International Heart and Vascular Disease Journal • Volume 9, № 32, December 2021

Journal of the Cardioprogress Foundation

LEADING ARTICLE

DOI 10.24412/2311-1623-2021-32-03-08

Genetic determinants of hypertriglyceridemia and cardiometabolic risks

Korneeva E.V.[1], Voevoda M.I.[2], Semaev S.E.[2], Maximov V.N.[2]

[1] Surgut State University, Surgut, Russia.

[2] The Institute of Internal and Preventive Medicine of the Federal Research Center Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russia.

Authors

Elena V. Korneeva*, Ph.D., docent of the Department of Internal Medicine of the Surgut State University, Surgut, Russia.

Mikhail I. Voevoda, doctor of medical science, professor, academician of the Russian Academy of Sciences, the Institute of Internal and Preventive Medicine of the Federal Research Center Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russia.

Sergey E. Semaev, junior researcher of the Laboratory of Molecular Genetics of Internal Diseases of the Institute of Internal and Preventive Medicine of the Federal Research Center Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russia.

Vladimir N. Maximov, doctor of medical science, docent, head of the Laboratory of Molecular Genetics of Internal Diseases of the Institute of Internal and Preventive Medicine of the Federal Research Center Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russia.

Summary

Objective. *To assess the combined effect of genetic associations on the development of hypertriglyceridemia as the risk factor for the development of cardiometabolic complications among young residents of the North.*

Materials and methods. *The study included 883 young participants who were examined between 2015 and 2020–749 patients had metabolic syndrome (MS), 134 — had no symptoms of MS. All the participants underwent anthropometric investigation, studies of lipid and carbohydrate metabolism, blood pressure (BP) monitoring. Using phenol-chloroform extraction genomic DNA was extracted from the peripheral blood of each individual. Gene polymorphism was assessed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) test. The following polymorphisms were studied: rs1378942 of the CSK gene, rs1801133 (C677T) of the MTHFR gene, ITGA2B, rs7903146 of the TCF7L2 gene, rs1799752 of the ACE gene.*

* Corresponding author. Tel. +7(922)252-6867. E-mail: evkorneeva39@rambler.ru

Results. *The prevalence of hypertriglyceridemia among all participants was 66.6 %, and 78.1 % among participants with MS. Hypertriglyceridemia was more common among the non-indigenous population, mainly among non-indigenous rural women (83.2 %). High levels of triglycerides were revealed in 56.2 % of the examined patients. More often hypertriglyceridemia was associated with heterozygous variants of the TG single nucleotide polymorphism rs1378942 of the CSK gene (50.7 %) (OR — 1.676, 95 % CI 1.268–2.214, p=0.142) and heterozygous variant rs1799752 of the ACE gene (52.2 %) (OR 0,54, 95 % CI 0.571–0.997, p=0.142). Patients with the combination of abdominal obesity and hypertriglyceridemia more often showed intergenic interactions of heterozygous genotypes ID of the ACE, ITGA2B gene, homozygous CC genotypes of TCF7L2 and MTHFR genes, heterozygous TG genotype of the CSK gene (47.4 %), the most common among rural female population and indigenous women (22.3 %).*

Conclusion. *The study revealed high prevalence of hypertriglyceridemia among study participants. Hypertriglyceridemia was associated with heterozygous TG variants of the single nucleotide polymorphism rs1378942 of the CSK gene and heterozygous rs1799752 variant of the ACE gene in the majority of patients with MS. The determination of genetic predictors of the hypertriglyceridemia will allow to timely identify individuals at increased cardiometabolic risk.*

Keywords: *hypertriglyceridemia, metabolic syndrome, genetic polymorphism.*

Conflict of interest: None declared.

Received: 29.07.2021 Accepted: 14.09.2021

Hypertriglyceridemia (hyperTG) is a defined as triglyceride (TG) levels>1,7 mmol/l. This condition is a common form of lipid imbalance in obesity, metabolic syndrome (MS), and type 2 diabetes (T2D). Today, hyperTG is considered a major risk factor (RF) of CVD and pancreatitis. According to our research, the prevalence of hyperTG is from 10 % to 30 % [1, 2]. The European Atherosclerosis Society recommends the following thresholds: mild and moderate hyperTG (2,0–9,9 mmol/l) and severe hyperTG (≥10,0 mmol/l) [3]. Mild and moderate hyperTG is associated with CV risk. Severe hyperTG develops due to monogenic mutations, is quite rare and can lead to pancreatitis [3]. HyperTG in adults is a multifactorial condition that involves both genetic and nongenetic factors. By now over 300 genetic loci that determine clinical phenotypes including hyperTG have been identified [1]. It is known that there are common and rare types of genetic factors that predispose to hyperTG. The types of these factors include mononucleotide variants and structural variations such as inclusion, deletion, and duplication of various parts of a gene or of a complete chromosome [4].

