ORIGINAL RESEARCHES

N.N. Gotovtsev, N.A. Barashkov, T.V. Borisova, M.V. Pak, M.P. Alekseeva, N.N. Innokentieva, K.S. Loskutova, V.G. Pshennikova, A.M. Rafailov, S.N. Lekhanova, S.A. Fedorova

ANALYSIS OF THE CLINICAL OUTCOMES OF GASTRODUODENAL DISEASES IN YAKUTIA DEPENDING ON THE PRESENCE OF THE CYTOTOXIN-ASSOCIATED GENE A (*CAGA*) IN THE *HELICOBACTER PYLORI*

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ABSTRACT

Introduction. The cytotoxin associated gene A (*cagA*) in the *Helicobacter pylori* genome is often associated with the formation of cytotoxins and induction of interleukin 8 (IL8) by gastric epithelial cells, which directly affects the immune response and entails inflammatory processes, affecting on clinical outcomes in patients with gastroduodenal diseases, caused by *Helicobacter pylori*. The clinical outcomes of gastroduodenal diseases, depending on the presence of *Helicobacter pylori cagA* gene, circulating in Yakutia, were not previously studied. The aim of this work is to study clinical outcomes in patients with gastroduodenal diseases in Yakutia, depending on the presence of the cytotoxin associated gene A in the *Helicobacter pylori*.

Materials and methods. Gastric biopsy specimens were obtained from 311 patients. According to the results of histological analysis, 172 patients had the presence of *H. pylori* and divided into two groups: chronic gastritis and chronic gastritis with erosions and ulcers.

Results. Chronic gastritis was established in 91 samples (52,9%), and the diagnosis of chronic gastritis with erosions and ulcers was established in 81 samples (47,1%). Strains with *cagA*+ status were identified in 118 samples (68,6%), and *cagA*- in 54 samples (31,4%). In the group from 18 to 70 years, a higher incidence of *cagA*+ strains were found in comparison with the group of patients from 3 to 17 years which more often had *cagA*- strains ($p<0,001$). The cross-sectional analysis showed that statistically significant differences were found in the *cagA*+ and *cagA*- strains between the clinical outcomes within a group of children ($\chi^2=9,03$, $p<0,001$) (73,7%).

Conclusion. We showed relationship between *cagA*+ strains of *Helicobacter pylori* and more severe clinical outcomes (erosions and ulcers) in patients with gastroduodenal diseases in Yakutia. Obtained result confirms previously known data that *cagA*+ strains are more virulent and pathogenic than *cagA*- strains of *Helicobacter pylori*.

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

Introduction

Helicobacter pylori (H. pylori) is one of the most common bacterial human pathogens, which is spread all over the world [20]. *H. pylori* infection is associated with the development of chronic gastritis, gastric or duodenal ulcers, gastric cancer and MALT-lymphoma [5, 12, 28]. In the absence of treatment, individuals who have been infected with *H. pylori* remain colonized during their lifetime due to increased viability and adaptability of the pathogen [4]. Previously, various virulence and pathogenicity genes of *H. pylori* infection have been described, such as *cagA*, *vacA*, *iceA* and *oipA* [6, 8, 10, 14]. The cytotoxin associated gene A (*cagA*) is often associated with the formation of cytotoxins and the induction of interleukin 8 (IL8) by gastric epithelial cells [19]. Most studies have shown that the presence *H. pylori* CagA protein, the relative risk of more severe gastroduodenal diseases is increased by 2-3 times [6, 15, 18]. Besides, some data indicate an increased risk of gastric cancer when patient infected by *cagA*+ strains of *H. pylori* about 28,4 times [24]. It has been established that *cagA*+ strains of *H. pylori* are also associated with more pronounced inflammation, cell proliferation and metaplasia of the gastric mucosa [25]. The first significant breakthrough in the study of CagA protein was the realization that its gene is part of a large so-called island of pathogenicity (*cag* PAI), a region of horizontally acquired DNA that is embedded in the genome of more virulent *H. pylori* strains [7]. There is a hypothesis that *cag* PAI *H. pylori* serves as a transport system for other genes of virulence factors [13]. In addition to the direct effect of CagA proteins on epithelial synapses, the transmission of growth factor pulses and the cytoskeleton, CagA also has a pronounced pro-inflammatory effect [21]. Currently relevant is the study of the prevalence of *cagA* gene and its association with clinical outcomes of gastroduodenal diseases worldwide. For example, in some studies it has been shown that the presence of the *cagA* gene is associated with peptic ulcer diseases of the stomach and duodenum [2, 16, 26]. The clinical outcomes of gastroduodenal diseases, depending on the *H. pylori cagA* gene circulating in Yakutia, was not previously studied.

