In conclusion, inflation, which continues for more than a quarter of a century, does not make it very likely to determine the amount of conditionally underexploited national income in monetary terms. However, the overall economic damage caused by deaths from malignant formations to the population of Yakutia was quite significant. Due to the death of the population of the Republic from malignant neoplasms every year loses 3.1 thousand person-years of life, including 0.72 thousand of working age, which is 23.3% of the total loss.

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ORIGINAL RESEARCHES

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THE ANALYSIS OF ASSOCIATIONS OF *HELICOBACTER PYLORI BABA* GENE IN PATIENTS WITH CLINICAL OUTCOMES OF GASTRODUODENAL DISEASES IN YAKUTIA

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Introduction: *Helicobacter pylori* has several of the most characteristic adhesins that have the property of a targeted effect on epithelial cells of human stomach, among which the *babA* gene is the most studied and exists in several variants – *babA1*, *babA2*. The BabA protein is high-affinity and binds to mono or difucosylated blood group antigens and each can be modified into blood group A, B, or 0 and expressed on epithelial cells of the stomach. The clinical outcomes of gastroduodenal diseases, depending on the *babA* variants of *Helicobacter pylori* circulated in Yakutia, has not been previously studied. The aim of this work is to analyze of associations of *Helicobacter pylori babA* gene in patients with clinical outcomes of gastroduodenal diseases in Yakutia.

Materials and methods: Gastric biopsy specimens were obtained from 322 patients. According to the results of histological analysis, 188 patients had the presence of *Helicobacter pylori* and divided into two groups: chronic gastritis and chronic gastritis with erosions and ulcers.

Results: Chronic gastritis was established in 96 samples (51,1%), and the diagnosis of chronic gastritis with erosions and ulcers was established in 92 samples (48,9%). *Helicobacter pylori babA2* gene variant were identified in 65 samples (34,5%), and *babA1* in 123 samples (65,4%). In the male patients the frequency of the *babA2* gene was almost two times higher (69,6%) than in the female patients (38,3%) (p<0,001). In contrast, in female patients more common was the *babA1* gene (61,6%) than in male patients (30,3%) (p<0,001). It was found that the *babA2* gene variant was significantly more common in samples of patients with chronic gastritis associated with erosions and ulcers of stomach and duodenum (43,4%) than in patients with chronic gastritis (26,0%) (p<0,05). Patients diagnosed with chronic gastritis had more often the *babA1* gene variant (73,9%), than patients with erosive gastritis (56,5%) (p<0,05). In comparing group of patients with different degrees of inflammation there were no statistically significant difference in the activity of inflammation with the presence of the *babA* gene, but there was a slight statistical difference with the second degree of dissemination which had the *babA1* gene variant.

Conclusion: We showed relationship between *babA2* gene of *Helicobacter pylori* and more severe clinical outcomes (erosions and ulcers) in patients with gastroduodenal diseases in Yakutia. Obtained result confirms previously known about data *babA2* which are more virulent and pathogenic than *babA1* gene of *Helicobacter pylori*. The data about *babA2* gene was more frequent in male patients and it may be an additional risk factor for more severe gastroduodenal diseases.

Keywords: *Helicobacter pylori*, gastroduodenal diseases, *babA* gene, Yakutia.

Introduction. In 1994, the US National Institute of Health published an expert opinion stating that the majority of recurrent gastric ulcers and gastritis with increased acidity are caused by infection with the bacterium *Helicobacter pylori* (*H. pylori*). Since then, evidence has gradually accumulated that duodenal ulcers and duodenitis are also associated with *H. pylori* infection. [17, 18]. In 2005 Robin Warren and Barry Marshall were awarded the Nobel Prize in Medicine about the medical significance of the bacteria. Recently, a lot of research has been done on the *H. pylori*. Most studies have found that *H. pylori* is a proven cause of gastroduodenal diseases (chronic gastritis, erosion, ulcers, and cancer of the human stomach). According to the latest data, the proportion of peptic ulcer associated with *H. pylori* infection accounts for 38% of gastric ulcers and 56% of duodenal ulcers worldwide [1].

