ACCSCIENCE PUBLISHING

Global Translational Medicine

ORIGINAL RESEARCH ARTICLE

Association between the *FTO* polymorphic variants and obesity in the Belarusian population

Maxim D. Ameliyanovich[1], Maxim L. Lushchyk[2], Irma B. Mosse[1]*, and Larisa I. Danilova[2]

[1]Institute of Genetics and Cytology of the National Academy of Sciences of Belarus, Minsk, Republic of Belarus

[2]Belarusian Medical Academy of Postgraduate Education, Minsk, Republic of Belarus

Abstract

Overweight and obesity refer to the abnormal and excessive deposition of adipose tissue in the human body causing significant harm to health. Unfortunately, there has always been a persisting upward trend in the number of overweight people. The development of obesity may be caused by a combination of excessive food intake, low physical activity, and a hereditary predisposition to it. Studies of the genotypes of obese individuals allowed identifying a number of polymorphic variants of genes that contribute to a genetic predisposition to an excessive weight gain. One of the most significant predictors of obesity is the *FTO* gene (a fat mass and obesity-associated gene). Genotyping of 655 representatives of the Republic of Belarus was carried out for 13 polymorphic variants of the *FTO* gene. Genomic DNA extraction was carried out from the peripheral venous blood samples. Real-time PCR was performed for the evaluation of polymorphic variants of the *FTO* gene. A significant association of the genotype with the body mass index was observed in eight polymorphic variants of the *FTO* gene: In the carriers of minor homozygotes of polymorphic variants rs11075990, rs1121980, rs1421085, rs17817449, rs3751812, rs9939609, rs9940128, and rs9941349, the body mass index (BMI) was much higher compared with the carriers of corresponding major homozygotes $P = 0.0022 – 0.021$. An analysis of the linkage disequilibrium of 13 polymorphic variants of the *FTO* gene was carried out. It was found that eight polymorphic variants of the *FTO* gene for which a statistically significant association with BMI was shown constitute one block of linkage disequilibrium ($r^2 = 0.82 – 1.0$, $P < 0.001$) and form two most common haplotypes: A/G/T/T/G/T/G/C (51.9%) and G/A/C/G/T/A/A/T (42.8%). Therefore, to determine the risk for obesity development, it is sufficient to conduct genetic testing for one of these polymorphic variants. This greatly facilitates the process of determining a genetic predisposition to excess weight.

Keywords: Obesity; Body mass index; *FTO* polymorphic variants; Polymerase chain reaction

***Corresponding author:**
Irma B. Mosse
(i.mosse@igc.by)

Citation: Ameliyanovich MD, Lushchyk ML, Mosse IB, *et al.*, 2023, Association between the *FTO* polymorphic variants and obesity in the Belarusian population. *Global Transl Med*.
https://doi.org/10.36922/gtm.352

Received: February 3, 2023
Accepted: March 27, 2023
Published Online: April 10, 2023

1. Introduction

Overweight and obesity refer to abnormal and excessive deposition of adipose tissue in the human body, causing significant harm to health[1]. The most commonly used method for determining obesity in adults is the calculation of body mass index (BMI) — the

ratio of body weight in kilograms to the square of height in meters (kg/m^2). BMI is the most convenient measure for determining the level of obesity and overweight in a population, since it is the same for both sexes and all age categories of adults. However, BMI should be considered an approximate criterion due to the fact that in different people it may correspond to different degrees of completeness.

According to the World Health Organization (WHO) recommendations, a diagnosis of "overweight" or "obesity" in adults should be made based on these criteria: (i) Overweight if BMI is equal to or more than 25; (ii) obesity if BMI is equal to or more than 30. High BMI significantly increases the risk of cardiovascular diseases, metabolic syndrome, diabetes mellitus, etc. Morbid obesity reduces life expectancy by about 7 years in women and 6 years in men[2].

According to 2016 data, 39% of the world's adult population over 18 years old (39% of men and 40% of women) was overweight and about 13% of adults (11% of men and 15% of women) were obese[3]. Unfortunately, there has always been a persisting upward trend in the number of overweight people. Previously, a big population of obese patients was used to be a characteristic of developed countries with a high income per capita, but this phenomenon has recently become more apparent in low- and middle-income countries. According to the WHO, the number of overweight children under 5 years old has increased by 24% in Africa compared to that in 2000[4].

If the mass of fat consumed exceeds the body's ability to oxidize it, obesity develops and progresses. Saturated fatty acids excessively supplied with food have a tendency to cause structural changes in cell membrane phospholipids and disruption in the expression of genes that control the conduction of insulin signal into the cell. In addition, fats are more caloric than proteins and carbohydrates: 1 g of fat contains 9 kcal; 1 g of proteins and carbohydrates contains 4 kcal each[5]. Therefore, with the same volume, fatty foods give the body twice as many calories as protein and carbohydrate foods.

Apart from overeating, lack of physical activity is another important environmental factor contributing to obesity development. Low physical activity leads to a slowdown in the lipolysis and utilization of triglycerides in the muscle and adipose tissue[6], as well as a decrease in the translocation of glucose transporters in muscles[7], which results in overweight and obesity. The development of obesity may be caused by a combination of excessive food intake, lack of physical activity, and a hereditary predisposition to it. Studies of the genotypes of obese individuals allowed identifying a number of polymorphic variants of genes that contribute to a genetic predisposition to an excessive weight gain. However, an association of these polymorphic variants with obesity requires clarification for each specific population.

