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HUMAN GENETICS

The Role of Polymorphic Variants of Several Genes of Matrix Metalloproteinases and Their Tissue Inhibitors in the Development of Gastric Cancer

L. F. Gallyamova[a, *], A. Kh. Nurgalieva[a], I. I. Khidiyatov[b], T. R. Nasibullin[c], F. R. Munasypov[d], Sh. M. Khusnutdinov[d], R. R. Rakhimov[d], R. R. Abdeev[d], D. D. Sakaeva[b], and E. K. Khusnutdinova[a, c]

[a] *Bashkir State University, Ufa, 450076 Russia*
[b] *Bashkir State Medical University, Ufa, 450008 Russia*
[c] *Institute of Biochemistry and Genetics of the Ufa Federal Research Center of the Russian Academy of Sciences, Ufa, 450054 Russia*
[d] *Republican Clinical Oncology Dispensary, Ufa, 450054 Russia*
**e-mail: liliyagallyamova@mail.ru*

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Abstract—The main function of matrix metalloproteinases is the degradation of the extracellular matrix and participation in signal transduction. In addition, it is known that they are involved in all stages of the progression of the tumor process. The activity of metalloproteinases can be regulated by interactions with specific inhibitors of matrix metalloproteinases, so the latter are also able to participate in tumor growth. The genes of matrix metalloproteinases and their inhibitors, as well as many other genes, are characterized by polymorphism. We have analyzed the frequency distribution of the alleles and genotypes of the polymorphic loci rs1799750 and rs494379 of the *MMP1* gene, rs2285053 of the *MMP2* gene, rs3025058 of the *MMP3* gene, rs3918242 and rs17576 of the *MMP9* gene, rs2276109 of the *MMP12* gene, rs8179090 of the *TIMP2* gene, and rs9619311 of the *TIMP3* gene in 314 patients with gastric cancer, as well as in 339 unrelated healthy individuals from the Republic of Bashkortostan. It was shown that the markers of the increased risk of developing gastric cancer are the genotypes rs1799750**1G/2G* of the *MMP1* gene and rs2276109**A/A* of the *MMP12* gene for Tatars and the genotype rs9619311**T/T* of the *TIMP3* gene for Russians. The association of the rs494379**G* allele of the *MMP1* gene and increased risk of developing malignant tumors of the stomach were reported in men. Using the APSampler algorithm, we identified combinations of alleles/genotypes associated with an increased and a reduced risk of developing gastric oncopathologies. The data obtained confirm the influence of the studied polymorphic variants of the genes of matrix metalloproteinases and their tissue inhibitors on the risk of developing gastric cancer and are important for understanding the genetic structure of the studied pathology.

Keywords: gastric cancer, matrix metalloproteinases, tissue inhibitors of matrix metalloproteinases, association, polymorphic variant

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INTRODUCTION

Gastric cancer (GC) is one of the leading causes of cancer-related mortality worldwide. In the Russian Federation, gastric cancer is the sixth leading cause among all malignant tumors in terms of morbidity and the second in terms of mortality. In 2018, 36941 new cases of GC were identified. Disease morbidity was 25.16 cases per 100000 population, which corresponded to the sixth leading cause (5.9%) of morbidity in the structure of cancer diseases. Disease mortality achieved the level of 19.42 cases per 100000 population (9.5%), which corresponds to second place among men (10.4%) and third place among women (8.4%) [1]. The Republic of Bashkortostan (RB) is also characterized by high rates of morbidity and mortality from GC. In 2017, gastric tumors with malignant neoplasms were the second leading cause of mortality in the population from the Republic of Bashkortostan (10.5%, or 703 cases) (http://02.rospotrebnadzor.ru/content/228/37374/). Since the mortality rate from GC remains at high level, it requires the development of novel concepts for the diagnosis, prognosis, and treatment of the disease.

The transformation of cells into cancer ones and progression of the oncological process are related to

Table 1. Characteristics of the samples of patients with gastric cancer and control group

Characteristics	Patients with gastric cancer ($N = 314$)	Control ($N = 339$)
Mean age (mean ± SE), years	62.67 ± 0.58	58.06 ± 0.73
	Ethnicity, *n* (%)	
Russians	134 (42.67)	170 (50.15)
Tatars	145 (46.18)	129 (38.05)
Bashkirs	29 (9.24)	28 (8.26)
Other ethnicities (Chuvash, Jewish, Ukrainians, and individuals of mixed ethnicity)	6 (1.91)	12 (3.54)
	Sex, *n* (%)	
Men	180 (57.32)	201 (59.29)
Women	134 (42.68)	138 (40.71)
	TNM stage, *n* (%)	
I	17 (5.52)	–
II	56 (18.18)	–
III	207 (67.21)	–
IV	28 (9.09)	–
	Degree of tumor differentiation, *n* (%)	
Highly and moderately differentiated GC	135 (45.30)	–
Poorly and undifferentiated GC	163 (54.70)	–
Died in the following 2–3 years after surgery, *n* (%)	61 (19.43)	–

the accumulation of genetic and epigenetic changes in the genome resulting from abnormal functioning [2].

The study of genetic liability to developing GC is accompanied by a specific interest in the class of genes encoding matrix metalloproteinases and their tissue inhibitors. Matrix metalloproteinases (MMP) represent a family of zinc-dependent endopeptidases able to impair the main components of the extracellular matrix (ECM) and play a crucial role in the processes of its regulated (physiological) degradation, i.e., in tissue morphogenesis, tissue repair, embryogenesis, and angiogenesis. Several pathological states, including peptic ulcer disease, tumor invasion, and metastasis, are developed as a result of impaired regulation of ECM degradation, thus involving MMPs [3]. To date, MMPs are known to be involved in all stages of tumor progression in GC and other oncological pathologies [4].

