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Associations of Cytokines Genetic Polymorphisms with Hypertension Progress.

Irina Vasilyevna Krivoshei*, Snezhana Nikolaevna Milanova, Pyotr Konstantinovich Alpferov, Olga Alekseevna Efremova, Victor Aleksandrovich Ruzhenkov, and Alexey Valeryevich Polonikov.

Belgorod State National Research University, 85, Pobedy St., Belgorod, 308015, Russia.

ABSTRACT

The article presents results of comparative analysis of cytokines genes polymorphous variants occurrence among hypertension patients with burdened familial history regarding this disease and in a control group. It was revealed that genetic variants *-308A TNFα*, *+252G Ltα,+36G TNFR1*, *-308GA TNFα* and *+252AG Ltα* are associated with hypertension progress in case of persons with hereditary load.

Key words: hypertension, hereditary background, genetic polymorphism, cytokines.

Corresponding author

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INTRODUCTION

Hypertension is one of the most widespread cardiovascular diseases [1]. This is the most important factor of risk of progress of ischemic heart disease, cardiac insufficiency, and also such severe cardiovascular complications as myocardial infarction, acute cerebrovascular disease [2, 3]. According to the literature data, hypertensive patients with hereditary load can have disease progressed for 8 years earlier than people without burdened familial history [4].

One of significant components of vessels affection hypertensive process is a low-grade inflammation [5, 6]. A leading role in the low-grade inflammation progress belongs to a cytokine cascade [7] and also tumour necrosis factors, which have some biomedical effects which are pathogenetically significant for hypertension (proinflammatory, immunomodulatory, cytotoxic action, activation of hemostasis system, apoptosis induction etc.) [8, 9, 10]. At the same time results of works dedicated to involvement of genetic polymorphisms of tumour necrosis factors and their receptors into hypertension evolution are contradictory in different populations, and there are few such works in Russian Federation.

MATERIALS AND METHODS

The research group consisted of 736 individuals, of which 205 hypertensive patients with burdened familial history and 531 persons of the control group. Both subgroups comprised Russian inhabitants of Central Black Earth region of Russia, not related to each other. Patients were subsumed under a corresponding subgroup after diagnosing hypertension which was confirmed by clinical and laboratory instrumental examination technics. The control subgroup included individuals without cardiovascular diseases.

The group under research passed through genotyping of four polymorphous markers of cytokines genes - tumour necrosis factor α (*-308G/A TNFα*), lymphotoxin α (*+252A/G Ltα*), receptor of tumour necrosis factor of the 1 type (*+36A/G TNFR1*) and receptor of tumour necrosis factor of the 2 type (*+1663G/A TNFR2*).

As research material we used venous blood – 8-9 ml from a proband's median cubital vein. Extraction of genomic DNA from peripheral blood was performed with the help of standard methods [11]. Molecular genetic analysis of all loci was carried out with the help of the method of DNA synthesis polymerase chain reaction using oligonucleotide primers and probes [12, 13, 14, 15]. DNA-markers genotyping was performed with the help of the method of detection of TaqMan probes according to data on value of level of relative fluorescence of each probe, using the amplifier "CFX96" with real-time detection system. Associations of alleles and genotypes of the studied DNA-markers with hypertension progress of individuals with burdened familial history were estimated with the help of analysis of cross tables 2x2 calculating the criterion $\chi 2$ with Yates correction for continuity and odds ratio (OR) with 95% confidence intervals (CI).

RESULTS

We studied 205 hypertensive patients with hereditary load and 531 persons of the control subgroup. Main characteristics of the studied subgroups (hypertensive patients and control subgroup) are shown in table 1. The control subgroup is completely equatable with the hypertensive patients regarding sex, age, ethnicity and birth place. It should be noted that hypertensive patients with hereditary load had values of body mass index and arterial blood pressure level that were much higher than those of the control subgroup ($p<0.01$-0.001).

Table 1: Characteristics of the subjects from the case and control groups.

Characteristics	Cases	Controls
Total	205	531
Male	67,03%	67,04%
Female	32,96%	32,96%
Age, yrs	54,74±13,08	52,20±14,68
BMI, kg/m2	32,60±3,08	25,70±4,05
SBP, mm Hg	176.4 ± 26.5	126.1 ± 4.4
DBP, mm Hg	100.7 ± 14.0	81.6 ± 2.0

Study of population genetic characteristics of the genetic markers under research has shown (table 2) that in case of all studied loci, for both hypertensive patients and control subgroup, observed distribution of genotypical variants corresponds to the theoretically expected one under Hardy–Weinberg equilibrium (p>0.05) .

