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The contribution of *FTO* rs9939609 and *RETN* rs1862513 polymorphisms in predisposing resettled indigenous (Orang Asli) Temiar to metabolic syndrome

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Abstract

Purpose Metabolic syndrome (MetS) is characterized by visceral obesity, elevated blood pressure and fasting blood glucose, increased triglycerides, and lower high-density lipoprotein cholesterol. MetS related with intricate gene-environment interactions. *FTO* and *RETN* variants were linked to the occurrence of MetS, but inconsistent results were reported. Therefore, this study was conducted to evaluate the potential role of *FTO* rs9939609 and *RETN* rs1862513 polymorphisms and their susceptibility risk to MetS among resettled indigenous or Orang Asli (OA) of Temiar subtribe under resettlement scheme by the Malaysia government.

Methods A cross sectional study was performed involving 123 Temiar volunteers located in Gua Musang, Kelantan. MetS was identified using modified NCEP-ATP III. DNA extraction was done using peripheral blood. Polymerase Chain Reaction–Restriction Fragment Length Polymorphism (PCR–RFLP) was employed to genotype *FTO* rs9939609 and *RETN* rs1862513 polymorphisms. Susceptibility risk of the polymorphisms (*FTO* rs9939609 and *RETN* rs1862513) with MetS was determined by binary logistic regression analysis and odds ratios (ORs).

Results *FTO* rs9939609 and *RETN* rs1862513 were associated with risk of MetS susceptibility among the Temiar subtribe with estimated OR 19.9 ($P<0.001$) and 20.7 ($P=0.006$) for heterozygous (T/A) and homozygous (A/A) genotype at *FTO* rs9939609 locus, respectively; OR 222.5 ($P<0.001$) and 26.2 ($P=0.005$) for heterozygous (C/G) and homozygous (G/G) genotype at *RETN* rs1862513 locus, respectively.

Conclusion The genetic polymorphisms of *FTO* rs9939609 and *RETN* rs1862513 were associated with the risk of MetS among the Temiar subtribe. The findings contribute toward the fundamental prevention plan to decrease the probability of MetS development.

Keywords Metabolic syndrome, Temiar subtribe, Orang Asli, *FTO* rs9939609, *RETN* rs1862513

Introduction

Metabolic syndrome (MetS) is described as a cluster of metabolic chaos comprising elevated level of both fasting glucose and blood pressure, visceral obesity, higher triglycerides and lower high-density lipoprotein (HDL) cholesterol [1]. The increment in its prevalence is alarming. It has been reported that MetS may create an increment at five-times and two-times risk progressing into

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type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD), respectively [2]. The prevalence of MetS is reported to be parallelly increasing with the epidemic of obesity. Rapid urbanization has resulted in behavioral alteration and exposing the world population to obesogenic environment. The occurrence of MetS is impacted by the progression of genetic predisposition and environmental factors. The pathogenesis of MetS is however, not completely recognized [3]. Apart from insulin resistance (IR) and visceral obesity [3, 4], MetS is also identified with strong genetic predisposition [5–7]. Approximately 24% of the MetS cases are associated with genetic factors [8].

Fat mass and obesity associated (*FTO*) that was acknowledged to be located on chromosome 16 (16q12.2) encodes 2-oxoglutarate-dependent nucleic acid demethylase. It is extensively secreted in various tissues, such as the hypothalamus and crucially govern the energy balance system [9, 10]. *FTO* was the first gene identified by genome-wide association studies (GWAS) to be linked with obesity [9, 10]. Since obesity or adiposity and T2DM are the MetS traits, it is expected that genetic variants in *FTO* may associated with the risks for MetS. The significant association linking MetS and single nucleotide polymorphism (SNP) of *FTO* rs9939609 was first demonstrated in a study among Caucasian populations [11]. *FTO* rs9939609 was also observed to have significant association with other MetS components including elevated fasting glucose and triglycerides and low level of HDL cholesterol through elevated body mass index (BMI) [11].