Therefore, the study of polymorphic loci of matrix metalloproteinase genes and their tissue inhibitors in GC cases is one of the most important and clinically relevant issues.

The present study aimed to search for associations of polymorphic variants of matrix metalloproteinase genes *MMP1* (rs1799750 and rs494379), *MMP2* (rs2285053), *MMP3* (rs3025058), *MMP9* (rs3918242 and rs17576), *MMP12* (rs2276109) and genes of tissue inhibitors of matrix metalloproteinases *TIMP2* (rs8179090) and *TIMP3* (rs9619311) with the risk for developing gastric cancer in the Republic of Bashkortostan.

MATERIALS AND METHODS

The material for the study included DNA samples obtained from GC patients and healthy donors aged 21 to 88 years from the Republic of Bashkortostan. The group of patients consisted of 314 individuals clinically diagnosed with "gastric cancer" who were treated at the Republican Clinical Oncology Dispensary. The diagnosis was based on clinical and histological screening. A group of healthy donors without any gastrointestinal disease served as a control and consisted of 339 individuals. The characteristics of the samples of patients and control group are shown in Table 1.

All individuals completed a questionnaire considering ethnicity up to three generations, year of birth, smoking status, diet, and familial history of cancer and signed an informed consent to participate in the study in accordance with the Helsinki Declaration of the World Medical Association "Ethical Principles for Medical Research Involving Human Subjects".

Genomic DNA was isolated from the peripheral blood lymphocytes via phenol-chloroform extraction according to C.G. Mathew [5]. The selection of polymorphic loci for the study was conducted on the basis of the following criteria: (1) the association with the

examined trait according to the previous association (including replication) studies; (2) the association with phenotypes characterized by biological pathways in common with the examined trait; (3) the regulatory potential; (4) the influence on gene expression; (5) the association with nonsynonymous substitutions; (6) minor allele frequency above 5% [6]. Amplification of the examined DNA loci was performed using a polymerase chain reaction of DNA synthesis on a GeneAmp PCR System 2720 (Applied Biosystems, United States). Nucleotide substitutions were assigned via PCR with subsequent analysis of restriction fragment length polymorphism (RFLP). The list of examined loci, the sequences of specific oligonucleotide primers, restriction endonucleases, and the sizes of amplified fragments are shown in Table 2. The results of PCR and RFLP analysis were evaluated by electrophoresis in 7% polyacrylamide gel followed by staining with ethidium bromide and visualization in transmitted ultraviolet light.

Statistical analysis of the results of the study was conducted via MS Office Excel. A pairwise comparison of allele and genotype frequencies between the groups of patients and healthy donors was performed using the χ^2 criterion for 2×2 contingency tables with Yates correction for continuity (http://www.biometrica.tomsk.ru/). All statistical tests were performed for 2 df significance level. The correction for multiple testing was carried out using the false discovery rate (FDR) method, which controls for false-positive results (Benjiamini, Hochberg), implemented in the Plink 1.9 program package. Statistically significant differences were considered at $p_{fdr} < 0.05$, where p is the level of significance of the criterion. When statistically significant differences were detected between the studied samples, the odds ratio (OR) and its 95% confidence interval (95% CI) were estimated [7].

The search for combinations of alleles/genotypes associated with GC was carried out using APSampler 3.6.1 (http://sourceforge.net/projects/apsampler/). The main algorithm of this program is described in the article by A.V. Favorov et al. [8]. A permutation test was used to correct for multiple comparisons; the differences were considered statistically significant at $p_{perm} < 0.05$.

RESULTS

The analysis of the distribution of allele and genotype frequencies in nine polymorphic loci (rs1799750 and rs494379 of the *MMP1* gene, rs2285053 of the *MMP2* gene, rs3025058 of the *MMP3* gene, rs3918242 and rs17576 of the *MMP9* gene, rs2276109 of the *MMP12* gene, rs8179090 of the *TIMP2* gene, and rs9619311 of the *TIMP3* gene) was conducted in patients with GC and a control group from the Republic of Bashkortostan. The observed distribution of genotype frequencies across all examined gene polymorphisms corresponded to that expected from the Hardy–Weinberg equilibrium. Since the population of the Republic of Bashkortostan is ethnically heterogeneous, the examined sample was divided into the subgroups depending on the ethnicity. Russians and Tatars represented the separate subgroups. Other nationalities are not separately examined in view of the small sample size in both representative samples. A comparison of the distribution of allele frequencies and genotype frequencies of DNA loci was conducted to detect the markers of increased and reduced risk of developing GC between patients and individuals of the control group of the corresponding sex and ethnicity.

The *MMP1* gene is located on the long arm of chromosome 11 and encodes collagenase, i.e., enzyme involved in the cleavage of intercellular matrix collagen [9]. We performed an analysis of association of alleles and genotypes of rs1799750 (–1607 *1G>2G*) and rs494379 (–519 *A>G*) polymorphisms, which are located in the promoter region of the *MMP1* gene, with the risk of developing GC in individuals from the Republic of Bashkortostan.

A comparative analysis of the distribution of allele and genotype frequencies of the polymorphic locus rs1799750 of the *MMP1* gene among GC patients and healthy individuals revealed that heterozygous genotype rs1799750**1G/2G* was the marker of increased risk of developing GC in Tatars ($\chi^2 = 7.82$; $p_{fdr} = 0.016$; OR = 2.08; 95% CI 1.27–3.41) (Table 3).

