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Association of SNPs in Lipid Metabolism Gene Single Nucleotide Polymorphism with the Risk of Obesity in Children

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Background: Obesity is one of the most common metabolic disorders in the world, which develops due to an imbalance in energy consumption and expenditure, and both genetic and environmental factors are of great importance. We investigated the potential interactions of single nucleotide polymorphisms that might contribute to the development of polygenic obesity in children.
Objective: The study involved 367 children and adolescents of both sexes aged from 4 to 18 years. The control group (normal weight) and the overweight groups included 65 and 302 children respectively.
Methods: DNA for analysis was isolated from peripheral blood lymphocytes, then allelic variants rs99305069 of the *FTO* gene (chr16:53786615), *Gln192Arg* of the *PON1* gene (chr7: 95308134), *-250G>A* of the *LIPC* gene (chr15: 58431740), and *Ser447Ter* of the *LPL* gene (chr8:19957678) were studied using the SNP-Express reagent kit. The results of allelic interactions were analyzed using the multifactor dimensionality reduction method.
Results and Discussion: Among overweight children, the distribution of genotype and allele frequencies for the studied single nucleotide polymorphisms of the four genes corresponded to those of the control group ($p > 0.05$). It was found that in obese children *SerSer* homozygotes at the *Ser447Ter* polymorphism of the *LPL* gene, had serum triglyceride (TG) levels 2.3 times higher than in children with the same genotype from the control group. In overweight *Ser447Ter* heterozygotes ($p < 0.0001$), the TG level exceeded the control values by only 13% ($p = 0.044$). A two-locus genotype *FTO AT/LPL SerTer*, was associated with a reduced risk of childhood obesity.

Keywords: overweight, gene polymorphism, lipid metabolism, FTO, gene/gene interactions

Introduction

Obesity is the one of the most common metabolic disorders in the world, which develops due to an imbalance in energy consumption and expenditure, and both genetic and environmental factors are of great importance here. This disease causes not only psychophysical discomfort but also causes other health problems, such as cardiovascular diseases, diabetes, and high blood pressure (Hsu *et al.*, 2006; Li *et al.*, 2006; Singh *et al.*, 2013).

Now, obesity is becoming an increasingly important medical problem in children and adolescents (Choquet and Meyre, 2011). In 2011 Redsell *et al.* (2011) found that overweight in children during active growth plays a key role in the development of obesity in adulthood and correlates with risk factors for chronic diseases. In 2017, the NCD Risk Factor Collaboration (2016) analyzed global trends in body mass index (BMI), underweight, overweight, and obesity from 1975 to 2016 in more than 128 million people, including both adults and children. As a result, the number of obese children increased from 0.7% and 0.9% to 5.6% and 7.8% for girls and boys, respectively (Abarca-Gómez *et al.*, 2017).

The most common causes that can lead to obesity are eating disorders, sedentary lifestyle, environmental factors, or genetic predisposition (Biswas *et al.*, 2017). In the genetic context, forms of obesity are divided into monogenic and polygenic. Monogenic obesity is rare, approximately in 3.5% of patients (Gao *et al.*, 2015). Polygenic obesity is more common in the population. In the context of the influence on this form of obesity, genes such as *FTO*, *ADRB2*, *VDR*, *LPL*, *PPARG*, *LIPC*, *ACE*, *PON1*, *UCP1*, *UCP2*, *UCP3*, and *ApoE* are studied (Rankinen *et al.*, 2006).

