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V.M. Nikolaev, E.K. Rumyancev, S.I. Sofronova, A.A. Grigoreva, S.A. Fedorova

SEARCH FOR ASSOCIATION OF DELETION POLYMORPHISMS OF GLUTATHIONE-S-TRANSFERASE *GSTM1* AND *GSTT1* GENES WITH RISK OF LUNG CANCER IN THE YAKUT POPULATION

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In the structure of oncological morbidity, lung cancer occupies one of the leading positions. According to scientific sources, lung cancer is a multifactorial disease in which both external and internal factors are involved. The aim of this work is to search for an association of deletion polymorphisms of the enzyme glutathione-S-transferase *GSTM1* and *GSTT1* with the risk of lung cancer in the Yakut population. Analysis of polymorphic variants of specific loci of genes *GSTM1*, *GSTT1* was carried out in a sample of patients with lung cancer (n = 112) and control (n = 65). In our study, in the Yakut population, we did not find a significant association between the null genotypes *GSTT1* and *GSTM1* and their combinations. We found that the genotype *GSTM1* * + / *GSTT1* * 0 in the group of patients with non-small cell lung cancer occurred 3.7 times less frequently than in the control group (OR 0.226 (CI 95%: 0.0609-0.841); $\chi 2 = 5.621$, $p = 0.0177$).

Keywords: glutathione-S-transferase, genes for biotransformation of xenobiotics, xenobiotic detoxification enzymes, lung cancer, isozymes, deletion.

Introduction. Lung cancer occupies a leading position in the structure of cancer morbidity in Yakutia. In the Sakha Republic (population: 982.1 thousand) lung cancer affects approximately 400 people yearly [1]. The severity of the problem is due not only to the high prevalence of the disease, but also to late diagnosis, unsatisfactory treatment results and, as a result, high mortality.

According to our sources, the development of lung cancer can be promoted by external background factors, such as: asbestos [15], radon [27], arsenic [28] polycyclic aromatic hydrocarbons [19], etc. According to many researchers, one of the most important causes of lung cancer worldwide is smoking [7,9,24], but lung cancer does not develop in all smokers, only in 5-10% [22]. Tobacco smoke contains about 4,000 known chemical substances. It has been established that 60 of them cause oncological diseases [29]. These carcinogenic substances are neutralized by enzymes of the xenobiotic detoxification system. An important role in this process is played by enzymes of the glutathione-S-transferase family [16; 26].

Glutathione-S-transferases (GST; EC 2.5.1.18) are enzymes of the second phase of xenobiotic biotransformation that catalyze the conjugation reaction of glutathione with a wide range of nonpolar compounds of endogenous and exogenous origin containing electrophilic carbon, sulfur, nitrogen and phosphorus atoms [20]. In humans, GST enzymes are represented mainly by the cytosolic GST family, while there are eight classes of dimeric enzymes, which are classified based on the basis of their amino acid sequence and substrate specificity of α (A), (K), μ (M), π (P), θ (T), σ (S), ω (O), ζ (Z) [25]. The spectrum of substrates of these isoenzymes partially overlaps. For example, for all GST isoenzymes, the substrate is the substance 1-chloro-2,4-dinitrobenzene, the only exception is the isoenzyme GSTT1 [23]. But despite this, GST isoforms show their specificity, as

Yakut Scientific Center for Complex Medical Problems: **NIKOLAEV Vyacheslav Mikhailovich** – Candidate of Biological Sciences, Director, Nikolaev1126@mail.ru, **RUMYANTSEV Egor Konstantinovich** – junior researcher, tzeentch1993@mail.ru, **SOFRONOVA Sargylana Ivanovna** – Candidate of Medical Sciences, Director, sara2208@mail.ru, **GRIGORIEVA Anastasia Anatolyevna** – researcher, nastiagrigoryeva@gmail.com, **FEDOROVA Sardana Arkadyevna** – Doctor of Biological Sciences, Head of the scientific research lab, M.K. Ammosov NEFU, sa.fedorova@s-vfu.ru.

class-A enzymes predominantly bind to cumene hydroperoxide, class-P - ethacrynic acid, class-M - epoxides, benzo(a) pyrene, styrene-7, 8-oxide, trans-stilbene oxide, class-T - epoxybutane, ethylene oxide, halomethane and methyl bromide, etc. [12].

