	26.86 ± .80	.890	27.03 ± .25	26.31 ± .47	.207	26.95 ± .27	26.66 ± .41	.540
WC, cm	91.88 ± .53	91.65 ± 1.83	.903	92.00 ± .58	91.37 ± 1.08	.606	91.76 ± .61	92.09 ± .94	.769
WHR[a]	.91 ± .01	.90 ± .02	.362	.91 ± .01	.92 ± .01	.448	.91 ± .01	.91 ± .01	.954
TBF[a], %	33.07 ± .31	32.54 ± 1.05	.815	33.26 ± .33	32.23 ± .62	.194	33.23 ± .35	32.56 ± .54	.546
SF, %	27.27 ± .36	25.70 ± 1.23	.221	27.46 ± .39	26.06 ± .73	.091	27.48 ± .41	26.38 ± .63	.146
VFL[a], %	12.05 ± .27	12.03 ± .94	.962	12.16 ± .30	11.66 ± .55	.396	12.10 ± .31	11.92 ± .48	.691
RM[a], kcal	1416.70 ± 1.06	145.34 ± 34.57	.355	1422.78 ± 1.98	1407.45 ± 2.40	.493	1416.41 ± 11.55	1426.21 ± 17.74	.658
SM[a], %	24.82 ± .17	25.25 ± .59	.394	24.82 ± .19	24.96 ± .35	.630	24.72 ± .20	25.17 ± .30	.171
SBP[a], mm Hg	14.82 ± .87	139.45 ± 2.97	.589	141.34 ± .94	138.56 ± 1.75	.198	14.92 ± .99	14.22 ± 1.52	.811
DBP, mm Hg	81.41 ± .52	82.13 ± 1.80	.703	81.69 ± .57	8.72 ± 1.06	.424	81.66 ± .60	81.03 ± .92	.567
FBG[a], mg/dL	7.73 ± .14	7.10 ± .50	.318	7.74 ± .15	7.49 ± .28	.267	7.76 ± .16	7.52 ± .25	.597
FI[a], μIU/mL	12.65 ± .66	13.63 ± 2.31	.627	13.17 ± .72	11.09 ± 1.35	.088	13.17 ± .75	11.61 ± 1.18	.700
HOMA-IR[a]	4.55 ± .28	4.33 ± .98	.997	4.75 ± .30	3.74 ± .57	.042[b]	4.73 ± .32	4.04 ± .50	.487
TC, mmol/L	4.44 ± .04	4.21 ± .15	.139	4.42 ± .045	4.42 ± .08	.954	4.42 ± .05	4.41 ± .07	.889
TG[a], mmol/L	1.49 ± .05	1.46 ± .17	.646	1.47 ± .05	1.53 ± .10	.900	1.51 ± .06	1.43 ± .09	.845
HDL-C[a], mmol/L	1.21 ± .01	1.21 ± .05	.445	1.20 ± .01	1.25 ± .03	.223	1.22 ± .01	1.19 ± .02	.168
LDL-C, mmol/L	2.55 ± .03	2.35 ± .12	.107	2.55 ± .04	2.49 ± .07	.420	2.52 ± .04	2.58 ± .06	.430
TC/HDL-C ratio[a]	3.76 ± .04	3.66 ± .14	.429	3.78 ± .04	3.69 ± .08	.297	3.73 ± .04	3.83 ± .07	.228
Plasma Adiponectin[a], ng/mL	6326.88 ± 216.39	524.79 ± 761.52	.120	614.54 ± 235.79	6618.95 ± 445.36	.342	6319.63 ± 247.68	6064.10 ± 387.83	.458
Plasma IL-6[a], pg/mL	8.90 ± .78	1.59 ± 2.75	.041[b]	9.13 ± .85	8.64 ± 1.61	.615	9.78 ± .89	7.18 ± 1.39	.254

BMI, body mass index; WC, waist circumference; WHR, waist-hip ratio; TBF, total body fat; SF, subcutaneous fat; VFL, visceral fat level; RM, resting metabolism; SM, skeletal muscles; SBP, systolic blood pressure: DBP, diastolic blood pressure; FBG, fasting blood glucose; FI, fasting insulin; HOMA-IR, homeostasis model assessment-estimated insulin resistance; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; IL-6, Interleukin-6

a. Values were log transformed before analysis; values are presented as adjusted mean ± SEM (estimated marginal means ± standard error of the mean) by univariate analysis of variance (General Linear Model), adjusted for co-variates: age and ethnicity.

b. *P* significant at <.05.

also not associated with lipid profile, glucose metabolism parameters and adiponectin, consistent with previous studies in other populations.[31,32,36,37,41] However, Gu et al[42] and Yilmaz-Aydogan et al[43] reported that the T161 allele carriers had higher serum TG.

