

Association of genetic variants of the Fat Mass and Obesity (FTO) gene and obesity in children

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Abstract

Introduction and Objectives: Single nucleotide variants (SNVs) of the gene associated with fat mass and obesity (FTO) make a significant contribution to the violation of energy metabolism and the development of obesity. Study the associations between SNVs of the FTO gene and the development of metabolic disorders in children with obesity. **Methods:** 252 obese children aged between six and 18 were examined. The main group (n = 152) represented children with metabolically unhealthy obesity (MUO). The control group (n = 100) consisted of children with metabolically healthy obesity (MHO). Whole genome sequencing (CeGat, Germany) was performed in 31 children from the main group and 21 children from the control group. **Results:** The association with the development of obesity is higher for the A allele rs2287142 (t = 2.29) and the T allele SNV rs17823223 (t = 6.34) compared to healthy individuals. Serum IL-6 levels in individuals with MHO depend on SNV rs2287142 (r = 0.73). The A allele of SNV rs1080312 is associated with basal hyperglycemia (r = 0.43) and impaired carbohydrate tolerance (r = 0.33), but negatively correlates with low serum cholesterol and low-density lipoprotein cholesterol (LDL-C) (r = -0.42 and r = -0.39, respectively). The T allele of SNV rs778691805 is associated with high levels of LDL-C in blood serum (r = 0.33). The T allele of SNV rs17823223 is negatively associated with basal hyperglycemia (r = -0.51) and directly correlates with high-density lipoprotein cholesterol (r = 0.33) (p < 0.05). **Discussion:** In obese children, SNV rs2287142 is associated with pro-inflammatory status and SNVs rs1080312, rs17823223, and rs778691805 of the FTO gene are associated with metabolic markers.

Keywords: Gene associated with fat mass and obesity. Analysis of single nucleotide gene variants. Children. Metabolically unhealthy obesity. Metabolically healthy obesity.

Associação de variantes genéticas do gene Fat Mass and Obesity (FTO) e obesidade em crianças

Resumo

Introdução e Objetivo: Variantes de nucleotídeo único (single nucleotide variants - SNV) do gene associado à massa gorda e obesidade (fat mass and obesity - FTO) contribuem significativamente para a violação do metabolismo energético e o desenvolvimento da obesidade. O objetivo é estudar as associações do SNV do gene FTO com o desenvolvimento de distúrbios metabólicos em crianças com obesidade. **Métodos:** Foram examinadas 252 crianças com obesidade de 6 a 18 anos. O grupo principal (n = 152) foi representado por crianças com obesidade metabolicamente não saudável (metabolically unhealthy obesity - MUO). O grupo controle (n = 100) consolidou-se de crianças com obesidade metabolicamente saudável

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(metabolically healthy obesity - MHO). O sequenciamento completo do genoma (CeGat, Alemanha) foi realizado em 31 crianças do grupo principal e 21 crianças do grupo controle. **Resultados:** A associação com o desenvolvimento de obesidade é maior para o alelo A rs2287142 ($t = 2,29$) e o alelo T SNV rs17823223 ($t = 6,34$) do que em indivíduos saudáveis. O nível sérico de IL-6 em MHO depende de SNV rs2287142 ($r = 0,73$). O alelo A do SNV rs1080312 está associado à hiperglicemia basal ($r = 0,43$) e tolerância prejudicada a carboidratos ($r = 0,33$), mas se correlaciona negativamente com baixo colesterol sérico, colesterol de lipoproteína de baixa densidade (LDL-C): $r = -0,42$, $r = -0,39$, respectivamente. O alelo T do SNV rs778691805 está associado a um alto nível de LDL-C no soro sanguíneo ($r = 0,33$). O alelo T do SNV rs17823223 está negativamente associado à hiperglicemia basal ($r = -0,51$) e se correlaciona diretamente com o colesterol de lipoproteína de alta densidade ($r = 0,33$), $p < 0,05$. **Discussão:** Em crianças obesas, o SNV rs2287142 está associado ao estado pró-inflamatório, e o SNV rs1080312, rs17823223, rs778691805 do gene FTO está associado a marcadores metabólicos.

