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Research of the Genotype Association by Locus Rs7903146 of the Tcf7l2 Gene and the Risk of Abdominal Obesity Development among Young Residents of the North

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ABSTRACT
Currently, interest in studying obesity as a chronic inflammatory disease continues to grow. Despite numerous recommendations for reducing excess weight, the majority of the population does not assess the importance of this pathology for the development of serious cardiovascular diseases. Eating disorders and physical inactivity continue to prevail among the majority of the population, and especially, it is common among young people. Climatic factors also play an important role in changing fat metabolism. This is peculiar, especially to residents of the northern regions, where, under the influence of cold, lipid and carbohydrate metabolism is often disturbed, which contributes to the accumulation of abdominal fat. However, a genetic predisposition to obesity is one of the common causes of this disorder. The TCF7L2 gene (localization - 10q25.3) controls the synthesis of a transcription factor that regulates the expression of the proglucagon gene involved in carbohydrate metabolism [1]. So, the CT and TT alleles of rs7903146 of the TCF7L2 gene lead to insulin deficiency in the body. In addition, the TCF7L2 gene regulates the differentiation of adipose tissue cells [2; 3]. To study the association of rs7903146 of the TCF7L2 gene with a risk of developing abdominal obesity among young residents of the north.

Keywords: Genotype, Locus RS7903146, TCF7L2 Gene, Abdominal, North

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INTRODUCTION

MATERIALS AND METHODS

The formation of a group of patients was carried out on the bases: "Fedorovskaya City Hospital", a branch of the hospital in the village of Russkinskaya, "Surgut City Clinical Polyclinic No. 1". All patients signed an informed consent to participate in the study. For the period 2015-2018 a total of 882 people aged 18-44 years were selected (average age 36.62 ± 5.12 years). Non-indigenous inhabitants (n = 599) are represented by the city population - 245 people (146 women and 99 men) and the village population - 354 people (108 men and 246 women). The indigenous small population of the north (indigenous peoples) is 283 khanty, of which 72 are men and 211 are women [4]. Conducted: questionnaire survey, anthropometric examination: measurement of height, body weight, body mass index (BMI = kg/m²), waist circumference (OT) [4]. In accordance with the clinical recommendations "Diagnosis and treatment of metabolic syndrome" (Moscow, 2019), the following criteria were used to establish the presence of abdominal obesity: waist circumference > 80 cm in women and > 94 cm in men.

Molecular genetic research was carried out at NIITPM - a branch of the Federal Research Center of Cytology and Genetics SB RAS. Genomic DNA was isolated from venous blood by phenol-chloroform extraction. The rs7903146 polymorphism of the TCF7L2 gene was tested using a polymerase chain reaction with restriction fragment length polymorphism (PCR with RFLP). All patients received informed consent [4].

Statistical processing of the results was carried out using the R 3.5.3 package (R Foundation for Statistical Computing) and additional BioConductor repository packages (HardyWeinberg 1.6.3, SNPassoc 1.9-2). To analyze the deviation of the observed genotype frequencies from theoretical frequencies determined by the Hardy-Weinberg equilibrium, the $\chi 2$ test was used for the cohort as a whole and groups of participants (city, village residents and khanty), deviations were considered statistically significant at $p < 0.05$. To assess the effect, we used the odds ratios (OR) with the corresponding 95% CI [4].

RESULTS

Table 1 presents the empirical distributions of the studied alleles and genotypes in the cohort of study participants as a whole and in groups. In addition, we studied the association of the genotype at the rs7903146 locus and the values of the waist circumference and body mass index. Table 2 and Figure 1 provide estimates of the marginalized probabilities of developing abdominal obesity in the population as a whole and in the studied groups, depending on the genotype at the rs7903146 locus of the TCF7L2 gene. Table 3 and Figure 2 show LS (least square, marginalized means, i.e., regardless of gender and age and their differences between groups) estimates of the average waist circumference, regardless of gender and age; in table 4 and figure 3– LS estimates of BMI regardless of gender and age of the genotype at the rs7903146 locus of the TCF7L2 gene.

