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The association between variant rs9939609 in the FTO gene with free leptin index and the risk of obesity in the Indonesian children population

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Abstract

Background: Several studies have reported that fat mass and obesity-associated gene (FTO), especially the *rs9939609* polymorphism, are associated with obesity and high leptin levels. The free leptin index (FLI) is known to be accurate in determining the function of leptin. The aim of this study was to determine the association between the *rs9939609* variant in the FTO gene and FLI and the risk of obesity among children living in Medan, Indonesia.

Methods: This case–control study included 212 children aged 6–12 years who were genotyped for variants of the *rs9939609* FTO gene. The case group consisted of children with obesity who were < 6 years old, and the control group had a normal body mass index and came from the Bataknese or Chinese ethnicities. Anthropometric measurements were performed. Serum leptin and soluble leptin receptor (sOB-R) levels were measured. Odds ratio and 95% confidence intervals were calculated to determine the risk of having obesity associated with the risk allele.

Results: In this study, there was no significant association between leptin, soluble leptin receptor, or free leptin index and the *rs9939609* FTO gene; however, the risk allele (A) of FTO rs9939609 had a significant association with obesity in Chinese ethnicity subjects ($p < 0.05$). The *AA/AT* genotype had an increased risk of FLI 5.889 times compared to the *TT* genotype. Multivariate analysis showed that the *rs9939609* polymorphism in the FTO gene played a role in obesity through the FLI.

Conclusion: It was concluded that the *rs9939609* polymorphism played a significant role in obesity through FLI. Further studies are still needed.

Keywords: Polymorphism, *rs9939609*, Obesity, FLI, FTO

Background

Childhood obesity has been alarmingly growing, and it is the most common nutritional problem among children in developed and developing countries. It is related to substantial morbidity and mortality, which includes cardiovascular, respiratory, gastrointestinal, endocrine, and psychosocial morbidities. [1] Along with the consistent increase in the prevalence, the morbidity and mortality resulting from the condition should be considered. Among the many factors that contribute to the increasing prevalence of childhood obesity are environmental and genetic factors. [2]

Some genes, such as the fat-mass and obesity-associated gene (FTO), are strongly related to obesity and overweight. FTO acts as a gene that has been recently studied and identified to be associated with obesity. Some of

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these gene polymorphisms are associated with obesity and metabolic disorders. [3, 4] The FTO gene role to date has not been fully understood, nor do the variants of this gene act as the most critical genetic determinants for body weight and obesity. [5] The FTO gene was found to be a highly polymorphic gene with more than 1500 single-nucleotide polymorphisms (SNPs).[6] *rs9939609* is known to be the most frequent polymorphism associated with the obesity phenotype. [3]

Leptin regulates energy balance and food intake through different pathways in the central and nervous systems. [7] Soluble leptin receptor (SOB-R) levels give an idea of free leptin levels and free leptin index (FLI), which is the ratio between leptin and sOB-R. This free leptin index is known to be accurate in determining the function of leptin. [8]

This study aimed to determine the association between the *rs9939609* polymorphism of the FTO gene and the free leptin index and the risks of obesity in children. This study conducted the first FTO research focusing on children with obesity in Indonesia.

Methods

This is an observational analytic study using a case–control design. The minimum sample size for this study was estimated using the formula of two group proportion, with an α at 0.05, power of 80%, p1 0.42, and p2 0.58. The final minimum sample size was 80 cases for each group. The case subjects of this study need to meet the inclusion criteria, including children aged 6–12 years old with body mass index (BMI) > 95th percentile according to the Center for Disease (CDC) 2000 BMI curve, who were obese since < 6 years old and came from Bataknese or Chinese ethnicities. Meanwhile, the control subjects' inclusion criteria consisted of children with BMI 3–85th percentile according to the CDC 2000 BMI curve and came from a similar population to the case subjects. The research was conducted at ten elementary schools in Medan with dominant ethnicities of Bataknese and Chinese.

During the study period, parents or caregivers completed a structured questionnaire to obtain information about age at onset of obesity, family history of obesity, and sedentary lifestyle. All participants provided informed consent before the data were collected.

