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Investigation of the association of *AGTR1* A1166C rs5186 and *FTO* rs9939609 polymorphisms with the obesity in children and adolescents

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Abstract:

Obesity is a risk factor for a number of chronic conditions. Obesity is clinically defined using the body mass index (BMI) as weight in kg divided by (height)^2 in m^2 correlated with obesity. Currently, genetic markers of obesity are being studied. This study focused on the association between the angiotensin II receptor *AGTR1* gene (A1166C) and fat mass and obesity-associated protein also known as alpha-ketoglutarate-dependent dioxygenase *(FTO)* (rs9939609) in obese children and adolescents patients in Rostov region, Russia. Five-hundreds of Russian nationality child and adolescent were recruited for the obesity-control studies. The relationship between the A1166C polymorphism of the AGTR1 gene in 300 children and adolescents included as the unhealthy group, compared with healthy group of 200 participants were investigated. Genotyping of A1166C polymorphisms of the *AGTR1* rs5186 gene was performed using PCR allele-specific primers. Polymorphisms of the *AGTR1* A1166C (rs5186) genes in donor DNA samples were typed by the electrophoretic method using commercial test systems from the Lytech research and production company. The relationship between obesity and *AGTR1* gene polymorphism (A1166C) was not established between the obesity and control groups in terms of the frequency of occurrence of the CC genotype (P = 1.000) and (OR 1.05; 95% CI (0.53 – 2.10)) and the C allele (P = 0.942) and (OR 1.01; 95% CI (0.76 – 1.35)). However, in the occurrence of frequency genotype of AA (P = 0.003; OR 0.57; 95% CI (0.39 – 0.82)) and T (P = 0.006) of allele and (OR 1.44; 95% CI (1.11 – 1.87)) the rs9939609 of the *FTO* gene were revealed differences (P <0.05) between patients and control groups. The association between genotypes obesity risk was indicated, and a significant relationship was shown between the occurrence of obesity with the *FTO* rs9939609 polymorphism.

Keywords: AGTR1 A1166C (rs5186), Children and adolescents, *FTO* rs9939609, Obesity, Polymorphism.

Introduction:

Obesity is a global problem with potentially devastating consequences, as described by the World Health Organization as the abnormal or excessive accumulation of fat representing a health hazard[1]. During the last years, there was significantly an increase in subjects number with obesity in addition to severity and an epidemic[2]. Also one of the biggest global health challenges remains the obesity epidemic in children and adolescents[3]. Therefore, obesity is one of the world's major public health problems, especially due to the increasing incidence in different age groups in recent years [3]. The prevalence of obesity in children and adolescents (5 to 19 years) increased more than four times higher from 1975 to 2016 (from 4% to 18%)[3]. Knowing the incidence of overweight and obesity in children and adolescents, as well as identifying the groups most predisposed to this outcome is significant. Since the earlier interventions in these specific groups actually

occur, the greater the impact and persistence of this disorder in adulthood can be avoided or reduced. Furthermore, it has been noticed that the treatment of obesity in adults was burdensome, and the situation becomes much more concerning because obese children are five times more likely to become obese in adults than non-obese children[4]. In addition, obesity may be seen as a metabolic disease that results in the development of abdominal fat content, especially in adipose tissues [5-7].

The *FTO* gene association (fat mass and obesity-related) is significant, as discovered by multiple genome-wide association studies (GWAS) [8], *FTO* gene plays an important role in the evolution of BMI and fat tissue growth[6]. The rs9939609 single nucleotide polymorphism (SNP) within *FTO* first intron was the most studied intensively and established to have a clear association with the obesity in adults, and also children and adolescents[9,10]. The FTO gene appears to have 9 exons and encodes the non-heme Fe(II) and 2-Oxoglutarate-dependent Dioxygenases A 505-amino acid protein and is located on the 16q12.2 chromosome[11]. The most significant polymorphism rs9939609 T > A in intron one within the *FTO* gene, which has been linked to a variety of metabolic problems as well as brain and cancer diseases[12–15]. Numerous studies have revealed a clear link between the uncommon allele (A) of the rs9939609 polymorphism in the *FTO* gene and an increased incidence of obesity in various peoples [16–19].