Table 1. Generalized characteristic of empirical distributions of variables included in generalized linear models

	Cohort	City	Village	Khanty	p-value*
TT	52 (5,9%)	20 (7,2%)	18 (5,3%)	14 (5,3%)	0,8099
CT	285 (32,3%)	90 (32,5%)	112 (33,0%)	83 (31,2%)	
CC	545 (61,8%)	167 (60,3%)	209 (61,7%)	169 (63,5%)	
T	389 (22,1%)	130 (23,5%)	148 (21,8%)	111 (20,9%)	0,5769
C	1375 (77,9%)	424 (76,5%)	530 (78,2%)	421 (79,1%)	

Table 2. Estimates of the likelihood of developing abdominal obesity depending on the genotype of the rs7903146 locus in the targeted population, city residents, village residents and khanty

Group	Genotype	Average value	95% CI
Codominant Model			
City	CC	0,617	0,538-0,690
	CT	0,603	0,497-0,701
	TT	0,748	0,518-0,892
Village	CC	0,519	0,448-0,588
	CT	0,446	0,355-0,540
	TT	0,151	0,049-0,382
Khanty	CC	0,411	0,337-0,490
	CT	0,417	0,315-0,528
	TT	0,479	0,242-0,726
Cohort	CC	0,520	0,474-0,565
	CT	0,491	0,431-0,551
	TT	0,466	0,335-0,602
Dominant model			
City	CC	0,617	0,539-0,690
	CT/TT	0,630	0,534-0,717
Village	CC	0,519	0,449-0,589
	CT/TT	0,404	0,322-0,492
Khanty	CC	0,412	0,338-0,491
	CT/TT	0,427	0,331-0,529
Cohort	CC	0,520	0,474-0,565
	CT/TT	0,487	0,432-0,542

Table 3. Estimates of the average waist circumference depending on the genotype at the rs7903146 locus in the target population, city residents, village residents and khanty

Group	Genotype	Average waist circumference	95% CI
Codominant Model			
City	CC	90,8	88,7-92,8
	CT	89,7	87,0-92,5
	TT	93,3	87,5-99,2
Village	CC	88,5	86,6-90,3
	CT	87,4	84,9-89,9

	TT	79,3	73,2-85,4
Khanty	CC	83,9	81,8-85,9
	CT	83,7	80,8-86,6
	TT	84,7	77,8-91,7
Cohort	CC	87,9	86,7-89,1
	CT	87,2	85,5-88,8
	TT	86,2	82,5-89,9
Dominant model			
City	CC	90,8	88,7-92,8
	CT/TT	90,4	87,9-92,9
Village	CC	88,5	86,6-90,3
	CT/TT	86,3	84,0-88,6
Khanty	CC	83,9	81,8-86,0
	CT/TT	83,9	81,2-86,6
Cohort	CC	87,9	86,6-89,1
	CT/TT	87,0	85,5-88,5

Table 4. LS of BMI estimate depending on the genotype at the rs7903146 locus in the target population, city dwellers, village residents and khanty

Group	Genotype	Risk assessment	95% CI
Codominant Model			
City	CC	31,2	30,4-31,9
	CT	32,0	31,0-33,0
	TT	32,1	30,0-34,2
Village	CC	31,5	30,8-32,2
	CT	31,7	30,8-32,6
	TT	30,4	28,2-32,6
Khanty	CC	31,0	30,2-31,7
	CT	30,3	29,3-31,4
	TT	30,3	27,8-32,8
Cohort	CC	31,3	30,8-31,7
	CT	31,4	30,9-32,0
	TT	31,0	29,7-32,3
Dominant Model			
City	CC	31,2	30,4-31,9
	CT/TT	32,0	31,1-32,9
Village	CC	31,5	30,8-32,2
	CT/TT	31,5	30,7-32,4
Khanty	CC	31,0	30,2-31,7
	CT/TT	30,3	29,4-31,3
Cohort	CC	31,3	30,8-31,7
	CT/TT	31,4	30,8-31,9

