Long Non-Coding RNA Genes *ANRIL*, *MEG3*, and *NEAT1* - Novel Players in Childhood Obesity and Insulin Resistance

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Abstract

Background: long-noncoding RNAs ANRIL, MEG3, and NEAT1, are involved in the pathogenesis of obesity. The association between genetic variants rs564398 in *ANRIL*, rs7158663 in *MEG3*, and rs674485 in *NEAT1* and childhood obesity in the Russian population has not been assessed previously. **The aim of this study:** we conducted this study in order to assess, for the first time in the Russian population, the association between genetic variants in long non-coding RNA genes (rs564398 in *ANRIL*, rs7158663 in *MEG3*, and rs674485 in *NEAT1*) and childhood obesity, as well as their potential impact on insulin resistance. **Materials and methods:** The genotyping of the studied polymorphisms was performed using TaqMan genotyping assay. **Results:** our results revealed associations between rs564398 of *ANRIL* and rs7158663 of *MEG3* and obesity risk ($p < 0,0001$), ($p = 0,0101$) respectively. The homozygous of the minor allele CC of rs564398 had an impact on insulin resistance risk ($p = 0,042$). Although the genetic variant rs674485 in *NEAT1* did not exhibit any notable associations, the heterozygote GA showed a higher distribution in the insulin-resistant group compared to the homozygote of the ancestral allele GG ($p = 0,047$). **Conclusion:** our findings

provided evidences of a significant association between genotypes of polymorphisms rs564398 in *ANRIL* and rs7158663 in *MEG3* and susceptibility to develop childhood obesity in the Russian population.

Keywords: lncRNA; ANRIL; MEG3; NEAT1; rs564398; rs7158663; rs674485; childhood obesity; insulin resistance.

Гены длинных некодирующих РНК *ANRIL*, *MEG3* и *NEAT1* являются новыми участниками в развитии ожирения и инсулинорезистентности у детей и подростков

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Аннотация

Введение: длинные некодирующие РНК ANRIL, MEG3 и NEAT1 вовлечены в патогенез ожирения. Ассоциация между генетическими вариантами rs564398 в *ANRIL*, rs7158663 в *MEG3* и rs674485 в *NEAT1* и риском развития ожирения у детей и подростков Российской популяции ранее не оценивалась. **Цель исследования:** данное исследование было проведено с целью впервые в Российской популяции оценить ассоциацию между генетическими вариантами в генах длинных некодирующих РНК (rs564398 в *ANRIL*, rs7158663 в *MEG3* и rs674485 в *NEAT1*) и риском развития ожирения в детской и подростковой популяции , и их потенциальные влияния на инсулинорезистентность.

Материалы и методы: генотипирование исследуемых полиморфных вариантов

проводилось с использованием метода TaqMan для генотипирования. **Результаты:** нами были выявлены ассоциации между rs564398 гена *ANRIL* и rs7158663 гена *MEG3* и риском развития ожирения ($p < 0,0001$), ($p = 0,0101$) соответственно. Гомозиготность по минорному аллелю CC rs564398 влияла на риск развития инсулинорезистентности ($p = 0,042$). Несмотря на то, что генетический вариант rs674485 в *NEAT1* не проявил заметных ассоциаций, гетерозигота GA показала более высокое распределение в группе с инсулинорезистентностью по сравнению с гомозиготой мажорного аллеля GG ($p = 0,047$). **Заключение:** полученные нами результаты свидетельствуют о значимой ассоциации между полиморфными локусами rs564398 гена *ANRIL* и rs7158663 гена *MEG3* и предрасположенностью к развитию ожирения у детей и подростков Российской популяции.

Ключевые слова: lncRNA; ANRIL; MEG3; NEAT1; rs564398; rs7158663; rs674485; детское ожирение; инсулинорезистентность.

