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HUMAN GENETICS

Role of Allelic Genes of Matrix Metalloproteinases and Their Tissue Inhibitors in the Risk of Peptic Ulcer Disease Development

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Abstract—Peptic ulcer disease is a chronic disease of the gastrointestinal tract, mainly manifesting itself in the formation of the fairly persistent ulcer defect of the mucous membrane of the stomach and/or duodenum. Association analysis of common polymorphisms of matrix metalloproteinases genes *MMP-1* (*rs1799750*, *rs494379*), *MMP-2* (*rs2285052*), *MMP-3* (*rs3025058*), *MMP-9* (*rs3918242*, *rs17576*), and *MMP-12* (*rs2276109*) and their tissue inhibitors *TIMP-2* (*rs8179090*) and *TIMP-3* (*rs9619311*) was carried out in 353 patients with a gastric ulcer or duodenal ulcer and in 325 unrelated healthy individuals from the Republic of Bashkortostan. Associations of polymorphic variants *rs1799750* and *rs494379* of gene *MMP-1*, *rs3025058* of gene *MMP-3*, *rs3918242* and *rs17576* of gene *MMP-9*, and *rs9619311* of gene *TIMP-3* with the risk of peptic ulcer disease in Russians and Tatars were revealed.

Keywords: peptic ulcer disease, polymorphic variants of gene, matrix metalloproteinases, association

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INTRODUCTION

Despite the improvement of methods of examination and treatment of patients with peptic ulcer disease (PUD), it continues to be one of the most common reasons why people having digestive diseases ask for medical care [1]. In particular, in the world each year, about four million people are diagnosed with PUD, and 10–20% of them have PUD with complications, 2–14% of which are perforations [2–4]. According to the Federal Research Institute for Health Organization and Informatics of the Ministry of Health of the Russian Federation, there are about three million people with this disease in Russia. In total, the distribution of patients first diagnosed with PUD is as follows: 89.5 per 100000 of the total population in the Central Federal District and 134 per 100000 of the total population in the Volga Federal District [5].

For many years, the main cause of PUD was considered to be an excess of hydrochloric acid, and now it is believed that a major factor in the development of peptic ulcers is bacterium *Helicobacter pylori*, found in 70–90% of people with this disease [6]. Helicobacteriosis concerns so-called slow infections: only 20% of infected people have peptic ulcer or gastric cancer [7]. This is due to the fact that ulcergenecity of *H. pylori* depends on many endogenous and exogenous risk factors, such as mental stress and use of tobacco, alcohol, tea, coffee, and spicy foods, and genetic predisposition [8, 9].

Despite the fact that *H. pylori* does not penetrate tissues, bacteria cause an intense inflammatory and immune response: increased production of proinflammatory cytokines, which in turn leads to the activation of matrix metalloproteinases (MMPs), including collagenase, accompanied by increased degradation of carbohydrate-protein components of connective tissue against the background of suppression of anabolic processes in mucosa of the stomach and duodenum [10, 11]. Thus, MMPs play an important role in the development of gastric (GU) and duodenal ulcers (DU). So, in this regard, it is relevant to study polymorphisms of key matrixins to determine their role in the development of PUD.

The purpose of this work is to study the association of polymorphic variants of genes *MMP-1* (*rs1799750*, *rs494379*), *MMP-2* (*rs2285052*), *MMP-3* (*rs3025058*), *MMP-9* (*rs3918242*, *rs17576*), and *MMP-12* (*rs2276109*) and their tissue inhibitors *TIMP-2* (*rs8179090*) and *TIMP-3* (*rs9619311*) with PUD in the Republic of Bashkortostan (RB).

Table 1. Polymorphisms, primer sequences, and nomenclature of alleles of analyzed DNA loci

Gene	Polymorphism	Primer sequences, 5'–3'	Restriction enzyme, alleles, size of fragments, bp (source)
MMP-1	*rs494379* *–519A > G*	GTCTTCCCATTCTTCTTACC ATTGATTTGAGATAAGTCAGATC	*Kpn*I, *G*—200, *A*—176 + 24 (Armstrong et al., 2007)
MMP-1	*rs1799750* *–1607G > GG*	TGAGGAAATTGTAGTTAAATCCTTAGAAAG TCCCCTTATGGATTCCTGTTTTCTT	*Bsl*I, *GG*—118, *G*—29 + 89 (Hinoda et al., 2002)
MMP-2	*rs2285052* *–735C > T*	ATAGGGTAAACCTCCCCACATT GGTAAAATGAGGCTGAGACCTG	*Hin*fI, *C*—300, *T*—254 + 46 (Armstrong et al., 2007)
MMP-3	*rs3025058* *–11715A > 6A*	GGTTCTCCATTCCTTTGATGGGGGGAAAGA CTTCCTGGAATTCACACTACTGCCACCACT	*Psy*I (*Tth*111I), 6*A*—130, 5*A*—97 + 32 (Gnasso et al., 2000)
MMP-9	*rs3918242* *–1562C > T*	TTCGTGACGCAAAGCAGA AGCAGCCTCCCTCACTCCT	*Sph*I, *C*—560, *T*—300 + 260 (Joos et al., 2002)
MMP-9	*rs17576* *836A > G*	AATTCACCCTCCCGCACTCT GTTTTGGGGGCCAATACATGA	*Sma*1, *A*—397, *G*—173 + 224 (Ganter et al., 2005)
MMP-12	*rs2276109* *–82A > G*	GAGATAGTCAAGGGATGATATCAG AAGAGCTCCAGAAGCAGTGG	*Pvu*II, *A*—199, *G*—175 + 24 (Joos et al., 2002)
TIMP-2	*rs8179090* *–418G > C*	CGTCTCTTGTTGGCTGGTCA CCTTCAGCTCGACTCTGGAG	*Eco*88I (*Ava*I), *G*—230 + 51 + 23, *C*—253 + 51 (Zhou et al., 2004)
TIMP-3	*rs9619311* *–1296T > C*	CAAAGCAGAATCAAGATGTCAAT CTGGGTTAAGCAACACAAAGC	*Alu*BI, *C*—204 + 160 + 69 + 55, *T*—204 + 128 + 69 + 55 + 32 (Armstrong et al., 2007)

MATERIALS AND METHODS

The materials for the study were DNA samples of patients with PUD and healthy donors aged 18–80 years living in the city of Ufa, Republic of Bashkortostan. The group of patients comprised 353 people (of which 264 were diagnosed with DU and 89 with GU and combined forms of GU and DU) of different ethnicities (102 Russians, 144 Tatars, 71 Bashkirs, and 36 people of mixed blood) under dispensary observation of clinical databases of polyclinics nos. 1, 5, 21, 22, 46, 47, 49, and 50 in Ufa. Of them, 182 patients were infected with the bacterium *H. pylori*, the presence of which was determined by urease test, as well as by serology and histology. As the control group, we studied healthy donors without evidence of abnormalities of the gastrointestinal tract; this group consisted of 325 people of different ethnicities (113 Russians, 137 Tatars, 44 Bashkirs, and 31 people of mixed blood).

