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## Studying the Impact of the Genetic Polymorphisms of Chemokines on the Arterial Pressure Level and Kidney Function in Patient with the Chronic Glomerulonephritis.

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### ABSTRACT

The associations of polymorphisms of the chemokine genes (+1931A/T *MIP1B*, A/G *I-TAC* (rs4512021), -403A/G *RANTES*, C/G *MCP1* (rs2857657), -801G/A *SDF1*) with arterial hypertension and renal insufficiency were investigated in 238 patients with chronic glomerulonephritis and 462 individuals of the control group. It has been established that the genetic marker A *I-TAC* (rs 4512021) is the risk factor for genesis of the severe arterial hypertension at the chronic glomerulonephritis (OR=1,65) and the genotypes AA and AG *I-TAC* are the risk factors of depression of the kidney function.

**Keywords:** chronic glomerulonephritis, arterial hypertension, glomerular filtration rate, creatinine rate, genetic polymorphism, chemokines.

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## INTRODUCTION

Chronic glomerulonephritis (CGN) is a multi-factor progressive kidney disease as the result of which a long-standing inflammatory process is developed which proceeds undulately which results in the genesis of sclerosis, hyalinosis, desolation of glomerular filtration function, genesis of the chronic kidney disease. [1,2].

Chronic glomerulonephritis more often than the other kidney disorders results is genesis of arterial hypertension (AH). There is a strong interrelation between arterial hypertension and kidney functional status. The failure of the kidney function lying in the insufficient sodium and water clearance rate is considered to be the most significant pathogenic link of the essential hypertension [3-5].

Among the immune factors of the CGN genesis an important role belongs the chemotactic factors (chemokines) that control migration of leucocytes of different kinds to the area of inflammation; activate the motile cells, have an impact on the production of anti-inflammatory cytokines. [6].

Therefore, the researchers demonstrate the increasing interest in the polymorphic chemokine genes in respect of the kidney disorders [7, 8, 9] referring them to the potential genetic glomerulopathy risk factors. In pursuance of the foregoing within this research there has been performed the study of the role of genetic chemokine polymorphisms (+1931A/T *MIP1B*, A/G *I-TAC* (rs4512021), -403A/G *RANTES*, C/G *MCP1* (rs2857657), -801G/A *SDF1*) in formation of arterial hypertension and depression of the kidney function in patients with chronic glomerulonephritis.

## MATERIALS AND PROCEDURES

There was performed analysis of polymorphisms of the chemokine genes in 700 persons: 238 patients with chronic glomerulonephritis and 462 persons of the control group (average age  $39,58 \pm 14,58$  years varying from 15 to 76 years) and 462 persons of the control group ( $42,20 \pm 6,28$  years varying from 18 to 79 years,  $p > 0,05$ ). The patient and control samplings included the Russian individuals born in the Central Black Earth Region of Russia and being unrelated against each other. The patients were included in a patients' group only after making the diagnosis confirmed by means of the clinical and laboratory and instrumental examination techniques. The clinical-laboratory examination of the patients was carried out on the basis of the nephrology department by the Belgorod Regional Clinical Hospital.

During the period of the blood sampling (surveying) when the patients were in inpatient treatment for the term from two to four weeks the blood pressure (BP) was measured daily. Further on at the outpatient stage the patients were keeping a diary of the blood pressure (BP) measurements with everyday blood pressure measurement carried out by themselves and examination by a nephrologist once a month within a period from 6 months up to 1 year. The AH criteria were systolic blood pressure (SBP)  $\geq 140$  mm Hg and/or diastolic blood pressure (DBP)  $\geq 90$  mm Hg. The AH was considered to be severe at BP  $\geq 160/100$  mm Hg in the course of treatment with antihypertensive drugs.

The general clinical examination of the patients included detailed study of the disease history, physical examination, complete blood count, common urine analysis with microscopic evaluation of urine sediment, determination of the daily proteinuria, blood biomedical measurement (total protein, albumin, protein fractions, creatinine, uric acid, urea, cholesterol), glomerular filtration rate (calculation according to the Cockcroft-Gault formula, 1976).

The exclusionary criteria for a group of the CGN patients were diabetes mellitus (in the patient's history or detected during examination), high blood pressure.