It is assumed that disorders in the detoxification system enzymes' functioning can provoke the development of oncological diseases. Particularly interesting for studying the association with oncological diseases are two polymorphic genes *GSTT1* and *GSTM1,* which have a mutation in the form of an extensive deletion, which is characterized by a complete absence of expression of the corresponding forms of enzymes. According to some references, it is known that carriers of these mutations have a higher risk of developing oncopathologies [22; 10]. The prevalence of null alleles *GSTM1* and *GSTT1* varies greatly among different ethnic groups [5].

The aim of this study is to search for associations of deletion polymorphisms of the enzyme glutathione-S-transferase *GSTM1* and *GSTT1* with the risk of lung cancer in the Yakut population.

Material and methods of researc. This work was carried out within the framework of research titled: "Epidemiological aspects of malignant tumors in the Far North, the development of modern methods of early diagnosis and prevention using highly informative fundamental research methods" in the Department of Adaptation Mechanisms Research of the Yakut Science Centre of Complex Medical Problems.

112 patients with lung cancer were examined. The patients were diagnosed with lung cancer based on histopathological examination. Histological types of lung cancer included non-small cell lung cancer, squamous cell lung cancer and lung adenocarcinoma. Other types of lung cancer included: large cell carcinoma, mesothelioma and bronchial carcinoid, etc. As a control group, 65 people were studied without signs of oncological and pre-oncological or any chronic or acute inflammatory diseases. Obtaining the informed consent of the respondents to the study (according to the protocol of the Ethics Committee of the YSC CMP No. 49 of 25.03.2018) was mandatory.

Table 1 presents the general characteristics of the studied groups. According to the questionnaire data, almost all lung cancer patients are long-term smokers, of which only 15 people (13.4%) are non-smokers. Compared with cancer patients, the control group had a greater proportion of non-smokers – 23 people (35.4%),. The patients were divided into three groups according to their histological type of tumor.

Venous blood was taken on an empty stomach from the median cubital vein. DNA was isolated using the standard method of phenol-chloroform extraction [14]. The analysis of polymorphic variants of specific regions *of the GSTM1 and GSTT1* genes was carried out using polymerase chain reaction methods using the structure of primers described earlier [21]. The amplification products were detected in a 7% polyacrylamide gel. The presence of null deletion polymorphisms *of the GSTM1* and *GSTT1 genes* was indicated by the absence of the corresponding bands 271bp and 480bp. The 183bp-sized CYP1A1 gene was amplified as an internal control (Fig. 1, 2).

The study used computational methods of mathematical statistics implemented in the licensed integrated statistical package for complex data processing SPSS for Windows 10.0. To check the reliability when comparing the frequency of occurrence of genotypes in groups, the standard Pearson's $\chi 2$ criterion or the Fisher's exact test for small samples were used. The relationship between genotypes and the risk of lung cancer was evaluated by the odds ratio (OR) with a 95% confidence interval (95% CI)

Results. The frequency of occurrence of null deletion polymorphisms *of the GSTM1*0 and GSTT1*0* genes in patients with lung cancer (n=112) was 50.9% and 32.1%, in the control sample (n=65) - 41.5% and 36.9%, respectively.

According to the data obtained by us, in the total sample of patients with lung cancer, the frequency of occurrence of the "null" genotype *GSTM1*0* was 1.2 times higher compared to healthy individuals, but the differences between the groups did not reach the level of statistical significance. At the same time, the odds ratio of developing lung cancer when carrying the null genotype *GSTM1*0* was 1.5 times higher (OR 1.458 (CI 95%: 0.787-2.703)) (Table 2). According to the frequency of occurrence of the "null" genotype *GSTT1*0*, there were also no statistically significant differences between the total sample of lung cancer patients and the control at OR 0.809; CI 95% (0.426-1.536) (Table 2).

