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HUMAN GENETICS

TOMM40 Gene Polymorphisms Association with Lipid Profile

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Abstract—The distribution of the allele and genotype frequency for the *TOMM40* gene polymorphic variants rs741780, rs157580, rs1160985, rs2075650, and rs8106922 was analyzed in a sampling of ethnic Russians from the city of Kemerovo. The study of the structure of linkage disequilibrium in terms of five studied polymorphic variants showed the presence of a haplotype block 2 Kb in length, which includes three polymorphic variants, i.e., rs741780, rs1160985, and rs8106922. The differences in the frequencies of alleles and genotypes in terms of the polymorphic rs2075650 and rs157580 variants between ethnic Russians from the city of Kemerovo and other European populations were detected. It was discovered that polymorphic variants of *TOMM40* rs741780, rs1160985, and rs8106922 are associated with serum triglyceride concentrations. In men, the polymorphic variant rs2075650 is associated with low-density lipoprotein cholesterol levels. In women, the polymorphic variant rs741780 is associated with diastolic blood pressure levels.

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INTRODUCTION

The *TOMM40* gene (12470 bp, 10 exons) is localized on the long arm of chromosome 19 (19p13) in the same cluster with the *APOE*, *APOC1*, *APOC2*, and *APOC4* genes. It encodes protein tom40, consisting of 361 amino acid residues. The tom40 protein forms a central subunit of the TOM complex that carries out the transfer of almost all proteins required for the normal functioning of mitochondria [1, 2].

According to the results of several genome-wide association studies (GWAS), allelic variants of the *TOMM40* gene may contribute to the genetic predisposition to several widespread multi-factorial diseases. To date, associations have been shown between the *TOMM40* gene allelic variants (rs2075650, rs10524523) with Alzheimer's disease [1–3], body mass index (rs2075650), cholesterol levels in fractions of lipoprotein, and triglycerides, as well as C-reactive protein in blood serum [4–9].

The data on the distribution of allelic variants of the *TOMM40* gene in populations of the world are limited to the results of few studies [4, 9]. For most functionally relevant genetic variants, there are interethnic and interpopulation differences in the distribution of allele frequencies. These differences largely determine features of the structure of the genetic component for the susceptibility to multifactorial diseases in different populations around the world. Therefore, the study of the allelic variants of candidate genes that affect the formation of a predisposition to a particular disease should be supplemented by the evaluation of the population specifics of distribution of allele frequencies and the study of the structure of linkage disequilibrium.

The purpose of our work was to study the polymorphic variants of the *TOMM40* gene selected based on the literature on genome-wide association studies and the results of phylogenetic analysis of the fragment of chromosome 19 carried out in Lutz et al. [2].

MATERIALS AND METHODS

The sampling of relatively healthy individuals ($N = 188$) was composed of individuals (32% men and 68% women) who expressed consent for participation in the study. The average age of the surveyed was 45.0 ± 9.1 years and almost did not differ in subgroups of men and women: 45.6 ± 9.1 and 44.7 ± 9.2 years, respectively.

DNA was isolated by phenol–chloroform extraction from peripheral blood leukocytes [10]. The allelic variants of the *TOMM40* gene (Table 1) were identified by the polymerase chain reaction in real time using presets of reagents and fluorescently-labeled TaqMan samples produced by Applied Biosystems (United States). The polymerase chain reaction was performed according to the manufacturer's protocol. The first stage involved activation of the AmpliTaq Gold-poly-

Table 1. Characteristics of studied polymorphic variants of *TOMM40* gene

Polymorphism	Locus	Localization	Rare allele frequency*	Link
c.844-34*T>C*	rs741780	Intron 8	*C* 0.456	
c.275-31*A>G*	rs2075650	Intron 2	*G* 0.134	
c.644-575*C>T*	rs1160985	Intron 6	*T* 0.457	[11, 12]
c.274+320*G>A*	rs157580	Intron 2	*G* 0.380	
c.644-2321*A>G*	rs8106922	Intron 6	*G* 0.420	

* Table presents average values for entire world population obtained within 1000 Genomes project.

merase (95°C for 10 min). This was followed by 40 cycles: denaturation (92°C for 15 s) and annealing/elongation (60°C for 1 min), followed by the detection of fluorescently labeled amplification products after each cycle.