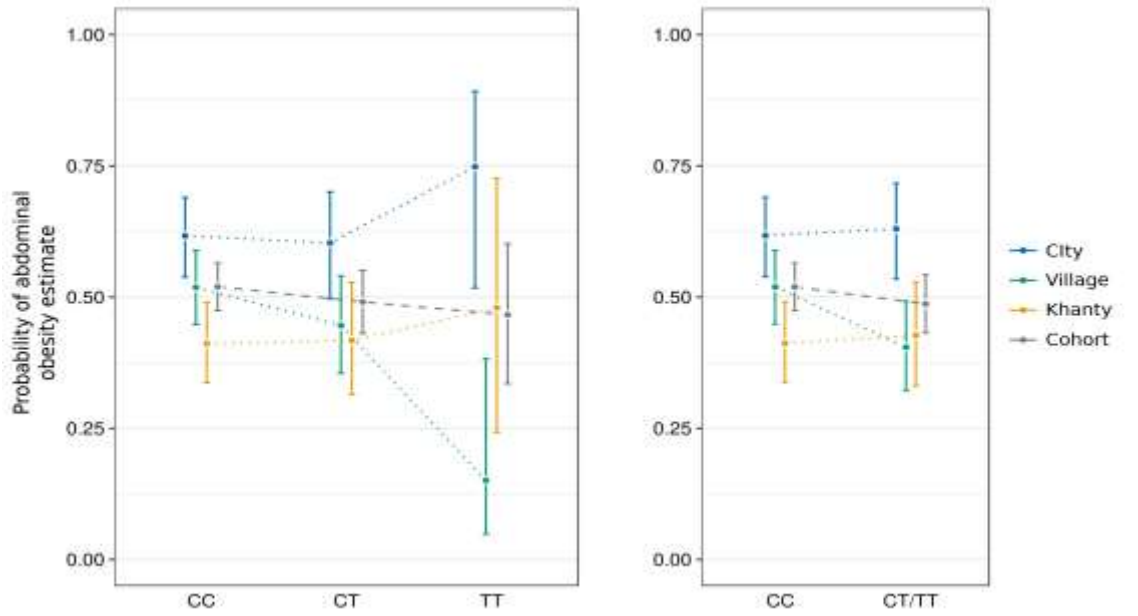

Figure 1. Estimates of the likelihood of developing abdominal obesity depending on the genotype at the rs7903146 locus of the TCF7L2 gene

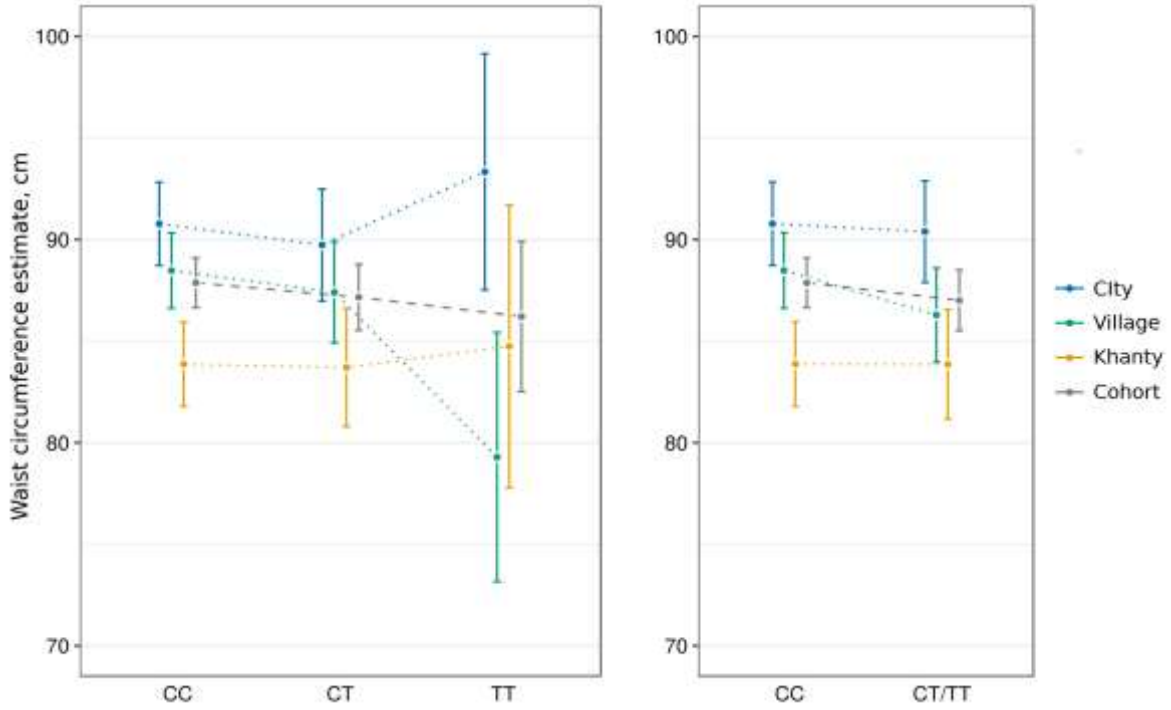

Figure 2. LS of the waist circumference estimate depending on the genotype at the locus rs7903146 of the TCF7L2 gene