Angiotensin II, the most biologically active component of the Renin-Angiotensin system (RAS), acts through two unique subtypes of angiotensin II receptors: angiotensin II type 1 receptor (*AGTR1*) [20]. The *AGTR1* protein is a part of the 7-transmembrane G family, and its expression is increased in the majority of tumors [21]. The *AGTR1* gene consists of 5 exons on the 3q chromosome, of which the first four are the 5' untraduced region. The A1166C (rs5186) polymorphism in the angiotensin II types I receptor gene (*AGTR1*) consists of an A/C nucleotide transversion and is localized at the 1166 position in the *AGTR1* of the 3'-untranslated region and resulting in the transversion of an adenine (A) base to a cytosine (C) base at the 1166 position. And as a result, there are three potential genotypes in the human population: homozygotes—AA, CC, and heterozygote—AC [22]. In previous meta-studies and another study, the polymorphism of A1166C in *AGTR1* was found to be related to myocardial infarction and the risk of hypertension [23–25]. Obesity, on the other hand, was linked to higher *AGTR1* expression in both visceral and subcutaneous adipose tissue in human participants, with increased *AGTR1* expression in visceral adipocytes at any time and body weight[26, 27]. As noted, polymorphisms in the Angiotensin II receptor 1 (*AGTR1*) A1166C gene were linked to body mass index in a Romanian populations [28]. As a result, this is thought to play a substantial role in the pathogenesis of obesity, especially extreme obesity, and they may also play a role in the pathogenesis of T2DM, which is linked to obesity [29].

Thus, the aim of this study is to investigate the possible interaction relationship between FTO (rs9939609) and AGTR1 (rs5186) genotype in obesity. Also, to analyze the distribution of the *FTO* and *AGTR1* gene polymorphic variants with obese in the Rostov on Don, Russian population patients.

Material and Methods:

In compliance with the World Medical Association's Helsinki Declaration, "Ethical Principles for Scientific Medical Research with Human Participation" (as modified in 2000), as well as, all children and young people participating in studies were informed and agreed to the "Rules of Clinical Practice in the Russian Federation," in addition to(approved by order of the Ministry of Health Russia dated June 19, 2003 No. 266).

This study investigated in 500 children and adolescents from 3 to 17 years the relationships between rs 9939609 and A1166C (s5186) polymorphisms with obesity: The overweight group included 300 unhealthy, while the healthy group included 200 children and adolescents. Moreover, the BMI was employed as the major criterion of the selection for the research. Participants with a BMI more than 30 kg/m2 comprised the obese group, while children and adolescents without obesity (BMI ranging from 18.5 to 24.9 kg/m2) comprised the control group. The research also shows that participants with grade III overweight participated in the evaluation in a WHO-based age-sex classification and the tasks of this study didn't even include their classification related to physical activity, nutrition, and other criteria in the tasks for that study. Participants were diagnosed in the Science of Medical Center, and genotyping analyses were conducted at the Southern Federal University Department of Genetics.

Methods for Extraction and Genotyping of DNA

A blood DNA-expression reagent was used to separate genomic DNA from entire blood leukocytes according to the DNA-sorb-AM (NextBio, Russia) reagent kit protocol. And a NanoDrop 2000c spectrophotometer was used to evaluate the quality of DNA samples spectrophotometer (USA). The polymorphisms

rs9939609 (T>A) and A1166C (rs5186) the standard NPF Lyteh test system with electrophoresis analysis was used for DNA samples (Table 1).