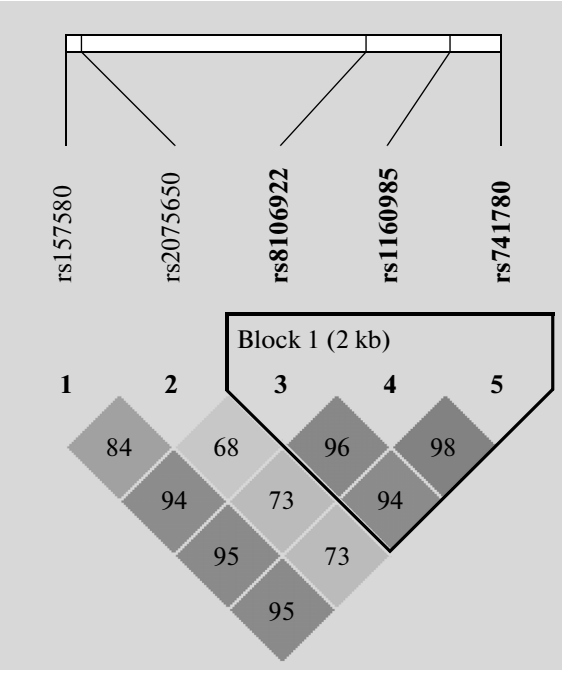
The associations of polymorphic variants of the *TOMM40* gene were analyzed with quantitative traits, such as total cholesterol content (TC), fractions of cholesterol in lipoproteins of high (HDL) and low density (LDL), triglycerides (TG), and serum glucose using standard test systems produced by Thermo Fisher Scientific (Finland) on a Konelab 30i biochemical analyzer. The cholesterol content in the fractions of lipoprotein, triglycerides, and glucose was determined based on the clinical diagnostic laboratory of the Research Institute for Complex Issues of Cardiovascular Diseases, Siberian Branch, Russian Academy of Medical Sciences, Kemerovo. These figures are known risk factors for cardiovascular diseases. In addition, the associations of polymorphic variants of the *TOMM40* gene with levels of systolic (SBP) and diastolic (DBP) blood pressure were analyzed.

The correspondence between the observed distribution of frequencies of genotypes and the theoretically expected Hardy–Weinberg equilibrium distribution was assessed using the χ^2 criterion, and the differences in frequencies of genotypes and alleles between different populations were assessed by χ^2 with Yates' correction for continuity [13]. The correspondence of the distribution of the values of quantitative traits in the studied sampling to normal distribution was assessed using the Kolmogorov-Smirnov test. A comparison of the mean values of quantitative traits in subgroups of individuals with different genotypes was carried out using single-factor ANOVA or nonparametric Mann–Whitney and Kruskal–Wallis tests. Statistical processing was carried out using the Statistica software package for Windows, v. 6.0. Linkage disequilibrium was assessed using the coefficient of Lewontin *D'* and Pearson's correlation coefficient r^2 using the HaploView program 4.2 [14].

RESULTS

For all of the studied polymorphic variants of the *TOMM40* gene, the correspondence of the empirical distribution of frequencies of genotypes to the theoretically expected Hardy–Weinberg equilibrium distribution was observed (Table 2). All of them are characterized by a high level of polymorphism. The minimum level of the observed heterozygosity was 0.33 ± 0.03 for locus rs2075650, and maximum was 0.45 ± 0.04 for locus rs1160985.

