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ASSOCIATION OF DELETION POLYMORPHISMS *GSTT1* AND *GSTM1* WITH INCREASED ACTIVITY OF HEPATIC TRANSAMINASES IN THE BLOOD OF PATIENTS RECEIVING ANTI-TUBERCULOSIS DRUG THERAPY

Tuberculosis is one of the most common infectious diseases worldwide. According to the approved clinical recommendations, combined anti-tuberculosis therapy with isoniazid, rifampicin, pyrazinamide and ethambutol. Isoniazid is one of the most effective anti-tuberculosis drugs for the treatment of drug–sensitive tuberculosis, however, it has a wide range of undesirable side effects, including drug-induced liver injury. The enzyme glutathione S-transferase is involved in the detoxification of toxic metabolites of isoniazid. There are a number of studies in which the role of deletion genotypes GSTM1 and GSTT1 of the enzyme glutathione S-transferase has been investigated and established, both individually and in combination to increase the frequency of undesirable adverse reactions when using drugs. However, the data obtained are ambiguous and contradictory. In this regard, we have presented an article aimed at studying the effect of polymorphic genes *GSTM1* and *GSTT1* on the activity of alanine aminotransferase and aspartate aminotransferase in blood serum in patients with newly diagnosed tuberculosis of the respiratory system.

Preliminary results of our study showed that carrying a combination of deletion genotypes in the *GSTM1* and *GSTT1* genes statistically significantly increases the activity of ALT and AST in tuberculosis therapy in patients of Yakut nationality. An increase in ALT and AST levels in the blood indicates the likelihood of hepatocellular liver damage during anti-tuberculosis therapy in carriers of a combination of deletion genotypes (*GSTM1(del)/GSTT1(del)*) of the enzyme glutathione-S transferase.

Keywords: Glutathione-S transferase, alanine aminotransferase, aspartate aminotransferase, deletion polymorphism, tuberculosis, isoniazid.

Introduction. Tuberculosis is one of the most common infectious diseases worldwide. According to the World Health Organization, about 10 million people in the world get tuberculosis every year, about 1.4 million of them die, the mortality rate from this disease is about 14% [21]. Despite this, in the Russian Federation there is a stabilization and a persistent trend towards a decrease in morbidity and mortality from tuberculosis. In Russia in 2020, the incidence of tuberculosis was 32.4 cases per 100,000 population [10]. Among patients diagnosed with active tuberculosis, the majority are patients with tuberculosis of the respiratory system. According to Vasilyeva et al., in 2022, the pandemic of a new coronavirus infection made its negative contribution to the clinical structure of tuberculosis. There was an increase in the proportion of newly diagnosed tuberculosis patients with destruction of lung tissue, massive bacterial excretion and fibrous-cavernous tuberculosis [3]. Therefore, at present, along with anti-epidemic and preventive measures, effective anti-tuberculosis drug therapy plays an important role in the fight against the tuberculosis epidemic.

According to approved clinical recommendations, combined anti-tuberculosis therapy with isoniazid, rifampicin, pyrazinamide and ethambutol is prescribed for the treatment of patients with newly diagnosed tuberculosis with established sensitivity of mycobacterium tuberculosis to isoniazid and rifampicin, as well as patients without bacterial excretion and the risk of developing multidrug resistance of the pathogen [6]. Anti-tuberculosis therapy with these drugs can cause a number of undesirable side effects, which can worsen the results of treatment. According to literature data, in the treatment of tuberculosis, undesirable adverse reactions occur in 7 to 69% of cases [42], the proportion of serious adverse reactions reaches 22.2%, complete withdrawal of drug therapy is required in 7.4% of cases [16]. Hepatotoxic reaction (drug-induced liver damage) is the main adverse reaction to anti-tuberculosis therapy [5] and the reason for drug withdrawal [4]. Most often, in 10-20% of cases, the hepatotoxic reaction is manifested by a transient increase in the activity of aminotransferases in blood plasma [29]. There are many factors leading to the development and progression of the hepatotoxic effect of anti-tuberculosis drugs: age, gender, pre-existing liver diseases, ethnicity, chronic intoxication, etc. [37, 38, 40, 41, 50].