Palavras-chave: Gene associado à massa gorda e obesidade. Análise de variantes de genes de nucleotídeo único. Crianças. Obesidade metabolicamente não saudável. Obesidade metabolicamente saudável.

Keypoints

What is known

– The role of the FTO gene in the accumulation of body fat mass.

What is added

– SNVs rs1080312, rs17823223, and rs542356043 of the FTO gene in children with obesity were identified by us for the first time.

Introduction

According to World Health Organization (WHO) experts worldwide, by 2030 more than one billion people will be obese. Obesity induces the development of metabolic disorders, which significantly worsen a person's state of health and can cause premature death. Overweight and obesity are thought to cause 2.8 million deaths each year^{1,2}. A significant contribution to the development of obesity, especially in children, is brought by genetic factors. One of the genes associated with the development of obesity has been identified as a gene associated with fat mass and obesity (FTO)³⁻⁵.

The human FTO gene is located on the long arm of chromosome 16 (16q12.2), consists of nine exons and eight introns, and encodes RNA demethylase, 2-oxoglutarate (2-OG) Fe(II)-dependent dioxygenase of the AlkB family^{6,7}.

The FTO gene is mainly expressed in neurons of the arcuate nucleus of the hypothalamus, adipocytes, and skeletal muscle myocytes⁸.

The RNA demethylase protein, FTO protein, contains the canonical binding motif of the substrate and cofactor α -ketoglutarate (RxxxxR) and the binding motif of Fe²⁺ (HxDxNH). RNA demethylase FTO demethylates the methylated sixth nitrogen atom of adenine (N6-methyladenosine [m6A]) and N6,2'-O-dimethyladenosine (N6,2'-O-dimethyladenosine [m6Am]) of messenger RNA (mRNA); m6A into U6RNA; m6Am small nuclear RNA and N1-methyladenosine (N1-methyladenosine [m1A]) transfer RNA. The main nitrogenous substrate of FTO is

m6A, which is the most common methylation modification of the region between the stop codon and the start codon of the 3' untranslated region of messenger RNA^{9,10}.

Methylation of 6A modulates the activity of alternative splicing, translation, transport, and mRNA degradation. FTO-mediated mRNA demethylation of factors involved in appetite regulation (ghrelin), adipogenesis (RUNX1T1), and autophagy (ATG5 and ATG7) promotes obesity¹¹. It has been demonstrated that overexpression of the FTO gene in experimental animals is accompanied by fat accumulation and an increase in body weight, while FTO gene knockout is characterized by a deficiency in body weight and adipose tissue¹²⁻¹⁴.

Genome-wide association studies (GWAS) have demonstrated a high frequency of single nucleotide variants (SNVs), such as rs9939609, rs17817449, rs8050136, rs1477196, rs6499640, rs16953002, rs11075995, and rs1121980, in the FTO gene in patients with obesity¹⁵⁻¹⁷.

It has been demonstrated that SNVs rs9930506, rs1421085, rs8050136, rs1121980, rs17817449, rs3751812 and rs7202116, located in the region of intron 1 of the FTO gene, are highly associated with overweight and obesity¹⁸⁻²⁴.

The classic SNV of the FTO gene is rs9939609, the presence of which increases the risk of developing obesity by 1.67 times²⁵⁻²⁸.

At the same time, associations of SNVs of the FTO gene with metabolic disorders in obese children remain virtually unexplored.

The aim of the study was to explore the associations of SNVs of the FTO gene with the development of metabolic disorders in children with obesity.

Materials and methods

Ethical approval

Participants provided written informed consent, and research protocols and procedures were approved according to the ethical standards of the Helsinki Declaration 2013 and by the Human Research Ethics Committee (ethical approval DSMU/EC/19/1107). Time of data collection: January 2020 – February 2023.

Study design

Observational, analytical, longitudinal, cohort study²⁹.

Inclusion criteria

Children with polygenic obesity (BMI \geq 97th percentiles) aged between six and 18.