The frequency distribution of genotypes and alleles in ethnic Russians (inhabitants of the city of Kemerovo) was compared with that of the populations of other nations of Caucasoid and Mongoloid origin, for which the frequency spectrum of alleles of the *TOMM40* gene was presented in the 1000 Genomes project [15] (Table 3). It was found that the sampling of Russians was statistically significantly different from that of Italians and British in terms of the frequencies of alleles and genotypes of polymorphic variant rs2075650. The *G**rs2075650 allele is identified at a higher rate (21%) in Russians compared to that of



Structure of linkage disequilibrium of five polymorphic loci of *TOMM40* gene in Russians of Kemerovo.

Table 2. Distribution of allele frequencies of polymorphic variants of *TOMM40* gene from Russian residents of Kemerovo

Polymorphism	Rare allele frequency, %	$H_e \pm$ s.d.	$H_o \pm$ s.d.	D	χ^2, $d.f. = 1$	p
rs741780	*C* (45.1)	0.49 ± 0.01	0.44 ± 0.04	–0.119	2.69	>0.05
rs2075650	*G* (20.9)	0.33 ± 0.03	0.33 ± 0.03	+0.004	0.003	>0.05
rs1160985	*T* (45.7)	0.49 ± 0.01	0.45 ± 0.04	–0.099	1.87	>0.05
rs157580	*G* (31.4)	0.43 ± 0.02	0.40 ± 0.04	–0.061	0.70	>0.05
rs8106922	*G* (40.4)	0.48 ± 0.01	0.44 ± 0.04	–0.078	1.14	>0.05

H_e and H_o are the theoretically expected and observed heterozygosity, correspondingly; s.d. is standard deviation; D is relative deviation of the observed heterozygosity from expected; χ^2 criterion was used to assess whether the observed distribution of genotypes corresponds to the Hardy–Weinberg equilibrium; *d.f.* is number of degrees of freedom; p is level of significance.

British (12.4%, $p = 0.018$) and Italians (9.7%, $p = 0.001$). There are statistically significant differences in frequencies of alleles of the polymorphic variant rs157580 in Russians compared to the sampling of people in the United Kingdom. When comparing Russians and populations of Mongoloid origin, differences were revealed between them in allele and genotype frequencies of all of the studied polymorphic loci of the *TOMM40* gene (Table 3).

In the study of the linkage disequilibrium of polymorphic variants of the *TOMM40* gene, it was shown that the values *D'* were close to one for polymorphisms rs1160985 and rs741780. The haplotype block length of more than 2 kb was isolated, including the polymorphic variants rs8106922, rs1160985, and rs741780 (figure). The pattern of linkage disequilibrium obtained by analyzing the frequencies of the studied polymorphisms presented in the 1000 Genomes project for European populations (Finns and British) was the same, i.e., these variants are also closely linked [15].

In analyzing the association of polymorphic variants of the *TOMM40* gene with quantitative traits showed no statistically significant differences in the content of total cholesterol, HDL cholesterol and glucose levels between the groups of carriers of different genotypes in terms of the genetic variants studied. It was shown that, in Russians, three polymorphic variants (rs741780, rs1160985, and rs8106922) are associated with the content of triglycerides in the blood serum, and the TG level in carriers of the heterozygous genotypes *TC**rs741780, *CT**rs1160985, and *AG**rs8106922 was higher than in carriers of homozygous genotypes (Table 4).

When analyzing associations that take into consideration the gender identity of persons surveyed, it was showed that, in the subgroup of men, the polymorphic variant rs2075650 is associated with the content of LDL cholesterol in the blood serum ($p < 0.001$). In the sampling of men with the *AG**rs2075650 genotype, there were higher levels of LDL-C (5.23 ± 0.72 mmol/L) than among men with the *AA**rs2075650 genotype (3.86 ± 1.16 mmol/L) (Table 5). No associations with the content of cholesterol in the blood serum lipoprotein fractions in women were found for any of the studied variants of the *TOMM40* gene. The association of the polymorphic variant rs741780 with the TG level shown in the total sampling was also observed in the subgroups of men and women ($p = 0.036$ and 0.041, respectively) (Table 5).

