

Identification Variant of FTO, LEP, and LEPR Gene Prevalence in Patients with Obesity at Panti Rapih Hospital, Yogyakarta

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HIGHLIGHTS

- ❖ FTO (rs9939609, rs1421085), LEP (rs10487505), and LEPR (rs1137100, rs2186248) variants were identified in obese patients from Panti Rapih Hospital Yogyakarta
- ❖ LEP rs10487505 and LEPR rs2186248 variants showed the highest prevalence (100%) among all subjects.
- ❖ These variants may serve as genetic biomarkers for obesity risk and early family-based screening

ABSTRACT

Obesity is a complex chronic disease marked by excessive body fat and serious health risks, rising globally. In Indonesia, 13.5% of adults are overweight, and 28.7% are obese. Variants of the FTO, LEP, and LEPR genes may increase obesity risk. This study identified and analyzed the prevalence of FTO (rs9939609, rs1421085), LEP (rs17151919, rs10487505), and LEPR (rs1137100, rs2186248) gene variants in obese patients at Panti Rapih Hospital, Yogyakarta. These variants could serve as biomarkers for obesity risk assessment and early detection through family screening. Saliva samples from ten obese patients were tested for FTO variants (rs9939609, rs1421085) using ARMS-PCR, while LEP (rs17151919, rs10487505) and LEPR (rs1137100, rs2186248) variants were amplified by PCR and sequenced via Sanger sequencing. Results showed that five patients carried FTO variants (rs9939609, rs1421085), nine had the LEPR rs1137100 variant, all ten carried the LEP rs10487505 and LEPR rs2186248 variants, while LEP rs17151919 was undetected. The study found a 50% prevalence of FTO variants (rs9939609, rs1421085), 90% for LEPR rs1137100, and 100% for LEP rs10487505 and LEPR rs2186248 in obese patients at Panti Rapih Hospital.



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INTRODUCTION

Obesity is a growing global public health issue. Being overweight means having a body weight above the normal range for someone's height and body mass index, which can lead to health risks if not addressed (Guh et al., 2009). Obesity, on the other hand, is a condition where someone's body weight is excessively high due to an overconsumption of nutrients like carbohydrates, proteins, and fats compared to their energy needs (Nurcahyo, 2011). A person is considered obese if their body mass index (BMI, kg/m²) is ≥ 30.00 (Lin & Li, 2021). Obesity and overweight are different conditions, but both reflect excess fat accumulation in the body, characterized by a body mass index above the normal range (Bangkele & Sumarni, 2023). In 2018, according to The Indonesia Health Ministry, over 13% of adults and nearly 19% of children aged 5-12 are overweight, while around 29% of adults and 11% of children are obese (Seidell & Halberstadt, 2015). The increasing prevalence of obesity has become a global problem affecting both developed and developing countries, including Indonesia. Obesity is one of the major public health issues in Indonesia. Mortality rates from obesity-related diseases have become significant in several Asian countries, even at relatively low BMI levels. Despite having a relatively low prevalence, Indonesia has experienced an increase in obesity-related diseases compared with developed countries (Nugraha et al., 2022). Globally, obesity reduces quality of life and contributes to illnesses like cancer, osteoarthritis, diabetes, cardiovascular disease, and sleep apnea (Indonesian Ministry of Health, 2018). The *FTO* (Fat Mass and Obesity-Associated) gene influences body mass index and susceptibility to obesity (Fawcett & Barroso, 2010). In addition, the *LEP* (*LEP*tin) and *LEPR* (*LEP*tin Receptor) genes have been recognized as obesity-causing genes (Mahmoud et al., 2022). Some variants of the *FTO*, *LEP*, and *LEPR* genes have been linked to increased body mass index and obesity risk. However, there is still minimal research on *FTO* (rs9939609, rs1421085), *LEP* (rs17151919, rs10487505), and *LEPR* (rs1137100, rs2186248) gene variants in the Yogyakarta Special Region. Therefore, this study aimed to identify the presence and determine the prevalence of the *FTO* gene (rs9939609, rs1421085), *LEP* gene (rs17151919, rs10487505), and *LEPR* gene (rs1137100, rs2186248) variants in obese patients at Panti Rapih Hospital, Yogyakarta Special Region, as this information is crucial for developing preventive strategies against obesity risk genetic variants.

MATERIALS AND METHODS

Participants and ethical consideration

Ethical clearance was granted by the Ethics and Legal Commission of Panti Rapih Hospital Yogyakarta (Ref. No.: 126/SKEPK-KKE/XI/2023). Saliva samples were collected from obese patients at the hospital who voluntarily participated using the Saliva Collection Kit (NEST, Jiangsu, China). Inclusion criteria were patients aged 16–35 years with a body mass index over 25. Exclusion criteria included diabetes mellitus, pregnancy, and smoking. Before sample collection, participants received detailed information and provided informed consent. Data confidentiality was ensured.

Molecular detection for *FTO* gene variants with ARMS-PCR

Ten participants met the inclusion criteria and were purposefully recruited to undergo molecular testing. Genomic DNA was extracted from their samples using the DNA Mini Kit (Geneaid, Taipei, Taiwan). The DNA extraction results were analyzed using NanoDrop to determine DNA concentration and purity. The *FTO* gene variants rs9939609 and rs1421085 were detected through the amplification refractory mutation system (ARMS) technique, which involved using a set of inner forward, inner reverse, outer forward, and outer reverse primers, as shown in **Tables 1 & 2** (Mozafarizadeh et al., 2019; Al-Ogaidi et al., 2020). A specific DNA fragment spanning intron 1 of the *FTO* gene was amplified via standard polymerase chain

reaction (PCR). The quality of the PCR products and the extracted DNA was assessed qualitatively by visualizing the amplicon sizes through gel electrophoresis using the Gel-Doc 1000 UV transilluminator. The analysis process involved verifying the suitability of the amplicon sizes and correlating variant detection results with participants' clinical conditions.

Table 1. Primers for rs9939609 variant of the *FTO* gene detection

SNP	Primary Sequence	Product Size	References
rs9939609 (T>A)	5'-GCTGCTATGGTTCTACAGTTCCA-3' (outer forward)	461 bp	Mozafarizadeh et al., 2019
	5'-TGTTCAAGTCACACTCAGCCTC-3' (outer reverse)		
	5'-CCTTGCGACTGCTGTGAATATA-3' (inner forward)	211 bp, A allele	
	5'-CAGAGACTATCCAAGTGCATCTCA-3' (inner reverse)	296 bp, T allele	

Table 2. Primers for rs1421085 variant of the *FTO* gene detection

SNP	Primary Sequence	Product Size	References
rs1421085 (T>C)	5'- GGTTGTAATGAAGTTTTAGGCCTCA -3' (outer forward)	450 bp	Al-Ogaidi et al., 2020
	5'- AGCCATCCATCAGGTAAATAAATG -3' (outer reverse)		
	5'- TAGCAGTTCAGGTCCTAAGGCATTAT -3' (inner forward)	213 bp, T allele	
	5'- CAAATTCTCATCAGACACTTAATCACTG -3' (inner reverse)	291 bp, C allele	

Molecular detection for *LEP* and *LEPR* gene variants with PCR and Sanger Sequencing

Ten participants fulfilling the inclusion criteria were deliberately chosen for molecular testing. The samples underwent genomic DNA extraction using the DNA Mini Kit (Geneaid, Taipei, Taiwan) and were subsequently assessed with NanoDrop to measure concentration and purity. *LEP* gene variants rs17151919 and rs10487505, and *LEPR* gene variants rs1137100 and rs2186248 were amplified using PCR with forward and reverse primers shown in **Tables 3 & 4**. The integrity of the PCR products and extracted DNA was evaluated qualitatively by examining the amplicon sizes through gel electrophoresis, utilizing the Gel-Doc 1000 UV transilluminator for visualization. The amplified DNA was subsequently sequenced, and sequencing data analysis was performed by aligning the results with the reference sequence.

