Polymorphic locus rs1061624 of the TNFR2 gene is associated with the development of arterial hypertension in males

Aim
To study the involvement of cytokine polymorphic loci in development of arterial hypertension (AH) in men from the Central Black Earth region of Russia.

Materials and methods
821 men were evaluated, including 564 patients with AH and 257 individuals of the control group. Analysis of 8 cytokine mononucleotide polymorphisms (MNP) was performed using the real-time polymerase chain reaction with TagMan probes. Statistical analysis was performed with the STATISTICA (v.10.0) and PLINK (v.1.06) software. The regulatory potential of MNP was analyzed with the HaploReg (v.4.1) service (http://archive.broadinstitute.org).

Results
The rs1061624 TNFR2 polymorphic locus was associated with development of AH in men in recessive (odd ratio (OR), 0.33; 95% confidence interval (CI): 0.18–0.61, pperm=0.0004) and additive (OR, 0.50, 95% CI: 0.34–0.74, pperm=0.0006) genetic models and exerted a protective effect in development of AH. The rs1061624 MNP of the TNFR2 gene has a regulatory significance; it is located in the DNA sites hypersensitive to the action of DNAse 1 and in binding sites for transcriptional factors and histones that mark enhancers and promoters in different organs and tissues.

Conclusion
The rs1061624 TNFR2 gene polymorphism is involved in the development of AH in men of the Central Black Earth region of Russia.

Keywords
Arterial hypertension; cytokine genes; mononucleotide polymorphism

For citation
Moskalenko M.I., Ponomarenko I.V., Milanova S.N., Verzilina I.N., Efremova O.A., Polonikov A.V. Polymorphic locus rs1061624 of the TNFR2 gene is associated with the development of arterial hypertension in males. Kardiologiia. 2020;60(8):78–83. [Russian: Москаленко М. И., Пономаренко И. В., Миланова С. Н., Верзилина И. Н., Ефремова О. А., Полоников А. В. Полиморфный локус rs1061624 TNFR2 ассоциирован с развитием артериальной гипертонии у мужчин. Кардиология. 2020;60(8):78–83]

Corresponding author
Moskalenko M.I. E-mail: mariam31011989@yandex.ru

Introduction
Hypertension is the most common cardiovascular disease. Each year it causes fatal complications in more than 9.4 million people worldwide, Elevated blood pressure (BP) levels are registered in 1.13 billion people in the general population, of whom 52.8% are male [1].

The molecular mechanisms of hypertension are not fully understood. However, the latest data shows an essential pathogenetic role of non-specific inflammation [2, 3]. The endothelium is known to be involved in the initiation and development of vascular wall inflammation. The inflammatory cascade adversely affects the endothelium-dependent processes and the mechanical properties of arteries [4]. The inflammation process is inevitably accompanied by the active production of inflammation mediators, such as cytokines [5]. Cytokines are a large group of low-molecular-weight proteins that regulate inflammation, angiogenesis, non-specific protective reactions of the body, and induce cell growth and differentiation and tissue regeneration [6].

Previous studies have shown that cytokine gene polymorphic loci are involved in developing hypertension and its complications [7–10]. However, this issue requires further research.

Objective
To study the involvement of cytokine polymorphic loci in the development of hypertension in male patients in the Central Black Earth Region of Russia.

Material and Methods
The study included 821 male patients: 564 patients with hypertension and 257 control individuals. Male patients were included in the study after diagnosis of hypertension...
The polymorphic cytokine markers were analyzed by means of the Hardy-Weinberg equilibrium. The inclusion criteria in the hypertension group were systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg; the absence of symptomatic hypertension, hepatic and renal failure. Inclusion criteria in the control group were SBP <140 mm Hg and DBP <90 mm Hg, the absence of metabolic syndrome, autoimmune diseases, and cancer. The study included patients of Russian ethnic origin, native to the Central Black Earth Region of Russia, who were not related. Hypertension and control groups were formed between 2013 and 2016 in the Cardiology Department of the St. Joasph Belgorod Regional Clinical Hospital. The mean age of patients with hypertension was 57.60 ± 8.36 years, healthy individuals 57.54 ± 9.73 years, and comparable (Mann–Whitney U-test) (r=0.86). The clinical characteristics of the study groups have been described earlier [12]. It should be noted that of the patients with hypertension included in the study, 145 (25.71%) had a history of ischemic stroke, 24 (4.25%) had a myocardial infarction, and 69 (12.23%) had coronary artery disease. The study was carried out following the Good Clinical Practice and the Declaration of Helsinki. The Ethics Committee of the Medical Institute under the Belgorod State National Research University approved the study. All individuals included in the study were subjected to an informed consent.