The area of chromosome 19p13, known to be the location of *RETN*, was recognized by genome-wide linkage analysis (GWLA) to have susceptibility loci for traits associated with MetS [12, 13]. *RETN* encodes cysteine-rich peptide hormone (resistin) expressed in adipose tissue [14] and was suggested to modulate glucose tolerance and insulin activity, therefore potentially contributes in the pathophysiology of obesity and IR in humans [15–17]. Approximately, 70% of the deviation in circulating levels of resistin were described by genetic factors and few SNPs in the *RETN* itself [18, 19]. Abnormal resistin may induce the onset of obesity-related health conditions such as hypertension, T2DM, and atherosclerosis eventually leads to MetS [20]. Certainly, resistin is considered as a possible inducement and biomarker for the onset of MetS based on its association with obesity, inflammation, IR and comorbidities of CVD [21, 22]. Additionally, few studies found that the GG genotype of *RETN* rs1862513 was correlated with increased prevalence of MetS [23–26].

Despite the reported association linking the SNPs of *FTO* rs9939609 and *RETN* rs1862513 with MetS as mentioned above, several studies reported null relationship [27–33]. The interaction between gene and environment is immensely intricate due to various lifestyle characteristics, different environmental conditions or genetic background resulting in such divergence reports. The isolated population of indigenous or named as Orang Asli (OA) of Temiar subtribe located in the Peninsular of Malaysia serves an exceptional chance to study gene-environment interactions as they had undergone the resettlement under a scheme named "Rancangan Penempatan Semula" (RPS) over the last two decades by the government, exposing them to obesogenic environments of modern living. Rare inter-marriage providing an opportunity to observe gene-environment interaction. However, there is no available data reported on the association of both polymorphism with MetS among them. Thus, the present study was undertaken to investigate the association between SNPs of *FTO* rs9939609 and *RETN* rs1862513 with the risk of MetS onset among the Temiar subtribe.

Methods

Study subjects

Ethical approval was obtained from Universiti Sultan Zainal Abidin (UniSZA) Human Research Ethics Committee (UHREC) (UHREC/2016/3/012). Participants were invited via the heads of the respective villages via Jabatan Kemajuan Orang Asli (JAKOA). Communication and information with the subject were through JAKOA. Cross sectional study was selected as the study design. Simple random sampling was used where smaller group of the study subjects from the whole Temiar community located at the RPS Kuala Betis in Gua Musang, Kelantan was selected based on termed inclusion and exclusion criteria. The inclusion criteria comprised Temiar subtribe aged 18 years and above from RPS Kuala Betis, Gua Musang in Kelantan, volunteered and agreed to participate in the study. Excluded was subjects who had major psychiatric illness, neurological deficits, and body dysmorphia. One hundred and twenty-three participants who gave written informed consents were recruited. The recruitment of subjects were done gradually with two times visit toward the resettlement. At enrollment, subjects were advised to fast (at least 8 h) prior to actual study procedures. They were then asked to complete a standardized interviewer-based to collect socio-demographics information including age, gender, marital status, educational level, working status, income, family history, tobacco, and alcohol consumption. They were also subjected to anthropometric measurements. All of the included study subjects were then divided into two groups, which are MetS and non-MetS based on modified National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III guidelines as described in "Metabolic syndrome" section.

Metabolic syndrome

MetS assessed as per the modified criteria of NCEP-ATP III that requires any three of the following [1]:

I. Waist circumference (WC) population-based specific cut-offs; ≥ 90 cm in males, and ≥ 80 cm in females.
II. Blood pressure; systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg or current use of antihypertensive drugs.
III. Impaired fasting glucose; fasting plasma glucose ≥ 5.6 mmol/L.
IV. Triglycerides; ≥ 1.7 mmol/L.
V. HDL cholesterol; ≤ 1.03 mmol/L in males and ≤ 1.29 mmol/L in females.

Anthropometric measurements

Anthropometric measurements recorded including blood pressure, weight, height, BMI, and WC. Automated body composition analyzer (Model HBF-36, Karada Scan, Bioelectrical Impedance principle, Omron, Japan) was utilized to evaluate weight and BMI. WC was obtained using a non-stretchable measuring tape to the nearest 0.1 cm. Digital blood pressure monitor (Omron HEM-757, Japan) was used to measure blood pressure in sitting position and on the right arm. Participants were instructed not to eat, exercise, smoke, or climb stairs 30 min prior to blood pressure measurement and were advised to rest (at least 5 min) before the assessment.