Currently, the role of genes controlling the synthesis and operation of drug metabolism enzymes, in particular cytochrome P450 isoenzymes (*CYP2D6, CYP2C9, CYP2C19*) and biotransformation phase II enzymes (N-acetyltransferase (*NAT2*), UDP-glucuronyltransferase (*UGT*), thiopurine methyltransferase (*TPMT*), glutathione S-transferase (*GST*), etc.). In recent years, the effect of

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polymorphism of drug transporter genes on drug pharmacokinetics has been studied: organic anion transporters (*SLCO1B1, OAT-1, OAT-3*), organic cation transporters (*OST-1*) and glycoprotein-P (*ABCB1*). It is the polymorphism of genes that determines the individual pharmacological response – resistance (low efficacy or lack thereof at all) or the development of an adverse side reaction when using drugs, including anti-tuberculosis drugs [1].

Isoniazid is one of the most effective anti-tuberculosis drugs for the treatment of drug–sensitive tuberculosis, however, it has a wide range of undesirable side effects, including drug-induced liver injury. The hepatotoxicity of isoniazid is due to the high toxicity of the drug, whose chemical structure contains the hydrazide group -C(O)-NHNH and its metabolites – hydrazine and acetylhydrazine [11].

In the body, isoniazid is metabolized by acetylation with the participation of the enzyme NAT2. Studies evaluating the metabolism of isoniazid in patients with tuberculosis have shown the presence of many single-nucleotide substitutions in the structural region of the *NAT2* gene causing genetic changes in enzyme activity [8], leading to a decrease or, conversely, an increase in the metabolic rate of isoniazid.

Currently, the effect of polymorphisms of genes of enzymes of the *CYP2E1* and *GST* biotransformation system on the frequency of hepatotoxic reactions when using isoniazid is being established [11].

GST is an enzyme involved in the detoxification process. GST conjugates the sulfhydryl group of glutathione with xenobiotics or their metabolites formed in the first phase of biotransformation. Xenobiotics with different chemical structures, including isoniazid, undergo conjugation with glutathione. GST exist in several isoforms differing in tissue-specific expression. GSTT1 and GSTM1 are the most important enzymes of the GST family [1]. There are a number of studies in which the role of deletion genotypes *GSTM1* and *GSTT1*, both individually and in combination, has been investigated and established to increase the frequency of undesirable adverse reactions when using drugs [7]. However, the data obtained on the effect of carrying homozygous null genotypes *GSTM1 and GSTT1* on the risk of hepatotoxic reactions induced by anti-tuberculosis drugs [14] are ambiguous and contradictory.

The aim of the study was to research the effect of polymorphic genes *GSTM1* and *GSTT1* on the activity of alanine aminotransferase and aspartate aminotransferase in serum in patients with newly diagnosed respiratory tuberculosis.

Material and methods of research. A retrospective comparative single-center cohort study was conducted on a clinical site in Yakutsk (hereinafter SBI RS(Y) SPC "Phthisiology"). The protocol of the study was reviewed and approved by the Ethics Committee at the SBI RS(Y) SPC "Phthisiology".

53 patients of Yakut nationality with newly diagnosed respiratory tuberculosis, hospitalized in the therapeutic department of the State Budgetary Institution of the Republic of Sakha (Yakutia) "Science and Practical Center "Phthisiology" named after E.N. Andreev" (group 1) participated in the study. Among them were 23 (44%) women and 30 (56%) men aged 41.4±4.2 years. Inclusion criteria: 1) respiratory tuberculosis detected for the first time; 2) age of 18 years and older; 3) intensive phase of anti-tuberculosis chemotherapy with mandatory inclusion of isoniazid; 4) signed informed consent of the patient. Exclusion criteria: generalized tuberculosis, HIV infection, the presence of malignant neoplasms, pregnancy, duration of the intensive phase less than 60 days. In accordance with clinical recommendations, all patients in the intensive phase of tuberculosis treatment received izoniazid at a dose of 5-10 mg/ kg/ day (no more than 600 mg/ day); ethambutol at a dose of 15-25 mg/ kg/ day (no more than 2000 mg/day); rifampicin at a dose of 10 mg/kg/day (no more than 600 mg / day); pyrazinamide at a dose of 25-30 mg / kg / day (more than 2500 mg / day) [6].