Exclusion criteria

Monogenic and secondary forms of obesity; hereditary syndromes accompanied by obesity; diseases, the treatment of which requires the use of medications that affect the metabolism of carbohydrates and lipids; pregnancy.

Setting

The Children's Endocrinology Department. 252 children of the Caucasian group, aged between six and 18, with a diagnosis of obesity were examined. To verify the diagnosis, the obesity classification recommended in clinical practice was used: Order of the Ministry of Health of Ukraine No. 254 of 27.04.2006 "Protocol for the provision of medical care to obese children" and Order of the Ministry of Health of Ukraine No. 1732 of 24.09.2022 On the approval of standard medical assistance for "obesity in children".

The main group (n = 152) represented children with metabolically unhealthy obesity (MUO) and the control group (n = 100) consisted of patients with metabolically healthy obesity (MHO).

Criteria for inclusion in the main group

The presence of abdominal obesity³⁰ and two of the following criteria: hyperglycemia and/or hyperinsulinemia;

dyslipidemia; systolic blood pressure (SBP) and diastolic blood pressure (DBP) above the 90th percentile for a given age, gender, and height³¹. Anthropometric data were collected by a nurse in the emergency department; children wore underwear, but no shoes. Height (m) was measured using a Heightronic Digital Stadiometer® to the nearest 0.01 m. Body mass (kg) was measured using a Tefal Bodysignal body composition analyzer (France). Waist circumference (WC) and hip circumference (HC) were measured using a standardized anthropometric tape, establishing the circumference at the midpoint between the top of the iliac crest and the lower part of the lateral rib cage to the nearest 0.01 m. Body Mass Index (BMI) was converted to standardized BMI (BMI SDS) by means of the current WHO growth references³². SBP and DBP were measured using the Dinamap ProCare (GE Healthcare) digital oscillometric device.

Immunochemical examination

The studies were carried out in a certified Synevo laboratory (Dnipro, Ukraine). The material for the study was venous blood.

To study carbohydrate metabolism disorders, the levels of basal glycemia and insulinemia were determined through immunochemical testing with electrochemiluminescence detection (ECLIA). Included in the main group were obese children with a glycemic level equal to or greater than 5.6 mmol/L and/or an increase in insulinemia > 90th percentile according to the percentile curves recommended by the Identification and prevention of Dietary - and lifestyle-induced health Effects In Children and infantS (IDEFICS) consortium for the European population according to the child's age and gender³³⁻³⁴.

To study lipid metabolism disorders, levels of high-density lipoproteins (HDL-C), low density lipoproteins (LDL-C), and triglycerides (TG) were determined through the enzymatic-colorimetric method using kits from Roche Diagnostics (Switzerland) and a Cobas 6000 analyzer. The main group included obese children with HDL-C < 1.03 mmol/l or under the 10th percentile of the age norm or increased TG \geq 1.7 mmol/l or above the 90th percentile of the age norm³⁵.

Molecular and immunological examination

To study the role of pro-inflammatory markers in the development of meta-inflammation in obesity in children, IL-1 β and IL-6 levels in blood serum were determined in the certified Synevo laboratory (Dnipro, Ukraine). Interleukin-1 β

was investigated through immunochemical methods with chemiluminescence detection (CLIA). Analyzer and test system: Immulite (Siemens AG), Germany. The reference value was considered to be IL-1 β 0-5 pg/ml. Interleukin-6 was determined by an enzyme-linked immunosorbent assay (ELISA) using a Cobas 6000/Cobas 8000 kit provided by Roche Diagnostics (Switzerland). The reference value was considered to be IL-6 1.5-7.0 pg/ml.

Leptin was determined using ELISA. Analyzer and test system: Tecan Sunrise, LDN (Germany). The reference value of leptin levels for boys was 2-5.6 ng/ml and for girls it was 3.7-11.1 ng/ml. Adiponectin was tested using ELISA. Analyzer and test system: Mediagnost GmbH (Germany). The results were interpreted as follows: over 10 μ g/ml represented a low cardiovascular risk; 7-10 μ g/ml represented a moderate cardiovascular risk; 4-7 μ g/ml represented a high cardiovascular risk; under 4 μ g/ml represented a very high cardiovascular risk.