Genotyping of *FTO* rs9939609 and *RETN* rs1862513 polymorphisms

Commercially available DNA extraction kit, QIAamp DNA Blood Mini kit (Qiagen, Hilden, Germany) was utilized to extract genomic DNA using peripheral blood samples as specified by prescribed protocols. Genotyping for *FTO* rs9939609 and *RETN* rs1862513 polymorphisms was employed using Polymerase Chain Reaction–Restriction Fragment Length Polymorphism (PCR–RFLP). The PCR product with the polymorphic sites of *FTO* and *RETN* was amplified using appropriate primers (*FTO* rs9939609 FW: 5′ AGCTGTGAG GAATACTAGGAGA 3′, *FTO* rs9939609 RV: 5′ ACT CAGCCTCTCTACCATCTTA 3′, *RETN* rs1862513 FW: 5′ CATTCTCACCCAGAGACATAAT 3′, *RETN* rs1862513 RV: 5′ CAGCTGTCACTTACCCTCTC 3′) to produce 508 bp and 552 bp fragments, respectively. Amplification was carried out in a total volume of 20 µl containing 1 X GeneAmp PCR Buffer II (Applied Biosystems, California, USA), 0.375 mM dNTPs (Applied Biosystems, California, USA), 1.875 mM $MgCl_2$ (Applied Biosystems, California, USA), 1 unit of AmpliTaq Gold DNA Polymerase (Applied Biosystems, California, USA), 0.5 µM of both forward and reverse specific primers, and 4 ng/µl of DNA template. The PCR protocols were as follows: 96 °C of pre-denaturation for 5 min, 95 °C of denaturation for 1 min, 50 °C for 1 min and 72 °C for 1 min in 40 cycles followed by 72 °C of final extension for 7 min in Veriti™ 96-Well Thermal Cycler (Applied Biosystems, CA, USA). Amplicons were then subjected to electrophoresis at 80 V for 70 min in a 2% agarose gel.

PCR product with the polymorphic site of *FTO* rs9939609 and *RETN* rs1862513 was digested using *Apo*I and *Bbs*I restriction enzymes (New England Biolabs Inc., Ipswich, MA, USA) for 30 min at 37 °C. The homozygous wildtype (T/T) for the SNP of *FTO* rs9939609 would produce three fragments (182, 173, and 153 bp), while the A-allele would not be digested

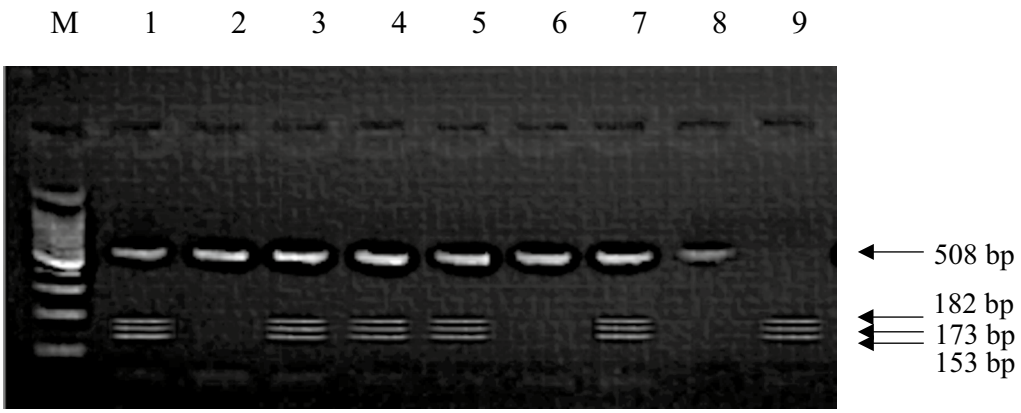

Fig. 1 Representative gel electrophoresis of PCR–RFLP analysis of *FTO* rs9939609 polymorphism. Lane: M, 100 bp DNA ladder; Lane 1, 3, 4, 5, and 7 are heterozygous genotype (508, 182, 173, and 153 bp); Lane 2, 6, and 8 are homozygous variant genotype (508 bp); Lane 9, homozygous wildtype genotype (182, 173, and 153 bp)

