Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Apr 04; 10(A):782-786.
https://doi.org/10.3889/oamjms.2022.9185
eISSN: 1857-9655
Category: *A - Basic Sciences*
Section: *Gentics*

OPEN ACCESS

Perilipin Genetic Variation Correlated with Obesity and Lipid Profile in Metabolic Syndrome

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Edited by: Slavica Hristomanova-Mitkovska
Citation: Hastuti P, Mus R, Puspasari A, Maharani C, Setyawati I. Perilipin genetic variation correlated with obesity and lipid profile in metabolic syndrome. Open Access Maced J Med Sci. 2022 Apr 04; 10(A):782-786. https://doi.org/10.3889/oamjms.2022. 9185
Keywords: Perilipin; Genetic variation; Metabolic syndrome; Obesity; Fat gene
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Received:03-Mar-2022
Revised: 20-Mar-2022
Accepted: 25-Mar-2022

Funding: This research was funded by directorate general of universities through the basic research of universities (no. 2760/UN1.DITLIT/DIT-LIT/PT/2020)
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Perilipin is very important for the regulation of the deposition and mobilization of fats. The human perilipin gene (*PLIN*) is near the locus for risk of obesity and hypertriglyceridemia. The *PLIN* gene is thought to be involved in the occurrence of metabolic syndrome.

AIM: The aim of this research is to determine the role of variations of the *PLIN* gene (PLN4 11482 G>A) as a risk factor for component of metabolic syndrome.

METHODS: This study involved a total of 160 subjects consisting of 80 with metabolic syndrome and 80 controls. Genotype analysis was done with the polymerase chain reaction-restriction fragment length polymorphism method. The data were analyzed with *t*-tests to compare the subjects' characteristics between metabolic syndrome groups and controls. Risk factors of *PLIN* genotypes were calculated with odds ratio and multivariate regression analysis was used to determine the role of the *PLIN* gene with each biochemical characteristic.

RESULTS: The result was significant differences between the characteristics of the metabolic syndrome subjects with controls ($p < 0.05$). There was no difference in genotypes between patients with metabolic syndrome and controls. The multivariate analysis of the genetic role with biochemical components showed the *PLIN* gene in AA carriers as a risk factor for metabolic syndrome compare GA+GG, risk of obesity, and hypercholesterolemia with $p < 0.05$.

CONCLUSION: It can be concluded that *PLIN* variation has a role in the incidence of metabolic syndrome, especially in relation to obesity and hypercholesterolemia. Further study is needed to determine the role of other gene variations as a risk factor for metabolic syndrome.

Introduction

Metabolic syndrome is a metabolic disorder that increases the risk of cardiovascular diseases, diabetes, and certain cancers. Components of metabolic syndrome are hypertriglyceridemia, low high-density lipoprotein-cholesterol (HDL-C) level, hypertension, abdominal obesity, and insulin resistance. The pathogenesis of this disease is a complex interaction of risk factors and high adipocyte fat levels seem to play an important role in triggering metabolic syndrome through the interaction of genetic variants involved in dyslipidemia, hypertension, and insulin resistance [1]. Genetic factors play an important role in regulation of obesity because there are specific genes involved in the control of energy expenditure, appetite, lipid metabolism, adipogenesis, thermogenesis, and differentiation of cells [2]. Excess consumption of energy such as fats can become deposited as triglycerides and stored in lipid droplets in adipocyte tissues. Lipid droplets are surrounded by a single layer of phospholipids and proteins. Perilipin is one of the phosphorylated proteins surrounding lipid droplets and is only found in adipocyte cells [3]. Perilipin plays a major role in synthesizing and maintaining fat deposits in adipocytes [4].

In humans, the perilipin gene (*PLIN*) is located on chromosome 15q 26.1 [5]. Perilipin is a target of protein kinase A, and non-phosphorylated perilipin can inhibit hormone-sensitive lipase (HSL) which affects the lipolysis of the triglycerides in lipid droplets [6]. Accordingly, *PLIN* maintains the homeostasis of lipogenesis and lipolysis in the adipose tissues. The existence of *PLIN* variations may influence the excess of lipid storage in the adipose tissues as obesity and change the balance of lipid metabolism. Some studies found correlations between the expression of the *PLIN* gene and obesity but the results were inconclusive [7].