The analysis of the distribution of allele and genotype frequencies of *MMP1* rs494379 gene polymorphism among GC patients and healthy individuals from the Republic of Bashkortostan demonstrated that men carrying the rs494379**A* allele and rs494379**A/A* genotype had a reduced risk of developing GC ($\chi^2 = 8.95$; $p_{fdr} = 0.030$; OR = 0.62; 95% CI 0.46–0.84 and $\chi^2 = 6.13$; $p_{fdr} = 0.040$; OR = 0.58; 95% CI 0.39–0.88, respectively), while the presence of the rs494379**G* allele by men, on the contrary, increased the risk of developing the disease ($\chi^2 = 8.95$; $p_{fdr} = 0.030$; OR = 1.62; 95% CI 1.19–2.20) (Table 4).

The *MMP2* gene is located on chromosome 16 at 16q12.2. The *MMP2* gene encodes metalloproteinase-2, which is specifically active against type IV collagen, known to be the main component of basal membranes [10]. The production of MMP2 by tumor cells is thought to provide their invasive potential [11, 12]. We conducted a comparative analysis of the distribution of allele and genotype frequencies of rs2285053 (–735 *C>T*) located in the *MMR2* gene among patients with GC and healthy donors from the Republic of Bashkortostan. However, the data obtained demonstrated no statistically significant differences between the groups of GC patients and healthy donors.

Together with the *MMP1* gene, the *MMP3* gene is located on the long arm of the chromosome 11. Several authors suggested the possibility of using MMP3 as a

Table 2. Polymorphic loci, primers sequences, and nomenclature of alleles of analyzed DNA loci

Gene, location	dbSNP	Primer sequence	Restriction endonuclease	Alleles, fragment size
MMP1, 11q22.2	rs1799750 (g.3471del)	TGAGGAAATTGTAGTTAAATCCTTAGAAAG TCCCCTTATGGATTCCTGTTTTCTT	*Bse*LI	*2G*—118 bp, *1G*—29 + 89 bp
MMP1, 11q22.2	rs494379 (g.102798479 *A*>*G*)	CATGGTGCTATCGCAATAGGGT TGCTACAGGTTTCTCCACACAC	*Kpn*I	*G*—200 bp, *A*—176 + 24 bp
MMP2, 16q12.2	rs2285053 (g.4297 *C*>*T*)	ATAGGGTAAACCTCCCCACATT GGTAAAATGAGGCTGAGACCTG	*Hin*fI	*C*—300 bp, *T*—254 + 46 bp
MMP3, 11q22.2	rs3025058 (g.13452_13453ins*A*)	GGTTCTCCATTCCTTTGATGGGGGGAAAGA CTTCCTGGAATTCACACTACTGCCACCACT	*Psy*I	*6A*—129 bp, *5A*—97 + 32 bp
MMP9, 20q13.12	rs3918242 (g.3430 *C*>*T*)	TTCGTGACGCAAAGCAGA AGCAGCCTCCCTCACTCCT	*Sph*I	*C*—560 bp, *T*—300 + 260 bp
MMP9, 20q13.12	rs17576 (g.7679 *A*>*G*)	AATTCACCCTCCCGCACTCT GTTTTGGGGGCCAATACATGA	*Sma*I	*A*—397 bp, *G*—224 + 173 bp
MMP12, 11q22.2	rs2276109 (g.4974 *A*>*G*)	GAGATAGTCAAGGGATGATATCAG AAGAGCTCCAGAAGCAGTGG	*Pvu*II	*A*—199 bp, *G*—175 + 24 bp
TIMP2, 17q25.3	rs8179090 (g.76921889 *C*>*G*)	CGTCTCTTGTTGGCTGGTCA CCTTCAGCTCGACTCTGGAG	*Eco*881	*G*—230 + 51 + 23 bp, *C*—253 + 51 bp
TIMP3, 22q12.3	rs9619311 (g.4892 *T*>*C*)	CAAAGCAGAATCAAGATGTCAAT CTGGGTTAAGCAACACAAAGC	*Alu*I	*C*—204 + 160 + 69 + 55 bp, *T*—204 + 128 + 69 + 55 + 32 bp

Table 3. Distribution of allele and genotype frequencies of rs1799750 of the *MMP1* gene in patients with gastric cancer and control group with respect to ethnicity