SNP-Express reagent kit was used to investigate allelic variants of A1166C (rs5186) of the AGTR1 gene rs99305069 of the FTO gene were studied using SNP-express reagent kits (Lytekh, Russia). The analysis is based on carrying out amplification reactions with two pairs of allele-specific primers. The tubes were prepared and numbered for conducting amplification with a capacity of 0.5 ml. For each sample, 2 test tubes are required - norm and polymorphism. Two test tubes were prepared for each sample allele one and allele two. Then a working mixture of reagents for amplification was prepared from the calculation for 1 sample: 17.5 µl of diluent, 2 µl of a reaction mixture, and 0.2 µl of Taq-polymerase. Ready for two working mixtures: a normal mixture and a polymorphism reaction mixture. Before using the working mixture, they were defrosted, stirred, and placed on the vortice. And the amplification mixture was added at a rate of 20 µL to all appropriate tubes for amplification. Then added 5 µl of the DNA sample into the test tube with the "norm" working mixture and into the test tube with the "polymorphism" working mixture, and the tubes were placed on the vortices. Finally, the test tubes were transferred to the amplifier to conduct the reaction of the amplification. The amplification program was as follows: hot start, 93 °C for 1 min, then 35 cycles at 93 °C for 10 s, 64 °C for 10 s, 72 °C for 20 s; then 72 °C for 1 min. PCR products were analyzed on 3% agarose gel plates exposed to horizontal electrophoresis and under the ultraviolet trans illuminator GelDoc (BioRad, USA).

Table 1. Type of polymorphism, primer sequences and nomenclature of alleles of polymorphic DNA *loci*.

Locus	Polymorphism (rs number)	Primers
AGTR1	A1166C rs662	F:5´-GCA GCA CTT CAC TAC CAA ATG GGC-3´
	rs5186	R:5´-CAG GAC AAA AGC AGG CTA GGG AGA-3´
FTO	A23525T	F:5´-AACTGGCTCTTGAATGAAATAGGATTCAGA-3´
	rs9939609	R:5´-AGAGTAACAGAGACTATCCAAGTGCAGTAC-3´

Statistical analysis

To evaluate gene-gene correlations, the Reduction of the multifactor dimensionality (MDR) method was utilized. Multi-locus genotypes were grouped into low and high-risk categories, to limit genotype predictors to the same dimension. The Cross-Validation Consistency (CVC) and Testing Balanced Accuracy (TBA) the best general model was selected by the indices after a series of models was obtained. To reduce the statistical mistake with the first kind in the evaluation of intergenic interactions, a multiplicity of comparisons correction (Bonferroni correction) was used, which has been found by dividing the original level of significance p (= 0.05) by the total of analyzed combinations of 2 SNPs. If the associated p values were less than or equal to (P = 0.025), the differences were considered significant [30].

In analysis, the $\chi 2$ test was used to examine the concordance of the genotype and allelic variant/genotype empirical distribution of the rs99305069 and rs5186 polymorphisms in theoretical terms anticipated distribution at HWE [31]. The analysis of this data, the combination of the genotype and the odds ratio (OR) was used to calculate obesity and the 95% CI for assessment of obesity-associated with alleles studied, with non-parametric data is represented using $\chi 2$ and Fisher exact probability using the WinPepi computer application version 11.6 [32].

Results:

In the obesity and control group of children and adolescents, the associational analysis of the polymorphisms of the gene investigated was performed with obesity in 2 variations: obesity associated with rs9939609 of *FTO* and with rs5186 of *AGTR1*, rs9939609.

Moreover, the MDR analysis discovered rs9939609 T>A of the *FTO* gene (p=0.002) obesity association model with a 56% TBA prediction accuracy, a 10/10 CVC, and a 100% repeatability. MDR analysis indicates obesity association models. The prediction accuracy (TBA) of the *AGTR1* A1166C- *FTO* rs9939609 T>A was likewise 55% (p=0.002, for the analysis) of the intergenic interactions in obesity; the model CVC – 10/10 and 100% reproductively (Table 2). Genes interacted with two polymorphisms in the model associated with obesity significantly increased the obesity risk (OR: 1.76; 95 percent CI: 1.21-2.56).

