ISSN: 3032-3134 (ONLINE)
InaJBCS | Indonesian Journal of Biomedicine and Clinical Sciences

Association of fat mass and obesity associate (FTO) single nucleotide polymorphisms in the first intron and obesity risk among Indonesians

Benedikta Diah Saraswati[1], Luluk Yunaini[2]*, Dwi Anita Suryandari[2]

[1]Master's Programme in Biomedical Sciences, Faculty of Medicine Universitas Indonesia, Jakarta.
[2]Departement of Medical Biology Faculty of Medicine Universitas Indonesia, Jakarta

https://doi.org/10.22146/inajbcs.v56i01.11771

Submitted: 2022-01-13
Accepted : 2023-09-18

ABSTRACT

Obesity is one of the global pandemics characterized by an excessive fat buildup due to disruption of energy homeostasis in the body. As obesity is a risk factor for many other non-communicable diseases such as diabetes and coronary heart disease, it is crucial to understand the risk factors that contribute to the pathogenesis of obesity. Although obesity is mainly caused due to unhealthy lifestyles, genetic predisposition also plays a part in the pathogenesis of obesity. Individuals who carry risk alleles for genes that control energy balance in the body have a greater risk of developing obesity. Fat mass and obesity associate (FTO) is a gene strongly correlated with obesity and is widely expressed in the hypothalamus. This gene is predicted to have 89 common variations that affect obesity-related phenotypes. Among Indonesians, the three most studied single nucleotide polymorphisms (SNPs) in the first intron of the FTO gene are rs1421085, rs17817449, and rs9939609. They are strongly associated with obesity's related traits such as weight gain, fat mass, body mass index (BMI), waist, and hip sizes. rs993609 is the most studied among diverse ethnicities in Indonesia, with AA genotype and allele A as a risk allele.

ABSTRAK

Obesitas termasuk ke dalam salah satu permasalahan global yang didefinisikan sebagai dengan adanya penimbunan lemak berlebih akibat terganggunya homeostatis energi pada tubuh. Obesitas merupakan faktor risiko dari berbagai penyakit seperti diabetes melitus, jantung, dan berbagai jenis kanker. Oleh sebab itu pengetahuan mengenai etiologi dari obesitas penting untuk diteliti, termasuk perihal mencari faktor genetik yang sekiranya terlibat dalam patogenesis obesitas. Walaupun bersifat poligenik, individu yang memiliki alel risiko untuk gen yang terlibat dalam mengontrol keseimbangan energi dalam tubuh memiliki risiko lebih besar terkena obesitas. FTO diketahui berkorelasi kuat dengan obesitas dan diekspresikan secara luas di hipotalamus. Gen ini diperkirakan memiliki 89 variasi umum yang memberikan berbagai efek pada fenotipe terkait obesitas. Pada populasi di Indonesia, tiga *single nucleotide polymorphisms* (SNP) yang paling banyak dipelajari pada intron pertama gen FTO adalah rs1421085, rs17817449, dan rs9939609. Ketiga titik tersebut sangat terkait dengan sifat terkait obesitas seperti penambahan berat badan, massa lemak, indeks massa tubuh, lingkar pinggang, dan ukuran pinggul. rs993609 adalah titik yang paling banyak dipelajari di antara beragam etnis di Indonesia, dengan alel A dan genotipe AA sebagai faktor risiko terhadap obesitas.

Keywords:
obesity;
FTO;
risk alleles;
SNP;
polymorphisms

INTRODUCTION

Obesity can be defined as abnormal and excessive fat accumulation that may impair health with a body mass index (BMI) of more than 30 kg/m^2. Because of its high prevalence in many countries, the World Health Organization (WHO) classified obesity as a global pandemic.[1] Obesity is the risk factor of many non-

Corresponding author: luluk.yunaini@ui.ac.id

communicable diseases, especially coronary heart disease, type 2 diabetes, cancer, hypertension, dyslipidemia, and stroke, thus indirectly leading to death.[2] The WHO predicted about 2.8 million adults in 2018 die from being overweight or obese.[3] Most deaths are caused by diabetes, ischemic heart disease, and the increased risk of cancer from being overweight or obese. Indonesia is one of the top nations with the highest obesity-related cancer death rates.[4]

Obesity is caused mainly by a discrepancy in energy intake and expenditure. The intake of energy-dense meals high in fat and carbohydrates and a lack of physical exercise has increased due to more sedentary lives and poor diets.[5] Moreover, genetic factors also play a part in obesity pathogenesis. It is believed that about 5% obesity in children due to that runs in the family.[6]

According to Genome-Wide Association Studies (GWAS), since 2006, more than 50 genes and 300 single nucleotide polymorphisms (SNPs) have contributed to obesity's incidences and traits.[7] Of all these genes, FTO, which encodes fat mass and obesity associate (FTO), is estimated to have the most remarkable association with obesity incidences in various countries worldwide.[8] Fat mass and obesity associate is a dioxygenase enzyme that plays a role in repairing alkylated DNA and RNA. Overexpression of FTO can influence the expression of m^6A-dependent transcription factors to control preadipocyte differentiation.[9] Fat mass and obesity associate has 89 common variations that exert various effects on obesity-related phenotypes.[8] Single nucleotide polymorphisms rs1421085, rs8050136, and rs9939609 are among the most studied variations in an increased risk of obesity. These three variations are associated with various parameters related to obesity, such as weight gain, fat mass, body mass index (BMI), and waist and hip size.

It is important to mention that FTO's polymorphisms have been related to obesity and being overweight in Asian, African, Hispanic, and Native American populations, in both adults and children, suggesting that FTO polymorphisms significantly influence obesity.[10] Indonesian, a broad and multicultural populations from the crossing point of Asia and the Pacific, is the source of genetic diversities.

MATERIAL AND METHODS

This paper aimed to assess the possible mechanism of how the FTO gene interactions with other energy-regulating genes will contribute to the pathogenesis of obesity. This paper also discuss FTO's common intronic variations (rs1421085, rs8050136, and rs9939609) associations with obesity-related traits and their possible mechanism, especially in the Indonesian population. Hence, the reviewer searches for some research journal articles from 2009 and above published through electronic databases as part of the review process. Among other electronic databases, Google Scholar, PubMed, and ResearchGate were used. The keywords "Obesity gene FTO", "FTO SNPs related to obesity", and "FTO variants in Indonesian" were used to search the articles needed to write this review.