Table 3. Primers for rs17151919 and rs10487505 variants of the *LEP* gene detection

SNP	Primer	Primary Sequence	Product Size
rs17151919 G>A/G>C	Forward	5'-CTGGGTGCAGGATACAAG-3'	595 bp
	Reverse	5'-TTCAATCCTGGAGATACCTG-3'	
rs10487505 G>C/G>T	Forward	5'- CCAATCCCAGTTTTCTCCAA- 3'	323 bp
	Reverse	5'- AGCATGCAGTGCTTTGTCTG- 3'	

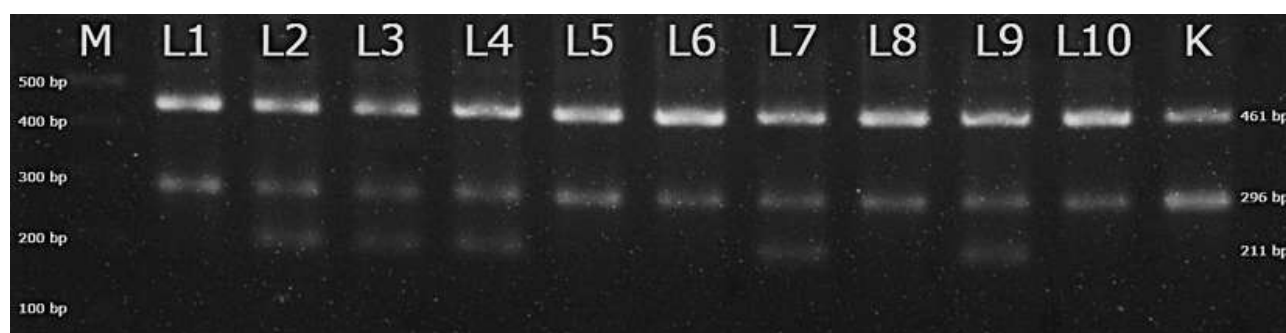
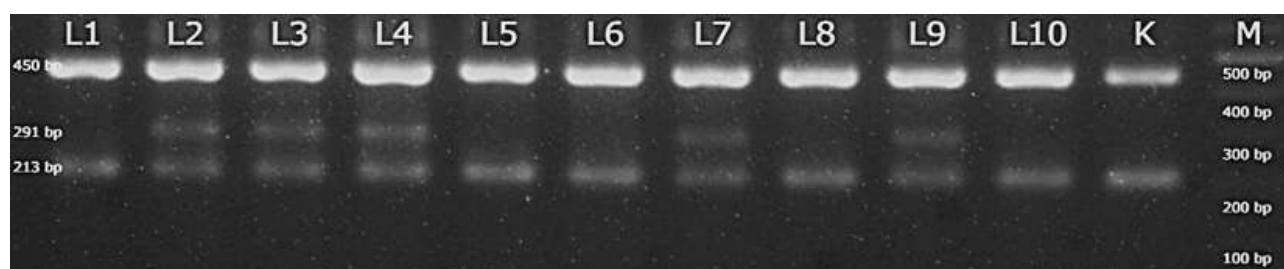
Table 4. Primers for rs1137100 and rs2186248 variants of the *LEPR* gene detection

SNP	Primer	Primary Sequence	Product Size
rs1137100 (A>G/T)	Forward	5'-CTCCTTGGAGATTTAAGTTGTC-3'	660 bp
rs2186248 (G>T/A/C)	Reverse	5'-CAGAGATATTCCTTGCCTGA-3'	

RESULTS

Visualization of the amplification of *FTO* gene variant using Tetra-ARMS PCR

Later, the DNA extracts were amplified using Tetra-ARMS PCR for both variants rs9939609 and rs1421085. The PCR results were then visualized using agarose gel electrophoresis to obtain amplicons, as shown in **Figures 1 & 2**.

**Figure 1.** rs9939609 variant of the *FTO* gene detected in subject samples**Figure 2.** rs1421085 variant of the *FTO* gene detected in subject samples

The results of the molecular investigation are illustrated in **Figures 1 & 2**. We identified the rs9939609 variant, as evidenced by the presence of amplicon bands of 461 base pairs (bp) in all samples, which corresponds to the expected PCR product size of approximately 461 bp for the amplification of the

rs9939609 variant, as documented in the literature (7). Regarding the rs1421085 variant, consistent amplicon bands of 450 bp were detected in every sample, matching the anticipated PCR product size of around 450 bp for the amplification of the rs1421085 variant, as reported in the literature (8). Notably, distinct amplicon patterns were observed for the rs9939609 variant in samples L2, L3, L4, L7, and L9, with two additional bands at 211 bp and 296 bp. A similar pattern emerged for the rs1421085 variant in the same samples, with two additional bands at 213 bp and 291 bp. These distinct band patterns indicate a heterozygous allelic state (AT) and (CT) for the rs9939609 and rs1421085 variants, respectively, in samples L2, L3, L4, L7, and L9. This finding suggests that these samples carry both allelic variants concurrently, with one copy of the reference allele and one copy of the variant allele for each investigated genetic marker.

Visualization of *LEP* and *LEPR* gene amplification results

The amplified DNA results from PCR for variants rs17151919 and rs10487505 *LEP* gene and variants rs1137100 and rs2186248 *LEPR* gene are visualized using agarose gel electrophoresis to obtain amplicons, as shown in **Figures 3–5**.