Table 2. Intergenic interaction analysis with reduction of dimensions MDR.

Interacting SNPs	Testing Balanced Accuracy (TBA)	Cross validation consistency (CVC)	X^2	*P*-value	OR (95% CI)
FTO rs9939609	0.565	10/10			1.76
AGTR1 rs5186, rs9939609	0.552	10/10	9.074	0.002	(1.21 – 2.56)

p= probability of significance level.

There was thus a significant gene combination interaction of obesity between the polymorphic variations of two gene loci in participants (Table 2). Association of polymorphous variations of those genes with the increased obesity risk was identified when investigating the link between the polymorphic loci rs9939609 of the *FTO* and rs5186 of the *AGTR1* genes (Fig. 1).

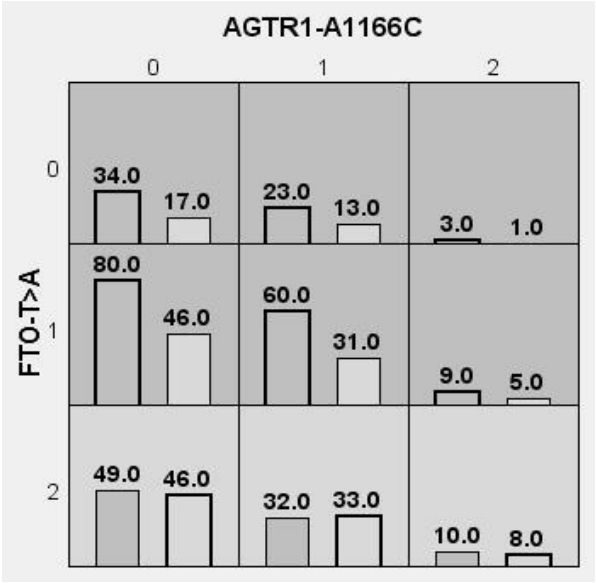

Figure 1. Distribution of frequency in participants of the two groups of tow locus genotypes *FTO* re9939609 T>A and *AGTR1* A1166C. High-risk — dark gray cells, low-risk — light-gray cell, lack of this genotype — white cells; left cell columns are obesity; right cell columns are number of controls; zero — homozygotes for first allele, one — heterozygotes, two — homozygotes for a second allele.

In addition, (Fig. 2) demonstrates an image of the entropy, the nature, and degree of the intergenic connection in obese children and adolescents rs99939609 T>A of the *FTO* and rs5186 of the *AGTR1* A1166C polymorphisms. The relationship between rs5186 and rs9939609 polymorphisms was shown to be pronounced antagonistic (Blue is the line color).

Figure 2. *FTO* rs9939609 and *AGTR1* rs5186 graph of entropy intergenic interactions in children and adolescents in the development of obesity. At the edges the marker data values and the locus pair's information interaction value is indicated as a percentage of entropy, the colored pattern is blue = no interaction and the interaction strength and direction is displayed.

For the display and understanding of potential interaction using an analysis of MDR, a dendrogram was created (Fig. 3) showing that antagonistic interactions between *AGTR1* and *FTO* form were low interactions with obesity.

Figure 3. Dendrogram that refers to the nature of the interactions for obese and control groups between two SNPs *FTO* and *AGTR1*. Blue: connection adversarial.

Frequency of genotype distribution in control groups of children and adolescents and those suffering from obesity of *AGTR1* and *FTO* genes. When analyzing the frequency distribution of the *AGTR1* A1166C genotypes in control group children and adolescents and those with obesity, it was shown that the AA, AC, and CC genotypes were (54.3%), (38.4%) and (7.3%) respectively of cases of children and adolescents of suffering from obesity, whereas the incidence of genotypes of the healthy group was equal with the obesity group. The genotypic frequencies of the *AGTR1* A1166C SNPs between both studies are summarized in (Table 3), where were no significant differences in the genotypic frequencies of the SNPs between these groups (Pearson's chi-square $\chi 2 = 0.020$; P = 1.000) for all genotypes in *AGTR1* A1166C.