Introduction:

Pediatric obesity has become a global health issue, with its steadily increasing prevalence worldwide (Jebeile et al., 2022). Estimation by the World Obesity Federation predicted that by 2030, the number of obese children and adolescents may reach 254 million (Lobstein, 2019). The persistence of childhood obesity into adulthood is well-documented and linked to reduced life quality and expectancy (Horesh et al., 2021), as well as increased risk of developing various metabolic comorbidities (Head, 2015). Obesity pathogenesis is caused by a complex interplay between different environmental, lifestyle, socioeconomic, genetic, and epigenetic factors (Meldrum et al., 2017).

In recent years, the discovery of functional noncoding parts of the human genome, particularly the long noncoding RNAs (lncRNAs), has shed light on their involvement in various physiological and pathological processes (Villegas, Zaphiropoulos, 2015). LncRNAs have emerged as important contributors in developing metabolic disorders such as obesity, type 2 diabetes (T2D), and insulin resistance (Rey et al., 2021) (Alipoor et al., 2021) (Yang et al., 2022). Among these lncRNAs are the ANRIL, MEG3, and NEAT1 (Wei et al., 2016) (Kong et al., 2016) (Ghafouri-Fard, Taheri, 2019). In an attempt to characterize their implications in diseases susceptibility, multiple investigations are currently underway to explore the associations between genetic variants within these genes and obesity-related traits. A pivotal role in this pursuit is played by genome-wide association studies (GWAS), which have identified a multitude of single-nucleotide polymorphisms linked to an increased risk of obesity (https://www.ebi.ac.uk/gwas/efotraits/EFO_0001073).

The antisense non-coding RNA in the *INK4* locus gene (*ANRIL*), or *CDKN2B-AS1* on human chromosome 9p21.3 (Ammar et al., 2022), plays a role in cellular

proliferation and metabolism through its control of gene expression via chromatin-modifying complexes and influencing microRNAs abundance and activity (Kong et al., 2018b) (Chen et al., 2020). It has been linked to various diseases, including malignancies, atherosclerosis, cardiovascular diseases, and diabetes (Tano, Akimitsu, 2012) (Ma et al., 2018) (Chen et al., 2020) (Cheng et al., 2017) (Ng et al., 2022) (Zeggini et al., 2007a) (Peng et al., 2013). Specifically, SNPs within the *ANRIL* gene have been associated with the risk of cancer, cardiovascular disease, T2D, and obesity (Scott et al., 2007) (Kong et al., 2016) (Kong et al., 2018a). In particular, SNP rs564398 within the second exon of *ANRIL* has been identified as a risk factor for reduced β-cell proliferation, and insulin dysregulation (Scott et al., 2007) (R et al., 2007) (Zeggini et al., 2007) (Kong et al., 2018a) (Pascoe et al., 2007) (Groenewoud et al., 2008).

MEG3 is an imprinted maternally expressed gene located on chromosome 14q32.3 (Al-Rugeebah et al., 2019) (Zhou et al., 2012). It has been associated with cancer and is implicated in the pathogenesis of obesity by regulating gene related to lipogenesis, insulin resistance, and glucose intolerance (Al-Rugeebah et al., 2019) (Zhou et al., 2012) (P. Huang et al., 2019) (X. Huang et al., 2019) (Zhu et al., 2016) (Liao et al., 2019). Elevated levels of MEG3 have been observed in human livers with nonalcoholic fatty liver disease (NAFLD) and subcutaneous adipose tissue of obese individuals (Cheng et al., 2021) (Daneshmoghadam et al., 2021). Additionally, the rs7158663 polymorphic variant within *MEG3*, has been significantly associated with the risk of cancer and T2D (Cao et al., 2016) (Mohammed et al., 2022) (Ghaedi et al., 2018a).