The venous blood (8-9 ml) taken from the median cubital vein of the proband was used as the test material. Extraction of the genomic DNA from the peripheral blood was performed with the use of standard methods [10].

Analysis of all the locuses was carried out by means of the polymerase chain reaction (PCR) method of the DNA synthesis with the use of the standard oligonucleotide primers and probes [11-13].

Genotyping assay of the DNA-markers was performed by means of the allelic discrimination analysis with the use of the TagMan probes. The associations of alleles and genotypes of the studied DNA-markers with arterial hypertension in patients with chronic glomerulonephritis were evaluated by means of the contingency table analysis 2x2 with calculation of the  $\chi^2$  criterion with Yates' correction for continuity and odd ratio (OR) with 95% confidence intervals (CI). By investigation of the figures of glomerular filtration rate and creatinine rate the median (Me) and interquartile range (Q25-Q75) was used, and for the comparative analysis – the Mann-Whitney test. («STATISTICA 6.0»).

### RESULTS

The analysis of rates of genotypes of the studied polymorphic gene markers has shown that no statistically significant differences have been detected by comparative analysis of the rates of alleles and genotypes of the investigated chemokine locuses between the patients with CGN and the control group (Table 1).

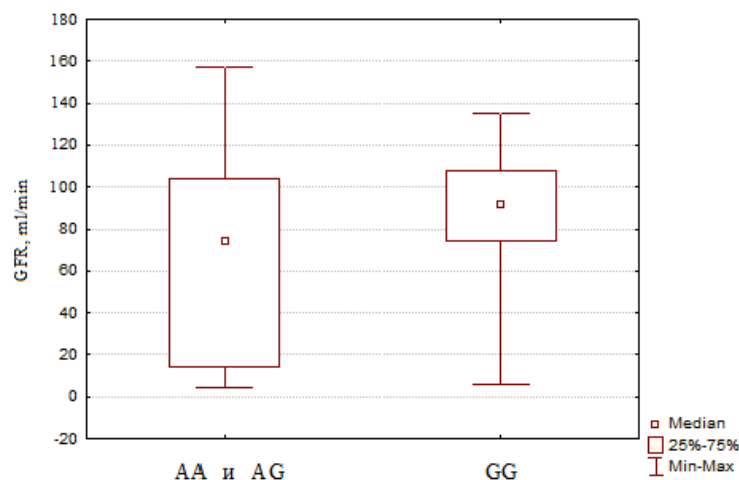
**Table 1: Summary information about the studied polymorphisms.**

Polymorphism	Studied groups	Minor allele	MAF (%)	HWE	
				$\chi^2$	p
(+1931)A/T <i>MIP1B</i>	Case	(+1931)A <i>MIP1B</i>	27.78	1.24	>0.05
(+1931)A/T <i>MIP1B</i>	Control	(+1931)A <i>MIP1B</i>	27.27	0.36	>0.05
A/G <i>I-TAC</i> (rs4512021)	Case	G <i>I-TAC</i> (rs4512021)	39.07	0.10	>0.05
A/G <i>I-TAC</i> (rs4512021)	Control	G <i>I-TAC</i> (rs4512021)	43.96	0.10	>0.05
(-403)G/A <i>RANTES</i>	Case	(-403)A <i>RANTES</i>	17.12	0.52	>0.05
(-403)G/A <i>RANTES</i>	Control	(-403)A <i>RANTES</i>	17.88	0.04	>0.05
C/ G <i>MCP-1</i> (rs2857657)	Case	G <i>MCP-1</i> (rs2857657)	18.86	0.67	>0.05
C/ G <i>MCP-1</i> (rs2857657)	Control	G <i>MCP-1</i> (rs2857657)	15.56	0.10	>0.05
(-801)G/A <i>SDF1</i>	Case	(-801)A <i>SDF1</i>	17.04	0.46	>0.05
(-801)G/A <i>SDF1</i>	Control	(-801) A <i>SDF1</i>	17.14	0.23	>0.05

Notes: MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium. P values were calculated using the  $\chi^2$  test.