The frequency analysis of polymorphic genotypes rs9939609 in the control group of the participants is as follows: observed the frequency of the TT, AT and AA genotypes in the unhealthy group were (20.0%), (49.7%) and (30.3) respectively and the healthy group were (15.5%),

(41.0%) and (43.5) respectively. Therefore, it appears from the current study results that FTO rs9939609 was a significant association of the rs9939609 polymorphism of the gene FTO and established highly with the obesity risk ($\chi 2 = 9.130$; P = 0.011) than another gene.

Table 3. The distribution of frequency of *AGTR1* and *FTO* genes polymorphisms in the studied groups.

Gene/ polymorphisms	Genotypes	Cases n=300 (%)	Controls n = 200 (%)	χ^2	*P*
	AA	163 (54.3)	109 (54.5)		
AGTR1 A1166C	AC	115 (38.4)	77 (38.5)	0.020	1.000
	CC	22 (7.3)	14 (7.0)		
	TT	60 (20.0)	31 (15.5)		
FTO rs9939609 (T>A)	AT	149 (49.7)	82 (41.0)	9.130	**0.011**
	AA	91 (30.3)	87 (43.5)		

X^2: Pearson chi-square, *P*: Fisher's exact probability (two tailed).

Frequency distribution analysis of the genotype frequencies of *AGTR1* A1166C and *FTO* rs9939609 T>A, the genes in both groups were by the expectations in the analyses observed (Table 2, 3). A search of the A1166C SNP of the gene *AGTR1* showed that the distributions of the genotypes were statistically not significant (P> 0.05) in both groups.

The distribution in both groups of the genotype frequencies of *FTO* genes was consistent with assumptions through this observed analysis. The frequencies of the genotype AA *FTO* gene were shown when calculating common homozygotes for obesity over the OR (P = 0.003; OR 0.57; 95% CI (0.39 – 0.82)) was significantly increased in the control group compared with the obese group. Therefore, not statistically significant distributions were relative risk of the genotype frequency AT (P = 0.067; OR 1.42; 95% CI (0.99 – 2.04)) and TT (P = 0.237; OR 1.36; 95% CI (0.85 – 2.19)) in obesity and in the participants of the healthy group (Table 4).

Table 4. The *AGTR1* and *FTO* frequency distribution analysis and in both groups.

Gene/ polymorphisms	Genotypes	Cases n =300	Controls n =200	χ^2	*P*	OR (95% CI)
AGTR1 A1166C rs5186	AA	163	109	0.001	1.000	0.99 (0.69 – 1.42)
	AC	115	77	0.001	1.000	0.99 (0.69– 1.43)
	CC	22	14	0.020	1.000	1.05 (0.53 – 2.10)
FTO rs9939609 T>A	TT	60	31	1.632	0.237	1.36 (0.85 – 2.19)
	AT	149	82	3.626	0.067	1.42 (0.99 – 2.04)
	AA	91	87	9.074	0.003	0.57 (0.39 – 0.82)

X2: chi-square, P: probability (two tailed), OR: odds ratio, (95% CI: 95%) confidence interval.

In comparing the distribution of the AGTR1 allele, the frequency of the A allele was found to be higher in study groups (73. %), whereas it was lower than the frequency of the C allele (27%). Therefore, no significant differences were observed in the distribution in these groups of alleles of the AGTR1 A1166C gene (P > 0.05).

When FTO gene alleles were analyzed in the frequency distribution of the obese group, the frequency of the T allele was (44.8%) and the A allele - (55.2%). The frequency distribution in the healthy group of these alleles where the frequency of their occurrence was (36.0%) and (64.0%) respectively. The difference between both groups of children and adolescents in terms of the distribution of these frequencies was highly significant (P = 0.006), (OR 1.44; 95% CI (1.11 – 1.87)) (Table 5).

Table 5. Distribution of allele frequency *AGTR1* and *FTO* gene polymorphisms between both groups.