A total of 67 articles were used to write basic theories of FTO gene and their SNPs located in the first intron. Journals were identified based on the following inclusion criteria: 1) full-text articles published in English or Bahasa; 2) able to address the role of the FTO in etiology of obesity; 3) had enough information regarding how FTO and its variations interact with environment to affect how obesity manifests itself. Especially for the purpose to show FTO first intron SNPs' possible effects in Indonesian population, we used any data available online with following criteria: 1) SNPs located on the first intron of FTO, 2) had and effects towards obesity and

obesity related symptoms and diseases and 3) using Indonesian population aged range from adolescent to adult. For a summary of FTO first intron SNPs among Indonesian we used a total of 9 articles.

RESULTS

Etiology and pathogensis of obesity

Numerous factors contribute to obesity. Obesity, rather than solely emerging from the passive deposition of extra weight, appears to be a disease of the energy balance system. Obesity is caused by two different but linked processes: a prolonged positive energy balance and resetting the body weight "set point" to a higher number.[11] Obesity is mainly caused by the environment or behavior, including excessive energy-dense food consumption and physical inactivity. Pathological overeating and physical inactivity appear to be connected with altered brain circuits and neuroendocrine feedback that lead to obesity.[12] The link between obesity and energy homeostasis is significantly influenced by the adipocyte hormone leptin, which circulates at concentrations proportionate to body fat mass.[11] Dietary variables contributing to the development of obesity include eating a high-fat diet, consuming large amounts of sugar-sweetened beverages, and the predominance of a wide variety of food at the markets. The other key factor in the etiology of obesity is reduced energy expenditure relative to calorie intake.[13] However, Obesity as a multifactorial disease results from the interactions of environmental and genetic variables.

Although genetic factors alone are unlikely to account for the rapid rise in obesity prevalence, it is believed that some genetic influences increase the risk of obesity brought on by environmental impacts in ways that favor positive energy balance (higher calorie intake, decreased physical activity, or both) and/or result in the biological defense of increased fat mass.[11] Genetic factors that may lead to obesity in a variety of ways, generically categorized as: 1) Single gene mutation on the leptin-melanocortin pathway, which is the key site for monogenic causes; 2) Obesity with additional characteristics, such as neurodevelopmental disorders and other organ/system anomalies, is referred to as syndromic obesity; 3) polygenic obesity which includes a significant number of genes together contribute to polygenic obesity, which is exacerbated by an environment that promotes weight gain.[14]

Monogenic mutations are single-gene mutations that produce a variety of rare forms of obesity. These mutations have been found in genes that code for the hormone leptin, the leptin receptor, pro-opiomelanocortin, and the melanocortin-4 receptor, all of which are involved in appetite control, food intake, and energy balance.[14] Various studies have found mutations in several alleles that have the predisposition to trigger obesity. In addition, human body weight and disposition are believed to be regulated by various genes. These genes include the obesity (OB), diabetes mellitus (DB), and FTO. The OB is associated with the secretory process of the hormone leptin, while the DB encodes the leptin receptor. Someone with mutations in OB and DB mostly experiences obesity problems.[3]

About 835 gene loci and 317 SNPs are associated with obesity, including FTO, MC4R, GNPDA2, TMEM18, NRXN3, SEC16B TNNI3K, QPCTL, and BDNF loci.[15] Among these loci, FTO is thought to have the most significant association with obesity in various countries globally. FTO was only known for its role in the pathogenesis of obesity; through the genome-wide analysis study (GWAS) in 2007, it was found that various variations in the FTO gene turned out to be associated with obesity in individuals with European ancestors.[16] People who have one of these gene variations have a greater risk of obesity and other obesity-

related traits than those who do not.

The first large-scale GWAS for quantitative BMI and height in East Asian ancestry populations showed that the FTO locus, which has long been recognized as a critical contributor to polygenic obesity in European people, also had the strongest connection result.[17] Following the GWAS meta-analysis, FTO variations are also relevant in many Asian ethnicities, including Singaporean, Malay, and Asian-Indian.[18] Thus, variations in the FTO locus are among the strongest candidates to be studied in the Indonesian population because there is a similar genetic distribution among the Malaysian and Singaporean people. However, a large-scale GWAS study using Indonesian ancestry has yet to be done.

The physiological function of FTO

Fat mass and obesity associate is encoded by the *FTO* gene, located on chromosome 16q12.2. This locus is from 53,737,875 bp to 54,155,853 bp of chromosome 16 and consists of 9 exons.[19,20] Bioinformatics analysis showed that FTO is a Fe(II) and 2-oxoglutarate-dependent oxygenase, characterized by a site for nucleic acid demethylation.[21,22] Although FTO is often associated with the risk of obesity, this gene's primary physiology function in humans remains unknown other than restoring damaged DNA and RNA by the demethylation process. Duplication of the FTO gene region causes mental retardation, obesity, and other disorders.[23]

Animal studies have shown a correlation between FTO and other hunger hormones like leptin. Still, no evidence supports the idea that human FTO *expression* is regulated at the transcriptional level in a leptin-dependent manner.[23] However, it is believed that FTO alters hypothalamic nuclear factor-kappa β (NF-κβ) signaling, impacts the metabolic consequences of a high-fat diet and requires leptin resistance induced by high-fat eating.[24] Leptin itself is known to suppress appetite, although the impact appears to be indirect. FTO and its neighbor gene RPGRIP1L are predicted to be coregulated because they share the same CpG island. RPGRIP1L is known to regulate leptin production.[25]

Fat mass and obesity associate is a crucial regulator in energy management. Fasting/feeding cycles regulate the expression of the FTO, which is strongly expressed in the hypothalamus. This geographical expression pattern is remarkable because the hypothalamus controls energy balance and food intake control.

