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HUMAN GENETICS

Association of Polymorphic Variants of *FTO* and *MC4R* Genes with Obesity in a Tatar Population

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Abstract—Obesity is a chronic relapsing disease that leads to numerous ailments and requires lifelong treatment. Genetic predisposition is one of the mostly discussed aspects of obesity development, and genome-wide association studies have provided evidence that several variants of the *FTO* and *MC4R* genes are significantly associated with obesity. In this study the association of *FTO* (*rs9939609, rs7202116,* and *rs9930506*) and *MC4R* (*rs12970134* and *rs17782313*) genes' SNPs with obesity in Tatar women has been analyzed. In the investigation 340 women with obesity (Body Mass Index (BMI) ≥ 30 kg/m^2) and 330 women from a control group (BMI up to 24.9 kg/m^2) took part. The *FTO rs9939609* ($p = 0.0002$) and *rs9930506* ($p = 0.0005$) SNPs were shown to be associated with obesity risk following an additive model, while the *MC4R rs12970134* ($p = 0.0076$) and *rs1778231* ($p = 0.021$) SNPs were associated by a recessive model. We also showed an association of quantitative parameters (age, weight, and BMI) with two the *FTO rs9939609* and *rs9930506* SNPs and the association of age and the *MC4R rs12970134* SNP. Our study demonstrates the role of genetic variability in *FTO* and *MC4R* genes in obesity development in Tatar women from Russia.

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INTRODUCTION

Obesity today is a global problem of humanity [1]. Excessive weight and obesity are among the five main risk factors for death. At least 2.8 million of adults die annually because of excessive weight or obesity. Besides, 44% of diabetes, 23% of ischemic heart disease, and 7–41% of cancers are caused by excessive weight and obesity [1]. According to the World Health Organization (WHO), the number of persons suffering from obesity increased at least twice since 1980 by 2012. In Russia the prevalence of excessive weight—obesity is 46.5% among men and 51.7% among women [2]. Obesity is a chronic relapsing disease leading to numerous ailments and requires lifelong treatment. Nevertheless, until now many people considered excessive weight and obesity a problem that can be resolved without any assistance.

The accelerated increase of body mass in different populations is primarily associated with changed environment conditions (food, chemical exposure, and sedentary life) [3]. One of the discussed aspects of this problem is genetic predisposition to obesity. The genetic component is confirmed by several studies of twins, who inherit such traits as body mass index (BMI) with a 40–70% probability among children and adults [4].

There are monogenic and syndromic forms of obesity caused by mutations in the genes controlling appetite. In both cases there is a marked pathological morbid obesity developing in childhood when there is a twofold or higher increase of the body mass in comparison to the ideal mass of the person (BMI ≥ 40 kg/m^2).

Syndromic obesity is accompanied by numerous abnormalities in the structure of different organs, intellectual disability, and neurological disorders [5]. Prader–illi and Beckwith–Wiedemann syndromes, caused by a disturbance of genomic imprinting, represent syndromic forms of obesity. Monogenic forms are caused by inactivation of the appetite-controlling genes on the melanocortin system level. Clinical manifestation is characterized by early onset of the disease, a rapidly progressive course, morbid obesity, hyperphagia, and secondary hypogonadism [5].

The problem of monogenic obesity today is fairly well studied, whereas the genetic basis of common polygenic obesity remains controversial. Since 2007 there have been several genome-wide association studies (GWAS) of obesity and anthropometric features. As a result of these projects, 54 loci were identified as being associated with an obesity risk in different populations [6–13]. Several genes were shown to be expressed in the central nervous system (CNS) and to participate in the regulation of energy intake and

expenditure, adipocyte differentiation, appetite control, etc. [7, 12, 14].

According to GWAS, an association of polymorphic variants of two genes—melanocortin 4 receptor (*MC4R*) and the gene associated with fat mass (*FTO*)—with the development of obesity and excessive weight was detected in many populations [7, 8, 11, 13, 14].