All individuals included in the study were subjected to genotype assessment on the basis of eight cytokine gene loci: rs1061624 TNFR2, rs909253 TNFβ, rs1800629 TNFa, rs767455 TNFR1, rs833061 VEGFA, rs2981582 FGFR-2, rs6214 IGF-1, and rs1800469 TGFβ-1. The polymorphic loci were selected depending on their regulatory potential and influence on gene expression (http://archive.broadinstitute.org/haploreg.php).

Genomic DNA was isolated from the peripheral blood leukocytes in a standard phenol-chloroform extraction [13]. The polymorphic cytokine markers were analyzed by means of a polymerase chain reaction, DNA synthesis in a CF-96 Real-Time System (Bio-Rad, USA) using oligonucleotide primers and probes (OOO «Synthol», Russia). 100% reproducibility was registered in a repeat genotyping of 5% of samples randomly selected in the hypertension and control groups. Correspondence of the distribution of genotype and allele frequencies with the Hardy-Weinberg equilibrium was evaluated using the χ² test. The frequencies of genotypes and alleles in the study groups were analyzed in the 2×2 contingency tables and the Yates’ χ² test.

The results obtained were processed using STATISTICA for Windows 10.0. The Bonferroni amendment equal to 8 was made to correct the number of SNPs analyzed, after which rbonf≤0.006 was considered statistically significant. The nature of the associations of polymorphisms with hypertension was estimated using the odds ratio (OR), and its 95% confidence interval (95% CI). SNP associations with hypertension were analyzed using logistic regression analysis in three genetic models (dominant, recessive, additive) using the Plink 1.06 software (http://pngu.mgh.harvard.edu/~purcell/plink). An adaptive permutation test was performed to minimize false positives with rperm≤0.05 being statistically significant. The power of associations in the genetic models was analyzed using Quanto v.1.2.4 (http://biostats.usc.edu/Quanto.html) and a two-tailed test taking into account the prevalence of hypertension in the adult Russian population (40%), as well as the probability of a false positive equal to 5% (α=0.05). The regulatory potential of the cytokine polymorphic loci was analyzed in Haploreg v4.1 (http://archive.broadinstitute.org/haploreg.php).

Results and Discussion

For all cytokine polymorphic loci analyzed (p>0.05), the observed distribution of genotypes corresponded to the anticipated distribution in the Hardy-Weinberg equilibrium. The allele frequencies of the cytokine genes SNPs in patients with hypertension and the control group are presented in Table 1. The rs1061624 TNFR2 and rs909253 TNFβ differences were significant.

It was identified that allele A (OR=0.73) and genotypes AA (OR=0.65), GG (OR=1.51) of polymorphic locus rs1061624, and allele G (OR=0.79) and genotypes AG (OR=0.71), AA (OR=1.43) of locus rs909253 (r<0.05) were associated with hypertension in male patients. However, the differences remained significant after correction for multiple comparisons (rbonf≤0.006) only for allele A of rs1061624 of TNFR2 acting as a protective factor in the development of the disease (OR<1). The analysis showed no associations of rs1800629 TNFa, rs767455 TNFR1, rs833061 VEGFA, rs2981582 FGFR-2, rs6214 IGF-1, and rs1800469 TGFβ-1 with hypertension in male patients.

Results of the logistic regression analysis of the associations of cytokine genotypes with hypertension are provided in Table 2.