Fat mass and obesity associate is also implicated in the adipogenesis process.[26] Adipocytes accumulate excessively in the adipose tissue of obese people. Fat mass and obesity associate mRNA levels in subcutaneous adipose tissue were shown to have a positive relationship with BMI, with greater levels of FTO mRNA in obese persons' fatty tissues.[27] Fat mass and obesity associate is involved in the development of obesity by affecting the level of hormones that control eating behavior or other molecules related to adipogenesis. Animal studies show that fto directly affects fat mass and, as a result, is likely to have a role in human obesity.[28] Fat mass and obesity associate protein has an oxidative demethylation activity towards N^6-methyladenosine (m^6A), the most common mRNA alteration in humans and mice considered involved in mRNA stability, splicing, and translation control.[22]

By influencing the m^6A level around the splice site of the adipogenic regulator, RUNX1T1, FTO contributes to modulating adipose cell differentiation.[27] Fat mass and obesity associate influences adipogenesis by controlling the mitotic clonal expansion (MCE). It is required for adipocyte differentiation within 48 h of adipogenic stimulation.[9] Overexpression of the FTO gene is

known to activate adjacent genes involved in energy balance and white adipocyte development.[29] After FTO has been identified as an obesity-associated gene via GWAS, many discoveries found that several variations in the FTO's first intron may be linked to obesity and other obesity characteristics.[23]

Overexpression of FTO increased m^6A demethylation, thus increasing the ghrelin mRNA level simultaneously. Ghrelin can only be synthesized after FTO demethylates m^6A.[30] The synthesized ghrelin will then penetrate the blood-brain barrier to exert its effect on the hypothalamus to increase appetite. According to research conducted in animals such as mice, the FTO gene might be a significant target for early dietary programming.[31,32] FTO is thought to affect the central nervous system's global energy sensors by interacting with mammalian target of rapamycin (mTOR), 5'-Adenosine monophosphate-activated protein kinase (AMPK), and uncoupling protein 2 (UCP2) (FIGURE 1).[23]

According to studies on mouse embryonic fibroblasts, cells with FTO-overexpression are resistant to amino acid shortages. Obesity is believed to be influenced by FTO's downstream mammalian target of rapamycin complex 1 (mTORC1).[28] mTORC1 controls the metabolism of glucose and glutamine, as well as the primary carbon sources used by mitochondria. It is known as a target for various hormones that play a role in regulating energy balance, such as leptin and ghrelin.[33] Fat mass and obesity associate is also controlled by the CUX1 transcription factor that governs leptin receptors' traffic, which modulates eating behaviour.[34]

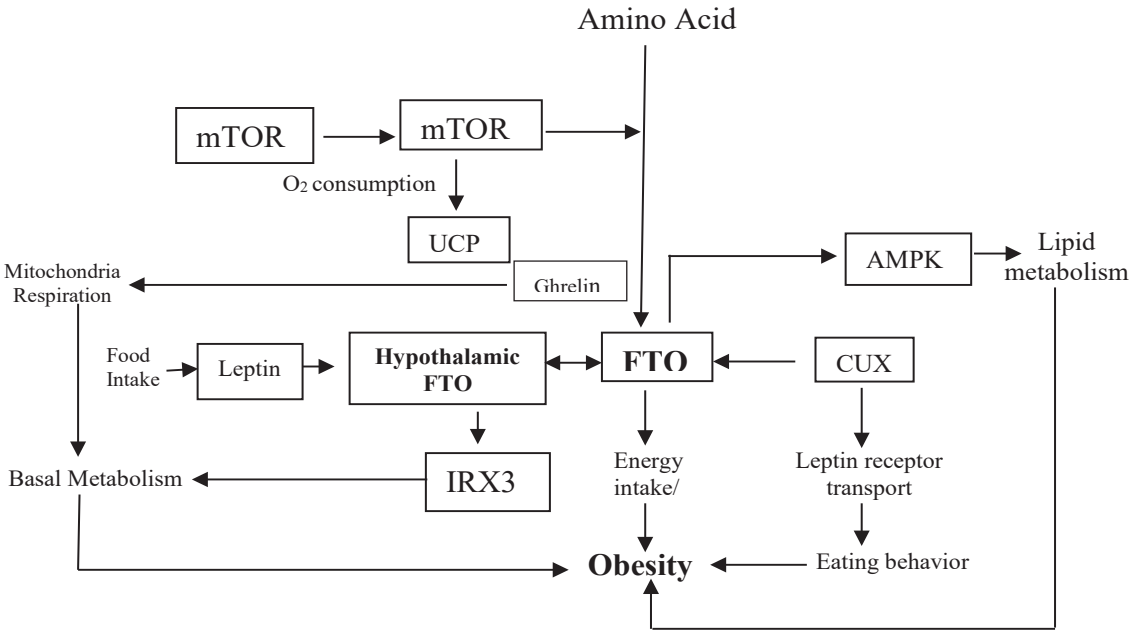

FIGURE1. Possible mechanism of how FTO causes obesity by interacting with other components. Fat mass and obesity associate is predicted to interact with hormones that regulate food intake such as ghrelin and leptin. In addition, FTO also plays a role in amino acid sensors through the mTOR signaling pathway. Adapted from Zhou *et al.*,[20] Abbreviation mTOR: mammalian target of rapamycin, UCP: uncoupling protein, CUX: Cut Like Homeobox, AMPK: 5' AMP-activated protein kinase, IRX3: Iroquois homeobox 3.

By modifying the expression of lipid-related genes, FTO-mediated m6A demethylation controls lipid metabolism and diseases associated with lipid disorders. Skeletal muscles' ability to consume lipids is restricted by FTO-dependent m^{6}A demethylation, which inhibits the AMPK pathway.[35] AMPK is a critical cellular energy sensor activated when cellular AMP levels rise. AMPK activation conserves energy for the cell under food deprivation by phosphorylating many substrates to inhibit anabolic activities, boost catabolic ones, transmit signals to mTORC1 and slow cell development.[36]

First intron variations of FTO and their association with obesity and other obesity's traits