The *FTO* gene is associated with the accumulation of fat mass and is localized on chromosome 16. This gene encodes the enzyme alpha-ketoglutarate-dependent dioxygenase, which participates in demethylation of nucleic acids. This indicates the presence of epigenetic mechanisms in the development of obesity [14–16]. Polymorphic variants of the *FTO* gene influence the tissue-specific expression of the gene in the brain centers responsible for the control of energy balance [15]. It was shown that carriers of the certain alleles of the gene not only eat more high-calorie foods but also show specific food preferences [16]. One of the most probable causes of obesity development is a change of appetite under the influence of the proteins of the *FTO* gene [15].

The *MC4R* gene encodes a neuronal melanocortin receptor. The stimulation of MC4R by melanocortin leads to an increase of the activity of the sympathetic nervous system, a decrease of appetite, an increase of the speed of fat metabolism, and a decrease in the insulin level; accordingly, a low activity of melanocortin leads to obesity. Analysis of the investigations of model animals shows that a *MC4R* block in mice leads to the development of the hyperphagia and hyperinsulinemia phenotype. Some investigators showed that SNPs of the *MC4R* gene are associated with quantitative characteristics determining metabolic disorders and changes of anthropometric characteristics, as well as changes in feeding behavior [17].

In light of the tissue-specific expression of the *FTO* and *MC4R* genes in the brain centers responsible for the control of the energy balance, a significant influence of the products of these genes on the characteristics of the feeding behavior (but not on the metabolism in general) can be suggested.

The relevance of the present work is determined by the small number of data concerning the detection of the frequencies of alleles and genotypes of the *FTO* and *MC4R* genes in Russian populations [18, 19].

The present work was aimed at an analysis of the associations of *FTO* (*rs9939609*, *rs7202116*, and *rs9930506*) and *MC4R* (*rs12970134* and *rs17782313*) SNPs with the risk of obesity and clinical and anthropometric characteristics of metabolic disorders in Tatar women.

MATERIALS AND METHODS

DNA from 670 women from a random sampling in the Republic of Bashkortostan (RB) was used in the work. Ethnicity was clarified by questionnaire.

The samples were collected in the Center for the Correction of Weight and Comorbidities of the Emergency Hospital. The samples were formed according to the body mass index (BMI). The group with obesity (BMI $\geq$ 30 kg/m^2) included 340 women. The control group included women according to the following criteria: BMI < 25 kg/m^2 and the absence of obesity and diabetes in anamnesis ($N = 330$).

The study included questionnaires, anthropometric measurements, and medical examinations were performed. Anthropometric measurements included the measurement of weight, height, waist and hip circumference, and a determination of the waist-to-hip ration. Biochemical analyses (cholesterol, triglyceride, low density lipoprotein (LDL), high density lipoprotein (HDL), aspartate aminotransferase (AST), and alanine aminotransferase (ALT)) and blood pressure were taken into consideration in women with obesity and in the control. The clinical description of women with obesity and of the control group is shown in Table 1.

The present study was approved by the Ethics Committee of the Institute of Biochemistry and Genetics, Ufa Scientific Center, Russian Academy of Science. Informed voluntary consent for the use of biological material was obtained from all participants.

Genotyping of single nucleotide substitutions. DNA was extracted from leukocytes of peripheral blood by the phenol-chloroform method. Genotyping of *FTO* (*rs9939609*, *rs7202116*, *rs9930506*) and *MCR4* (*rs12970134* and *rs17782313*) SNPs was performed by TaqMan technology. The amplification was performed using a CFX 96 cycler (Bio-Rad, United States) according to the manufacturer's protocol (Limited Liability Company TestGen, http://testgen.ru/).

Mathematical treatment of the results was performed using MS Office Excel 2003 (Microsoft) and Statistica v. 6.0. (StatSoft) software. Comparison of the clinical data for women with obesity and the control group was performed using the Mann–Whitney test.