The rs1061624 TNFR2 polymorphism was shown to be associated with hypertension in male patients in the recessive (pperm=0.0004, power 57.21%) and additive (pperm=0.0006, power 83.08%) genetic models and has a protective effect in the development of the disease (OR=0.33–0.50).

According to the HaplReg (v4.1) database, the rs1061624 TNFR2 polymorphism is located in the DNA region hypersensitive to DNase-1 in stem cells and peripheral blood monocytes. This SNP is located in DNA fragments which bind to modified histones (H3K4me1 and H3K4me3) that label enhancers and promoters in 12 different organs and tissues. These include the peripheral...
blood cells, the heart, the brain, the digestive system, etc. rs1061624 was shown in the field of regulatory DNA motifs. Its allele A reduces the affinity to transcriptional factors BCL-disc9, Myc-disc10, NRSF-disc9, and VDR-2 (http://archive.brodinstitute.org/haploreg.php). The associations of rs1061624 with hypertension may be based on the established regulatory effects of this SNP and the general biological functions of the tumor necrosis factor type II. According to the GeneCards database, TNFR2 is synthesized in circulating T lymphocytes, endotheliocytes, macrophages and induces cell proliferation and migration. Tumor necrosis factor receptor type II and TNFR1 form a heterocomplex with ubiquitin ligase activity protecting cells from apoptosis by stimulating antioxidant pathways (http://www.genecards.org/).

The impaired production of TNFR2 and other cytokines was shown to aggravate endothelium-dependant vasodilation and induce the vasoconstrictor synthesis. This leads to the rigidity of the vascular wall and the retention of BP at high levels [14]. Shai et al. showed that an increase in the TNFR2 serum levels correlates with a high risk of myocardial infarction (OR=2.48, r=0.034) and coronary artery disease (OR=2.02, r=0.003) in the North American population [15].