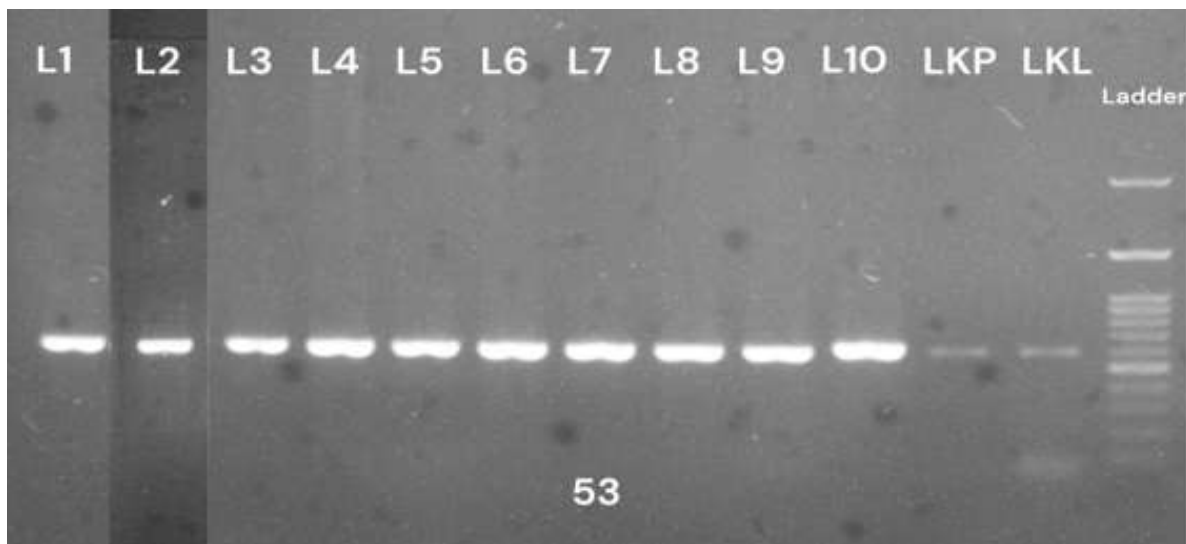


Figure 3. Visualization of the rs17151919 *LEP* gene amplification results

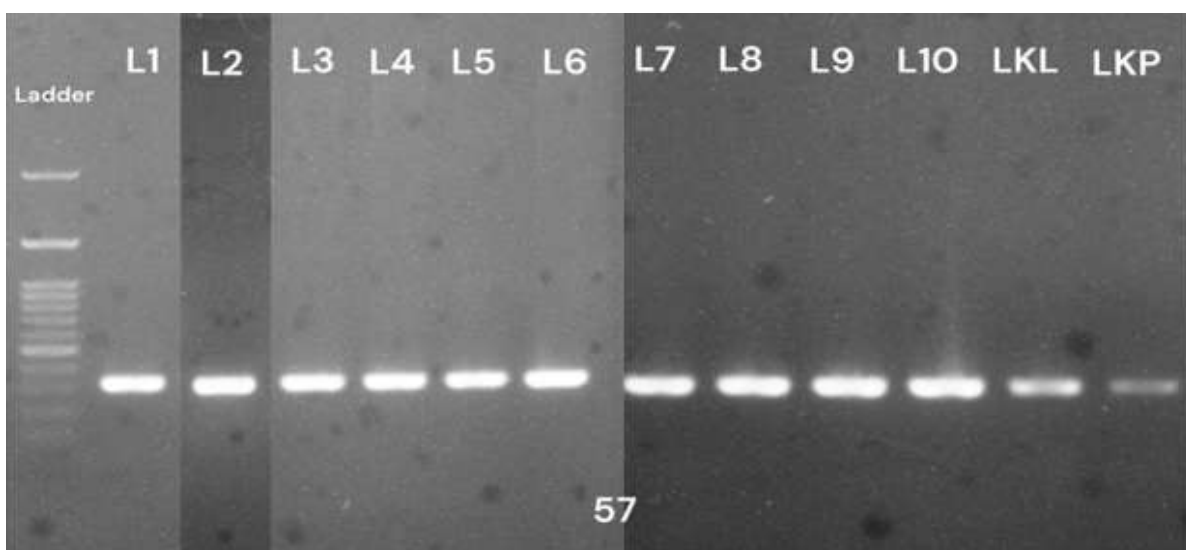


Figure 4. Visualization of the rs104875905 *LEP* gene amplification results

Based on **Figure 3**, electrophoresis of the *LEP* gene variant rs17151919 shows an amplicon size of 595 bp in all test samples, consistent with Primer3Plus predictions and BLAST validation on NCBI. This confirms successful amplification with the expected product size. Similarly, **Figure 4** shows that electrophoresis of the *LEP* gene variant rs10487505 produced a 323 bp amplicon in all test samples, consistent with the predicted primer design. This result verifies the accuracy of the amplification process.

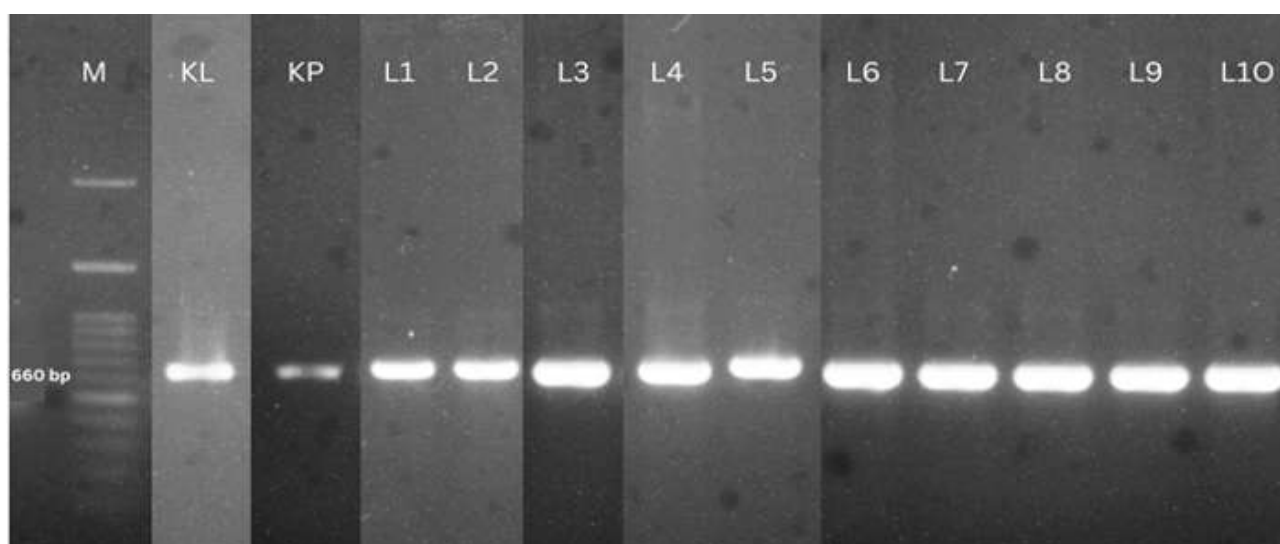


Figure 5. Visualization of the rs1137100 and rs2186248 variants of *LEPR* gene amplification result

Based on **Figure 5**, electrophoresis visualized using the Gel Doc 1000 UV transilluminator shows that the amplicon size is 660 bp in all samples. The primer design using Primer3Plus and validation using the BLAST feature on NCBI also indicate an amplicon size of 660 bp. Additionally, the electrophoresis gel shows a single band. Therefore, it can be confirmed that DNA amplification was successfully performed, and the PCR product can proceed to sequencing.

Alignment to reference sequence with Benchling

This study detects polymorphism variants in the *LEP* and *LEPR* genes through sequencing. Sequencing was performed on PCR products from 10 obese patients and 2 control samples. The obtained nucleotide sequences were then aligned using the Benchling software as shown in **Figures 6–10**.