Nuclear enriched abundant transcript 1 gene (*NEAT1*) located on chromosome 11q13.1, is exclusively expressed in the nucleus and acts as a scaffolding factor in

paraspeckle formation (Clemson et al., 2009) (Naganuma, Hirose, 2013) (R et al., 2016). NEAT1 paraspeckles are involved in gene transcription activation (West et al., 2014) (Lin, 2016). *NEAT1* promotes adipogenesis and preadipocyte differentiation by interacting with microRNAs, such as miR-140 (Sun et al., 2013) (R et al., 2016). The SNP rs674485, located within the single exon of *NEAT1*, has been associated with BMI-adjusted hip circumference and body mass index (Christakoudi et al., 2021).

Examining the involvement of SNPs rs564398 *ANRIL*, rs7158663 *MEG3*, and rs674485 *NEAT1* in disease susceptibility is a recent and perspective area of interest. However, their association with childhood obesity, especially within the Russian population, has largely gone unexplored. Consequently, we conducted our current study.

The aim of this study is to assess any potential associations between the polymorphisms rs564398, rs7158663, and rs674485 and the susceptibility to develop obesity and insulin resistance among Russian children and adolescents. Understanding the impact of various SNPs in elevating the risk of obesity and its related traits is of paramount importance, as it can pave the way for the identification of potential diagnostic markers and the development of lncRNA-based strategies to combat and manage the obesity epidemic.

Materials and methods

1. Research subjects and ethics statement

The bioethics committee of the Academy of Biology and Biotechnology named after D. I. Ivanovsky at Southern Federal University in Rostov on Don, Russian Federation, had approved this case-control study with Protocol № 2 of January 17, 2018. 150 children and adolescents, aged 5 to 17 years old, were included in this research. Participants were recruited at Children's Municipal Polyclinic No. 4 in Rostov-on-Don,

Russian Federation, between January 2018 and December 2019. The case-control study design and applied methods were carried out in accordance with articles 20, 22, and 23 of Federal Law N 323-FZ of November 21, 2011 in the Russian Federation ("Russian Federation - Federal Law No. 323-FZ of 21 November 2011 on Basics of Health Protection of the Citizens in the Russian Federation as amended to 29 December 2015.," n.d.), as well as the World Medical Association Declaration of Helsinki ("World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects," 2013). Parents of all participating children and adolescents have signed a written informed consent form.

2. Obesity and insulin resistance assessment

We conducted assessments of each participant, encompassing measurements of their weight and height, as well as the collection of whole blood samples following an overnight fast. To evaluate the body weight status, we calculated both their Body Mass Index (BMI) and z-score BMI. Additionally, we characterized the metabolic profiles of children and adolescents included in the study by measuring various parameters at the Nauka Medical Center in Rostov-on-Don, Russian Federation. These parameters included total cholesterol concentration, high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol (LDLc), very low-density lipoprotein cholesterol (vLDLc), triglycerides (TG), circulating levels of glucose, and insulin. To assess insulin resistance within the study groups, we employed the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR).

Obesity diagnosis criteria followed the magnitude of the standard deviation from the normal BMI of the same-age, same-sex child (zBMI) as recommended by WHO (malnutrition, zBMI < -2.0 SD, normal weight, zBMI between -1.00 to +1.00 SD,

overweight, between +1.00 to +2.00 SD, and obesity, zBMI > +2.00 SD) (Anderson et al., 2017). Accordingly, the studied population consisted of the main comparison groups: 50 controls and 100 obese children and adolescents. Then, based on the value of the HOMA-IR, two subgroups were formed out of the obese group with 50 insulin-sensitive (INS-S) and 50 insulin-resistant (INS-R).

Genomic DNA was extracted and genotyped using the TaqMan assay, as described in our previous study (Shkurat et al., 2023). Instruction for PCR program and used primers / probes are available upon request.