| Table 1. Frequencies of alleles and genotypes of the cytokine gene polymorphic markers in male patients depending on the presence of hypertension (n = 821) |
|----------------------------------|----------------------------------|----------------------------------|
| rs1061624 TNFR2                  | Alleles, genotypes               | Male patients with hypertension (n = 564) | Male patients without hypertension (n = 257) | OR (95% CI) χ2, p     |
| A                                | 42.86%                           | 50.59%                          | 0.73 (0.59–0.90); χ2 = 8.47, p = 0.004* |
| GG                               | 32.14%                           | 23.83%                          | 1.51 (1.07–2.15); χ2 = 5.44, p = 0.02* |
| AG                               | 50.00%                           | 51.17%                          | 0.95 (0.70–1.30); χ2 = 0.06, p = 0.81 |
| AA                               | 17.86%                           | 25.00%                          | 0.65 (0.45–0.95); χ2 = 5.15, p = 0.02* |
| rs909253 TNFβ                    | G                                | 26.02%                          | 30.86%                          | 0.79 (0.63–0.99); χ2 = 4.12, p = 0.04* |
|                                  | AA                               | 56.16%                          | 47.26%                          | 1.43 (1.05–1.94); χ2 = 5.22, p = 0.02* |
|                                  | AG                               | 35.65%                          | 43.76%                          | 0.71 (0.52–0.71); χ2 = 4.55, p = 0.03* |
|                                  | GG                               | 8.19%                           | 8.98%                           | 0.91 (0.52–1.58); χ2 = 0.06, p = 0.81 |
| rs1800629 TNFa                   | A                                | 13.03%                          | 13.09%                          | 0.99 (0.73–1.35); χ2 = 0.01, p = 0.99 |
|                                  | GG                               | 75.89%                          | 75.78%                          | 1.01 (0.70–1.44); χ2 = 0.01, p = 0.99 |
|                                  | AG                               | 22.16%                          | 22.27%                          | 0.99 (0.69–1.43); χ2 = 0.01, p = 0.99 |
|                                  | AA                               | 1.95%                           | 1.95%                           | 0.99 (0.32–3.33); χ2 = 0.01, p = 0.99 |
| rs833061 VEGFA                   | T                                | 46.80%                          | 44.90%                          | 1.19 (0.87–1.33); χ2 = 0.51, p = 0.47 |
|                                  | GG                               | 30.02%                          | 30.20%                          | 0.99 (0.71–1.39); χ2 = 0.01, p = 0.99 |
|                                  | CT                               | 46.36%                          | 49.80%                          | 0.87 (0.64–1.18); χ2 = 0.70, p = 0.40 |
|                                  | TT                               | 23.62%                          | 20.00%                          | 1.24 (0.85–1.81); χ2 = 1.12, p = 0.29 |
| rs2981582 FGFR-2                 | C                                | 35.68%                          | 33.27%                          | 1.11 (0.89–1.39); χ2 = 0.89, p = 0.34 |
|                                  | TT                               | 40.57%                          | 46.46%                          | 0.79 (0.58–1.07); χ2 = 2.25, p = 0.14 |
|                                  | CT                               | 47.51%                          | 40.55%                          | 1.33 (0.97–1.81); χ2 = 3.14, p = 0.08 |
|                                  | CC                               | 11.92%                          | 12.99%                          | 0.91 (0.57–1.45); χ2 = 0.10, p = 0.75 |
| rs767455 TNFR1                   | G                                | 49.90%                          | 49.98%                          | 0.98 (0.84–1.28); χ2 = 0.13, p = 0.71 |
|                                  | AA                               | 24.37%                          | 22.66%                          | 1.04 (0.72–1.51); χ2 = 0.02, p = 0.88 |
|                                  | AG                               | 51.25%                          | 52.73%                          | 0.94 (0.69–1.28); χ2 = 0.10, p = 0.75 |
|                                  | GG                               | 24.38%                          | 24.61%                          | 0.98 (0.69–1.41); χ2 = 0.01, p = 0.99 |
| rs6214 IGF-1                     | A                                | 37.41%                          | 39.13%                          | 0.92 (0.75–1.15); χ2 = 0.44, p = 0.51 |
|                                  | GG                               | 39.46%                          | 35.58%                          | 1.18 (0.86–1.63); χ2 = 0.96, p = 0.33 |
|                                  | AG                               | 46.25%                          | 50.59%                          | 0.84 (0.62–1.14); χ2 = 1.15, p = 0.28 |
|                                  | AA                               | 14.29%                          | 13.83%                          | 1.04 (0.66–1.63); χ2 = 0.01, p = 0.95 |
| rs1800469 TGFβ-1                 | T                                | 34.94%                          | 34.45%                          | 1.02 (0.82–1.27); χ2 = 0.04, p = 0.85 |
|                                  | CC                               | 44.74%                          | 43.31%                          | 1.06 (0.78–1.44); χ2 = 0.09, p = 0.76 |
|                                  | CT                               | 40.64%                          | 44.49%                          | 0.85 (0.63–1.17); χ2 = 0.91, p = 0.34 |
|                                  | TT                               | 14.62%                          | 12.20%                          | 1.23 (0.77–1.96); χ2 = 0.66, p = 0.42 |

OR, odds ratio; CI, confidence interval; p, significance level, significant differences are marked with an asterisk.
Для предупреждения тромботических осложнений у пациентов с ОКС, которым проводится ЧКВ

Более выраженное действие по сравнению с клопидогрелом в снижении частоты ПКТ и ВКТ с 3-го года и до 450 дней

Среди пациентов, которым показан прасугрел (Эффицент®) 10 мг, нет отличий от терапии клопидогрелом 75 мг по риску «болливых» по классификации TIMI, не связанных с АКВ кровотечений