Molecular genetic testing

To study the contribution of SNVs of the FTO gene in the formation of MUO, a molecular genetic study was carried out using next-generation whole-genome sequencing (NGS) according to the recommendations of the American College of Medical Genetics and Genomics (ACMG)³⁶ in 52 patients (31 children from the main group and 21 controls) with venous blood sampling in a certified CeGat laboratory (Tubingen, Germany) using the Illumina CPro[®] Certified service provider platform.

The average amount of DNA (μ g) in samples was 0.875. Library Preparation: Quantity used 50 ng. Library Preparation Kit: Twist Human Core Exome plus Kit (Twist Bioscience). Sequencing parameters: NovaSeq 6000; 2 x 100bp. QC values of sequencing, Q30 value: 96.07%.

Bioinformatics analysis

Bioinformatic analysis – demultiplexing of the sequencing reads was performed with Illumina bcl-2fastq (version 2.20). Adapters were trimmed using Skewer (version 0.2.2)³⁷. DNA-Sequencing: trimmed raw reads were aligned to the human reference genome (hg19-cegat) using the Burrows-Wheeler Aligner (BWA – mem version 0.7.17-cegat)³⁸⁻⁴¹.

ABRA (version 2.18) and Genotype Harmonizer v.1.4.20 were used for local restructuring of readings in target regions to improve accuracy in the detection of indels in the genome during mutagenesis^{42,43}.

The reference sequence was obtained from the National Center for Biotechnology Information RefSeq database⁴⁴.

Statistical analysis

A statistical analysis of the results obtained was carried out using the Statistica 6.1 software package (No. AGAR909E415822FA) with the help of a personal computer with an Intel Pentium 4 processor. Depending on the test result, parametric and nonparametric statistical methods were used. Correlation analysis was used to analyze 100 indicators of clinical, laboratory-instrumental, and molecular genetic examinations in 252 children. The Pearson correlation method was used to assess the relationship between quantitative traits and Spearman's analysis (r), a non-parametric ranking method, was used to assess qualitative traits. Only essential connections were taken into account ($p < 0.05$).

Results

Molecular immunological studies showed obesity levels of pro-inflammatory and anti-inflammatory adipokines and cytokine IL-6 in the blood serum (Table 1).

As a result of whole-genome sequencing in 52 children with obesity, we identified five SNVs: rs1080312 (G > A), rs2287142 (G > A), rs17823223 (C > T), rs542356043 (G > A), and rs778691805 (G > T). We did not find significant associations of SNVs in the FTO data with body mass and BMI in children.

The distribution of genotype frequencies was in Hardy-Weinberg equilibrium in both groups of children with different obesity phenotypes.

Molecular genetic characteristics of the identified SNVs of the FTO gene are presented in table 2.

Among the identified SNVs of the FTO gene, the most highly pathogenic are three nonsynonymous variants: rs778691805, rs542356043, and rs1080312 (CADD = 17.32, 8.63, and 7.84, respectively).

Associations between SNVs of the FTO gene and obesity phenotypes in children

The frequency of occurrence of SNVs of the FTO gene in children with different obesity phenotypes is presented in table 3.

In children with the MHO phenotype, the allele frequency (AF) of the mutated A allele of SNV rs1080312 ($t = 3.32$) and rs2287142 ($t = 2.29$), and T allele SNV rs17823223 ($t = 6.34$) and rs778691805 ($t = 2.29$) of the FTO gene was significantly higher than the AF of these polymorphisms in healthy non-Finnish Europeans ($p < 0.05$). In children with MUO, the AF of the mutated A allele SNV rs2287142 ($t = 2.74$) and T allele SNV rs17823223 ($t = 3.27$) of the FTO gene was significantly

Table 1. Mean concentration ($M \pm m$) and median (Me)* values of blood serum inflammation markers in children with different phenotypes of obesity