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Table 1. Distribution of Children and Adolescents by Age and Body Mass Index

	Control		*Overweight*	
Age	*Abs. (% [95% CI])*	*BMI ± SD*	*Abs. (% [95% CI])*	*BMI ± SD*
Up to 10 years	22 (33.8% [22.3–45.3])	18.1 ± 0.12	84 (27.8% [22.8–32.9])	22.02 ± 0.17
11–15 years	18 (27.7% [16.8–38.6])	19.9 ± 0.26	123 (40.7% [35.2–46.3])	27.02 ± 0.13
15–18 years	25 (38.5% [26.6–50.3])	19.7 ± 0.18	95 (31.5% [26.2–36.7])	28.4 ± 0.29
Total	65	19.2 ± 0.15	302	26.06 ± 0.19

The values are presented as the mean ± SE where applicable.
Abs., Absolute; BMI, body mass index; CI, confidence interval; SE, standard error of the mean.

Dietary fat is broken down to triglyceride (TG)-rich lipoproteins. TG hydrolysis is performed by lipoprotein lipase encoded by the *LPL* gene. LPL is an enzyme that contributes to normal lipoprotein metabolism, delivery, and utilization of tissue-specific lipoproteins. Homozygous *LPL* knockout mice at birth have three times higher levels of TGs and seven times higher levels of very low-density lipoproteins (Weinstock *et al.*, 1995).

Another enzyme that plays an important role in lipid metabolism is hepatic lipase, encoded by the *LIPC* gene (Cai *et al.*, 1989). This enzyme catalyzes the hydrolysis of the fatty acyl chains of phospholipids and mono-, di-, and triacylglycerols bound to various lipoproteins, including high-density lipoproteins (HDLs). LIPC can also promote receptor-mediated uptake of lipoproteins (Brown *et al.*, 2004). Variations in the *LIPC* locus affect HDL metabolism.

HDLs are associated with paraoxonase 1, which can prevent the oxidation of low-density lipoproteins (LDLs) (Draganov *et al.*, 2005). In *PON1* knockout mice, HDLs are unable to prevent LDL oxidation. When fed on a diet high in fat and cholesterol, *Pon1*-zero mice were more susceptible to atherosclerosis than wild-type litters (Shih *et al.*, 1998).

Humbert *et al.* (1993) found that arginine (R) at position 192 of PON1 determines high activity of the enzyme, whereas glutamine (Q) at this position determines low enzyme activity. HDLs protect LDLs from oxidative modification regardless of the combination of PON1 isoforms present in it. However, QQ homozygotes are more effective in protection (Mackness *et al.*, 1998).

Regulation of appetite and satiety, energy consumption and expenditure is provided by a complex neurohumoral system with a cascade action. One of the important elements of this system is the FTO protein, which is involved in energy metabolism and affects metabolism in general. FTO is involved in controlling adipocyte differentiation, energy homeostasis, and leptin-independent appetite control, regulates energy consumption, affects muscle mass, and suppresses lipolysis (James, 2004).

The effect of variations in the *FTO* gene on body composition and the risk of overweight development were shown in childhood and persisted in adults (Loos and Bouchard, 2008). The results of studies in children aged 4–5 years with mutant alleles of the *FTO* gene (rs9939609) showed no sense of food saturation, that is, they were characterized by food consumption in the absence of hunger (Carnell and Wardle, 2009).

The aim of this work was to investigate the association of rs9939609 polymorphism of the *FTO*, *Gln192Arg* of the *PON1*, *-250G>A* of the *LIPC*, *Ser447Ter* of the *LPL* with the risk of overweight in children and adolescents in Rostov-on-Don.

Materials and Methods

The study was conducted on two groups of children and adolescents aged 4 to 18 years. The control group (normal weight) included 65 children of both sexes. The overweight group included 302 children. All procedures were in accordance with the Declaration of Helsinki as revised in 2013. This study was approved by an institutional review board of Federal State Autonomous Educational Institution of Higher Education, Southern Federal University, Academy of Biology and Biotechnology Protocol No. 2 of 29.03.2016.

Table 1 shows the distribution of children by age subgroup, indicating the average values of the BMI. The cut-points for the detection of excess weight were determined in accordance with the standards of the World Health Organization: for the age subgroup up to 10 years inclusive—cut-points BMI = 19.5; for the subgroup 11–15 years—24; for the subgroup 16–18 years inclusive—25.

