Association of *FTO* rs1421085 Single Nucleotide Polymorphism With Fat and Fatty Acid Intake in Indonesian Adults

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Research note

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Abstract

Objective

Recent studies showed that genetic polymorphisms in the fat mass and obesity-associated gene (*FTO*) were associated with obesity and dietary intake. In this study of 71 adults in Jakarta, Indonesia, we investigated *FTO* rs1421085 association with body mass index (BMI), macronutrient intake, and fatty acid intake. We genotyped *FTO* rs1421085 using amplification-refractory mutation system polymerase chain reaction (ARMS PCR). The association was evaluated using linear regression analyses assuming co-dominant, dominant, recessive, over-dominant, and additive genetic models.

Results

Only individuals with CC genotype had a considerably higher BMI (p<0.001), which indicates a recessive genetic trait, but the incidence for this genotype is low (68 TT+TC vs. 3 CC). Individuals with the minor C allele had an estimated increase of fat intake by 3.45%—4.06% across various genetic models (dominant: p<0.010, over-dominant: p<0.030, additive: p<0.010). Subjects with TC/CC genotypes had increased dietary monounsaturated fatty acid (MUFA; 1.14%, p = 0.046) and saturated fatty acid (SAFA; 2.06%, p = 0.023) intakes, compared to those with the TT genotype. In conclusion, our study provided evidence for the association between *FTO* rs1421085 risk allele with higher BMI and individual preferences for consuming more fat, MUFA, and SAFA.

Introduction

WHO reported that 13% of the global population of adults were obese in 2016 [1], and it is projected that 1 in 5 adults will be obese in 2025 [2]. The etiology of obesity is attributed to a complex interaction between overnutrition, sedentariness, and genetic factors [3]. Obesity incidence have increased significantly in Indonesia between 2007 (10.5%) and 2018 (21.8%) [4, 5]. There is a growing interest in the genetic predisposition of obesity in Indonesia, since mortality due to obesity comorbidities have risen to the nation's top [6, 7].

As a common risk factor, the fat mass and obesity-associated (*FTO*) association with obesity is well-documented, particularly in Caucasian populations, albeit the overall risk is modest [8–12]. Single nucleotide polymorphism (SNPs) in the *FTO* gene were associated with other obesity traits (e.g., body weight, leptin levels, body fat, waist circumference) [8–14]. East and South Asian populations showed comparable associations for common *FTO* variants (notably rs9939609, rs1558902, and rs1421085) [13–18], but the effect size may vary depending on ethnicity and dietary intake [19, 20]. Concurrent associations between *FTO* variants, obesity, and dietary intake have been noted in several ethnic groups [19–22], including our previous report that *FTO* rs9939609 TT genotype was associated with obesity and preference for a high-fat diet in adult individuals from Jakarta [23].

Overexpression of the *FTO* gene in the hypothalamus can regulate energy balance and appetite [3]. *FTO* rs9939609 is associated with elevated intake of polyunsaturated fatty acid (PUFA) and saturated fatty acid (SAFA), as well as with obesity, in children and adolescents in a Spanish population [24]. We expect that a similar influence can be observed for *FTO* rs1421085 – an intronic T→C mutation that has high linkage disequilibrium with *FTO* rs9939609 [23]. Several studies showed that *FTO* rs1421085 is associated with both obese-related phenotypes and dietary macronutrient intake [13, 14, 25]. *In vivo* and *in vitro* model studies showed that *FTO* rs1421085 can alter the binding of transcriptional repressors in nearby regions, affecting the expression of genes linked to adipocyte thermogenesis and food intake [26, 27].

Understanding the interaction between diet and *FTO* variants in Indonesia may provide invaluable insights for the management of obesity in the country, given that Indonesian cuisine is naturally fatty, owing to generous use of coconut milk and palm oil [28–30]. Dietary fat and SAFA intake in Indonesia was among the highest of countries across the globe (31.9% and 20.9%, respectively) [31].

As a continuation of our previous study [23], we performed genotyping for *FTO* rs1421085 and analyzed its association with obesity and dietary intake. We hypothesize that individuals with the minor risk allele have higher Body Mass Index (BMI), higher fat intake, and distinct fatty acid intake profile (PUFA, monounsaturated fatty acid/MUFA, and SAFA). Our findings provided valuable insights into the influence of the *FTO* rs1421085 risk allele on BMI and individual preferences for consuming more fat, particularly MUFA and SAFA.