These facts contributed to the emergence of a large number of works that devoted to the study of characteristics, prevalence and clinical significance of various on the genetic structure and on the virulence of *H. pylori* strains, including its molecular genetic characteristics. It has been shown that genetic factors of *H. pylori* – virulence and pathogenicity can have a great influence on the development and clinical outcomes of diseases of the upper gastrointestinal tract, as well as on the morphological changes in the gastric mucosa. Recently, the spectrum of genetic factors of pathogenicity of *H. pylori* is expanding and their role in

the development of pathological changes at gastroduodenal diseases is becoming more and more obvious [2].

Currently it is known that the genome of the *H. pylori* strain "26695" is represented by 1 667 867 base pairs, and contains 1 630 genes, which 1 576 encode proteins [15]. The study of the *H. pylori* genome is conducted mainly in order to improve the understanding of the pathogenesis of gastritis and peptic ulcer disease, the causes of ability to be the cause of disease. Currently, in the database of *H. pylori* genome, 62 genes are classified as "pathogenic" (their presence in the bacterium correlates with its pathogenicity).

In 2002, the results of study of two sequences of *H. pylori* genomes were published, which has a large family of 32 bound outer membrane proteins (*Helicobacter* outer membrane protein) was discovered. They include the most well-known adhesin *H. pylori* [15], which allow firmly attached to epithelial cells due to numerous bacterial components. The most typical for *H. pylori* are few adhesins, which have the property of a targeted action on epithelial cells of the human stomach, among which the *babA* gene is the most studied and exists in the form of several variants – *babA1*, *babA2* [19]. The *babA2* gene variant creates a start codon in the signal peptide sequence and functions as an adhesin that is identical to the *babA1* variant (91% identity) except for 10 b.p. insertion with a repeat motif that ends with the creation of a translational initiation codon and has the ability to bind Lewis-like antigens (Le^b) in the blood of a human.

The BabA protein is high-affinity and binds to mono- or difucosylated blood group antigens, and each can be modified into blood group A, B, or 0 and expressed on epithelial cells of the stomach [4, 9, 10, 14]. There is a hypothesis that the bacterial adhesion factor BabA, may contribute to the pathogenesis of gastric ulcer and/or gastric cancer by mediating anchorage to the epithelium of the stomach [3]. The clinical outcomes of gastroduodenal diseases, depending on the *babA* gene variants of *H. pylori* circulating in Yakutia, has not been previously studied.

The purpose of this work is to analyze the associations of *Helicobacter pylori babA* gene in patients with clinical outcomes of gastroduodenal diseases in Yakutia.

MATHERIALS AND METHODS. Gastric biopsy specimens were obtained from April 2014 to January 2018 from 322 patients that admitted to the endoscopic department for fibrogastroduodenoscopy (FGDS) in endoscopic department of State autonomous institution of Republic Sakha (Yakutia) «Republican Hospital No. 1 – National Center of Medicine» (RH No.-1 NCM). To confirm the presence of *H. pylori* infection, gastric biopsy specimens were sent for histological examination to the pathoanatomical department of RH No.-1 NCM. According to the results of histological analysis, 188 patients (out of 322) were included in the study, who had the presence of *H. pylori*. The average age was 25,2 years (from 3 to 70). In accordance with macroscopic analysis of the mucosa and histological results, patients were divided into two groups: chronic gastritis and chronic gastritis with erosions and ulcers.

Genomic DNA of *H. pylori* was isolated from frozen gastrobiopsies of the examined patients by using phenol-chloroform extraction [7]. To perform the genotyping of babA H. pylori DNA fragments, the sequences of oligonucleotide primers proposed earlier by Rad R. et al., which flanks the region containing the babA gene, were used. (817 b.p.) – 5'-AATCCAAAAAGGAGAAAAAACATGAAA-3' (babA2-F), 5'-TGTTAGTGATTTCGGTGTAGGACA-3' (babA2-R) [16]. Polymerase chain reaction (PCR) was performed on «Bio-Rad» thermocycler. Separation of amplification products was carried in the horizontal electrophoresis camera in a 2% agarose gel. Visualization of PCR products was performed by «Bio-Rad» gel video documentary device using Image Lab ™ Software.

The surveys, provided by the framework of research work, were carried out strictly after the informed consent of participants, parents or legal representatives of minor patients without violations of ethical standards. This study was approved by the local committee on biomedical ethics of the Yakutsk Scientific Center for Complex Medical Problems. Protocol No. 41 of November 12, 2015. Decision №5.

