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ORIGINAL ARTICLE

Polymorphisms of the Resistin Gene and Their Association with Obesity and Resistin Levels in Malaysian Malays

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Abstract Single nucleotide polymorphisms (SNP) in the resistin gene (*RETN*) are linked to obesity and resistin levels in various populations. However, results have been inconsistent. This study aimed to investigate association between polymorphisms in the resistin gene with obesity in a homogenous Malaysian Malay population. This study is also aimed to determine association between resistin levels with certain SNPs and haplotypes of *RETN*. A total of 631 Malaysian Malay subjects were included in this study and genotyping was carried out using Sequenom MassARRAY. There was no significant difference found in both allelic and genotype frequencies of each of the *RETN* SNPs between the obese and non-obese groups after Bonferroni correction. *RETN* rs34861192 and rs3219175 SNPs were significantly associated with log-resistin levels. The GG genotype carriers are found to have higher levels of log-resistin compared to A allele carriers. The *RETN* haplotypes (CAG, CGA and GA) were significantly associated with resistin levels. However, the haplotypes of the *RETN* gene were not associated with obesity. Resistin levels were not correlated to metabolic parameters such as body weight, waist circumference, body mass index, and lipid parameters. *RETN* SNPs and haplotypes

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are of apparent functional importance in the regulation of resistin levels but are not correlated with obesity and related markers.

Keywords Body mass index · RETN · BMI · Obesity haplotypes

Introduction

The recent rise in the prevalence of obesity is mainly contributed by environmental changes in modern lifestyle and a genetic predisposition to fat deposition (O'Rahilly and Farooqi 2006). Obesity is a serious issue as it leads to many serious health problems such as diabetes mellitus, insulin resistance, hypertension, fatty liver disease, cardiovascular disease, and certain types of cancer (Boffetta et al. 2011; Isomaa et al. 2001; Schwimmer et al. 2006; Calle and Kaaks 2004).

Resistin is an adipocyte-secreted hormone which belongs to the cystein-rich C-terminal domain proteins called resistin-like molecules (Holcomb et al. 2000; Kim et al. 2001; Steppan et al. 2001a). Resistin concentration is positively associated with obesity and also with metabolic parameters (Degawa-Yamauchi et al. 2003; Azuma et al. 2003). Resistin levels is correlated with obesity, diabetes mellitus, and insulin resistance (McTernan et al. 2006; Conneely et al. 2004; Liu et al. 2006) in which circulating resistin levels were significantly elevated and have been concordant with increasing levels of insulin, glucose, and lipid (Haugen et al. 2001). Resistin is increased in the obese subjects compared to lean controls (Vendrell et al. 2004; Schaffler et al. 2004; Degawa-Yamauchi et al. 2003). Resistin is positively correlated with alterations in BMI and visceral fat (Azuma et al. 2003; Vozarova de Courten et al. 2004). Circulating resistin levels are elevated in diet-induced and genetically induced obese mice and decreased with administration of the antidiabetic drug rosiglitazone (Steppan et al. 2001b). Improvement in insulin action and blood sugar in mice with diet-induced obesity was observed with administration of anti-resistin antibody (Steppan et al. 2001b). Nevertheless, numerous controversial findings have been reported on the role of resistin as a potential risk factor for insulin resistance, obesity, and diabetes mellitus (Pfutzner et al. 2003; Kusminski et al. 2005; Barnes and Miner 2009; Ye et al. 2013). Latest data showed that the resistin levels are under genetic control in different populations (Ukkola et al. 2008; Asano et al. 2010; Cho et al. 2004; Hivert et al. 2009). The mechanism underlying expression, regulation, secretion, and circulating levels of resistin remain unclear. The effect of resistin on the central nervous system and β-cell function is still yet to be explored.

Genetic variations in *RETN* reported to play an important role in pathogenesis of obesity, diabetes, and insulin resistance; however, results are inconsistent (El-Shal et al. 2013; Ochi et al. 2003; Kimbell et al. 2008). Many studies have shown significant association between single nucleotide polymorphism *RETN* and determinants of metabolic syndrome and resistin levels (Azuma et al. 2004; Cho et al. 2004; Hivert et al. 2009; Norata et al. 2007; Kumar et al. 2014). Several studies reported that the polymorphisms in the promoter region of *RETN* including rs1862513 (−420C>G) and rs3219175 have potential functional role for