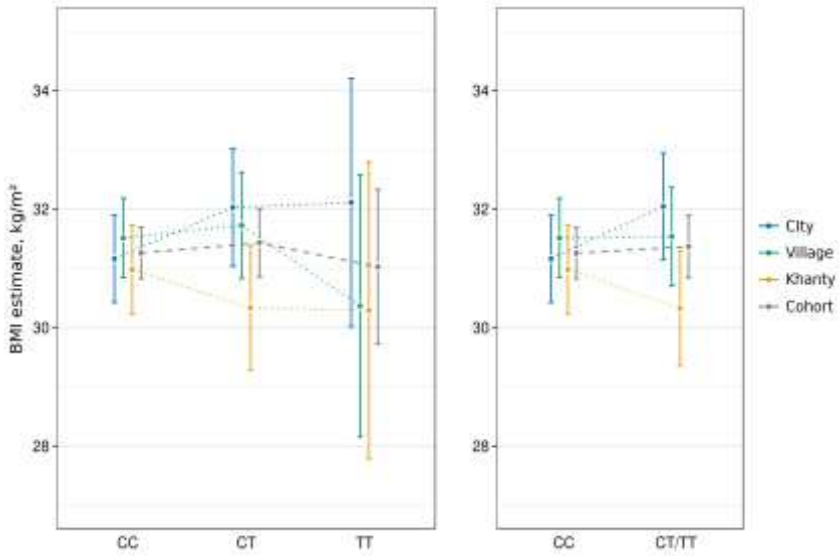

Figure 3. LS of BMI estimate depending on the genotype at the rs7903146 locus of the TCF7L2 gene

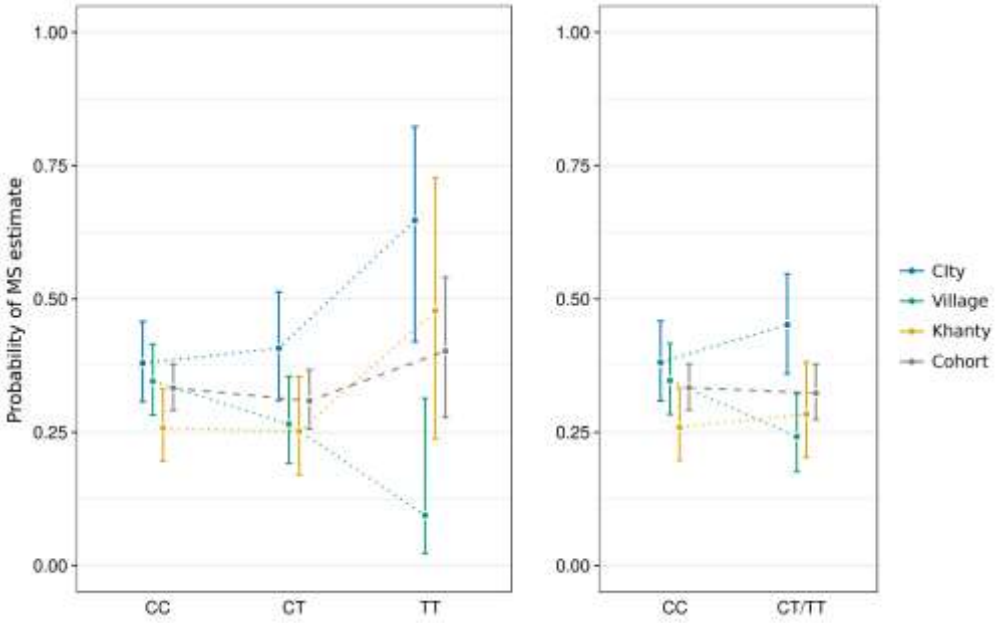

Figure 4. Estimates of the likelihood of developing a metabolic syndrome depending on the genotype at the rs7903146 locus of the TCF7L2 gene

Table 5 presents estimates of the effect of genotypes on the risk of abdominal obesity (odds ratio and 95% CI) in the cohort and in the subgroups obtained in the dominant and codominant logistic models regardless of gender and age.

Tables 6 and 7 show estimates of the size of the effect of genotypes (absolute differences and 95% CI for them) on the waist circumference and body mass index, regardless of gender and age.

Table 5. Estimates of the odds ratio of developing abdominal obesity between genotypes at the rs7903146 locus in the target population, city residents, village residents and khanty

	Contrast	OR	95% CI	P-value
Codominant model (AIC = 1193,7)				
City	CC - CT	1,060	0,620-1,810	0,8324
	CC - TT	0,541	0,186-1,578	0,2610
	CT - TT	0,511	0,169-1,547	0,2348
Village	CC - CT	1,338	0,841-2,129	0,2184
	CC - TT	6,066	1,695-21,714	0,0056
	CT - TT	4,532	1,235-16,632	0,0227
Khanty	CC - CT	0,976	0,573-1,661	0,9280