3. Statistical analysis

The statistical analysis was performed using GraphPad Prism 8.0.1 software (https://www.graphpad.com). Continuous data were presented as means ± standard deviation (SD) and analyzed using the analysis of variance test (ANOVA). To assess if the control group in the study adhered to the Hardy-Weinberg equilibrium (HWE), we compared the expected distribution of genotypes with observed one in the control group using chi-squared (χ^2) test. Differences in genotypes distribution between cases and control were evaluated using Fisher's exact test. The association between genotypes and alleles of the studied SNPs and the risk of obesity, increased zBMI, and insulin resistance was assessed by calculating odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was determined as a *p*-value < 0.05.

Results

1. Characteristics of study population

Mean ages of participants in the control, insulin-sensitive, and insulin-resistant groups were (11.58 ± 3.45), (10.99 ± 3.78), and (13.02 ± 2.77) respectively. By comparing the continuous data from the biochemical analysis using one-way ANOVA

test, we found that, even though there were notable differences in the levels of HDL (p = 0.0008), LDL (p = 0.0034), VLDL (p < 0.0001), and TG (p < 0.0001) among groups, the concentration of total cholesterol was essentially the same (p = 0.0501). The levels of glucose (p = 0.0411), insulin (p < 0.0001), and consequently, the HOMA-IR (p < 0.0001) significantly vary among the three groups in the study.

HDL and LDL levels were notably higher in the control group when compared to the obese group. In contrast, the insulin-resistant group exhibited significantly elevated concentrations of VLDL and TG in comparison to both the control and insulin-sensitive groups. Although glucose levels showed minimal variation across the studied groups, insulin concentrations and HOMA-IR values demonstrated significant increase from the control group to the insulin-sensitive group, with even higher levels recorded in the insulin-resistant group.

2. Association of SNP rs564398 *ANRIL* genotypes with childhood obesity and insulin-resistance risk

For SNP rs564398 in *ANRIL*, no notable deviation from the Hardy-Weinberg equilibrium was detected (p = 0,68). As shown in Table 1, the SNP rs564398 has a positive association with the risk of childhood obesity (p < 0,0001). Moreover, the TC heterozygous genotype has a significantly different distribution compared to the TT genotype (p = 0,0001). Additionally, three genetic models, dominant (CT+CC vs. TT), recessive (CC vs. TT+TC), and allelic (C vs. T) — were also used to assess the association with obesity risk. SNP rs564398 showed an association under the dominant (p < 0,0001), recessive (p = 0,0010), and allelic (p < 0,0001) genetic models.

Table 1 — Genotype distribution and allele frequency of rs564398 in ANRIL in the obese vs. control groups

	Case	Control	*p*	OR (95% CI)

	n (%)	n (%)		
genotype	100	50	< 0,0001	
TT	11 (11%)	24 (48%)		
TC	46 (46%)	18 (36%)	0,0001	5,58 (2,30 to 14,05)
CC	43 (43%)	8 (16%)	0,0010	3,96 (1,74 to 8,79)
TC+CC	89	26	< 0,0001	7,47 (3,20 to 16,65)
alleles				
T	68 (34%)	66 (66%)		
C	132 (66%)	34 (34%)	< 0,0001	3,77 (2,25 to 6,13)

Further subgroup analysis was conducted using the same three genetic models. Our findings showed that SNP rs564398 is associated with an increased zBMI (p = 0,0010) under the dominant (p = 0,0004) and allelic (p = 0,0006) models, but not the recessive one (p = 0,1000). Moreover, SNP rs564398 showed an association with insulin resistance only under the recessive model (p = 0,0428). Results are displayed in table 2.

Table 2 — Genotype distribution and allele frequency of rs564398 in ANRIL in (A) INS-S vs. control and (B) INS-R vs. INS-S groups.