Table 2: Summary information about the studied polymorphisms.

Polymorphism	Studied groups	Minor allele	MAF (%)	HWE	
				χ^2	p
(-308)G/A TNFα (rs 1800629)	Case	*(-308) A TNFα*	2.44	1.70	>0.05
(-308)G/A TNFα (rs 1800629)	Control	*(-308) A TNFα*	1.32	0.00	>0.05
(+252)A/G Ltα (rs 909253)	Case	*(+252) G Ltα*	27.10	0.18	>0.05
(+252)A/G Ltα (rs 909253)	Control	*(+252) G Ltα*	26.93	1.48	>0.05
(+36)A/G TNFR1 (rs 767455)	Case	*(+36)A TNFR1*	46.02	0.80	>0.05
(+36)A/G TNFR1 (rs 767455)	Control	*(+36) A TNFR1*	49.72	1.18	>0.05
***(+**1663)A/G TNFR2 (rs 1061624)*	Case	***(+**1663)A TNFR2*	41.60	0.18	>0.05
***(+**1663)A/G TNFR2 (rs 1061624)*	Control	***(+**1663) A TNFR2*	45.20	0.40	>0.05

Notes: MAF, minor allele frequency; Hardy – Weinberg equilibrium. P values were calculated using the χ2 test.

It has been found that factors of hypertension progress risk for persons with hereditary load regarding this disease are alleles *-308A TNFα* (χ2=21.69, p=0.0005, OR=2.06, 95%Cl 1.51-2.83), *+252G Ltα* (χ2=30.44, p=0.0005, OR=1.96, 95%Cl 1.53-2.51)*,+36G TNFR1* (χ2=3.78, p=0.05, OR=1.26, 95%Cl 1.00-1.60) and genotypes -308*GA TNFα* (χ2=13.13, p=0.001, p_{cor}=0.003, OR=1.97, 95%Cl 1.35-2.86), *+252AG Ltα* (χ2=23.03, p=0.0005, p_{cor}=0.0015, OR=2.26, 95%Cl 1.60-3.18), and protective factors are genetic variants *-308GG TNFα* (χ2=19.10, p=0.0005, p_{cor}=0.0015, OR=0.45, 95%Cl 0.32-0.66), *+252AA Ltα* (χ2=36.40, p=0.0005, p_{cor}=0.0015, OR=0.34, 95%Cl 0.24-0.49).

SPECULATION

In our work we revealed involvement of tumour necrosis factors genes and their receptors into susceptibility to hypertension in case of individuals with burdened familial history. A significant role in susceptibility to hypertension in case of individuals with hereditary load is played by genetic variants *-308A TNFα, -308GA TNFα, +252G LTα, +252AG LTα, +36G TNFR1*, which are factors of risk of hypertension progress (OR>1.0), and also alleles and genotypes *-308G TNFα, -308GG TNFα, 252A LTα, +252AA LTα*, which have a protective impact during hypertension evolution (OR<1.0).

Pathogenetic significance of these cytokines genes for hypertension evolution among individuals with burdened familial history, which was revelead during our research, is coherent with the literature data on their biomedical effects in an organism (proinflammatory, cytotoxic action, endothelium dysfunction, activation of cardiomyocytes oxidative stress processes, apoptosis induction and so on) [8, 16, 17]. We should note the fact that the risk of hypertension progress among individuals with burdened familial history is increased by genetic variants *-308A TNFα, +252G LTα* (in the form of allele variants or in composition of genotypes *-308GA TNFα* and *+252AG LTα*), which, according to information in the literature, are highly productive [18, 19]. Due to this, hypertensive patients with highly productive alleles *-308A TNFα* and *+252G LTα* may have more expressed manifestations of their biomedical effects.

CONCLUSION

Thus, the work's results allow us to make a conclusion that there are following molecular genetic markers of a high risk of hypertension progress in case of individuals with burdened familial history: genetic variants *-308A TNFα* (OR=2,06), -308*GA TNFα* (OR=1,97), *+252G Ltα* (OR=1,96)*, +252AG Ltα* (OR=2,26), *+36G TNFR1* (OR=1,26), and there are such protective factors of hypertension evolution: genotypes *-308GG TNFα* (OR=0,45), *+252AA Ltα* (OR=0,34).

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