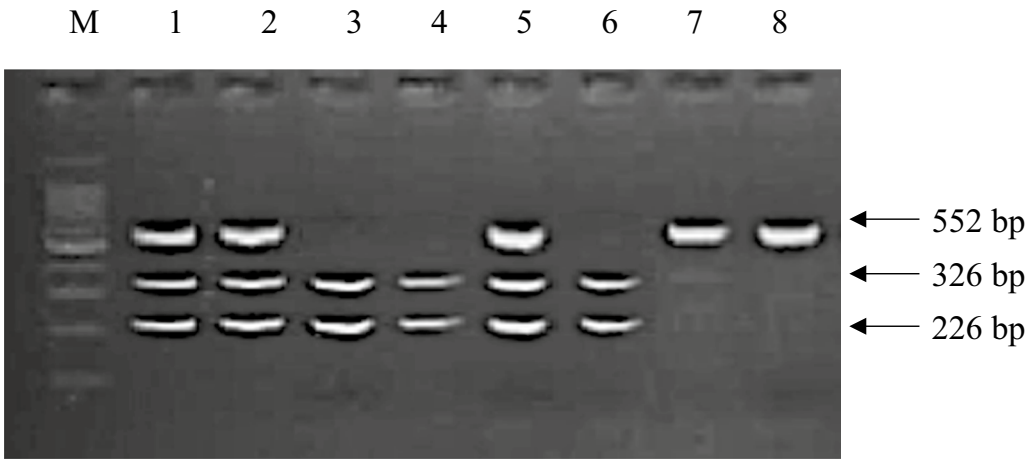

Fig. 2 Representative gel electrophoresis of PCR–RFLP analysis of *RETN* rs1862513 polymorphism. Lane: M, 100 bp DNA ladder; Lane 1, 2, and 5 are heterozygous genotype (552, 326, and 226 bp); Lane 3, 4, and 6, homozygous wildtype genotype (326 and 226 bp); Lane 7 and 8 are homozygous variant genotype (552 bp)

by *Apo*I and produced 508 bp fragment. The appearance of four fragments (508, 182, 173 and 153 bp) represented the heterozygous genotype (Fig. 1). Wildtype C allele of *RETN* rs1862513 was digested with *Bbs*I, to produce a 326 and 226 bp fragments, respectively, with the G allele remaining undigested (552 bp). Heterozygous genotype for *RETN* rs1862513 polymorphism was confirmed with the presence of three fragments (552, 326, and 226 bp). The genotype was classified as homozygous wildtype (C/C), heterozygous (C/G), and homozygous variant (G/G) according to fragment sizes as shown in Fig. 2. The results for PCR–RFLP genotyping were validated by DNA sequencing based on representative samples.

Statistical analysis

The Chi-square test was utilized to calculate the genotype frequency of *FTO* rs9939609 and *RETN* rs1862513 polymorphisms among Temiar with MetS and non-MetS individuals. Descriptive analysis using mean and standard deviation for numerical and continuous variable. Frequency and percentage used for categorical variables. Independent t test was used to compare the mean of all related variables between groups of MetS and non-MetS. Binary logistic regression (SPSS 18.0, IBM Corporation, Armonk, New York, USA) was used to evaluate the Odds Ratios (ORs) and 95% Confidence Interval (CI) of the association risk between *FTO* rs9939609 and *RETN* rs1862513 polymorphisms with MetS. All statistical tests were two sided and $P < 0.05$ was considered as statistically significant.

Results

Of the 123 subjects enrolled, thirty-seven (37) were males and 86 females, and 49 (39.8%) subjects fulfilled the criteria of MetS. The mean age was 40.9 ± 16.6 and 34.5 ± 11.9 years for males and females, respectively. The association between anthropometric measurements and MetS components among the subjects are shown in Table 1. Genotype frequencies of *FTO* and *RETN* variants comparing MetS and non-MetS subjects are shown in Table 2.