Human obesity risk is related to genetic polymorphisms in non-coding regions of the FTO locus, which have small but statistically significant impacts. It is predicted that the possible mechanism by which these non-coding variations increase obesity risk is mediated through effects on adjacent genes that alter brain development and the formation of beige adipose tissue.[37] It was shown that individuals with the obesity-promoting FTO variation were 23% more likely to be obsessed than those without.[38] On the other hand, physical exercise has been shown to reduce the risk of obesity, with active persons with the obesity-promoting gene having a 30% lower risk than sedentary adults.[11] Fat mass and obesity associate SNPs, primarily located in the first intron, have been associated with individual variation in appetite rating scales, loss of control, bulk eating, and eating without hunger (FIGURE 2).[23]

As mentioned above, FTO and RPGRIP1L have co-regulation mechanisms. Besides sharing the same CpG island, there is an overlapping regulatory region inside FTO's first intron with at least two putative transcription factor binding sites (CUX1), one of which coincides with other obesity-related SNPs.[39] Thus, the possibility that changes in both FTO and RPGRIP1L mediate the link between FTO SNPs and body weight control expression.[16]

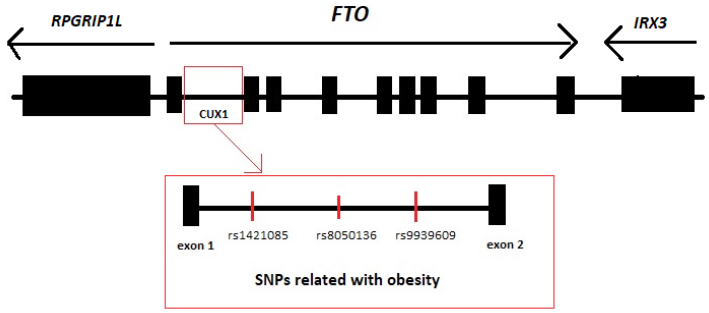

FIGURE 2. This paper reviewed the construction of the FTO gene structure and the location of the first intron SNPs. Fat and mass obesity associate is located on chromosome 16q12.2. A GWAS found a link between a common variant in single nucleotide polymorphisms in FTO's first intron with obesity. Three of the most studied SNPs are shown in this figure.

Another possible mechanism is by affecting the expression of IRX3, which plays a role in the differentiation process of adipocyte cells. These interactions are essential in regulating feeding behavior and detecting cellular nutritional status. Polymorphisms in the first intron of the *FTO* are strongly linked to increased BMI. Variations of FTO have also been linked to increased body fat composition, metabolite parameters, and metabolic diseases, including type 2 diabetes mellitus (T2DM).[40] Because the relevant risk alleles are relatively common, they are predicted to be responsible for many obesity cases in almost all human populations, especially among Europeans.[29]

Several studies show that some FTO polymorphisms may enhance calorie intake while decreasing satiety, resulting in weight gain. The mechanisms underlying the association between those variations with obesity are thought to be related to :1) the direct effect of FTO function in controlling body fat mass or 2) the presence of a non-random association (disequilibrium linkage) between the variant alleles tested with other causative changes in different alleles, which is still in the same area as FTO gene locus.[23]

Despite progress made, the actual mechanism by which SNPs in FTO impact human body mass remains unknown but is predicted to correlate with appetite and whole-body energy expenditure circuits in the brain and peripheral energy expenditure pathways. Most FTO expression variation is attributable to cis-regulatory variation in this gene's first intron.[41] Variations of the FTO gene in the first intron include rs9939609, rs1421085, rs17817449, rs9939973, rs1121980, and rs8050136. These FTO variants are in one cluster on the first intron of the FTO gene. All FTO variants identified by GWAS have a linkage disequilibrium (LD) of $r^2 > 0.80$, which indicates that the alleles are correlated, thus having almost the same significance level for obesity.[16] Among them, rs1421085, rs8050136, rs9939609, and rs17817449 were the most associated with obesity status and measures of obesity.

The effect of FTO polymorphism varies from one population to another. Ethnic variations in FTO allele frequencies, population sampling and age, and underlying patterns of significant environmental exposures might explain these inconsistencies.[27] This review specifically summarized all the first intron SNP of FTO using a population from Indonesia. Those variants and their association with obesity characteristics such as increased BMI, waist-hip ratio (WHR), waist circumference (WC), visceral fat accumulation (VFA), as well as metabolic abnormalities related to obesity such as T2DM, in Indonesian populations are summarized in (TABLE 1).

TABLE 1. FTO 1st intron's SNPs and their effect in obesity phenotype among Indonesians

rsID	Study population	Cases/controls	Genotype	Effects	Ref.
s9939609	Adult aged 19 –59 yr in Jakarta	40/40	AT/AA	Higher risk to obesity and tendency to consume excessive dietary fat	42
	Adult aged 20–30 yr in Jakarta	38/40	AA	increased visceral fat deposition with significantly higher WC, WHR, and VFA in males	43
	Balinese adults from both urban and rural area	612 cases	AA	Tendency to higher BMI, particularly in in rural and female population	44
	Chinese or Bataknese children (6-12 y.o., both sex)	Bataknese: 56/61 Chinese: 49/46	TT	Higher risk to Obesity in Chinese children but not in Bataknese children.	45
	Minangkabau's Adolescent girls	130/145	AA/AT	Tendency to eat more fried food and less fruit	46
	Minangkabau Women (25-60 y.o. with BMI under 40 kg/m^2)	133 non-obese women	AA/AT	higher BMI	47
rs1421085	Balinese adults from both urban and rural area	612 cases	CC	Higher BMI, particularly in females	44
	Javanese adults in Yogyakarta	94/94	CC	Increased the risk of and percentage of total body fat only in male subjects	40
	Adults aged 19 –59 yr in Jakarta	40 cases and 40 control	TC/CC	higher BMI and dietary fat food	48
rs8050136	Minangkabau Women (25-60 yr) with BMI (under 40 kg/m^2)	133 non-obese women	AA/AC	higher BMI	47

Abbreviations: BMI, body mass index; WC, waist circumference; WHR, a waist-hip ratio; and VFA, visceral fat area

rs9939609

The minor allele for the FTO rs9939609 significantly enhanced the risk of obesity.[49] Variation in FTO (rs9939609) was the most strongly linked locus in a GWAS for BMI in 7,861 Koreans.[50] In Malay ethnicity living in Singapore. rs9939609 strongly related to obesity traits.[51] rs9939609 is positively correlated with increased calorie intake in adults. Individuals with the AT or AA genotypes consumed foods with higher calories than individuals with the TT genotype in individuals of Caucasian ethnic descent in Europe. However, the same thing also happened to other ethnicities in South East Asia, including races in Indonesia.[52]