Genotype, allele		Patients (in total)	Control (in total)	Russians, GC	Russians, control	Tatars, GC	Tatars, control
1G/1G	n_i	79	81	39	35	29	38
	$p_i \pm s_p$ (95% CI)	25.16 ± 2.45 (20.45–30.34)	25.47 ± 2.44 (20.77–30.63)	29.10 ± 3.92 (21.58–37.57)	21.88 ± 3.27 (15.73–29.09)	20.00 ± 3.32 (13.82–27.44)	32.20 ± 4.30 (23.90–41.43)
	χ^2	0.000001		1.66		4.48	
	p (p_{fdr})	0.999 (0.999)		0.198 (0.475)		0.034 (0.051)	
1G/2G	n_i	170	163	70	94	84	47
	$p_i \pm s_p$ (95% CI)	54.14 ± 2.81 (48.45–59.75)	51.26 ± 2.80 (45.62–56.87)	52.24 ± 4.32 (43.44–60.93)	58.75 ± 3.89 (50.71–66.46)	57.93 ± 4.10 (49.46–66.07)	39.83 ± 4.51 (30.93–49.25)
	χ^2	0.42		1.00		7.82	
	p (p_{fdr})	0.518 (0.777)		0.316 (0.475)		**0.005 (0.016)**	
	OR (CI)					2.08 (1.27–3.41)	
2G/2G	n_i	65	74	25	31	32	33
	$p_i \pm s_p$ (95% CI)	20.70 ± 2.29 (16.36–25.61)	23.27 ± 2.37 (18.74–28.31)	18.66 ± 3.37 (12.45–26.30)	19.38 ± 3.12 (13.56–26.36)	22.07 ± 3.44 (15.61–29.70)	27.97 ± 4.13 (20.10–36.98)
	χ^2	0.47		0.00005		0.92	
	p (p_{fdr})	0.494 (0.777)		0.994 (0.994)		0.338 (0.927)	
1G	n_i	328	325	148	164	142	123
	$p_i \pm s_p$ (95% CI)	52.23 ± 1.99 (48.24–56.20)	51.10 ± 1.98 (47.14–55.05)	55.22 ± 3.04 (49.05–61.28)	51.25 ± 2.79 (45.63–56.85)	48.97 ± 2.94 (43.08–54.88)	52.12 ± 3.25 (45.54–58.64)
	χ^2	0.12		0.77		0.40	
	p (p_{fdr})	0.730 (0.819)		0.380 (0.512)		0.528 (0.955)	
2G	n_i	300	311	120	156	148	113
	$p_i \pm s_p$ (95% CI)	47.77 ± 1.99 (43.80–51.76)	48.90 ± 1.98 (44.95–52.86)	44.78 ± 3.04 (38.72–50.95)	48.75 ± 2.79 (43.15–54.37)	51.03 ± 2.94 (45.12–56.92)	47.88 ± 3.25 (41.36–54.46)
	χ^2	0.12		0.77		0.40	
	p (p_{fdr})	0.730 (0.819)		0.380 (0.512)		0.528 (0.955)	

Table 4. Distribution of allele and genotype frequencies of rs494379 of the *MMP1* gene in patients with gastric cancer and control group with respect to sex

Genotype, allele		Men, GC	Men, control	Women, GC	Women, control
A/A	n_i	73	103	51	54
	$p_i \pm s_p$ (95% CI)	40.78 ± 3.67 (33.51–48.36)	54.21 ± 3.61 (46.85–61.44)	38.64 ± 4.24 (30.29–47.50)	41.54 ± 4.32 (32.97–50.51)
	χ^2	6.13		0.12	
	p (p_{fdr})	**0.013 (0.040)**		0.724 (0.999)	
	OR (CI)	0.58 (0.39–0.88)			
A/G	n_i	71	65	63	52
	$p_i \pm s_p$ (95% CI)	39.66 ± 3.66 (32.44–47.23)	34.21 ± 3.44 (27.50–41.43)	47.73 ± 4.35 (38.97–56.59)	40.00 ± 4.30 (31.51–48.95)
	χ^2	0.96		1.29	
	p (p_{fdr})	0.328 (0.854)		0.256 (0.555)	
G/G	n_i	35	22	18	24
	$p_i \pm s_p$ (95% CI)	19.55 ± 2.96 (14.01–26.13)	11.58 ± 2.32 (7.40–17.00)	13.64 ± 2.99 (8.29–20.69)	18.46 ± 3.40 (12.20–26.21)
	χ^2	3.90		0.80	
	p (p_{fdr})	0.048 (0.073)		0.370 (0.555)	
A	n_i	217	271	165	160
	$p_i \pm s_p$ (95% CI)	60.61 ± 2.58 (55.34–65.71)	71.32 ± 2.32 (66.48–75.81)	62.50 ± 2.98 (56.36–68.36)	61.54 ± 3.02 (55.33–67.48)
	χ^2	8.95		0.02	
	p (p_{fdr})	**0.003 (0.030)**		0.891 (0.892)	
	OR (CI)	0.62 (0.46–0.84)			
G	n_i	141	109	99	100
	$p_i \pm s_p$ (95% CI)	39.39 ± 2.58 (34.29–44.66)	28.68 ± 2.32 (24.19–33.52)	37.50 ± 2.98 (31.64–43.64)	38.46 ± 3.02 (32.52–44.67)
	χ^2	8.95		0.02	
	p (p_{fdr})	**0.003 (0.030)**		0.891 (0.892)	
	OR (CI)	1.62 (1.19–2.20)			

marker of invasion, metastasis, and a prognostic marker of GC progression [13]. The conducted comparative analysis of the distribution of allele and genotype frequencies of rs3025058 (–1171 *5A>6A*) of the *MMP3* gene demonstrated no significant differences between GC patients and individuals of the control group.

The *MMP9* gene encodes gelatinase B, which is involved in inflammation (together with MMP2, it may possess pro- and anti-inflammatory activity), tissue remodeling and repair, mobilization of matrix-related growth factors, and cytokine processing [10]. In addition, gelatinase B provides angiogenesis, including that in tumor tissue, thus promoting its growth [12]. Within the framework of the present study, an analysis of association of *MMP9* gene polymorphisms and GC development was conducted in individuals from the Republic of Bashkortostan: rs3918242 (–1562 *C>T*) located in the gene promoter and rs17576 (836 *A>G*) located in exon 6, which results in amino acid substitution in the protein (Gln279Arg). A comparative analysis of the distribution of allele and genotype frequencies of rs3918242 and rs17576 of the *MMP9* gene between GC patients and healthy donors from the Republic of Bashkortostan patients failed to detect associations of described DNA loci with a risk of developing GC stratified by sex and ethnicity.