At present, much attention is paid to the prevention of obesity, which includes a normalized diet, higher level of physical activity, and maintenance of a healthy lifestyle. Molecular genetic diagnostics will make it possible to identify individuals with an increased risk for obesity so that preventive measures can be taken in a timely manner.

One of the most significant predictors of obesity is the *FTO* gene (a fat mass and obesity-associated gene) encoding the Fe(II)/2-oxoglutarate-dependent demethylase, which is the ninth AlkB family protein found in mammals (also called ALKBH9)[8] and involved in the regulation of metabolic rate, energy balance, thermogenesis, and control over adipocyte differentiation into brown or white fat cells[9].

The human *FTO* gene is located on the chromosome 16q12.2 with a total length of 410,50 kb, including nine exons and eight introns and is extensively expressed in the adipose tissue and the skeletal muscles of human with the highest expression in the hypothalamus, in the region that controls energy balance. In the genome-wide association study (GWAS) performed by Frayling *et al.* in 2007, the *FTO* gene was found to be able to influence the risk for Type 2 diabetes development[10]. It was shown that A allele homozygous carriers of the *FTO* rs9939609 polymorphic variant had an average weight of 3 kg, and the risk for obesity was 1.67 times higher than that of T/T homozygotes[10]. Further studies identified a large number of polymorphic variants in the *FTO* gene associated not only with an increased body mass index[11-15], but also with other metabolic conditions, such as increased levels of fasting insulin, glucose, triglycerides, and low levels of high-density lipoproteins[16].

Obese (or overweight) single-nucleotide polymorphisms (SNPs) in the *FTO* gene were replicated in large European populations[17,18]. According to the 1000 Genomes Project data, significant differences in the frequencies of minor alleles for some polymorphisms were noted depending on the population (Figure 1). For instance, the minor allele frequency of the rs9939609 polymorphic variant among Europeans is 34 – 44%, among Asians 11 – 20%, among Spaniards 31 – 37%, and about 17% among South Americans[12]. In our study, the minor allele frequencies of the polymorphic variants tested correspond to Europeans.

The present study aimed to identify an association between 13 polymorphic variants of the *FTO* gene (Table 1) and obesity risks in the representatives from the Belarusian population.

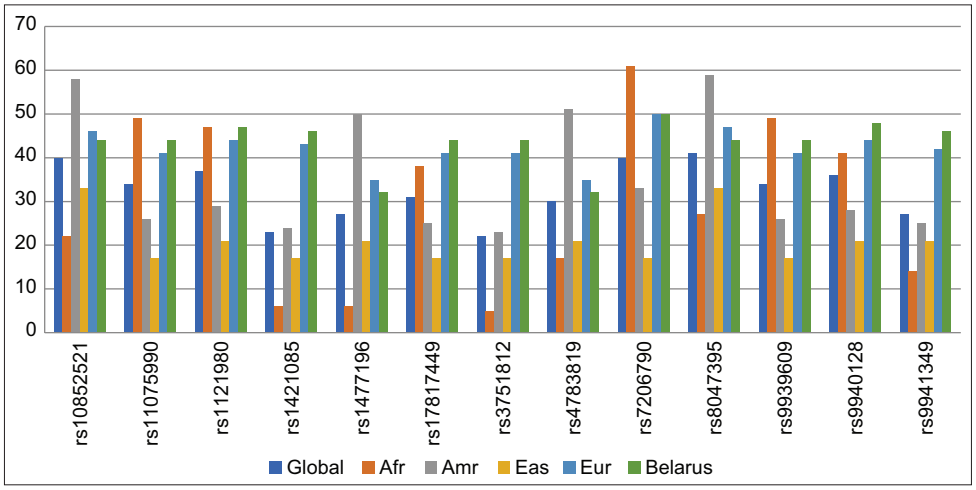

Figure 1. Minor allele frequency in populations.

Table 1. Candidate polymorphic variants included in the study

SNP	SNP Location	SNP Type	MAF Global
rs10852521 C/T	Chr. 16:53771053	Intron 1	0.40 (T)
rs11075990 A/G	Chr. 16:53785981	Intron 1	0.34 (G)
rs1121980 C/T	Chr. 16:53775335	Intron 1	0.37 (T)
rs1421085 C/T	Chr. 16:53767042	Intron 1	0.23 (C)
rs1477196 A/G	Chr. 16:53774346	Intron 1	0.27 (A)
rs17817449 G/T	Chr. 16:53779455	Intron 1	0.31 (G)
rs3751812 G/T	Chr. 16:53784548	Intron 1	0.22 (T)
rs4783819 G/C	Chr16:53782735	Intron 1	0.30 (G)
rs7206790 G/C	Chr16:53763996	Intron 1	0.40 (G)
rs8047395 A/G	Chr16:53764611	Intron 1	0.41 (G)
rs9939609 T/A	Chr16:53786615	Intron 1	0.34 (A)
rs9940128 A/G	Chr16:53766842	Intron 1	0.36 (A)
rs9941349 C/T	Chr16:53791576	Intron 1	0.27 (T)