Daya *et al.*[42] found that the risk allele A (AT or AA) at rs9939609 could modulate the consumption preferences of high-fat foods in the adult population. Susmiati *et al.*[46] tried to link the association of rs9939609 with a person's food preferences. It is estimated that the risk allele A at rs9939609 is thought to interfere with circulating levels of the hormone acyl-ghrelin. Increased

circulating ghrelin will inappropriately repress leptin production, which causes the body to feel hungry and increases the desire to consume high-calorie foods.[30]

Priliani *et al.*[44] found that the AA genotype also had a higher BMI than other genotypes in the Balinese population, especially in women and rural populations. This was predicted due to eating behavior and different body composition between women and men.[33] A diminished resting energy expenditure (REE) in the A allele of FTO might be the plausible reason it had a higher BMI than the TT genotype.[53] FTO rs9939609 also had high linkage disequilibrium with IRX3. IRX3 disturbed energy balance by directly inhibiting white adipose tissue browning. As a result, FTO rs9939609 Increased IRX3 expression may reduce energy expenditure and enhance fat storage if a risk allele is present.[54]

However, Lubis *et al.*[45] reported that the distribution of AA homozygote for the rs9939609 FTO gene was lower in the case group than in the control group compared to the TT genotype in a North Sumatera population of Chinese origin.[45] It was found that children with the AA genotype may be less likely to gain weight, whereas those with the TT genotype may gain weight more easily. Nevertheless, more study is needed to determine if the two alleles play distinct roles, such as one predisposing and the other protecting, or whether one of the two alleles causes function gain or loss. These inconsistencies might be due to variations in ethnic groupings, sample sizes, physical activity, and environmental exposure. According to a meta-analysis by Kilpelainen *et al.*[55] using 200.000 adults and about 20.000 children participants, 27% of subjects with these FTO variations most consistently related to obesity could reduce their risk through physical exercise.[55]

rs1421085

The genotypes CC and CT/CC of rs1421085 were linked to 59% and 71% higher odds of childhood obesity in Chinese children aged 3-6 years old.[56] The BMI growth in the Korean population was revealed to be highly correlated with the rs1421085 C allele.[57] rs1421085 correlated with an increase in BMI in Indonesia's Balinese population, with homozygous CC individuals having an approximately 1.12 kg/m^2 higher BMI than other genotypes.[58] This finding is similar to Cha *et al.*[59] also found that individuals in the Korean population who carry the C risk allele are known to be significantly associated with increased BMI. The increase in BMI is predicted to be caused by an unhealthy diet. Individuals with the rs1421085 variation with the C allele tend to have an eating behavior disorder known as binge eating or huge portions. Other parameters such as waist and hip size were also bigger in individuals with the C risk allele.

The *FTO* SNP rs1421085 (T> C) is known to have an enhancer element of the *IRX3* gene. Fat mass and obesity associate directly plays a role in adipocyte cells' biological activity by activating the thermogenin cascade in the browning process of fatty cells. It causes differentiation from the energy-dissipating beige adipocytes to energy-storing white adipocytes, followed by a decrease in the thermogenesis process, increased triglycerides in the blood, and increased storage of body fat reserves. The regulatory connections between FTO SNPs and IRX3 expression were also supported because alterations in the rs1421085 risk allele (C allele) caused a two-fold production of IRX3 and IRX5 in the early stages of adipocyte development by disrupting the ARID5B repressor's conservative motif.[60]

rs8050136

Meta-analysis from 2404 cases and 5713 control subjects showed that rs8050136 was significantly associated with obesity risk in East Asia populations.[61] A study in the Han Chinese population showed that rs8050136 is a risk factor for T2DM but independent of BMI.[62]

In Indonesia itself, using Minangkabau ethnicity groups, rs8050136 risk allele A is known to have a higher BMI than allele C. Like other studies covering different populations, this SNP is also associated with T2DM among the same ethnicity in Padang, Indonesia, one of the obesity-related diseases.[63]

rs8050136 mutation causes a change in factor binding Cut-like Homeobox 1 (CUX1) transcription and later decreases the expression of both FTO and RPGRIP1L in the hypothalamus. This risk allele (A allele) also can affect the expression of the RPGRIP1L, located FTO, by providing a regulatory element on the promoter part RPGRIP1L <100 bp from the FTO, by providing a regulatory element on the promoter part RPGRIP1L, which later acts as a repressor.[26] RPGRIP1L plays a role in controlling the leptin signaling process in the hypothalamus.[64] This caused a reduction of the leptin signaling process, thereby increasing the risk of obesity.[62]

rs17817449

FTO SNPs rs17817449 show the highest significant connection with BMI among people of Chinese descent, according to a large-scale meta-analysis focusing on GWAS investigation of East Asian populations. However, no research has been concluded using the Indonesian people, so this SNP is not discussed further in this review.

In our investigation, some potential limitations should be taken into account. First, not all of the studies SNPs in the first intron of FTO are included in this review. Other than that, there is still little research that examines the relationship of the first intron variation of FTO with the risk of obesity in Indonesia. Also, if variables like gender, age, food preferences, and lifestyle were changed, a more accurate analysis should also be considered. Additionally, there are discrepancies in results between ethnic groups due to different lifestyle interventions, different target populations (for instance, in terms of age group), surveying different polymorphisms in multiple research, and ignoring additional genetic factors that affect obesity.

CONCLUSION

SNP rs1421085, rs8050136, and rs9939609 were the most studied variations in an increased risk of obesity study in the Indonesian population. The most studied FTO SNP for obesity risk among diverse ethnicities in Indonesia is rs9939609 with risk allele A. Nevertheless, further data from a broader population and ethnic groups in Indonesia is needed to determine the impact of the first intron SNP of the FTO on obesity risk among Indonesians. It is essential to remember that even if FTO is the most promising among other candidate genes, it is only responsible for a small portion of obesity predisposition caused by genetic factors. Gaining a better understanding of how the FTO polymorphism impacts the body's fat mass can aid in the pathophysiology of obesity and the possible application of *FTO* inhibitors for obesity treatments.