The study identified the association of the polymorphic variant rs741780 with the level of diastolic blood pressure ($p = 0.034$). The highest values of diastolic blood pressure were observed in carriers of the heterozygous genotype *TC**rs741780 (80.7 ± 11.2 mm Hg (Table 4)). The mean DBP in carriers of the genotype *TT**rs741780 was 76.4 mm Hg. When analyzing the values of blood pressure in subgroups of men and women, it was found that statistically significant differences were only discovered in the subgroup of women (Table 5).

DISCUSSION

The study of variability of the five polymorphic loci of the *TOMM40* gene in the sampling relatively to healthy individuals showed that the frequencies of alleles and genotypes by polymorphic variants rs741780, rs1160985, and rs8106922 are within the values presented in the genetic databases for a number of Caucasoid populations [12, 15]. The frequencies of *G* allele and *GG* genotype of the rs2075650 locus in the studied sampling are statistically significantly higher than those described for the populations of Caucasoid origin. It is shown that, in terms of the frequency of the *G* allele of the polymorphic rs157580 variant, Russians (Kemerovo) differ from the residents of the UK. When comparing the results of this study with the data on the frequencies of alleles and genotypes of the studied markers in populations of Mongoloid origin, significant differences were found in terms of all polymorphic variants.

The *TOMM40* gene is actively being studied in relation to Alzheimer's disease [16, 17]. It has been shown that the polymorphic rs157580, rs2075650, and rs11556505 variants of the *TOMM40* gene are associated with the age of the onset of the disease.

Table 3. Frequency distribution of genotypes and alleles by polymorphic variants of *TOMM40* gene in Russians of Kemerovo and in subpopulations of nations of Caucasoid and Mongoloid origin

SNP	Genotype, allele	Frequency distribution of genotypes and alleles*										
		Kemerovo	GBR	*p*	TSI	*p*	CHB	*p*	CHS	*p*	JPT	*p*
rs741780	*CC*	44 (33.0)	14 (15.7)		25 (25.5)		11 (11.3)		5 (5.0)		9 (10.1)	
	CT	82 (43.6)	48 (53.9)	0.216	49 (50.0)	0.340	40 (41.2)	**0.014**	43 (43.0)	**0.022**	32 (36.0)	<**0.001**
	TT	62 (23.4)	27 (30.3)		24 (24.5)		46 (47.4)		52 (52.0)		48 (53.9)	
	C	170 (45.1)	79 (42.7)	0.584	99 (50.5)	0.251	62 (32.0)	**0.002**	53 (26.5)	<**0.001**	50 (28.1)	<**0.001**
rs157580	*GG*	21 (11.2)	18 (20.2)		11 (11.2)		27 (27.8)		34 (34.0)		31 (34.8)	
	AG	76 (40.4)	39 (43.8)	0.057	52 (53.1)	0.096	56 (57.7)	<**0.001**	56 (56.0)	<**0.00**1	36 (40.4)	<**0.001**
	AA	91 (48.4)	32 (36.0)		35 (35.7)		14 (14.4)		10 (10.0)		22 (24.7)	
	G	118 (31.4)	75 (42.1)	**0.017**	74 (37.8)	0.136	110 (56.7)	**0.006**	124 (62.0)	<**0.001**	98 (55.1)	<**0.001**
rs2075650	*GG*	8 (4.2)	2 (2.2)		1 (1.0)		0 (0)		1 (1.0)		2 (2.2)	
	AG	62 (33.2)	18 (20.2)	**0.049**	17 (17.3)	**0.003**	22 (22.7)	**0.011**	14 (14.0)	<**0.001**	19 (21.3)	0.079
	AA	117 (62.6)	69 (77.5)		80 (81.6)		75 (77.3)		85 (85.0)		68 (76.4)	
	G	78 (20.9)	22 (12.4)	**0.018**	19 (9.7)	**0.001**	22 (11.3)	**0.005**	16 (8.0)	<**0.001**	23 (12.9)	**0.025**
rs1160985	*CC*	60 (31.9)	27 (30.3)		24 (24.5)		46 (47.4)		52 (52.0)		48 (53.9)	
	CT	84 (44.7)	49 (55.1)	0.165	49 (50.0)	0.432	40 (41.2)	**0.01**	43 (43.0)	<**0.001**	32 (36.0)	**0.001**
	TT	44 (23.4)	13 (14.6)		25 (25.5)		11 (11.3)		5 (5.0)		9 (10.1)	
	T	172 (45.7)	75 (42.1)	0.464	99 (50.5)	0.291	62 (32.0)	**0.002**	53 (26.5)	<**0.001**	50 (28.1)	<**0.001**
rs8106922	*GG*	34 (18.2)	12 (13.5)		20 (20.4)		3 (3.1)		0 (0)		7 (7.9)	
	AG	83 (44.4)	45 (50.6)	0.522	47 (48.0)	0.620	32 (33.0)	<**0.001**	35 (35.0)	<**0.001**	25 (28.1)	<**0.001**
	AA	70 (37.4)	32 (36.0)		31 (31.6)		62 (63.9)		65 (65.0)		57 (64.0)	
	G	151 (40.4)	69 (38.8)	0.780	39 (21.9)	0.372	38 (19.6)	<**0.001**	35 (17.5)	<**0.001**	39 (21.9)	<**0.001**