Methods

Study design and subjects

We performed a follow-up case-control genetic association study of *FTO* rs1421085 on a study population from Daerah Khusus Ibukota (DKI) Jakarta, Indonesia. Study enrollment and collection of informed consent were done as described previously by Daya *et al.* (2019) [23]. Ethical approval for this study was obtained from the Medical Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia (No.1137/UN2/F1/ETIK/2017, protocol number 17-12-1212). Age, gender, and residence data were collected at enrollment. BMI was calculated as body weight (kg) per squared height (m^2). We used the International Obesity Task Force (IOTF) definitions for Asian obesity (BMI ≥ 25 kg/m²) and non-obesity (BMI < 23 kg/m²) [32]. Dietary data were obtained with questionnaires and dietary calculations were done using NutriSurvey 2007 as previously described [23, 33].

Genotyping

Archived DNA samples from our previous study [23] were assessed for quantity and purity using a Nanodrop-1000 (Perkin Elmer Biosystem, USA). *FTO* rs1421085 was genotyped with amplification-refractory mutation system polymerase chain reaction (ARMS PCR) using primer sets and PCR cycles described in Priliani *et al.* [34] in a GeneAmp PCR System 9700 (Applied Biosystems, USA). PCR products were separated on 2% agarose gel electrophoresis (Lonza, Basel, Switzerland) and visualized using the Gel Doc XR Imaging System (BioRad, USA). The primer sequences are in Additional File 1: Table S1.

Statistical analysis

We used R version 4.0.3 for all statistical tests. Data distribution normality was assessed using the Shapiro-Wilk test. Differences in anthropometric values and dietary intake between obese and non-obese participants were calculated using the unpaired t-test for normally distributed variables and Mann–Whitney U test for non-normal variables. The R package "genetics" was used to calculate allele and genotype frequencies and perform Hardy–Weinberg equilibrium test. Association analyses were carried out using either a linear regression analysis for the normally distributed variables ("stats" package) or a rank-based linear regression analysis for non-normal variables ("Rfit" package), adjusted for age and sex (formula: outcome ~ SNP + age + sex). We assessed the following genetic models: co-dominant (factorial variables: TT = 0, TC = 1, and CC = 2), dominant (TT = 0, TC + TT = 1), recessive (TT + TC = 0, CC = 1), over-dominant (TT + CC = 0, TC = 1), and additive (continuous variables: TT = 0, TC = 1, and CC = 2). Upper and lower intervals were calculated at 95% confidence levels with no adjustments for multiple comparisons. The value of $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Available archived DNA samples consisted of 36 non-obese and 35 obese individuals, aged 19–52 years. The proportion of females was higher than males (51 female, 29 male). The difference in gender proportions between the non-obese and obese group was significant ($\chi^2 = 7.36$, $p = 0.013$). The median BMI for the obese and non-obese groups were 31.86 and 20.86, respectively ($p < 0.001$). Age and dietary parameters are comparable in obese and non-obese samples (all $p > 0.05$, Additional File 1: Table S2).

Genotype and allele distributions

The *FTO* rs1421085 genotype and allele distribution are shown in Table 1. The minor allele frequency (MAF) was 22% in total samples (n = 71), 24% in obese samples (n = 35), and 19% in non-obese samples (n = 36). The genotype distribution did not depart from Hardy–Weinberg equilibrium for total, obese, and non-obese samples (all $p = 1$). The frequency of CC genotype was notably low.

Table 1
FTO rs1421085 genotype and minor allele frequency (MAF), Hardy-Weinberg equilibrium test

	Total, n (%)	Obese, n (%)	Non-obese, n (%)
Genotype	**n = 71**	**n = 35**	**n = 36**
TT	43 (60.6%)	20 (57.1%)	23 (63.9%)
TC	25 (35.2%)	13 (37.1%)	12 (33.3%)
CC	3 (4.2%)	2 (5.7%)	1 (2.8%)
MAF	22%	24%	19%
p-HWE	1	1	1
MAF: minor allele frequency, HWE: Hardy-Weinberg equilibrium			

Associations of FTO rs1421085 with BMI and diet

By evaluating various genetic models, we found several notable associations between *FTO* rs1421085 with BMI, macronutrient intake, and fatty acid intake (Table 2). BMI is greater by 12.58 kg/m^2 ($p = 0.001$) and 12.38 kg/m^2 ($p < 0.001$) in individuals with the CC genotype under the co-dominant and recessive model, respectively. These individuals also reported lower carbohydrate intake. Individuals with CC genotype were lower in carbohydrate intake by 7.84% ($p = 0.029$) and 7.59% ($p = 0.031$) under the co-dominant and recessive model, respectively. This data suggests that *FTO* rs1421085 associations with higher BMI and lower carbohydrate intake might be a recessive trait that showed only in individuals with CC genotype. However, we consider these findings inconclusive since the CC genotype frequency was very low (n = 3).