	Case n (%)	Control n (%)	*p*	OR (95% CI)
(A) INS-S vs. Control				
genotype	50	50	0,0010	
TT	7 (14%)	24 (48%)		
TC	27 (54%)	18 (36%)	0,0021	5,14 (1,89 to 13,10)
CC	16 (32%)	8 (16%)	0,1000	2,47 (0,99 to 6,50)
TC+CC	43	26	0,0004	5,67 (2,13 to 14,01)
alleles				
T	41 (41%)	66 (66%)		
C	59 (59%)	34 (43%)	0,0006	2,79 (1,56 to 4,97)
(B) INS-R vs. INS-S				
genotype	50	50	0,0811	
TT	4 (8%)	7 (14%)		
TC	19 (38%)	27 (54%)	> 0,9999	1,23 (0,306 to 4,17)
CC	27 (54%)	16 (32%)	0,0428	2,49 (1,08 to 5,63)
TC+CC	46	43	0,5246	1,87 (0,53 to 6,00)
alleles				
T	27 (27%)	41 (41%)		
C	73 (73%)	59 (59%)	0,0519	1,88 (1,04 to 3,32)

3. Association of SNP rs7158663 *MEG3* genotypes with childhood obesity and insulin-resistance risk

The genotype distribution of SNP rs7158663 in the control group was in HWE (p = 0,34). SNP rs7158663 is associated with the risk of developing childhood obesity (p = 0,0101). Compared to the GG genotype, there was a significant difference in the distribution of the heterozygous genotype GA (p = 0,0252) between the case and control groups. The dominant GA+AA vs. GG (p = 0,0120), and the allelic A vs. G (p = 0,0148) genetic models showed significant associations with obesity risk but not the recessive model AA vs. GG+GA (p = 0,0633). Results are shown in Table 3.

Table 3 — Genotype distribution and allele frequency of rs7158663 in MEG3 in the obese vs. control groups.

	case n (%)	control n (%)	*p*	OR (95% CI)
genotype			0,0101	
GG	12 (12%)	15 (30%)		
GA	68 (68%)	31 (62%)	0,0252	2,74 (1,13 to 6,26)
AA	20 (20%)	4 (8%)	0,0633	2,87 (1,00 to 8,13)
GA+AA	88	35	0,0120	3,14 (1,34 to 6,97)
alleles				
G	92 (46%)	61 (61%)		
A	108 (54%)	39 (39%)	0,0148	1,84 (1,13 to 2,97)

Subgroup analysis revealed an association between SNP rs7158663 and increased zBMI in the studied population (p = 0,0195), under the dominant (p = 0,0479) and allelic (p = 0,0232) models. No significant association with insulin resistance was demonstrated, table 4.

Table 4 – Genotype distribution and allele frequency of rs7158663 in MEG3 in (A) INS-S vs. control and (B) INS-R vs. INS-S groups.

	case n (%)	control n (%)	*p*	OR (95% CI)
(A) INS-S vs. Control				
genotype			0,0195	
GG	6 (12%)	15 (30%)		
GA	32 (64%)	31 (62%)	0,0845	2,58 (0,88 to 7,67)
AA	12 (24%)	4 (8%)	0,0538	3,63 (1,16 to 10,83)
GA+AA	44	35	0,0479	3,14 (1,13 to 9,00)
alleles				
G	44 (44%)	61 (61%)		
A	56 (56%)	39 (39%)	0,0232	1,99 (1,13 to 3,44)
(B) INS-R vs. INS-S				
genotype			0,5959	
GG	6 (12%)	6 (12%)		
GA	36 (72%)	32 (64%)	> 0,9999	1,12 (0,30 to 4,18)
AA	8 (16%)	12 (24%)	0,4539	0,60 (0,22 to 1,66)
GA+AA	44	44	> 0,9999	1,00 (0,28 to 3,57)
alleles				
G	48 (48%)	44 (44%)		
A	52 (52%)	56 (56%)	0,6705	0,85 (0,48 to 1,50)

4. Association of SNP rs674485 *NEAT1* genotypes with childhood obesity and insulin-resistance risk

The genotype distribution of SNP rs674485 in *NEAT1* in the controls did not respect the HWE (p = 0,03). Our finding did not reveal any association between rs674485 in *NEAT1* and obesity risk (p = 0,1302). Moreover, the genotypes of rs674485 also showed no association with increased zBMI (p = 0,7754) or insulin resistance (p =

0,0954). However, the heterozygous genotype GA showed a slight difference in distribution compared to the homozygous allele GG (p = 0,0474) in the subgroup analysis of INS-S vs. INS-R groups. Results are clarified in Table 5.