ACKNOWLEDGEMENT

The author appreciates everyone's help in making this literature review possible especially Dr. Dra. Ria Kodariah, M.S. and Master's Programme in Biomedical Sciences, Faculty of Medicine

Universitas Indonesia for encouraging us to write this article.

REFERENCE

1. WHO. Obesity [Internet]. [cited 2023 Apr 20]. Available from: https://www.who.int/health-topics/obesity#tab=tab_1
2. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, *et al*. Obesity and cardiovascular disease: A scientific statement from the American Heart Association. Circulation 2021; 143(21):e984-e1010. https://doi.org/10.1161/CIR.0000000000000973
3. Hussain A, Mahawar K, Xia Z, Yang W, EL-Hasani S. Obesity and mortality of COVID-19. Meta-analysis. Obes Res Clin Pract 2020; 14(4):295-300. https://doi.org/10.1016/j.orcp.2020.07.002
4. Nurcahyo F. Kaitan antara obesitas dan aktivitas fisik. Medikora 2015; (1):87-96. https://doi.org/10.21831/medikora.v0i1.4663
5. Hill JO, Wyatt HR, Peters JC. Energy balance and obesity. Circulation 2012; 126(1):126-32. https://doi.org/10.1161/CIRCULATIONAHA.111.087213
6. Bouchard C. Childhood obesity: are genetic differences involved? Am J Clin Nutr 2009; 89(5):1494S-501. https://doi.org/10.3945/AJCN.2009.27113C
7. Goodarzi MO. Genetics of obesity: what genetic association studies have taught us about the biology of obesity and its complications. Lancet Diabetes Endocrinol 2018; 6(3):223-36. https://doi.org/10.1016/S2213-8587(17)30200-0
8. Loos RJF, Bouchard C. FTO: The first gene contributing to common forms of human obesity. Obes Rev 2008; 9(3):246-50. https://doi.org/10.1111/j.1467-789X.2008.00481.x
9. Merkestein M, Laber S, McMurray F, Andrew D, Sachse G, Sanderson J, *et al*. FTO influences adipogenesis by regulating mitotic clonal expansion. Nature Communications 2015; 6:6792. https://doi.org/10.1038/ncomms7792
10. Sun C, Kovacs P, Guiu-Jurado E. Genetics of obesity in East Asians. Front Genet 2020; 11:575049. https://doi.org/10.3389/fgene.2020.575049
11. Schwartz MW, Seeley RJ, Zeltser LM, Drewnowski A, Ravussin E, Redman LM, *et al*. Obesity pathogenesis: An endocrine society scientific statement. Endocr Rev 2017; 38(4):267-96. https://doi.org/10.1210/ER.2017-00111
12. Oussaada SM, van Galen KA, Cooiman MI, Kleinendorst L, Hazebroek EJ, van Haelst MM, *et al*. The pathogenesis of obesity. Metabolism 2019; 92:26–36. https://doi.org/10.1016/j.metabol.2018.12.012
13. Bray GA. Epidemiology, risks and pathogenesis of obesity. Meat Sci 2005; 71(1)2-7. https://doi:10.1016/j.meatsci.2005.04.009
14. Thaker VV. Genetic and epigenetic causes of obesity. Adolesc Med State Art Rev 2017; 28(2):379-405.
15. Kalantari N, Mohammadi NK, Izadi P, Doaei S, Gholamalizadeh M, Eini-Zinab H, *et al*. A haplotype of three SNPs in FTO had a strong association with body composition and BMI in Iranian male adolescents. PloS One 2018; 13(4):e0195589 https://doi.org/10.1371/journal.pone.0195589
16. Loos RJF, Yeo GSH. The bigger picture of FTO – The first GWAS-identified obesity gene. Nat Rev Endocrinol 2014; 10(1):51-61. https://doi.org/10.1038/nrendo.2013.227
17. Cho YS, Go MJ, Kim YJ, Heo JY, Oh JH, Ban HJ, *et al*. A large-scale genome-wide association study of Asian populations uncovers genetic factors influencing eight quantitative traits.

Nat Genet 2009; 41(5):527-34. https://doi.org/10.1038/ng.357
18. Tan JT, Dorajoo R, Seielstad M, Sim XL, Ong RTH, Chia KS, *et al*. FTO variants are associated with obesity in the Chinese and malay populations in Singapore. Diabetes 2008; 57(10):2851-7. https://doi.org/10.2337/db08-0214
19. Yang Q, Xiao T, Guo J, Su Z. Complex relationship between obesity and the fat mass and obesity locus. Int J Biol Sci 2017; 13(5):615-29. https://doi.org/10.7150/ijbs.17051
20. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, *et al*. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007; 316(5826):889-94. https://doi.org10.1126/SCIENCE.1141634
21. Gerken T, Girard CA, Tung YCL, Webby CJ, Saudek V, Hewitson KS, *et al*. The obesity-associated FTO gene encodes a 2-oxoglutarate–dependent nucleic acid demethylase. Science 2007; 318(5855):1469-72. https://doi.org/10.1126/science.1151710
22. Jia G, Fu Y, Zhao X, Dai Q, Zheng G, Yang Y, *et al*. N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO. Nat Chem Biol 2011; 7(12):885-7. https://doi.org/10.1038/nchembio.687
23. Zhou Y, Hambly BD, McLachlan CS. FTO associations with obesity and telomere length. J Biomed Sci 2017; 24(1):65. https://doi.org/10.1186/s12929-017-0372-6
24. Tung YCL, Gulati P, Liu CH, Rimmington D, Dennis R, Ma M, *et al*. FTO is necessary for the induction of leptin resistance by high-fat feeding. Mol Metab 2015; 4(4):287-98. https://doi.org/10.1016/j.molmet.2015.01.011
25. Martin-Carli JF. RPGRIP1L and FTO – genes implicated in the effects of FTO intronic sequence variants on food intake – also affect adipogenesis and adipocyte biology. 2017 https://doi.org/10.7916/D8PV6XT2
26. Ben-Haim MS, Moshitch-Moshkovitz S, Rechavi G. FTO: linking m6A demethylation to adipogenesis. Cell Res 2015; 25(1):3-4. https://doi.org/10.1038/cr.2014.162
27. Zhao X, Yang Y, Sun BF, Zhao YL, Yang YG. FTO and obesity: Mechanisms of association. Curr Diab Rep 2014; 14(5):486. https://doi.org/10.1007/s11892-014-0486-0
28. Church C, Moir L, McMurray F, Girard C, Banks GT, Teboul L, *et al*. Overexpression of FTO leads to increased food intake and results in obesity. Nat Genet 2010; 42(12):1086-92. https://doi.org/10.1038/ng.713
29. Pulit SL, Stoneman C, Morris AP, Wood AR, Glastonbury CA, Tyrrell J, *et al*. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. Hum Mol Genet 2019; 28(1):166-74. https://doi.org/10.1093/hmg/ddy327
30. Karra E, O'Daly OG, Choudhury AI, Yousseif A, Millership S, Neary MT, *et al*. A link between FTO, ghrelin, and impaired brain food-cue responsivity. J Clin Invest 2013; 123(8):3539-51. https://doi.org/10.1172/JCI44403
31. Sébert SP, Hyatt MA, Chan LY, Yiallourides M, Fainberg HP, Patel N, *et al*. Influence of prenatal nutrition and obesity on tissue specific fat mass and obesity-associated (FTO) gene expression. Reproduction 2010; 139(1):265-74. https://doi.org/10.1530/REP-09-0173
32. Caruso V, Chen H, Morris MJ. Early hypothalamic FTO overexpression in response to maternal obesity – potential contribution to postweaning hyperphagia. PLoS One 2011; 6(9):e25261. https://doi.org/10.1371/journal.pone.0025261