The levels of TG, HDL, LDL, cholesterol, and glucose were determined in samples by enzymatic methods using commercial kits (Vector-Best, Russia). All measurements were performed with an autoanalyzer (MIURA 200, Italy). No differences were found for the biochemical parameters by sex, as well as between the age subgroups within the same group. Table 2 shows the average values of the indicators for the groups as a whole. In the group of overweight children, the average values of cholesterol, HDL, and glucose did not differ from those of the control group. At the same time, the levels of TGs and LDL were significantly higher compared with the control group.

DNA samples isolated from peripheral blood leukocytes were used for molecular genetic research. DNA was isolated by the thermocoagulation method using the ''DNA-Express-blood'' reagent (Lytech, Russia). Allelic variants rs99305069 of the *FTO* gene, *Gln192Arg* of the *PON1* gene, *-250G>A* of the *LIPC* gene, and *Ser447Ter* of the *LPL* gene

Table 2. Participant Characteristics

	Control	*Overweight*	p
Sex			
Female	39 (60%)	163 (54%)	
Male	26 (40%)	139 (46%)	
Triglyceride (mM)	0.69 ± 0.06	1.06 ± 0.03	<0.0001
Cholesterol (mM)	3.87 ± 0.09	4.01 ± 0.59	0.98
HDL (mM)	1.35 ± 0.04	1.34 ± 0.02	0.57
LDL (mM	2.22 ± 0.07	3.04 ± 0.99	0.02
GLU (mM)	4.76 ± 0.07	4.68 ± 0.06	0.25

GLU, glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 3. The Allele and Genotype Frequencies [Absolute (%)] for Polymorphic Variants of the *FTO*, *PON1*, *LIPC*, and *LPL* Genes in Children

Genotype, allele	*Control*	*Overweight*	χ^2 (p)
rs9939609, *FTO* gene			
AA	19 (29.23)	90 (29.80)	5.76 (0.06)
AT	39 (60)	142 (47.02)	
TT	7 (10.77)	70 (23.18)	
A allele	0.592	0.533	1.28 (0.26)
HWE, χ^2 (p)	3.82 ($p>0.05$)	0.93 ($p>0.05$)	
Gln192Arg, *PON1* gene			
GlnGln	32 (49.23)	139 (46.02)	0.79 (0.67)
GlnArg	30 (46.15)	140 (46.36)	
ArgArg	3 (4.62)	23 (7.62)	
Arg allele	0.288	0.308	0.35 (0.55)
HWE, χ^2 (p)	1.51 ($p>0.05$)	2.32 ($p>0.05$)	
-250G>A, *LIPC* gene			
GG	38 (58.46)	185 (61.25)	0.77 (0.68)
GA	24 (36.92)	109 (36.10)	
AA	3 (4.62)	8 (2.65)	
A allele	0.231	0.207	0.23 (0.63)
HWE, χ^2 (p)	0.10 ($p>0.05$)	2.99 ($p>0.05$)	
Ser447Ter, *LPL* gene			
SerSer	54 (83.07)	253 (83.77)	0.25 (0.88)
SerTer	11 (16.93)	48 (15.90)	
TerTer	0 (0)	1 (0.33)	
Ter allele	0.084	0.082	0.005 (0.94)
HWE, χ^2 (p)	0.55 ($p>0.05$)	0.66 ($p>0.05$)	

HWE, Hardy–Weinberg equilibrium.

were studied using the SNP-Express reagent kit (Lytech, Russia). The analysis is based on amplification reactions with two pairs of allele-specific primers. Amplification products were separated by horizontal electrophoresis in 3% agarose gel.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 8.4.2. Quantitative variables were expressed as mean ± standard error of the mean, and qualitative variables as percentages. Normality test was performed using the Shapiro–Wilk test. Comparisons of quantitative variables were made using the appropriate nonparametric Mann–Whitney test.

