International Journal of Biomedicine 8(2) (2018) 134-138
http://dx.doi.org/10.21103/Article8(2)_OA5

INTERNATIONAL JOURNAL OF BIOMEDICINE

ORIGINAL ARTICLE

Pulmonology

Polymorphisms of Genes Involved in Endothelial Dysfunction in the Yakuts with COPD and Metabolic Syndrome

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Abstract

The aim of our research was to study the association of the -675 4G/5G (rs1799889) SNP of the SERPINE1 (PAI-1) gene and the Arg353Gln G>A (rs6046) SNP of the F7 gene with metabolic syndrome (MetS) in the Yakuts with COPD.

Methods and Results: A molecular-genetic examination was conducted in 200 COPD patients of Yakut ethnicity. The main group (MG) consisted of 100 COPD patients with MetS, the comparison group (CG) included 100 COPD patients without MetS. The distribution of genotypes of studied SNPs was in Hardy-Weinberg equilibrium in all cases. Studying the SERPINE1 -675 4G/5G SNP, we found the prevalence of a 4G allele in MG, compared to CG (OR=1.84, 95% CI 1.23 – 2.74; χ^2=9.06, *P*=0.003). Incidence of the homozygous 4G/4G mutation was rather high in MG, compared to CG (OR=2.35, 95% CI 1.24 – 4.44; χ^2=9.31, *P*=0.002). According to our data, the presence of MetS in Yakut patients with COPD has been associated with the carrier of the 4G/4G genotype. Studying the F7 Arg353Gln SNP, we found the prevalence of an Arg253 allele in both groups (0.72 in MG and 0.71 in CG; χ^2=0.01, *P*=0.91). The homozygous Gln353/Gln353 mutant genotype was rare in both groups (0.12 in MG and 0.10 in CG; OR=1.23, 95% CI 0.50–2.99; χ^2=0.01, *P*=0.92). In our study, the F7 Arg353Gln SNP was not associated with protection against MetS in COPD patients. **(International Journal of Biomedicine. 2018;8(2):134-138.)**

Key Words: SERPINE1 gene • F7 gene • metabolic syndrome • chronic obstructive pulmonary disease

Abbreviations

BMI, body mass index; **ED**, endothelial dysfunction; **F7**, coagulation factor VII; **MetS**, metabolic syndrome; **COPD**, chronic obstructive pulmonary disease; **PAI-1**, plasminogen activator inhibitor-1; **SNP**, single nucleotide polymorphism; **WC**, waist circumference.

Introduction

COPD is a major source of morbidity and mortality internationally.[1] In 1997, COPD was predicted to become the third leading cause of global death by 2020,[2] but a subsequent analysis found that COPD had become the third leading cause of global death by 2010.[3] According to Global Strategy For The Diagnosis, Management, And Prevention Of Chronic Obstructive Pulmonary Disease (GOLD, 2017), COPD has substantial manifestations beyond the lungs—the so-called systemic effects.[4] The chronic systemic inflammation that is linked to COPD may also initiate or exacerbate comorbid diseases, such as cardiovascular disease, osteoporosis, anemia, MetS, type 2 diabetes, lung cancer, and depression. It is one of the key mechanisms underlying these extrapulmonary effects.[5-7] The active involvement of the vascular endothelium in the inflammatory process is recognized in this disease.[8] Metabolic abnormalities like type 2 diabetes, obesity and MetS are common in COPD.[9] Obesity, physical inactivity, cigarette smoking, corticosteroid use, as well as inflammation and hypoxia, are mechanisms responsible for the development of MetS in COPD patients.[10-14]

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MetS is a prothrombotic condition as a result of ED and an imbalance between coagulation factors and substances regulating fibrinolysis.[15] It is known that the development of MetS is due to both environmental factors and genetic predisposition. An important point in the study of MetS is the identification of its characteristics in different ethnic groups, since the peculiarities of culture and lifestyle determine the genetic aberrations that lead to MetS development.[16] The study of genetic determinants in the development of MetS in COPD patients is of undoubted interest.