MAF: Minor allele frequency; SNP: Single nucleotide polymorphism

2. Materials and methods

2.1. Study participants

The study involved 655 volunteers over the age of 18 years living in the territory of the Republic of Belarus. Among them, the control group included 273 volunteers with BMI < 25, 170 obese patients with BMI > 30, and 212 individuals in the pre-obesity state. The minimum sample size was estimated in the study using the two-group proportion formula with α at 0.05, power of 80%, p1 = 0.40 and p2 = 0.56. The final minimum sample size was 150 cases per group. The study participants gave informed consent to participate in the study in accordance with the Declaration of Helsinki (as amended in 2013) and were invited to the survey. The informed consent form and the study program were approved by the Bioethics Committee of the Belarusian Medical Academy of Postgraduate Education.

2 ML of peripheral venous blood samples was collected into EDTA tubes. Genomic DNA extraction was carried out by the Eppendorf epMotion 5075 multifunctional automatic station using Art NK Magnit kits (ArtBioTech LLC, the Republic of Belarus) for nucleic acid extraction on magnetic particles in accordance with manufacturer's instructions. The DNA quantity was measured using the GloMax Explorer (Promega, USA), a multimode microplate reader, and the extracted DNA was stored at −20°C until use.

2.2. Clinical examination

Clinical examination and the collection of blood samples were performed at the clinical bases of the Department of Endocrinology of the Belarusian Medical Academy of Postgraduate Education. Clinical examination included an assessment of anthropometric characteristics and an endocrinologist checkup to exclude patients with severe somatic conditions, concomitant chronic diseases at the decompensation stage, pregnancy or lactation periods, severe infectious processes (HIV infection, tuberculosis, syphilis, and a progressive course of viral hepatitis B and C). Anthropometric measurements were performed in accordance with the WHO and International Diabetes Federation requirements. Height was measured with an accuracy of 0.1 cm and body weight was measured with an accuracy of 0.1 kg using TANITA floor bioimpedance scales (a body composition analyzer; TF-780, Japan) to analyze the percentage of adipose tissue distribution.

Body mass index was calculated using the following formula: BMI = Body weight (kg)/height $(m)^2$. The study participants were categorized into groups based on the

generally accepted criteria as follows: Normal weight (BMI <25); overweight (BMI ≥25 but <30); obesity degree I (BMI ≥30 but <35); obesity degree II (BMI ≥35 but <40); and obesity degree III (BMI ≥40).

2.3. Genotyping

TaqMan assays (Thermo Fisher Scientific, USA) for the polymorphic variants of the *FTO* gene (rs10852521, rs11075990, rs1121980, rs1421085, rs1477196, rs17817449, rs3751812, rs4783819, rs7206790, rs8047395, rs9939609, rs9940128, and rs9941349) were used for genotyping. Real-time PCR was performed in 25-μL reactions, which consisted of 12.5 μL of the TaqMan Genotyping Master Mix; 0.625 μL of the TaqMan genotyping assay mix (×40), which includes a primer and a probe; 11.25 μL of DNase- and RNase-free water; and 20 ng of template DNA. Thermal cycling was performed on the Bio-Rad CFX96 (Bio-Rad, Germany). The method was applied at the temperature of 95°C for 10 min, 40 cycles at 95°C for 15 s, and 60°C for 90 sec. The CFX96TM Real-Time PCR software (Bio-Rad, Germany) was used to conduct the allelic discrimination method for SNP genotyping.

2.4. Statistical analysis

Statistical analysis of the data was carried out using the standard STATISTICA software package for Windows (StatSoft Inc., USA). A Pearson's χ^2 test was used to analyze the distribution of genotype frequencies in the groups under study. Distribution of corresponding genotypes in the groups under study for all analyzed polymorphisms corresponded to the expected Hardy-Weinberg distribution.

Haplotype frequency was estimated using SNPStats software[19]. Linkage disequilibrium (LD) analysis and LD-heatmap generation were carried out using the R package Gaston[20].

To assess the effect of polymorphisms with respect to the risk of obesity development, the odds ratio (OR) was used taking into account the 95% confidence interval (95% CI).

Multiple linear regression was applied to evaluate adjusted associations between the polymorphism alleles and the anthropometric indices by adjusting potentially important confounders (e.g., gender, age). In this study, statistical significance was obtained when $P < 0.05$.

3. Results and discussion

Characteristics of the studied population are shown in Table 2.

The cohort included 655 participants: 273 normal weight (the median BMI = 21.7 [20.1; 23.4] kg/m^2) and 170 obese (the median BMI = 35.1 [31.8; 37.7] kg/m^2) individuals. The controls were significantly younger than the obese patients (Figure 2). Gender and age variables were included as covariates in the case–control association analysis to remove bias from confounding factors.

Table 3 presents the analysis results on the BMI association in the group of patients with the genotypes of various *FTO* polymorphic variants.

A significant association of the genotype and the body mass index was observed for eight polymorphic variants of the *FTO* gene: In the carriers of minor homozygotes of polymorphic variants rs11075990, rs1121980, rs1421085, rs17817449, rs3751812, rs9939609, rs9940128, and rs9941349, BMI was 1.51 – 1.84 kg/m^2 higher compared with the carriers of corresponding major homozygotes ($P = 0.0022 – 0.021$).