The association between SNPs and obesity was estimated using a logistic regression model. Groups with a BMI of $\geq$30 kg/m^2 and BMI < 25 kg/m^2 were compared. Genotypes were marked as 0, 1, and 2, depending on the risk allele copy. Risk alleles were determined based on previous studies [14, 20]. Comparison of the genotypes and risk alleles was performed according to three models. In the first case, the assessment was performed in an additive model, when every copy of a rare allele changes the risk of disease development. In the second case, a dominant model was considered when one copy of a rare allele is enough to change the risk. In this case the risk is related both to

Table 1. Clinical characteristics of the examined women

Indicator	Women with obesity ($N = 150$)	Control group ($N = 100$)	p
Age, years	44.16 ± 9.04	42.98 ± 9.52	0.12
Weight, kg	91.10 ± 12.30	57.02 ± 6.36	<0.001
Height, m	164.05 ± 7.25	160.58 ± 5.72	0.003
Body mass index, kg/m^2	33.57 ± 5.32	22.01 ± 1.88	<0.001
Waist circumference, cm	110.11 ± 10.29	72.54 ± 8.80	<0.001
Hip circumference, cm	113.22 ± 8.42	95.94 ± 5.09	<0.001
Waist/hip ratio, cm	0.972 ± 0.06	0.724 ± 0.08	<0.001
Cholesterol, mol/L	5.92 ± 0.78	4.36 ± 0.93	<0.001
Triglycerides, mol/L	1.78 ± 0.64	1.07 ± 0.43	<0.001
HDL, mol/L	1.01 ± 0.14	1.06 ± 0.21	0.019
LDL, mol/L	3.16 ± 0.22	2.58 ± 0.67	0.019
AST, units/L	24.21 ± 11.92	24.83 ± 8.22	0.82
ALT, units/L	26.32 ± 12.87	22.56 ± 7.42	0.06
Systolic pressure	152.26 ± 11.77	114.42 ± 7.46	<0.001
Diastolic pressure	88.23 ± 5.43	69.36 ± 3.86	<0.001
Type II diabetes mellitus, %	60	0	not defined

Mean values and error of the mean are shown in the Table. HDL, high density lipoproteins; LDL, low density lipoproteins; AST, aspartate aminotransferase; ALT, alanine aminotransferase; p, statistical significance.

the genotype homozygous for the rare allele and the heterozygous genotype. In the third case, a recessive model was analyzed to estimate the association with the homozygote for the rare allele, when two copies of the rare allele are needed to change the risk of disease development.

Linkage disequilibrium for *FTO rs9939609*, *rs7202116*, and *rs9930506* and *MCR4 rs12970134* and *rs17782313* SNPs and the Hardy–Weinberg equilibrium were calculated with Haplo-view 4.2 software [21]. Deviation from the Hardy–Weinberg equilibrium was shown only for the *rs17782313* loci of the *MC4R* gene in the group of women with obesity ($p = 0.037$).

The comparison of clinical data with different genotypes was performed using a logistic regression model in SNPStats [22].

RESULTS

The clinical characteristics of women with obesity and those from the control group are shown in Table 1. As we supposed, the sample of women with obesity and the control group differed significantly on the basis of characteristics associated with metabolic disorders: fat distribution and the level of cholesterol and triglycerides, as well as blood pressure. Statistically significant differences were obtained when BMI values were compared in women with obesity and in the control group (33.57 ± 5.32 kg/m^2 in the group with obesity and 22.01 ± 1.88 kg/m^2 in the control, $p < 0.001$). Among women with obesity, 10.0% suffered from morbid obesity ≥40 kg/m^2, 44.8% had second-degree obesity (35 kg/m^2 ≤ BMI < 40 kg/m^2), and first-degree obesity accounted for 49.2% (30 kg/m^2 ≤ BMI < 34.9 kg/m^2). Comparison of the groups by age and AST and ALT levels did not reveal statistically significant differences.