Measurements of body weight, height, and waist circumference were also performed. Weighing scales used the SECA brand scale (sensitivity 0.1 kg) to measure the child's weight (kg); height was measured by the SECA brand standing height meter (sensitivity 0.1 cm), while an elastic measuring tape (cm) was used to measure waist circumference. The CDC 2000 BMI curve, ages 2–20 years, was used to determine the child's nutritional status. Waist circumference was measured in a standing position by attaching an anthropometric tape to the waist, passing through a point on the side of the body, between the 12th costae and the upper end of pelvis, and one centimeter below the navel.

Blood samples were collected by Prodia laboratory personnel under the provision of researchers. Leptin and sOB-R levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit based on the manufacturer's instructions and standard guidelines. The free leptin index is the ratio between leptin and sOB-R levels.

For the genetic studies, a whole blood sample was collected from each child and mixed with ethylenediaminetetraacetic acid (EDTA). A TaqMan assay for the *rs9939609* polymorphism (Assay ID C_25638153_10; Applied Biosystems, Foster City, CA) was used to perform genotyping. Real-time PCR was performed in 25-µl reactions, which consisted of 12.5 µl of TaqMan Genotyping Master Mix, 1.25 µl of TaqMan genotyping assay mix (20X) that includes the primer and probe, 11.25 µl of DNase-free, RNase-free water, and approximately 20 ng of template deoxyribonucleic acid (DNA) in 5 µl. Thermal cycling was performed on a Biorad CFX96 (Biorad, Munchen, Germany). This method was performed at a temperature of 95 °C for 10 min and 40 cycles of 95 °C for 15 s and 60 °C for 90 s. CFX96TM Real-Time PCR software (Bio-Rad, Munich, Germany) was used to conduct the allelic discrimination method for SNP genotyping. Three selected genotypes, *AA*, *AT*, and *TT*, were regenotyped using *oligonucleotides 5'-AAGAGATGATCTCAA ATCTACTTTATFAFFATA-3'* (forward) and *5'-AGGATA GTTTCGATCTATTGACCTC-3'* (reverse) (IDT DNA, Singapore) through sequencing by Sanger's dideoxy chain termination reaction using Big-Dye Terminator v.1.1 Cycle Sequencing Kit and the ABI 3500 sequencer (Applied Biosystems, Foster City, USA).

Univariate analysis was performed to explain the characteristics of each studied variable. Normally distributed data were analyzed using the chi-square test and are presented as the mean ± SD. Data are presented in tables and diagrams. The association between the *rs9939609* polymorphism in the FTO gene and leptin levels, soluble leptin receptor, and free leptin index was assessed using one-way ANOVA. The odds ratio (OR) between the *rs9939609* polymorphism in the FTO gene and the free leptin index was determined using multiple logistic regression tests. Multivariate analysis was conducted to evaluate and confirm the hypotheses and control for confounding variables. The backward LR method of multiple logistic regression analysis was used. Statistical significance in this study was obtained when the *p*-value was less than 0.05.

Results

A total of 212 children were included in this study, divided into 105 subjects in the case group and 107 subjects in the control group. Table 1 shows that more than 50% of Bataknese subjects in the case and control groups had the *TT* allele, as did Chinese subjects. The TT allele was found in the majority of male and female subjects in both groups, with 64.1% in the case group and 36.4% in the control group for males, and 63.2% in the case group and 51.2% in the control group for females. In the case group, 66.7% of the *TT* allele group had a family history of obesity, followed by 31.9% in the *AT* allele group and 1.4% in the *AA* allele group. Finding in the control group was also similar, with 53.9% in the *TT* allele group, 34.6% in *AT* allele group, and 11.5% in *AT allele* group. There was a significant difference in age between *AA*, *AT*, and *TT* in the control group, while family history of obesity exhibited significance in the case group with a *p*-value of < 0.05. Children in the Chinese ethnic group had a significant difference between *AA*, *AT*, and *TT* both in the case group and control group, with a *p*-value < 0.05.

Table 2 reports no significant association between leptin, soluble leptin receptor, and free leptin index with the *rs9939609* FTO gene in all alleles because the *p* values were 0.559, 0.091 and 0.464, respectively.