determining circulating resistin levels by altering the transcriptional activity and elevating resistin messenger ribonucleic acid levels in abdominal fat (Osawa et al. 2004; Onuma et al. 2010; Cho et al. 2004). In addition, the rs34861192, which is monomorphic in Caucasians, is reported to be associated with higher plasma resistin levels in Asians (Azuma et al. 2004; Asano et al. 2010). *SREBP1c*, a transcription factor known to regulate expression of *RETN* binds to the resistin gene promoter in the vicinity of rs34861192 was also shown to play a crucial role in determining the plasma resistin levels (Seo et al. 2003; Asano et al. 2010). Furthermore, haplotypes of rs1862513 and rs3219175 (GA) have been reported to confer the highest plasma levels in both functional data using in vitro luciferase promoter assay and human genetic data (Onuma et al. 2010). To clarify the role of *RETN* variants with resistin levels and their potential link with metabolic disorders, we investigated the association between rs34861192, rs3219175, and rs1862513 *RETN* single nucleotide polymorphisms (SNPs) with obesity and resistin levels in Malaysian Malays. This study was also carried out to determine the link between resistin levels with obesity and lipid parameters.

Methods

Study Subjects

Candidate gene association study was performed in a convenient sample of Malaysian Malays. Obesity was defined using the WHO body mass index cut-off of 30 kg/m^2. Participants with BMI of 30 kg/m^2 and above were grouped as obese and those with BMI below 30 kg/m^2 were grouped as non-obese. From the 631 participants, 469 were non-obese, while 162 were obese. The study population included participants from the annual health screening program for staff members of a public university in Kuala Lumpur and from a health screening program in Bera, Pahang, Malaysia.

All participants self-reported as being of Malay ethnic origin for at least three generations. The Medical Ethics Committee of the university medical center approved the study protocol (MEC reference number: 672.23). Written informed consent was obtained from all the participants.

Blood Collection

Approximately 10–15 mL of blood was drawn, in a sitting position, from overnight fasted participants. Total serum cholesterol, serum high-density lipoprotein cholesterol (HDL), serum low-density lipoprotein cholesterol (LDL), and triglyceride levels were measured using standard clinical laboratory techniques by the fully accredited clinical diagnostic laboratory of the medical center. Resistin levels were measured in duplicates using Human Resistin Platinum ELISA kit (eBioscience).

Anthropometric and Clinical Measurements

Height and weight were measured using calibrated stadiometers and weighing scales. Waist and hip measurements were made by a circumference measurement tape. Waist circumference (WC) was measured at the midpoint between the lower border of the rib cage (costal margin) and the iliac crest. Hip circumference (HC) was measured at the widest circumference over the buttocks and below the iliac crest. Body mass index (BMI) was defined as the ratio of weight (kg) divided by height squared (m^2). Blood pressure was measured using a digital automatic blood pressure monitor (Omron HEM-907, Omron Healthcare, Kyoto, Japan).

Genotyping of the SNPs

Genomic DNA was extracted using buccal swabs. DNA extraction was performed using i-genomic CTB DNA extraction kit (iNtRON Biotechnology, Inc., Gyeonggi, Korea). *RETN* rs34861192, rs1862513, and rs3219175 SNPs were genotyped using Sequenom MassARRAY.

Statistical Analysis

Hardy–Weinberg equilibrium were tested (Shi and He 2005). Genotype and allelic frequencies among obese and non-obese were calculated using Pearson's chi-squared test. Generalized linear model (GLM) was used in assessing effects of SNPs on obesity parameters, adjusted for age and gender. All data were presented as mean ± standard deviation. Bivariate analysis was performed to determine correlation between resistin levels and demographic variables. Statistical analysis was performed using SPSS 16 software. Genotype-based association test was carried out using chi-square test with 2 degree of freedom, while allele-based test was carried out using chi-square test with 1 degree of freedom. Bonferroni correction was used to adjust the p values for multiple testing on multiple markers ($\alpha = 0.05/3$). Three *RETN* SNPs were included in this study, therefore α was 0.016 after Bonferroni correction.

Sample size and power of the study was calculated using Quanto version 1.2.4 software (Menashe et al. 2008). Haploview software (version 4.2) was used for calculating linkage disequilibrium (LD) and constructing the LD blocks and haplotype association analysis. Permutation test with 5000 permutations was used to access the statistical significance. Measurement of linkage disequilibrium coefficient (D') was performed to determine the strength of LD. Association analysis of haplotypes with resistin levels was performed using GLMs.