Indicator	Reference values	MUO (n = 152)		MHO (n = 100)		p
		M \pm m	Me	M \pm m	Me	
IL-1 β (pg/ml)	0-5	2.5 \pm 0.3	1.9	1.8 \pm 0.7	1.7	> 0.05
IL-6 (pg/ml)	1.5-7	7.4 \pm 0.5	6.8	4.3 \pm 0.3	3.4	< 0.05
Leptin (ng/ml)						
Boys	2-5.6	29.3 \pm 8.9	25	26.0 \pm 6.4	24.4	> 0.05
Girls	3.7-11.1	47.8 \pm 4.4	45.2	32.5 \pm 4.3	28.5	< 0.05
Adiponectin (μ g/ml)	\geq 10	3.9 \pm 0.8	3.1	7.7 \pm 2.4	6.5	< 0.05

*Me with 95% CI median.

Table 2. Characteristics of SNV types of the FTO gene

SNV	Position	GnomAD_maxPOP	Ref	Alt	Consequence	Base change	CADD	RawScore	Clinical significance (ClinVar)
rs1080312*	53745367	AFR	G	A	Intronic	c. 45+7226G>A	7.84	0.35	not reported
rs2287142	53945351	EAS	G	A	Synonymous	c. 60G>A	0.14	-0.44	not reported
rs17823223	53999638	NFE	C	T	Intronic	c. 230+31617C>T	1.88	-0.05	not reported
rs542356043*	54013348	NFE	G	A	Intronic	c. 1364+45327G>A	8.63	0.42	not reported
rs778691805*	53859781	NFE	G	T	Missense	c. 129G>T	17.32	1.68	not reported

*SNV of the FTO associated with high levels of CADD.

GnomAD_maxPOP: frequency distribution of FTO mutations; AFR: African; EAS: East Asian; NFE: Non-Finnish European; Ref: reference allele; Alt: alternative allele; Consequence: functional consequence of the variation in relation to the transcript; c: the nucleotide change and position relative to the coding sequence of the affected transcript in HGVS nomenclature; CADD: combined annotation dependent depletion. CDS Position Reference Base > Alternative Base. Example: c. 223A>T (c.¹ - interpretation for DNA coding sequence)⁴⁴. This column is empty if the variant is intergenic.**Table 3.** The frequency of occurrence of the SNV of the FTO gene in children with different obesity phenotypes

SNV	gnomAD browser		The frequency of occurrence of major and minor options (%)				The value of Student's t-test in Welch's modification		
	Popmax AF (HOM ^p), %	AF NFE, (HOM ^p), %	MHO		MUO		t ₁	t ₂	t ₃
			(HOM ^N), %	(HET/HOM ^p), %	(HOM ^N), %	(HET/HOM ^p), %			
rs1080312	0.17	0.02	90	10	97	3	3.32*	1.74	2.03*
rs2287142	0.06	0.002	95	5	93	7	2.29*	2.74*	0.6
rs17823223	0.12	0.13	71	29	90	10	6.34*	3.27*	3.49*
rs542356043	0.00005	0.0002	100	0	97	3	0.01	1.76	1.76
rs778691805	0.000003	0.00002	95	5	100	0	2.29*	0	2.29*

*Critical value of Student's t-test modified by Welch >1.97, at which the differences in the compared groups are significant (p < 0.05).

HOM^p: homozygous variant (biallelic single nucleotide substitution); HET: heterozygous variant (single allelic single nucleotide substitution); HOM^N: homozygous variant (absence of nucleotide substitutions); Popmax AF: maximum population allele frequency in the genome (gnomAD browser); AF NFE: allele frequency for non-Finnish Europeans in the genome (gnomAD browser); t₁: student's test of significance modified by Welch in the comparison groups MHO and healthy Non-Finnish Europeans; t₂: Student's test of significance modified by Welch in the comparison groups MUO and healthy Non-Finnish Europeans; t₃: Student's test of significance modified by Welch in the MUO and MHO comparison groups.

higher than the AF of these polymorphisms in healthy non-Finnish Europeans ($p < 0.05$). The allele frequency of the mutated A allele SNV rs1080312 ($t = 2.03$) and T allele SNV rs17823223 ($t = 3.49$) and rs778691805 ($t = 2.29$) of the FTO gene in MUO was also significantly lower than in children with MHO ($p < 0.05$). We found no significant differences in the allelic frequency of the mutated A allele SNV rs542356043 of the FTO gene among obese children and healthy non-Finnish Europeans ($p < 0.05$).