Table 1 Genotype Differences of rs9939609 based on Subject Characteristics

	Case			*p*	Control			*p*
	AA	**AT**	**TT**		**AA**	**AT**	**TT**	
Age (Years)	9,8 ± 1,6	9,9 ± 1,4	9,9 ± 1,5	0,998	7,9 ± 1,6	9,5 ± 1,7	9,1 ± 1,5	0,037[a]*
Sex (N%)								
Male	5 (7,5)	19 (28,4)	43 (64,1)	0,531	5 (4,7)	19 (18,7)	40 (36,4)	0,428
Female	1 (2,6)	13 (28,4)	24 (63,2)		18 (41,9)	18 (41,9)	22(51,2)	
Ethnicities								
Bataknese	6 (10,7)	22 (39,3)	28 (50)	0,19	3 (4,9)	24 (39,3)	34 (55,7)	0.48
Chinese	0 (0)	10 (20,4)	39 (79,6)	0,001*	5 (10,9)	13 (28,3)	28 (60,9)	0,028*
Waist circumference (cm)	78,0 ± 8,8	75,0 ± 7,1	76,9 ± 9,6	0,580	57,0 ± 4,1	59,5 ± 8,8	56,7 ± 5,9	0,167[a]
Family history of obesity								
Yes	1 (1,4)	23 (31,9)	48 (66,7)	0,019*	3 (11,5)	9 (34,6)	14 (53,9)	0,651
No	5 (15,1)	9 (27,3)	19 (57,6)		5 (6,2)	28 (34,5)	48 (59,3)	
Sedentary life style								
< 5 h	0 (0,0)	6 (26,2)	7 (53,8)		3 (8,1)	14 (37,8)	20 (54,1)	0,581
5–10 h	2 (18,2)	5 (45,5)	4 (36,3)	0,273	4 (8,9)	16 (35,5)	25 (55,6)	
11–14 h	0 (0,0)	3 (30)	7 (70,0)		1 (7,1)	4 (28,6)	9 (64,3)	
15–20 h	3 (8,8)	8 (23,5)	23 (67,6)		0 (0,0)	0 (0,0)	6 (100,0)	
> 20 h	1 (2, 7)	10 (27,0)	26 (70,3)		0 (0,0)	3 (60,0)	2 (40,0)	

[a]One way Anova test

*Represents significance at $p < 0.05$

Table 2 Association between Leptin, Soluble Leptin Receptor and Free Leptin Index with Polymorphism *rs9939609* (FTO Gene)

	rs9939609	**n**	**Mean ± SD**	**95% Confidence interval**	***p***
Leptin	AA	14	8750.90 ± 7163.38	4614.89–12,886.92	0.559
	AT	69	12,315.07 ± 10,369.39	9824.07–14,806.07	
	TT	129	12,003.49 ± 12,263.18	9867,09–14,139,89	
sOB-R	AA	14	31.86 ± 8.07	27.21–36.52	0.091
	AT	69	30.09 ± 8.09	28.15–32.04	
	TT	129	33.15–9.99	31.41–34.89	
FLI	AA	14	302.53 ± 274.79	143.87–461.19	0.464
	AT	69	481.68 ± 464.64	370.07–593.30	
	TT	129	456.75 ± 524.65	365.35 ± 548.16	

We generated a receiver operating characteristic (ROC) curve to determine the value of the leptin, sOB-R, and FLI cutoff points. The results were 8.63, 30.75, and 0.28 for leptin, soluble leptin receptor, and free leptin index, respectively. The odds ratio between genetic variation and leptin, sOB-R, and FLI in the ethnic groups is shown in Table 3. Subjects in the control group who had the *AT/AA* genotype had a 3.69 times risk of rising leptin, a 2.29 times increased risk of having high sOB-R, and a 5.889 times increased risk of having a high FLI. It has been shown that the case group had a lower risk than the control group in all analyses.

Multivariate analysis was performed to determine and control the confounding factors in this study, as shown in Table 4. It is observed that the 15–20 h and > 20 h sedentary lifestyle had a significant effect on the occurrence of obesity with *p*-value < 0.05 and had a risk of 17.17 and 18.11 times for the occurrence of obesity. This multivariate analysis also showed that the *rs9939609* polymorphism in the FTO gene played a significant role in obesity by influencing FLI.