Differences in genotype distribution between the groups were obtained using the chi-square test. The risk of developing overweight was judged by the odds ratio (OR). OR is specified with a 95% confidence interval (CI).

To analyze intergenic interactions, we used a bioinformatic approach—Multifactor Dimensionality Reduction, for modeling genomic interactions (MDR program, V.1.1.0).

Table 4. The Level of Triglycerides (mM) in the Blood Serum of Children, Depending on the Body Mass Index and Genotype by Polymorphism *Ser447Ter* of the *LPL* Gene

Group/genotype	*SerSer*	*SerTer*	*p1*
Control	0.67 ± 0.06	0.80 ± 0.22	0.87
Overweight	1.57 ± 0.51	0.91 ± 0.08	0.18
p2	<0.0001	0.044	

p1, comparison between genotypes within the same group; p2, comparison between groups for the same genotype.

Results

The results of the study of genotype and allele frequencies for polymorphic variants of the *FTO, PON1, LIPC*, and *LPL* genes are presented in Table 3. The Hardy–Weinberg equilibrium is observed for all four genes in both the control group and the comparison group.

According to the rs99305069 polymorphism of the *FTO* gene, *AT* heterozygotes predominate in the samples. The frequency distribution of genotypes and alleles according to the rs99305069 polymorphism of the *FTO* gene is the same in two groups of children ($p>0.05$). According to the *Ser447-Ter* polymorphism of the *LPL* gene, *SerSer* homozygotes predominate in both groups. For the polymorphisms, *-250G>A* of the *LIPC* gene *GG* homozygotes is dominated also. The proportion of *GlnGln* homozygotes and *GlnArg* heterozygotes for the *Gln192Arg* polymorphism of the *PON*1 is the same in both groups (Table 3). Among overweight children, the distribution of genotype and allele frequencies for the studied single nucleotide polymorphisms (SNPs) of four genes corresponds to the control group ($p>0.05$).

Table 5. The Level of Triglycerides (mM) in the Blood Serum of Children, Depending on the Body Mass Index and Genotype According to rs99305069 Polymorphism of the *FTO* Gene

Group/genotype	*AA*	*AT*	*TT*
Control	0.62 ± 0.08	0.70 ± 0.07	0.84 ± 0.32
Overweight	0.98 ± 0.05	1.04 ± 0.06	1.08 ± 0.09
p	0.0013	0.0002	0.082

p, comparison between groups for the same genotype.

Table 6. The Level of High-Density Lipoproteins (mM) in the Blood Serum of Children, Depending on the Body Mass Index and Genotype *Gln192Arg* Polymorphism of the *PON1* Gene

Group/genotype	*ArgArg*	*p1*	*GlnArg*	*p1*	*GlnGln*
Control	1.15 ± 0.19	>0.05	1.48 ± 0.06	0.017	1.26 ± 0.06
Overweight	1.28 ± 0.06	>0.05	1.41 ± 0.03	0.009	1.29 ± 0.02
p2	>0.05		>0.05		>0.05

p1, comparison with the *GlnGln* genotype within the same group; p2, comparison between groups for the same genotype.

Next, we analyzed the level of biochemical parameters of lipid metabolism, depending on the genotype for the studied SNPs. It was found that in overweight children, Ser447Ser homozygotes of the *LPL* gene, the level of TGs in the blood serum is 2.3 times higher than in children with the same genotype from the control group (Table 4). In Ser447Ter heterozygotes with excess weight, the level of TGs exceeds the control values by only 13% (Table 4).

Elevated serum TG levels in overweight children are also associated with the *AA* and *AT* genotypes of the rs99305069 polymorphism of the *FTO* gene (Table 5).

In both study groups of children, *Gln192Arg* heterozygotes of the *PON1* gene are characterized by a higher level of HDL compared with *GlnGln* homozygotes (Table 6). Children with different BMI, but the same genotype for the *PON1* gene polymorphism, have a similar level of HDL in the blood serum.