	CC - TT	0,759	0,252-2,284	0,6237
	CT - TT	0,778	0,248-2,442	0,6669
Cohort	CC - CT	1,122	0,794-1,586	0,4336
	CC - TT	1,240	0,624-2,464	0,4638
	CT - TT	1,104	0,541-2,252	0,7442
Dominant model (AIC = 1195,9)				
City	CC - CT/TT	0,947	0,570-1,572	0,8333
Village	CC - CT/TT	1,591	1,019-2,482	0,0409
Khanty	CC - CT/TT	0,940	0,567-1,559	0,8116
Cohort	CC - CT/TT	1,140	0,866-1,499	0,3502

As can be seen from Figure 4 and Table 5, as in the case of the risk of developing metabolic syndrome, the effect of the mutant allele at the rs7903146 locus of the TCF7L2 gene tends to be multidirectional in different groups of participants: the presence of the T allele is associated with a 1.5% reduction in the chance of developing abdominal obesity in village residents times (dominant model) and, in addition, there is a pronounced "dose dependence" of the effect in the codominant model. There was no significant association of this polymorphism with the risk of metabolic syndrome among khanty and city residents. Interestingly, despite a generally similar picture regarding waist circumference, regardless of gender and age, no statistically significant differences were found between the average BMI values. The results of the analysis of the polymorphism association at a given locus and the above variables are also presented in Figures 5-7.

Table 6. Estimates of the difference between the average waist circumference between genotypes at the rs7903146 locus in the target population, city residents, village residents and khanty, regardless of gender and age.

	Contrast	Absolute difference	95% CI	P-value
Codominant model				
City	CC - CT	1,039	-2,362-4,441	0,5488
	CC - TT	-2,562	-8,722-3,598	0,4145
	CT - TT	-3,602	-10,034-2,830	0,2720
Village	CC - CT	1,074	-1,973-4,120	0,4893
	CC - TT	9,179	2,788-15,571	0,0049
	CT - TT	8,106	1,501-14,711	0,0162
Khanty	CC - CT	0,171	-3,320-3,662	0,9233
	CC - TT	-0,874	-8,113-6,364	0,8127
	CT - TT	-1,046	-8,564-6,472	0,7849
Cohort	CC - CT	0,700	-1,600-3,000	0,4684
	CC - TT	1,700	-3,000-6,300	0,3969
	CT - TT	0,900	-3,800-5,700	0,6420
Dominant model				
City	CC - CT/TT	0,388	-2,815-3,591	0,8123
Village	CC - CT/TT	2,195	-0,718-5,109	0,1395
Khanty	CC - CT/TT	0,015	-3,311-3,341	0,9929
Cohort	CC - CT/TT	0,900	-1,000-2,700	0,3578

Table 7. Estimates of the difference between the average BMI between genotypes at the rs7903146 locus in the target population, city residents, village residents and khanty regardless of gender and age

	Contrast	Absolute difference	95% CI	P-value
Codominant model				
City	CC - CT	-0,869	-2,094-0,357	0,1644
	CC - TT	-0,950	-3,170-1,269	0,4008
	CT - TT	-0,082	-2,399-2,236	0,9449
Village	CC - CT	-0,210	-1,308-0,888	0,7073
	CC - TT	1,146	-1,156-3,449	0,3288
	CT - TT	1,356	-1,023-3,736	0,2636
Khanty	CC - CT	0,646	-0,612-1,904	0,3135
	CC - TT	0,689	-1,918-3,297	0,6040
	CT - TT	0,043	-2,665-2,752	0,9750
Cohort	CC - CT	-0,200	-1,000-0,600	0,6211
	CC - TT	0,200	-1,400-1,900	0,7382
	CT - TT	0,400	-1,300-2,100	0,5744
Dominant model				
City	CC - CT/TT	-0,884	-2,034-0,267	0,1320
Village	CC - CT/TT	-0,023	-1,069-1,023	0,9661
Khanty	CC - CT/TT	0,652	-0,543-1,846	0,2845
Cohort	CC - CT/TT	-0,100	-0,800-0,500	0,7385