Currently, there are no data on the association of SNPs in genes, related to ED, in particular, -675 4G/5G insertion/deletion promoter polymorphism (rs1799889) of the SERPINE1 (PAI-1) gene and Arg353Gln polymorphism of the F7 gene, with MetS in Yakut people with COPD.

PAI-1 also known as endothelial plasminogen activator inhibitor, encoded by the SERPINE1 gene, is an inhibitor of fibrinolysis [17] and, as such, genetic mutations of SERPINE1 resulting in alterations in plasma levels or function of the expressed protein may be important determinants for COPD and MetS.

Previous studies have suggested that a single guanosine insertion/deletion (4G/5G) polymorphism in the promoter region is associated with circulating levels of PAI-1.[18] Studies carried out in different populations have consistently shown that individuals, homozygous for the 4G allele, have significantly higher plasma PAI-1 levels than those homozygous for the 5G allele.[19] This SNP is associated with the risk of insulin resistance and thrombosis formation.[20,21]

Factor VII (FVII), a vitamin K-dependent glycoprotein secreted by the liver, plays an important role in the initiation of coagulation by tissue factor.[22] Plasma FVIIc levels are regulated by environmental factors, such as age, BMI, dietary fat intake, plasma lipids, especially triglycerides, and diabetes,[23-25] and by a genetic component.[26,27]

The F7 Arg353Gln SNP located in exon 8 causes an exchange of arginine to glutamine, which in turn results in decreased FVII activity by 20% to 30%.[28-30] It has been suggested that the Gln353 allele protects against myocardial infarction.[28] Thus, presence of the Gln353 allele may consequently also be protective in other situations in which thrombus formation is a fundamental pathophysiological mechanism.

The aim of our research was to study the association of the -675 4G/5G (rs1799889) SNP of the SERPINE1 (PAI-1) gene and the Arg353Gln G>A (rs6046) SNP of the F7 gene with MetS in the Yakuts with COPD.

Materials and methods

A molecular-genetic examination of 200 COPD patients was conducted at the emergency department at the Republican Hospital No.2 in Yakutsk. The study was performed in the period between 2009 and 2013. The study was carried out within the framework of the project "Metabolic syndrome and chronic non-communicable diseases among the inhabitants of Yakutia" (State Project No. 11-01M.2009.). The study was approved by the Ethics Committee of the Yakut Science Center of Complex Medical Problems. Written informed consent was obtained from all patients.

Patients were divided into 2 groups. The main group (MG) consisted of 100 COPD patients (70 women and 30 men; mean age of 50.9±0.91 years) with MetS, the comparison group (CG) included 100 COPD (80 women and 20 men; mean age of 48.9±1.35 years) patients without MetS. All patients were of Yakut ethnicity and did not have kinship with each other.

Anthropometric parameters in MG and CG were as follows: BMI - 32.7±0.44 kg/m^2 and 23.2±0.35 kg/m^2, WC - 102.9±0.95 cm and 77.2±0.96 cm, HC - 108.7±1.84 cm and 93.5±0.98 cm, WC/HC ratio - 1.03±0.87 and 0.8±0.01, respectively. COPD diagnosis was based on the integral assessment of symptoms, medical history, health status, and spirometry values according to GOLD. MetS was diagnosed according to the IDF consensus criteria.[31] The patients filled out a questionnaire approved by the ethics committee, which contained questions on these blocks: socio-demographic characteristics, anamnestic data, heredity research, behavior and health, a validated questionnaire for assessing respiratory symptoms, and a symptom scale of COPD patients (Paggiaro PL, 1998).

Total cholesterol (TC), low-density cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were determined in plasma using biochemical analyzer Olympus AU 400 (Beckman Coulter, USA). Patients did not receive lipid-lowering treatment at the time of the examination.