Mice with null perilipin showed increased lipolysis and decreased adipocyte fat deposits. They remained skinny even when fed with a high-fat diet [4], [8] but they developed insulin resistance [9], [10]. Therefore, in addition to its role in energy homeostasis, *PLIN* has a role in maintaining adipocyte lipolysis which is essential for metabolic homeostasis [11]. One study comparing perilipin levels in obese patients with metabolic syndrome found perilipin levels were higher in the obese subjects

with metabolic syndrome than non-metabolic syndrome obese patients [12]. Variants in the *PLIN* gene have been identified and examined and were previously associated with obesity and high lipid levels in humans [13], [14], [15], [16], [17], [18] with controversial results.

Indonesia consists of several islands with some diversity in anthropologically, archaeologically, linguistically, and genetically and has two different gene groups. Western of Indonesia is an austronesid genetic pool and eastern of Indonesia is melanesid pool. This study aimed to determine the role of polymorphism in the *PLIN* gene (PLN4 rs 894160, 11482G >A) as a risk factor for metabolic syndrome in the western of Indonesia.

Methods

This research was a case–control study that involved 160 participants consisting of 80 patients with metabolic syndrome and 80 participants as controls, with ages between 25 and 66 years from the western of Indonesian ethnic groups (three generation, that were subject, their father and mother as well as grandparents, living in the western of Indonesia) which has a larger population than the eastern of Indonesia. Patients were categorized as metabolic syndrome if they met 3 out of 5 criteria based on the NCEP ATP-III: obesity with body mass index (BMI) >30 kg/m^2, systolic blood pressure >130 mmHg/diastolic blood pressure >85 mmHg or consume antihypertensive drugs, HDL-C levels <40 mg/dL for men and <50 mg/dL for women, waist circumference >90 cm for men and >85 cm for women, triglyceride levels >150 mg/dL, and blood fasting sugar levels >100 mg/dL or taking diabetic medications. Dislipidemia included hypercholesterolemia if total cholesterol levels >200 mg/dL.

Biochemical analysis

After 8 h of fasting, subjects' blood samples were taken and collected in ethylenediaminetetraacetic acid test tubes. Then, plasma and buffy coat were separated. Plasma was used to determine the lipid profile and fasting blood glucose levels and analyzed enzymatically with an automated analyzer (Cobas c111R analyzer with the protocol of Glucose HK, HDL-C Gen4, Triglycerides, Cholesterol Gen2 from Roche DiagnosticR, Germany). Buffy coat was used for DNA extraction using the FavorPrep™ blood genomic DNA extraction mini Kit (Favorgen) with standard protocol and stored at -20°C.

Genotyping analysis

Perilipin genotype was analyzed with polymerase chain reaction (PCR)-restriction fragment length polymorphism. The primers were F-CTGTTTGT GG GGC TCCCTCG, R-CCTCCCAGATCTTTTAAGAG. The PCR conditions were as follows: initial denaturation of 94°C for 5 min, followed by 35 cycles of denaturation of 94°C for 1 minute, annealing 52°C for 1 min, elongation at 72°C for 1 min, and the final elongation at 72°C for 10 min. The PCR product 126 bp was then digested by XhoI endonuclease enzyme with the result of 100+ 26 bp for AA genotype, 126, 100 and 26 bp for GA genotype and 126 bp for GG genotype [19]. Digested products were electrophoresed with 2% agarose gel with florosafe as contrast.

The study was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada-Dr. Sardjito General Hospital, Yogyakarta with number KE/FK/0944/EC 13 Agustus 2019. All participants in this study signed an informed consent form.

Statistical analysis

Data were analyzed with SPSS 17 (IBM Corp., Chicago, Illinois, India). Differences in subjects' characteristics in the metabolic syndrome and control groups were compared with independent T-tests if data had normal distribution and were expressed as mean ± standard deviation and Mann–Whitney tests if not normally distributed with median (min-max) and 95% confidence interval. The frequencies of the genotypes in the two groups were compared with bivariate analysis then continued with multivariate regression analysis to know the role of the genotype as a risk factor for components of metabolic syndrome. $p < 0.05$ was considered significant.