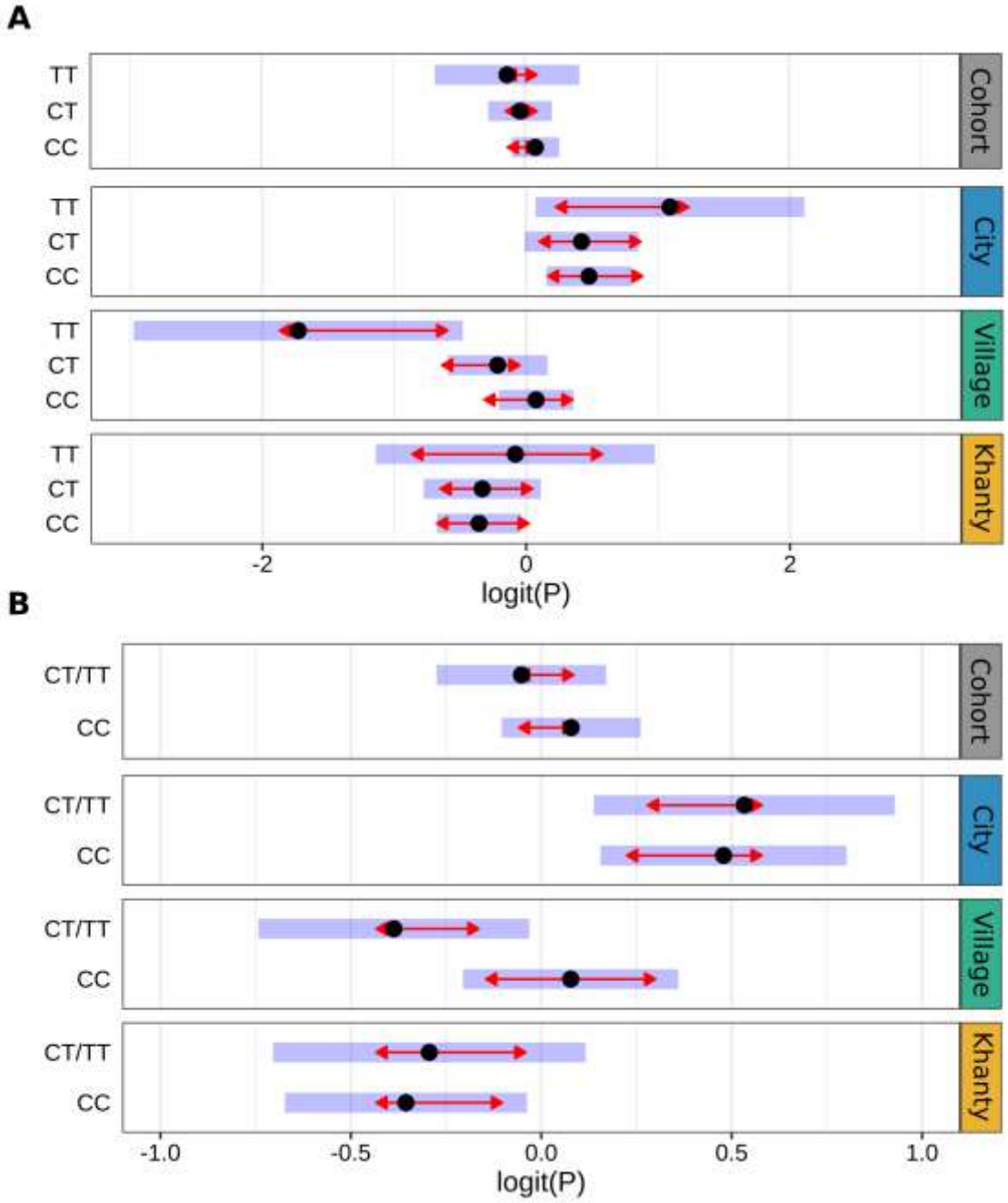

Figure 5. Estimates of the risk of developing abdominal obesity in the context of codominant (A) and dominant (B) inheritance models. Black dots - estimates of the likelihood of developing a metabolic syndrome, blue line - 95% CI, red line - shows a comparison of genotypes within the corresponding models and subgroups.