Analysis of distribution of haplotypes of FTO and MC4R genes. It has been shown that *FTO* gene *rs9939609* (*A*) and *rs9930506* (*G*) are in linkage disequilibrium ($D' = 91.8$, LOD = 133.74, $r^2 = 0.72$), while no linkages between loci *rs9939609* and *rs7202116, rs9930506,* and *rs7202116* have been defined ($D' = 22.4$, LOD = 5.3, $r^2 = 0.045$; $D' = 25.5$,

Table 2. Associations of *FTO* and *MC4R* genes SNPs with obesity in Tatar women

Gene locus	Chromosome	Genotypes	Obesity (BMI > 30.0 kg/m^2) $N = 340$	Control (BMI to 24.9) $N = 330$	Additive model		AIC	Dominant model		AIC	Recessive model		AIC
					OR (95% CI)	p		OR (95% CI)	p		OR (95% CI)	p	
FTO/rs9939609	16	*TT/AT/AA*	100/169/71 (29.41/49.71/20.88)	136/152/42 (41.21/46.06/12.73)	1.51 (1.21–1.88)	0.0002	611.4	1.68 (1.23–2.30)	0.0012	613.8	1.79 (1.17–2.74)	0.0056	614.8
FTO/rs7202116	16	*AA/AG/GG*	97/162/81 (28.53/47.65/23.82)	78/176/76 (23.64/53.33/23.03)	0.92 (0.71–1.20)	0.55	396	0.78 (0.51–1.19)	0.24	396	1.05 (0.68–1.62)	0.84	396.1
FTO/rs9930506	16	*AA/AG/GG*	92/167/81 (27.06/49.12/23.82)	128/150/52 (38.79/45.45/15.76)	1.47 (1.18–1.83)	0.0005	574.6	1.70 (1.23–2.34)	0.0014	576.4	1.63 (1.09–2.44)	0.014	578.9
MCR4/rs12970134	18	*GG/AG/AA*	193/123/24 (56.76/36.18/7.06)	194/129/7 (58.79/39.09/2.12)	1.22 (0.92–1.63)	0.17	487.6	1.09 (0.78–1.54)	0.61	489.4	3.43 (1.20–9.78)	0.0076	485.5
MC4R/rs17782313	18	*CC/CT/TT*	191/119/30 (56.18/35.00/8.82)	200/118/12 (60.61/35.76/3.64)	1.27 (0.96–1.67)	0.096	487	1.19 (0.84–1.68)	0.32	488	2.41 (1.06–5.45)	0.021	488.9

LOD = 7.77, $r^2 = 0.063$). Analysis of the haplotypes of *FTO* gene *rs9939609* and *rs9930506* loci showed an association of the *AA* haplotype with obesity in women (OR = 1.71 (CI 95% 1.36–2.15), $p < 0.0001$). The frequency of the *AA* haplotype among women with obesity is 45.10%, compared with 29.36% in the control group.

Linkage disequilibrium was shown for two investigated *MC4R* gene loci, *rs12970134* and *rs1778231* ($D' = 67.5$, LOD = 27.37, $r^2 = 0.25$). Analysis of the *MC4R* gene haplotype distribution showed an association of the *AT* haplotype with obesity risk in women (OR = 2.52 (CI 95% 1.04–6.10), $p = 0.041$). The frequency of the *AT* haplotype in the group of women with obesity was 3.68%, compared to 1.65% in the control.

Furthermore, an analysis of the frequency distribution of genotypes and alleles of *FTO* and *MC4R* SNPs in women with obesity and in the control group was performed. Results of the analysis of an association of *FTO* gene SNPs *rs9939609, 7202116*, and *9930506* and *MC4R* gene SNPs *rs12970134* and *rs17782313* with obesity in women are shown in Table 2. The association with obesity was determined in three models: additive, dominant, and recessive. In accordance with the significance level (p) and Akaike criterion (AIC) for the analysis of *FTO* gene frequencies, the additive model was selected as most accurately describing the obtained associations (Table 2). The odds ratio was OR = 1.51 (CI 95% 1.21–1.88), $p = 0.0002$ for the *rs9939609* locus, and OR = 1.47 (CI 95% 1.18–1.83), $p = 0.0005$ for the *rs9930506* locus of the *FTO* gene.

