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

DOI 10.25789/YMJ.2018.63.04

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

sickle-cell anemia in Africa [6].

The high carrier frequency of the c.-23+1G>A mutation in Eastern Siberia may indicate a possible, but unknown, mechanism of the selective advantage of carriers of this mutation. Considering, that the *GJB2* gene is expressed not only in the tissues of the inner ear but also in the epidermal skin [7], and the formation storage center of the c.-23+1G>A mutation in Eastern Siberia probably explained by the increased survival rate of carriers of this mutation. Currently known that heterozygous carriers of p.Arg143Trp mutation in *GJB2* gene in some African country (Ghana), demonstrated a thicker layer of epidermis than in individuals without this mutation. The authors consider that epidermal thickening can protect against insect bites and limit cellular invasion of certain bacterial infections [8]. In 2009 was published the results studies of thicker layer of epidermis in heterozygous carriers of c.35delG mutation in Europe (Italy), where the same way confirmed data on a thicker layer of epidermis in individuals with c.35delG mutation in heterozygous state [5]. Moreover, *in vitro* studies conducted on cell cultures show that *GJB2*-mutant cells were more resistant to the infection of dysentery - *Shigella flexneri* [1], this data confirmed by the study of the frequency of cases of diarrhea in heterozygous carriers of c.35delG mutation in *GJB2* gene, where cases of diarrhea occurred significantly less than in individuals without this mutation [4].

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.

Research materials 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 (Fig. 1, B), and indicated the most characteristic form of their stool, according to the Bristol scale (Fig. 1, A). All respondents were healthy, there were no persons with Crohn's disease, cholecystitis and other diseases of the digestive tract. The mean age in respondents was 20.3 ± 2.04 years, of them 62.4% of female and 37.5% of male.

The genomic DNA was extracted from lymphocytes of the peripheral blood. Amplification of the noncoding exon 1 and flanking intronic regions was performed using primers Ex1-F/Ex1-R

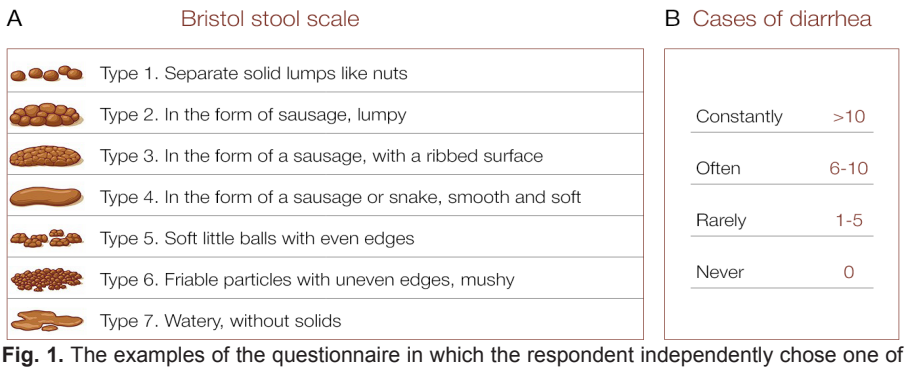

Fig. 1. The examples of the questionnaire in which the respondent independently chose one of the proposed options.
Note: A - Bristol stool scale. B - Number of diarrhea cases in the last year.

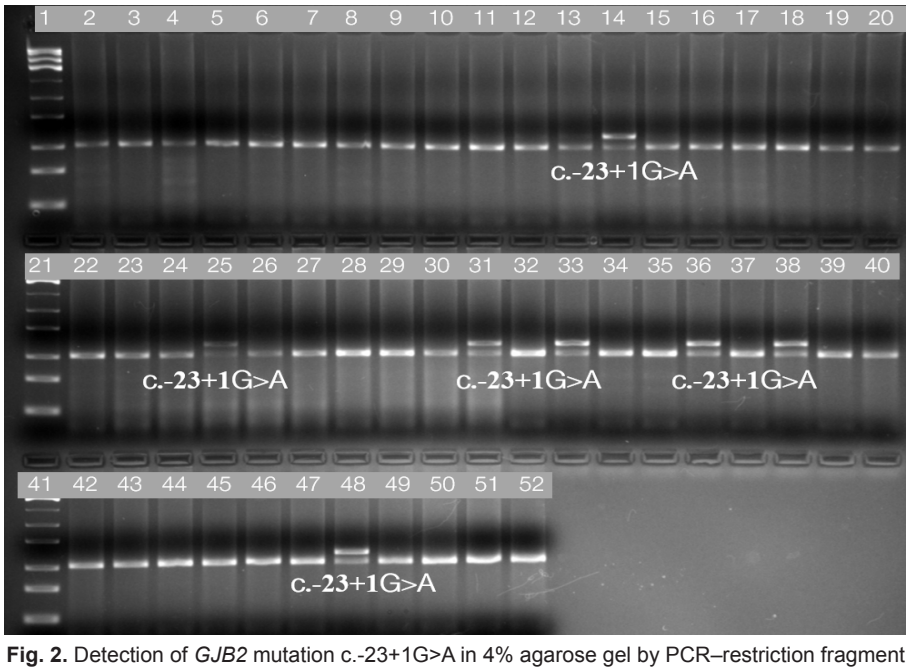

Fig. 2. Detection of *GJB2* mutation c.-23+1G>A in 4% agarose gel by PCR–restriction fragment length polymorphism analysis (*HphI*).
Note: Columns 1, 21, 41 - marker, columns 2-13, 15-24, 26-30, 32, 34, 35, 37, 39-47, 49-52 - individuals without mutation c.-23+1G>A, columns 14, 25, 31, 33, 36, 38, 48 - individuals with c.-23+1G>A mutation in heterozygous state.