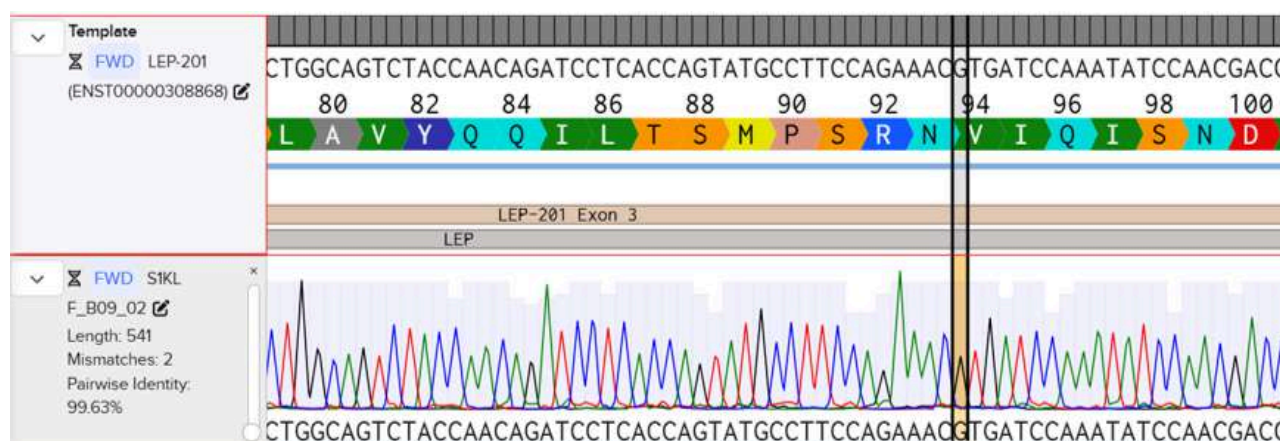


Figure 6. Alignment result for identification of the rs17151919 variant of the *LEP* gene

Based on the sequencing results, the alignment shown in **Figure 6** indicates no nitrogenous base change at the rs17151919 variant position at genomic position g.128254539, according to the reference sequence of the *LEP* transcript NM_000230.3:c.280G>C (National Center for Biotechnology Information, 2024). At this position, the nitrogenous base G in the reference sequence matches the sequencing result. Therefore, the rs17151919 variant is not detected in this sample. The rs17151919 variant is detected when a G>A/C substitution occurs.

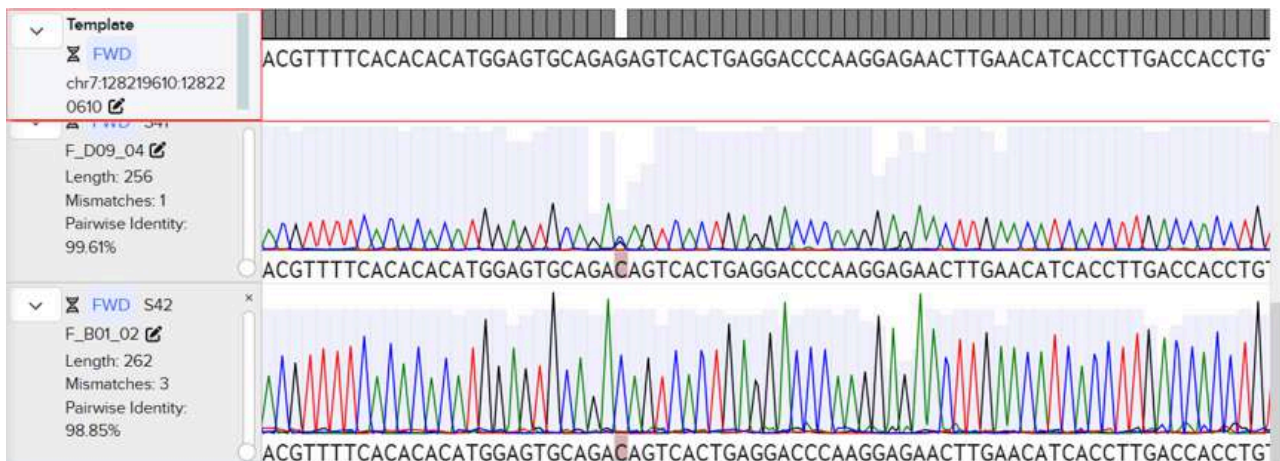


Figure 7. Alignment result for identification of the rs10487505 variant of the *LEP* gene

Based on **Figure 7**, the alignment of one DNA sequence from an obese patient sample for the detection of the rs10487505 polymorphism variant in the *LEP* gene shows a mismatch or nucleotide difference between the target and reference sequences, indicating genetic variation. A nitrogenous base change occurs at the rs10487505 variant position at genomic position g.128220110, according to the reference sequence of the *LEP* transcript NC_000007.14:g.128220110G>C (National Center for Biotechnology Information, 2024). Based on the figure, two samples exhibit different chromatogram patterns: one sample shows a double peak at the rs10487505 variant position, while the other does not. The double peak indicates that the individual carries two different alleles at this position, categorizing them as heterozygous.

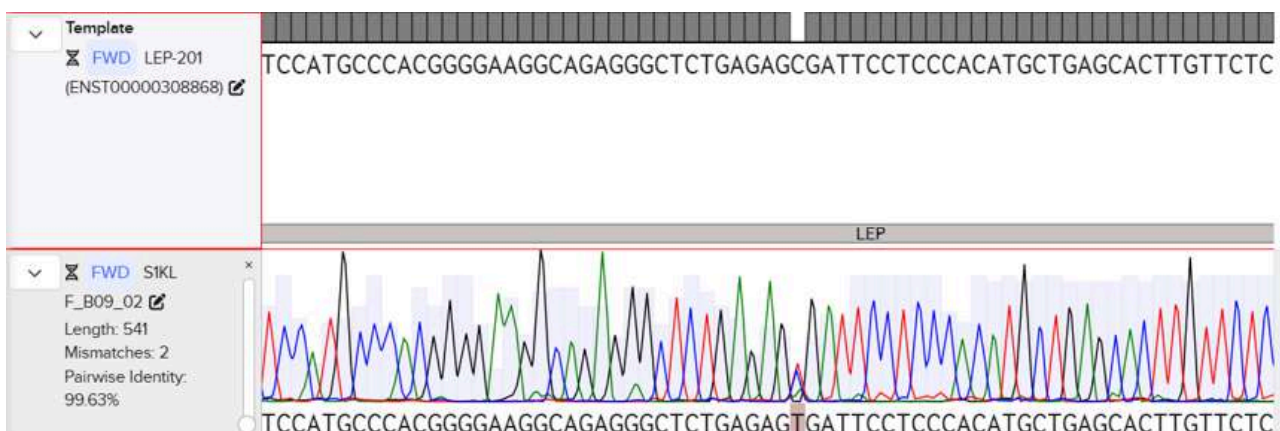


Figure 8. Alignment result for identification of the rs17151914 variant of the *LEP* gene

Based on **Figure 8**, there is a nitrogenous base change: C changes to T at genomic position g.128254354. According to the reference sequence of the *LEP* transcript NC_000007.14:g.128254354C>T,

the allele change at genomic position g.128254354 corresponds to the rs17151914 variant in the *LEPR* gene (National Center for Biotechnology Information, 2024).

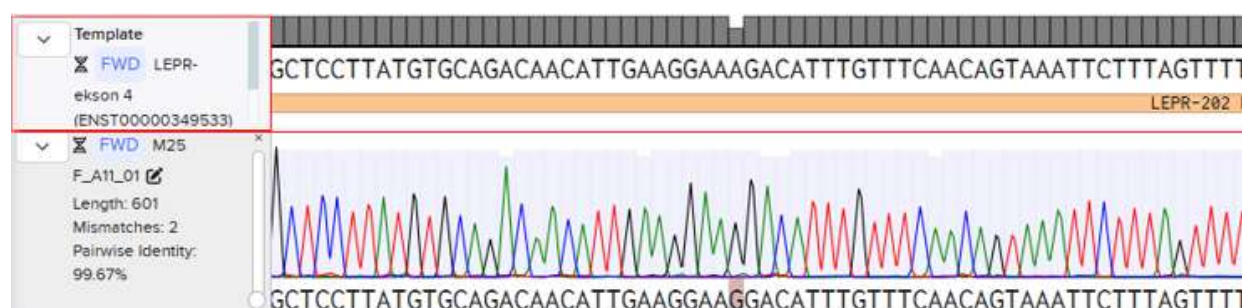


Figure 9. Alignment result for identifying the rs1137100 variant of the *LEPR* gene

Based on the sequencing results aligned in **Figure 9**, a transition substitution was identified, specifically a base change from A to G at chromosome 1, position 65,570,758, according to RefSeq accession number NC_000001.11:g.65570758A>G. This variation changes the amino acid from lysine (Lys) to arginine (Arg) at position 109 of the protein, known as Lys109Arg. The rs1137100 variant is also referred to as c.326A>G, which indicates a nucleotide substitution of adenine (A) to guanine (G) at position 326, based on RefSeq accession number NM_002303.6:c.326A>G (National Center for Biotechnology Information, 2021).