Analysis of the *rs12970134* and *17782313* SNPs of the *MC4R* gene showed an association with obesity risk in the recessive model: OR = 3.43 (CI 95% 1.20–9.78), $p = 0.0076$ for the *rs12970134* locus and OR = 2.41 (CI 95% 1.06–5.45), $p = 0.021$ for the *rs17782313* locus.

Quantitative clinical and anthropometric characteristics were compared according to the genotypes of the *FTO* and *MC4R* gene loci. Data are shown for the additive model (Table 3). The associations were obtained when the genotype distributions of the *rs9939609* and *rs9930506* loci of the *FTO* gene were compared by age, weight, and BMI. Analysis of the genotype distribution in samples of women differentiated by age showed statistically significant differences in the additive model for the *FTO* gene *rs9939609* and *rs9930506* loci and the *MC4R* gene *rs12970134* locus ($\beta = -2.69$ (CI 95% 1.80–4.57), $p = 0.005$; $\beta = -1.85$ (CI 95% 1.02–3.67), $p = 0.04$; $\beta = 0.67$ (CI 95% 0.49–0.92), $p = 0.012$, respectively).

For interpretation of the associative data with age, an analysis of the frequency distribution of alleles and genotypes of the *FTO* gene *rs9939609* and *rs9930506* loci and the *MC4R rs12970134* in women with obesity with respect to age was performed. Since the mean age of the women was 44.16 years, they were divided into groups under and over 44, and pairwise comparison was further performed. In this case a tendency toward an increase in the frequency of rare alleles of the *FTO* gene *rs9939609* and *rs9930506* loci was determined in women with obesity of the younger group (under 44 years); however, the results were not statistically significant ($p \geq 0.05$). Analysis of the genotype distribution of the *MC4R* gene *rs12970134* locus showed a statistically significant increase in the frequency of the genotype homozygous for the rare allele in the group of women with obesity under 44 years, up to 5.3% as compared to 0% in the older group. This result is in agreement with the data of Sentinelli et al. and Andreasen et al. [23, 24]. According to the results of these authors, the genotype that is homozygous for the rare allele is more frequent among the younger group suffering from obesity.

Statistically significant differences were shown when the level of BMI and *FTO* gene *rs9939609* ($\beta = 1.05$ (CI 95% 1.00–1.63), $p = 0.0004$) and *rs9930506* ($\beta = 1.20$ (CI 95% 1.06–2.15), $p = 0.0039$) SNPs were compared. These data were obtained in the additive model.

Analysis of the genotype distribution of the *FTO* gene *rs9939609* locus with respect to weight showed that the body weight of homozygous carriers of allele *A* (*AA*) is 8 kg greater than the weight of homozygous carriers of allele *T* (*TT*). The weight of homozygous carriers of allele *A* (*AA*) of the *rs9930506* locus is 3.93 kg greater than the weight of homozygous carriers of allele *G* (*GG*).

Analysis of the association of metabolic disorders, such as cholesterol, triglycerides, LDL, and HDL levels, as well as ALT and AST, with respect to the *FTO* (*rs9939609, 7202116*, and *rs9930506*) and *MC4R* (*rs12970134* and *rs17782313*) SNPs did not show statistically significant differences (Table 3). Analysis of the association of the anthropometric characteristics of waist and hip circumference and waist-to-hip ratio and polymorphic variants of the *FTO* and *MC4R* genes also did not determine statistically significant differences (Table 3).

Analysis of the haplotype distribution the of *FTO* gene *rs9939609* and *rs9930506* loci showed that the *AG* haplotype (carriers of risk alleles) is associated with increased weight ($p = 0.014$) and a high level of triglycerides ($p < 0.0001$). Analysis of the distribution of *MC4R* gene haplotypes did not show statistically significant differences with respect ot quantitative characteristics and anthropometric parameters of metabolic disorder.