RESULTS. *Analysis of the H. pylori babA frequency occurrence in patients with gastroduodenal diseases*

Endoscopic and histological studies carried out in the first step of work have shown that only in 188 (58,3%) out of 322 patients confirmed the presence of *H. pylori*. The diagnosis of chronic gastritis was established in 96 cases (51,1%), and the diagnosis of chronic gastritis with erosions and ulcers in 92 cases (48,9%). We analyzed the frequency of the *H. pylori babA* gene occurrence among 188 samples with histologically confirmed of *H. pylori* infection. The *babA2* gene variant was identified in 65 samples (34,5%), and *babA1* in 123 (65,4%).

Comparison of the occurrence of H. pylori babA1 and babA2 gene variants in patients depending on the clinical outcomes of *gastroduodenal diseases (erosive or chronic gastritis)*

It was found that the *babA2* gene variant was significantly more common in sample of patients with chronic gastritis associated with erosions and ulcers of stomach and duodenum (43,4%). Patients diagnosed with chronic gastritis more often had the *babA1* gene variant (73,9%) (p<0,05) (Table 1).

Comparison of the occurrence of H. pylori babA1 and babA2 gene variants in patients depending on the activity of inflammation and dissemination degree

There were no found statistically significant difference between comparing group of patients with different degrees of inflammation and with presence of the *H. pylori babA* gene variants (Fig. 2). However, a slight statistical difference was found in comparison with the second degree of dissemination and the variant of the *babA1* gene (Fig. 3).

Comparison of H. pylori babA1 and babA2 gene variants in group of patients depending on gender, age, place of birth and residence

There were no significant differences depending on age, place of birth or residence in patients with *H. pylori babA* gene variants (p>0,05), however, statistically significant differences were found while comparing male and female group (p<0,001) (Table 1). Thus, the frequency of occurrence of the *babA2* gene variant was almost twice as high in group of male patients (69,6%) than in female patients (38,3%) (p<0,001). On the contrary, *babA1* gene (61,6%) was significantly more common in female patients than in male patients (30,3%) (p<0,001) (Table 1).

DISCUSSION. In this paper, for the first time in Yakutia, the frequency of occurrence of *H. pylori babA* gene variant in patients with gastroduodenal diseases was investigated. Thus, it was found that the frequency of the *babA2* gene variant in patients with erosive gastritis was 43,4% (Table 1). Earlier, a meta-analysis of the frequencies of the *babA* gene variants in different countries of the world was performed by Chen M. Y. Obtained results are concordant with data from Turkey, China-1, Portugal-1, Brazil-1 and Italy (46,6%, 39,5%, 47,3%, 40,0% and 48,7%, respectively), but differ from the results of most other countries (India 52,7%, Iran from 18,1-74,1%, Japan from 84,8-100%, South Korea from 96,5-

Comparison of the frequency of *babA* genes depending on the presence of erosions and ulcers, age and sex and demographic factors

Factors	n (188)	*babA1* (%)	*babA2* (%)	χ^2	*p*
Dependence on the presence of erosions and ulcers					
CG with erosions and GU/DU	92	52 (56.5%)	40 (43.4%)	**6.314**	**<0.05**
CG	96	71 (73.9%)	25 (26.0%)		
Dependence of age					
Children (3-17 years)	112	77 (68.7%)	35 (31.2%)	1.354	>0.05
Adults (18-70 years)	76	46 (60.5%)	30 (39.4%)		
Comparison by gender					
♂	89	27 (30.3%)	62 (69.6%)	**18.417**	**<0.001**
♀	99	61 (61.6%)	38 (38.3%)		
Comparison on place of residence					
Urban population	32	23 (71.8%)	9 (28.1%)	0.709	>0.05
Rural population	156	100 (64.1%)	56 (35.8%)		

Note: GU/DU – gastric ulcers/chronic ulcers, CG – chronic gastritis; ♂ – male, ♀ – female.

100%, Thailand 91,1%, China 64,9%-2, Taiwan 100%, Portugal 50,0%-2, France 81,4%, Sweden 83,3%, Germany-1 77,7%, USA 84,8%, Brazil 20,0%-2, Finland 70,9%, Colombia from 82,8-85,0% and Germany-2 100%) (Fig. 1) [3].