Gene/polymorphisms	Allele	Cases n = 600%	Controls n = 400%	χ^2	*p*	OR95% CI	
AGTR1 A1166C	A	441 (73.5)	295 (73.7)	0.008	0.942	0.99	0.74 – 1.32
rs5186	C	159 (26.5)	105 (26.3)			1.01	0.76 – 1.35
FTO rs9939609	T	269 (44.8)	144 (36.0)	7.725	0.006	1.44	1.11 – 1.87
	A	331 (55.2)	256 (64.0)			0.69	0.53 – 0.90

X2: chi-square, P: probability (two tailed), OR: odds ratio, (95% CI: 95%) confidence interval.

Table 6. shows the genotypes and frequencies of alleles observed. The distribution of the genotypes yielded from the Hardy-Weinberg equilibrium was as calculated for A1166C and rs9939609 polymorphisms in the patients and control.

Table 6. frequencies the genotyping of *FTO* and *AGTR1* in patients group compared to control group.

Gene	Genotyping	Cases n=540(%)		Chi-squared (chi2)	*P*-HWE	Control n = 330(%)		Chi-squared (chi2)	*P*-HWE
		Observed	Expected			Observed	Expected		
AGTR1	AA	163	162.1	0.076	0.782	109	108.8	0.006	0.936
A1166C	AC	115	116.9			77	77.4		
rs5186	CC	22	21.1			14	13.8		
FTO	TT	60	60.3	0.004	0.944	31	25.9	2.430	0.118
rs9939609	AT	149	148.4			82	92.2		
T>A	AA	91	91.3			87	81.9		

P-HWE: probability of Hardy-Weinberg equilibrium, X^2: Chi-squared value – HWE.

The risk of obesity has been observed to increase with one combination of genotype distribution while developing recessive and dominant models. Therefore, in the recessive model, the statistic difference of AA vs AT + TT in gene *FTO* was statistically significant (P = 0.003; OR 0.57; 95% CI (0.39 – 0.82)). While in the dominant model AA + AT vs TT of the gene *FTO*, moreover, no significant variations in the distribution of genotypes were listed (Table 7).

In addition, the frequencies of genotypes for *AGTR1* A1166C are AA, AC and CC in the analyzed groups were not different a dominant and recessive models CC + AC vs AA (p = 1.000 OR: 1.01; 95% CI: 0.70 – 1.44 and p = 1.000; OR: 1.05; 95% CI: 0.53 – 2.10) respectively. There was no statistically significant difference in the construction of dominant and recessive models between the two groups.

Table 7. The genotypes of *FTO* and *AGTR1* polymorphisms in the study groups for dominant and recessive models.

Gene/polymorphisms	Genotypes	Cases n=540(%)	Controls n =330(%)	χ^2	*P*	OR (95% CI)
AGTR1 A1166C	[a]CC + AC	137 (45.7)	91 (45.5)	0.001	1.000	1.01 (0.70 – 1.44)
rs5186	*vs* AA	163 (54.3)	109 (54.5)			
	[b]CC *vs*	22 (7.3)	14 (7.0)	0.020	1.000	1.05 (0.53 – 2.10)
	AC + AA	278 (927)	186 (93.0)			
FTO rs9939609 T>A	[a]AA + AT	240 (80.0)	169 (84.5)	1.632	0.237	0.73 (0.46 – 1.18)
	vs TT	60 (20.0)	31 (15.5)			
	[b]AA *vs*	91 (30.3)	87 (43.5)	9.074	0.003	0.57 (0.39 – 0.82)
	AT + TT	209 (69.7)	113 (56.5)			

(a) dominant model (b) recessive model.