The aim of this work is to study the analysis of the clinical outcomes of gastroduodenal diseases in Yakutia, depending on the presence of the cytotoxin associated gene A in the *Helicobacter pylori*.

Matherials and methods

Gastric biopsy specimens were obtained from April 2014 to January 2018 from 311 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, 172 patients (out of 311) were included in the study, who had the presence of *H. pylori*. The average age was 24,7 years (from 3 to 70). In accordance with macroscopic analysis of the mucosa and histological results, patients were divided into two

Table 1

Design of oligonucleotide primers for *H. pylori* cagA gene detection

Gene, fragment	Name of oligonucleotide primer	Sequence from 5' → 3'	The size of amplified fragment
cagA	*cagA*	F5'-GATAACAGGCAAGCTTTT-3' R5'-CTGCAAAAGATTGTTTGGCAG-3'	349 b.p.

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 [9]. Amplification of the required DNA fragments of *H. pylori* was performed using of the oligonucleotide primers described previously (Table 1), that flanking region, containing *cagA* gene [27]. 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 (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 No. 5.

Results

In the course of endoscopic and histological examination, in 172 (55,3%) out of 311 individuals had histologically confirmed the presence of *H. pylori* (fig. 1, a). The diagnosis of chronic gastritis was established in 91 cases (52,9%), and the diagnosis of chronic gastritis with erosions and ulcers was established in 81 samples (47,1%) (fig. 1, b). Strains which have *cagA*+ status were identified in 118 samples (68,6%), and *cagA*- status – in 54 samples (31.4%) (fig. 1, c).

There were no significant differences in clinical outcomes of gastroduodenal diseases in patients infected by *cagA*+ *or cagA*- strains of *H. pylori* depending on the gender of the patients, as well as the place of birth and residence (p>0,05) (fig. 2, a, b). However, statistically significant differences between adult and child samples were shown, depending on the presence of *cagA*+ and *cagA*- strains of *H. pylori*. Thus, in the group from 18 to 70 years, a higher incidence of *cagA*+ strains were found in comparison with the group of patients from 3 to 17 years which more often had *cagA*-strains (p<0,001) (fig. 2, c).

Also, significant differences were found in the comparison group for the clinical outcomes of gastroduodenal diseases, depending on the presence