1. Данные отдельных исследований ведущих производителей

2. Средняя длительность терапии в группе высокого риска TIMI 30

3. Средняя длительность терапии в группе среднего риска TIMI 30

4. Средняя длительность терапии в группе низкого риска TIMI 30

5. Средняя длительность терапии в группе высокого риска TIMI 30

6. Средняя длительность терапии в группе среднего риска TIMI 30

7. Средняя длительность терапии в группе низкого риска TIMI 30

8. Средняя длительность терапии в группе высокого риска TIMI 30

9. Средняя длительность терапии в группе среднего риска TIMI 30

10. Средняя длительность терапии в группе низкого риска TIMI 30

11. Средняя длительность терапии в группе высокого риска TIMI 30

12. Средняя длительность терапии в группе среднего риска TIMI 30

13. Средняя длительность терапии в группе низкого риска TIMI 30

14. Средняя длительность терапии в группе высокого риска TIMI 30

15. Средняя длительность терапии в группе среднего риска TIMI 30

16. Средняя длительность терапии в группе низкого риска TIMI 30

17. Средняя длительность терапии в группе высокого риска TIMI 30

18. Средняя длительность терапии в группе среднего риска TIMI 30

19. Средняя длительность терапии в группе низкого риска TIMI 30

20. Средняя длительность терапии в группе высокого риска TIMI 30

21. Средняя длительность терапии в группе среднего риска TIMI 30

22. Средняя длительность терапии в группе низкого риска TIMI 30

23. Средняя длительность терапии в группе высокого риска TIMI 30

24. Средняя длительность терапии в группе среднего риска TIMI 30

25. Средняя длительность терапии в группе низкого риска TIMI 30

26. Средняя длительность терапии в группе высокого риска TIMI 30

27. Средняя длительность терапии в группе среднего риска TIMI 30

28. Средняя длительность терапии в группе низкого риска TIMI 30

29. Средняя длительность терапии в группе высокого риска TIMI 30

30. Средняя длительность терапии в группе среднего риска TIMI 30

31. Средняя длительность терапии в группе низкого риска TIMI 30

32. Средняя длительность терапии в группе высокого риска TIMI 30

33. Средняя длительность терапии в группе среднего риска TIMI 30

34. Средняя длительность терапии в группе низкого риска TIMI 30

35. Средняя длительность терапии в группе высокого риска TIMI 30

36. Средняя длительность терапии в группе среднего риска TIMI 30

37. Средняя длительность терапии в группе низкого риска TIMI 30

38. Средняя длительность терапии в группе высокого риска TIMI 30

39. Средняя длительность терапии в группе среднего риска TIMI 30

40. Средняя длительность терапии в группе низкого риска TIMI 30

41. Средняя длительность терапии в группе высокого риска TIMI 30

42. Средняя длительность терапии в группе среднего риска TIMI 30

43. Средняя длительность терапии в группе низкого риска TIMI 30

44. Средняя длительность терапии в группе высокого риска TIMI 30

45. Средняя длительность терапии в группе среднего риска TIMI 30

46. Средняя длительность терапии в группе низкого риска TIMI 30

47. Средняя длительность терапии в группе высокого риска TIMI 30

48. Средняя длительность терапии в группе среднего риска TIMI 30

49. Средняя длительность терапии в группе низкого риска TIMI 30

50. Средняя длительность терапии в группе высокого риска TIMI 30

51. Средняя длительность терапии в группе среднего риска TIMI 30

52. Средняя длительность терапии в группе низкого риска TIMI 30

53. Средняя длительность терапии в группе высокого риска TIMI 30

54. Средняя длительность терапии в группе среднего риска TIMI 30

55. Средняя длительность терапии в группе низкого риска TIMI 30

56. Средняя длительность терапии в группе высокого риска TIMI 30

57. Средняя длительность терапии в группе среднего риска TIMI 30