Table 4 Effect of FLI, Polymorphism of rs9939609 FTO Genes and A Confounding Factor on Obesity

	p	OR	95% Confidence interval	
Sedentary life style			Lower limit	Upper Limit
< 5 h	0.000			
6 – 10 h	0.725	0.81	0.26	2.58
11 – 14 h	0.10	3.28	0.81	13.33
15 – 20 h	0.000*	17.17	4.3	69.06
> 20 h	0.000*	18.11	27.21–36.52	0.091
FLI > 0.28	0.000*	28.87	4.35	75.31
Constant	0.000	0.058	11.46	72.76

The backward LR method of multiple logistic regression analysis

*Represents significance at $p < 0.05$

Discussion

The FTO gene has been identified and associated with obesity by genome-wide association studies (GWAS), and several polymorphisms of this gene were associated with obesity or obesity phenotypes, such as high BMI. Subsequent studies also found that children who had the FTO risk allele had an increase in energy intake. This gene was relatively frequent (it was estimated that 16% of the population had one allele variant). The presence of this gene was associated with an average increase of 1.5 kg of body weight. [9]

The FTO gene's most critical genetic polymorphism is *rs9939609*, and it is known that this polymorphism is associated with BMI and predisposition to obesity in childhood and adulthood. [10] Children and adults who held at least one risk allele of *rs9939609* in the FTO gene (homozygous = *AA* and heterozygous = *AT*) had a more significant energy intake than the wild-type allele (*TT*). [11]

In this study, we found a significant difference between Chinese ethnicity and the *rs9939609* FTO gene. Along with our study, a study in Malaysia also reported a significant association between Chinese ethnicity and the *rs9939609* FTO gene in children with obesity. [12] A study conducted in Singapore found an association between the FTO gene variant and obesity in Chinese and Malay ethnicities living in Singapore. [13] A study in Beijing reported an association between the *rs9939609* FTO gene and BMI and the risk of obesity in children and

Table 3 Odds Ratio Between Genetic Variation with Leptin, sOB-R, and FLI in Ethnic Groups

	Case groups		Genotype		OR	95% confidence interval	
			AT/AA	TT		Lower limit	Upper limit
Leptin	Case	Leptin ≤ 8,63 ng/mL	9	6	0,83	0,27	2,54
		Leptin > 8,63 ng/mL	58	32			
	Control	Leptin ≤ 8,63 ng/mL	57	34	3,69	1,18	11,52
		Leptin > 8,63 ng/mL	5	11			
sOB-R	Case	sOB-R > 30,75 ng/mL	19	13	0,76	0,32	1,79
		sOB-R ≤ 30,75 ng/mL	48	25			
	Control	sOB-R > 30,75 ng/mL	47	26	2,29	1,00	5,25
		sOB-R ≤ 30,75 ng/mL	15	19			
FLI	Case	FLI ≤ 0,28	10	5	1,16	0,36	3,68
		FLI > 0,28	57	33			
	Control	FLI ≤ 0,28	58	32	5,889	1,77	19,57
		FLI > 0,28	4	13			

Multiple logistic regression test

adolescents. [14] Another study conducted on Han children aged 7–18 years also showed that the genetic variation *rs9939609* was associated with obesity and dietary choices in children and adolescents in China. [15] We were only able to compare the Chinese ethnicities in this study with Chinese in Malaysia or in China, and we found that the frequency of polymorphism *rs9939609* of the FTO gene in our research was almost similar to that in the Chinese ethnic groups in these countries.

We obtained different results in Bataknese patients, and there was no significant difference between the Bataknese and *rs9939609* FTO genes. The possible explanation for this different result is that obesity is a condition with multifactorial and heterogeneous causes that can occur due to the interrelated interactions between gene factors and the environment such as diet, physical activity patterns, the interaction between gene factors and genes, and the interaction between genetic factors and the environment. These interactions make it difficult to explain the specific relationship between genetic variants and obesity. In addition, the FTO gene was involved in the pathophysiology of obesity and played a role in controlling food intake and energy output. [16] The FTO gene is also known to be part of the neuroregulation (leptin) pathway of energy metabolism in adipose tissue, and barriers to leptin signaling can inhibit downstream changes in adipose tissue that stimulate FTO expression; thus, it was thought that there was a relationship between the leptin signaling pathway and FTO [17]