* Data were collected during the 1000 Genomes project in subpopulations of Caucasoid and Mongoloid origin: GRB (British in England and Scotland), English and Scots; TSI (Toscani in Italy), Italians; CHB (Han Chinese in Bejing, China), Chinese, residents of Beijing; CHS (Southern Han Chinese), Chinese from southern provinces; JPT (Japanese in Tokyo, Japan), Japanese.

Table 4. Results of analysis of associations of polymorphic variants of *TOMM40* gene with parameters of blood pressure, lipid profile, and glucose levels in blood serum

Locus	Genotype*	SBP, mm Hg	DBP, mm Hg	Glucose, mmol/L	TC, mmol/L	LDL cholesterol, mmol/L	HDL cholesterol, mmol/L	TG, mmol/L
rs741780	*TT* (62)	120.2 ± 15.1	76.4 ± 10.3	5.99 ± 0.87	6.05 ± 1.69	4.25 ± 1.78	1.42 ± 0.51	1.78 ± 1.13
	TC (82)	124.0 ± 17.6	80.7 ± 11.2	5.69 ± 0.61	5.77 ± 1.53	3.97 ± 1.29	1.63 ± 0.50	2.29 ± 1.92
	CC (44)	120.1 ± 15.0	78.2 ± 10.4	5.41 ± 0.55	5.75 ± 1.68	4.28 ± 1.30	1.50 ± 0.44	1.26 ± 0.86
	p	0.226	**0.034**	0.087	0.519	0.667	0.152	**0.010**
rs2075650	*AA* (117)	120.9 ± 15.6	77.9 ± 11.0	5.65 ± 0.64	5.70 ± 1.56	4.03 ± 1.32	1.50 ± 0.49	1.75 ± 1.32
	GA (62)	121.9 ± 15.8	79.6 ± 10.5	5.76 ± 0.83	6.14 ± 1.70	4.47 ± 1.69	1.58 ± 0.50	1.96 ± 1.76
	GG (8)	136.3 ± 23.7	81.9 ± 11.3	6.08 ± 0.47	5.82 ± 1.73	2.88 ± 1.90	1.18 ± 0.46	1.50 ± 1.10
	p	0.215	0.509	1.000	0.357	0.325	0.650	0.536
rs1160985	*CC* (44)	120.1 ± 15.0	78.2 ± 10.4	5.41 ± 0.55	5.75 ± 1.68	4.28 ± 1.30	1.50 ± 0.44	1.26 ± 0.86
	CT (84)	123.9 ± 17.4	80.4 ± 11.2	5.69 ± 0.60	5.76 ± 1.51	3.98 ± 1.27	1.62 ± 0.50	2.26 ± 1.91
	TT (60)	120.3 ± 15.3	76.6 ± 10.3	5.99 ± 0.89	6.08 ± 1.72	4.25 ± 1.80	1.44 ± 0.52	1.81 ± 1.13
	p	0.257	0.059	0.100	0.619	0.682	0.229	**0.014**
rs157580	*AA* (91)	121.9 ± 16.3	79.1 ± 9.9	5.57 ± 0.68	5.84 ± 1.65	4.18 ± 1.33	1.62 ± 0.50	1.73 ± 1.62
	GA (76)	121.9 ± 17.3	78.6 ± 11.5	5.85 ± 0.67	5.96 ± 1.58	4.29 ± 1.162	1.44 ± 0.52	1.93 ± 1.35
	GG (21)	120.9 ± 12.7	77.1 ± 12.4	5.87 ± 0.90	5.50 ± 1.63	3.51 ± 1.48	1.50 ± 0.44	1.97 ± 1.38
	p	0.984	0.475	0.211	0.525	0.204	0.839	0.747
rs8106922	*AA* (34)	120.3 ± 14.7	78.2 ± 10.3	5.46 ± 0.59	6.03 ± 1.45	4.36 ± 1.36	1.50 ± 0.41	1.18 ± 0.51
	AG (83)	123.9 ± 17.6	80.5 ± 11.4	5.61 ± 0.58	5.67 ± 1.62	3.96 ± 1.27	1.58 ± 0.50	2.26 ± 1.96
	GG (70)	120.3 ± 15.2	76.8 ± 10.2	6.00 ± 0.83	5.98 ± 1.71	4.23 ± 1.72	1.47 ± 0.53	1.77 ± 1.10
	p	0.338	0.127	1.000	0.602	0.709	0.336	**0.028**