DISCUSSION

An association of the *FTO* gene *rs9939609* and *rs9930506* SNPs with obesity in Tatar women was shown. This conclusion is fully consistent with previously published data from the various world samples

Table 3. Analysis of anthropometric and metabolic characteristics of women according to *FTO* and *MC4R* genes SNPs

Gene/polymorphism	Genotype	Age, years ($N = 670$)	Height, cm ($N = 250$)	Body weight, kg ($N = 250$)	Body mass index, kg/m^2 ($N = 250$)	Waist circumference, cm ($N = 250$)	Hip circumference, cm ($N = 250$)	Waist/hip ratio ($N = 250$)	Cholesterol, mol/L ($N = 250$)	Triglycerides, mol/L ($N = 250$)	HDL, mol/L ($N = 250$)	LDL, mol/L ($N = 250$)	AST, units/L ($N = 250$)	ALT, units/L ($N = 250$)
FTO/rs9939609	*TT*	48.1 (0.97)	164.5 (0.75)	79.0 (1.78)	27.3 (0.37)	104.8 (2.2)	111.0 (1.21)	0.95 (0.01)	5.6 (0.13)	1.7 (0.1)	1.03 (0.02)	3.15 (0.02)	22.5 (1.54)	24.2 (1.5)
	AT	45.1 (0.6)	164.6 (0.62)	81.8 (1.38)	28.3 (0.35)	105.2 (1.62)	111.0 (1.07)	0.95 (0.01)	5.9 (0.11)	1.7 (0.07)	1.03 (0.02)	3.16 (0.03)	25.8 (1.41)	25.1 (1.16)
	AA	45.3 (0.63)	167.3 (0.84)	87.0 (1.79)	29.4 (0.46)	107.6 (1.74)	111.0 (1.07)	0.99 (0.01)	5.8 (0.1)	1.8 (0.07)	1.04 (0.02)	3.2 (0.02)	25.0 (1.77)	27.9 (1.78)
FTO/rs7202116	*AA*	48.9 (0.9)	166.9 (0.76)	84.3 (1.55)	28.8 (0.47)	106.7 (1.45)	111.2 (1.02)	0.97 (0.01)	5.8 (0.1)	1.8 (0.09)	1.02 (0.02)	3.15 (0.02)	22.7 (1.3)	25.7 (1.34)
	AG	46.1 (0.75)	164.9 (0.67)	82.0 (1.49)	28.7 (0.4)	105.3 (1.84)	110.6 (1.05)	0.96 (0.01)	5.7 (0.11)	1.8 (0.07)	1.05 (0.02)	3.2 (0.03)	24.5 (1.41)	25.0 (1.43)
	GG	47.6 (1.03)	165.0 (0.82)	82.8 (1.88)	29.2 (0.51)	105.4 (2.17)	110.7 (1.31)	0.97 (0.01)	5.9 (0.16)	1.7 (0.08)	1.02 (0.02)	3.15 (0.03)	27.2 (2.02)	26.7 (1.7)
FTO/rs9930506	*GG*	47.6 (0.92)	164.7 (0.81)	81.2 (1.87)	29.3 (0.45)	104.6 (2.16)	110.5 (1.17)	0.95 (0.01)	5.6 (0.13)	1.7 (0.07)	1.03 (0.02)	3.15 (0.02)	22.3 (1.52)	23.9 (1.5)
	AG	45.4 (0.6)	164.7 (0.63)	80.9 (1.34)	28.1 (0.35)	104.8 (1.66)	110.8 (1.1)	0.95 (0.01)	5.9 (0.12)	1.7 (0.07)	1.03 (0.02)	3.16 (0.03)	25.7 (1.44)	25.4 (1.2)
	AA	45.9 (0.73)	166.6 (0.77)	85.0 (1.83)	27.3 (0.4)	108.3 (1.7)	111.9 (1.09)	0.98 (0.01)	5.8 (0.11)	1.9 (0.11)	1.04 (0.02)	3.2 (0.02)	25.4 (1.73)	27.6 (1.7)
MCR4/rs12970134	*GG*	47.7 (1.52)	164.8 (0.53)	81.7 (1.18)	28.4 (0.31)	105.4 (1.45)	111.3 (0.88)	0.96 (0.01)	5.8 (0.08)	1.8 (0.05)	1.03 (0.01)	3.14 (0.02)	23.8 (1.11)	25.8 (1.06)
	AG	46.4 (0.76)	166.1 (0.77)	81.4 (1.58)	28.5 (0.39)	106.1 (1.63)	110.7 (1.03)	0.96 (0.01)	5.8 (0.13)	1.7 (0.06)	1.05 (0.02)	3.21 (0.03)	26.1 (1.71)	25.6 (1.5)
	AA	46.7 (0.61)	167.1 (1.72)	88.5 (3.29)	30.5 (1.18)	110.0 (4.07)	110.7 (2.4)	1.02 (0.03)	5.7 (0.22)	2.1 (0.49)	0.92 (0.05)	3.24 (0.03)	23.0 (3.01)	20.1 (2.32)
MC4R/s17782313	*TT*	47.8 (1.4)	164.7 (0.5)	82.0 (1.16)	28.4 (0.29)	105.3 (1.42)	111.2 (0.86)	0.96 (0.01)	5.8 (0.09)	1.7 (0.05)	1.04 (0.01)	3.14 (0.01)	24.7 (1.21)	26.5 (1.11)
	CT	47.4 (0.93)	166.5 (0.88)	81.8 (1.72)	28.8 (0.46)	106.7 (1.43)	111.8 (1.01)	0.96 (0.01)	5.7 (0.1)	1.8 (0.07)	1.03 (0.02)	3.23 (0.04)	24.5 (1.53)	24.3 (1.36)
	CC	46.4 (0.57)	167.4 (1.8)	82.7 (3.23)	30.1 (0.98)	108.6 (3.93)	108.1 (1.98)	1 (0.03)	5.7 (0.23)	2 (0.29)	0.96 (0.04)	3.17 (0.05)	23.7 (2.23)	22.7 (1.62)