Analysis of intergenic interactions revealed a statistically significant two-locus model that includes polymorphic loci of the *LPL* and *FTO* genes (Table 7). The studied model has a high predictive ability.

A two-locus genotype *FTO AT/LPL SerTer* associated with a reduced risk of overweight in children was identified (χ^2 4.88, $p = 0.027$; OR = 0.35; 95% CI 0.15–0.83) (Fig. 1).

Children and adolescents with the *FTO AT/LPL SerTer* genotype do not differ from children of the control group in terms of biochemical parameters of lipid metabolism (Table 8).

Discussion

We studied the frequencies of genotypes and alleles of four SNPs of genes, the protein products of which are involved in lipid metabolism. The obtained minor alleles frequencies (MAF) correspond to the data for other populations of Caucasians. For the *Gln192Arg* polymorphism of the *PON1*, MAF is 0.25 for residents of Brazil (Barris-Oliveira *et al.*, 2012); 0.31 for residents of Pakistan (Idrees *et al.*, 2018); and 0.38 among Caucasians of European descent (Pauer *et al.*, 2010). In India, MAF is higher—0.47–0.51 among residents of different regions (Mitra *et al.*, 2015). In our study, the MAF for the *Gln192Arg* polymorphism of the *PON1* gene was 0.29.

Table 7. Statistical Characteristics of the Two-Locus Model

General characteristics of the two-locus model	
Parameter	*Two-locus model LPL-FTO*
Balanced accuracy	0.57
Accuracy	0.39
Sensitivity	0.28
Specificity	0.89
Odds ratio	3.24 (1.42–7.39)
χ^2 (p)	8.6 ($p = 0.0034$)
Precision	0.92

LPL-FTO, two-locus model of SNP interaction in the LPL and FTO genes.

The frequency of *-250A* allele of the *LIPC* is 0.32 among Brazilians (de Andrade *et al.*, 2004); and 0.28 and 0.39 among residents of various China provinces (Li Meng *et al.*, 2010). In India, the MAF is 0.05 (Verma *et al.*, 2016). In our study, the MAF for *-250G>A* SNP of the *LIPC* was 0.23. This value is lower than in other studies for Caucasians with MAF = 0.387 (Liao *et al.*, 2021).

According to rs99305069 of the *FTO*, MAF in our data was 0.59. This value is higher compared with the data for other populations of Caucasians. Among non-Hispanic whites in the United States, the MAF was 0.39 (Hallman *et al.*, 2012). In the group of children in Germany, the MAF was 0.44 (Müller *et al.*, 2008). The MAF among Iranian residents was 0.45 (Mehrdad *et al.*, 2020). The average MAF value for Caucasians is 0.44 (Elouej *et al.*, 2016). Among Asians, the frequency of the *A* allele of the *FTO* is lower. For example, in China, the MAF was 0.22 (Xi *et al.*, 2010). Thus, the MAF value we identified for rs99305069 is one of the highest.

The MAF for the *Ser447Ter* SNP of the *LPL* in our study was 0.08. This frequency of the allele corresponds to the literature data. Thus, among the residents of Kazakhstan, the MAF was 0.14 (Shakhanova *et al.*, 2020), among the residents of Saudi Arabia—0.05 (Daoud *et al.*, 2013), in India, the MAF was 0.096–0.15 (Ayyappa *et al.*, 2017).

The study group of overweight children is characterized by an increased level of TGs and LDL in the blood serum compared with the control group. Changes in the level of these biochemical parameters may be associated with the peculiarities of the functioning of lipoprotein lipase. LPL is an enzyme, the concentration and activity of which determine the risk of metabolic disorders related to energy balance, insulin action, and body weight regulation. In the *LPL* gene, we considered the *Ser447Stop* (rs328) polymorphism.