Some studies have found not only ethnic but also gender differences in the BMI genotype association. For example, a significant association of rs11075990 and rs3751812 polymorphic variants with BMI in women ($P = 2.26 \times 10^{-6}$ and 3.04×10^{-6}, respectively) and its absence in men was

Table 2. Characteristics of the studied population

Group	BMI	Gender		Age
	Mean (SD)	Male (n)	Female (n)	Mean (SD)
Control	21.7 (1.9)	77	196	33.3 (9.7)
Pre-obesity	27.3 (1.4)	90	122	38.2 (11.7)
Obesity (degree I)	32.3 (1.4)	34	72	46.9 (9.9)
Obesity (degree II)	37.6 (1.4)	9	33	47.9 (9.1)
Obesity (degree III)	43.6 (3.2)	3	19	53.1 (6.3)
Total	26.9 (6.0)	213	442	38.5 (11.8)

BMI: Body mass index; SD: Standard deviation

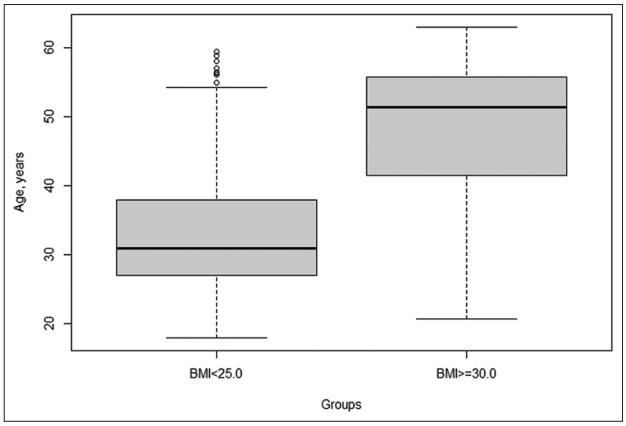

Figure 2. Age distribution by group.

Table 3. Association of the studied polymorphic variants with average BMI values in the Belarusian population

SNP	Genotype	n	Mean BMI (SD)	Difference (95% CI)	*P*
rs10852521	C/C	184	27.43 (6.55)	0.00	0.23
	C/T	322	26.94 (6.05)	−0.49 (−1.59 – 0.61)	
	T/T	114	26.18 (5.21)	−1.25 (−2.66 – 0.17)	
rs11075990	A/A	197	25.64 (5.02)	0.00	0.0022
	A/G	316	27.47 (6.30)	1.83 (0.76 – 2.89)	
	G/G	121	27.39 (6.55)	1.74 (0.39 – 3.10)	
rs1121980	C/C	165	25.72 (5.05)	0.00	0.015
	C/T	340	27.27 (6.19)	1.55 (0.43 – 2.66)	
	T/T	130	27.36 (6.56)	1.65 (0.27 – 3.02)	
rs1421085	T/T	182	25.95 (5.07)	0.00	0.021
	C/T	335	27.38 (6.23)	1.43 (0.35 – 2.50)	
	C/C	129	27.46 (6.41)	1.51 (0.16 – 2.85)	
rs1477196	G/G	291	27.1 (6.16)	0.00	0.62
	A/G	281	27.14 (6.00)	0.04 (−0.95 – 1.03)	
	A/A	62	26.33 (5.40)	−0.77 (−2.42 – 0.88)	
rs17817449	T/T	207	25.78 (5.03)	0.00	0.0027
	G/T	312	27.48 (6.18)	1.70 (0.66 – 2.73)	
	G/G	124	27.56 (6.47)	1.77 (0.46 – 3.08)	
rs3751812	G/G	204	25.88 (5.03)	0.00	0.0072
	G/T	319	27.48 (6.24)	1.60 (0.56 – 2.65)	
	T/T	125	27.41 (6.49)	1.53 (0.20 – 2.85)	
rs4783819	C/C	293	27.05 (6.18)	0.00	0.55
	G/C	293	27.1 (5.91)	0.05 (−0.92 – 1.01)	
	G/G	64	26.21 (5.39)	−0.84 (−2.46 – 0.78)	
rs7206790	C/C	152	26.41 (5.07)	0.00	0.25
	G/C	351	27.33 (6.27)	0.92 (−0.22 – 2.06)	
	G/G	146	26.79 (6.15)	0.38 (−0.98 – −1.74)	
rs8047395	A/A	190	27.24 (6.28)	0.00	0.62
	A/G	340	27.03 (6.04)	−0.21 (−1.27 – 0.85)	
	G/G	113	26.55 (5.29)	−0.69 (−2.09 – 0.70)	
rs9939609	T/T	205	25.83 (5.05)	0.00	0.0037
	T/A	319	27.54 (6.26)	1.71 (0.66 – 2.75)	
	A/A	123	27.47 (6.49)	1.64 (0.31 – 2.97)	
rs9940128	G/G	168	25.85 (5.08)	0.00	0.015
	A/G	342	27.36 (6.17)	1.51 (0.41 – 2.61)	
	A/A	138	27.48 (6.39)	1.63 (0.29 – 2.97)	
rs9941349	C/C	190	25.73 (5.05)	0.00	0.003
	C/T	325	27.41 (6.07)	1.68 (0.63 – 2.73)	
	T/T	132	27.58 (6.47)	1.84 (0.54 – 3.15)	

BMI: Body mass index; CI: Confidence interval; SD: Standard deviation.

shown[21]. In addition, pronounced population differences were observed for these polymorphic variants – an association of BMI and a risk for obesity among Europeans was shown, while this kind of relationship was not observed in Chinese and Hispanic or African Americans[22].