Mean values and error of mean are shown in the Table.

[6, 13, 20]. The most significant differences in the distribution of alleles and genotypes were shown for the *FTO* gene *rs9939609* locus. It is known that this locus has statistically significant associations with obesity risk, both among Europeans and among Mongoloids [13, 23, 24]. There are controversial data concerning the *FTO* gene *rs9930506* locus, because the frequency of the rare allele in populations is different. The association with obesity risk was shown both for allele *G* in the European population [6, 23] and for allele *A* in the Mongoloid population [14, 25, 26]. In our work an association with obesity risk was shown for women with rare allele *G*.

We did not determine the associations of such characteristics of metabolic disorders as the level of cholesterol, triglycerides, ALT, and AST with genotypes of the *FTO* and *MC4R* genes. One of the possible explanations of the absence of differences may be the relatively young age of women suffering from obesity (the mean age is 44.16 years), when metabolic disorders have not achieved a high level.

However, the analysis of the distribution of *FTO* gene SNPs with such characteristics as age, body weight, and BMI showed a statistically significant association. An increase in the BMI level and body weight in carriers of the rare alleles of the *FTO* gene *rs9939609* and *rs9930506* loci was shown.

The obvious reasons for an association of SNPs of the *FTO* gene intron 1 with obesity have not yet been established. This may be determined by the close linkage with other genetic variants directly affecting the metabolism. However, there is a suggestion that functionally significant variants are determined just by the region of the *FTO* gene itself [13]. From bioinformatics methods of investigating the functional activity of proteins, it was shown that the *FTO* gene encodes demethylase of nucleic acids. It is known that the processes of demethylation play an important role in the mechanisms of DNA repair and epigenetic regulation of the expression of genes participating in metabolism and causing obesity development on the epigenetic level.

MC4R gene SNPs were shown to make a smaller contribution in the development of pathogenic mechanisms of metabolic disorders in comparison with the *FTO* gene [20]. In the present work an association with obesity development for two *MC4R* gene *rs12970134* and *rs17782313* loci was shown only in the recessive model. Analysis of the association of anthropometric and metabolic characteristics of women in accordance with SNPs of the *MC4R* gene showed the presence of association only with age for the *rs12970134* locus.

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