Results

This study included metabolic syndrome and control groups consisting of 80 participants in each group. Analysis of the subjects' characteristics (Table 1) showed that there were significant differences statistically in BMI, waist circumference, blood pressure, and lipid profile in the metabolic syndrome group compared to the controls.

The bivariate analysis found that there were no differences statistically between metabolic syndrome and control groups in the genotyping frequency of PLIN 4 11482 G>A, neither in the additive model (Table 2).

In the comparison of the metabolic syndrome components with PLIN4 11482 G>A genotypes using multivariate regression analysis, carriers of the AA PLIN 4 genotype had 2 times higher risk of metabolic syndrome, almost 9 times higher risk for obesity and 3 times higher risk for hypercholesterolemia than the GG genotype or GG + GA genotype (Table 3).

Table 1: Baseline subject characteristics of metabolic syndrome and control groups

Characteristic	Met-S (n = 80)	Control (n = 80)	p
Age (years)	46.22 ± 12.88	46.69 ± 12.34	0.799[a]
Sex (male/female) (*n*)	33/47	47/33	0.747[c]
BMI (kg/m^2)	29.40 ± 4.63	22.15 ± 3.21	<0.001[a]
Obese (n)	57	17	<0.001[c]
Waist circumference (cm)	93.00 (77.00–126.00)	81.61 (62.00–104.00)	<0.001[b]
Systolic blood pressure (mmHg)	130.00 (100.00–190.00)	115.00 (90.00–155.00)	<0.001[b]
Diastolic blood pressure (mmHg)	85.00 (60.00–145.00)	75.00 (60.00–95.00)	<0.001[b]
Plasma fasting glucose (mg/dL)	73.10 (44.05–227.60)	73.60 (43.20–171.00)	0.213[b]
Plasma fasting HDL (mg/dL)	37.02 ± 6.79	44.00 ± 9.68	<0.001[a]
Plasma fasting triglyceride (mg/dL)	191.53 ± 94.09	102.40 ± 94.09	<0.001[a]
Total cholesterol (mg/dL)	185.00 (88.00–380.00)	160.00 (95.00–250.00)	<0.001[b]
Hypercholesterolemia (*n*)	21	8	0.008[c]

[a]Independent *t*-test, [b]Mann–Whitney test, [c]Pearson Chi-squared, p significant < 0.05. BMI: Body mass index, HDL: High-density lipoprotein, Met-S: Metabolic syndrome.

Discussion

The results of our study showed that there was 2 times greater risk of developing metabolic syndrome in carriers of AA genotype of PLIN4 11492 G>A than other genotypes. Patients with the genotype of AA PLIN4 11492 G>A had 9 times greater risk to become obese and develop hypercholesterolemia. In this study, the AA genotype was not correlated with the level of triglycerides, low-density lipoprotein-cholesterol and HDL-C and the genotype was not different among genders. The genotype also was neither correlated with blood pressure nor glucose level.

Table 2: Bivariate analysis of the association of genetic variance of perilipin 4 gene 11482 G > A with metabolic syndrome

Genotype	Met-S	Control	P	OR	95% CI
AA	35	29	0.828	1.092	0.495–2.411
AG	24	32	0.351	0.679	0.300–1.534
GG	21	19	Ref		
AA	35	29	0.333	1.368	0.725–2.580
AG + GG	45	51	Ref		
AA + AG	59	61	0.715	0.875	0.428–1.791
GG	21	19	Ref		

Met-S: Metabolic syndrome, OR: Odds ratio, CI: Confident interval, Ref: Reference genotype.

Other research found that similar results indicating the polymorphism of PLIN 4 11452 G > A were a risk factor for metabolic syndrome in obese children and adolescent [20], and correlated with higher BMI, waist circumference and triglyceride level in middle-aged Japanese men [21]. The same results were also reported by Qi *et al*. in multiethnic Asian population in Singapore, especially Indian and Malays ethnics [16]. In addition, gender differences were correlated with the genetic mutation effect as an indicator of obesity, which is also different from other study [15]. This same result was not found in the study in French Caucasian men and women, children, and adolescence in Turkey and Carribean Hispanic population [19], [22], [23].