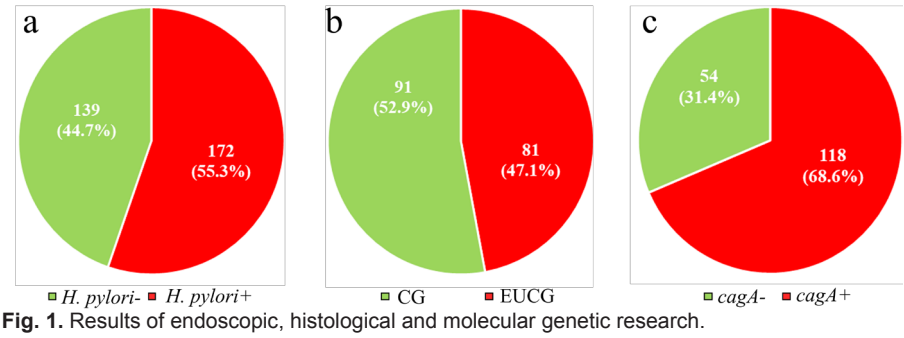

Fig. 1. Results of endoscopic, histological and molecular genetic research.
A. Number of patients, infected by *H. pylori*; B. The frequency of the sample of patients according to clinical diagnosis, depending on the presence or absence of erosions and ulcers; C. Sample of patients which have different *H. pylori* strains.
Note: CGEU – chronic gastritis with erosions and ulcers; CG – Chronic gastritis; *cagA*+ – strains, which have *cagA* gene; *cagA*- – strains, which have not *cagA* gene.