Therefore, the objective of this study was to evaluate the role of genetic factors in the development of hyperTG — a risk factor for cardiometabolic events in the young people of the North.

Materials and methods

This is a prospective study that was carried out in Fedorov City Hospital and Surgut City Clinic № 1 from 2015 to 2020 and included 883 people. Oh those, 749 had metabolic syndrome (MS). The mean duration of residency in the North was 27,9± 0,005 years. MS was diagnosed based on the 2009 Metabolic Syndrome Clinical Guidelines: the presence of three out of five metabolic disorders — increased waist circumference (over 80 cm in women and 94 cm in men), arterial hypertension (AH) (BP over 135 and 90 mmHg), hyperTG (≥ 1,7 mmol/l), decreased levels of low-density lipoproteins (LDL) (3,0 mmol/l), fasting hyperglycemia (≥ 6,1 mmol/l). Age characteristics of the groups are presented in Table 1.

Exclusion criteria were: exacerbation of any chronic condition, age< 18 years and>45 years, pregnancy.

TG levels were considered normal if<1,7 mmol/l (low CVD risk), intermediate — 1,7–2,2 mmol/l (moderate risk) and high —>2,3 mmol/l.

Molecular genetic testing was performed in the Research Institute of Internal and Preventive Medicine — an affiliated center of The Federal Research Center Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences. DNA was isolated from venous blood using the phenol–chloroform extraction technique. Gene polymorphisms were assessed using the polymerase chain reaction (PCR) with various restrictive fragments length [5]. We studied the following gene polymorphisms: rs1378942, CSK gene; rs1801133 (C677T) MTHFR gene; ITGA2B gene; rs7903146 TCF7L2 gene; rs1799752 ACE gene.

Table 1. **Age characteristics of the groups**

Parameters	Non-native population, n=601				Native population, n= 282	
	Urban population, n=247		Rural population, n=354			
	MS, n=211	No MS, n=36	MS, n=294	No MS, n=60	MS, n=244	No MS, n=38
Men	84	19	92	16	62	14
Age, years	37,6± 0,0009	36,5± 0,0001	37,4± 0,0008	39,9± 0,001	35,0± 0,0001	37,9± 0,003
Women	127	17	202	44	182	24
Age, years	35,7± 0,0002	39,4±0,004	36,4±0,0004	37,5± 0,003	36,1± 0,0004	39,0± 0,0001

Note. MS — metabolic syndrome.

Table 2. **The prevalence of hypertriglyceridemia in patients with MS**

Parameters		Men, n=238		Women, n=511		All	
		n	%	n	%	n	%
City	MS	62	73,8	99	78,0	161	76,3
	mmol/l	2,83± 0,04		2,75± 0,05		2,79± 0,05	
Rural area	MS	73	79,3	168	83,2	241	82,0
	mmol/l	2,67± 0,02		2,75± 0,003		2,71± 0,01	
The Khanty	MS	45	72,6	138	75,8	183	75,0
	mmol/l	2,77± 0,03		2,70± 0,004		2,74± 0,02	
All	MS	180	75,6	405	79,3	585	78,1
	mmol/l	2,76± 0,03		2,73± 0,019		2,75± 0,02	

Statistical analysis was performed using the SPSS 16.0 software. First, we assessed the frequencies of genotypes and alleles of the polymorphisms of interest in patients with MS and in control group. Secondly, we checked in the genotype frequencies followed the Hardy-Weinberg equilibrium using the χ^2 test. The risk of MS in the presence of a specific allele was calculated as the odds ratio (OR) using the Fisher exact test and Pearson's chi-squared test. Confidence interval (CI) was also calculated. P<0,05 was considered statistically significant [5].

Informed consents were obtained prior to participation.

Results

The prevalence of hyperTG was 66,6% (n=588); 78,1% (n=585) in patients with MS and 2,2% in individuals without MS. In healthy participants 3 individuals who lived in rural area (2 men and 1 women) and high levels of TG (m=1,9±0,001 mmol/l). In some non-native patients with MS the prevalence of hyperTG was by 4,6% higher compared with the natives — 79,6% (n=402) and 75,0% (n=183), respectively. The prevalence of hyperTG in rural population was by 5,7% higher than in the participants with MS who lived in the urban areas and by 7,0% higher than in the natives. HyperTG was also more prevalent in women (by 3,7%) in general and in some women living in rural areas (83,2%) (Table 2). Mean levels of TG in all groups were 2,75± 0,02 mmol/l (Table 2).