58. Средняя длительность терапии в группе низкого риска TIMI 30

59. Средняя длительность терапии в группе высокого риска TIMI 30

60. Средняя длительность терапии в группе среднего риска TIMI 30

61. Средняя длительность терапии в группе низкого риска TIMI 30

62. Средняя длительность терапии в группе высокого риска TIMI 30

63. Средняя длительность терапии в группе среднего риска TIMI 30

64. Средняя длительность терапии в группе низкого риска TIMI 30

65. Средняя длительность терапии в группе высокого риска TIMI 30

66. Средняя длительность терапии в группе среднего риска TIMI 30

67. Средняя длительность терапии в группе низкого риска TIMI 30

68. Средняя длительность терапии в группе высокого риска TIMI 30

69. Средняя длительность терапии в группе среднего риска TIMI 30

70. Средняя длительность терапии в группе низкого риска TIMI 30

71. Средняя длительность терапии в группе высокого риска TIMI 30

72. Средняя длительность терапии в группе среднего риска TIMI 30

73. Средняя длительность терапии в группе низкого риска TIMI 30

74. Средняя длительность терапии в группе высокого риска TIMI 30

75. Средняя длительность терапии в группе среднего риска TIMI 30

76. Средняя длительность терапии в группе низкого риска TIMI 30

77. Средняя длительность терапии в группе высокого риска TIMI 30

78. Средняя длительность терапии в группе среднего риска TIMI 30

79. Средняя длительность терапии в группе низкого риска TIMI 30

80. Средняя длительность терапии в группе высокого риска TIMI 30

81. Средняя длительность терапии в группе среднего риска TIMI 30

82. Средняя длительность терапии в группе низкого риска TIMI 30

83. Средняя длительность терапии в группе высокого риска TIMI 30

84. Средняя длительность терапии в группе среднего риска TIMI 30

85. Средняя длительность терапии в группе низкого риска TIMI 30

86. Средняя длительность терапии в группе высокого риска TIMI 30

87. Средняя длительность терапии в группе среднего риска TIMI 30

88. Средняя длительность терапии в группе низкого риска TIMI 30

89. Средняя длительность терапии в группе высокого риска TIMI 30

90. Средняя длительность терапии в группе среднего риска TIMI 30

91. Средняя длительность терапии в группе низкого риска TIMI 30

92. Средняя длительность терапии в группе высокого риска TIMI 30

93. Средняя длительность терапии в группе среднего риска TIMI 30

94. Средняя длительность терапии в группе низкого риска TIMI 30

95. Средняя длительность терапии в группе высокого риска TIMI 30

96. Средняя длительность терапии в группе среднего риска TIMI 30

97. Средняя длительность терапии в группе низкого риска TIMI 30

98. Средняя длительность терапии в группе высокого риска TIMI 30

99. Средняя длительность терапии в группе среднего риска TIMI 30

100. Средняя длительность терапии в группе низкого риска TIMI 30
There are few studies of the contribution of tumor necrosis factor receptor genes in the development of cardiovascular diseases. For example, Allen et al. studied the association of rs1061624 TNFR2 and rs4149570 TNFR1 with the development of coronary artery disease in the British population (n=430) although they did not find any significant associations (p>0.05) [10]. However, data has been published showing the association of TNFα polymorphisms with hypertension, with TNFα encoding tumor necrosis factor and acting through TNFR2. In the Asian population, Liaquat et al. established the associations of polymorphic marker -238G/A TNFα with cardiomyopathy in hypertension (p=0.01) [7], and Tong et al. showed that locus -308GA TNFα was involved in the development of ischemic stroke (p=0.03) [9]. Interestingly, Conen et al. found no associations of rs909253 TNFβ with hypertension in the American population (p=0.53) [16], which is consistent with our findings.