To conduct a more detailed assessment of the association of polymorphic variants of genes with an obesity progression risk selected for the study, a BMI > 30 subgroup was formed from the general group of patients. Table 4 presents the comparison of genotype frequencies in the group of BMI > 30 patients in comparison with the BMI < 25 control.

The results demonstrated in Table 4 were fully confirmed by the data obtained when comparing the *FTO* gene association with average BMI values in the Belarusian population. A significant association of the genotype with the body mass index was observed for the same eight polymorphic variants of the *FTO* gene. The most significant differences between the groups were observed in the distribution of genotypes of the rs11075990 polymorphic variant (P = 0.0042). The observed differences remained significant after adjustment for age and gender. The minor G/G genotype was found in 22.5% of obese patients. It turned out to be more frequently occurring than the major A/A genotype.

In this study, no association of polymorphic variants rs10852521, rs1477196, rs4783819, rs7206790, and rs8047395 with a risk for obesity was found. At the same time, there is evidence that rs1477196 provokes the development of obesity in the case of insufficient physical activity[23], and rs7206790 is associated with a risk of weight gain, waist circumference and BMI[24].

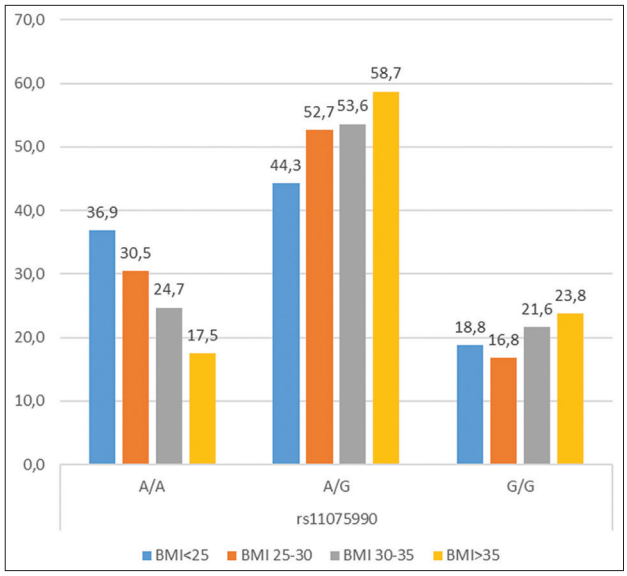

Figure 3. The distribution of genotypes of the *FTO* rs11075990 polymorphic variant in the studied groups.

Table 4. Comparison of genotype frequencies of various *FTO* polymorphic variants in the BMI >30 patient and control groups

SNP	Genotype	BMI <25	BMI >30	OR (95% CI)	*P*
rs10852521	C/C	76 (28.8%)	52 (32.7%)	1.00	0.35
	C/T	136 (51.5%)	84 (52.8%)	0.90 (0.58 – 1.41)	
	T/T	52 (19.7%)	23 (14.5%)	0.65 (0.35 – 1.18)	
rs11075990	A/A	100 (36.9%)	35 (21.9%)	1.00	0.0042
	A/G	120 (44.3%)	89 (55.6%)	2.12 (1.32 – 3.40)	
	G/G	51 (18.8%)	36 (22.5%)	2.02 (1.14 – 3.58)	
rs1121980	C/C	84 (30.9%)	31 (19.4%)	1.00	0.029
	C/T	132 (48.5%)	90 (56.2%)	1.85 (1.13 – 3.02)	
	T/T	56 (20.6%)	39 (24.4%)	1.89 (1.06 – 3.37)	
rs1421085	T/T	88 (32.8%)	36 (21.6%)	1.00	0.037
	C/T	128 (47.8%)	92 (55.1%)	1.76 (1.10 – 2.81)	
	C/C	52 (19.4%)	39 (23.4%)	1.83 (1.04 – 3.24)	
rs1477196	G/G	126 (48.1%)	78 (47%)	1.00	0.66
	A/G	108 (41.2%)	74 (44.6%)	1.11 (0.74 – 1.67)	
	A/A	28 (10.7%)	14 (8.4%)	0.81 (0.40 – 1.63)	
rs17817449	T/T	103 (38.4%)	39 (23.6%)	1.00	0.0055
	G/T	116 (43.3%)	88 (53.3%)	2.00 (1.26 – 3.18)	
	G/G	49 (18.3%)	38 (23%)	2.05 (1.17 – 3.59)	
rs3751812	G/G	99 (36.5%)	40 (24.1%)	1.00	0.023
	G/T	121 (44.6%)	89 (53.6%)	1.82 (1.15 – 2.88)	
	T/T	51 (18.8%)	37 (22.3%)	1.80 (1.03 – 3.14)	
rs4783819	C/C	126 (46.7%)	79 (47%)	1.00	0.7
	G/C	115 (42.6%)	75 (44.6%)	1.04 (0.69 – 1.56)	
	G/G	29 (10.7%)	14 (8.3%)	0.77 (0.38 – 1.55)	
rs7206790	C/C	66 (24.4%)	33 (19.6%)	1.00	0.42
	G/C	139 (51.5%)	96 (57.1%)	1.38 (0.84 – 2.26)	
	G/G	65 (24.1%)	39 (23.2%)	1.20 (0.67 – 2.14)	
rs8047395	A/A	78 (29.3%)	51 (30.5%)	1.00	0.8
	A/G	140 (52.6%)	90 (53.9%)	0.98 (0.63 – 1.53)	
	G/G	48 (18.1%)	26 (15.6%)	0.83 (0.46 – 1.50)	
rs9939609	T/T	101 (37.4%)	40 (23.8%)	1.00	0.011
	T/A	119 (44.1%)	91 (54.2%)	1.93 (1.22 – 3.05)	
	A/A	50 (18.5%)	37 (22%)	1.87 (1.07 – 3.27)	
rs9940128	G/G	84 (31.2%)	33 (19.8%)	1.00	0.028
	A/G	129 (48%)	92 (55.1%)	1.82 (1.12 – 2.94)	
	A/A	56 (20.8%)	42 (25.1%)	1.91 (1.08 – 3.37)	
rs9941349	C/C	95 (35.2%)	36 (21.6%)	1.00	0.009
	C/T	122 (45.2%)	90 (53.9%)	1.95 (1.22 – 3.12)	
	T/T	53 (19.6%)	41 (24.6%)	2.04 (1.17 – 3.57)	