Results

General characteristics of the study participants are shown in Table 1. There were 469 non-obese (BMI: 25.01 ± 3.07 kg/m^2) and 162 obese (BMI: 33.83 ± 3.16 kg/m^2) subjects in this study. Non-obese and obese participants are in the mean age

Table 1 General characteristics of the study participants

Parameters	Non-obese	Obese	*p*
Height (m)	1.59 ± 0.09	1.57 ± 0.09	0.005
Weight (kg)	63.51 ± 10.79	83.26 ± 11.66	<0.001
BMI	25.01 ± 3.07	33.83 ± 3.16	<0.001
WC (cm)	85.57 ± 10.12	100.51 ± 8.52	<0.001
HC (cm)	98.37 ± 7.24	113.24 ± 8.04	<0.001
WHR (cm)	0.87 ± 0.08	0.89 ± 0.07	0.004
SBP (mmHg)	128.67 ± 17.82	137.60 ± 18.54	<0.001
DBP (mmHg)	80.63 ± 11.37	87.64 ± 12.38	<0.001
TC (mmol/L)	5.51 ± 0.92	5.45 ± 0.99	0.508
LDL (mmol/L)	3.55 ± 0.83	3.47 ± 0.88	0.371
HDL	1.32 ± 0.28	1.25 ± 0.25	0.032
TG	1.44 ± 0.93	1.58 ± 0.72	0.001
Resistin (ng/mL)	0.58 ± 0.04	0.06 ± 0.03	0.729
Age	48.33 ± 10.13	48.43 ± 9.05	0.912

BMI body mass index, *DBP* diastolic blood pressure, *HC* hip circumference, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *SBP* systolic blood pressure, *TC* total cholesterol, *TG* triglyceride, *WC* waist circumference, *WHR* waist–hip ratio

groups of 48.33 and 48.43, respectively. There were no significant differences in the resistin levels between the obese and non-obese participants. Resistin concentration did not correlate with age, BMI, waist–hip ratio, blood pressure, waist, and HC, and neither did it correlate with lipid profile in the general population (Supplementary File 1). There was no gender specific effect observed in this group. Table 2 summarizes genotype and allele frequencies in the obese and non-obese participants of the *RETN* SNPs. *RETN* rs34861192, rs1862513, and rs3219175 SNPs did not deviate from the Hardy–Weinberg equilibrium. There was no significant difference was found in both genotype and allelic frequencies of each of the *RETN* SNPs between the obese and non-obese group after Bonferroni corrections. The *RETN* rs1862513 SNP had the highest minor allele frequency (MAF) (0.46) and *RETN* rs3219175 SNP had the lowest MAF (0.14).

Table 3 shows the association between the *RETN* SNPs with log-resistin following adjustment for age and gender under dominant model. *RETN* rs3219175 and rs3481192 SNPs were significantly associated with log-resistin levels after Bonferroni correction and adjustment with age and gender. GG genotype carriers of *RETN* rs3219175 and rs3481192 SNPs presented higher levels of log-resistin compared to A allele carriers. However, *RETN* rs1862513 SNP was not associated with log-resistin levels. In addition, the haplotypes CAG and CGA in block 1 (rs3219175, rs1862513 and rs3481192 SNPs) and GA in the block 3 (rs34861192 and rs3219175) were significantly associated with log-resistin levels (Table 4).

Figure 1 shows the haplotype block and LD pattern of resistin gene in obese and non-obese subjects. *RETN* rs3219175 SNP was in complete LD with *RETN* rs1862513 SNP ($D' = 1.0$). *RETN* rs3219175 SNP was in strong LD with *RETN* rs34861192 SNP ($D' = 0.99$). Strong LD was also observed at *RETN* rs34861192 with rs1862513 SNPs ($D' = 0.90$). There were three haplotypes found in the *RETN* gene. There was no significant difference in haplotype frequencies of *RETN*

Table 2 Genotype and allelic distribution of RETN SNPs

	MAF	Genotype frequency			p ($df = 2$)	Allele frequency		p ($df = 1$)	OR	95% [CI]	p HWE
rs34861192	0.15	A/A (freq)	A/G (freq)	G/G (freq)		A (freq)	G (freq)				
Non-obese		12 (0.03)	127 (0.27)	330 (0.70)	0.381	151 (0.16)	787 (0.84)	0.224	0.8	[0.55–1.15]	0.443
Obese		4 (0.03)	35 (0.22)	123 (0.76)		43 (0.13)	281 (0.87)				0.958
rs1862513	0.46	C/C (freq)	C/G (freq)	G/G (freq)		C (freq)	G (freq)				
Non-obese		101 (0.22)	233 (0.50)	135 (0.29)	0.812	435 (0.46)	503 (0.54)	0.792	1.03	[0.80–1.33]	0.98
Obese		34 (0.21)	85 (0.53)	43 (0.27)		153 (0.47)	171 (0.53)				0.503
rs3219175	0.14	A/A (freq)	A/G (freq)	G/G (freq)		A (freq)	G (freq)				
Non-obese		10 (0.02)	122 (0.26)	337 (0.72)	0.528	142 (0.15)	796 (0.85)	0.413	0.86	[0.59–1.24]	0.434
Obese		4 (0.03)	35 (0.22)	123 (0.76)		43 (0.13)	281 (0.87)				0.788