p is level of significance; DBP is diastolic blood pressure; SBP is systolic blood pressure; TC is total cholesterol; LDL cholesterol and HDL cholesterol are cholesterol within lipoproteins of low and high density, respectively; TG is triglycerides.

* Absolute value of frequency is given in parentheses; for Tables 4 and 5.

Table 5. Analysis of associations of polymorphic variants of *TOMM40* gene with blood pressure, lipid profile, and glucose levels in blood sera of men and women

Locus	Genotypes*	SBP, mm Hg	DBP, mm Hg	Glucose, mmol/L	TC, mmol/L	LDL cholesterol, mmol/L	HDL cholesterol, mmol/L	TG, mmol/L
rs2075650	Men							
	AA (38)	124.5 ± 11.6	83.0 ± 10.5	6.05 ± 0.77	5.26 ± 1.15	3.86 ± 1.16	1.21 ± 0.41	1.18 ± 0.69
	AG (21)	126.4 ± 18.9	82.6 ± 12.2	5.79 ± 0.49	5.93 ± 1.77	5.23 ± 0.72	1.28 ± 0.47	1.19 ± 0.68
	GG (3)	150.0 ± 26.5	86.7 ± 11.6	6.45 ± 0.64	4.65 ± 0.35	–	–	–
	p	0.077	0.862	0.347	0.149	**<0.001**	0.626	0.924
	Women							
	AA (79)	119.2 ± 17.0	75.5 ± 10.5	5.47 ± 0.48	5.92 ± 1.69	4.12 ± 1.41	1.65 ± 0.47	2.06 ± 1.47
	AG (41)	119.5 ± 13.6	78.1 ± 9.4	5.74 ± 1.01	6.23 ± 1.67	4.12 ± 1.89	1.71 ± 0.46	2.29 ± 1.99
	GG (5)	128.0 ± 20.2	79.0 ± 11.4	5.83 ± 0.12	6.29 ± 1.88	2.88 ± 1.90	1.17 ± 0.46	1.50 ± 1.10
	p	0.567	0.263	0.312	0.588	0.510	0.293	0.727
rs741780	Men							
	TT (24)	124.8 ± 16.9	80.2 ± 11.1	6.09 ± 0.89	5.96 ± 1.10	4.51 ± 1.15	1.19 ± 0.48	1.48 ± 0.79
	TC (25)	128.8 ± 16.4	85.2 ± 11.0	6.00 ± 0.61	5.17 ± 1.23	4.19 ± 1.27	1.26 ± 0.46	1.17 ± 0.64
	CC (13)	124.6 ± 13.1	84.2 ± 10.4	5.55 ± 0.21	5.18 ± 1.61	4.15 ± 1.27	1.27 ± 0.34	0.81 ± 0.22
	p	0.535	0.119	0.510	0.087	0.649	0.871	**0.036**
	Women							
	TT (38)	117.3 ± 13.2	73.9 ± 9.2	5.93 ± 0.89	6.11 ± 1.87	4.05 ± 2.14	1.58 ± 0.48	1.98 ± 1.28
	TC (57)	121.9 ± 17.8	78.7 ± 10.7	5.46 ± 0.51	6.04 ± 1.58	3.92 ± 1.30	1.74 ± 0.46	2.63 ± 2.03
	CC (31)	118.2 ± 15.6	75.7 ± 9.5	5.38 ± 0.59	5.98 ± 1.68	4.35 ± 1.34	1.62 ± 0.44	1.51 ± 0.98
	p	0.290	**0.039**	0.088	0.954	0.436	0.419	**0.041**