BMI: Body mass index; CI: Confidence interval; OR: Odds ratio

Figure 3 shows a comparison of genotype frequencies of the rs11075990 polymorphic variant in the group of patients with normal weight (BMI < 25), overweight (25 < BMI < 30), obesity degree I (30 < BMI < 35), and obesity degree II (BMI > 35).

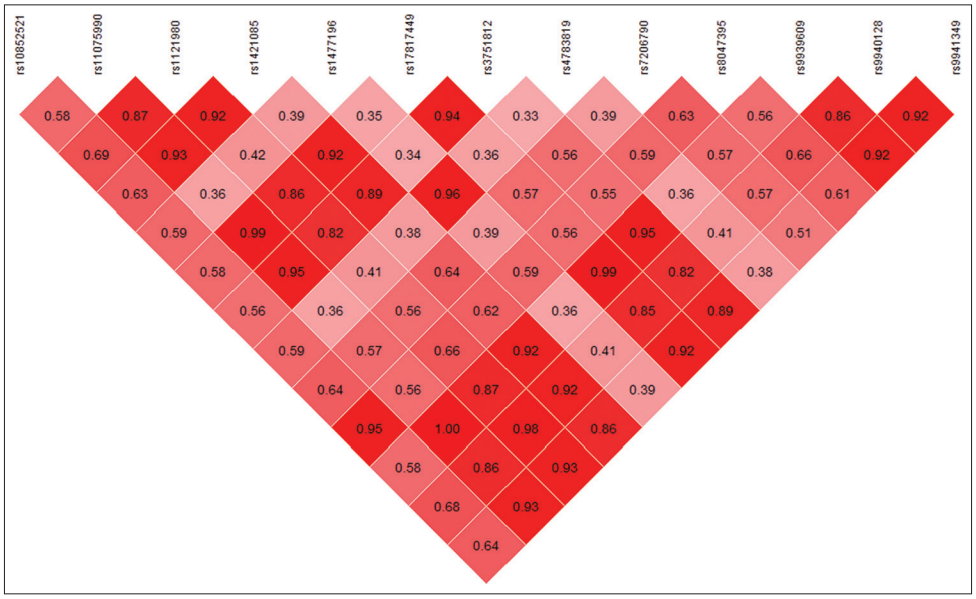

Figure 4. Map of the linkage disequilibrium of *FTO* polymorphic variants.

As shown in Figure 3, the genotype frequencies of *FTO* rs11075990 polymorphic variants correlate with BMI. The A/A genotype occurs less frequently with an increasing BMI in the groups under study. People with the A/A genotype are more often characterized by normal weight compared to heterozygote and minor G/G homozygote carriers.

A meta-analysis performed by Peng *et al.*[12], which includes 59 studies, showed a significant association between a risk for obesity and five polymorphic variants of the *FTO* gene located in the 47-kb linkage disequilibrium block covering the parts of the first two introns and the exon 2: rs9939609 (OR = 1.31, 95% CI = 1.26–1.36), rs1421085 (OR = 1.43, 95% CI = 1.33–1.53), rs8050136 (OR = 1.25, 95% CI = 1.13–1.38), rs17817449 (OR = 1.54, 95% CI = 1.41–1.68), and rs121980 (OR = 1.34, 95% CI = 1.10–1.62). rs9940128 variant, associated with a risk for early and severe obesity development, belongs to the same block of linkage disequilibrium[25]. However, the formation of linkage disequilibrium blocks seems to have ethnic features. Thus, the strength of the linkage disequilibrium of rs10852521 at rs9939609 varied, according to the HapMap data, from D' = 0.48 to D' = 1.0 depending on the population[26].