Genomic DNA was isolated from peripheral blood lymphocytes by phenol-chloroform extraction [12]. Amplification of investigated loci of DNA was carried out using the polymerase chain reaction of DNA synthesis on a GeneAmp PCR System 2720 thermocycler manufactured by Applied Biosystems (United States). Nucleotide substitutions were determined by restriction fragment length polymorphism (RFLP) analysis. The list of investigated loci, primer sequences, sizes of amplified fragments, and names of restriction enzymes are shown in Table 1 [13–16]. The results of RFLP analysis were evaluated by electrophoresis in 7% polyacrylamide gel followed by staining with ethidium bromide and visualizing in transmitted ultraviolet light. Statistical processing of the results was carried out using MS Office Excel. Pairwise comparison of allele frequencies and genotypes in patients and the control group was carried out using the χ^2 test for contingency tables 2×2 with Yates correction for continuity (http://www.bi-ometrica.tomsk.ru/). When detecting statistically significant differences ($p < 0.05$) between the samples, the odds ratio (OR) and the boundaries of its 95% confidence interval (CI 95%) were estimated [17].

Meta-analysis of the results for the samples of Russians, Tatars, and Bashkirs was carried out using the program WinPepi v. 11.32 (http://www.brixton-health.com/pepi4windows.html) [18]. To calculate the average value of OR and the significance level, we considered models with fixed (Mantel–Haenszel test) and random (DerSimonian and Laird method) effects. To estimate the statistical heterogeneity between different samples, we used the I^2 test (percentage of variability due to heterogeneity of samples) [19]. For $I^2 < 30\%$, the heterogeneity was assessed as mild; for I^2 within 30–50%, as moderate; and for $I^2 > 50\%$, as heterogeneous.

Analysis of intergenic reactions was carried out using GMDR (generalized multifactor-dimensionality reduction) [20].

Table 2. Frequency distribution of genotypes and alleles (number (%)) of polymorphisms *rs494379* and *rs1799750* of gene *MMP-1* in patients with PUD and healthy donors

Genotype, allele	Tatars				Russians				Bashkirs			
	control	*H. pylori*	DU	total sample	control	*H. pylori*	DU	total sample	control	*H. pylori*	DU	total sample
rs494379												
**G/G*	15 (15.46)	6 (8.69)	8 (8.79)	14 (11.11)	18 (15.93)	7 (19.44)	10 (15.38)	12 (13.63)*	3 (9.68)	1 (3.44)	2 (4.00)	2 (3.33)
**A/G*	30 (30.93)	35 (50.72)*	49 (53.84)	65 (51.58)*	40 (35.40)	15 (41.66)	31 (47.69)	42 (47.72)	11 (35.48)	15 (51.72)	23 (46.00)	28 (46.66)
**A/A*	52 (53.61)**	28 (40.57)	34 (37.36)	47 (37.30)	55 (48.67)	14 (38.88)	24 (36.92)	34 (38.63)	17 (54.84)	13 (44.82)	25 (50.00)	30 (50.00)
**G*	60 (30.30)	47 (34.05)	65 (35.71)	93 (36.90)	76 (33.62)	29 (40.27)	51 (39.23)	66 (37.5)	17 (27.41)	17 (29.31)	27 (27.00)	32 (26.66)
**A*	138 (69.70)	91 (65.95)	117 (64.28)	159 (63.10)	150 (66.37)	43 (59.72)	79 (60.77)	110 (62.5)	41 (72.59)	41 (70.68)	73 (73.00)	78 (73.34)
rs1799750												
**1/1*	28 (31.11)	10 (22.22)	17 (20.48)	23 (23.00)	25 (21.55)	7 (31.81)	17 (36.17)	26 (42.62)	6 (23.08)	10 (22.22)	13 (29.55)	14 (26.41)
**2/1*	29 (32.22)	27 (60.00)	42 (50.60)	48 (48.00)	65 (56.03)	11 (50.00)	23 (48.93)	27 (44.26)	13 (50.00)	27 (60.00)	22 (50.00)	29 (54.71)
**2/2*	33 (36.67)	8 (17.77)	24 (28.91)	29 (29.00)	26 (22.41)	4 (18.18)	7 (14.89)	8 (13.11)	7 (26.92)	8 (17.78)	9 (20.45)	10 (18.86)
**1*	85 (47.22)	47 (52.22)	76 (45.78)	94 (47.00)	115 (49.57)	25 (56.81)	57 (60.63)	79 (64.75)	57 (53.77)	71 (37.37)	48 (54.55)	57 (53.77)
**2*	95 (52.78)	43 (47.77)	90 (54.21)	106 (53.00)	117 (50.43)	19 (43.18)	37 (39.37)	43 (35.25)	49 (46.22)	119 (62.63)	40 (45.45)	49 (46.22)

Total sample combines patients with GU and DU (for Tables 2–6).

* $p < 0.05$, accuracy of differences compared to control; ** $p < 0.05$, accuracy of differences compared to patients with PUD.

RESULTS

Patients with PUD and individuals of the control group from the Republic of Bashkortostan were analyzed for allele and genotype frequencies of a number of polymorphisms of genes *MMP-1* (*rs1799750*, *rs494379*), *MMP-2* (*rs2285052*), *MMP-3* (*rs3025058*), *MMP-9* (*rs3918242*, *rs17576*), and *MMP-12* (*rs2276109*) and their tissue inhibitors *TIMP-2* (*rs8179090*) and *TIMP-3* (*rs9619311*).

The population of the Republic of Bashkortostan is ethnically heterogeneous. Our study sample included individuals of the most numerous ethnic groups: Russians, Tatars, and Bashkirs. In order to identify markers of increased and decreased risk of PUD in these ethnic groups, we compared the distribution of allele and genotype frequencies of polymorphic DNA loci between the samples of patients with PUD and individuals of control groups of the respective ethnicity.

The allele and genotype frequencies of polymorphic variants *rs494379* (*–519A > G*) and *rs1799750* (*–1607G > GG*) of gene *MMP-1* are presented in Table 2. The most frequently detected allele was *rs494379*A*, which was identified on 62.50–73.34% of chromosomes in patients from different ethnic groups and 66.37–72.59% of chromosomes in healthy donors. Among genotypes, the most common were heterozygous genotype *rs494379*A/G* (patients 46.66–51.58%, control 30.93–35.48%) and homozygous genotype *rs494379*A/A* (patients 37.30–50.00%, control 48.67–54.84%). Comparative analysis of the allele and genotype frequency distribution of the polymorphic locus *rs494379* among patients with PUD and healthy individuals showed statistically significant differences in Tatars and Russians: genotype *rs494379*A/G* was identified in individuals of the Tatar ethnic group with PUD in 51.58% and Russians in 47.72% cases, whereas in the relevant control groups it was identified only in 30.93 and 35.40% of cases, respectively; thus, they are markers of increased risk of the disease for individuals of these ethnic groups ($\chi^2 = 8.74$, $p = 0.001$; OR = 2.37; 95% CI 1.36–4.14 and $\chi^2 = 2.62$, $p = 0.05$; OR = 1.66; 95% CI 0.94–2.94, respectively). It was revealed that homozygous genotype *rs494379*A/A* (53.61%) was significantly more frequent in the control group of Tatars than in the respective group of patients (37.30%) ($\chi^2 = 5.26$, $p = 0.01$; OR = 0.51; 95% CI 0.30–0.88). Analysis of duplication of guanine in position *–1607G > GG*

Table 3. Frequency distribution of genotypes and alleles (number (%)) of polymorphisms *rs2285052* of gene *MMP-2* and *rs3025058* of gene *MMP-3* in patients with PUD and healthy donors