Table 5 — Genotype distribution and allele frequency of rs674485 in NEAT1 in the (A) obese vs. control, (B) INS-S vs. control, and (C) INS-R vs. INS-S groups.

	case n (%)	Control n (%)	*p*	OR (95% CI)
(A) obese vs. Control				
genotype			0,1302	
GG	13 (13%)	13 (26%)		
GA	29 (29%)	11 (22%)	0,0735	2,64 (0,88 to 7,33)
AA	58 (58%)	26 (52%)	0,4916	1,27 (0,65 to 2,49)
GA+AA	87	37	0,0661	2,35 (0,96 to 5,53)
alleles				
G	55 (27,5%)	37 (37%)		
A	145 (72,5%)	63 (63%)	0,1109	1,55 (0,92 to 2,57)
(B) INS-S vs, Control				
genotype			0,7754	
GG	10 (20%)	13 (26%)		
GA	12 (24%)	11 (22%)	0,7683	1,42 (0,42 to 4,16)
AA	28 (56%)	26 (52%)	0,8411	1,17 (0,52 to 2,66)
GA+AA	40	37	0,6353	1,40 (0,57 to 3,59)
alleles				
G	32 (32%)	37 (37%)		
A	68 (68%)	63 (63%)	0,5520	1,25 (0,70 to 2,24)
(C) INS-R vs. INS-S				
genotype			0,0954	
GG	3 (6%)	10 (20%)		

GA	17 (34%)	12 (24%)	0,0474	4,72 (1,09 to 17,99)
AA	30 (60%)	28 (56%)	0,8396	1,18 (0,52 to 2,53)
GA+AA	47	40	0,0713	3,92 (1,00 to 13,82)
alleles				
G	23 (23%)	32 (32%)		
A	77 (77%)	68 (68%)	0,2050	1,57 (0,86 to 2,99)

Discussion

Recent genome-wide association studies have uncovered numerous single nucleotides polymorphisms in lncRNA genes that are associated with an elevated risk of developing metabolic disorders, including obesity. However, there is a dearth of research investigating the association between specific SNPs and the susceptibility to obesity and insulin resistance in Russian children and adolescents. To address this knowledge gap, we conducted this case-control study involving participants aged 5 to 17 from the Russian Federation. Our study aimed to explore the association between three SNPs in lncRNA genes: rs564398 in *ANRIL*, rs7158663 in *MEG3*, and rs674485 in *NEAT1*, and the likelihood of developing obesity and insulin resistance.

ANRIL has drawn special attention because it is situated within the *CDKN2A/B* gene cluster, which houses genes involved in cellular proliferation, cancer susceptibility and metabolic homeostasis. *ANRIL* regulates gene expression at this locus, and may be regarded as a genomic site for epigenetic responses to environmental factors (Lillycrop et al., 2017) (Kong et al., 2018a) (Gu et al., 2013). SNPs within *ANRIL* can influence its activity through various mechanisms, and these changes may be linked to a raised susceptibility to diseases, as exemplified by rs564398, that demonstrated a significant association with obesity risk and increased zBMI in our study, although GWAS did not indicate a direct link between SNPs at *ANRIL* and obesity risk. Subgroup analysis also illustrated that the homozygous genotype of the minor allele CC is associated with