More than a half of all patients with MS (56,2%, n=421) had higher mean levels of TG (>2,3 mmol/l) that were associated with high risks of coronary artery disease (CAD). Non-native participants the prevalence of hyperTG>2,3 mmol/l was 58,8% (n=297) — 8,0% higher than in native people (50,8%, n=124). Intermediate levels of TG were identified overall in 21,9%. Of those, 29,8% were non-natives, and 24,2% were natives. TG<1,7 mmol/l were present in 25,0% of native and in 20,4% non-natives (Figure 1).

We have investigated intergenic associations of mononucleotide rs1378942 polymorphisms of CSK gene, rs1801133 (C677T) polymorphisms of MTHFR genes, TCF7L2 genes, rs7903146 ITGA2B genes, rs1799752 polymorphisms of ACE genes and their prevalence in patients with MS. The results of the genotypes and polymorphism alleles prevalence analysis in patients with MS are presented in Table 3. In most patients with MS hyperTG was associated with heterozygous TG variations of of mononucleotide rs1378942 polymorphism of CSK gene (n=278, 50,7%) (OR 1,676, 95% CI 1,268–2,214, p=0,142), heterozygous rs1799752 variant of gene ACE (n=286, 52,2%) (OR — 0,754, 95% CI 0,571–0,997, p=0,142). Mutations in G allele of CKS gene were identified in 45,3% of cases (OR — 1,210, 95% ДИ 0,009–0,086, p=0,027) and D allele in ACE gene in 52,6% of cases

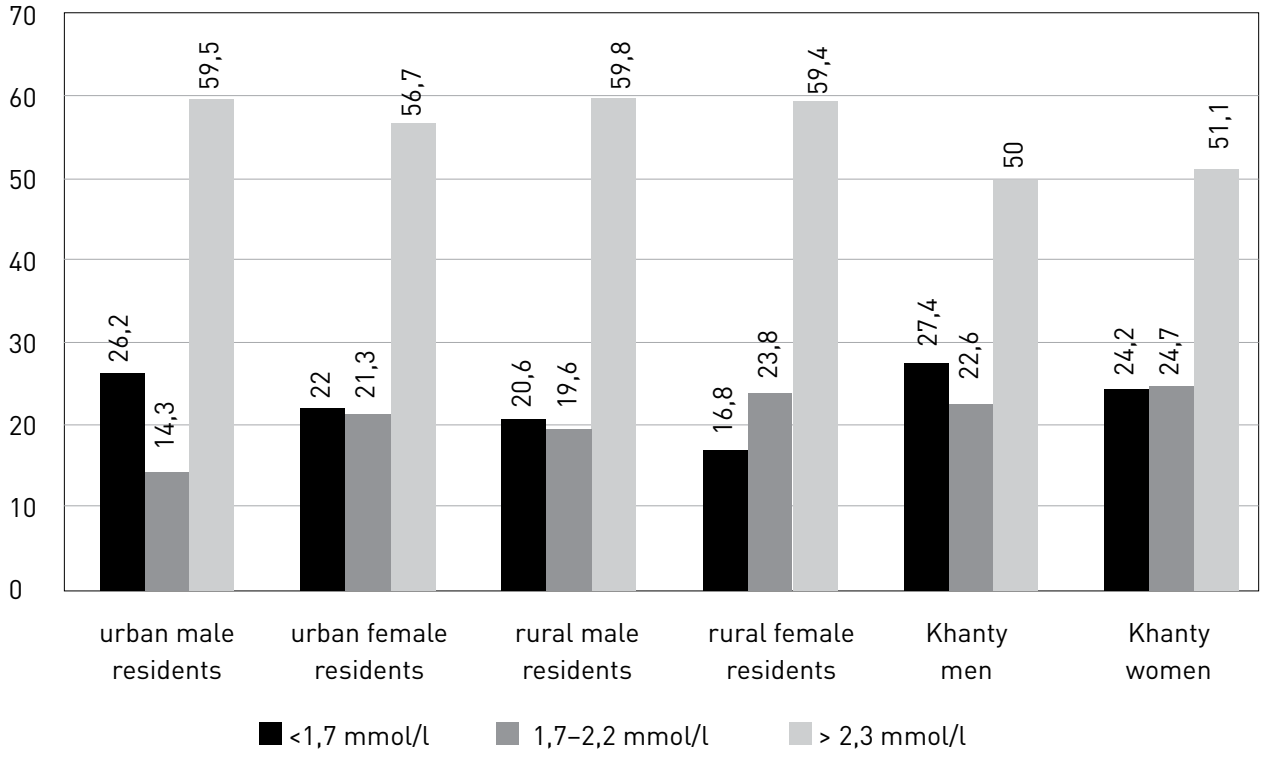

Figure 1. Coronary artery disease risks and mean triglyceride levels in patients with metabolic syndrome