Genotype, allele	Tatars				Russians				Bashkirs			
	control	*H. pylori*	DU	total sample	control	*H. pylori*	DU	total sample	control	*H. pylori*	DU	total sample
rs2285052 of gene *MMP-2*												
**C/C*	74 (84.09)	51 (85.00)	61 (80.26)	89 (84.76)	93 (83.04)	45 (88.24)	41 (73.21)	60 (80.00)	14 (63.64)	20 (90.91)	37 (88.10)	45 (88.240)
**C/T*	13 (14.77)	9 (15.00)	14 (18.42)	15 (14.29)	18 (16.07)	6 (11.76)	14 (25.00)	14 (18.67)	6 (27.27)	2 (9.09)	5 (11.90)	6 (11.76)
**T/T*	1 (1.14)	0 (0.00)	1 (1.32)	1 (0.95)	1 (0.89)	0 (0.00)	1 (1.79)	1 (1.33)	2 (9.09)	0 (0.00)	0 (0.00)	0 (0.00)
**C*	161 (91.48)	111 (92.50)	136 (89.47)	140 (89.74)	204 (91.07)	140 (89.74)	96 (85.71)	91 (85.85)	161 (91.48)	42 (95.45)	79 (94.05)	140 (89.74)
**T*	15 (8.52)	9 (7.50)	16 (10.53)	16 (10.26)	20 (8.93)	16 (10.26)	16 (14.29)	15 (14.15)	15 (8.52)	2 (4.55)	5 (5.95)	16 (10.26)
rs3025058 of gene *MMP-3*												
**5/5*	17 (18.48)	9 (22.5)	18 (23.07)	23 (24.73)	46 (36.51)	8 (40.00)	17 (36.95)	25 (43.85)	6 (20.00)	2 (10.00)	5 (11.91)	7 (13.73)
**6/5*	65 (46.74)**	11 (27.5)	30 (38.46)	38 (40.86)	38 (30.16)	7 (35.00)	15 (32.61)	16 (28.075)	16 (53.33)	11 (55.00)	23 (54.76)	26 (50.98)
**6/6*	32 (34.78)	20 (50.00)	30 (38.46)	32 (34.41)	42 (33.33)	5 (25.00)	14 (30.43)	16 (28.075)	8 (26.67)	7 (35.00)	14 (33.33)	18 (35.29)
**5*	77 (41.84)	29 (36.25)	66 (42.30)	84 (45.16)	115 (49.57)	23 (57.50)	51 (54.25)	40 (39.22)	28 (46.66)	15 (37.50)	33 (39.29)	40 (39.21)
**6*	107 (58.16)	51 (63.75)	90 (57.70)	102 (54.84)	117 (50.43)	17 (42.50)	43 (45.75)	62 (60.78)	32 (53.34)	25 (62.50)	51 (60.71)	62 (60.79)

**$p < 0.05$, accuracy of differences compared to patients with PUD.

showed that allele *rs1799750*1* was the most frequent, being identified on 47.00–64.75% of chromosomes in patients from different ethnic groups and 47.22–53.77% of chromosomes in the control. The frequency of genotype *rs1799750*2/1* was much higher in Tatars with PUD (48.00%) as compared with the control group ($\chi^2 = 4.25$, $p = 0.02$, OR = 1.94; 95% CI 1.07–3.50). It was found that the combination of genotypes *rs494379*A/A–rs1799750*1/1* of gene *MMP-1* is a marker of reduced risk of PUD for Tatars ($\chi^2 = 3.46$, $p = 0.03$; OR = 0.35; 95% CI 0.13–0.96).

Patients with DU without combination with GU were allocated to a separate group for a special study. Their comparison with the combined sample of healthy donors showed that, in the development of mucosal lesions of the duodenum, a marker of increased risk for Tatars is genotype *rs494379*A/G* of polymorphic locus *rs494379* of gene *MMP-1*, which occurred with a frequency of 53.84% in patients and 30.93% in the control ($\chi^2 = 9.6$, $p = 0.0009$; OR = 1.80; 95% CI 1.25–2.60). In the control group, homozygous genotype *rs494379*A/A* (53.61%) was found significantly more often than in the described group of patients (37.36%): $\chi^2 = 4.24$, $p = 0.01$; OR = 0.67; 95% CI 0.47–0.96.

Patients with GU and DU who at the time of collecting the material were found to be infected with the bacterium *H. pylori* were also allocated to a separate subgroup. Comparative analysis of the frequency distribution of alleles and genotypes described by polymorphisms *rs1799750* and *rs494379* of gene *MMP-1* in the group of patients infected with the bacterium *H. pylori* and in the combined sample of healthy donors showed that heterozygous genotype *rs494379*A/G* was significantly more often (in 50.72% of cases) observed in Tatar patients with *H. pylori* than in the control group (30.93% of cases): $\chi^2 = 5.82$, $p = 0.007$; OR = 2.29; 95% CI 1.21–4.35.

Table 3 shows the frequency of distribution of alleles and genotypes of polymorphism *rs2285052* of gene *MMP-2* in patients with GU and healthy donors. The most frequent allele was *rs2285052*C* identified on

Table 4. Frequency distribution of genotypes and alleles (number (%)) of polymorphisms *rs17576* and *rs3918242* of gene *MMP-9* in patients with PUD and healthy donors

Genotype, allele	Tatars				Russians				Bashkirs			
	control	*H. pylori*	DU	total sample	control	*H. pylori*	DU	total sample	control	*H. pylori*	DU	total sample
rs17576												
*G/G	15 (15.46)	8 (11.42)	13 (14.44)	18 (13.95)	18 (15.93)	3 (8.82)	6 (9.67)	10 (11.90)	6 (22.22)	5 (18.52)	6 (13.33)	7 (12.72)
*A/G	30 (30.93)	35 (50.00)*	43 (47.77)*	64 (49.91)*	40 (35.40)	13 (38.23)	25 (40.33)	38 (45.24)	14 (51.85)	12 (44.44)	19 (42.22)	26 (47.27)
*A/A	52 (53.61) **	27 (38.57) **	34 (37.77)	47 (36.43)	55 (48.67)	18 (52.94)	31 (50.00)	36 (42.86)	7 (25.93)	10 (37.04)	20 (44.44)	22 (40.00)
*G	60 (39.92)	51 (36.42)	69 (38.33)	100 (38.75)	76 (33.62)	19 (27.94)	37 (29.83)	58 (34.52)	26 (48.15)	71 (37.37)	31 (34.44)	40 (36.36)
*A	134 (69.08)	89 (63.58)	111 (61.67)	158 (61.24)	150 (66.37)	49 (72.05)	87 (70.17)	110 (65.48)	28 (51.85)	119 (62.63)	59 (65.56)	70 (63.64)
rs3918242												
*C/C	79 (80.61)	40 (83.33)	74 (83.15)	90 (83.33)	97 (73.48)	21 (87.50)	43 (86.00)	52 (82.54)	23 (82.14)	20 (83.33)	38 (80.85)	45 (77.59)
*C/T	18 (18.37)	18 (16.67)	15 (16.85)	18 (16.67)	34 (25.76)	3 (12.50)	7 (14.00)	11 (17.46)	4 (14.29)	4 (16.67)	9 (19.15)	13 (22.41)
*T/T	1 (1.02)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.76)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.57)	0 (0.00)	0 (0.00)	0 (0.00)
*C	176 (89.79)	198 (91.67)	163 (91.57)	198 (91.67)	228 (86.36)	45 (93.75)	93 (93.00)	45 (93.75)	50 (89.29)	44 (91.67)	85 (90.43)	103 (88.79)
*T	20 (10.21)	18 (8.33)	15 (8.42)	18 (8.33)	36 (13.64)	3 (6.25)	7 (7.00)	3 (6.25)	6 (10.71)	4 (8.33)	9 (9.57)	13 (11.21)

* $p < 0.05$, accuracy of differences compared to control; ** $p < 0.05$, accuracy of differences compared to patients with PUD.