Discussion:

As evidence of the involvement of genetics in the development of overweight and obesity grows, polymorphisms in various obesity candidate genes have been the focus of intense investigation for the *FTO* gene, but only a few studies have looked into a possible link between obesity and the RAS. As a result, this study aims to investigate the relationship between *AGTR1* A1166C and *FTO* rs9939609 SNPs and obesity status, as well as control groups, in the Rostov-on-Don, Russia population. Furthermore, childhood obesity raises the probability of adult obesity, emphasizing the relevance of identifying the causes of obesity in children and preventing it. The advancement of personalized genomics will lead to identifying genetic disease risk factors in the particular cases. When compared to adults' obesity, the obesity in children phenotype is much more suitable for investigation since it is not too much connected with the environment even more with gene variation. This is supported by researches which show that BMI which genetic predetermination in children is 40%-90%[33]. Nonetheless, the prevalence of overweight and obesity in children and adolescents has been identified as a source of attention due to its link to cardiovascular, psychological, and social diseases [34,35]. Furthermore, being overweight or obese at these ages increases the likelihood that these problems will stay throughout adulthood [4].

In this study, for the first time, the association between SNPs *AGTR1* A1166C and *FTO* rs9939609 with cases in participants were studied.

As a result, the purpose of this study was to see if there was a link between the two major polymorphisms in the rs5186 and rs9939609 polymorphisms and cases in the Rostov-on-Don population from Russia. Interestingly, obese people

were statistically different higher than non-obese controls in the homozygote model of the rare genotype (AA) of *FTO* rs9939609 polymorphism (p = 0.003). GWASs also looked at the link between the polymorphism rs9939609 of the *FTO* gene and a high obesity risk[36]. A recent study of Emirati subjects found an association between the rare genotype (AA) of the *FTO* (rs9939609) variant and increased obesity and BMI values (p =0.027)[17]. Several studies have also demonstrated a relationship between the *FTO* gene and obesity [37–39]. The rs9939609 polymorphism correlates with physical activity and food intake and may sedentary lifestyles and eating problems has been shown to affect the prevalence of obesity[40–42]. The presence of the *FTO* gene genotypes TA and AA shows that allele A predicts the risk of higher *FTO* gene expression, including in children [43,44]. A further study found a link between in the Nigerian population, the rs9939609 polymorphism allele A is associated with increased obesity risk ($p < 0.001$) [45]. In addition, another research was done on Croatian obese women demonstrated that the risk genotype (AA) of *FTO* polymorphism (rs9939609) and the risk of obesity is statistically significant (p = 0.04) [46].

With regard to the *AGTR1* A1166C (rs5186) polymorphism, there were no statistically significant differences in the distribution of genotypes AA, AC, and CC of the *AGTR1* gene A1166C polymorphism between the study and control group of obese patients in this study ($p>0.05$). As a result, such research give support and explanation for the non association between (rs5186) in *AGTR1* and obesity revealed in the current study. Therefore, the present study findings suggest that carriers with genotypes in the *AGTR1* SNP (rs5186) had a protective effect against obesity. In several studies it was observed that Egyptian and Tunisian studies showed no statistically significant results, and this is consistent with the current study[47,48]. Other research, contradicting the present study findings, in the Romanian and Kazakhs populations carriers with either genotype had the inverse effect, particularly being related to an increased obesity risk [28,49]. There is also another study in Poland that revealed no statistically significant results, therefore does not agree with the current study results [50].

Therefore, the objective of the present study was to analyze the distribution of the *FTO* and *AGTR1* gene polymorphic variants with obese in the Rostov-on-Don, Russian population patients. Also, to investigate the possible interaction between FTO (rs9939609) and AGTR1 (rs5186) genotype in obesity. The current results also offered insights into the possible association between obesity risk with both *FTO* (ss9939609) and *AGTR1* (ss5186). Hence, it is possible to recommend future researches with a larger sample to confirm the present findings.

Conclusions:

In the present study, it showed that *AGTR1* (rs5186) gene polymorphism was not associated with the risk of obesity. While the genotypes of increased and decreased obesity risk were identified. Also, a significant relationship was shown between the occurrence of obesity in Rostov-on-Don with the rs9939609 polymorphism of the *FTO* gene, as well as the absence of an association of the A1166C locus of the *AGTR1* gene with obesity. This polymorphism is in an antagonistic relationship with the rs9939609 polymorphism of the *FTO* gene.

