GENETICS

Arg25Pro Polymorphism of Transforming Growth Factor-β_1 and Its Role in the Pathogenesis of Essential Hypertension in Russian Population of the Central Chernozem Region

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We studied the relationship between Arg25Pro polymorphism of *TGFb1* gene and predisposition to essential hypertension in the Russian population of Central Chernozem Region (n=402). An association was found between 25Pro allele and 25ArgPro genotype with low risk of essential hypertension in male individuals.

Key Words: *essential hypertension; DNA polymorphism; transforming growth factor-β_1; analysis of association*

Transforming growth factor β_1 (TGF-β_1) is a multifunctional cytokine regulating various biological processes, *e.g.* cell proliferation and differentiation, cell adhesion, cell-cell signaling, production and degradation of extracellular matrix proteins, *etc.* [2,6]. Numerous biological effects of TGF-β_1 attracted much attention of cardiologists investigating etiology and pathogenesis of essential hypertension (EH) [3-5,7,8]. Activity and expression of TGF-β_1 greatly varies in individuals in various populations of the world. This can be explained by the presence of single-nucleotide polymorphic sites in the corresponding gene. Some functionally important polymorphisms were described, *e.g.* nucleotide substitution 74G→C in exon 1 resulting in substitution of arginine (Arg) with proline (Pro) in position 25 of the animo acid sequence of TGF-β_1 [1-4,7]. Foreign investigators demonstrated a relationship between Arg25Pro polymorphism of *TGFb1* gene and the development of EH [3-5,8].

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Here we studied association of Arg25Pro *TGFb1* gene polymorphism with predisposition to EH in the Russian population.

MATERIALS AND METHODS

The main group comprised 200 individuals with EH, patients of Cardiological Departments of Kursk Regional Hospitals and Kursk Emergency Hospital. Control group comprised 202 healthy volunteers. All examinees were Russian, native of Central Chermozem Region of the Russian Federation. The main and control groups were sex- and age-matched (p>0.05). Venous blood was obtained from all examinees for genotyping of Arg25Pro *TGFβ1* gene polymorphism. Genomic DNA was isolated by phenol-chloroform extraction. Genotyping was performed using PCR and restriction analysis as described previously. PCR products were treated with AspS9I endonuclease (Sibenzim), separated in 2% agarose gel with ethidium bromide, and visualized in UV. Association of alleles and genotypes of *TGFβ1* gene

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with predisposition to ES was analyzed using χ^2 test and odds ratio (OR) at 95% confidence intervals (CI). The data were processed using Statistica 6.0 software ("StatSoft").

RESULTS

The genotype distributions of Arg25Pro *TGFβ1* polymorphisms in healthy individuals and EH patients corresponded to expected values of Hardy—Weinberg equilibrium ($p>0.05$). The frequencies of alleles and genotypes of Arg25Pro *TGFβ1* polymorphisms were similar in the groups of EH patients and healthy individuals (Table 1). However, comparative analysis of allele and genotype frequencies for men and women separately revealed associations of Arg25Pro polymorphic variants of *TGFβ1* gene with predisposition to EH (Table 2). For men, the frequency of the 25Pro allele in the group of EH patients was lower than in the control group (OR=0.31; CI=0.11-0.89; $p=0.03$). Moreover, the wild-type homozygous genotype was associated with the risk of EH development (OR=0.30; CI= 0.10-0.91; $p=0.04$). The heterozygous genotype was 2-fold less frequent in EH patients than in healthy individuals (OR=0.33; CI=0.11-0.99; $p=0.06$). In women, no association of alleles and genotypes of Arg25Pro *TGFβ1* polymorphism with predisposition to EH was found.

These findings confirm the protective value of 25Pro allele variant of *TGFβ1* gene in men for EH development in the studied population of Russians in Central Chernozem Region, which is consistent with the results obtained for other populations of the world [5,8]. It is well known that in carriers of wild-type 25ArgArg genotype of *TGFβ1* gene, the phenotypic effect is characterized by more pronounced expression of TGF-β_1 compared to carriers of heterozygous genotype 25ArgPro [1]. In light of this, the protective value of 25Pro allele for the risk

TABLE 1. Distribution of Frequencies of Alleles and Genotypes of Arg25Pro *TGFβ1* Polymorphisms in Groups of EH Patients and Healthy Individuals

Group	Arg25Pro *TGFβ1* allele frequency		Arg25Pro *TGFβ1* genotype frequency, *n* (%)		
	25Arg	25Pro	25ArgArg	25ArgPro	25ProPro
Control (*n*=202)	0.931	0.069	175	26	1
			(86.6)	(12.9)	(0.5)
EH patients (*n*=200)	0.948	0.053	179	21	0
			(89.5)	(10.5)	(0.0)
χ^2	0.99		0.79	0.55	0.00002

TABLE 2. Distribution of Frequencies of Alleles and Genotypes of Arg25Pro *TGFb1* Polymorphisms in Women and Men with EH and Healthy Individuals

Group	Arg25Pro *TGFβ1* allele frequency		Arg25Pro *TGFβ1* genotype frequency, *n* (%)		
	25Arg	25Pro	25ArgArg	25ArgPro	25ProPro
Men					
control (*n*=84)	0.899	0.101	68	15	1
			(81.0)	(17.9)	(1.2)
EH patients (*n*=65)	0.969	0.031	61	4	0
			(93.8)	(6.2)	(0.0)
χ^2	4.53		4.19	3.52	0.02
Women					
control (*n*=118)	0.953	0.047	107	11	0
			(90.7)	(9.3)	(0.0)
EH patients (*n*=135)	0.937	0.063	118	17	0
			(87.4)	(12.6)	(0.0)
χ^2	0.64		0.68	0.68	

of EH development is determined by less pronounced activation of *TGFβ1*. In carriers of 25ArgArg genotype, enhanced activity of TGF-β_1 can led to stimulation of endothelin-1 expression and release of renin and antiogensin II [4] mediating the hypertensive effects of TGF-β_1.

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