85.85–89.74% of chromosomes in patients from different ethnic groups and on 91.07–91.48% of chromosomes in the control. Genotype *rs2285052*C/C* homozygous for the frequent allele was found at the rate of 80.00–88.24% in patients and 63.64–84.09% in healthy donors; genotype *rs2285052*T/T* homozygous for the relevant allele was rare, on average 0.00–1.33% in patients and 0.89–9.09% in healthy individuals.

The frequency distribution of alleles and genotypes of this locus among patients with PUD and healthy donors of the Russian, Tatar and Bashkir ethnic groups was not significantly different ($p > 0.05$). No associations of polymorphism *rs2285052* of gene *MMP-2* with the risk of DU or the risk of the development of PUD against the background of infection with *H. pylori* was found.

The study of the distribution of genotypes and alleles of polymorphism *rs3025058* of gene *MMP-3* in patients with PUD from different ethnic groups and healthy donors revealed that the frequencies of genotypes in patients and healthy subjects were almost identical (Table 3).

Comparative analysis of the frequency distribution of alleles and genotypes of the described polymorphism *rs3025058* of gene *MMP-3* among patients of the Tatar ethnicity infected with *H. pylori* and the combined sample of healthy donors was carried out. It showed that genotype *rs3025058*6A/5A* was significantly more frequent (46.7% of cases) among individuals of the control group than among patients (27.50% of cases): $\chi^2 = 3.51$, $p = 0.03$; OR = 0.43; 95% CI 0.19–0.96.

Table 4 shows the frequency distribution of alleles and genotypes of polymorphisms *rs3918242* and *rs17576* of gene *MMP-9* in patients with PUD and healthy donors. The most common allele was *rs17576*A*, identified on 61.24– 65.48% of chromosomes in patients from different ethnic groups and 51–69.08% of chromosomes in the control. Genotype *rs17576*A/A* homozygous for the frequent allele and heterozygous genotype *rs17576*A/G* were found with roughly the same frequency; homozygous for the rare allele, genotype *rs17576*G/G* of the described polymorphism occurred with a frequency of 11.90–

Table 5. Frequency distribution of genotypes and alleles (number (%)) of polymorphism *rs2276109* of gene *MMP-12* in patients with PUD and healthy donors

Genotype, allele	Tatars				Russians				Bashkirs			
	control	*H. pylori*	DU	total sample	control	*H. pylori*	DU	total sample	control	*H. pylori*	DU	total sample
**G/G*	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.88)	2 (1.75)	0 (0.00)	1 (1.72)	1 (1.33)	1 (3.23)	0 (0.00)	0 (0.00)	0 (0.00)
**A/G*	24 (25.26)	12 (21.43)	14 (18.66)	21 (18.58)	17 (14.91)	4 (12.90)	9 (15.52)	13 (17.33)	2 (6.46)	5 (21.74)	8 (19.51)	10 (20.41)
**A/A*	71 (74.74)	44 (78.57)	61 (81.33)	91 (80.54)	95 (83.33)	27 (83.10)	48 (82.56)	61 (81.34)	28 (90.31)	18 (78.26)	33 (80.49)	39 (79.59)
**G*	24 (12.63)	12 (10.71)	14 (9.33)	23 (10.18)	21 (9.21)	4 (6.45)	11 (9.48)	15 (10.00)	4 (6.45)	5 (10.87)	8 (9.76)	10 (10.20)
**A*	166 (87.37)	100 (89.29)	136 (90.67)	203 (89.82)	207 (90.79)	58 (93.55)	105 (90.52)	135 (90.00)	58 (93.55)	41 (89.13)	74 (90.24)	88 (89.80)

13.95% in patients and 15.46–22.22% in healthy individuals without any signs of gastrointestinal pathology.

Comparative analysis of the frequency distribution of alleles and genotypes *rs17576* of gene *MMP-9* showed that Tatar patients with PUD in relation to the similar group of healthy individuals revealed a trend toward an increase in the frequency of allele *rs17576*G* (38.75 and 39.92%, respectively) and, consequently, a downward trend in the frequency of allele *rs17576*A* (61.24 and 69.08%, respectively), $p = 0.05$. It was found that Tatars more frequently than other ethnic groups had allele *rs17576*A* of gene *MMP-9* (69.08, 66.37, 51.85%, respectively). For Tatars, genotype *rs17576*A/A* homozygous for the frequent allele is a marker of reduced risk of PUD, whereas heterozygous genotype *rs17576*A/G* is a marker of increased risk for this disease ($\chi^2 = 5.95$, $p = 0.007$; OR = 0.49; 95% CI 0.29–0.84 and $\chi^2 = 7.20$, $p = 0.003$; OR = 2.19; 95% CI 1.26–3.81, respectively).

Comparison of individuals with DU to the combined sample of healthy donors revealed that genotype *rs17576*A/G* occurred with a significantly higher frequency in patients than in healthy donors ($\chi^2 = 5.42$, $p = 0.009$; OR = 1.57; 95% CI 1.08–2.27), while homozygous genotype *rs17576*A/A* was detected with the approximately equal frequency ($p = 0.05$).

It was found that polymorphism *rs17576* of gene *MMP-9* is associated with the risk of PUD against the background of infection with *H. pylori*. Representatives of the Tatar ethnic group were revealed to have a relationship between the presence of genotype *rs17576*A/G* and the risk of the disease under study ($\chi^2 = 5.44$, $p = 0.009$; OR = 2.23; 95% CI 1.18–4.21), whereas the frequency of genotype *rs17576*A/A* in Tatar patients with PUD against the background of infection was lower than in the control (38.57 and 53.61%, respectively; $\chi^2 = 3.10$, $p = 0.03$; OR = 0.54; 95% CI 0.29–1.01).

The most frequent allele of polymorphism *rs3918242* of gene *MMP-9* was allele *rs3918242*C*, which was found in patients of different ethnic groups with the frequency of 88.79–93.75% and in the control with the frequency of 86.36–89.79%. Among the genotypes, the most frequent was homozygous genotype *rs3918242*C/C* (patients 77.59–83.33%, healthy donors 73.48–82.14%), while genotype homozygous for the rare allele *rs3918242*T/T* of the described polymorphic locus in patients in our sample was not found and in the group of healthy individuals was diagnosed with a frequency of less than 4%. Analysis of the frequency distribution of alleles and genotypes of this DNA locus showed no statistically significant differences between the studied samples of patients with GU and the control ($p > 0.05$).