Table 1 Anthropometric parameters and MetS criteria among study subjects ($n = 123$)

Variables	MetS ($n = 49$)	Non-MetS ($n = 74$)	*P* value*
Age	38.61 ± 12.65	35.04 ± 14.25	0.025
Time of birth			0.073
Before relocation	14 (28.6)	33 (44.6)	
After relocation	35 (71.4)	41 (55.4)	
Height (cm)	149.77 ± 18.2	153.87 ± 13.03	0.152
Weight (kg)	62.24 ± 14.07	60.38 ± 13.38	0.460
BMI (kg/m^2)	31.56 ± 4.14	22.51 ± 3.19	< 0.001
WC (cm)	91.46 ± 12.89	74.91 ± 8.3	< 0.001
Systolic BP (mmHg)	136.98 ± 21.23	126.67 ± 18.15	0.005
Diastolic BP (mmHg)	90.37 ± 13.1	81.33 ± 11.28	< 0.001
Fasting blood glucose (mmol/L)	7.214 ± 3.37	5.62 ± 2.02	0.001
Fasting triglyceride (mmol/L)	1.86 ± 0.63	1.29 ± 0.2	< 0.001
Fasting HDL-C (mmol/L)	0.94 ± 0.35	1.42 ± 0.23	< 0.001

*P value < 0.05 is considered statistically significant based on independent t test/Chi-square

Table 2 Genotype and allele frequencies of *FTO* rs9939609 and *RETN* rs1862513 polymorphism in study subjects ($n=123$)

	MetS $n=49$ (%)	Non-MetS $n=74$ (%)	*P* value
Genotype	*FTO* rs9939609		
Homozygous wildtype (TT)	20 (40.8)	70 (94.6)	< 0.001
Heterozygous (TA)	23 (46.9)	4 (5.4)	
Homozygous variant (AA)	6 (12.2)	0 (0.0)	
Allele			
T	63 (64.3)	144 (97.3)	< 0.001
A	35 (35.7)	4 (2.7)	
Genotype	*RETN* 1862513		
Homozygous wildtype (CC)	11 (22.4)	73 (98.6)	< 0.001
Heterozygous (CG)	34 (69.4)	1 (1.4)	
Homozygous variant (GG)	4 (8.2)	0 (0.0)	
Allele			
C	56 (57.1)	147 (99.3)	< 0.001
G	42 (42.9)	1 (0.7)	

The ORs for the association between *FTO* rs9939609 and *RETN* rs1862513 polymorphisms with susceptibility risk of developing MetS were calculated, where wildtype T/T (*FTO* rs9939609) and the C/C (*RETN* rs1862513) were used as a reference genotype. The OR for the occurrence of MetS was 222.5 ($P<0.001$) for those having the heterozygous (C/G) genotype and 26.2 ($P=0.005$) for those harboring the homozygous (G/G) genotype, at the *RETN* rs1862513 locus. Homozygous (A/A) genotype and heterozygous (T/A) genotype of *FTO* rs9939609 polymorphism were also associated with higher risk of developing MetS with OR 19.83 ($P<0.001$) and OR 20.7 ($P=0.006$), respectively (Table 3).

Table 3 Association of *FTO* rs9939609 and *RETN* rs1862513 polymorphisms with MetS susceptibility risk among Temiar subtribe ($n=123$)

Polymorphism	MetS $n=49$ (%)	Non-MetS $n=74$ (%)	OR (95% CI)	*P* value*
FTO rs9939609				
TT	20 (40.8)	70 (94.6)	1.000 (Ref)	
TA	23 (46.9)	4 (5.4)	19.83 (6.14–64.09)	< 0.001*
AA	6 (12.2)	0 (0.0)	20.7 (2.35–182.16)	0.006
RETN rs1862513				
CC	11 (22.4)	73 (98.6)	1.00 (Ref)	
CG	34 (69.4)	1 (1.4)	222.545 (27.60, 1794.50)	< 0.001*
GG	4 (8.2)	0 (0.0)	26.182 (2.67, 256.31)	0.005*