DNA was isolated from peripheral blood leukocytes by a standard procedure based on phenol- chloroform extraction. Determination of gene polymorphism was performed by PCR using the Applied Biosystems amplifier and reagent kits SNP-Express (LITEH). DNA amplification for molecular detection of SNPs was performed by an allele-specific analysis. PCR products were analyzed on 2% agarose gel after staining with ethidium bromide and were visualized using a UV transilluminator.

Statistical processing and data analysis was carried out using the SPSS package (version 19). Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean±SD for continuous variables. The chi-square test was used to determine the deviation from Hardy-Weinberg equilibrium (HWE) (P>0.05) and the differences in genotypes and alleles between groups. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. We calculate ORs using multiplicative model for alleles and additive model for genotypes. Multiple comparisons were performed with one-way ANOVA and post-hoc Tukey HSD test. A probability value of P<0.05 was considered statistically significant.

Results and Discussion

The distribution of alleles and genotypes of studied SNPs in groups is shown in Table 1. The distribution of genotypes of studied SNPs was in Hardy-Weinberg equilibrium in all cases. Studying the SERPINE1 -675 4G/5G SNP, we found the prevalence of a 4G allele in MG, compared to CG (OR=1.84, 95% CI 1.23–2.74; χ^2= 9.06, P=0.003).

Table 1.

The distribution of alleles and genotypes of studied SNPs in MG and CG

Gene	Allele Frequency		OR (95% CI)	*P*-value	Genotype Frequency		OR (95% CI)	*P*-value
	MG (n=100)	CG (n=100)			MG	CG		
SERPINE1	5G: 77(0.38) 4G: 123(0.62)	5G: 107(0.54) 4G: 93(0.46)	0.54 (0.37-0.81) 1.84 (1.23-2.74)	0.003	5G/5G: 14(0.14) 4G/4G: 37(0.37) 5G/4G: 49(0.49)	5G/5G: 27(0.27) 4G/4G: 20(0.20) 5G/4G: 53(0.53)	0.44 (0.21-0.90) 2.35 (1.24-4.44) 0.85 (0.49-1.48)	0.002
F7	Arg353: 143(0.72) Cln353: 57(0.28)	Arg353: 142(0.71) Cln353: 58(0.29)	1.02 (0.66-1.58) 0.98 (0.63-1.50)	0.91	Arg353/Arg353: 55(0.55) Cln353/Cln353: 12(0.12) Arg353/Cln353: 33(0.33)	Arg353/Arg353: 52(0.52) Cln353/Cln353: 10(0.10) Arg353/Cln353: 38(0.38	1.13 (0.65-1.97) 0.80 (0.45-1.44) 1.23 (0.50-2.99)	0.92

Incidence of the homozygous 4G/4G mutation was rather high in MG, compared to CG (OR=2.35, 95% CI 1.24–4.44; χ^2=9.31, *P*=0.002). Thus, according to our data, the presence of MS in Yakut patients with COPD has been associated with the carrier of the 4G/4G genotype. Similar data were obtained by V.Khavinson.[32] Thus, the study showed that the presence of the 4G/4G genotype significantly correlated with systolic hypertension and hyperglycemia in the Russian population. Our data also agree with earlier studies performed in Turkey and Italy. Thus, according to results by Berberoğlu and colleagues,[33] in obese children, frequency of the 4G/4G genotype was more than the 4G/5G and 5G/5G genotypes in the PAI-1 gene. Sartori and colleagues showed that the 4G/5G polymorphism may influence PAI-1 expression in obesity, with a crucial role in central but not peripheral adiposity.[34]

Studying the F7 Arg353Gln SNP, we found the prevalence of an Arg253 allele in both groups (0.72 in MG and 0.71 in CG; χ^2=0.01, *P*=0.91). Allelic frequency of the Gln353 mutation was 0.28 and 0.29 in MG and CG, respectively (*P*=0.91). The homozygous Gln353/Gln353 mutant genotype was rare in both groups (0.12 in MG and 0.10 in CG; OR=1.23, 95% CI 0.50–2.99; χ^2=0.01, *P*=0.92). In our study, the F7 Arg353Gln SNP was not associated with protection against MetS in COPD patients.