33. Lan N, Lu Y, Zhang Y, Pu S, Xi H, Nie X, *et al*. FTO – A common genetic basis for obesity and cancer. Front Genet 2020; 11:559138. https://doi.org/10.3389/fgene.2020.559138
34. Stratigopoulos G, LeDuc CA, Cremona ML, Chung WK, Leibel RL. Cut-like homeobox 1 (CUX1) regulates expression of the fat mass and obesity-associated and retinitis pigmentosa GTPase regulator-interacting protein-1-like (RPGRIP1L) genes and coordinates leptin receptor signaling. J Biol Chem 2011; 286(3):2155-70. https://doi.org/10.1074/jbc.M110.188482
35. Yang Z, Yu G, Zhu X, Peng T, Lv Y. Critical roles of FTO-mediated mRNA m6A demethylation in regulating adipogenesis and lipid metabolism: Implications in lipid metabolic disorders. Genes Dis 2021; 9(1):51-61. https://doi.org/10.1016/j.gendis.2021.01.005
36. Jewell JL, Guan KL. Nutrient signaling to mTOR and cell growth. Trends Biochem Sci 2013; 38(5):233-42. https://doi.org/10.1016/j.tibs.2013.01.004
37. Aldiss P, Betts J, Sale C, Pope M, Budge H, Symonds ME. Exercise-induced 'browning' of adipose tissues. Metabolism 2018; 81:63–70. https://doi.org/10.1016/j.metabol.2017.11.009
38. Hruby A, Hu FB. The Epidemiology of Obesity: A big picture. Pharmacoeconomics 2015; 33(7):673-89. https://doi.org/10.1007/S40273-014-0243-X
39. Sedaghati-khayat B, Barzin M, Akbarzadeh M, Guity K, Fallah MS, Pourhassan H, *et al*. Lack of association between FTO gene variations and metabolic healthy obese (MHO) phenotype: Tehran Cardio-metabolic Genetic Study (TCGS). Eat Weight Disord 2020; 25(1):25-35. https://doi.org/10.1007/S40519-018-0493-2
40. Maharani Citra, Puspasari. A. Peran variasi gen FTO pada obesitas. Jmj 2019; 7(2):161-6. https://doi.org/10.22437/jmj.v7i2.8018
41. Berulava T, Horsthemke B. The obesity-associated SNPs in intron 1 of the FTO gene affect primary transcript levels. Eur J Hum Genet 2010; 18(9):1054-6. https://doi.org/10.1038/EJHG.2010.71
42. Daya M, Pujianto DA, Witjaksono F, Priliani L, Susanto J, Lukito W, *et al*. Obesity risk and preference for high dietary fat intake are determined by FTO rs9939609 gene polymorphism in selected Indonesian adults. Asia Pac J Clin Nutr 2019; 28(1):183-91. https://doi.org/10.6133/apjcn.201903_28(1).0024
43. Salim S, Kartawidjajaputra F, Suwanto A. Association of FTO rs9939609 and cd36 rs1761667 with visceral obesity. J Nutr Sci Vitaminol (Tokyo) 2020; 66(Supplement):S329-35. https://doi.org/10.3177/jnsv.66.S329
44. Priliani L, Oktavianthi S, Hasnita R, Nussa HT, Inggriani RC, Febinia CA, *et al*. Obesity in the Balinese is associated with FTO rs9939609 and rs1421085 single nucleotide polymorphisms. PeerJ 2020; 8:e8327. https://doi.org/10.7717/peerj.8327
45. Lubis SM, Fattah M, Damanik HA, Batubara JRL. Association of fat mass and obesity-associated gene (FTO) rs9939609 variant with early onset obesity among Bataknese and Chinese Children in Indonesia: A Case-control study. Indones Biomed J 2017; 9(3):147-52. https://doi.org/10.18585/inabj.v9i3.322
46. Susmiati, Lipoeto NI, Surono IS, Jamsari. Association of Fat mass and obesity-associated rs9939609 polymorphisms and eating behaviour and food preferences in adolescent Minankabau girls. Pak J Nut 2018; 17(10):471-9. https://doi.org/10.3923/PJN.2018.471.479
47. Alsulami S, Aji AS, Ariyasra U, Sari SR, Tasrif N, Yani FF, *et al*.