Our study demonstrated that children in the control group who had the *AA/AT* genotype had an increased risk of high leptin of 3.69 times and high FLI 5.889 times compared to children with the *TT* genotype. However, we found no significant association between the FTO gene and leptin, sOB-R or FLI. Several studies have identified an association between the *rs9939609* FTO gene polymorphism and leptin and leptin receptors. Studies from Austria and Spain reported a similar result to our study, which found no significant association between the *rs9939609* FTO gene and leptin in children and adults with obesity and normal weight. [18, 19] A study in Poland showed an association between waist circumference and higher FTO expression. [20]

Meanwhile, another study identified an association between the *rs9939609* FTO gene and a high level of leptin, and this single-nucleotide polymorphism role was thought to trigger leptin resistance and induce dysregulation of food intake and energy output, resulting in obesity. [21] A study in Denmark also reported an association between the *rs9939609* polymorphism in the FTO gene and an increase in serum leptin levels, which was thought to occur due to an increase in adipocytes. [22] A study conducted in Pakistan reported that the *rs9939609* FTO gene polymorphism was associated with leptin and leptin receptors in adult women (aged > 18 years) but not in children. [23] A study in Iran showed that the homozygous risk allele (A) for FTO *rs0039609* had higher serum leptin ($p = 0{,}005$; F: 5,131), and there were no significant differences between the *TT* and *AT* genotypes. [24]

Our multivariate analysis found a significant association between the *rs9939609* polymorphism in the FTO gene and obesity through FLI. Unfortunately, we were unable to compare our study results with those of previous studies because no study reported an association between the rs9939609 polymorphism in the FTO gene and the FLI.

One study demonstrated that sedentary behavior of > 22 h a week acted as a vital risk factor for overweight and obesity. [25] In this study, we also looked for an association between sedentary lifestyle, such as the number of times children spent sitting in activities, excluding time spent in school, and the incidence of obesity in children. This study obtained results that were similar to those in previous studies, i.e., we found that the majority of children with obesity had a sedentary lifestyle of > 20 h per week compared to the control group. Additionally, FLI > 0.28 was significantly associated with the weekly duration of sedentary habits in subjects. It is essential to prevent obesity in children by increasing physical activity and limiting their sedentary activities.

The strength of this study is that there has not been a similar previously conducted study in Indonesia. This study is the first to evaluate the association between the *rs9939609* polymorphism in the FTO gene and the free leptin index in children in Indonesia. This study obtained a significant difference between the *rs9939609* polymorphism and the occurrence of obesity in the Chinese ethnic group in Medan, Sumatera Utara, Indonesia.

This study has limitations. We only examined one polymorphism of the FTO gene, *rs9939609*, because based on the literature, *rs9939609* was the most frequent polymorphism associated with the obesity phenotype; therefore, in this study, we chose the *rs9939609* polymorphism to determine whether it has an association with obesity in children in Medan. From the literature, it is known that several other FTO gene variants have been reported to be associated with obesity, namely, *rs1421085, rs8050136, rs17817449*, and *rs1121980*; thus, further research is recommended to determine the role of other FTO gene polymorphisms in the incidence of obesity in children in Indonesia.

Conclusion

Our study provided evidence that the *rs9939609* polymorphism played a significant role in obesity indirectly through FLI. Nevertheless, further studies and analyses

are needed. The results of this study are expected to improve public health services in preventing obesity and providing education to children and parents to change their lifestyles, especially children who have a risk allele for the tendency to have obesity in the future.

Abbreviations
BMI: Body mass index; CDC: Center for disease control; DNA: Deoxyribonucleic acid; EDTA: Ethylene diamine tetraacetic acid; FLI: Free leptin index; FTO: Fat mass and obesity associated gene; GWAS: Genome wide association study; ROC: Receiver operating characteristic; SNP: Single nucleotide polymorphism; sOB-R: Soluble leptin receptor.

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Author contributions
Research idea and study design: SML, MF, and JRB; data acquisition: SML, MF; data analysis/interpretation: SMF; supervision or mentorship: JRB; primary responsibility to drafting the paper: SML All authors contributed important intellectual content during manuscript drafts or revisions, accepted personal accountability, reviewed the document submitted for the review, and agreed to ensure that questions on the accuracy of the work were appropriately assessed and explored. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by The Ethics Committee of The Medical School, Universitas Sumatera Utara, Medan, Indonesia, and informed consent was received from participants and legal guardians at the time of participation.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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