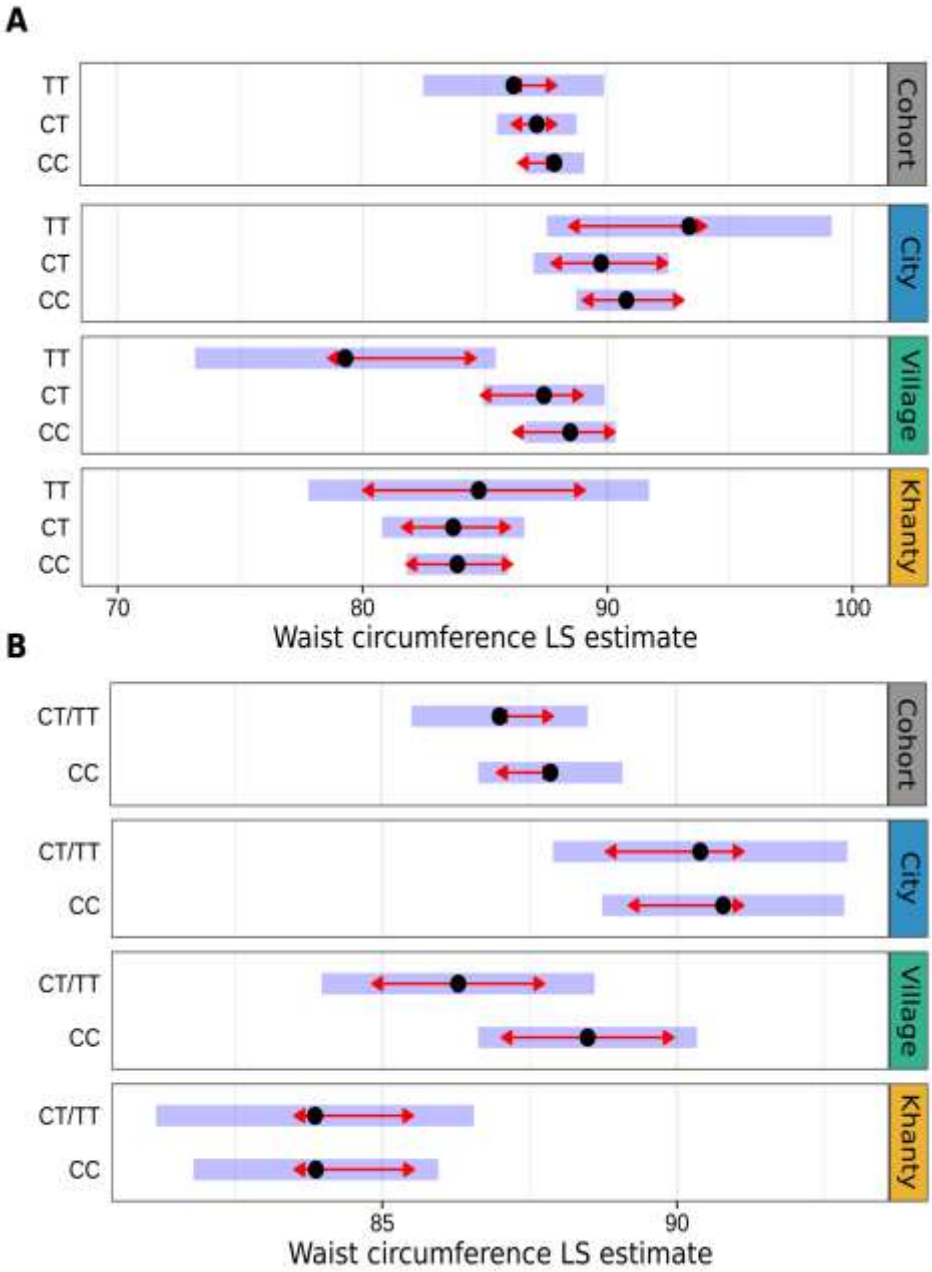

Figure 6. LS of the estimate (marginalized means) of average waist circumference in the context of codominant (A) and dominant (B) inheritance models. Black dots - estimates of the likelihood of developing a metabolic syndrome, blue line - 95% CI, red line - shows a comparison of genotypes within the corresponding models and subgroups.