When studying the relationship between the genotypes *GSTT1, GSTM1* and various histological types of lung cancer, it was found that in the group of patients with squamous cell lung cancer, the chance of meeting the null genotype *GSTM1*0* is 2.8 times higher than in persons without cancer (OR 2.814; 95% CI (0.769-10.304)), but these differences did not reach the level of statistical significance. The frequency of occurrence of the null genotype *GSTT1*0* in the groups of patients with adenocarcinoma was 1.7 times higher compared to the control (OR 1.708; CI 95% (0.319-9.145)), but these differences were also not significant (Table 2).

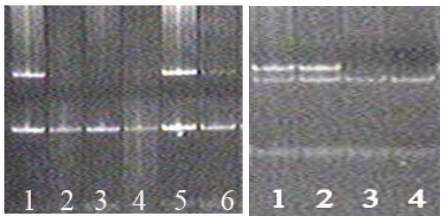
We analyzed the combined occurrences of the *GSTM1* and *GSTT1* genotypes in the control group and in patients suffering from lung cancer. The combined null genotype *GSTM1*0/GSTT1*0* was 1.2 times more common in the total group of patients compared to healthy ones (OR 1,200 (CI 95%: 0.540-2.666);, but the differences did not reach the level of statistical significance (p=0.654). If we look at the histological types of cancer, then in patients suffering from non-small cell lung cancer, adenocarcinoma and squamous cell cancer, the frequency of occurrence of the combined null genotype was similar to the control group and did not differ significantly. However, in other types of cancer, the incidence of the zero combined genotype *GSTM1*0/GSTT1*0* was 1.5 times higher than the control (OR 1.753 (95% CI: 0.664-4.627); χ^2=1.303, p=0.253).

Among all combinations of the studied genotypes, a significant change in the frequency of occurrence of the *GSTM1*+/GSTT1*0* genotype was noted by us in people suffering from non-small cell lung cancer. The combination of genotypes *GSTM1*+/GSTT1*0* was 3.7

Table 1

Characteristics of the control group and patients with lung cancer by histological type

Groups	Men n (%)	Women n (%)	n	Age X * SD
All patients	84 (75.0)	28 (25.0)	112	59.99±0.80
Non-small cell lung cancer	43 (76.8)	13 (23.2)	56	59.68±0.96
Adenocarcinoma	2 (33.3)	4 (66.7)	6	69.83±3.90
Squamous cell lung cancer	10 (83.3)	2 (16.3)	12	56.82±2.45
Other types of cancer	29 (76.3)	9 (23.7)	38	59.74±1.26
Control	49 (75.4)	16 (24.6)	65	55.69±1.02



a b

Examples of identification: a - GSTT1 * 0 and GSTT1 * + genotypes for the *GSTT1* gene; CYP1A1 - internal PCR control (183bp); 2, 3, 4, 6 - "GSTT1 * 0" genotype; 1, 5 - "GSTT1 * +" genotype; b - GSTM1 * 0 and GSTM1 * + genotypes for the *GSTM1* gene; CYP1A1 - internal PCR control (183bp); 3, 4 - "GSTM1 * 0" genotype; 1,2 - "GSTM1 * +" genotype.

times less common in the group of patients with non-small cell lung cancer (OR 0.226 (CI 95%: 0.0609-0.841); χ^2=5.621, p=0.0177) compared with the control group. In other combinations, we did not find an association of deletion genotypes of the *GSTM1* and *GSTT1 genes* with the risk of developing different histological types of lung cancer (Table 3).

Discussion. The lungs are most vulnerable to the action of carcinogens contained in polluted air, since they are directly in contact with them. The tissues and cells of each organ have a unique set of isozymes of the detoxification system. Both *GSTM1* and *GSTT1* genes are actively expressed in lung tissues, which is confirmed by the data of the UniProt consortium [https://www.uniprot.org].