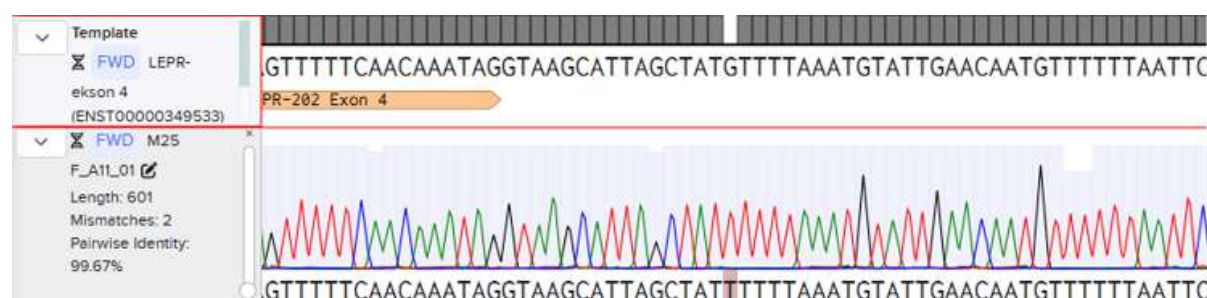


Figure 10. Alignment result for identifying the rs2186248 variant of the *LEPR* gene

Based on the sequencing results aligned in **Figure 10**, a transversion substitution was identified, specifically a base change from G to T at chromosome 1, position 65,570,818, according to RefSeq accession number NC_000001.11:g.65570818G>T (National Center for Biotechnology Information, 2021). This variant is intronic, meaning it is located within an intron (non-coding segment) of the *LEPR* gene.

Interpretation of chromatograms

Chromatogram interpretation verifies sequencing quality by assessing peak shape, intensity, and spacing. High-quality chromatograms have distinct, evenly spaced peaks, while poor-quality ones show overlaps or signal drop-offs. The alignment results in Benchling were also confirmed by the chromatograms in **Figures 11–14**.

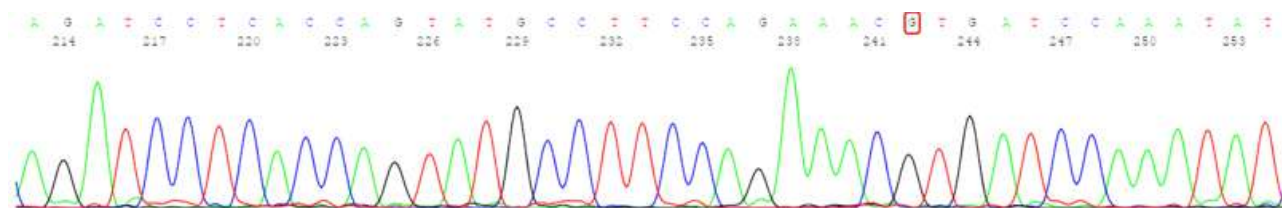


Figure 11. Chromatogram representation of sequencing results of identification the rs17151919 variant of the *LEP* gene

Based on **Figure 11**, the nucleotide sequence from the sequencing results shows a black peak at this position, indicating the presence of Guanine (G). The rs17151919 variant is detected as a G>A/C substitution. This variant was not found in the female control group or in the overall samples of obese patients.

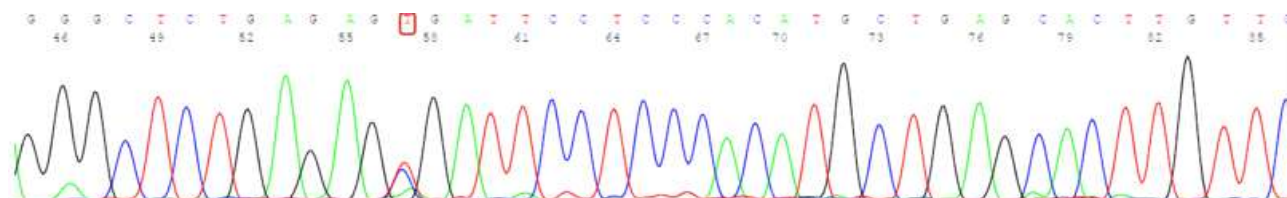
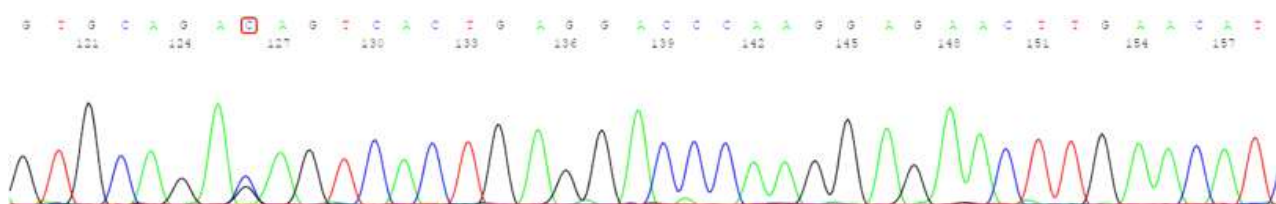
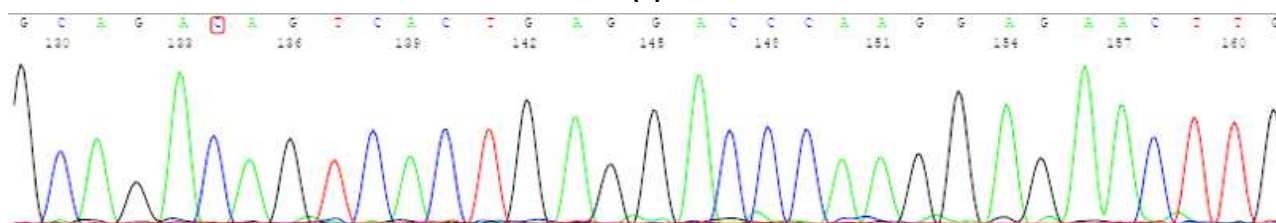


Figure 12. Chromatogram representation of sequencing results showing detection of the rs17151914 variant and identification of the rs17151919 variant in the *LEP* gene.

Based on **Figure 12**, the sequencing results show a blue peak representing Cytosine (C) and a red peak representing Thymine (T). The rs17151914 variant is detected when there is a C>A/T substitution. This result reinforces that the sequencing findings are consistent with the alignment data from Benchling. This variant is located before exon 3, meaning it is not translated into an amino acid in the alignment.