We found that in children with obesity, certain SNVs of the FTO gene that we identified are associated with both the level of inflammatory activity and laboratory markers of metabolic disorders.

Associations between SNVs of the FTO gene and markers of inflammatory activity

Based on the correlation analysis data, we found that the level of IL-6 in the blood serum of children with the MHO phenotype depended exclusively on SNV rs2287142 of the FTO gene ($r = 0.73$), whereas the content of pro-inflammatory interleukins (IL-1 β and IL-6) in children with the MUO phenotype did not depend on the SNV of the FTO gene. We did not establish a significant correlation between the levels of leptin, adiponectin, and SNV of the FTO gene in obese children.

Associations between SNVs of the FTO gene and carbohydrate metabolism disorders

According to the correlation analysis data, indicators of carbohydrate metabolism are only associated with SNVs of the FTO gene in children with the MHO phenotype. Thus, SNVs rs17823223 and rs1080312 of the FTO gene are associated with glucose metabolism. The presence of the T allele of SNV rs17823223 is associated with a lower concentration of fasting serum glucose ($r = -0.51$), while carriage of the A allele of SNV rs1080312 is associated with a higher level of fasting glycemia ($r = 0.43$) and impaired carbohydrate tolerance ($r = 0.33$).

Associations between SNVs of the FTO gene and lipid metabolism disorders

It was found that in children with the MHO phenotype, SNVs rs778691805 and rs1080312 of the FTO gene are associated with lipid metabolism markers. And, if the T allele of SNV rs778691805 was associated with a high level of LDL-C in the blood serum ($r = 0.33$), then the A allele of SNV rs1080312 was associated with a low level of cholesterol and LDL-C in the blood serum

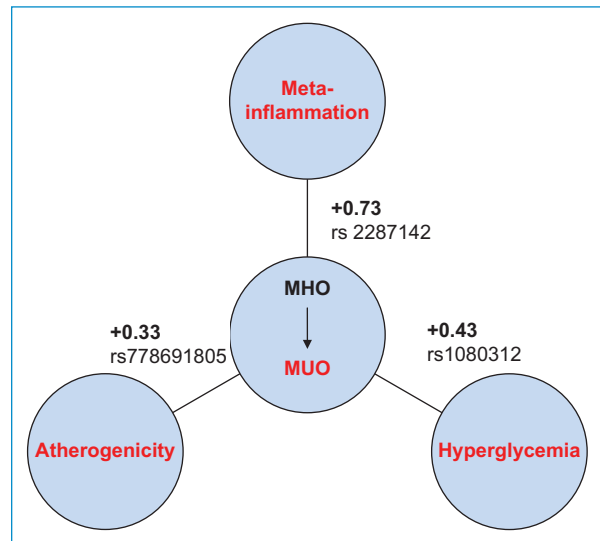


Figure 1. Correlation pleiad of associations between SNVs of the FTO gene and the development of metabolic disorders in children with obesity.

($r = -0.42$ and $r = -0.39$, respectively). In children with the MUO phenotype, only SNV rs17823223 was associated with lipid profile parameters; in individuals with the T allele of SNV rs17823223, a higher level of HDL-C in blood serum was noted ($r = 0.33$) (Fig. 1).

Discussion

We have identified SNVs of the FTO gene based on whole-genome sequencing in children with obesity, such as rs1080312, rs2287142, rs17823223, rs542356043, and rs778691805. It should be noted that SNVs rs1080312, rs17823223, and rs542356043 of the FTO gene in children with obesity were identified by us for the first time.