The symbols are the same as in Table 4. Dash means absence of genotypes.

Several recent papers have marked the association of polymorphic variants of the *TOMM40* gene [4, 8, 18] with risk factors for cardiovascular diseases, such as body mass index, blood pressure, and blood lipid profile. In particular, it was shown that the *G**rs2075650 allele is associated with lower values of the body weight (the association detected is characteristic for all races [19]); with an increasing concentration of total cholesterol [4]; apolipoprotein B, E; and also with increasing degree of liver fibrosis in patients with hepatitis C virus [20] and with a reduction in life expectancy [7]. The study of associations of the polymorphic loci of large spectrum of genes with 13 different biochemical parameters in a group of 20000 people, including twins, showed that the polymorphic rs2075650 locus of the *TOMM40* gene contributes to the variation in the content of HDL cholesterol, LDL cholesterol, C-reactive protein, and TG in the blood serum [5]. Interestingly, associations of this locus with the content of lipids and C-reactive protein are multidirectional, i.e., the carriage of the *G* allele predisposes individuals to the development of hyperlipidemia, but prevents the development of inflammatory processes.

An association was found between rs2075650 and the level of LDL cholesterol in men. The variability in the TG levels was associated with the rs741780, rs1160985, and rs8106922 variants of the *TOMM40* gene. Also, the association of the polymorphic rs741780 variant with the level of DBP in women was revealed.

Thus, the association of the polymorphic variant rs2075650 of the *TOMM40* gene with LDL-C was shown, which is consistent with the previously described data obtained from other populations. We have shown a number of new associations of the *TOMM40* gene polymorphic variants rs741780, rs1160985, and rs8106922 with TG, and rs741780 with DBP.

The studied polymorphic variants of the *TOMM40* gene are located in its intron regions. Presumably, these loci have a regulatory effect on the functional activity of the *TOMM40* gene and closely spaced genes encoding apolipoproteins. For example, in the study

by Bekris et al. [21], it was demonstrated that polymorphic variants of the *TOMM40* and *APOE* genes mutually influence promoter activity of each other. The single nucleotide polymorphisms selected in this study are linked to a poly-T repeat in intron 6 of the *TOMM40* gene. Different versions of the repeat length are associated with different ages of the manifestation of Alzheimer's disease [2, 22]. In the study of this disease, it has been shown that the product of the *TOMM40* gene (tom40) binds to the precursor protein of amyloid β, forms a stable complex, and hinders the transmembrane transport of precursor proteins of respiratory chain, thereby causing mitochondrial dysfunction [23]. The violation of mitochondrial transport, followed by mitochondrial dysfunction, may be one of the mechanisms that mediate associations of allelic variants of the studied gene with risk factors for cardiovascular disease.

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