(a)



(b)

Figure 13. Chromatogram representation of sequencing results for identifying the rs10487505 variant in the *LEP* gene.
(a) Heterozygous GC genotype; (b) Homozygous CC genotype

Based on **Figure 13**, in the nucleotide sequence from the sequencing results, a blue peak indicates Cytosine (C), while a black peak represents Guanine (G). In the chromatogram representation, both patients were detected with the rs10487505 variant, characterized by a G>C substitution. In the first sample, shown

in **Figure 13(a)**, the detected variant is classified as heterozygous, as indicated by two peaks at the variant position. Meanwhile, in the second sample, shown in **Figure 13(b)**, the detected variant is classified as a homozygous mutation, identified by a single peak at the allele position, despite the individual carrying a different allele. Further analysis of these allele differences indicates two mutation types: heterozygous and homozygous. Heterozygous mutations were found in the male control sample (L4KL) and two obese patients (L41 and L43), while homozygous mutations were identified in the female control sample (L4KP) and eight obese patient samples (L42, L44, L45, L46, L47, L48, L49, and L410).

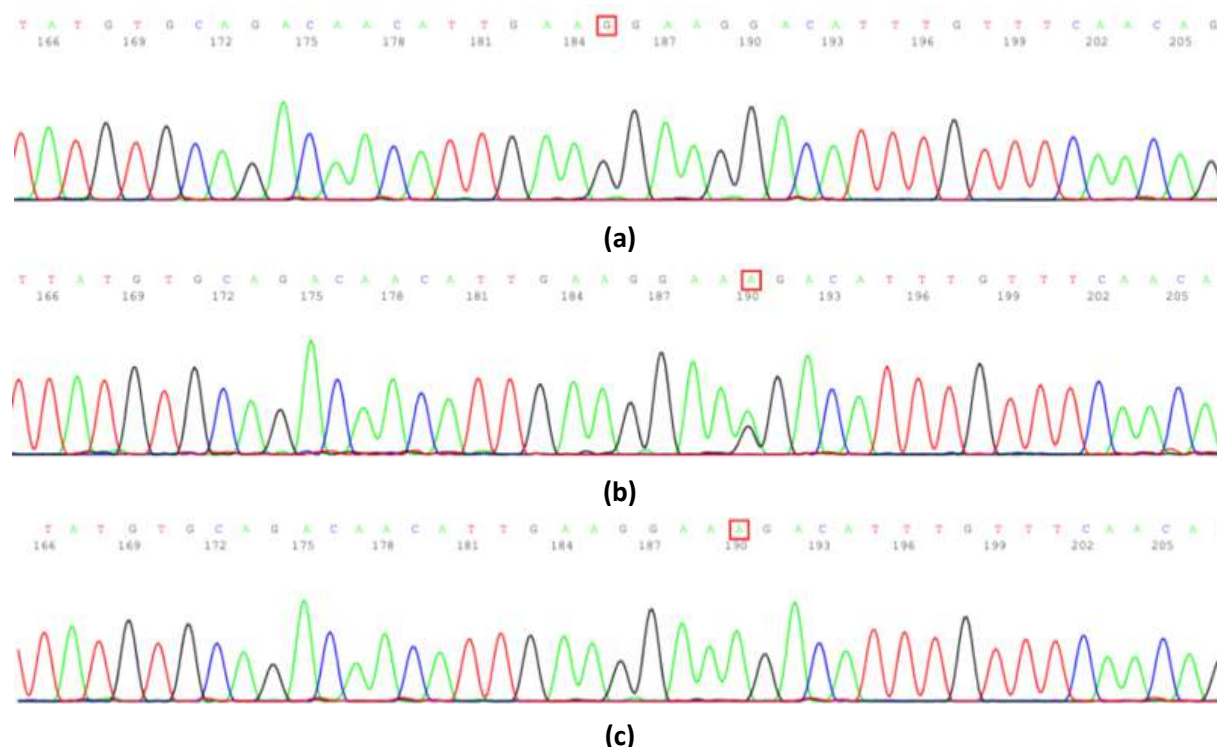


Figure 14. Chromatogram representation of sequencing results for identifying the rs113700 variant in the *LEPR* gene. (a) Homozygous GG genotype; (b) Heterozygous AG genotype; (c) Homozygous AA genotype

In **Figure 14(a)**, there is a black peak, which corresponds to the guanine (G) base. The substitution of guanine (G) to adenine (A) signifies the presence of the rs1137100 (A>G/T) variant. This variant is homozygous, as only a single peak is present, specifically the black peak, which refers to the guanine (G) nucleotide base. This variant is also found in other samples, including L4, L5, L6, L9, and L10, as shown in **Figure 12(a)**. In **Figure 12(b)**, samples KL, KP, L1, L2, L3, and L7 are heterozygous, as indicated by both a green peak (adenine, A) and a black peak (guanine, G). In **Figure 12(c)**, sample L8 is homozygous, as shown by a single green peak indicating the adenine (A) base.

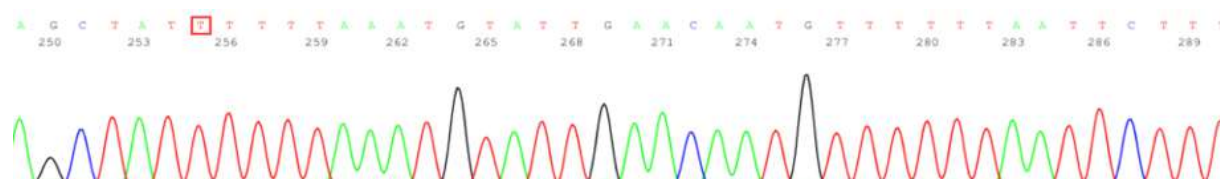


Figure 15. Chromatogram representation of sequencing results for identifying the rs2186248 variant in the *LEPR* gene

In **Figure 15**, the red peak indicates the thymine (T) base. The substitution of guanine (G) to thymine (T) signifies the presence of the rs2186248 (G>T/A/C) variant. This variant is homozygous, as only a single peak is present, specifically the red peak, which refers to thymine (T). This variant is found in all obese patient samples, including the control samples labeled KL and KP.

DISCUSSION

This study was conducted to identify the presence of the *FTO* gene rs9939609 and rs1421085 variants in obese patients at Panti Rapih Hospital Yogyakarta. Genotype analysis of the aforementioned variants of the *FTO* gene was carried out by gender and obesity classification, as described in **Tables 3 & 4**.