According to the results of our study, the frequency of heterozygotes for the *Ser447Ter* polymorphism of the *LPL* gene among children in Rostov-on-Don was 15–16%. There was no association of this SNP with changes in the risk of overweight. This polymorphism is located in exon 9 of the *LPL*, in which replacing C with G leads to premature completion of reading. The result is a truncated protein lacking two carboxyl terminal amino acids. The frequency of carriers of this genetic variant is from 10% to 25% (Fisher *et al.*, 1997). Carriers of the S447X variant have a reduced level of TG, which, accordingly, reduces the risk of vascular pathologies (Clee *et al.*, 2001; Gao *et al.*, 2015). The data obtained by us indirectly confirm the possible protective effect

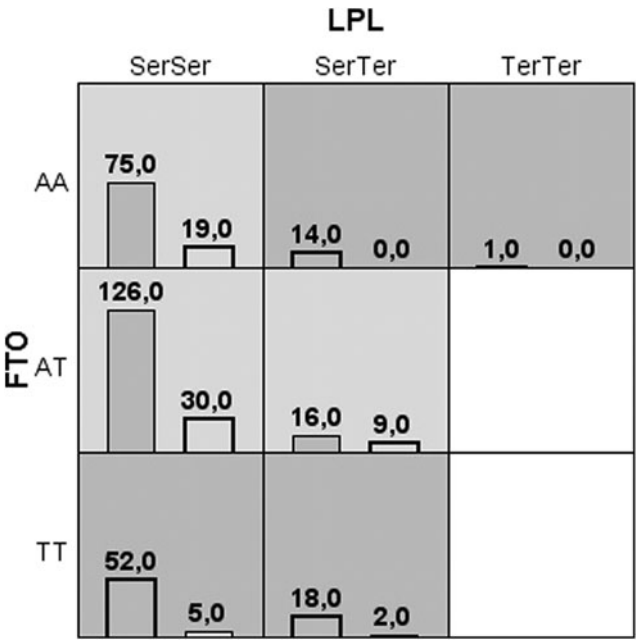

FIG. 1. Distribution of *LPL* and *FTO* genotypes in a two-locus model (*dark gray* cells, high-risk genotypes; *light gray* cells, low-risk genotypes; *white* cells, absence of this genotype; *left columns* in cells, overweight children; *right columns* in cells, control).

of heterozygosity on the *Ser447Ter*. In heterozygotes from the group of overweight children, the level of TGs in the blood serum is 42% lower compared with homozygotes of the *SerSer,* who are also overweight. However, no such differences were found in the control group, which indicates multifactorial control of TG levels.

SNP *T>A* (rs9939609) of the *FTO* was initially associated with a predisposition to type 2 diabetes. However, there is strong evidence that this polymorphism affects the accumulation of fat in the human body (Frayling *et al.*, 2007).

Data show that the *A* allele of the *FTO* is associated with an increased risk of obesity. In our work, the association of the *A* allele of the *FTO* with an increased risk of overweight was not revealed. At the same time, the level of TG is increased in overweight children with *AT* or *AA* genotypes compared with the control group.

Rutters *et al.* (2011) studied 58 boys aged 12–17 years and identified an association of the *A* allele (rs9939609) of the *FTO* with a high BMI, obesity, and high leptin levels in children aged 12 and 15–17 years. In boys aged 13–14 years, the association was not observed, which was explained by the onset of puberty, accompanied by endocrine changes and a drop in leptin levels relative to fat mass (Rutters *et al.*, 2011). Such data indicate the need to take into account age characteristics, as well as the degree of maturation of the reproductive system when analyzing the genetic causes of overweight in children and adolescents. In our study, the analysis of the frequencies of genotypes and alleles for the studied SNPs, depending on the age of children, did not reveal statistically significant differences.