Interaction between the genetic risk score and dietary protein intake on cardiometabolic traits in Southeast Asian. Genes Nutr 2020; 15(1):19. https://doi.org/10.1186/S12263-020-00678-w
48. Al-Jawadi AA, Priliani L, Oktavianthi S, Febinia CA, Daya M, Artika IM, *et al*. Association of FTO rs1421085 single nucleotide polymorphism with fat and fatty acid intake in Indonesian adults. BMC Res Notes 2021; 14(1):411. https://doi.org/10.21203/rs.3.rs-690802/v1
49. Li H, Kilpeläinen TO, Liu C, Zhu J, Liu Y, Hu C, *et al*. Association of genetic variation in FTO with risk of obesity and type 2 diabetes with data from 96,551 East and South Asians. Diabetologia 2012; 55(4):981-95. https://doi.org/10.1007/S00125-011-2370-7
50. Cho YS, Go MJ, Kim YJ, Heo JY, Oh JH, Ban HJ, *et al*. A large-scale genome-wide association study of Asian populations uncovers genetic factors influencing eight quantitative traits. Nat Genet 2009; 41(5):527-34. https://doi.org/10.1038/NG.357
51. Tan JT, Dorajoo R, Seielstad M, Sim XL, Ong RTH, Chia KS, *et al*. FTO variants are associated with obesity in the Chinese and Malay populations in Singapore. Diabetes 2008; 57(10):2851-7. https://doi.org/10.2337/DB08-0214
52. Solak M, Ozdemir Erdogan M, Yildiz SH, Ucok K, Yuksel S, Arıkan Terzi ES, *et al*. Association of obesity with rs1421085 and rs9939609 polymorphisms of FTO gene. Mol Biol Rep 2014; 41(11):7381-6. https://doi.org/10.1007/s11033-014-3627-2
53. Arrizabalaga M, Larrarte E, Margareto J, Maldonado-Martín S, Barrenechea L, Labayen I. Preliminary findings on the influence of FTO rs9939609 and MC4R rs17782313 polymorphisms on resting energy expenditure, leptin and thyrotropin levels in obese non-morbid premenopausal women. J Physiol Biochem 2014; 70(1):255-62. https://doi.org/10.1007/S13105-013-0300-5
54. Ferreira Todendi P, de Moura Valim AR, Klinger E, Reuter CP, Molina S, Martínez JA, *et al*. The role of the genetic variants IRX3 rs3751723 and FTO rs9939609 in the obesity phenotypes of children and adolescents. Obes Res Clin Pract 2019; 13(2):137-42. https://doi.org/10.1016/J.ORCP.2019.01.005
55. Kilpeläinen TO, Qi L, Brage S, Sharp SJ, Sonestedt E, Demerath E, *et al*. Physical Activity Attenuates the Influence of FTO variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. PloS Med 2011; 8(11):e1001116. https://doi.org/10.1371/journal.pmed.1001116
56. Wang L, Yu Q, Xiong Y, Liu L, Zhang X, Zhang Z, *et al*. Variant rs1421085 in the FTO gene contribute childhood obesity in Chinese children aged 3-6 years. Obes Res Clin Pract 2013; 7(1):e14-22 https://doi.org/10.1016/j.orcp.2011.12.007
57. Bo X, Mi J. FTO polymorphisms are associated with obesity but not with diabetes in East Asian populations: a meta-analysis. Biomed Environ Sci 2009; 22(6):449-57. https://doi.org/10.1016/S0895-3988(10)60001-3
58. Priliani L, Oktavianthi S, Hasnita R, Nussa HT, Inggriani RC, Febinia CA, *et al*. Obesity in the Balinese is associated with FTO rs9939609 and rs1421085 single nucleotide polymorphisms. PeerJ 2020; 8:e8327 https://doi.org/10.7717/peerj.8327
59. Cha SW, Choi SM, Kim KS, Park BL, Kim JR, Kim JY, *et al*. Replication of genetic effects of FTO polymorphisms on BMI in a Korean population. Obesity. 2008; 16(9):2187-9. https://doi.org/10.1038/oby.2008.314
60. Claussnitzer M, Dankel SN, Kim KH, Quon G, Meuleman W, Haugen C, *et al*. FTO obesity variant circuitry and

adipocyte browning in humans. N Engl J Med 2015; 373(10):895-907. https://doi.org/10.1056/NEJMoa1502214
61. Xi B, Mi J. FTO polymorphisms are associated with obesity but not with diabetes in East Assian populations: a metaanalysis. Biomed Environ Sci 2009; 22(6):449-57. https://doi.org/10.1016/S0895-3988(10)60001-3
62. Qian Y, Liu S, Lu F, Li H, Dong M, Lin Y, *et al*. Genetic variant in fat mass and obesity-associated gene associated with type 2 diabetes risk in Han Chinese. BMC Genet 2013; 14:86. https://doi.org/10.1186/1471-2156-14-86
63. Adhiyanto C, Mutia Nasir N, Sari FR, Pamungkas G, Azis I, Harriyati Z, *et al*. Preliminary study: identification of DNA variation with SNP numbers rs1137101 and rs8050136 in patient's type 2 diabetes mellitus at Salsabila clinic Bogor Indonesia. Biotech Env Sc 2019; 21(4):112–5
64. Kwon O, Kim KW, Kim MS. Leptin signalling pathways in hypothalamic neurons. Cell Mol Life Sci 2016; 73(7):1457-77. https://doi.org/10.1007/S00018-016-2133-1
65. Dorris ER, O'Neill A, Treacy A, Klocker H, Teltsh O, Kay E, *et al*. The transcription factor CUX1 negatively regulates invasion in castrate resistant prostate cancer. Oncotarget 2020; 11(9):846-57. https://doi.org/10.18632/oncotarget.27494
66. Lan N, Lu Y, Zhang Y, Pu S, Xi H, Nie X, *et al*. FTO – A Common Genetic Basis for Obesity and Cancer. Front Genet 2020; 11:559138. https://doi.org/10.3389/fgene.2020.559138
67. Schlauch KA, Read RW, Lombardi VC, Elhanan G, Metcalf WJ, Slonim AD, *et al*. A Comprehensive Genome-Wide and Phenome-Wide Examination of BMI and Obesity in a Northern Nevadan Cohort. G3: Genes, Genomes, Genetics 2020; 10(2):645-64. https://doi.org/10.1534/G3.119.400910