Table 5. Genotypes of *FTO*, *LEP*, and *LEPR* variants based on the gender and obesity classification of research subjects

Factors	<i>FTO</i> gene				<i>LEP</i> gene				<i>LEPR</i> gene			
	rs9939609		rs1421085		rs17151919		rs10487505		rs1137100		rs2186248	
	**G	**N	G	N	G	N	G	N	G	N	G	N
Gender												
Male	TT	3	TT	3	GG	5	GG	0	AA	1	GG	0
	*AT	2	*CT	2	*GC	0	*GC	0	*AG	1	*GT	0
	*AA	0	*CC	0	*CC	0	*CC	5	*GG	3	*TT	5
Female	TT	2	TT	2	GG	5	GG	0	AA	0	GG	0
	*AT	3	*CT	3	*GC	0	*GC	2	*AG	3	*GT	0
	*AA	0	*CC	0	*CC	0	*CC	3	*GG	2	*TT	5
Classification												
Overweight	TT	2	TT	2	GG	4	GG	0	AA	0	GG	0
	*AT	2	*CT	2	*GC	0	*GC	0	*AG	1	*GT	0
	*AA	0	*CC	0	*CC	0	*CC	4	*GG	3	*TT	4
Obesity I	TT	2	TT	2	GG	4	GG	0	AA	1	GG	0
	*AT	2	*CT	2	*GC	0	*GC	1	*AG	2	*GT	0
	*AA	0	*CC	0	*CC	0	*CC	3	*GG	1	*TT	4
Obesity II	TT	1	TT	1	GG	1	GG	0	AA	0	GG	0
	*AT	0	*CT	0	*GC	0	*GC	1	*AG	1	*GT	0

	<i>FTO</i> gene				<i>LEP</i> gene				<i>LEPR</i> gene			
	*AA	0	*CC	0	*CC	0	*CC	0	*GG	0	*TT	1
	TT	0	TT	0	GG	1	GG	0	AA	0	GG	0
Obesity III	*AT	1	*CT	1	*GC	0	*GC	0	*AG	0	*GT	0
	*AA	0	*CC	0	*CC	0	*CC	1	*GG	1	*TT	1

*Shows the genotypes of variants from the *FTO*, *LEP*, and *LEPR* genes

**G, genotype; N, number

Based on **Table 5**, the genotype distribution by sex in the detection of the rs17151919 (G>C) variant shows that the GG genotype was found in 10 samples (all samples), consisting of 5 male samples and 5 female samples. Meanwhile, in the detection of the rs10487505 (G>C) variant, the GC genotype was found in 2 samples, both female. Additionally, the CC genotype was detected in 8 samples: 5 males and 3 females.

The genotype distribution for obesity classification in the detection of the rs17151919 (G>C) variant shows that the GG genotype was found in 10 samples, consisting of 4 samples classified as overweight, 4 samples as obesity class I, 1 sample as obesity class II, and 1 sample as obesity class III, as shown in **Table 5**. Meanwhile, for the rs10487505 (G>C) variant, the GC genotype was found in 2 samples: 1 sample classified as obesity class I and 1 sample as obesity class II. Additionally, the CC genotype was detected in 8 samples: 4 classified as overweight, 3 as obesity class I, and 1 as obesity class III.

According to **Table 5**, analysis of the rs9939609 variant in the *FTO* gene (T>A) showed that 5 samples had the TT genotype, comprising 3 male samples and 2 female samples. Concurrently, the remaining 5 samples displayed the AT genotype, with 2 male and 3 female samples. Meanwhile, examination of the rs1421085 (T>C) variant of the *FTO* gene genotypes showed that 5 samples carried the TT genotype (3 male and 2 female samples), while the other 5 samples possessed the CT genotype (2 male and 3 female samples). Based on these findings, the rs9939609 (T>A) and rs1421085 (T>C) variants of the *FTO* gene were more frequently detected among female individuals in the obese patient population at Panti Rapih Hospital Yogyakarta. For the rs1137100 (A>G/T) variant in the *LEPR* gene, the AA genotype was found in 1 sample and was present only in male subjects. The AG genotype was observed in 4 samples: 1 male and 3 females. Meanwhile, the GG genotype was found in 5 samples: 3 in males and 2 in females. Furthermore, the rs2186248 (G>T/A/C) of the *LEPR* gene variant in the TT genotype was present in 10 samples: 5 male and 5 female samples. The results indicate that the rs1137100 variant of the *LEPR* gene in the obese patient population at Panti Rapih Hospital, Yogyakarta, was more commonly found in female subjects, whereas the rs2186248 variant of the *LEPR* gene was found in equal numbers in both male and female subjects.

The genotypes related to obesity classification were identified during the detection of the variant rs9939609 (T>A) of the *FTO* gene, as shown in **Table 5**. The TT genotype was observed in 5 samples: 2 categorized as overweight, 2 in obesity classification I, and 1 in obesity classification II. Similarly, the AT genotype was present in 5 samples, with 2 classified as overweight, 2 as obese I, and 1 as obese III. For the rs1421085 (T>C) variant of the *FTO* gene, the TT genotype was found in 5 samples, with 2 categorized as overweight, 2 as obesity classification I, and 1 as obesity classification II. Conversely, the CT genotype was identified in 5 samples, including 2 classified as overweight, 2 as obese I, and 1 as obese III. Variants rs1137100 (A>G/T) of the *LEPR* gene in the AA genotype was found in 1 sample, which belonged to obesity

level I. The AG genotype was observed in 4 samples: 1 in the overweight category, 2 in obesity level I, and 1 in obesity level II. Meanwhile, the GG genotype was found in 5 samples: 3 in the overweight category, 1 in obesity level I, and 1 in obesity level III. Furthermore, variant rs2186248 (G>T/A/C) of the *LEPR* gene in 10 obese patient samples had the TT genotype, consisting of 4 samples in the overweight category, 4 samples in obesity level I, 1 sample in obesity level II, and 1 sample in obesity level III.

Hence, in a sample population of obese patients at Panti Rapih Hospital Yogyakarta, variants rs9939609 and rs1421085 of the *FTO* gene and variant rs1137100 of the *LEPR* gene were identified across overweight, obesity I, and obesity III classifications, predominantly in women. Women exhibit a heightened susceptibility to physical and psychological comorbidities associated with obesity, with a twofold greater risk of mortality compared to overweight men (Kapoor et al., 2021). In the United States, the prevalence of obesity stands at 40.4% for women and 35.0% for men, with even higher rates among women in the severe obesity category, reaching 9.9%. Over the past two decades, there has been a notable rise in obesity prevalence among women, notably from 2005 to 2014 (Tauqeer et al., 2018). Key factors contributing to differential risk between genders include variances in the insulin growth factor axis, the influence of gonadal hormones, and the emerging role of adipocytokines. Overall, obesity-associated malignancies are more frequently observed in women, encompassing endometrial, ovarian, and post-menopausal breast cancers (Kapoor et al., 2021).

In this study, heterozygous allele outcomes were identified for the rs9939609 (AT) and rs1421085 (CT) variants of the *FTO* gene. Individuals carrying the homozygous genotype for the rs9939609 (AA) and rs1421085 (CC) variants exhibit an elevated risk of obesity compared to carriers of the heterozygous genotype for the rs9939609 (AT) and rs1421085 (CT) variants, as well as those with the wild-type (TT) genotype (7, 8). Nevertheless, the presence of heterozygous alleles for both variants still impacts obesity occurrence in an individual. In the case of the rs9939609 variant, individuals carrying the A allele tend to favor high-energy foods, experience increased body weight, and exhibit tendencies toward excessive eating behaviors (Mehrdad et al., 2020). Conversely, the CC and TC alleles of the rs1421085 variant of the *FTO* gene were positively correlated with body mass index, macronutrient intake, and fatty acid intake (Al-Jawadi et al., 2021).

Based on the obtained data, it was found that in the population of obese patients at Panti Rapih Hospital, Yogyakarta, the rs17151919 variant was not detected in either male or female samples. This was determined from the sequencing results, which showed that all observed samples had the wild-type genotype. This variant has a functional consequence as a missense variant and a coding-sequence variant, but it is likely not a major factor in obesity occurrence in this population. Clinically, this variant is classified as likely benign or benign, meaning it has a low probability of causing pathological effects.