Table 2
Associations between FTO rs1421085, macronutrient intake, and dietary fatty acids intake in various geneti

Genetic Model	*n*	BMI (kg/m2)			Carb. Intake (%)			Protein Intake (%)			Fat Intake (%)			PUFA Intake (%)		
		Coef.	(95% CI)	*p*	Coef.	(95% CI)	*p*	Coef.	(95% CI)	*p*	Coef.	(95% CI)	*p*	Coef.	(95% CI)	*p*
Co-dominant																
TT	43	Ref.			Ref.			Ref.			Ref.			Ref.		
TC	25	0.47	(-2.66–3.6)	0.766	-0.70	(-3.64–2.25)	0.639	0.27	(-1.18–1.73)	0.709	3.87	(0.69–7.05)	0.018	0.45	(-0.72–1.63)	0.4
CC	3	12.58	(5.15–20.01)	0.001	-7.84	(-14.84 - -0.83)	0.029	0.77	(-2.68–4.22)	0.657	5.63	(-1.92–13.18)	0.141	0.84	(-1.96–3.64)	0.5
Dominant																
TT	43	Ref.			Ref.			Ref.			Ref.			Ref.		
TC + CC	28	0.70	(-2.27–3.67)	0.640	-1.47	(-4.38–1.44)	0.316	0.35	(-0.98–1.68)	0.602	4.06	(1.01–7.11)	**0.010**	0.54	(-0.59–1.67)	0.3
Recessive																
TT + TC	68	Ref.			Ref.			Ref.			Ref.			Ref.		
CC	3	12.38	(5.3–19.46)	< 0.001	-7.59	(-14.47 - -0.71)	0.031	0.70	(-2.7–4.1)	0.681	4.24	(-3.48–11.97)	0.277	0.71	(-1.97–3.39)	0.5
Over-dominant																
TT + CC	46	Ref.			Ref			Ref.			Ref.			Ref.		
TC	25	0.20	(-2.84–3.25)	0.894	-0.20	(-3.2–2.8)	0.895	0.22	(-1.24–1.68)	0.766	3.51	(0.34–6.68)	0.030	0.41	(-0.73–1.54)	0.4
Additive	71	1.17	(-1.38–3.72)	0.363	-1.99	(-4.42–0.45)	0.109	0.32	(-0.84–1.48)	0.586	3.45	(0.86–6.04)	0.010	0.43	(-0.51–1.38)	0.3

BMI, Body Mass Index (kg/m2). Carb., carbohydrate. PUFA, polyunsaturated fatty acid. MUFA, monounsaturated fatty acid. SAFA, saturated fatty acid. Coef., genotype in a particular genetic model. *p*, *p*-values obtained through linear model analyses for normally distributed variables (carbohydrate, fat, and SAFA int variables (BMI, protein, PUFA, and MUFA). CI, confidence interval. All analyses were adjusted for age and sex. Significant associations were marked in bold (*p*

No associations with *FTO* rs1421085 were found for protein intake, but associations with fat intake (%) were significant (Table 2). Individuals with TC genotype showed a slightly higher fat intake by 3.87% ($p = 0.018$) and 3.51% ($p = 0.030$) under the co-dominant and over-dominant models, respectively. The increase was comparable under the dominant (TC + CC: 4.06%, $p = 0.010$) and additive model (3.45%, $p = 0.010$). Given these findings, *FTO* rs1421085 association with higher fat intake appeared as a dominant or an additive trait since it was overall stronger in individuals with the minor risk allele.

There were notable associations with MUFA and SAFA intake (Table 2). The association with MUFA was minor; individuals with TC + CC genotypes intake were projected with 1.14% ($p = 0.046$) higher MUFA intake only in the dominant model, whereas the associations under the co-dominant, over-dominant, and additive models were marginal ($p < 0.100$). The co-dominant model showed that individuals with TC and CC genotype had respectively greater SAFA intake by 1.77% ($p = 0.058$) and 4.49% ($p = 0.043$) when compared to individuals with TT genotype. The dominant (TC + CC: 2.06%, $p = 0.023$) and additive model (1.96%, $p = 0.011$) showed comparable results. This data showed that the association with SAFA is likely a dominant or an additive trait, and it is in line with our analysis of fat macronutrient intake.