An analysis of the association between components of MetS and the SERPINE1 -675 4G/5G SNP revealed significant differences in anthropometric parameters. The levels of BMI and WC were significantly greater in homozygous carriers of 4G/4G compared to carriers of 5G/4G and 5G5G genotypes (Table 2). Similar results were obtained in the study by Al-Hamodi et al.[35]: the Malaysian subjects with homozygous 4G/4G showed association with increased triglyceride levels (*P*=0.007), BMI (*P*=0.01) and diastolic blood pressure (BP) (*P*=0.03).

In our study, the F7 Arg353Gln SNP was not associated with MetS in COPD patients of the Yakut ethnic group. In study by A.Reiner et al.,[36] young-to-middle-aged women (US population) carrying a >or=1 copy of the low F7 expression level haplotype C (containing the -401T/-323del/-122C and Gln353 alleles) had a decreased BMI and an increased HDL-C level. According to a study by J.Pankow,[37] the Gln353 allele was associated with lower FVII coagulant activity in moderately obese adults, but obtained results did not support the hypothesis that the Arg-Gln353 polymorphism interacts with the plasma triglyceride level in determining FVIIc.

Table 2.

MetS components in COPD patients of MG depending on the SERPINE1 -675 4G/5G SNP

Variable	Genotype			Statistics
	5G/5G (n=14) [1]	5G/4G (n=49) [2]	4G/4G (n=37) [3]	
BMI, kg/m^2	25.8±0.83	27.8±0.59	29.3±0.79	F=3.5974 P=0.0311 P_{1-3}=0.0283
WC, cm	83.8±1.93	89.2±1.59	95.3±1.99	F=6.3574 P=0.0025 P=0.0037 P_{2-3}=0.0346
HC, cm	97.2±1.43	99.8±1.19	103.1±2.95	F=1.3449 P=0.2654
WC/HC	0.9±0.01	0.9±0.01	1.1±0.14	F=1.7155 P=0.1853
Heart rate, bpm	76.9±1.57	77.4±0.83	75.4±1.04	F=1.1869 P=0.3095
Systolic BP, mmHg	123.5±3.63	126.1±2.12	131.3±2.75	F=1.7928 P=0.1720
Diastolic BP, mmHg	75.1±1.79	76.6±1.19	80.0±1.39	F=2.6121 P=0.0785
Glucose, mmol/l	5.3±0.11	5.2±0.07	5.4±0.16	F=0.8575 P=0.4274
TC, mmol/l	4.9±0.18	5.3±0.12	5.3±0.14	F=1.4183 P=0.2471
LDL-C, mmol/l	3.1±0.12	3.4±0.09	3.5±0.12	F=1.9322 P=0.1504
HDL-C, mmol/l	1.3±0.04	1.4±0.04	1.4±0.07	F=0.5519 P=0.5777
TG, mmol/l	1.3±0.09	1.4±0.08	1.6±0.11	F=1.8720 P=0.1593

Conclusion

Thus, in the Yakut ethnic group, the SERPINE1 -675 4G allele was predominant in COPD patients with MetS compared to COPD patients without MetS (OR=1.84, 95% CI

1.23–2.74; χ^2= 9.06, *P*=0.003). Incidence of the homozygous 4G/4G mutation was rather high in COPD patients with MetS compared to COPD patients without MetS (OR=2.35, 95%CI 1.24–4.44; χ^2=9.31, *P*=0.002). The levels of BMI and WC were significantly greater in homozygous carriers of 4G/4G compared to carriers of the 5G/4G and 5G5G genotypes. The homozygous F7 Gln353/Gln353 mutant genotype was rare in COPD patients with and without MetS (0.12 in MG and 0.10 in CG; OR=1.23, 95% CI 0.50–2.99; χ^2=0.01, *P*=0.92). The F7 Arg353Gln SNP was not associated with protection against MS in COPD patients of the Yakut ethnic group.

Conflict of interest

The authors declare that they have no conflicts of interest to disclose.

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