We found that in obese children, SNV rs2287142 is associated with pro-inflammatory status, and SNVs rs1080312, rs17823223, and rs778691805 are associated with metabolic markers. The rs542356043 variant of the FTO gene was not associated with any of the pro-inflammatory or metabolic markers. It was shown that in children with the MHO phenotype, SNV rs2287142 of the FTO gene is highly associated with IL-6 fluctuations. Individuals with the A allele have a higher level of IL-6 in their blood serum. The rs2287142 variant is located in the enhancer/silencer region of the cis-regulatory element of the FTO gene, changes in which can lead to alternative RNA splicing and the generation of functionally different isoforms⁴⁵. FTO gene knockout has been shown to increase the level of IL-6 in adipose tissue⁴⁶. It is possible that the A allele of SNV rs2287142

is associated with the production of FTO isoforms with low functional activity.

It is of interest that two SNVs (rs17823223 and rs1080312) of the FTO gene are multi-directionally associated with lumen glucose in children with the MHO phenotype. Carriage of the T allele of the missense variant of SNV rs17823223 prevents the development of glycemia, while the A allele of the intron variant of SNV rs1080312 promotes the development of fasting glycemia. Given that FTO, by enhancing the activity of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase 1, induces gluconeogenesis⁴⁷, it is possible to suggest that SNV rs17823223 leads to a decrease in FTO activity, while SNV rs1080312 is accompanied by an increase in FTO expression. Missense variant rs17823223 is accompanied by the replacement of a threonine residue with a methionine residue at position 457 (Thr457Met), which can lead to a decrease in the functional activity of the FTO protein. However, the dependence of glucose metabolism and insulin secretion in these variants of the FTO gene remains unexplored. It should be noted that in experimental animals with a FTO gene knockout, hyperglycemia does not develop and high glucose tolerance was observed. At that time, SNV rs9939609, which is characterized by overexpression of the FTO gene, is accompanied by severe hyperglycemia^{48,49}.

Of interest is the fact that elevated levels of both mRNA and FTO protein in muscle are characteristic of type 2 diabetes mellitus, regardless of the presence of obesity and insulin resistance⁵⁰.

We found that SNVs rs1080312, rs17823223, and rs778691805 in children with obesity are associated with the concentration levels of some lipid fractions in blood serum. In all likelihood, SNVs rs1080312 and rs17823223 have a protective antiatherogenic effect, and rs778691805, on the contrary, has a weak but atherogenic effect. It is known that, on the one hand, FTO, by reducing the expression of mRNA of carnitine palmitoyltransferase 1, hormone-sensitive lipase, and triglyceride lipase, inhibits the activity of fatty acid oxidation and lipolysis; and on the other hand, by inducing the expression of activating transcription factor 4, it stimulates the expression of lipogenic genes, which leads to increased *de novo* lipogenesis in the liver^{47,51}.

Also, FTO stabilizes the mRNA of sterol regulatory element-binding transcription factor 1 (SREBF1) and carbohydrate-response element-binding protein (ChREBP), two major lipogenic transcription factors⁵². Thus, FTO promotes triglyceridemia. Based on these data, it is likely that SNVs rs1080312 and rs17823223 cause a decrease in FTO expression or activity, respectively. At the same time, rs778691805 leads to an increase in FTO

expression. However, further experimental and clinical studies are needed to confirm this assumption.

Conclusions

- In obese children, SNV rs2287142 is associated with pro-inflammatory status, and SNVs rs1080312, rs17823223, and rs778691805 of the FTO gene are associated with metabolic markers.
- In children with the MHO phenotype, SNVs rs17823223 and rs1080312 of the FTO gene have different associations with serum glucose values. Carriage of the T allele of the missense variant of SNV rs17823223 prevents the development of glycemia, while the A allele of the intron variant of SNV rs1080312 contributes to the development of basal hyperglycemia.
- SNVs rs1080312, rs17823223, and rs778691805 in children with obesity are associated with the concentration levels of some lipid fractions in blood serum. SNVs rs1080312 and rs17823223 have a protective antiatherogenic effect due to a corresponding decrease in the expression or activity of the FTO gene, and rs778691805, on the contrary, has a weak but atherogenic effect due to an increase in FTO expression.
- In obese children, the missense mutation SNV rs17823223 of the FTO gene is associated with the accumulation of fat mass but is not associated with metabolic disorders.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with

the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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