Comparative analysis of the frequency distribution of alleles and genotypes of polymorphism *rs2276109* of gene *MMP-12* among patients with PUD and individuals without signs of gastrointestinal pathology showed that the frequency of homozygous genotype *rs2276109*A/A* varied from 79.59 to 81.34% in the group of patients and from 74.74 to 90.31% in the control group, whereas genotype homozygous for the rare allele *rs2276109*G/G* of the described polymorphic locus was detected in patients and healthy individuals with a frequency of less than 4% (Table 5). Separation of the groups of subjects into subgroups according to their ethnicity identified no associations of this locus with the risk of GU ($p > 0.05$). Also, no association of polymorphism *rs2276109* of gene *MMP-12* with the risk of DU or the risk of PUD against the background of infection with *H. pylori* was found.

The study of polymorphism *rs8179090* of gene *TIMP-2* in patients with PUD and healthy donors found that, in all the studied groups, genotype *rs8179090*G/G* is the most frequent, occurring in 97.87–98.02% of patients with gastrointestinal diseases and 87.50–98.75% of the control, as well as its

Table 6. Frequency distribution of genotypes and alleles (number (%)) of polymorphisms *rs8179090* of gene *TIMP-2* and *rs9619311* of gene *TIMP-3* in patients with PUD and healthy donors

Genotype, allele	Tatars				Russians				Bashkirs			
	control	*H. pylori*	DU	total sample	control	*H. pylori*	DU	total sample	control	*H. pylori*	DU	total sample
rs8179090 of gene *TIMP-2*												
**G/G*	79 (98.75)	43 (97.72)	80 (97.56)	99 (98.02)	120 (92.24)	16 (100.00)	36 (97.30)	46 (97.87)	14 (87.50)	19 (95.00)	37 (100.00)	45 (97.83)
**C/G*	1 (1.25)	1 (2.27)	2 (2.44)	2 (1.98)	6 (4.76)	0 (0.00)	1 (2.70)	1 (2.13)	2 (12.50)	1 (5.00)	0 (0.00)	1 (2.17)
**C/C*	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
**G*	159 (99.37)	87 (98.86)	162 (98.78)	200 (99.00)	246 (97.62)	32 (100.00)	73 (98.65)	93 (98.94)	30 (93.75)	39 (97.50)	74 (100.00)	91 (98.91)
**C*	1 (0.63)	1 (1.13)	2 (1.22)	2 (1.00)	1 (1.06)	0 (0.00)	1 (1.35)	1 (1.06)	2 (6.25)	1 (2.50)	0 (0.00)	1 (1.09)
rs9619311 of gene *TIMP-3*												
**C/C*	19 (20.65)	4 (10.81)	6 (9.09)	8 (9.76)	18 (15.25)	1 (4.76)	3 (6.52)	5 (8.33)	5 (82.42)	4 (17.39)	6 (13.64)	7 (13.21)
**C/T*	35 (38.04)**	8 (21.62)**	14 (21.21)**	16 (19.51)	62 (52.54)**	6 (28.57)**	10 (21.74)**	14 (23.33)	14 (16.36)	5 (21.74)	14 (31.82)	17 (32.08)
**T/T*	38 (41.30)	25 (67.57)*	46 (69.70)*	58 (70.73)*	38 (32.21)	14 (66.67)*	33 (71.74)*	41 (68.33)*	8 (1.21)	14 (60.86)	24 (54.54)	29 (54.71)
**C*	73 (39.67)**	16 (21.62)	26 (19.70)**	32 (19.51)	98 (41.53)**	8 (19.05)	16 (17.39)**	24 (20.00)	24 (44.44)	13 (28.26)	26 (29.55)	31 (29.25)
**T*	111 (60.33)	58 (78.38)	106 (80.30)	132 (80.49)*	138 (58.47)	34 (80.95)	76 (82.61)	96 (80.00)*	30 (55.56)	33 (71.74)	62 (70.45)	75 (70.75)

* $p < 0.05$, accuracy of differences compared to control; ** $p < 0.05$, accuracy of differences compared to patients with PUD.

allele *rs8179090*G*, which was identified on 98.91–99.00% of chromosomes in patients from different ethnic groups (Table 6). Analysis of the frequency distribution of alleles and genotypes showed no statistically significant differences between the studied samples of patients with PUD and the control ($p > 0.05$). Also, no associations of polymorphism *rs8179090* of gene *TIMP-2* with the risk of DU or the risk of PUD against the background of infection with *H. pylori* was found.

The frequency distribution of alleles and genotypes of polymorphism *rs9619311* of gene *TIMP-3* is shown in Table 6. Common allele *rs9619311*T* was detected in patients from different ethnic groups with the frequency of 70.75–80.49% and in healthy donors with the frequency of 55.56–60.33%. The most common was genotype *rs9619311*T/T* homozygous for this allele (patients 54.71–70.73%, control 1.21–41.30%).

Comparative analysis of the frequency distribution of alleles and genotypes of polymorphic locus *rs9619311* between patients and healthy donors according to their ethnicity showed statistically significant differences in Tatars and Russians. In Tatars with PUD, genotype *rs9619311*T/T* (70.73%) and its allele *rs9619311*T* (80.49%) (in the healthy group, they were found only in 41.30 and 60.33% of cases) are markers of increased risk of combined forms of PUD ($\chi^2 = 14.01$, $p = 0.0001$; OR = 3.43; 95% CI 1.82–6.45 and $\chi^2 = 15.78$, $p = 0.0001$; OR = 2.71; 95% CI 1.67–4.41, respectively). For the Russian ethnicity, it was revealed that allele *rs9619311*T* and genotype *rs9619311*T/T* are also markers of increased risk of the disease ($\chi^2 = 15.42$, $p = 0.0001$; OR = 2.84; 95% CI 1.69–4.76 and $\chi^2 = 19.60$, $p = 0.0001$; OR = 4.54; 95% CI 2.33–8.85, respectively). It was found that heterozygous genotype *rs9619311*C/T* was found significantly more frequent in the control group of Tatars and Russians (38.04 and 52.54%, respectively) than in the described groups of patients (19.51 and 23.33%, respectively): $\chi^2 = 6.31$, $p = 0.006$; OR = 0.39; 95% CI 0.19–0.77 and $\chi^2 = 12.70$, $p = 0.0002$; OR = 0.27; 95% CI 0.13–0.55, respectively. For Russians and Tatars, it was found that a marker of reduced risk of PUD was a rare allele *rs9619311*C* identified at a frequency of 41.53 and 39.67% in the control as compared to the group of patients ($\chi^2 = 15.42$, $p = 0.0001$; OR = 0.35; 95% CI 0.20–0.59 and $\chi^2 = 15.78$, $p = 0.0001$; OR = 0.37; 95% CI 0.23–0.59, respectively).

Table 7. Results of meta-analysis of studied polymorphic loci in patients with peptic ulcer disease and individuals from control group of Russian, Tatar and Bashkir ethnicity

Gene	Polymorphic locus	Alleles	Fixed effect model		Random effect model		I^2, %
			P	OR	*P*(*R*)	OR(*R*)	
MMP-1	*rs1799750*	*1*	–	–	0.018	0.92	77.3
		2	–	–	0.018	0.92	77.3
	rs494379	*A*	0.137	–	–	–	0.0
		G	0.137	–	–	–	0.0
MMP-2	*rs2285052*	*C*	0.73	–	–	–	0.0
		T	0.73	–	–	–	0.0
MMP-3	*rs3025058*	*5*	0.20	–	–	–	37.6
		6	0.20	–	–	–	37.6
MMP-9	*rs3918242*	*C*	0.4	–	–	–	0.0
		T	0.4	–	–	–	0.0
	rs17576	*A*	0.089	–	0.089	–	58.6
		G	0.089	–	–	–	58.6
MMP-12	*rs2276109*	*A*	0.51	–	–	–	0.0
		G	0.51	–	–	–	0.0
TIMP-2	*rs8179090*	*C*	0.45	–	–	–	0.0
		G	0.45	–	–	–	0.0
TIMP-3	*rs9619311*	*C*	0.49	–	–	–	0.0
		T	0.49	–	–	–	0.0

P, p value fixed; *P*(*R*), p value random; I^2, Higgins heterogeneity test.