The *GSTM1* gene is located on the short arm of the 1st chromosome (1p13. 3), has a length of 5,929 kb and consists of 8 exons. The *GSTT1* gene (22q11.23) is located on chromosome 22, it occupies about 8,179 kb and consists of 6 exons (https://www.ncbi.nlm.nih.gov). A feature of these genes is the presence of extensive deletions having sizes of 15kb *(GSTM1)* and 50kb *(GSTT1)*. *GSTM1* and *GSTT1* mutations are polymorphic, occurring in different populations of the world with a frequency of 37-53% and 18-48%, respectively (Table 4). The phenotypic manifestation of deletions is the complete absence *of GSTM1* and *GSTT1 enzymes* [11].

Some researchers claim that deletion polymorphisms in *the GSTM1* and *GSTT1 genes* reduce the overall enzymatic activity of GST [31]. It should be noted that a decrease in the activity of important enzymes necessary for the neutralization of carcinogens can lead to an increased risk of developing oncological diseases. In this regard, many authors are looking for a relationship between the null genotypes *of GSTM1, GSTT1* and the development of oncopathologies [10,22].

Our results showed that the null genotypes *GSTM1* and *GSTT1* have no significant association with the risk of lung cancer in the Yakut population, as well as their null combinations *GSTM1*0/ GSTT1*0*. We found that in the Yakut population, the genotype *GSTM1*+/ GSTT1*0* in the group of patients with non-small cell lung cancer was 3,7 times less common than in the control group, and this value reached statistical significance. When analyzing studies conducted earlier in different populations, it became clear that many of the results contradict each other. For example, in the work of Carlsten et al., (2008) was found a significant association between the null genotype of *GSTM1* and the development of lung cancer pathology, while Liu et al., (2015) did not find a reliable association, and both studies took into account the Chinese population. In the study of Liu et al., (2020), the authors note that a reliable association was found between the zero genotype *of GSTT1* and lung cancer in the Asian population, but no reliable association was found in the populations of Europeans and Africans.

According to the results of a meta-analysis of the association of lung cancer risk with null genotypes *GSTM1* and *GSTT1* and their combinations conducted by a group of researchers Zhang et.

Table 2

Incidence of null genotypes of *GSTTM1* and *GSTT1* in patients with lung cancer and the control group

Groups	n	n (%)	OR	95% CI	χ^2	p
GSTM1*0						
All patients	112	57 (50,9)	1,458	0,787-2,703	1,443	0,229
Non-small cell lung cancer	56	27 (48,2)	1,31	0,637-2,691	0,542	0,461
Adenocarcinoma	6	3 (50,0)	1,407	0,264-7,511	0,161	0,688
Squamous cell lung cancer	12	8 (66,7)	2,814	0,769-10,304	2,58	0,108
Other types of cancer	38	19 (50,0)	1,407	0,629-3,147	0,694	0,404
Control	65	27 (41,5)				
GSTT1*0						
All patients	112	36 (32,1)	0,809	0,426-1,536	0,419	0,517
Non-small cell lung cancer	56	12 (21,4)	0,466	0,206-1,050	3,455	0,063
Adenocarcinoma	6	3 (50,0)	1,708	0,319-9,145	0,398	0,527
Squamous cell lung cancer	12	4 (33,3)	0,854	0,232-3,139	0,056	0,812
Other types of cancer	38	17 (44,7)	1,383	0,613-3,121	0,611	0,434
Control	65	24 (36,9)				
GSTM1*0/GSTT1*0						
All patients	112	22 (19,6)	1,2	0,540-2,666	0,2	0,654
Non-small cell lung cancer	56	9 (16,1)	0,94	0,358-2,502	0,015	0,899
Adenocarcinoma	6	1 (16,7)	0,981	0,104-9,248	0,0003	0,987
Squamous cell lung cancer	12	2 (16,7)	0,981	0,188-5,116	0,0005	0,982
Other types of cancer	38	10 (26,3)	1,753	0,664-4,627	1,303	0,253
Control	65	11 (16,9)				