The *MMP12* gene, which is located on the short arm of chromosome 11, encodes a macrophage metalloelastase (MMP12). MMP12 is a scarcely examined

Table 5. Distribution of allele and genotype frequencies of rs2276109 of the *MMP12* gene in patients with gastric cancer and control group with respect to ethnicity

Genotype, allele		Patients (in total)	Control (in total)	Russians, GC	Russians, control	Tatars, GC	Tatars, control
A/A	n_i	256	253	105	101	124	109
	$p_i \pm s_p$ (95% CI)	81.53 ± 2.19 (76.79–85.66)	78.09 ± 2.30 (73.18–82.47)	78.36 ± 3.56 (70.42–85.00)	83.47 ± 3.38 (75.63–89.60)	85.52 ± 2.92 (78.72–90.81)	69.87 ± 3.67 (62.02–76.95)
	χ^2	0.97		0.77		9.64	
	p (p_{fdr})	0.325 (0.547)		0.381 (0.572)		**0.002 (0.003)**	
	OR (CI)					2.55 (1.43–4.53)	
A/G	n_i	56	68	29	18	19	47
	$p_i \pm s_p$ (95% CI)	17.83 ± 2.16 (13.76–22.53)	20.99 ± 2.26 (16.68–25.83)	21.64 ± 3.56 (15.00–29.58)	14.88 ± 3.24 (9.06–22.49)	13.10 ± 2.80 (8.08–19.70)	30.13 ± 3.67 (23.05–37.98)
	χ^2	0.82		1.51		11.75	
	p (p_{fdr})	0.365 (0.547)		0.219 (0.572)		**0.0006 (0.002)**	
	OR (CI)					0.35 (0.19–0.63)	
G/G	n_i	2	3	0	2	2	0
	$p_i \pm s_p$ (95% CI)	0.64 ± 0.45 (0.08–2.28)	0.93 ± 0.53 (0.19–2.68)	0	1.65 ± 1.16 (0.20–5.84)	1.38 ± 0.97 (0.17–4.89)	0
	χ^2	0.001		0.16		0.14	
	p (p_{fdr})	0.972 (0.995)		0.687 (0.975)		0.705 (0.927)	
A	n_i	568	574	239	220	267	265
	$p_i \pm s_p$ (95% CI)	90.45 ± 1.17 (87.87–92.63)	88.58 ± 1.25 (85.88–90.93)	89.18 ± 1.90 (84.83–92.63)	90.91 ± 1.85 (86.56–94.21)	92.07 ± 1.59 (88.34–94.91)	84.94 ± 2.03 (80.48–88.72)
	χ^2	0.99		0.25		6.76	
	p (p_{fdr})	0.320 (0.577)		0.615 (0.644)		0.009 (0.159)	
G	n_i	60	74	29	22	23	47
	$p_i \pm s_p$ (95% CI)	9.55 ± 1.17 (7.37–12.13)	11.42 ± 1.25 (9.07–14.12)	10.82 ± 1.90 (7.37–15.17)	9.09 ± 1.85 (5.79–13.44)	7.93 ± 1.59 (5.09–11.66)	15.06 ± 2.03 (11.28–19.52)
	χ^2	0.99		0.25		6.76	
	p (p_{fdr})	0.320 (0.577)		0.615 (0.644)		0.009 (0.159)	

metalloelastase, whose role in tumor progression remains unclear; together with other MMPs, this molecule is known to inhibit angiogenesis [10, 14]. We conducted an association study of the distribution of allele and genotype frequencies of rs2276109 of the *MMP12* gene with the risk of developing GC in individuals from the Republic of Bashkortostan.

A comparative analysis of allele and genotype frequencies distribution of polymorphism rs2276109 (−82 *A>G*) of the *MMP12* gene between GC patients and healthy individuals revealed ethnicity-specific associations: the rs2276109**A/A* genotype was the marker of increased risk of developing the examined pathology for Tatars ($\chi^2 = 9.64$; $p_{fdr} = 0.003$; OR = 2.55; 95% CI 1.43–4.53), while the heterozygous rs2276109**A/G* genotype was the marker of reduced risk in the same subgroup of individuals ($\chi^2 = 11.75$; $p_{fdr} = 0.002$; OR = 0.35; 95% CI 0.19–0.63) (Table 5).

Experimental data reported by various authors indicate that tissue inhibitors of matrix metalloproteinases (TIMP) are multifunctional molecules which possibly affect tumor progression [15–17]. The mechanism of oncological transformation during the molecular-genetic modifications in the *TIMP2* gene may be caused by low activity of the promoter during TIMP2 expression, which results in

slow inhibition of metalloproteinases and, hence, in inflammatory changes in the microenvironment and carcinogenesis [18].

In the present study we analyzed rs8179090 (–418 *G>C*) polymorphism located in the promoter region of the *TIMP2* gene. A comparison of patients with healthy donors according to their sex and ethnicity failed to detect statistically significant differences in the distribution of allele and genotype frequencies of rs8179090 of the *TIMP2* gene in individuals from the Republic of Bashkortostan.

The *TIMP3* gene encodes the 24 kDa TIMP3 protein, which is exclusively bound to the extracellular matrix compared to other members of the TIMP family [19, 20]. There is evidence that TIMP3 can induce apoptosis of cancer cells and inhibit tumor growth and angiogenesis [20].