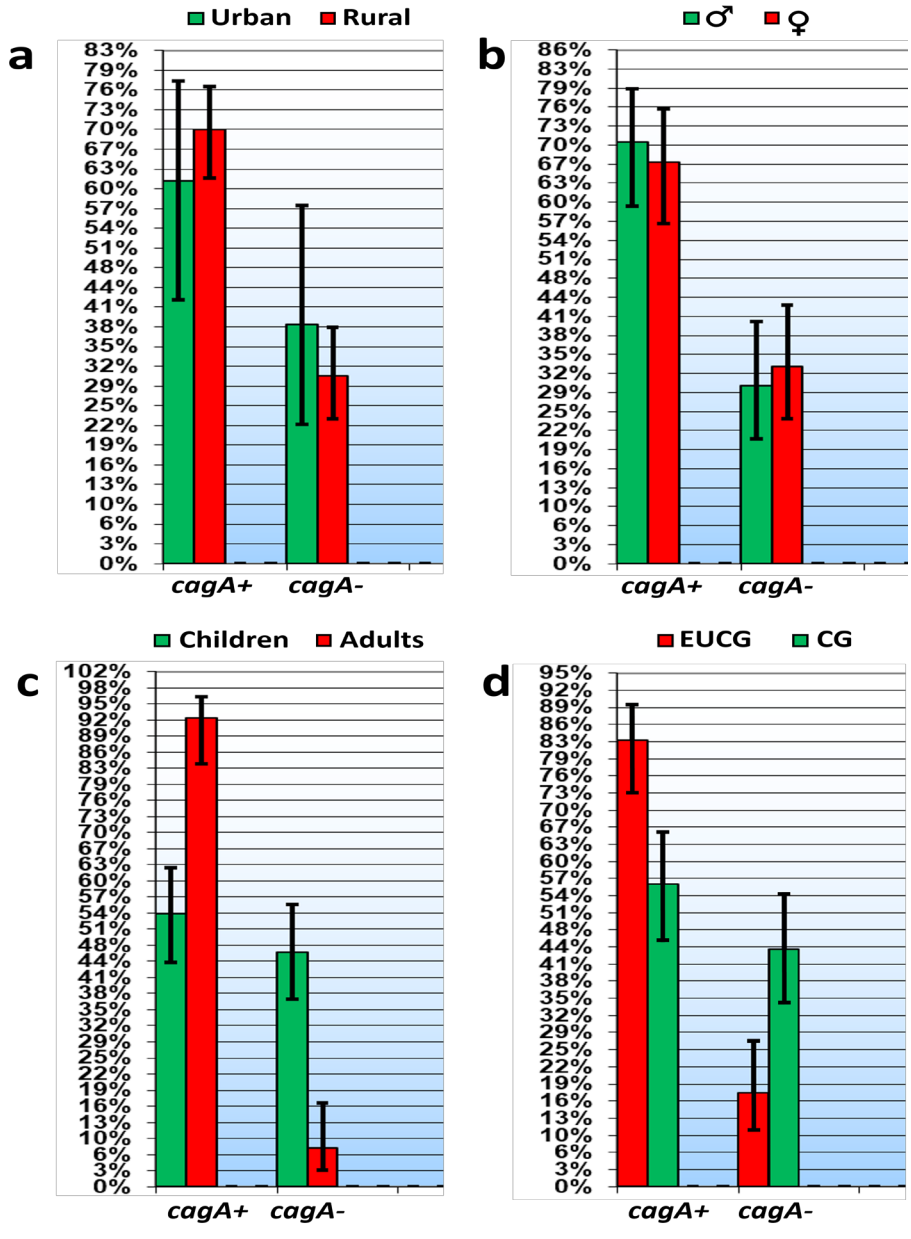

Fig. 2. Comparative analysis of the clinical outcomes of gastroduodenal diseases depending on the presence in patients of *cagA* gene.
a) depending by place of birth/residence; b) depending on the gender of patients; c) depending on the age (children/adults); d) depending by the established diagnosis.
Note: ♂ – male, ♀ – female.

of *cagA*+ and *cagA*- strains of *H. pylori* (p<0,001). Thus, it was found that *cagA*+ strains were significantly more frequent in the sample of patients diagnosed with chronic gastritis with erosions and ulcers of the stomach and duodenum than in patients diagnosed with chronic gastritis which more often had *cagA*- strains (p<0,001) (fig. 2, d).

A cross-sectional analysis of patients was performed for the presence of *cagA*+ and *cagA*- strains, taking into account age and established diagnoses. Statistically significant differences were found in the cross-comparison of *cagA*+ and *cagA*- strains between the clinical outcomes within a group of children (Table 2). Thus, in a sample of children diagnosed with chronic gastritis with erosions and ulcers, *cagA*+ strains were significantly more frequent (χ^2=9,03, p<0,001) (73,7%). In the sample of adults there were no significant differences by clinical outcomes (χ^2=0,018, p>0,05).

Table 2

The cross-comparison of clinical outcomes within a group of children and adults by *cagA*+ and *cagA*- strains

Children (n=105)	Chronic gastritis (n=67)	*cagA*+	29 (43,3%)	χ^2=9,03 p<0,001
		cagA-	38 (53,7%)	
	Chronic gastritis with erosive-ulcerative (n=38)	*cagA*+	28 (73,7%)	
		cagA-	10 (26,3%)	
Adults (n=67)	Chronic gastritis (n=24)	*cagA*+	22 (91,6%)	χ^2=0,018 p>0,05
		cagA-	2 (8,4%)	
	Chronic gastritis with erosive-ulcerative (n=43)	*cagA*+	39 (90,7%)	
		cagA-	4 (9,3%)	
Total: 172				

Discussion

The prevalence of *cagA*+ strains of *H. pylori* among patients with gastroduodenal diseases varies in different parts of the world [11]. In Yakutia the frequency of *cagA*+ strains of *H. pylori* in patients with gastroduodenal diseases was 68.6%. Our result corresponds with the frequency of *cagA*+ strains in Tunisia [22], Egypt [11], Palestine, Iran, Spain and Great Britain [references available on request]. However, obtained frequency of *cagA*+ strains of H. pylori in Yakutia is lower than in some countries of South America, Africa, Europe, Asia, and higher than in some countries of North America, Africa, the Middle East and Europe (fig. 3).

When analyzing a sample of patients infected with *cagA*+ and *cagA*- strains of *H. pylori*, statistically significant differences were found in the comparison group of patients, depending on the presence of erosive-ulcerous (fig. 2, d). Thus, in patients with erosions and ulcers, *cagA*+ strains of *H. pylori* were significantly more frequent than in patients with chronic gastritis (p<0,001). The result obtained by us is comparable with the results of similar studies of other authors [3, 17, 21, 23] and indicates about more pathogenic potential of *cagA*+ strains of *H. pylori.*