Table 3

Combined incidences of *GSTTM1* and *GSTT1* genotypes in patients with lung cancer and the control group

Groups	n	Genotype (*GSTM1*+ / GSTT1*+*) n (%)	Genotype (*GSTM1*0 / GSTT1*+*) n (%)	Genotype (*GSTM1*+ / GSTT1*0*) n (%)	Genotype (*GSTM1*0 / GSTT1*0*) n (%)
All patients	**112**	**41 (36.6)**	**35 (31.3)**	**14 (12.5)**	**22 (19.6)**
Non-small cell lung cancer	56	26 (46)	18 (32.1)	3 (5.4)*	9 (16.1)
Adenocarcinoma	6	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)
Squamous cell lung cancer	12	2 (16.7)	6 (50.0)	2 (16.7)	2 (16.7)
Other types of cancer	38	12 (31.6)	9 (23.7)	7 (18.4)	10 (26.3)
Control	**65**	**25 (38.5)**	**16 (24.6)**	**13 (20.0)**	**11 (16.9)**

* $p \leq 0.05$.

Table 4

Frequency of occurrence of deletion polymorphisms of the *GSTM1* and *GSTT1* genes in different populations

Populations	n	Genotype (*GSTM1*0*) n (%)	n	Genotype (*GSTT1*0*) n (%)	n	Genotype (*GSTM1*0/ GSTT1*0*) n (%)	Sources
Yakuts	65	27 (41.5)	65	24 (36.9)	65	11 (16.9)	
Buryats	130	49 (37.7)	130	53 (40.8)	129	21 (16.3)	Tabixanova et al., (2019)
Kazakhs	220	118 (46.4)	220	56 (25.5)	220	27 (12.3)	Balmukhanov et. al, 2013
Chinese	412	194 (47.1)	412	198 (48.1)	412	90 (21.8)	Zhang et. al, 2011
Japanese	457	236 (51.6)	457	205 (44.9)	457	333 (72.9)	Hidaka et. al, 2016
Turks	231	124 (53.6)	231	43 (18.6)	108	22 (20.40)	Ada et. al, 2012
Russians	341	164 (48.1)	341	132(38.7)	341	78 (22.9)	Korchagina et al., 2011

al, (2021), quite interesting results were obtained on a very large sample. Statistically significant associations with the development of lung cancer were found in the Japanese population for the null genotype *GSTM1*, and in the Chinese population for the null genotype *GSTT1*. A significant association between lung adenocarcinoma and null genotypes *of GSTM1* and *GSTT1* was found by Zhang et. al, (2021) in Asian populations

Thus, based on the data we have obtained, we can conclude that *the GSTT1* and *GSTM1 genes* may play different roles in cancer predisposition in different populations. This is explained by the fact that oncological diseases are multifactorial. The layering of various factors creates conditions in which the same combinations of zero genotypes *of the GSTT1* and *GSTM1* genes can be risk factors or have no association with the development of lung cancer. In the Yakut population, we did not find a significant association between the null genotypes *GSTT1* and *GSTM1* and their combinations with the risk of developing lung cancer, but we found that the genotype *GSTM1*+/GSTT1*0* was significantly less common in the group of patients with non-small cell lung cancer compared to the control group.

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K.V. Vereshchagina, A.V. Samodova, L.K. Dobrodeeva

FEATURES OF IMMUNE REACTIONS IN AUTOIMMUNE THYROIDITIS IN RESIDENTS OF THE NORTHERN REGION

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Aim: to reveal the features of immune responses in autoimmune thyroiditis (AIT) in residents of the northern region.