In the present study, we conducted an analysis of association of rs9619311 (–1296 *T>C*) polymorphism of the *TIMP3* gene with the risk of developing GC in individuals from the Republic of Bashkortostan. A comparative analysis of the distribution of allele and genotype frequencies of rs9619311 between patients and healthy donors revealed that the rs9619311**T/T* genotype was a marker of increased risk of developing malignant gastric tumors in Russians ($\chi^2 = 8.11$; $p_{fdr} = 0.013$; OR = 2.04; 95% CI 1.27–3.27), while the rs9619311**C/T* genotype represented a marker of reduced risk of developing GC in the same ethnic subgroup ($\chi^2 = 6.84$; $p_{fdr} = 0.013$; OR = 0.51; 95% CI 0.31–0.83) (Table 6).

Together with the assessment of the effect of polymorphic variants of certain genes of matrix metalloproteinases and their tissue inhibitors on the risk of developing GC, we also considered combinations of alleles and genotypes of the examined DNA loci. Using the APSampler algorithm, we identified combinations associated with an increased and a reduced risk of developing GC. The results with p_{perm} under 0.05 and OR above 3.50 or below 0.33 are shown in Table 7 [21] (Table 7).

In Russians, the most significant combinations associated with higher risk of developing GC were rs494379**A/G* of the *MMP1* gene + rs3025058**6A* of the *MMP3* gene + rs9619311**T* of the *TIMP3* gene and rs2276109**A* of the *MMP12* gene + rs8179090**G/G* of the *TIMP2* gene. In Tatars, the combinations included rs1799750**2G* of the *MMP1* gene + rs3025058**5A/6A* of the *MMP3* gene, rs1799750**1G/2G* of the *MMP1* gene + rs9619311**C* of the *TIMP3* gene, and rs1799750**2G* of the *MMP1* gene + rs494379**G* of the *MMP1* gene + rs3025058**5A* of the *MMP3* gene (Table 7).

DISCUSSION

The effect of polymorphisms of matrix metalloproteinase genes and their tissue inhibitors on GC development and progression has been widely studied by many research groups; however, such study was conducted in a sample from the Republic of Bashkortostan for the first time.

It is known that rs1799750, which is located in the promoter region of the *MMP1* gene, creates a binding site for the transcription factor Ets owing to insert of additional guanine. It has been experimentally shown that the mutant allele *2G* has an increased ability to bind to the recombinant factor ETS-1 in a complex with C-JUN [22]. As a result of the present study, we observed that the heterozygous rs1799750**1G/2G* genotype of the *MMP1* gene was a marker of an increased risk of developing GC in Tatars. Our findings are contrary to previous results obtained by S. Dey et al. [23]. The authors failed to detect association of rs1799750 polymorphism of the *MMP1* gene with the risk of developing GC in the population of India. However, the scientists demonstrated that the rs1799750**2G* allele was a major allele in a sample of patients and was likely to be a risky one [23]. In addition, in the Indian population, it was also reported that the presence of the rs494379**A/G* and rs494379**G/G* genotypes of the *MMP1* gene had a protective effect with respect to both metastases in the regional lymph nodes and distant metastasis [23]. In the present study, we revealed that the presence of the rs494379**G* allele of the *MMP1* gene was a marker of increased risk of developing GC, while the presence of the rs494379**A* allele and rs494379**A/A* genotype, on the other hand, represented a marker of reduced risk of developing GC in men from the Republic of Bashkortostan. Contradictory findings obtained by our research group and other scientists can be explained by differences in the genetic structure of the studied populations.

The nucleotide substitution –735 *C>T* (rs2285053) in the promoter region of the *MMP2* gene results in the extinction of the Sp-1 binding site, which significantly reduces promoter activity [24]. W. Shen et al. [25] as a result of their meta-analysis concluded that MMP2 overexpression had an adverse effect on patient survival and clinicopathologic specificity of GC. The authors concluded that MMP2 overexpression might serve as a prognostic marker of GC and indicate the possibility of distribution of metastases [25]. The study conducted by D.Y. Zhang et al. [26] in China demonstrated that the distribution of allele and genotype frequencies of rs2285053 of the *MMP2* gene in the group of GC patients was similar to that observed in healthy individuals and no statistically significant differences between the groups were observed. The results obtained in individuals from China correspond to the data presented in the present study.

The mutant allele of the *MMP3* –1171 *5A>6A* (rs3025058) polymorphism differs from the normal one in the insertion of additional adenosine. Experiments with reporter constructs demonstrated reduced transcription efficiency in the case of the *6A* allele.

Table 6. Distribution of allele and genotype frequencies of rs9619311 of the *TIMP3* gene in patients with gastric cancer and control group with respect to ethnicity