CI confidence interval, *HWE* Hardy–Weinberg equilibrium, *MAF* minor allele frequency, *OR* odds ratio

Table 3 Association between RETN SNPs with resistin levels

	rs3219175	rs3481192	rs1862513
Log-resistin	GG = −3.19 ± 0.59 (n = 70)	GG = −3.19 ± 0.59 (n = 69)	CC = −2.77 ± 0.68 (n = 24)
	AG + AA = −2.62 ± 0.65 (n = 23)	GA + AA = −2.62 ± 0.63 (n = 24)	GC + GG = −3.14 ± 0.61 (n = 69)
p (R^2)	**<0.001 (0.128)**	**<0.001 (0.133)**	0.018 (0.044)

R^2, r-squared

* p-Adjusted for age and gender

* Significant level was corrected for Bonferroni, $\alpha = 0.016$

Table 4 Association analysis of resistin haplotypes with resistin levels

Block	SNPs	Haplotypes	Frequencies	p
Block 1	rs1862513, rs3219175 and rs3481192	GAG	0.190	0.044
		CGG	0.206	0.565
		CAG	0.190	**<0.001**
		CGA	0.447	**0.002**
		GGG	0.447	0.810
		GGA	0.063	0.913
Block 2	rs1862513 and rs3219175	GA	0.120	0.071
		CG	0.120	0.784
		GG	0.730	0.230
		CA	0.120	0.010
Block 3	rs34861192 and rs3219175	AG	0.237	0.075
		GA	0.258	**0.001**

* Significant level was corrected for Bonferroni, Block 1 alpha is 0.008, Block 2 is 0.012 and Block 3 is 0.025

between obese and non-obese groups. After correcting for permutation testing with 5000 permutations, the haplotypes were not associated with obesity (Table 5).

Discussion

All the *RETN* rs34861192, rs1862513 (−420C>G), and rs3219175 SNPs were in high frequencies (>5%) in this population. There were no significant differences in allelic and genotype frequencies of *RETN* SNPs between the obese and non-obese groups. This indicates that the resistin gene does not play a major role in predisposition of obesity in the Malaysian Malays. The *RETN* rs1862513 SNP was not associated with obesity in the Koreans (Cho et al. 2004).

RETN rs34861192 and rs3219175 SNPs were significantly associated with plasma log-resistin levels in the Malaysian Malays. Similarly, the *RETN* rs34861192 SNP in the 5′ flanking regions is associated with plasma resistin levels in the Japanese and Finnish populations (Ukkola et al. 2008; Asano et al. 2010).

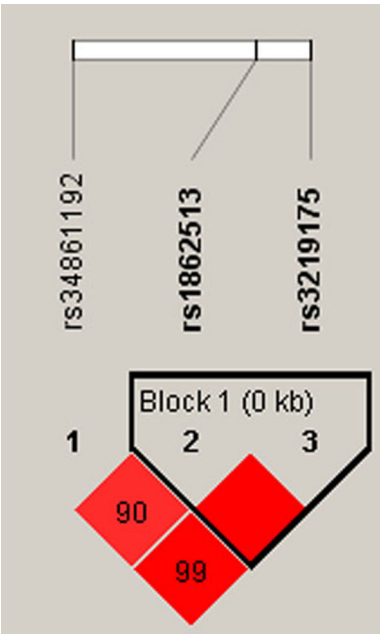

Fig. 1 Haplotype block of resistin gene in non-obese and obese participants. Patterns of linkage disequilibrium (LD) between the *RETN* single nucleotide polymorphisms (SNPs). The strength of LD measured by D' multiplying 100 displayed in the red diamonds. A *red cell* without number indicates a complete LD. Higher number in the cell indicates a higher degree of LD (Color figure online)

Table 5 Association analysis of resistin haplotypes with obesity

Block	Obese, frequencies	Non-obese, frequencies	χ^2	*p*
Block 1				
GG	0.528	0.54	0.13	0.953
CG	0.341	0.312	0.909	0.633
CA	0.131	0.148	0.567	0.755