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Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- Authors sign on ethical consideration's approval
- Ethics Approval: We declare that the above research got the approval from the Medical Research Ethics Committee of (Ministry of Health or Hospital administration / (Russia) and code number of Health Ministry Approval Which State Science Agreement No. 0852-2020-0028.

Authors' contributions statement:

The authors TE and BO collected the sample and analyzed, and were major contributors in the present study. AH, KG and TP made substantial contributions to conception and design of the study. Also AH and KG analyzed the data and write the manuscript. All authors read the manuscript carefully and approved the final manuscript.

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التحري عن ارتباط تعدد الأشكال *AGTR1* A1166C (rs5186) و *FTO* (rs9939609) بالسمنة لدى الأطفال والمراهقين

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الخلاصة:

تزيد السمنة من مخاطر الإصابة بالعديد من الأمراض المزمنة. ويتم تعريف السمنة سريريًا باستخدام مؤشر كتلة الجسم (BMI) الذي يعرف بأنه الوزن بالكيلوجرام مقسومًا على (الطول) 2 بالمتر المربع المرتبط بالسمنة .لذلك حاليا تم دراسة العلامات الجينية للسمنة. حيث كان الهدف من هذه الدراسة هو التحقق من ارتباط جين مستقبل الأنجيوتنسين الثاني من النوع الأول AGTR1 (A1166C) و جين كتلة الدهون والسمنة, أيضًا يُعرف باسم ديوكسجيناز المعتمد على ألفا كيتوجلوتارات المرتبطة بها (rs9939609) *FTO* في مرضى السمنة لدى الأطفال والمراهقين في منطقة روستوف (روسيا). تم تضمين خمسمائة مواطن روسي من أطفال ومراهقون لدراسة الحالات والشواهد وتم التحقيق في العلاقة بين تعدد الأشكال A1166C لجين AGTR1 مع 300 طفل ومراهق مدرجين في المجموعة غير الصحية ، والمجموعة الصحية - 200 مشارك. كما تم إجراء التنميط الجيني لتعدد الأشكال A1166C من جين re5186 *AGTR1* وجين re9939609 *FTO* التي استخدمت بادئات خاصة بأليل في تفاعل البلمرة المتسلسل. وتم تحديد تعدد الأشكال لجينات AGTR1 A1166C (rs5186) في عينات DNA المتبرع وبالطريقة الرحلان الكهربائي باستخدام أنظمة اختبار تجارية من شركة Lytech للابحاث والانتاج. اظهرت النتائج عدم تحديد العلاقة بين السمنة وتعدد الاشكال الجيني AGTR1 (A1166C) بين مجموعتي السمنة والسيطرة من حيث تكرار حدوث النمط الجيني CC وكان [OR 1.05 ; P = 1.000 ; 95% CI (0.05 – 2.10)] وكان الاليل C [OR 1.01 ; P = 0.942 ; 95% CI (0.76 – 1.35)] بينما كان في جين re9939609 *FTO* لحدوث تكرار النمط الجيني AA [OR 0.57 ; P = 0003 ; 96% CI (0.39 – 0.82)] و الاليل T كان [OR 1.44 ; P = 0.006 ; 95% CI (1.11 – 1.87)] لذلك كانت تعدد الاشكال لهذا الجين احصائيا عالية وبشكل معنوي (P <0.05) بين مجموعتي المرضى والسيطرة. كما تم تحديد الارتباط بين خطر الاصابة بالسمنة من الانماط الجينية، واظهرت علاقة كبيرة بين حدوث السمنة مع تعدد الاشكال لجين FTO re9939609.

الكلمات المفتاحية: AGTR1 A1166C (rs5186), الأطفال والمراهقون، FTO rs9939609، السمنة، تعدد الأشكال.