Comparison of *H. pylori babA* gene variants depending on the clinical outcomes of gastroduodenal diseases (erosive or chronic gastritis) showed that patients with erosions and ulcers of the stomach, *H. pylori babA2* gene variant (43,4%) was significantly more common than in patients with chronic gastritis (26,0%) ($p<0,05$) (Table 1). In this regard, obtained result may indicate a more expressed pathogenic potential of *H. pylori babA2* gene variant. The results of our study are consistent with previous data that the presence of the *babA2* gene variant in the *H. pylori* genome was found to be associated with a higher incidence of duodenal ulcer, a complicated course of *H. pylori* infection, and also with adenocarcinoma of the stomach [2].

When comparing the *H. pylori babA1* and *babA2* genes with the inflammation activity, there were no statistically significant differences. However, insignificant difference was found in comparison with the second degree of dissemination and the *babA1* gene variant (Fig. 3), which is probably due to stochastic causes and is a consequence of the small number of subgroups of observations.

When comparing of *H. pylori babA1* and *babA2* gene variants in patients depending on age, place of birth and residence, no statistically significant differences were obtained ($p>0,05$). However, in the analysis, depending on the gender of the patients, a higher frequency of *H. pylori babA2* gene variant occurrence was found among men – 69,6%, almost two times more often than among women – 38,3% ($p<0,001$). In the case of the *babA1* gene variant, the opposite picture was observed: female patients had *H. pylori babA1* gene variant (61,6%) twice often than in male patients (30,3%) (Table 1). Our obtained result is consistent with the study of Mattar et al., where the *babA2* gene variant was also more common in men than in women [12]. Recent studies have conducted studies on mice and macaques to study the determining factors of the host organism that affect the expression of *H. pylori* BabA proteins [5-8, 11, 13]. The determining factor was the gender of the host, which was associated with a higher bacterial load and loss of BabA expression, and generally was preserved in male mice. These results may indicate the possibility that the loss of BabA protein expression is not due to adaptive immunity or signaling toll-like receptors. This evidence may indicate that BabA may have other unrecognized functions besides adhesion that binds to Le^b antigens which do not require the effect of gender differences in glycosylation for loss of BabA expression [11].

CONCLUSION

1) An association has been established between *H. pylori babA2* gene with more severe cases of gastroduo-

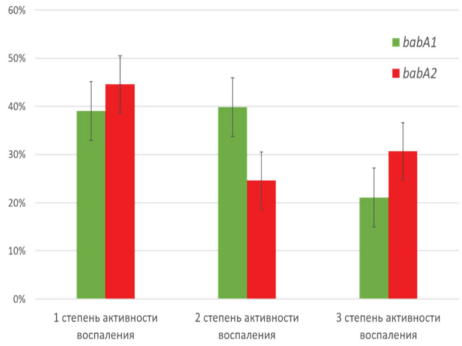

Fig. 1. Results of the frequency distribution of the *babA H. pylori* in the World. Note: China-1 – a study performed in 2006; China-2 – a study performed in 2004; Portugal-1 – a study performed in 2010; Portugal-2 – a study performed in 2009; Brazil-1 – study performed in 2006; Brazil-2 – study performed in 2005; Germany-1 – a study performed in 2009; Germany-2 – a study performed in 1999.

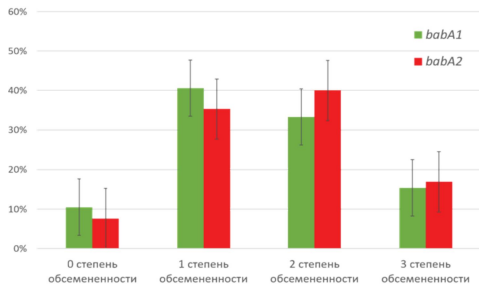

Fig. 2. Comparative analysis of *babA* gene with inflammation activity in patients with gastroduodenal diseases.

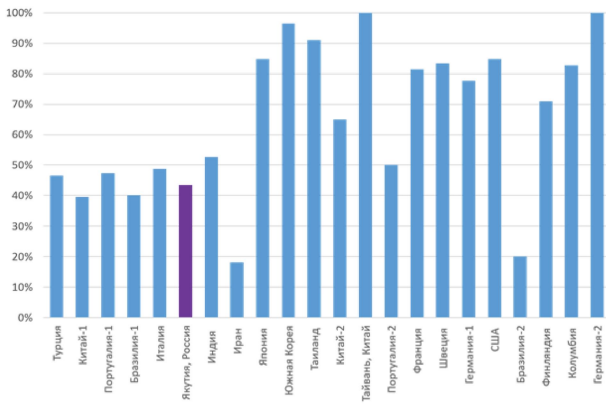

Fig. 3. Comparative analysis of *babA* gene with dissemination degree in patients with gastroduodenal diseases.

denal diseases (erosions and ulcers) in patients of Yakutia. Our results are consistent to previously known evidence that the presence of the *H. pylori babA2* gene may contribute to an increased risk of erosions and stomach ulcers.