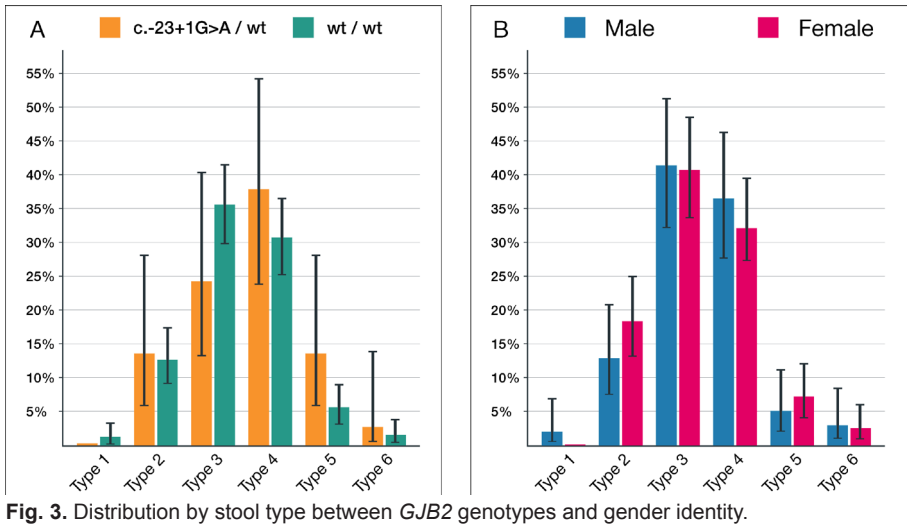

Fig. 3. Distribution by stool type between *GJB2* genotypes and gender identity.
Note: A – The distribution stool type according *GJB2* genotypes, the yellow color is individuals with c.-23+1G>A mutation in heterozygous state, the green color is individuals without mutation. B - The distribution stool type according gender identity, the blue color is male, the pink color is female.

The number of cases of diarrhea in the last year in heterozygous carriers and non-carriers of the mutation c.-23+1G>A in *GJB2* gene

The number of cases of diarrhea in the last year	All samples (n=272)				Female (n=170)				Male (n=102)			
	c.-23+1G>A/wt (n=34)	wt/wt (n=238)	χ^2	p	c.-23+1G>A/wt (n=23)	wt/wt (n=147)	χ^2	p	c.-23+1G>A/wt (n=11)	wt/wt (n=91)	χ^2	p
0 (never)	**8 (23,5%)**	**12 (5,0%)**	**14,93**	**<0,05**	**5 (21,7%)**	**7 (4,7%)**	**8,74**	**<0,01**	**3 (27,2%)**	**5 (5,4%)**	**6,44**	**<0,05**
1-5 (rarely)	14 (41,1%)	127 (53,3%)	1,77	>0,05	10 (43,4%)	83 (56,4%)	1,35	>0,05	4 (36,3%)	44 (48,3%)	0,57	>0,05
6-10 (often)	8 (23,5%)	56 (23,5%)	0,00	>0,05	5 (21,7%)	36 (24,4%)	0,08	>0,05	3 (27,2%)	20 (21,9%)	0,16	>0,05
>10 (constantly)	4 (11,7%)	43 (18,0%)	0,83	>0,05	3 (13,0%)	21 (14,2%)	0,03	>0,05	1 (9,0%)	22 (24,1%)	1,28	>0,05

Note: c.-23+1G>A/wt - individuals with c.-23+1G>A mutation in heterozygous state; wt/wt - individuals without c.-23+1G>A mutation; Differences were statistically significant when p<0.05, is in bold font.

(5'-CCGGGAAGCTCTGAGGAC-3', 5'-GCAACCGCTCTGGGTCTC-3') with 10% Betaine (Sigma, USA) [9]. Detection of *GJB2* mutation c.-23+1G>A in 4% agarose gel by PCR–restriction fragment length polymorphism analysis with use of *Hph*I endonucleases, according to manufacturer's specifications («New England Biolabs Inc», England).

Statistical analyzes were made on the MedStat, Biostat (McGraw-Hill, Inc. Version 3,03) software and Sampling (kindly provided by V. Macaulay and adapted by M. Metspalu). Differences between groups were tested with χ2-statistics. Differences were statistically significant when p<0.05.

The local bioethics committee at the Yakut Science Centre of Complex Medical Problems (Yakutsk, Protocol 16, on April 16, 2009) approved this work and questionnaire.