Materials and methods: We examined 223 people living in the city of Arkhangelsk, aged 21 to 55, including 108 patients with AIT and 115 practically healthy people. A database was formed, including the data of the subject: date of birth, date of examination, age, sex and indicators of the immune background. Statistical analysis of the data was carried out using the Statistics 21.0 software package.

Results. In patients with AIT, compared with the level of the studied parameters in practically healthy individuals, an increase in the content of mature T-lymphocytes (CD3+), T-helpers (CD4+), cytotoxic T-lymphocytes (CD8+), activated cells with a transferrin receptor (CD71+) and cells labeled for programmed cell death (CD95+). The inflammatory process in AIT is manifested by systemic reactions - thrombocytopenia (27%), an increase in the content of IL-6 and TNF-α (26 and 18%, respectively). In patients with AIT, in addition to increased concentrations of antibodies to thyroid peroxidase, a high frequency of detection of elevated levels is recorded. antibodies to DNA (ds-DNA) (52.3%), RNA (RNP) (60.3%), antiphospholipids (aPhL) of the IgM and IgG classes (16.17%).

Conclusion. It was found that the inflammatory process in AIT in 15-27% of cases is manifested by systemic reactions-thrombocytopenia, increased levels of IL-6 and TNF-α, lymphocytosis and monocytosis. With AIT, the concentration of cytotoxic T-lymphocytes increases 3 times with a low activity of natural killer cells and the phagocytic ability of neutrophilic granulocytes. The development of cell-mediated cytotoxicity is formed at a low background level of activity of mature T-lymphocytes (CD3+), natural killer cells (CD3-CD16+CD56+), activated T-lymphocytes with a transferrin receptor (CD71+) and lymphocytes capable of proliferation (CD10+).

Keywords: autoimmune thyroiditis, antibodies, T-lymphocytes, pro-inflammatory cytokines, inhabitants of the north.

VERESHCHAGINA Ksenia Vitalievna – Senior laboratory assistant, Laboratory of regulatory mechanisms of immunity of the Institute of Physiology of Natural Adaptations of the N. Laverov Federal Center for Integrated Arctic Research of the Ural Branch of the Russian Academy of Sciences. E-mail: vereschagina.ks@yandex.ru; **SAMODOVA Anna Vasilyevna** – candidate of Biological Sciences, Head of the laboratory of regulatory mechanisms of immunity of the Institute of Physiology of Natural Adaptations of the N. Laverov Federal Center for Integrated Arctic Research of the Ural Branch of the Russian Academy of Sciences. E-mail: annapoletaeva2008@yandex.ru; **DOBRODEEVA Liliya Konstantinovna** – Doctor of Medical Sciences, Professor, Honored Worker of Science, Chief Researcher of the laboratory of regulatory mechanisms of immunity, Director of the Institute of Physiology of Natural Adaptations of the N. Laverov Federal Center for Integrated Arctic Research of the Ural Branch of the Russian Academy of Sciences. E-mail: dobrodeevalk@mail.ru.

Introduction. The autoimmune process is a physiological process that regulates secretion, tissue metabolism, use, and clearance of hormones and other biologically active substances in the body [9, 18]. Currently, the understanding of the spectrum of autoantibodies, their concentrations and physiological regulatory role is expanding [3]. It was revealed that autoimmune processes have a clear tendency to increase [12]. Increased concentrations of autoantibodies to thyroid peroxidase are detected in residents of areas affected by the Chernobyl accident [2], as well as in unfavorable climatic conditions [9, 10], during physical exertion [11], stressful situations [4], and also depends on the degree tissue metabolism of the amount of metabolic products entering the blood [10].

In addition, with pathology, new structures with antigenic properties may appear as a result of conformational changes in the formed complex or destruction of any biologically active substance with antigenic properties [7].

In connection with the above, the aim of the work is identification of the features of immune responses in autoimmune thyroiditis (AIT) in residents of the northern region.

Materials and methods. The objects of the study were residents of the city of Arkhangelsk. The work includes the results of an immunological examination of 223 people aged 21-55 years, including 108 people with AIT, who applied to the