(OR — 0,903, 95% ДИ 0,689–0,964, p=0,086). In patients with co-existent abdominal obesity and hyperTG heterogenous ID genotypes of ACE, ITGA2B gene, homozygous CC genotypes of TCF7L2 and MTHFR genes, heterozygous phenotype TG of CSK (47,4%), that were most prevalent in female rural (31,7%) and native (22,3%) population. The combination of mutant alleles in the homozygous genotypes of all the genes that we studied were identified in 31 patients with MS (5,7%). The prevalence was the same in urban and rural residents (22,6% respectively). The combinations of homozygous genotypes of ITGA2B and ACE, homozygous genotypes TT of CSK gene, heterozygous CT variants in MTHFR and TCF7L2 were identified in 26,4% patients with MS (n=145). They were present in more rural residents (32,4%) and native residents (22,8%) (Table 3).

Discussion

High prevalence of hyperTG in patients with MS (78,1%) that we identified in our study is confirmed by other authors (80%) [6].

Genetic causes of lipid imbalance such as hyperTG involve mutations of genes encoding metabolism and homeostasis.

Mutations of genes that play a role in the development of hyperglycemia and insulin resistance are the main cause of MS. Insulin resistance in obesity causes increased production of very-low-density lipoprotein (VLDL) and TG because of high levels of free fatty acids that activate insulin-dependent tissues. The insulin receptor is a type of tyrosine kinase receptor that triggers autophosphorylation of the tyrosine residues [7]. Insulin binds to the extracellular alpha subunit, and in the process stimulates the autophosphorylation of the beta subunit and the expression of tyrosine kinase activity [7]. Tyrosine-protein kinase phosphorylates tyrosine residues [8]. TCF7L2 gene inhibits liver gluconeogenesis and pancreatic beta-cell proliferation and causes hyperglycemia [9, 10]. A few studies have confirmed the association between T2D and mononucleotide rs7903146 polymorphisms of TCF7L2 genes [11].

Insulin is known to increase production of endothelial NO, canal sodium reabsorption and angiotensin-converting enzyme production and, therefore, vasodilation. Obesity and hyperinsulinemia are associated with increased sympathetic activation and RAAS activity that causes rise in blood pressure [12]. Angiotensive peptides are present in all cells and tissues and have local effects on RAAS. Activation of RAAS leads to decreased satiety, less weight loss and increased adipocyte proliferation causing obesity and lipid imbalance [13, 14]. Uchiyama et al [15] have shown that angiotensin II reduces lipoprotein lipase expression in visceral adipose tissue.

Table 3. **Mononucleotide polymorphisms in patients with MS and hypertriglyceridemia**

Polymorphism	Genotype	n	%	OR, 95% CI, p
CSK rs1378942	GG	109	19,9	1,676, 1,268–2,214, p=0,142
	TG	278	50,7	
	TT	161	29,4	
	Allele G	496	45,3	1,210, 0,009–0,086, p=0,027
	Allele T	600	54,7	
MTHFR rs1801133 (C677T)	CC	288	52,6	0,163, 0,077–0,147, p=0,107
	CT	201	36,7	
	TT	58	10,6	
	Allele C	777	71,0	0,408, 0,138–0,200, p=0,094
	Allele T	317	29,0	
ITGA2B	DD	76	13,9	0,178, 0,133–0,239, p=0,150
	ID	260	47,4	
	II	212	38,7	
	Allele D	412	37,6	0,363, 0,305–0,431, p=0,088
	Allele I	684	62,4	
TCF7L2 rs7903146	CC	347	63,3	0,060, 0,023–0,052, p=0,205
	CT	170	31,0	
	TT	31	5,7	
	Allele C	864	78,8	0,269, 0,059–0,089, p=0,072
	Allele T	232	21,2	
ACE rs1799752	DD	117	21,4	0,754, 0,571–0,997, p=0,142
	ID	286	52,2	
	II	145	26,4	
	Allele D	520	52,6	0,903, 0,689–0,964, p=0,086
	Allele I	576	47,4	

Note. CSK — C-terminal Src kinase gene, MTHFR — Methylenetetrahydrofolate reductase, ITGA2B — Integrin Subunit Alpha 2b, TCF7L2 — Transcription Factor 7 Like 2, ACE — angiotensin converting enzyme gene.