Further analysis of patients age revealed a higher incidence of *cagA*+ strains of *H. pylori* among adults (from 18-70) – 92,4% compared to children (from 3-17) – 53,7% (p<0,001) (fig. 2, c). Our result agrees with the previously published work performed in Tunisia on a sample of patients with gastroduodenal diseases, where statistically significant difference was found between children and adults, with respect to the *cagA* gene [22]. Thus, *cagA*+ strains of *H. pylori* in adults were identified in 155 cases, and in children only in 18 cases [22]. It is known that the immune system of children has a number of features that make them more vulnerable to most infections [1]. Perhaps in the group of children *cagA*- strains can lead to chronic gastritis in the same way as *cagA*+ strains, since in the group of children *cagA*+ and *cagA*- strains were found with almost the same frequency (fig. 2, b). Perhaps obtained result indicates an imperfection of the immune system in children, which is more vulnerable to many infections, even having a small pathogenic potential [1].

Since the gender and place of birth/residence didn't show statistically significant differences (p>0,05), we cross-compared *cagA*+ and *cagA*- strains with clinical outcomes within the group of children and adults (Table 2). In the sample of children which were diagnosed with chronic gastritis with erosions and ulcers significantly more frequent *cagA*+ strains (73,7%) than in children diagnosed with chronic gastritis (43,3%) (p<0,001). In the sample of adults, this trend was not con-

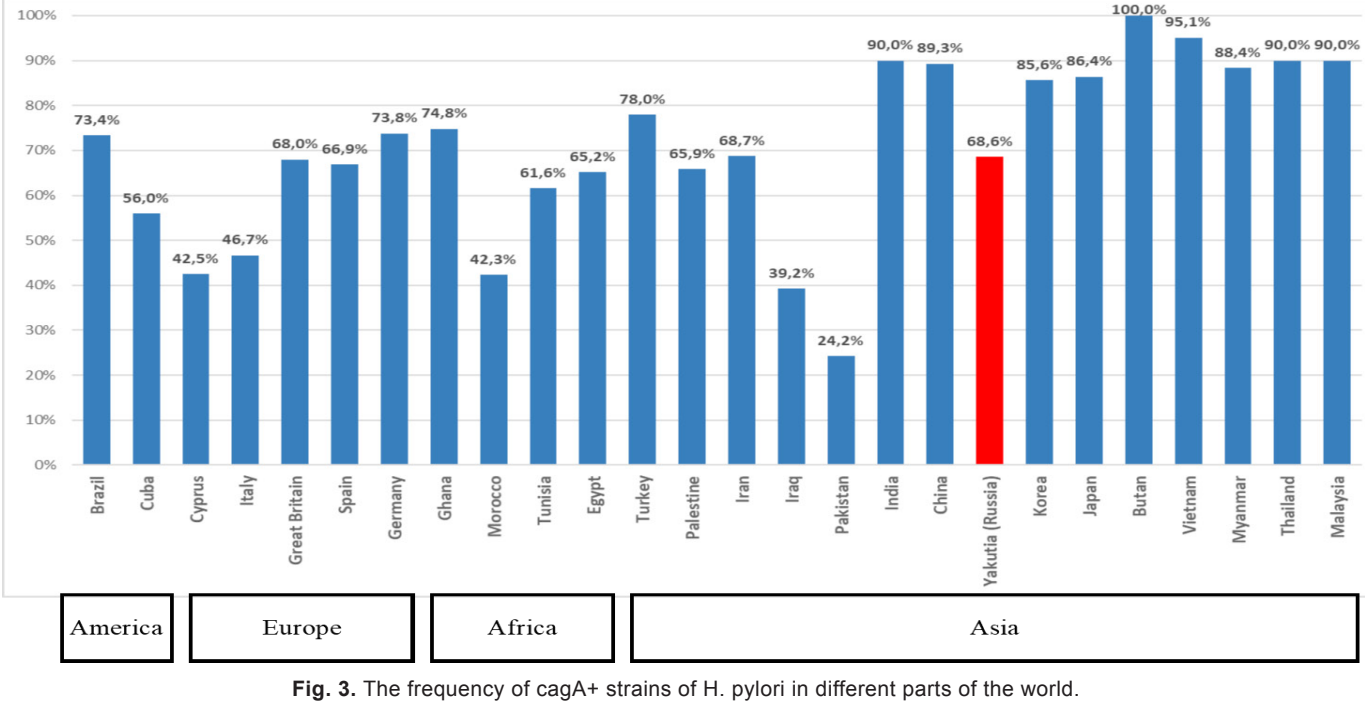

Fig. 3. The frequency of cagA+ strains of H. pylori in different parts of the world.