In this study, the rs10487505 (G>C) variant of the *LEP* gene was detected in all samples. This was identified through genotype analysis, where a G-to-C substitution occurred either in one allele (GC, forming a heterozygous variant) or in both alleles (CC, forming a homozygous variant). The rs10487505 variant was found in overweight, obesity class I, obesity class II, and obesity class III classifications. The rs10487505 variant in the *LEP* gene is classified as an intron variant, meaning the mutation occurs in a non-coding intron region. This variant does not directly affect the structure or function of the *LEP* protein, but it may still influence gene expression regulation.

In this study, both heterozygous (GC) and homozygous (CC) alleles of the rs10487505 variant were detected in the *LEP* gene. Individuals carrying the homozygous genotype (CC) have a higher likelihood of developing obesity compared to those with the heterozygous genotype (GC) or the wild-type (GG). This

finding aligns with previous research indicating that heterozygous variants can become pathogenic when in a homozygous state (Machha et al., 2024).

Research has shown that *LEP*tin, a hormone produced by the *LEP* gene, plays a crucial role in regulating food intake, body mass, and reproductive function. *LEP* functions through a negative feedback mechanism between adipose tissue and the hypothalamus to regulate body mass. *LEP*tin resistance, characterized by reduced satiety and increased nutrient intake, often leads to obesity (Obradovic et al., 2021).

Apart from the rs17151919 and rs10487505 variants, another variant, rs17151914 (C>T), was detected in the male control sample. This variant involves a cytosine (C) to thymine (T) substitution at a specific DNA position and is classified as a Single Nucleotide Variation (SNV) since it involves a single nucleotide change in the genome. This variant is located in an intron region, which is non-coding DNA, meaning it is removed during splicing before the RNA is translated into a protein (Bairqdar et al., 2023). The impact of intron mutations (intron variants) is often related to regulatory elements such as enhancers or silencers, which can affect gene expression levels and alter interactions with DNA-binding proteins, such as transcription factors, thereby influencing gene activity. However, some intron variants may be neutral, meaning they do not affect gene expression or protein function (Liu et al., 2015). A study has shown that the rs17151914 variant in the *LEP*tin gene is associated with overweight conditions in both males and females with depression, with a prevalence of 5.26% in the depressed population. In the general population, its frequency is reported to be 2% in Pakistan and 4% globally (Muscogiuri et al., 2024).

The rs1137100 variant of the *LEPR* gene was analyzed as a gene mutation that causes an amino acid substitution from lysine to arginine at codon 109 (A/G) (AAG to AGG). This change can affect *LEP*tin binding, receptor dimerization, and the signaling capacity of the *LEP*tin receptor. However, this mutation does not always occur, as many other factors contribute to obesity (Linjawi & Al-Harbi, 2014). According to Grzeszczak et al. (2018), there is no significant association between the rs1137100 variant of the *LEPR* gene and obesity. However, when subjects were categorized by gender, a study conducted by Gotoda et al. (1997) on the male population in England found no significant association between genotype and BMI in the male group. In contrast, a study by Rosmond et al. (2000) on the male population in Sweden found a significant association between BMI and the rs1137100 polymorphism. Additionally, there was a significant relationship between genotype and BMI in the female group. A study by Oliveira et al. (2013) found that the G allele and the GG genotype were less frequent in obese than in non-obese individuals in the Brazilian female population. In the Saudi Arabian population, no association was found between the rs1137100 polymorphism and obesity in males, but it was reported that this polymorphism was associated with obesity in females (Linjawi & Al-Harbi, 2014). These differences in results may be due to ethnic variations in study subjects, behavioral factors, and environmental influences. The rs2186248 variant of the *LEPR* gene undergoes a G-to-T base substitution in all obese patient samples, including the control samples. There are 10 types of nonsynonymous SNPs in the *LEPR* gene, with rs3790435, rs13306522, rs13306520, rs70940803, rs2186248, and rs1359482195 playing a role in the development of Metabolically Unhealthy Obesity (MUO) in Caucasian children. The rs2186248 SNP has a weak association with the MUO phenotype; however, the TT genotype is frequently found in children with MUO. Lifestyle factors and an inadequate diet showed a moderate association with MUO. These findings emphasize the importance of physical activity and nutritional interventions in preventing metabolic complications. Beyond environmental factors, genetic molecular mechanisms related to SNPs in the *LEPR* gene also contribute to the development of meta-inflammation in MUO (Abaturov & Nikulina, 2021).

The rs9939609 and rs1421085 variants of the *FTO* gene pose a risk linked to elevated body mass index and increased body fat, which serve as primary risk factors for metabolic and cardiovascular diseases. This risk escalates among individuals with homozygous and heterozygous genotypes for both variants. Several ailments, including metabolic disease, cancer, and neurological disorders, are associated with *FTO* variants such as rs9939609 and rs1421085 (Zhao, 2014). The impacts of these *FTO* gene variants can be magnified by environmental factors such as sedentary lifestyles and unhealthy dietary patterns. Therefore, individuals carrying the risk genotype for the rs9939609 and rs1421085 variants of the *FTO* gene are encouraged to adopt a healthy lifestyle, comprising a balanced diet and regular physical activity, as a nutritious, low-calorie diet can mitigate the effects of the *FTO* gene variant on alterations in body composition and fat distribution among overweight and obese individuals (Zhang et al., 2012). Obesity can be one of the contributing factors to the development of diseases such as type 2 diabetes mellitus (T2DM) (Cao et al., 2019). T2DM is also influenced by the interaction between genotype and environmental factors (Hu & Jia, 2018). To date, obesity is considered an environmental risk factor that interacts with susceptible genes to increase T2DM risk (Lv et al., 2017). The rs1137100 variant of the *LEPR* gene is associated with T2DM risk, even after adjusting for age, sex, BMI, waist-to-hip ratio (WHR), smoking status, alcohol consumption, socioeconomic status, and hypertension. Individuals with the GG genotype have a higher risk of developing T2DM compared to those with the AA/AG genotype in the rs1137100 variant of the *LEPR* gene (Cao et al., 2019). Although the rs1137100 variant may contribute to an individual's susceptibility to obesity and T2DM, adopting a healthy lifestyle is also an important factor in reducing the impact of this variant on the *LEPR* gene. Additionally, screening of the patient's siblings can serve as an early detection measure to identify *FTO*, *LEP*, and *LEPR* gene risk variants, potentially preventing and reducing the incidence of obesity-related diseases. Therefore, the *FTO*, *LEP*, and *LEPR* genes present compelling indications as biomarkers for detecting obesity risk.

CONCLUSION

We discovered the rs9939609 and rs1421085 variants of the *FTO* gene, rs10487505 of the *LEP* gene, and rs1137100 and rs2186248 of the *LEPR* gene in obese patients at Panti Rapih Hospital Yogyakarta. The prevalence of the rs9939609 and rs1421085 variants in the *FTO* gene is 50%, the rs10487505 variant in the *LEP* gene is 100%, the rs1137100 variant in the *LEPR* gene is 90%, and the rs2186248 variant in the *LEPR* gene is 100%.

AUTHOR CONTRIBUTIONS

LRP: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – Original Draft. **ESP:** Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – Original Draft. **MA:** Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – Original Draft. **NSNH:** Data Curation, Funding Acquisition, Supervision, Writing – Review & Editing.

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COMPETING INTERESTS

The authors declare no conflict of interest.

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ADDITIONAL INFORMATION

None.

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