Comparison of individuals with DU not combined with GU and the combined sample of healthy donors showed that a marker of increased risk was again genotype *rs9619311*T/T*, identified among patients of Tatar and Russian ethnicity at a frequency of 69.70–71.74% compared to the similar group of individuals with no signs of this disease ($\chi^2 = 11.32$, $p = 0.0004$; OR = 3.26; 95% CI 1.67–6.38 and $\chi^2 = 23.58$, $p = 0.0001$; OR = 6.94; 95% CI 3.10–15.55, respectively). In the control groups of the given ethnicities, heterozygous genotype *rs9619311*C/T* was found significantly more often than in the groups of patients (21.21 and 21.74% of cases, respectively): $\chi^2 = 4.33$, $p = 0.01$; OR = 0.43; 95% CI 0.21–0.91 and $\chi^2 = 11.53$, $p = 0.0003$; OR = 0.25; 95% CI 0.11–0.55. It was found that for persons of the Tatar and Russian ethnicity, a marker of reduced risk of ulceration of the mucous membrane of duodenum was allele *rs9619311*C*, found on 39.67 and 41.53% of chromosomes in the control and 19.70 and 17.39% in patients ($\chi^2 = 13.34$, $p = 0.001$; OR = 0.37; 95% CI 0.22–0.62 and $\chi^2 = 15.95$, $p = 0.0001$; OR = 0.29; 95% CI 0.16–0.53, respectively).

Associations of polymorphism *rs9619311* of gene *TIMP-3* with the risk of PUD against the background of infection with *H. pylori* were found. Representatives of the Russian and Tatar ethnic groups were revealed to have a relationship between the presence of genotype *rs9619311*T/T* and the risk of PUD ($\chi^2 = 6.27$, $p = 0.006$; OR = 2.96; 95% CI 1.32–6.61 and $\chi^2 = 7.63$, $p = 0.003$; OR = 4.21; 95% CI 1.57–11.28, respectively). The frequency of occurrence of genotype *rs9619311*C/T* in Tatar patients was lower than in the control ($p = 0.05$). It was found that heterozygous genotype *rs9619311*C/T* was detected significantly more often in healthy donors than in the similar group of *H. pylori*-positive Russian patients with PUD ($\chi^2 = 3.19$, $p = 0.03$; OR = 0.36; 95% CI 0.13–0.99).

We carried out meta-analysis of studies of polymorphic loci of genes of matrix metalloproteinases and their tissue inhibitors in Russians, Tatars, and Bashkirs. The results are shown in Table 7. Meta-analysis made it possible to detect statistically significant differences between samples of patients and healthy individuals for polymorphic locus *rs1799750* of gene *MMP-1*. Single nucleotide substitution *rs1799750* of gene *MMP-1* showed high sample heterogeneity, $I^2 = 77.3\%$ (95% CI 0.81–1.1). Since this value of heterogeneity was high, we considered the random effect model (DerSimonian–Laird method), and differences for this locus between the samples of patients infected with *H. pylori* and healthy individuals were statistically significant: $p = 0.018$ ($OR_C = 0.92$ (95% CI 0.49–1.73), $OR_T = 0.92$ (95% CI 0.55–1.56)). Meta-analysis failed to detect statistically significant differences between samples of patients with PUD and

healthy donors for polymorphic loci *rs494379* of gene *MMP-1*, *rs2285052* of gene *MMP-2*, *rs3025058* of gene *MMP-3*, *rs3918242* and *rs17576* of gene *MMP-9*, *rs2276109* of gene *MMP-12*, *rs8179090* of gene *TIMP-2*, and *rs9619311* of gene *TIMP-3*.

In addition to assessing the effect of individual polymorphisms on the risk of PUD, the program GMDR (generalized multifactor-dimensionality reduction) was used to model interaction models of the studied DNA loci of metalloproteinase genes and their tissue inhibitors. No statistically significant combinations of polymorphisms *rs1799750* and *rs494379* of gene *MMP-1*, *rs2285052* of gene *MMP-2*, *rs3025058* of gene *MMP-3*, *rs3918242* and *rs17576* of gene *MMP-9*, *rs2276109* of gene *MMP-12, rs8179090* of gene *TIMP-2*, and *rs9619311* of gene *TIMP-3* leading to predisposition to PUD were detected.

DISCUSSION

For the first time in the Republic of Bashkortostan, a study of associations with the risk of PUD was carried out in nine polymorphisms of five genes of matrix metalloproteinases: *MMP-1* (*rs1799750*, *rs494379*), *MMP-2* (*rs2285052*), *MMP-3* (*rs3025058*), *MMP-9* (*rs3918242*, *rs17576*), and *MMP-12* (*rs2276109*) and their tissue inhibitors *TIMP-2* (*rs8179090*) and *TIMP-3* (*rs9619311*). Interethnic comparison of the frequency distribution of alleles and genotypes in patients and healthy donors revealed the most statistically significant results in the study of polymorphisms *rs1799750* and *rs494379* of gene *MMP-1*, *rs17576* of gene *MMP-9*, and *rs9619311* of gene *TIMP-3*.

Elevated levels of mRNA of interstitial collagenase (MMP-1) and stromelysin-1 (MMP-3) were found in tissue samples of human gastric mucosa for various inflammatory diseases such as Crohn's disease and ulcerative colitis [21]. Our study revealed that genotype *rs494379*A/G* of gene *MMP-1* is a marker of increased risk of PUD in Russians and Tatars, as well as that this molecular marker is significantly more frequent in patients with DU as compared with the control group and in Tatar patients infected with *H. pylori*. Allele *rs1799750*1* and its resulting genotype *rs1799750*1/1* of gene *MMP-1* were also more common in the group of patients of Russian ethnicity, and the frequency of genotype *rs1799750*2/1* was much higher in Tatars with PUD as compared with the control group. In addition, in the same groups, we identified a marker of reduced risk of pathology—genotype *rs494379*A/A*; it was found that the combination of genotypes *rs494379*A/A–rs1799750*1/1* of gene *MMP-1* is a marker of reduced risk of PUD for Tatars. Meta-analysis made it possible to detect statistically significant differences between the samples of patients and healthy individuals for polymorphic locus *rs1799750* of gene *MMP-1*.

Changes in MMP activity (both increase and decrease) accompany many human diseases (tumors; fibrosing diseases of heart, lungs, liver, and kidneys; arthritis; gastric ulcer; etc.) [22]. In 2012, H.-C. Cheng et al. [23] showed that expression levels of genes *MMP-3*, *-7*, *-9*, and *TIMP-1* are increased in cells of the gastric mucosa in patients with GU as compared with similar tissue from healthy donors. M. Tomita et al. [24] revealed that patients with GU have high levels of concentrations of MMP-3 and tissue inhibitor of metalloproteinase-1 (TIMP-1), as well as several pro-inflammatory cytokines IL-1β, IL-6, and IL-8. Furthermore, the level of MMP-3 was significantly higher at the site of ulceration than in the antrum; thus, researchers assumed that stromelysin-1 (MMP-3) may perform an important function in the process of healing of ulcers [24].