Insulin resistance in MS increases thrombogenesis and changes blood rheology and, therefore, has toxic effects on vascular wall. ITGA2B and MTHFR cause these effects. It leads to hyperhomocysteinemia and atherosclerotic changes in vascular wall.

The genes that we described in the current paper play a role in the development of hypeTG and MS and, therefore, their mutations predispose to cardiometabolic syndrome.

Conclusion

We have identified high prevalence of hypertriglyceridemia in all young people that we've examined (66,6%) and in 78,1% patients with metabolic syndrome. ACE, TCF7L2, ITGA2B, CSK, MTHFR gene polymorphism play a role in hyperTG that is usually associated with heterozygous TG variants of mononucleotide rs1378942 polymorphism of CSK gene and heterozygous rs1799752 variant of ACE gene.

Conflict of interest: None declared.

References

1. Carrasquilla, G.D., Christiansen, M.R., Kilpeläinen, T.O. The Genetic Basis of Hypertriglyceridemia. Current Atherosclerosis Reports. 2021; 23:39.
2. Simha V. Management of hypertriglyceridemia. BMJ. 2020; 371.
3. ESC/EAS Guidelines for the Management of Dyslipidaemis Russ J. Cardiol. 2017; 5 (145): 7–77.
4. Dron J.S., Hegele R.A. Genetics of Hypertriglyceridemia. Front Endocrinol (Lausanne). 2020; 24; 11:455.
5. Korneeva E.V., Voevoda M.I., Semaev S.E., Maksimov V.N. The role of intergenic interactions in the development of metabolic disorders among young inhabitants of the north. Modern problems of science and education. 2020; 2. Russian
6. Ford E.S., Li C., Zhao G., Pearson W.S., Mokdad A.H. Hypertriglyceridemia and its pharmacologic treatment among US adults. Arch Intern Med. 2009; 169:572–8.
7. Boytsov S.A., Strazhesko I.D., Akasheva D.U., Dudinskaya E.N., Kruglikova A.S., Tkacheva O.N. State Research Centre for Preventive Medicine. Moscow, Russia. Insulin resistance: good or bad? Development mechanisms and the association with age-related vascular changes. Cardiovascular Therapy and Prevention, 2013; 12 (4): 91–97. Russian
8. Meng Y., Roux B. Locking the active conformation of c-Src kinase through the phosphorylation of the activation loop. J. Mol. Biol.2014; 426(2): 423–435.

9. Yi F., Brubaker P.L., Jin T. TCF-4 mediates cell type-specific regulation of proglucagon gene expression by beta-catenin and glycogen synthase kinase-3 beta. J. Biol. Chem. 2005; 280 (2): 1457–1464.
10. Muendlein A., Saely C.H., Geller-Rhomberg S., Sonderegger G., Rein P., Winder T., Beer S., Vonbank A., Drexel H. Single nucleotide polymorphisms of TCF7L2 are linked to diabetic coronary atherosclerosis. PLoS One. 201; 6(3): e17978.
11. Melnikova E.S., Rymar O.D., Ivanova A.A., Mustafina S.V., Shapkina M.Yu., Bobak M., Malyutina S.K., Voevoda M.I., Maksimov V.N. Association of polymorphisms of genes TCF7L2, FABP2, KCNQ1, ADIPOQ with the prognosis of the development of type 2 diabetes mellitus. Therapeutic archive. 2020; 92 (10): 40–47. Russian
12. Muñoz A.M., Bedoya G., Velásquez C. An approach to the etiology of metabolic syndrome. Colomb. Med.2013; 44(1): 57–63.
13. Borghi C., Urso R., Cicero A.F. Renin-angiotensin system at the crossroad of hypertension and hypercholesterolemia.Nutr. Metab.Cardiovasc.Dis.2017;27(2): 115–120.
14. Shakhanova A.T., Aukenov N.E., Nurtazina A.U., Shakhanov T.E., Kozhakhmetova D.K. The relationship between insulin resistance and polymorphisms of genes for lipid metabolism and the renin-angiotensin-aldosterone system. Literature review. Science and health care. 2019; 4: 50–59. Russian
15. Uchiyama T., Tomono S., Sato K., Nakamura T., Kurabayashi M., Okajima F. Angiotensin II Reduces Lipoprotein Lipase Expression in Visceral Adipose Tissue via Phospholipase C β4 Depending on Feeding but Increases Lipoprotein Lipase Expression in Subcutaneous Adipose Tissue via c-Src. PLoS One. 2015;10(10): e0139638.