In our work, none of the four studied polymorphisms showed an individual association with changes in the risk of overweight in children. Analysis of intergenic interactions revealed a two-locus genotype associated with a reduced risk of overweight. This genotype is conditioned by the heterozygous state for the rs9939609 of the *FTO* and the heterozygous state of the *Ser447Ter* polymorphism of the *LPL.* Children with this genotype do not differ from the control group in terms of biochemical parameters of lipid metabolism. This may be due to the increased activity of the LPL enzyme in the presence of the 447Ter mutation of the *LPL* in heterozygotes. A twofold increase in LPL activity during the cleavage of amino acids at the C-terminus of the peptide molecule was shown by Kozaki *et al.* (1993). This mutation is associated with an increase in HDL and a decrease in TG (Kuivenhoven *et al.*, 1997). Individuals with the *Ser447Ter* mutation have a significantly larger LDL particle size compared with those with the *SerSer* genotype (Sawano *et al.*, 2001). Thus, the *Ser447Ter* mutation can contribute to the normalization of the blood lipid profile.

On the contrary, a number of data indicate the existence of a relationship between lipid metabolism indicators and *FTO* rs9939609 (Khella *et al.*, 2017). It has been shown that the presence of a risk allele, especially in the homozygous state, leads to a decrease in the level of HDL (Franczak *et al.*, 2018: Mehrdad *et al.*, 2020). In our study, there was no association of the risk allele with a decrease in the level of HDL in the blood serum of children. We have shown that the combination of heterozygosity of *FTO* rs9939609 and *LPL Ser447Ter* polymorphisms is associated with the normal level of the main indicators of lipid metabolism in the blood serum of children. Probably, the effects of the presence of the A allele of the *FTO* gene can be leveled in the presence of a heterozygous state of the *Ser447Ter* polymorphism of the *LPL*. The presence of a truncated version of the LPL enzyme may increase the receptor-mediated capture of lipoproteins (Hayne *et al.*, 2017), but to confirm or refute this thesis, it is necessary to conduct an additional study. Also, it is possible that the heterozygotes of *FTO* rs9939609 polymorphism form a specific level of expression of genes encoding lipid metabolism enzymes.

Additional research is needed on the rs1421085 and rs17817449 polymorphisms of the *FTO*, which are associated with rs9939609 in the haplotype (Li *et al.*, 2006) and together may disrupt the *IRX3* gene enhancer motif associated with

Table 8. The Level of Biochemical Parameters of Lipid Metabolism in the Blood Serum of Children with the Genotype *FTO AT/LPL SerTer*

Parameter	*Overweight, FTO AT/LPL SerTer*	*Control (Total)*	p	*Control, FTO AT/LPL SerTer*	p
Cholesterol (mM)	3.93 ± 0.15	3.87 ± 0.09	0.65	3.39 ± 0.32	0.21
HDL (mM)	1.32 ± 0.10	1.35 ± 0.04	0.58	1.26 ± 0.09	0.83
LDL (mM)	2.08 ± 0.17	2.22 ± 0.07	0.56	2.06 ± 0.24	0.85
Triglyceride (mM)	1.06 ± 0.22	0.69 ± 0.06	0.08	0.82 ± 0.27	0.35

adipocyte differentiation (Chang *et al.*, 2018). In addition, the effect of *FTO* may depend on the level of leptin. Therefore, further studies should include the analysis of both leptin levels and genotyping of the leptin gene and its receptor.

Conclusion

In this study, it was shown that the *FTO AT/LPL SerTer* genotype is associated with a reduced risk of overweight in children and adolescents. Children with this genotype are characterized by a normal lipid profile.

Authors' Contributions

K.D.E. and V.V.V.: Analysis and interpretation of data, and drafting the article. O.V.B. and E.D.T.: Formation of groups of investigated children, and contributed to unpublished essential data. M.A.S.: Acquisition of data. E.G.D.: Drafting and revising of the article. E.V.M.: Acquisition of data, analysis and interpretation of data, and drafting and revising the article.

Author Disclosure Statement

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