### Table 2. Associations of the genotypes of cytokine gene polymorphic loci with hypertension in male patients

| Polymorphic locus | Model   | Compared genotypes | OR (95% CI)               | p       | pperm   |
|-------------------|---------|--------------------|---------------------------|---------|---------|
| rs1061624 TNFR2   | Dominant| AG/GG vs AA        | 0.51 (0.27-0.96)          | 0.04    | 0.04    |
|                   | Recessive| GG vs AG/AA         | 0.33 (0.18-0.61)          | 0.0004  | 0.0004*  |
|                   | Additive| AG vs GG vs AA      | 0.50 (0.34-0.74)          | 0.0005  | 0.0006*  |
| rs909253 TNFβ     | Dominant| AG/GG vs AA        | 0.94 (0.56-1.55)          | 0.80    | 0.99    |
|                   | Recessive| GG vs AG/AA         | 0.67 (0.26-1.70)          | 0.40    | 0.41    |
|                   | Additive| AG vs GG vs AA      | 0.89 (0.60-1.33)          | 0.58    | 0.86    |
| rs1800629 TNFa    | Dominant| AG/GG vs AA        | 0.76 (0.43-1.35)          | 0.34    | 0.39    |
|                   | Recessive| GG vs AG/AA         | 0.23 (0.03-1.81)          | 0.16    | 0.19    |
|                   | Additive| AG vs GG vs AA      | 0.72 (0.42-1.23)          | 0.23    | 0.24    |
| rs833061 VEGFA    | Dominant| TC/TT vs CC        | 1.64 (0.95-2.84)          | 0.07    | 0.08    |
|                   | Recessive| TT vs TC/CC         | 1.67 (0.89-3.12)          | 0.11    | 0.12    |
|                   | Additive| TC vs TT vs CC      | 1.45 (1.02-2.07)          | 0.04    | 0.04    |
| rs2981582 FGFR-2  | Dominant| TC/TT vs CC        | 1.41 (0.85-2.34)          | 0.18    | 0.28    |
|                   | Recessive| TT vs TC/CC         | 1.17 (0.43-3.17)          | 0.76    | 0.99    |
|                   | Additive| TC vs TT vs CC      | 1.29 (0.85-1.94)          | 0.23    | 0.24    |
| rs767455 TNFR1    | Dominant| AG/GG vs AA        | 1.57 (0.86-2.85)          | 0.14    | 0.15    |
|                   | Recessive| GG vs AG/AA         | 1.21 (0.67-2.19)          | 0.53    | 0.55    |
|                   | Additive| AG vs GG vs AA      | 1.28 (0.88-1.85)          | 0.20    | 0.23    |
| rs6214 IGF-1      | Dominant| AG/GG vs AA        | 1.06 (0.63-1.78)          | 0.83    | 0.86    |
|                   | Recessive| GG vs AG/AA         | 0.75 (0.37-1.54)          | 0.43    | 0.48    |
|                   | Additive| AG vs GG vs AA      | 0.95 (0.66-1.38)          | 0.81    | 0.87    |
| rs1800469 TGFβ-1  | Dominant| TC/TT vs CC        | 0.90 (0.54-1.49)          | 0.68    | 0.70    |
|                   | Recessive| TT vs TC/CC         | 1.28 (0.58-2.85)          | 0.54    | 0.75    |
|                   | Additive| TC vs TT vs CC      | 1.00 (0.69-1.45)          | 0.99    | 0.99    |

Produced by Plink software; OR, odds ratio; CI, confidence interval; p, significance level, significant differences are marked with an asterisk.

**Conclusion**

We analyzed the involvement of cytokine gene polymorphisms in the development of hypertension in male patients. Significant associations of rs1061624 TNFR2 with hypertension were established in the recessive (OR=0.33) and additive (OR=0.50) genetic models. Single nucleotide polymorphism TNFR2 is characterized by high regulatory potential. It is located in DNA fragments hypersensitive to Dnase-1 and the fragments to which transcription factors and histones, labelling promoters and enhancers in various organs, bind.

**Funding**

This study was supported by a grant from the President of the Russian Federation for leading scientific schools of the Russian Federation (project NSh-2609.2020.7).

**No conflict of interest is reported.**

The article was received on 12/01/2020
REFERENCES

1. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M et al. 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: ESC/ESH Task Force for the Management of Arterial Hypertension. Journal of Hypertension. 2018;36(12):2284–309. DOI: 10.1097/HJH.0000000000001961

2. Pietri P, Vlachopoulos C, Tousoulis D. Inflammation and Arterial Hypertension: From Pathophysiological Links to Risk Prediction. Current Medicinal Chemistry. 2015;22(23):2754–61. DOI: 10.2174/0928673226615042104727

3. Sirotina S, Ponomarenko I, Kharchenko A, Bykanova M, Bocharova A, Vagytseva K et al. A Novel Polymorphism in the Promoter of the CYP4A11 Gene Is Associated with Susceptibility to Coronary Artery Disease. Disease Markers. 2018;2018:5812802. DOI: 10.1155/2018/5812802

4. Teixeira BC, Lopes AL, Macedo RCO, Correa CS, Ramis TR, Ribeiro JL et al. Inflammatory markers, endothelial function and cardiovascular risk, Jornal Vascular Brasileiro. 2014;13(2):108–15. DOI: 10.1590/jvb.2014.054