Genotype, allele		Patients (in total)	Control (in total)	Russians, GC	Russians, control	Tatars, GC	Tatars, control
C/C	n_i	21	21	8	12	10	9
	$p_i \pm s_p$ (95% CI)	6.69 ± 1.41 (4.19–10.04)	6.69 ± 1.41 (4.19–10.04)	5.97 ± 2.05 (2.61–11.42)	7.69 ± 2.13 (4.04–13.05)	6.90 ± 2.10 (3.36–12.32)	7.56 ± 2.42 (3.52–13.87)
	χ^2	0.03		0.12		0.001	
	p (p_{fdr})	0.873 (0.995)		0.730 (0.975)		0.975 (1.000)	
C/T	n_i	106	129	40	71	53	40
	$p_i \pm s_p$ (95% CI)	33.76 ± 2.67 (28.54–39.28)	41.08 ± 2.78 (35.59–46.75)	29.85 ± 3.95 (22.26–38.36)	45.51 ± 3.99 (37.53–53.67)	36.55 ± 4.00 (28.72–44.95)	33.61 ± 4.33 (25.22–42.85)
	χ^2	3.29		6.84		0.14	
	p (p_{fdr})	0.070 (0.116)		**0.009 (0.013)**		0.713 (0.927)	
	OR (CI)			0.51 (0.31–0.83)			
T/T	n_i	187	164	86	73	82	70
	$p_i \pm s_p$ (95% CI)	59.55 ± 2.77 (53.90–65.03)	52.23 ± 2.82 (46.55–57.87)	64.18 ± 4.14 (55.44–72.27)	46.79 ± 3.99 (38.77–54.94)	56.55 ± 4.12 (48.08–64.75)	58.82 ± 4.51 (49.43–67.76)
	χ^2	3.13		8.11		0.06	
	p (p_{fdr})	0.077 (0.116)		**0.004 (0.013)**		0.805 (0.969)	
	OR (CI)			2.04 (1.27–3.27)			
C	n_i	148	171	56	95	73	58
	$p_i \pm s_p$ (95% CI)	23.57 ± 1.69 (20.30–27.09)	27.23 ± 1.78 (23.78–30.89)	20.90 ± 2.48 (16.19–26.26)	30.45 ± 2.61 (25.39–35.88)	25.17 ± 2.55 (20.28–30.58)	24.37 ± 2.78 (19.06–30.33)
	χ^2	2.03		6.35		0.01	
	p (p_{fdr})	0.154 (0.378)		0.012 (0.224)		0.911 (0.955)	
T	n_i	480	457	212	217	217	180
	$p_i \pm s_p$ (95% CI)	76.43 ± 1.69 (72.91–79.70)	72.77 ± 1.78 (69.11–76.22)	79.10 ± 2.48 (73.74–83.81)	69.55 ± 2.61 (64.12–74.61)	74.83 ± 2.55 (69.42–79.72)	75.63 ± 2.78 (69.67–80.94)
	χ^2	2.03		6.35		0.01	
	p (p_{fdr})	0.154 (0.378)		0.012 (0.224)		0.911 (0.955)	

The same allele was associated with higher binding efficiency with a specific protein complex, which is presumably a transcription repressor [27]. The impact of rs3025058 of the *MMP3* gene in developing GC was estimated by scientists from India [28]. The authors revealed that the rs3025058**5A* allele and rs3025058**5A/6A* genotype were the markers of higher risk of developing GC in the examined population [28]. The data obtained by our group are contradictory to the results of Indian researchers, which can be explained by significant ethnic differences between the studied populations.

It was reported that an increased transcriptional activity associated with a rare *T* allele of the –1562 *C>T* (rs3918242) polymorphism in the *MMP9* gene was related to the preferential binding of the transcription repressor to the wild-type allele [29]. In 2017, Z. Peng et al. [30] published the results of a systematic meta-analysis which aimed to estimate the association between rs3918242 (–1562 *C>T*) of the *MMP9* gene and the risk of developing gastric malignancies. As a result of this meta-analysis, the authors ascertained that the –1562 *C>T* polymorphism located in the promoter region of the *MMP9* gene increased the risk of developing GC [30]. R. Okada et al. [31] in the same

Table 7. Combinations of alleles/genotypes associated with gastric cancer and obtained via APSampler algorithm

Sample		Combination of alleles/genotypes	Frequency, %		p_{perm}	OR	95% CI
			patients	control			
Russians	Women	*MMP1.2*A/G + MMP3*6A + TIMP3*T*	38.18	9.09	0.0443	6.18	1.31–29.16
	Men	*MMP12*A + TIMP2*G/G*	100.00	91.36	0.0470	7.69	1.70–34.86
	Poorly and undifferentiated GC	*MMP3*5A + MMP9.1*C*	57.45	80.80	0.0071	0.32	0.15–0.67
	Highly and moderately differentiated GC	*MMP1.1*2G + MMP12*A + TIMP3*T*	56.00	79.78	0.0108	0.32	0.15–0.69
Tatars	Women	*MMP1.1*2G + MMP3*5A/6A*	43.33	8.00	0.0047	8.79	1.90–40.71
		*MMP1.2*A/A + MMP12*G*	3.33	18.52	0.0242	0.15	0.03–0.73
	Men	*MMP1.1*1G/2G + TIMP3*C*	27.38	5.36	0.0029	6.66	1.89–23.44
	Highly and moderately differentiated GC	*MMP1.1*2G + MMP1.2*G + MMP3*5A*	55.07	20.00	0.00002	4.90	2.38–10.12
		*MMP1.2*A + MMP12*G*	10.00	28.10	0.0184	0.28	0.12–0.68

MMP1.1—rs1799750 of the *MMP1* gene; *MMP1.2*—rs494379 of the *MMP1* gene; *MMP3*—rs3025058 of the *MMP3* gene; *MMP9.1*—rs3918242 of the *MMP9* gene; *MMP12*—rs2276109 of the *MMP12* gene; *TIMP2*—rs8179090 of the *TIMP2* gene; *TIMP3*—rs9619311 of the *TIMP3* gene.

year published the study which reported that the presence of the rs17576**G/G* genotype of the *MMP9* gene was significantly more common in Japanese with first- and second-degree relatives with malignant gastric tumors compared to those without family history of this disease. In our association study no statistically significant results were observed for individuals from our geographic region for rs3918242 and rs17576 of the *MMP9* gene. Published findings and the results obtained by our group emphasize the necessity to consider ethnicity in association studies.