The analysis results on the linkage disequilibrium of *FTO* polymorphic variants based on genotyping results are shown in Figure 4 (r^2 values provided).

According to the data, we were able to obtain, the rs10852521 polymorphic variant turned out to be linked to the rs8047395 variant (r^2 = 0.95) and rs1477196 to rs4783819 (r^2 = 0.96), while the rs7206790 variant was not linked to any of the polymorphic variants tested.

Eight polymorphic variants of the *FTO* gene for which a statistically significant association with BMI were shown constitute one block of linkage disequilibrium (r^2 = 0.82–1.0, $P < 0.001$) and form two most common haplotypes: A/C/T/T/G/T/G/C (51.9%) and G/T/C/G/T/A/A/T (42.8%). The frequency of occurrence of other haplotypes does not exceed 2%.

It is of particular interest that the variants associated with a risk for overweight form one block of linkage disequilibrium (r^2 = 0.82–1.0, $P < 0.001$). Therefore, to determine an obesity risk, carrying out genetic testing for one of these polymorphic variants seems to be sufficient. This greatly facilitates a process of determining a predisposition to excess weight with the aim to undertake preventive measures for identified individuals and reduce the relevant cost.

However, several limitations should also be noted. First, neither thyroid disease nor Type 2 diabetes and their pharmacological treatment were exclusion criteria for the present study. Second, we cannot completely exclude the role of environmental variables, which may impact the development of obesity, such as a lifestyle, physical activity, a diet, and alcohol consumption.

4. Conclusions

A group of 655 volunteers residing in the territory of the Republic of Belarus was genotyped for 13 polymorphic variants of the *FTO* gene. A significant association

of the genotype with the BMI was observed in eight polymorphic variants of the *FTO* gene: In the carriers of minor homozygotes of polymorphic variants rs11075990, rs1121980, rs1421085, rs17817449, rs3751812, rs9939609, rs9940128, and rs9941349, the BMI was much higher compared with the carriers of corresponding major homozygotes (P = 0.0022 – 0.021). Using the polymorphic variant rs11075990 as an example, it was shown that *FTO* genotype frequencies correlate with BMI. Thus, the frequency of the A/A genotype in the studied groups decreases with increasing BMI. Major A/A homozygote carriers are more likely to have normal weight compared to heterozygotes and minor G/G homozygote carriers. An analysis of linkage disequilibrium of 13 polymorphic variants of the *FTO* gene was carried out. It was found that the rs10852521 polymorphic variant is linked to the rs8047395 variant (r^2 = 0.95) and rs1477196 to rs4783819 (r^2 = 0.96), while the rs7206790 variant is not linked to any of the tested polymorphic variants. Eight polymorphic variants of the *FTO* gene for which a statistically significant association with the BMI was shown constitute one block of linkage disequilibrium (r^2 = 0.82 – 1.0, P < 0.001) and form two most common haplotypes: A/G/T/T/G/T/G/C (51.9%) and G/A/C/G/T/A/A/T (42.8%). The frequency of occurrence of other haplotypes does not exceed 2%. Therefore, to determine a risk of obesity, carrying out genetic testing for one of these polymorphic variants seems to be sufficient.

Acknowledgments

None.

Funding

This research was funded by NATIONAL ACADEMY OF SCIENCES OF BELARUS, scientific and technical program of the Union State "DNA-identification," grant number 6.1.

Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Irma B. Mosse, Larisa I. Danilova
Investigation: Maxim D. Ameliyanovich, Maxim L. Lushchyk
Methodology: Larisa I. Danilova
Writing – original draft: Irma B. Mosse
Writing – review & drafting: Maxim D. Ameliyanovich

Ethics approval and consent to participate

The informed consent form in accordance with the Declaration of Helsinki (as amended in 2013) and the study program were approved by the Bioethics Committee of the Belarusian Medical Academy of Postgraduate Education (protocol № 4 dated 04.12.2017).

Consent for publication

All participants gave written informed consent to publishing their anonymized data.

Availability of data

Data available on request from the corresponding author.

References

1. Kopelman PG, 2000, Obesity as a medical problem. *Nature*, 404: 635–643.

   https://doi.org/10.1038/35007508

2. Peeters A, Barendregt JJ, Willekens F, *et al.*, 2003, Obesity in adulthood and its consequences for life expectancy: A life-table analysis. *Ann Intern Med*, 138: 24–32.

   https://doi.org/10.7326/0003-4819-138-1-200301070-00008

3. World Health Organization. Overweight and Obesity Report Fact Sheet. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight [Last accessed on 2023 Jan 27].

4. UNICEF, World Bank. Levels and Trends in Child Malnutrition: UNICEF-WHO-World Bank Joint Child Malnutrition. Available from: https://www.who.int/publications/i/item/9789240025257 [Last accessed on 2023 Jan 27].