insulin-resistance risk. This is in line with similar observations made by Kong et al., who reported that the C allele of rs564398 is associated with a decreased pancreatic β-cell proliferation index in response to glucose stimulation (Kong et al., 2018a). Other cohort studies have also indicated a trend toward reduced insulin sensitivity associated with the C allele (Pascoe et al., 2007) (Groenewoud et al., 2008). Furthermore, there is evidence of a correlation between SNP rs564398 and a decrease in insulin content in human islets. This same study revealed that rs564398 leads to reduced methylation of local CpG sites in ANRIL, without affecting its expression (Dayeh et al., 2013). The involvement of SNP rs564398 in insulin resistance risk could potentially explain its association with the development of T2D (Scott et al., 2007) (R et al., 2007) (Zeggini et al., 2007b). However, it's important to note that the strength of this association with type 2 diabetes may vary depending on the ethnicity of the study population (Duesing et al., 2008) (Wu et al., 2008) (Horikawa et al., 2008) (Ammar et al., 2022). More importantly, there are many SNPs in linkage with rs564398 that, in combination, may influence pathological phenotypes instead of rs564398 alone. There is still much to learn about the biology of *ANRIL* in obesity, this field of study may provide an understanding of the pathogenesis of obesity and potential management strategies.

Another SNP, rs7158663 in the maternally expressed gene 3 (*MEG3)*, has showed a positive association with obesity risk and elevated zBMI in our studied population. Previous research has implicated *MEG3* in the regulation of lipogenesis, fat accumulation, glucose intolerance, insulin secretion, and sensitivity, suggesting its involvement in the pathogenesis of T2D and obesity in multiple populations (Kameswaran et al., 2014) (You et al., 2016) (Zhu et al., 2016) (Qiu et al., 2016) (P. Huang et al., 2019) (X. Huang et al., 2019) (Cheng et al., 2021) (Daneshmoghadam et

al., 2021) (Ghaedi et al., 2018a). The mechanism by which rs7158663 impacts *MEG3* regulation or function is still unknown. However, a study in the Egyptian population suggested that rs7158663 minor allele A is linked to decreased serum MEG3 levels (Ghaedi et al., 2018a). Moreover several studies reported an influence of rs7158663 on transcript secondary structure (Cao et al., 2016) (Ghaedi et al., 2018b) (Zeggini et al., 2007) (Ghaedi et al., 2018a).

Regarding rs674485 in *NEAT1*, a deviation from HWE was observed in the control group, this may be attributed to various factors such as the specific geographic region and demographic group from which our study population was recruited. Additionally, the small sample size and potential genetic diversity limitations could have influenced the results. Although no significant associations were found, it is important to mention that previous GWAS have linked rs674485 with phenotypes related to obesity (Christakoudi et al., 2021). The discrepancy may be attributed to the deviation from HWE in the control group or the ethnic differences in the studied populations. In general, there are limited number of studies investigating the SNP rs674485. However, the role of *NEAT* in adipogenesis has been confirmed in studies on mice (Wu et al., 2022). Another study revealed signaling networks between miR-140 and NEAT, that are necessary for adipogenesis (R et al., 2016) (Sun et al., 2013).

Our study has several limitations. Firstly, the study population represents a specific geographical and demographic region due to recruitment from a single polyclinic. Secondly, the sample size was relatively small. Thirdly, the age range of the enrolled children and adolescents was not specified by any criteria. Lastly, considering the complex nature of obesity with gene-environment interactions and a polygenic background, future research should consider integrating environmental factors and

examining the interactions between multiple SNPs to gain a comprehensive understanding of obesity pathogenesis and identify personalized prevention and treatment strategies.

Conclusion

Our findings provided preliminary evidence of the association between specific SNPs in lncRNA genes (rs564398 in *ANRIL* and rs7158663 in *MEG3*) and the susceptibility to develop obesity and insulin resistance in Russian children and adolescents. This contributes to the growing body of evidences on the role of lncRNAs in metabolic disorders. However, further investigations with larger and more diverse populations considering functional interactions with environmental factors are needed to gain deeper insights into the biology of lncRNAs in obesity and develop personalized approaches for prevention and treatment of obesity epidemic.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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