By evaluation of the BP level in the course of disease the patients were divided into three groups: patients with the BP<140/90 mm Hg (84 persons – 36,2%), BP from 140/90 to 159/100 mm Hg (96 persons – 41,4%), BP>160/110 mm Hg (52 persons – 22,4%). It has been established that in patients with severe arterial hypertension (blood pressure 160/110 and more mm Hg) the concentration of the A *I-TAC* allele made 68,78% and is the highest as compares to the control group (56,04%, OR=1,65 95% CI 1,02-2,69,  $\chi^2=4,13$ , p=0,04).

By evaluation of the glomerular filtration rate (Fig.1) and creatinine rate (Fig.2) in patients with CGN depending in the genetic polymorphisms of chemokines there have been established the significant associations of these characteristics with the genetic polymorphism A/G *I-TAC* (rs 4512021).



**Figure 1: Associations of the genetic polymorphism A/G I - TAC (rs4512021) with the figures of the glomerular filtration in patients with CGN**

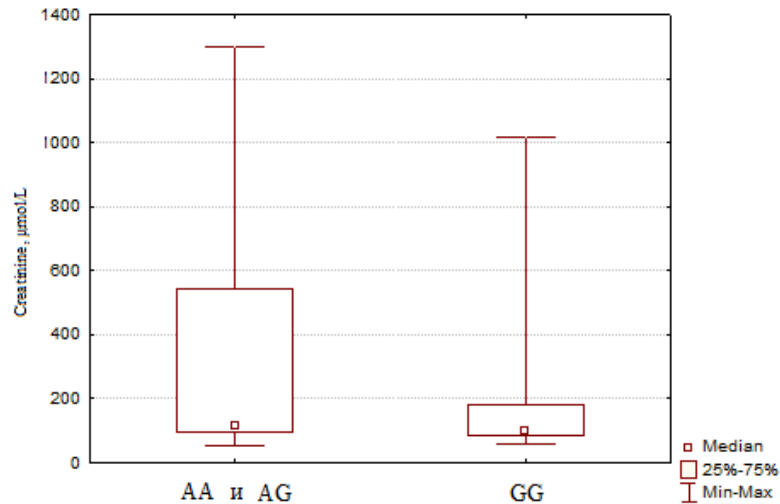


Figure 2: Creatinine rate in patients with CGN depending on the genetic polymorphism A/G I-TAC (rs 4512021)

It has been found out that the patients with CGN with the genotypes AA and AG *I-TAC* has a significantly lower indicator of the glomerular filtration (Me 74,0 ml/min, Q25-Q75 14,0-104,0 ml/min) and a higher creatinine rate (Me 119,0 µmol/l, Q25-Q75 94,4-541,0 µmol/l) as compared to the individuals with GG genotype (Me 92,0 ml/min, Q25-Q75 74,0-108,0 ml/min,  $p=0,047$  and Me 101,0 µmol/l, Q25-Q75 87,0– 81,0 ml/min,  $p=0,05$ , respectively).

### DISCUSSION

It has been found out that the polymorphic genetic marker A/G *I-TAC* (rs 4512021) has a pleiotropic effect on formation of an expressed arterial hypertension in the course of CGN, determines the reduction of the glomerular filtration rate and increase in the creatinine rate in patients with CGN.

The interferon chemokine the inducible  $\alpha$ -chemo attractant of the T-cells is not only a relevant chemotactic factor for T-lymphocytes but also has a significant role in activation of monocytes, natural killer cells in the inflammation area [12]. Its rate is regulated by interferon. The increase in concentration and activity of the separate leucocytes groups in the kidney glomerulus affected by the immune-inflammatory processes results in the enhanced production of the anti-inflammatory cytokines within the abnormal focus. The enhanced production of the cell response mediators, cytokines and growth factors provides the basis of the glomerulosclerosis genesis. By progressing not only in the affected but also in the remaining intact nephrons it causes the advance of glomerulonephritis and genesis of the chronic kidney disease [12, 13].

### CONCLUSIONS

Thus, the findings of the research allow deducing that the genetic marker A *I-TAC* (rs 4512021) is the risk factor in respect of progressing of the severe arterial hypertension in the course of the chronic glomerulonephritis (OR=1,65) and the AA and AG *I-TAC* genotypes are the risk factors that may cause depression of the kidney function.

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