For *PPARδ* T294C SNP, the MAF varies from .16 to 0.25 among Caucacians[6,44,45] and .28 among African Americans.[45] The MAF in Chinese Han population was reported as.30,[42,46] which is similar to the MAF of Malaysian Chinese population in our study. Similar with our study, several studies from other populations reported the lack of association of *PPARδ* T294C SNP with obesity,[38,47] Met-S and their related clinical variables.[47] Meanwhile, other studies found significant association with obesity,[46,48-50] increased plasma LDL-C,[6,51] and decreased plasma HDL-C.[6,49]

When participants with homozygous wild type for all the three SNPs were clustered together to compare with those with at least one mutant allele, no significant differences in the anthropometric and clinical measurements were observed. This finding suggests that polygenic obesity and Met-S have a multi-factorial etiology that involves complex interactions between many candidate genes, hormonal status, dietary habits, and other environmental factors.

One of the major limitations of our study is our relatively small

Table 4. Means of anthropometric and clinical variables according to *PPAR* genotype combinations

Variable	Subjects with homozygous wild type for all three SNPs[a] M:F = 1:.42 Mean age: 55.70 ± 11.49	Subjects without homozygous wild type for all three SNPs M:F = 1:.78 Mean age: 52.54 ± 14.86	*p*
Weight[b], kg	66.21 ± 1.68	67.87 ± .94	.438
BMI[b], kg/m^2	26.80 ± .65	26.88 ± .36	.977
WC, cm	9.03 ± 1.48	92.44 ± .83	.157
WHR[b]	.90 ± .01	.91 ± .01	.479
TBF[b], %	33.51 ± .86	32.88 ± .48	.632
SF, %	28.52 ± 1.00	26.71 ± .56	.117
VFL[b], %	11.64 ± .76	12.17 ± .43	.927
RM[b], kcal	1378.83 ± 28.04	1429.18 ± 21.57	.269
SM[b], %	24.46 ± .48	24.98 ± .27	.278
SBP[b], mm Hg	141.97 ± 2.41	14.32 ± 1.35	.698
DBP, mm Hg	81.27 ± 1.46	81.53 ± .82	.874
Pulse rate, bpm	78.41 ± 1.57	77.40 ± .88	.573
FBG[b], mg/dL	7.79 ± .38	7.65 ± .22	.581
FI[b], μIU/mL	13.02 ± 1.78	12.61 ± 1.04	.839
HOMA-IR[v]	4.81 ± .75	4.44 ± .44	.957
TC, Mmol/L	4.42 ± .11	4.42 ± .07	.987
TG[b], Mmol/L	1.38 ± .13	1.52 ± .08	.566
HDL-C[b], Mmol/L	1.24 ± .04	1.20 ± .02	.144
LDL-C, Mmol/L	2.56 ± .09	2.53 ± .54	.809
TC/HDL-C[b]	3.65 ± .11	3.79 ± .06	.237
Plasma adiponectin[b], ng/mL	6414.12 ± 586.59	6186.87 ± 344.19	.913
Plasma IL-6[b], pg/mL	11.83 ± 2.10	8.05 ± 1.23	.318

BMI, body mass index; WC, waist circumference; WHR, waist-hip ratio; TBF, total body fat; SF, subcutaneous fat; VFL, visceral fat level; RM, resting metabolism; SM, skeletal muscles; SBP, systolic blood pressure: DBP, diastolic blood pressure; FBG, fasting blood glucose; FI, fasting insulin; HOMA-IR, homeostasis model assessment-estimated insulin resistance; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; IL-6, Interleukin-6

a. Participants with homozygous wild-type genotypes for all three PPAR SNPs: LL for PPARα L162V, CC for PPARγ2 C161T and TT for PPARδ T294C
The total number of participants with homozygous mutated genotypes for all variables was 74/307, except for FBP, TC, TG, HDL-C, LDL-C, TC/HDL-C (70/280) and FI, HOMA-IR (67/260).

b. Values were log transformed before analysis; values are presented as adjusted mean ± SEM (estimated marginal means ± standard error of the mean) by univariate analysis of variance (General Linear Model), adjusted for co-variates: age and ethnicity.

sample size, thus limiting statistical power. As our participants were recruited from a health clinic, the findings on the SNPs prevalence and association may not be fully representative of the general Malaysian population. In addition, our study did not assess in detail the dietary habits and lifestyle factors, which are factors that may also affect the biochemical parameters in our study.

Conclusion

*PPAR*α L162V, *PPARγ2* C161T and *PPAR*δ T294C SNPs are not the major genetic determinants of obesity and metabolic syndrome in the multi-ethnic Malaysian population. Nevertheless, we found that *PPAR*α V162 allele carriers were associated with significantly higher plasma IL-6 level, while participants with *PPARγ2* T161 allele had significantly lower HOMA-IR, suggesting that the latter SNP may confer some protective effect on insulin sensitivity.

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Author Contributions

Research concept and design: Say. Acquisition of data: Chia, Fan, Say. Data analysis and interpretation: Chia, Fan, Say. Manuscript draft: Chia, Fan, Say. Statistical expertise: Chia, Fan, Say. Acquisition of funding: Say. Administrative: Say. Supervision: Say

Statement of Human Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

…we found that PPARα V162 allele carriers were associated with significantly higher plasma IL-6 level, while participants with PPARγ2 T161 allele had significantly lower HOMA-IR, suggesting that the latter SNP may confer some protective effect on insulin sensitivity.

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