**P* value < 0.05 is considered statistically significant based on binary logistic regression

Discussion

MetS is a multifactorial disease with many interrelated factors, such as genetic and environmental factors. There is some urgency in identifying the specific genetic influences on the pathophysiology of MetS. The present study suggested a potential role of *FTO* and *RETN* polymorphisms in predisposing individuals to MetS. The studied polymorphisms were found to be associated with higher risk of developing MetS. Our previous finding reported the highest prevalence of MetS among the Temiar subtribe (39.8%) [34] compared to the prevalence reported among major Malaysian populations: 26.4% (Malays), 26.2% (Chinese), and 35.6% (Indians) [35]. The prevalence of MetS was found to be increased with age. Jusoh et al., said that higher MetS prevalence was observed among subjects born after the relocation to RPS compared to the other group, therefore, indicating a distinct relation between the relocation to RPS and the prevalence of MetS among the Temiar subtribe [34]. Despite being a small study, the prevalence observed among this Temiar subtribe is definitely startling, considering the extended results among other substantial populations of relocated OA. Albeit the continuing upgrade of their quality of life and the gradual improvement of long-suffered illnesses, including malnutrition and stunting [20, 36, 37], the establishment of RPS in the Third Malaysia Plan (1976–1980) which previously planned to redevelop and resettle the OA community including the Temiar subtribe, however, has caused them to become vulnerable to non-communicable and lifestyle-related diseases such as MetS and T2DM [38, 39].

The present study indicated higher risk of developing MetS among the Temiar subtribe in association with

FTO rs9939609 with compelling odd ratio (OR: 19.83) (Table 3). Temiar subtribe with heterozygous (T/A) has 19-fold increasing risk of developing MetS, while 20-fold of increasing risk to develop MetS was reported with homozygous variant (A/A) compared to the Temiar subtribe with homozygous wildtype (T/T). The present finding was in agreement with previous GWAS among Caucasian [11] and non-Caucasian multi-ethnics [27] where increasing risk of developing MetS was observed among A-allele carriers of *FTO* rs9939609. Previous studies also reported significant associations between *FTO* rs9939609 and MetS among subjects in Southern Italy, Xinjiang and Tunisia [40–42]. However, few studies failed to demonstrate the association between *FTO* rs9939609 and MetS [43, 44]. It is known that obesity (reflects by BMI) and adiposity specifically visceral obesity (reflects by waist circumference) are acknowledged as parts of MetS components. In contrast to those without MetS, WC and BMI were significantly higher among the Temiar subtribe with MetS [34]. Indeed, BMI was reported as an independent predictor for MetS [34]. Hence, it is apparent that adiposity or visceral obesity is the intermediate implication in the association of the *FTO* rs9939609 and the development of MetS.

It is reported that the *FTO*'s overexpression in mice would cause obesity and elevated adiposity level [45]. *FTO* influences the biological activity through the effects on the DNA methylation [46]. *FTO* is predominantly expressed in hypothalamus, suggesting that *FTO* plays crucial biological activity in the hypothalamic controlling the food intake [45], energy homeostasis [47], cerebrocortical regulation of insulin [48], and body fat regulation through adipocyte lipolysis [49]. It is also suggested that *FTO* might crucially regulated sympathetic nervous system, modulating the cardiovascular system and blood pressure [50]. While precise function of *FTO* in the mechanism of human obesity and MetS remains debatable, *FTO* is the most identified genetic loci for frequent form of obesity. Reports on the risk association of *FTO* with obesity and its related traits, however, were inconsistent [30, 51–54]. Obesity has a fundamental contribution in MetS progression. The risk association of *FTO* rs9939609 in MetS observed in this study was in line with a large meta-analysis among Asian and European populations [55]. However, several studies were reported to contradict the observation [27–29].

The present study also indicated a higher risk of developing MetS with *RETN* rs1862513 polymorphism among the Temiar subtribe with a captivating odd ratio (OR: 222.55) (Table 3). Subjects with heterozygous (C/G) have two-hundred-twenty-two-fold increasing risk of developing MetS. In contrast, twenty-six-fold of increasing risk to develop MetS was reported among them with homozygous variant (G/G) compared to subjects with homozygous wildtype (T/T). Significant associations between *RETN* rs1862513 and MetS were also reported in studies among Japanese population [25, 26], but no such association was observed in a study among Malaysian men [31]. *RETN* rs1862513 polymorphism was found to be associated with the regulation of *RETN* expression and serum resistin level [56–58]. Resistin expression is induced during adipocyte differentiation, while in mature adipocytes, it is down-regulated, but is overexpressed in obesity [59, 60]. A recent study has reported a significant association between higher serum resistin level in GG carriers compared to CC and CG carriers of *RETN* rs1862513 polymorphism [61]. Albeit being reported as a controversial finding [62], such association was also reported in previous studies among Korean [56] and Malaysian population [63].