Results and discussion

The results of respondents answers about most characteristic form of stool, show that more than 75% of the subjects surveyed had a normal stool form (type 3 – 39%, type 4 – 36%). A small number of respondents registered a tendency to constipation (type 1 - 1%, type 2 - 15 %) or to diarrhea (type 5 - 7%, type 6 - 2%). After the distribution of the *GJB2* genotype, observed the same trend. A histogram of the distribution of stool types in individuals with c.-23+1G>A mutation in heterozygous state (n = 34) and individuals without c.-23+1G>A mutation (n = 238) is shown in Figure 3A. Distribution by gender and *GJB2*-genotype did not reveal statistically significant differences in stool types (p>0.05) (Fig. 3B).

In individuals with c.-23+1G>A mutation in heterozygous state (n = 34), cases of diarrhea in the last year were not registered in 8 individuals out of 34, which was 23%. In individuals without c.-23+1G>A mutation, in the last year were not registered in 12 individuals out of 238, which was 5% (Table 1). We indicate significant differences when comparing these groups, were significantly less detected cases of diarrhea in individuals with c.-23+1G>A mutation in heterozygous state than in individuals without this mutation (p<0.05) in the last year. The distribution of the sample by gender also revealed statistically significant differences among in the number of cases of diarrhea in male (p <0.05) and in female (p <0.01) (Table 1).

The results are consistent with previous studies in Italy, when to test hypothesis about that *GJB2* carriers might have an increased resistance to gastrointestinal infectious diseases, a cross-sectional study involving 203 subjects aged 19-65 years (63% women) was carried out. Subjects (170) were wildtype for the *GJB2* gene, whereas 33 carried one or more mutations variants. Significant effect for genotype was detected indicating lower diarrhea frequency for *GJB2* carriers. The present clinical results provide new insights on *GJB2* heterozygote advantage, further suggesting that it might consist in an increased resistance to gastrointestinal infections as already demonstrated by *in vitro* studies.

Conclusion

Thus, the results of this study support previous evidence that heterozygous carriers of *GJB2* gene mutations may have increased resistance to gastrointestinal diseases, in particular to diarrhea. The obtained results testify to the hypothesis of the selective advantage of heterozygous carriers of the mutant alleles of the *GJB2* gene, which can explain the extremely high frequency of heterozygous carriage (10.3%) c.-23+1G>A mutation in the Yakut population.

Acknowledgments

We thank all participants of this study.

The study was supported by the Ministry of Education and Science of the Russian Federation №6.1766.2017, Project NEFU M.K. Ammosov "Genetic features of the population of Yakutia: the structure of the gene pool, adaptation to cold, psychogenetic characteristics, the prevalence of certain hereditary and infectious diseases". Research of the YSC CMP "The study of the genetic structure and the load of hereditary diseases of the Sakha Republic (Yakutia) populations". Programs of Bioresource collections of the FASO Russia "Genome of Yakutia" (BRK: 0556-2017-0003) and Russian Foundation of Basic Research (#17-29-06016-ofi_m, #18-54-16004_NCNIL_a, #18-015-00212_A, #18-013-00738_A, #18-05-60035_Arctica).

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A STUDY OF THE POLYMORPHISM RS9939609 OF THE *FTO* GENE AND RS738409 OF THE *PNPLA3* GENE AS RISK FACTORS FOR THE DEVELOPMENT OF NAFLD IN THE YAKUT POPULATION OF TYPE 2 DIABETES MELLITUS

DOI 10.25789/YMJ.2018.63.05

ABSTRACT

In order to study the frequency distribution of the polymorphism alleles rs9939609 of the *FTO* gene and polymorphism rs738409 of the *PNPLA3* gene among the Yakuts, 132 DNA samples of patients with type 2 diabetes and 70 DNA samples of healthy volunteers were tested.

The study of the frequency distribution of the polymorphism alleles rs9939609 of the *FTO* gene and polymorphism rs738409 of the *PNPLA3* gene in both groups showed no significant differences. Analysis of the frequency distribution of alleles and genotypes of the polymorphic variant of the *FTO* gene (rs9939609) in the group of patients with type 2 diabetes and healthy revealed a predominance of the T allele and a homozygous genotype of *TT*, except for a group of practically healthy men, which despite the prevalence of the *T* allele was characterized by the highest level of the heterozygous genotype *AT*. When analyzing the frequency distribution of the alleles and genotypes of the polymorphic version of the *PNPLA3* gene (rs738409), the allele *G* and the homozygous genotype *GG* prevailed in both groups. In the men and both groups studied, the *G* allele significantly prevailed over the *C* allele ($p < 0.05$).

Keywords: *FTO* gene, adiponadine gene, type 2 diabetes mellitus, NAFLD, overweight, Yakuts.

Introduction

Currently, obesity is an actual problem, which is associated with its progressive spread and the severity of complications, which often cause the death of patients at a young age. To date, according to the World Health Organization in the world - 39% of adults are overweight, and 13% are obese. In Russia, among the able-