firmed, because *cagA*+ strains prevailed over *cagA*- as in the group of patients diagnosed with chronic gastritis (91,6% and 8,4%) and in the group of patients diagnosed with chronic gastritis with erosions and ulcers (90,7% and 9,3%). Perhaps this can be explained by sampling effect.

Conclusions

1) We have shown the relationship between *cagA*+ strains of *H. pylori* and more severe clinical outcomes (erosions and ulcers) in patients with gastroduodenal diseases in Yakutia. Obtained result confirms previously known data that *cagA*+ strains are more virulent and pathogenic than *cagA*- strains *H. pylori*.

2) It was shown that *cagA*- strains were more frequent among children (from 3 to 17) than in adults (from 18-70). Perhaps this can be explained by fact that in children the immune system is not as developed as in adults, which in turn explains the higher grade of susceptibility of children to many infections, not even so virulent and pathogenic.

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The authors:

1. GOTOVTSEV NYURGUN NAUMOVICH - Scientific researcher, Laboratory of Molecular Genetics, Federal State Budgetary Scientific Institution "Yakut Science Center of Complex Medical Problems". Address: 677010, Sakha Republic, Yakutsk, Sergelyakhskoye Shosse, 4. Phone: 89141062015, e-mail: Donzcrew@mail.ru
2. BARASHKOV NIKOLAI ALEKSEEVICH - Candidate of biological sciences, Head of laboratory of Molecular genetics, Federal State Budgetary Scientific Institution "Yakutsk Scientific Center of Complex Medical Problems". Address: 677010, Sakha Republic, Yakutsk, Sergelyakhskoye Shosse, 4. Phone: 8-(4112) 32-19-81; E-mail: barashkov2004@mail.ru
3. BORISOVA TUYARA VALERIEVNA - student, Institute of Natural Sciences, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University. M.K. Ammosov ", 677000, Yakutsk, Kulakovsky st. 48. Phone: 89644290223, e-mail: borisovatv96@gmail.com
4. PAK MARIA VLADIMIROVNA - endoscopist of the endoscopic department of the Republican Hospital No. 1 National Center of Medicine. Address: 677010, Sakha Republic, Yakutsk, Sergelyakhskoye Shosse, 4. e-mail: pakmv@mail.ru
5. ALEXEEVA MAVRA PAVLOVNA - endoscopist of the endoscopic department of the Republican Hospital No. 1 National Center of Medicine. Address: 677010, Sakha Republic, Yakutsk, Sergelyakhskoye Shosse, 4.
6. INNOKENTYEVA NATALYA NIKOLAEVNA - Post-graduate student, Medical Institute, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University. M.K. Ammosov ", 677010, Yakutsk, Oyunsky st. 27. Phone: 8-(4112) 36-30-46, e-mail: natalia_inn@mail.ru
7. LOSKUTOVA KIUNNIAI SAVVICHNA - Candidate of Medical Science, Head of the Pathoanatomical department of the Republican Hospital No. 1 National Center of Medicine. Address: 677010, Sakha Republic, Yakutsk, Sergelyakhskoye Shosse, 4. e-mail: loskutovaks@mail.ru
8. PSHENNIKOVA VERA GENNADIEVNA - Scientific researcher, Laboratory of Molecular Genetics, Federal State Budgetary Scientific Institution "Yakutsk Scientific Center for Complex Medical Problems", postgraduate student of NEFU. Address: 677010, Sakha Republic, Yakutsk, Sergelyakhskoye Shosse, 4. Phone: 8-(4112) 32-19-81, e-mail: pshennikovavera@mail.ru
9. RAFAILOV ADUM MIKHAILOVICH - Candidate of Biological Sciences, Associate Professor, Department of Biology, Institute of Natural Sciences, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University. M.K. Ammosov ". Address: 677010, Sakha Republic, Yakutsk, Kulakovsky st. 48. Phone: 8-(4112) 49-68-42, e-mail: archinay@mail.ru
10. LEKHANOVA SARGYLANA NIKOLAEVNA - Candidate of Medical Science, Associate Professor, Medical Institute, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University M.K. Ammosov", 677010, Yakutsk, Oyunsky st. 27. Phone: 8-(4112) 36-30-46, e-mail: lehanovasn@mail.ru
11. FEDOROVA SARDANA ARKADIEVNA - Doctor of biological sciences, Head of the Research Laboratory of Molecular Biology Institute of Natural Sciences, Federal State Autonomous Educational Institution of Higher Education "North-Eastern Federal University M.K. Ammosov". Address: 677010, Sakha Republic, Yakutsk, Kulakovsky st. 46., e-mail: sardaanafedorova@mail.ru.