However, *RETN* rs1862513 and *RETN* rs3219175 SNPs were not associated with plasma resistin levels in the Japanese population (Asano et al. 2010). The *RETN* rs1862513 SNP was associated with plasma resistin concentrations in the Koreans (Cho et al. 2004). A meta-analysis in the Europeans reported that *RETN* rs1862513 SNP was not associated with resistin levels in two European populations, the Framingham Offspring study and in a cohort from Italy (Menzaghi et al. 2006; Hivert et al. 2009). Haplotypes of *RETN* rs34861192, rs1862513, and rs3219175 SNPs (CAG and CGA) was associated with resistin levels in Malaysian Malays. Our results are consistent with another study which reported that these SNPs are in the same LD block and are strongly associated with circulating resistin levels (Onuma et al. 2010). However, GA haplotypes defined by rs1862513 and rs3219175 was associated with higher plasma resistin levels in Japanese in which these haplotypes showed highest activity in the luciferase promoter constructs (Onuma et al. 2010). However, this study was unable to provide evidence as to why the A allele from rs3219175 is required for G allele from rs1862513 to confer highest resistin levels in Japanese population, thereby indicating that ethnic differences might be a

contributing factor (Onuma et al. 2010). It is possible that variation in genetic patterns for each ethnic group might contribute to variation in circulating plasma resistin levels.

The *RETN* rs34861192 SNP was found to be monomorphic in the Hispanic and Europeans panel of dbSNP. The MAF of *RETN* rs34861192 SNP was 0.22 in the Japanese which was higher than in the Malaysian Malays. The MAF of *RETN* rs1862513 SNP was 0.37 in the Japanese which was lower than in the Malaysian Malays (0.46). The MAF of *RETN* rs3219175 SNP was 0.22 in the Japanese which was higher than in the Malaysian Malays (0.14) (Asano et al. 2010). A study in the Japanese men reported that MAF of *RETN* rs1862513 and rs3219175 SNPs was 0.34 and 0.21, respectively (Miyamoto et al. 2009). Ethnic differences may contribute to the differences in MAF. *RETN* rs1862513 was in complete LD ($D' = 1.0$) with *RETN* rs3219175 SNP in Malaysian Malays. The strength of LD between *RETN* rs1862513 and *RETN* rs3219175 SNPs was reduced in the Japanese (Asano et al. 2010; Miyamoto et al. 2009). The *RETN* rs34861192 and *RETN* rs3219175 SNPs was in perfect LD in the Japanese but the strength of LD between these two SNPs was slightly reduced in Malaysian Malays ($D' = 0.99$). None of the *RETN* haplotypes were significantly associated with obesity. This showed that the *RETN* variants do not play a major role in obesity in the Malaysian Malays.

Although resistin is an adipocyte-secreted hormone where it should be linked to adiposity; however, many studies have shown no association between resistin and adiposity (Lee et al. 2003; Zhang et al. 2002). Some studies have shown that resistin levels correlated with determinants of metabolic syndrome while few other studies failed to report any correlation of resistin levels with metabolic parameters (Reilly et al. 2005; Azuma et al. 2003; Bienertova-Vasku et al. 2014). Similarly, in the current study, there is no correlation between resistin and obesity markers. Correlations between plasma resistin levels and determinants of metabolic syndrome are reported to be gender specific in Caucasians particularly in women (Norata et al. 2007). No gender specific effects, however, were observed in Malaysian Malays. Despite these findings, the role of resistin in metabolic abnormalities is still controversial.

Limitation of this study is that findings from this study cannot be extrapolated to the other ethnic groups within the Malaysian population, such as the Chinese and Indians. In addition, lack of information on physical activities and dietary habits limit us from making conclusions regarding gene–environment interactions of *RETN* gene in this population. Since childhood obesity is on the increase in Malaysia, this study should be replicated in children. To our knowledge, this is the first study conducted in Malaysian Malays to elucidate effects on *RETN* haplotypes on obesity and resistin levels. We had genotyped only a limited number of SNPs, therefore future studies should include other possible causal SNPs covering upstream and downstream regions of *RETN*.

Conclusion

In summary, *RETN* SNPs and haplotypes have potential roles in determining the circulating resistin levels in Malaysian Malays. However, *RETN* variants are not involved in predisposition to obesity in this population. Haplotypes of *RETN* gene did

not appear to confer risk to obesity in Malaysian Malays. Resistin levels are found not to be associated with obesity parameters, blood pressure, and lipid profiles.

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Conflict of interest The authors declare no conflict of interest.

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