5. Zhao F, Zhang R, Zhao H, Liu T, Ren M et al. The role of TIMP1, TIMP2 and TIMP3 in the development of coronary artery disease. European Journal of Clinical Investigation. 2018;48(1):83–91. DOI: 10.1111/eci.13140

6. Levchenko A.S., Mezentseva O.Yu., Bushueva O.Yu., Vorobyova A.A., Freidin M.B., Polonikov A.V. Study of associations of polymorphism of matrix metalloproteinases genes with the development of arterial hypertension in men. Kardiologia. 2019;59(7S):31-9. DOI: 10.18087/cardio.59.7S-31-9

7. Lisakut A, Shauket U, Ahmad W, Javed Q. The tumor necrosis factor-α -238G/A and IL-6 -572G/C gene polymorphisms and the risk of idiopathic dilated cardiomyopathy: a meta-analysis of 25 studies including 9493 cases and 13,971 controls, Clinical Chemistry and Laboratory Medicine (CCLM). 2015;53(2):307–18. DOI: 10.1515/cclm-2014-0502

8. Ryvovanov A.V. Relationship between insulin-like growth factor-1 and indicators of the carbohydrate metabolism in patients with comorbidity of arterial hypertension and type 2 diabetes mellitus. Research Result. Medicine and Pharmacy. 2017;3(1):8–14. DOI: 10.1515/cclm-2014-0502

9. Tong Y, Geng Y, Xu J, Wang Z, Zhang Y, Lin L et al. The role of functional polymorphisms of the TNF-α gene promoter in the risk of ischemic stroke in Chinese Han and Uyghur populations: Two case–control studies. Clinica Chimica Acta. 2010;411(17–18):1291–5. DOI: 10.1016/j.cca.2010.05.007

10. Allen RA, Lee EM, Roberts DH, Park BK, Pirmohamed M. Polymorphisms in the TNF-alpha and TNF-receptor genes in patients with coronary artery disease. European Journal of Clinical Investigation. 2001;31(10):843–51. DOI: 10.1046/j.1365-2362.2001.00907.x

11. Britov A.N., Pozdnyakov Yu.M., Volkova E.G., Drapkina O.M., Egan Khan R.A., Kishyak O.A. et al. National recommendations of cardiovascular prevention. Cardiovascular Therapy and Prevention. 2011;10(6 S2):2–64. DOI: 10.1016/j.cca.2011.08.002

12. Moskalenko M.I., Milanova S.N., Ponomarenko I.V., Polonikov A.V., Churnosov M.I. Study of associations of polymorphism of matrix metalloproteinases genes with the development of arterial hypertension in women. Kardiologia. 2019;59(7S):31-9. DOI: 10.18087/cardio.59.7S-31-9

13. Moskalenko M.I., Ponomarenko I.V., Polonikov A.V., Churnosov M.I. Polymorphic locus rs652438 of the MMP12 gene is associated with the development of hypertension in women. Arterial Hypertension. 2019;25(4):60–5. DOI: 10.18705/1607-419X-2019-25-1-60-65

14. Konukoglu D, Uzun H. Endothelial Dysfunction and Hypertension. Advances in Experimental Medicine and Biology. 2017;956:511–40. DOI: 10.1007/5584_2016_90

15. Shai I, Schulze MB, Manson JE, Rexrode KM, Stampfer MJ, Manson C et al. A Prospective Study of Soluble Tumor Necrosis Factor-Receptor II (sTNF-RII) and Risk of Coronary Heart Disease Among Women with Type 2 Diabetes. Diabetes Care. 2005;28(6):1376–82. DOI: 10.2337/diacare.28.6.1376

16. Conen D, Cheng S, Steiner LL, Buring JE, Ridker PM, Zee RY. Association of 77 polymorphisms in 52 candidate genes with blood pressure progression and incident hypertension: the Women’s Genome Health Study. Journal of Hypertension. 2009;27(3):476–83. DOI: 10.1097/ HJH.0b013e28823104e8