Table 3: Multivariate analysis of the association of genetic variance of perilipin 4 gene 11482 G > A with metabolic syndrome

rs894160	Logistic regression model			
	B	SE	p	Adjusted OR (95% CI)
Genotype				
AA	0.459	0.429	0.351	1.583 (0.603–4.154)
GA	−0.539	0.506	0.241	0.553 (0.205–1.490)
GG	Ref			
Obesity	2.281	0.392	<0.001	9.791 (4.542–21.107)
Hypercholesterolemia	1.128	0.535	0.035	3.088 (1.082–8.816)
AA	0.804	0.399	0.044	2.234 (1.021–4.888)
GG + GA	Ref			
Obesity	2.242	0.386	<0.001	9.416 (4.419–20.064)
Hypercholesterolemia	1.133	0.529	0.032	3.104 (1.100–8.761)
AA + GA	NS			
GG	Ref			

Hosmer and Lemeshow test were performed for analyzed good fitness for both models. *P* value for all model was>0.05. B = Logistic regression model coefficient. Stepwise logistic regression model was performed by inserting obesity (BMI>30) and hypercholesterolemia (total cholesterol>200 mg/dL). NS: Non-significant, SE: Standard error, OR: Odds ratio with 95% CI, CI: Confident interval, Ref: Reference genotype, BMI: Body mass index.

One study in a Spanish population showed women's adipose tissue with homozygous of A11482 allele showed lower risk of obesity and lower levels of perilipin. In addition, the 11482G > A polymorphism also demonstrated significant relationships with fasting glucose and triglyceride levels [15]. The single nucleotide polymorphism was also investigated in a multiethnic population living in Singapore consisting of Chinese, Malay, and Indian Asian ethnics [16] and appeared to have a disequilibrium structure of the intragenic PLIN locus that differs with Caucasian populations compared to the Asian populations. In Caucasians, the 11482G >A polymorphism is associated with negative disequilibrium with 13041A > G and 14995A > T [19]. In Singapore with some ethnic populations, which included Chinese, Malay, and Indian, the results were reversed with the 11482G>A polymorphism having negative disequilibrium linkage with polymorphisms of 6209T > C and positive linkage disequilibrium with 13041A > G and 14995A > T polymorphisms [16]. The different results showed that the A allele, which was associated with a lower risk for obesity in the Caucasian population, was associated with an increased risk of obesity in the Asian population. However, the relationship was significant only in Asian and Malay populations, but not in the Chinese population [16] in line with our study.

In the Korean population, Jang *et al*. studied women who were given a low-calorie diet (−300 kcal per day) and found that the presence of A11482 allele was associated with greater weight loss in response to calorie restriction and the weight loss occurred especially in the visceral fat compartment [18]. Carriers of A allele in 11482G > A polymorphisms have been found to be resistant to weight loss with calorie restriction and treatment with rosiglitazone as a peroxisome agonist receptor-γ [24]. Therefore, a person who is overweight and obese carriers of the A allele may not show any beneficial effect with a dietary approach to weight loss, and another alternative approach is required, such as an anaerobic exercise program [17].

Pathogenesis of perilipin 11482 G>C gene variation increases the risk of metabolic syndrome possibly due to mutation of this gene causes the disruption of phosphorylation perilipin resulting the lipolysis by HSL to be abnormal. This disorders causes fat deposits to increase. Increasing the deposit of fat will increase very low-density lipoprotein production and lipid profile, especially cholesterol in the blood.

Different results in some populations with

the polymorphism effects to the phenotype may be due to differences in lifestyle and diet that affect the clinical markers. In addition, metabolic syndrome caused by obesity is a complex interaction between the environment and the genes. The variations of the intronic gene although it does not express directly to the protein but the variation will affect the stability of the expression and influence the incidence of obesity and cause changes in lipid metabolism in adipose tissues which present as risks of metabolic syndrome. The limitation of this study may be the number of samples is too small, but with the calculation, number of samples in this study is already above the minimum number of samples required.

Conclusion

This research concluded that the variation of Perilipin 4 11482G > A gene is a risk factor for metabolic syndrome primarily because of the susceptibility of obesity and dyslipidemia.

Acknowledgments

We would like to thank to directorate general of universities through the basic research of universities which funded this research no. 2760/UN1.DITLIT/DIT-LIT/PT/2020.

Disclosure Statement

This work has been approved by all of the contributing authors, has not been published previously, and has not been submitted elsewhere for consideration of publication. The authors declare that they have no competing interests.

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