A study carried out by Yeh et al. [25] found that genotype *rs3025058*6A/6A* of gene *MMP-3* was significantly more frequent in the group of patients with duodenal ulcer than in a similar group of patients with gastritis. Also, the same study found that this genotype is a marker of increased risk of DU for women infected with *H. pylori*. Our study revealed that heterozygous genotype *rs3025058*6A/5A* of gene *MMP-3* is a protective marker for the risk of PUD among *H. pylori*-infected patients of Tatar ethnicity. There are works of other researchers showing the association of this DNA locus and stomach cancer. For example, Dey et al. [26] showed that genotypes *rs3025058*6A/5A* and *rs3025058*5A/5A* serve as a risk factor in relation to the development of gastroduodenal pathology.

Some studies have shown that expression of MMP-2 and MMP-9 is highly pronounced in tumor tissues as compared with normal tissue and that polymorphisms *rs2285052* of gene *MMP-2* and *rs3918242* of gene *MMP-9* play an important role in the development of gastric ulcers and stomach cancer [27, 28]. MMP-9, one of the most important MMPs, is known for degrading the extracellular matrix and basement membrane, thereby contributing to disease progression of various cancers by increasing the migration, invasion, metastasis, and angiogenesis [29]. It was shown that high levels of MMP-9 are strongly correlated with tumor aggressiveness and poor prognosis in various human cancers, but the study of Lin et al. [30] found no association of polymorphism *rs2285052* of gene *MMP-2* with the size of a stomach cancer tumor, tissue differentiation, or invasion. In 2013, Zheng et al. [31] analyzed the association of expression of MMP-12 and the overall survival of patients with gastric cancer. It was found that the level of expression of MMP-12 in the tumor tissue was significantly higher than in the intact gastric mucosa. Analysis of the relationship of the level of expression of MMP-12 in tumors with clinical and morphological features of gastric cancer noted a higher content of MMP-12 in patients with lymph node metastases in distant organs with an increase in the degree of invasion and TNM stage. Moreover, patients with gastric cancer whose tumor expresses MMP-12 have a lower survival rate as

compared with patients who do not have expression of this proteinase. The authors consider MMP-12 as one of the main independent prognostic factors in patients with gastric cancer [31]. There are published data that indicate the relationship of polymorphism *rs2276109* of gene *MMP-12* with a number of diseases such as lung cancer, chronic obstructive pulmonary disease, and myocardial infarction [32–34].

In this paper, we analyzed the frequency distribution of alleles and genotypes of single nucleotide polymorphisms *rs2285052* of gene *MMP-2*, *rs3918242* and *rs17576* of gene *MMP-9*, and *rs2276109* of gene *MMP-12* in patients with PUD and healthy donors from the Republic of Bashkortostan. It was shown that homozygous genotype *rs17576*A/A* and allele *rs17576*A* of polymorphism *rs17576* of gene *MMP-9* are significantly more frequent in the control group of Tatar patients with PUD, as well as those *H. pylori*-positive, whereas heterozygous genotype *rs17576*A/G* is a marker of increased risk of PUD against the background of infection with the bacterium. Comparison of individuals with duodenal ulcer and the control group revealed a tendency toward an increase in the frequency of genotype *rs17576*A/G* in the patients, whereas the frequency of homozygous genotype *rs17576*A/A* in the studied groups was almost identical. Analysis of the frequency distribution of alleles and genotypes *rs2285052* of gene *MMP-2*, *rs3918242* of gene *MMP-9*, and *rs2276109* of gene MMP-12 showed no statistically significant differences between the studied samples of patients with PUD and the control.

MMP activation in vivo in the intercellular space is specifically inhibited by endogenous tissue inhibitors of metalloproteinases (TIMPs), which are connected to zinc-binding sites of active MMPs in an equimolar ratio. TIMPs form strong complexes with both active forms of MMPs and their secreted proenzymes, thereby regulating their activity [35]. The TIMP family consists of four structurally related proteins, three of which, TIMP-1, -2, and -4, are secreted in soluble form and one, TIMP-3, is associated with the extracellular matrix. TIMP-1 and -3 possess antiangiogenic properties, and TIMP-2 is involved in the activation of MMP-2. Structurally, TIMPs are highly specific to the active binding of MMP (according to "lock and key" model) [36]. All TIMPs inhibit the full range of MMPs, except for TIMP-1, which is not able to inhibit MT1-MMP [37]. In addition to inhibiting the activity of metalloproteinases, TIMPs have other biological functions. TIMP-2 (but not TIMP-1) specifically inhibits growth of endothelial cells induced by the fibroblast growth factor [36, 38].

Our study revealed that homozygous genotype *rs9619311*T/T* and its forming allele *rs9619311*T* are markers of increased risk of PUD, whereas genotype *rs9619311*C/T* and allele *rs9619311*C* of gene *TIMP-3* are markers of reduced risk of this pathology in Russians and Tatars, regardless of infection with *H. pylori*. Studies conducted by foreign authors demonstrated that polymorphism *rs9619311* of gene *TIMP-3* is associated with the risk of some diseases, such as bladder cancer [39].

On the whole, the results of this study confirm the important role of genes of metalloproteinases and their tissue inhibitors in the pathogenesis of gastric ulcers and duodenal ulcers.

REFERENCES

1. Konturek, S.J., *Helicobacter pylori and Its Involvement in Gastritis and Peptic Ulcer Formation*, Konturek, S.J. and Konturek, P.C., Eds., *J. Physiol. Pharmacol.*, 2006, vol. 57, no. 3, pp. 29–50.
2. Zelickson, M.S., Bronder, C.M., Johnson, B.L., et al., *Helicobacter pylori* is not the predominant etiology for peptic ulcers requiring operation, *Am. Surg.*, 2011, vol. 77, pp. 1054–1060.
3. Bertleff, M.J. and Lange, J.F., Perforated peptic ulcer disease: a review of history and treatment, *Dig. Surg.*, 2010, vol. 27, pp. 161–169.
4. Lau, J.Y., Sung, J., Hill, C., et al., Systematic review of the epidemiology of complicated peptic ulcer disease: incidence, recurrence, risk factors and mortality, *Digestion*, 2011, vol. 84, pp. 102–113.
5. http://www.mednet.ru
6. Baranovskii, A.Yu., *Gastroenterologiya: spravochnik* (Gastroenterology: Reference Book), Baranovskii, A.Yu., Ed., St. Petersburg: Piter, 2011.
7. Go, M.F., Natural history and epidemiology of *Helicobacter pylori* infection, *Aliment. Pharmacol. Ther.*, 2002, vol. 16, pp. 3–15.
8. Aljamal, A., Effects of turmeric in peptic ulcer and *Helicobacter pylori*, *Plant Sci. Res.*, 2011, vol. 3, pp. 25–28.
9. Snaith, A. and El-Omar, E.M., *Helicobacter pylori*: host genetics and disease outcomes, *Expert Rev. Gastroenterol. Hepatol.*, 2008, vol. 2, no. 4, pp. 577–585.
10. Pasieshvili, L.M. and Morgulis, M.V., State and role of cytokines in formation and progression of diseases of the alimentary channel, *Suchasna Gastroenterol.*, 2004, no. 3, pp. 8–11.
11. Tsaregorodtseva, T.M., Zotina, M.M., and Serova, T.I., Interleukins in chronic diseases of digestive organs, *Ter. Arkh.*, 2003, no. 2, pp. 7–9.
12. Mathew, C.C., The isolation of high molecular weight eukaryotic DNA, *Methods Mol. Biol.*, 1984, vol. 2, pp. 31–34.
13. Santtila, S., Savinainen, K., Hurme, M., et al., Presence of the IL-1RA allele 2 (IL-1RN*2) is associated with enhanced IL-1β production in vitro, *Scand. J. Immunol.*, 1998, vol. 47, pp. 195–198.
14. Hull, J., Ackerman, H., Isles, K., et al., Unusual haplotypic structure of IL8, a susceptibility locus for a common respiratory virus, *Am. J. Hum. Genet.*, 2001, vol. 69, pp. 413–419.
15. Karplus, T.M., Jeronimo, S.M., Chang, H., et al., Association between the tumor necrosis factor locus and the clinical outcome the *Leishmania chagasi* infection, *Infect. Immun.*, 2002, vol. 70, no. 12, pp. 6919–6925.
16. Hang, L.W., Hsia, T.C., Chen, W.C., et al., Interleukin-10 gene –627 allele variants, not interleukin-I beta gene