Discussion

The rapid increase of obesity incidence and mortality caused by its comorbid conditions have gathered concerns over genetic predispositions to obesity in Indonesia. The association between *FTO* genetic variants with obesity can differ by ethnicity and dietary preference [13, 19, 20, 22, 23]. Here we performed a genetic association study employing various genetic models to assess the impact of *FTO* rs1421085 on obesity and dietary preference in individuals residing in Jakarta, Indonesia. We found that *FTO* rs1421085 is a common mutation in our studied population; and showed evidence that the minor risk allele is associated with BMI, higher intake of dietary fat, MUFA, and SAFA.

The minor allele frequency of *FTO* rs1421085 in our studied population (22%) is lower than our findings in Balinese (41%) [34]. The frequency is only slightly higher than Asian populations (13–14%, excluding South Asians), but lower than South Asian (31%) and European populations (42%) [35, 36]. Our sample size was admittedly small compared to these studies, but the disparity might also be unique to this specific population due to Indonesia's population diversity [37], natural selection, genetic drift, and mutation [38]. A further study is required to confirm the allelic distribution in Jakarta.

We cautiously note that there is an indication of *FTO* rs1421085 association with BMI in our studied population, which agrees with previous studies [13, 14, 34, 39]. However, the frequency of the heterozygous CC genotype in our study is small. A study employing 84 individuals from Tehran has a similar sample

size to ours, and it did not find an association between *FTO* rs1421085 and BMI [20]. Our analysis suggests that the relationship between *FTO* rs1421085 and BMI is expressed as a recessive trait. Given that Asian populations have a low frequency of the risk allele, it is likely that a dataset smaller than a few hundred samples might not be sufficient to assess the association.

As expected, we found that *FTO* rs1421085 was associated with higher dietary fat intake, particularly with SAFA intake, although a minor association with MUFA intake was also observed. This data supports the findings in an adult Caucasian population, in which the risk allele of *FTO* rs1421085 was found associated with perceived hunger, higher intake of high-fat foods, and increased body weight [40]. Our findings are also in line with our previous assessment of the *FTO* rs9939609 risk allele in the same studied population, which showed an association to higher fat intake [23]. It is known that both SNPs have high linkage disequilibrium in our previous study of a Balinese population [29].

Our findings support that *FTO* gene expression is associated with fatty acid intake (MUFA and PUFA) [41]. *FTO* rs1421085 can influence the expressions of several genes linked to food intake and appetite [26, 27], which might explain why we found associations between the risk allele, dietary fat, and SAFA intake under the additive genetic model that imply incremental allelic influence. The direction of causality of these associations is not yet confirmed, but these findings highlight the importance of dietary fatty acids intake in *FTO* gene expression that may subsequently influence body weight.

Conclusions

Our analysis of individuals in Jakarta indicated that the *FTO* rs1421085 TC + CC genotypes were positively associated with BMI, higher dietary fat, MUFA, and SAFA. This study supports the notion of *FTO* gene involvement in food intake regulation.

Limitations

The sample size for this study was limited; so, a follow-up study with larger sample size is required to investigate the true effect of *FTO* rs1421085 and to confirm the interaction between the SNP and dietary intake. Our findings should be viewed with caution since we only sampled 71 individuals in Jakarta. Our dataset also has a skewed gender distribution (the majority samples were female). A more comprehensive collection of anthropometric and clinical data is recommended for future studies to assess other obesity parameters (e.g., waist circumference, leptin levels).

Abbreviations

ARMS-PCR: Amplification-refractory mutation system-polymerase chain reaction; **BMI:** Body mass index; **FTO:** Fat mass and obesity-associated; **HWE:** Hardy-Weinberg equilibrium; **LD:** Linkage disequilibrium; **MAF:** Minor allele frequency; **MUFA:** Monounsaturated fatty acid; **PUFA:** Polyunsaturated fatty acid; **SAFA:** Saturated fatty acid; **SNPs:** Single nucleotide polymorphisms

Declarations

Ethics approval and consent to participate

The ethical approval had been granted from the Medical Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia (No.1137/UN2/F1/ETIK/2017, protocol number 17-12-1212). Archived DNA samples were obtained from a previous study with written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The dataset analyzed in this study is provided in Additional File 2.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SGM and IMA conceived and supervised the study. AA and LP performed the ARMS PCR. AA, LP, SO, and CAF, performed data analysis. MD collected the samples, clinical and dietary assessment. AA, LP, SO, and CAF write original draft preparation. AA, LP, SO, CAF, IMA, and SGM revised the manuscript. All authors read and approved the final manuscript.

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