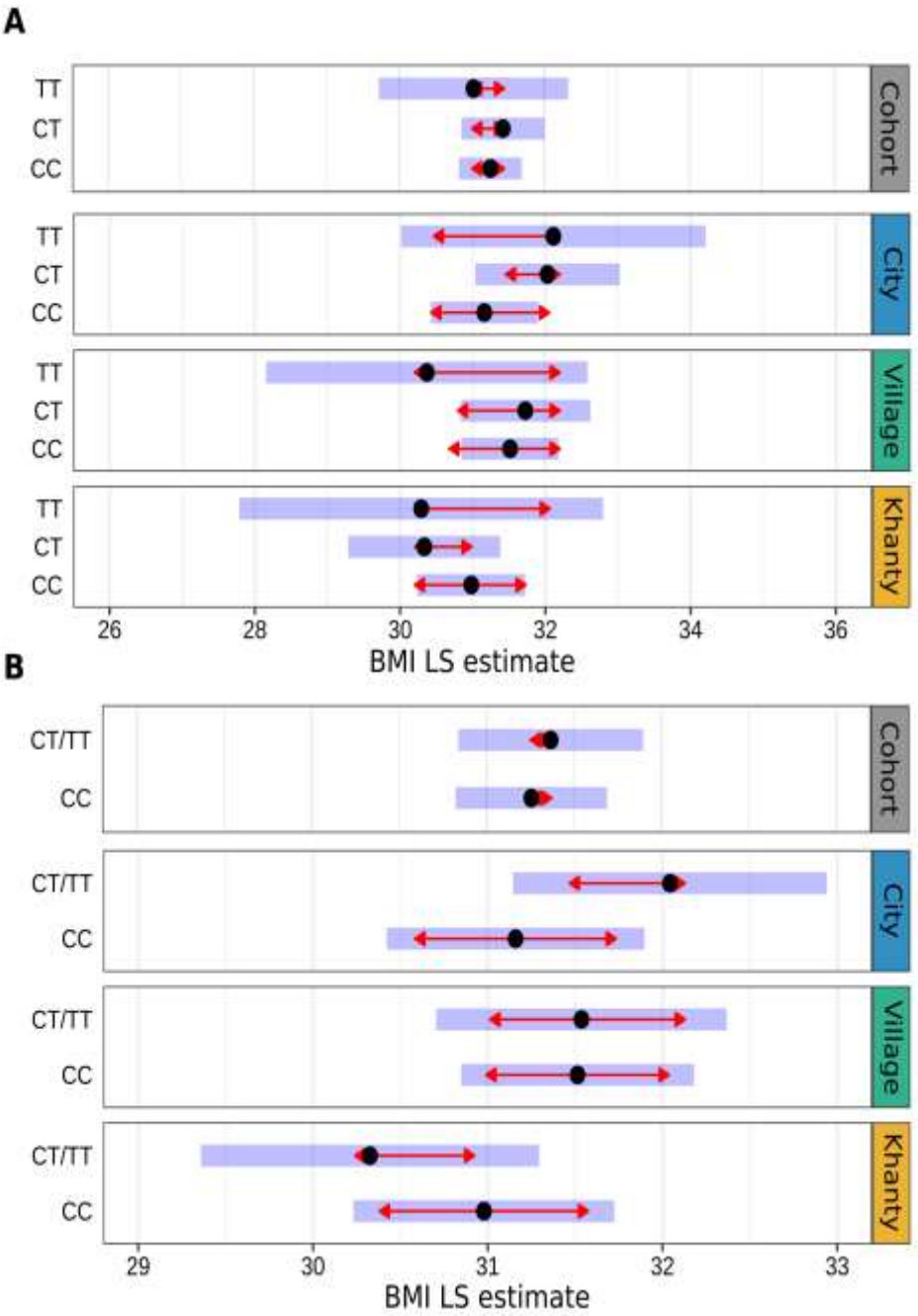

Figure 7. LS of the average BMI estimate in the context of codominant (A) and dominant (B) inheritance models. Black dots - estimates of the likelihood of developing a metabolic syndrome, the blue line - 95% CI, the red line - shows a comparison of genotypes within the corresponding models and subgroups.

DISCUSSION

A sufficient number of studies have been devoted to the TCF7L2 gene, but the relationship of the mutant alleles of this gene with the development of obesity remains unclear [5]. According to many researchers, the TCF7L2 gene is expressed in adipose tissue and is involved in Wnt-dependent regulation of adipogenesis, which supports preadipocytes in an undifferentiated state [6; 7; 8; 9]. Several studies do not exclude the association of the gene with TCF7L2 with obesity [10; 11].

An increase in the average BMI is often detected in carriers of the heterozygous CT genotype rs7903146 of the TCF7L2 gene [12]. Stolerman E.S. et al. (2009) consider that the rs7903146 minor allele T increases the risk of diabetes and confirmed that variants in TCF7L2 are strongly associated with an increased proinsulin/insulin ratio [12].

The so-called functional role of TCF7L2 in adipogenesis, mature adipocytes, and in the growth of obesity has been described [3]. The authors observed that with a decrease or loss of TCF7L2, insulin resistance developed in adipocytes. As a result, adipocytes hypertrophied, lipolysis was disturbed, and the content of triglycerides in the blood serum increased. [3].

It was revealed that the T allele of the rs7903146 genome is less able to bind to the protein than the C allele, and in TT carriers the expression of rs7903146 of the TCF7L2 gene decreases in subcutaneous adipose tissue when interfering with lifestyle (rational nutrition with calorie restriction, increased physical activity) [8].

In our study, the effect of the T allele rs7903146 of the TCF7L2 gene is multidirectional among city, village, and indigenous people. The risk of developing abdominal obesity in village residents is 1.5 times lower than among city residents and khanty.

Thus, a significant association of rs7903146 of the TCF7L2 gene with the risk of developing obesity, as the main component of the metabolic syndrome, was not found among the examined patients. Given that obesity models insulin resistance and the development of diabetes mellitus, individuals carrying the mutant T allele at the rs7903146 locus of the TCF7L2 gene need to develop methods for the timely prevention and treatment of metabolic disorders.

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