2) It has been established that the *H. pylori babA2* gene was more often found in males than in female patients, which suggests that the infection of men with the *H. pylori* strain with a *babA2* gene variant may be an additional risk factor for more severe gastroduodenal diseases.

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REPLICATIVE ANALYSIS OF HEREDITARY THROMBOPHILIA FACTORS IN THE DEVELOPMENT OF PREECLAMPSIA IN THE YAKUT POPULATION

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The study of the contribution of hereditary thrombophilia to the etiopathogenesis of preeclampsia (PE) is of particular interest, since the formation of blood clots in the microvasculature vessels have affects to the processes of implantation and placentation, which subsequently leads to disorders of uteroplacental perfusion, which is a key link in the pathogenesis of this disease.

The **aim** of this work was to conduct a replicative associations analysis of the single-nucleotide polymorphisms the four most significant genes of hereditary thrombophilia with the development of PE in the Yakut population: rs1801133 (C677T) in the *MTHFR* gene, rs1799963 (G20210A) in the *F2*, rs6025 (G999A) in the *F5* gene and rs1799889 (-675 4G/5G) in the *SERPINE1* gene.

The results of this study indicate a statistically significant association of 4G allele of polymorphic variant rs1799889 (-675 4G/5G) in the *SERPINE1* gene in formation of a hereditary predisposition to the development of this pregnancy complication in Yakuts, both in the general group of patients and in the subgroup of patients with severe PE.

Keywords: preeclampsia, hereditary thrombophilia, association study.

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Introduction. Preeclampsia (PE) is a severe multisystem complication of pregnancy, which is characterized by the presence of arterial hypertension and significant proteinuria after 20 weeks of gestation. For a long time, this pathology continues to be one of the leading causes of maternal mortality, accounting for at least 63,000 cases per year worldwide [27]. According to the study, which covered about 39 million women from 40 countries, the incidence of PE for the period from 2002 to 2010 was 4.6%, in addition, the frequency of this complication of pregnancy varied widely among different regions [19]. It should be noted that differences in the frequency of PE development in modern human populations are due to the characteristics of racial and ethnic affiliation of the studied individuals [21, 23, 28, 29]. In the Russian Federation, among healthy first-time pregnant women, PE is detected in 6-12% of cases, while in the presence of extragenital pathology, the frequency increases to 20-40%. In addition, in recent years, there has been an increase in the number of cases of this complication of pregnancy and its contribution to the structure of maternal mortality, which is from 6 to 29.6% depending on the region [5], the excess of the average Russian rate of PE is 1.5 times observed among the regions of Siberia and the Far East [10].

According to the Ministry of health of the Republic of Sakha (Yakutia) PE plays a significant role in the structure of diseases of pregnant women. Thus, for the period from 2000 to 2016, the frequency of this pathology of pregnancy varied within 12.8 – 22.2%, which means the development of PE in every sixth pregnant woman on average for this region. According to the Ministry of health of the Republic of Sakha (Yakutia) PE plays a significant role in the structure of diseases of pregnant women. Thus, for the period from 2000 to 2016, the frequency of this pathology of pregnancy varied within 12.8 – 22.2%, which means the development of PE in every sixth pregnant woman on average for this region. In addition, the results of the analysis of critical obstetric conditions in maternity institutions in 2016 among the regions of the far Eastern Federal district showed the largest number of cases of "near miss"("Almost lost" or "nearly dead" women) for the Republic of Sakha (Yakutia) it is noteworthy that a significant number of these cases (54.5%) is due to the development of severe PE and eclampsia [6]. This high incidence of "near miss" cases due to severe PE and eclampsia, along with the high incidence of PE among the population of this region, shows the importance of studies studied at studying the etiopathogenesis of this pregnancy complication in women from the Yakut population.

According to the most recognized hypothesis of PE, the basis for the forma-