A.V. Solovyev, N.A. Barashkov, K.E. Savvinova, N.N. Gotovtsev, F.M. Teryutin, V.G. Pshennikova, G.P. Romanov, A.M. Rafailov, N.N. Sazonov, L.U. Dzhemileva, O.L. Posukh, E.K. Khusnutdinova, S.A. Fedorova

THE ANALYSIS OF THE RESISTANCE OF HETEROZYGOUS CARRIERS OF THE C.-23+1G>A MUTATION IN *GJB2* GENE TO DIARRHEA

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ABSTRACT

The high carrier frequency of c.-23+1G>A mutation in the *GJB2* gene in Yakut population is might be explained not only by the factors of population dynamics (founder effect, genetic drift, small effective population size), but also can be due to the selective advantage of heterozygous mutations in the *GJB2* gene. Because the *GJB2* gene is expressed not only in the cochlea but also in other tissues, and in vitro studies conducted on cell cultures show that *GJB2*-mutant cells were more resistant to the infection of dysentery - *Shigella flexneri*. The **aim** of this study is the analysis of the resistance in heterozygous carriers of the c.-23+1G>A mutation in *GJB2* gene to diarrhea.

Material and methods. We examined 272 Yakut individuals, which was divided into two groups: the first group consisted from 238 individuals without c.-23+1G>A mutation, the second group consisted from 34 individuals with c.-23+1G>A mutation in heterozygous state. All respondents independently filled information about the number of cases of diarrhea in the last year, and indicated the most characteristic form of their stool.

Results and Discussion. In heterozygous carriers of the c.-23+1G>A mutation the cases of diarrhea in the last year were not registered in 22% of individuals, in individuals without mutation cases of diarrhea were not registered in 5% of individuals. According to the results of this study heterozygous carriers of the c.-23+1G>A mutation statistically significantly are less susceptible to diarrhea cases than individuals without this mutation. Thus, the obtained results can support the hypothesis about selective advantage of the *GJB2* gene mutant alleles carriers and partly explain the extremely high carrier frequency (10.3%) of the c.-23+1G>A mutation in the *GJB2* gene in Yakut population.

Keywords: *GJB2* gene, diarrhea, c.-23+1G>A mutation, heterozygous carriers.

INTRODUCTION

The results earlier studies in 6 population from Eastern Siberia (Yakuts, Dolgans, Evenks, Evens, Yukaghirs and Russians) show that carrier frequency c.-23+1G>A mutation in the *GJB2* gene was one of the highest in the world (4.7%) and in the Yakut population was a local maximum of 11.7% [3]. Then on a larger sample of Yakuts populations (n = 350), the extremely high incidence of heterozygous carriage was confirmed and amounted to 10.3%, which is comparable to the carrier frequency of the HbS allele (10%) associated with