This phenomenon probably resulted from elevated resistin promoter activity found with the G allele [56, 58]. Evidently, the G allele serves as a binding site for Sp1 and Sp3 transcription factors, where the binding of the factors was observed to elevate the resistin promoter activity [58]. The SNP rs1862513 has a real sequel on resistin expression, but the capacity of resistin in human obesity via the effect of *RETN* rs1862513 remains to be elucidated. Higher serum resistin level was acknowledged to be linked with increased obesity, visceral fat, IR and T2DM [64, 65]. The serum resistin level is closely linked to metabolic disorders and the onset of MetS itself. A clinical finding supported the association observing the increment of serum resistin level among adults with MetS, likened to those without MetS [66]. The Temiar subtribe was also reported to have a direct correlation between serum resistin with most of MetS components including visceral obesity, increasing fasting glucose and triglycerides levels. However, the HDL cholesterol was inversely correlated with the resistin level [67]. Correspondingly, serum resistin level was reported to be an independent predictor for MetS among the Temiar subtribe [34]. The *RETN* rs1862513 polymorphism was also observed to be linked with risk of MetS components including visceral obesity, and increased BMI, total cholesterol, and low-density-lipoprotein levels [69]. However, no such association was reported among Malaysian [30], Han Chinese [68], Tunisian [69], and Thais [70].

Nonetheless, the main limitation of this study was the small sample size. Their refusal to consent for blood specimens, the accessibility to the Temiars due to remote location, the layered procedures to recruit the Temiars, which involved OA officials and the Temiars village heads, as well as budget constraint are among the anticipated causative factors for the low response rate. Although the best efforts were made to ensure correct understanding on the procedures and requirements to the subjects, we regret that

there might be a possibility of poorly complied subjects to the overnight fasting instruction.

Conclusion

It is possible to postulate that the impact of genetic factors predisposes human to a disease was diverse across numerous ethnic populations and depends on various lifestyle or cultural characteristics and different environmental conditions. Therefore, the disparity among findings were reported among studies. The study subjects and its setting minimized the genetic background noises considering the Temiars living in a very close-knit society and tend to marry each other. Thus, the genetic admixture is reduced. The present study suggested a significant role of *FTO* rs9939609 and *RETN* rs1862513 polymorphisms in predisposing the Temiars to develop MetS with captivating high odds ratios. Further studies are necessary with larger sample size consisting of other ethnic groups with similar background to confirm the genetic influences in the development of MetS.

Abbreviations

BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
DNA	Deoxyribonucleic acid
dNTPs	Deoxyribose nucleotide triphosphate
FTO	Fat mass and obesity associated
GWAS	Genome-wide association studies
GWLA	Genome-wide linkage analysis
HDL	High-density lipoprotein
JAKOA	Jabatan Kemajuan Orang Asli
MetS	Metabolic syndrome
$MgCl_2$	Magnesium chloride
NCEP-ATP III	National Cholesterol Education Program Adult Treatment Panel-III
OA	Orang Asli
OR	Odd ratio
PCR	Polymerase Chain Reaction
PCR–RFLP	Polymerase Chain Reaction–Restriction Fragment Length Polymorphism
RPS	Rancangan Penempatan Semula
SNP	Single nucleotide polymorphism
SPSS	Statistical Packages for the Social Sciences
T2DM	Type 2 diabetes mellitus
UHREC	UniSZA Human Research Ethics Committee
UniSZA	Universiti Sultan Zainal Abidin
WC	Waist circumference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43042-023-00425-x.

Additional file 1. Ethical approval from UniSZA Human Research Ethics Committee (UHREC).

Additional file 2. Patient Information and Consent Form.

Additional file 3. Approval from Jabatan Kemajuan Orang Asli (JAKOA) for data collection.

Additional file 4. Sample of consent form signed by research participants.

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Author contributions

NSH, MNZ and AFWJ performed writing, analyzing and interpreting data, collected samples as well as performed the research. MAKR, RY and NASNH analyzed and collected samples. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from UniSZA Human Research Ethics Committee (UHREC) (UHREC/2016/3/012). All subjects gave consent to participate. Personal, demographic details and relevant data of the participants were collected and recorded after getting informed consent as in the patient information and consent form provided in Additional files 1, 2, 3 and 4.

Consent for publication

All authors gave consent to publish the paper.

Competing interests

The authors declared that they have no competing of interests.

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