5. Rolls BJ, 2017, Dietary energy density: Applying behavioural science to weight management. *Nutr Bull*, 42: 246–253.

   https://doi.org/10.1111/nbu.12280

6. Horowitz JF, Klein S, 2000, Lipid metabolism during endurance exercise. *Am J Clin Nutr*, 72: 558–563.

   https://doi.org/10.1093/ajcn/72.2.558S

7. Richter EA, Derave W, Wojtaszewski JF, 2001, Glucose, exercise and insulin: Emerging concepts. *J Physiol*, 535: 313–322.

   https://doi.org/10.1111/j.1469-7793.2001.t01-2-00313.x

8. Gerken T, Girard CA, Tung YC, *et al.*, 2007, The obesity-associated *FTO* gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. *Science,* 318: 1469–1472.

   https://doi:10.1126/science.1151710

9. Han Z, Niu T, Chang J, *et al.*, 2010, Crystal structure of the FTO protein reveals basis for its substrate specificity. *Nature*, 464: 1205–1209.

   https://doi.org/10.1038/nature08921

10. Frayling TM, Timpson NJ, Weedon MN, *et al.,* 2007, A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity.

Science, 316: 889–894.

https://doi.org/10.1126/science.1141634

11. Dina C, Meyre D, Gallina S, *et al*., 2007, Variation in *FTO* contributes to childhood obesity and severe adult obesity. *Nat Genet*, 39: 724–726.

https://doi.org/10.1038/ng2048

12. Peng S, Zhu Y, Xu F, *et al*., 2011, *FTO* gene polymorphisms and obesity risk: A meta-analysis. *BMC Med*, 9: 71.

https://doi.org/10.1186/1741-7015-9-71

13. Scuteri A, Sanna S, Chen WM, *et al*., 2007, Genome-wide association scan shows genetic variants in the *FTO* gene are associated with obesity-related traits. *PLoS Genet*, 3: 1200–1210.

https://doi.org/10.1371/journal.pgen.0030115

14. Cornes BK, Lind PA, Medland SE, *et al*., 2009, Replication of the association of common rs9939609 variant of *FTO* with increased BMI in an Australian adult twin population but no evidence for gene by environment (G x E) interaction. *Int J Obes (Lond)*, 33: 75–79.

https://doi.org/10.1038/ijo.2008.223

15. Tan JT, Dorajoo R, Seielstad M, *et al*., 2008, *FTO* variants are associated with obesity in the Chinese and Malay populations in Singapore. *Diabetes*, 57: 2851–2857.

https://doi.org/10.2337/db08-0214

16. Freathy RM, Timpson NJ, Lawlor DA, *et al*., 2008, Common variation in the *FTO* gene alters diabetes-related metabolic traits to the extent expected given its effect on BMI. *Diabetes*, 57: 1419–1426.

https://doi.org/10.2337/db07-1466

17. Hinney A, Nguyen TT, Scherag A, *et al*., 2007, Genome wide association (GWA) study for early onset extreme obesity supports the role of fat mass and obesity associated gene (*FTO*) variants. *PLoS One*, 2: e1361.

https://doi.org/10.1371/journal.pone.0001361

18. Loos RJ, 2009, Recent progress in the genetics of common obesity. *Br J Clin Pharmacol*, 68: 811–829.

https://doi.org/10.1111/j.1365-2125.2009.03523.x

19. Solé X, Guinó E, Valls J, *et al*., 2006, SNPStats: A web tool for the analysis of association studies. *Bioinformatics*, 22: 1928–1929.

https://doi.org/10.1093/bioinformatics/btl268

20. Dandine-Roulland C, Perdry H, 2018, Manipulation of Genetic Data (SNPs). Computation of GRM and Dominance Matrix, LD, Heritability with Efficient Algorithms for Linear Mixed Model (AIREML). In: Proceedings of the Forty-Sixth European Mathematical Genetics Meeting, 2018. p. 6.

21. Tan LJ, Zhu H, He H, *et al*., 2014, Replication of 6 obesity genes in a meta-analysis of genome-wide association studies from diverse ancestries. *PLoS One*, 9: e96149.

https://doi.org/10.1371/journal.pone.0096149

22. Peters U, North KE, Sethupathy P, *et al.,* 2013, A systematic mapping approach of 16q12.2/FTO and BMI in more than 20,000 African Americans narrows in on the underlying functional variation: Results from the Population Architecture using Genomics and Epidemiology (PAGE) study. *PLoS Genet*, 9: e1003171.

https://doi.org/10.1371/journal.pgen.1003171

23. Rampersaud E, Mitchell BD, Pollin TI, *et al*., 2008, Physical activity and the association of common *FTO* gene variants with body mass index and obesity. *Arch Intern Med*, 168: 1791–1797.

https://doi.org/10.1001/archinte.168.16.1791

24. Xu Y, Ling J, Yang M, *et al*., 2014, Rs7206790 and rs11644943 in *FTO* gene are associated with risk of obesity in Chinese school-age population. *PLoS One*, 9:e108050.

https://doi.org/10.1371/journal.pone.0108050

25. Li, X., Mei, L., Yang, K., *et al*., 2009, Identifying association under a previous linkage peak on chromosome 16 for body mass index using cross-sectional and longitudinal data of the Framingham Heart Study. *BMC Proc*, 3: S101.

https://doi.org/10.1186/1753-6561-3-s7-s101

26. Apalasamy YD, Ming MF, Rampal S, *et al.,* 2012, Genetic association of SNPs in the *FTO* gene and predisposition to obesity in Malaysian Malays. *Braz J Med Biol Res*, 45: 1119–1126.

https://doi.org/10.1590/s0100-879x2012007500134