The rs2276109 (–82 *A>G*) polymorphism in the *MMP12* gene affects the binding of the AP-1 transcription factor to its responsive element in the gene promoter. It was revealed that this binding was more effective for the *A* allele. The *G* allele is associated with a reduced transcription level of the *MMP12* gene. Obviously, this relation is caused by the difference in the efficiency of AP-1 binding to the *A* or *G* allele [32]. The rs2276109 polymorphism of the *MMP12* gene has been examined in multiple malignant tumors; nevertheless, the data of different scientific groups remain incompletely congruent and fail to make a certain conclusion on the effect of the examined locus. To be more precise, scientists from China [33] conducted a meta-analysis which examined the association of –82 *A>G* polymorphism of the *MMP12* gene and the risk of developing malignant tumors. In particular, nine nosologies were considered, including gastric adenocarcinoma. The authors succeeded in detecting an association only with epithelial ovarian carcinoma, and the rs2276109**G* allele was a genetic risk factor for this pathology. No association between –82 *A>G* polymorphism of the *MMP12* gene and susceptibility to other tumors was reported [33]. S. VAN Nguyen et al. [34] conducted a study to estimate the relation of rs2276109 of the *MMP12* gene to the development of colorectal cancer in Swedish patients. The study demonstrated that the rs2276109**A/A* genotype of the *MMP12* gene was associated with a higher risk of developing disseminated colorectal cancer [34]. In our study the rs2276109**A/A* genotype of the *MMP12* gene significantly increased the risk of malignant tumors in gastric cancer in the Tatar population, while the heterozygous rs2276109**A/G* genotype was protective for the examined pathology in this ethnic subgroup.

In the foreign literature, multiple publications have examined the effect of polymorphic loci of genes of tissue inhibitors of matrix metalloproteinases in carcinogenesis of different location. Recently, scientists from Turkey who studied the role of rs8179090 polymorphism in the *TIMP2* gene in hereditary predisposition to bladder cancer concluded that rs8179090 polymorphism was not associated with the development of this pathology [35]. The results obtained by Indian researchers reported that higher risk of developing gallbladder cancer was associated with the rs8179090**G/C* and (*C/C* + *G/C*) genotypes compared to the control group [17]. In the Chinese population [36], carriers of the rs8179090*(*C/C* + *G/C*) genotype had a 51% higher risk of developing GC compared to the carriers of the rs8179090**G/G* genotype. A higher risk was particularly obvious in young individuals under 58 years and in current smokers [36]. In the present study, no significant associations of rs8179090 of the *TIMP2* gene with the risk of developing GC was observed for individuals from the Republic of Bashkortostan. A possible explanation of such contradictory findings can include the presence of ethnic-

ity-specific associations between alleles of genes and clinical parameters of the studied pathology.

Published data reporting the effect of rs9619311 of the *TIMP3* gene on developing oncopathology remain contradictory. H.-T. Tsai et al. [37] revealed that the presence of the rs9619311**C/T* or rs9619311**C/C* genotype of the *TIMP3* gene was a protective marker for developing hepatocellular cancer in Taiwanese women compared to women with the rs9619311**T/T* genotype. Authors from Poland [38] published the results of a study which demonstrated that genetic variants of the rs9619311 polymorphism of the *TIMP3* gene were unrelated to increased risk of bladder cancer in the Polish population. In the present study, the presence of the rs9619311**T/T* genotype of the *TIMP3* gene was shown to significantly enhance the risk of developing gastric malignancies in Russians, while the heterozygous rs9619311**C/T* genotype was a marker of reduced risk of developing GC in this ethnic subgroup. The data obtained by our group together with the results of other studies point to the necessity of further research on the effect of rs9619311 of the *TIMP3* gene on the risk of developing malignant tumors of various location.

Special attention should be paid to the studies aimed at examining the effect of combinations of alleles/genotypes of polymorphic loci of matrix metalloproteinase genes and their tissue inhibitors on developing oncological pathology. Z. Rahimi et al. [39] explored the role of rs3918242 (–1562 *C>T*) of the *MMP9* gene and rs2285053 (–735 *C>T*) of the *MMP2* gene and concluded that the combination of the rs3918242**T* allele of the *MMP9* gene and rs2285053**C* allele of the *MMP2* gene significantly increased the liability of Kurdish women from Western Iran to breast cancer. The study conducted in the Netherlands [40] demonstrated that the presence of the *G* allele of –181 *A>G* polymorphism of the *MMP7* gene in combination with the *T* allele of 303 *C>T* polymorphism of the *TIMP2* gene was related to a worse survival prognosis for GC patients. In the present study, combinations of alleles and genotypes of polymorphic loci of matrix metalloproteinase genes and their tissue inhibitors in individuals from the Republic of Bashkortostan were shown to be associated with an increased and a reduced risk of developing GC (Table 7). The results obtained by our group are frequently contradictory to those obtained by other researchers; nevertheless, identified combinations of alleles and genotypes can be the basis for the development of a test system aimed at determining individuals at high risk of developing oncopathology in the case of positive replication on an independent sample.

Therefore, as a result of the present research, we obtained statistically significant results with high scientific novelty and practical significance, which allow us to better understand the mechanisms and molecular bases of gastric cancer pathogenesis and to identify important molecular-genetic markers of higher risk of developing the disease for individuals from the Republic of Bashkortostan.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest. The authors declare no conflict of interest.

Statement of compliance with standards of research involving humans as subjects. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants involved in the study.

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