and receptor antagonist gene polymorphisms, are associated with atopic bronchial asthma, *J. Clin. Lab. Anal.*, 2003, vol. 17, no. 5, pp. 168–173.

17. Schlesselman, J., *Case-Control Studies: Design, Conduct, Analysis*, New York: Oxford Univ. Press, 1982, pp. 58–96.
18. Abramson, J.H., WINPEPI updated: computer programs for epidemiologists, and their teaching potential, *Epidemiol. Perspect. Innovations*, 2011, vol. 8, pp. 1–9.
19. Higgins, J.P. and Thompson, S.G., Quantifying heterogeneity in a meta-analysis, *Stat. Med.*, 2002, vol. 21, pp. 1539–1558.
20. Lou, X.Y., Chen, G.B., Yan, L., et al., A generalized combinatorial approach for detecting gene-by-gene and gene-by-environment interactions with application to nicotine dependence, *Am. J. Hum. Genet.*, 2007, vol. 80, no. 6, pp. 1125–1137.
21. Saarialho-Kere, U.K., Vaalamo, M., Puolakkainen, P., et al., Enhanced expression of matrilysin, collagenase, and stromelysin-1 in gastrointestinal ulcers, *Am. J. Pathol.*, 1996, vol. 148, pp. 519–526.
22. Bobkova, I.N., Kozlovskaya, L.V., and Li, O.A., Matrix metalloproteinases in the pathogenesis of acute and chronic kidney disease (review of literature), *Nefrol. Dializ*, 2010, vol. 10, no. 2, pp. 105–111.
23. Cheng, H.-C., Yang, H.-B., Chang, W.-L., et al., Expression of MMPs and TIMP-1 in gastric ulcers may differentiate *H. pylori*-infected from NSAID-related ulcers, *Sci. World J.*, 2012, pp. 1–9.
24. Tomita, M., Ando, T., Minami, M., et al., Potential role for matrix metalloproteinase-3 in gastric ulcer healing, *Digestion*, 2009, vol. 79, pp. 23–29.
25. Yeh, Y.-Ch., Cheng, H.-Ch., Chang, W.-L., et al., Matrix metalloproteinase-3 promoter polymorphisms but not dupA-*H. pylori* correlate to duodenal ulcers in *H. pylori*-infected females, *Microbiology*, 2010, vol. 10, pp. 218–225.
26. Dey, S., Stalin, S., Gupta, A., et al., Matrix metalloproteinase3 gene promoter polymorphisms and their haplotypes are associated with gastric cancer risk in Eastern Indian population, *Mol. Carcinog.*, 2011, vol. 51, pp. 1–12.
27. Kim, S-J., Park, Y.S., Paik, H.D., et al., Effect of anthocyanins on expression of matrix metalloproteinase-2 in naproxen-induced gastric ulcers, *Br. J. Nutr.*, 2011, vol. 106, pp. 1792–1801.
28. Yang, T.-F., Guo, L., and Wang, Q., Meta-analysis of association between for polymorphisms in the matrix metalloproteinases gene in gastric cancer risk, *Asian Pac. J. Cancer Prev.*, 2014, vol. 15, no. 3, pp. 1263–1267.
29. Matsumura, S., Oue, N., Nakayama, H., et al., A single nucleotide polymorphism in the MMP-9 promoter affects tumor progression and invasive phenotype of gastric cancer, *J. Cancer Res. Clin. Oncol.*, 2005, vol. 131, pp. 19–25.
30. Lin, X.D., Chen, G., Li, C., et al., Association of polymorphism in matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-2 with genetic susceptibility of gastric cancer, *Chin. J. Prev. Med.*, 2011, vol. 45, no. 8, pp. 711–716.
31. Zheng, J., Chu, D., Wang, D., et al., Matrix metalloproteinase-12 is associated with overall survival in Chinese patients with gastric cancer, *J. Surg. Oncol.*, 2013, vol. 107, no. 7, pp. 746–751.
32. Li, S., Zhou, W., Assomaning, A., et al., Genotypes and haplotypes of matrix metalloproteinase 1, 3 and 12 genes and the risk of lung cancer, *Carciogenesis*, 2006, vol. 27, pp. 1024–1029.
33. Haq, I., Chappel, S., Johnson, S.R., et al., Association of MMP-12 polymorphisms with severe and very severe COPD: a case control study of MMPs-1,9 and 12 in a European population, *BMC Med. Genet.*, 2010, vol. 11, pp. 1–11.
34. Perez-Hernandes, N., Vargas-Alarcon, G., Martinaz-Rodrigues, N., et al., The matrix metalloproteinase-2—1575 gene polymorphisms is associated with the risk of developing myocardial infarction in Mexican patients, *J. Atheroscler. Thromb.*, 2012, vol. 19, pp. 718–727.
35. Ramnath, N. and Creaven, P.J., Matrix metalloproteinase inhibitors, *Curr. Oncol. Rep.*, 2004, vol. 6, no. 2, pp. 96–102.
36. Murphy, G. and Nagase, H., Progress in matrix metalloproteinase research, *Mol. Aspects Med.*, 2008, vol. 29, no. 5, pp. 290–308.
37. Sounni, N.E., Janssen, M., Foidart, J.M., and Noel, A., Membrane type-1 matrix metalloproteinase and TIMP-2 in tumor angiogenesis, *Matrix Biol.*, 2003, vol. 22, no. 1, pp. 55–61.
38. Brew, K., Dinakarpandian, D., and Nagase, H., Tissue inhibitors of metallo-proteinases: evolution, structure and function, *Biochim. Biophys. Acta*, 2000, vol. 1477, pp. 267–283.
39. Wieczorek, E., Reszka, E., Jablonowski, Z., et al., Genetic polymorphisms in matrix metalloproteinases (MMPs) and tissue inhibitors of MPs (TIMPs), and bladder cancer susceptibility, *BJU Int.*, 2013, vol. 8, pp. 1207–1214.

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