The control group (group 2) consisted of 74 conditionally healthy volunteers of Yakut nationality aged 41.7±3.2 years, 41 (55%) men and 33 (45%) women who signed informed consent.

For genotyping, DNA was isolated from whole blood by the standard two-stage method of phenol-chloroform extraction. DNA samples were sampled by deletion polymorphisms of the biotransformation genes: *GSTT1* and *GSTM1*, which encode the glutathione S-transferase enzymes θ1 and μ1, respectively. Typing of samples by the *GSTT1* and *GSTM1* genes was carried out using polymerase chain reaction (PCR) according to the method described in the work of Zehra et al. (2018).

The results were visualized electrophoretically in 3% agarose gel, with the addition of ethidium bromide. The PCR results were viewed in transmitted UV light on a transilluminator. The presence of deletion polymorphisms of the *GSTM1* and *GSTT1* genes was determined by the absence of the corresponding fragments: 219 bp for GSTM1 and 459 bp for GSTT1. The presence of these fragments indicates the presence of at least one normal (without deletion) copy of the genes. β-globulin with a 268 bp fragment was used as an internal control. Evidence of successful PCR analysis was the presence of an amplification of 268 bp, the *β-globulin* gene.

The activity of ALT and AST in blood serum was determined once on an XL-640 automatic biochemical analyzer (Erba Lachema, Czech Republic) using XL System Pack® reagents (ERBA Mannheim, Czech Republic). 8-9 ml of blood was taken from the ulnar vein in the morning on an empty stomach from all participants of the study and transfered into vacuum tubes without filler (Zhejiang Gongdong Medical Technology Co., Ltd, China)

Statistical processing was carried out using the software package SPSS 11.5 for Windows and Microsoft Excel. The data of the descriptive analysis are presented in the form of M ± m, where M is the average value, m is the standard error of the average value. The significance of the differences was assessed using the Mann-Whitney criterion. Comparison of genotype frequencies in groups of sick and healthy individuals was carried out using the Pearson chi-squared criterion. The differences were considered statistically significant at $p < 0.05$.

Results. Patients (group 1) and conditionally healthy volunteers (group 2) were comparable in age (U=97.0; p=0.65) and gender ($\chi 2 = 0.45$; p=0.2).

Analysis of the association of deletion polymorphisms of the GSTM1 and GSTT1 genes with tuberculosis showed that there were no differences in the frequencies of the *GSTM1* and *GSTT1* genotypes, as well as between their combinations, between the study groups, patients and healthy ones (Table 1).

In patients carrying the double deletion genotype *GSTM1(del)/GSTT1(del)*, the ALT level in the blood serum was significantly higher than in healthy volunteers with the same genotype. For other genotypes of the *GST* gene and its combinations, no significant differences were found among the 1st and 2nd groups (Table 2).

When comparing the activity levels of ALT and AST enzymes among patients, we found a significant increase in transaminase activity (**p=0.038 and p=0.047**, respectively) in carriers of the double deletion genotype of the *GSTM1* and *GSTT1 genes,* compared with carriers

of genotypes without deletions in these genes (Table 2). We have not established a comparison of ALT and AST activity in carriers of other variants of deletion genotypes and their combinations in the group of patients.

Discussion. The main pathways of isoniazid metabolism include the reaction of acetylation by the enzyme NAT2 to form N-acetylisoniazid, as well as hydrolysis by the enzyme amidase to form hydrazine and concomitant formation of isonicotinic acid. N-acetylisoniazide is hydrolyzed by amidase to the toxic metabolite acetylhydrazine and isonicotinic acid. Acetylhydrazine can be further hydrolyzed by amidase to hydrazine and acetylated by NAT2 to diacetylhydrazine. The low activity of the enzyme NAT2 leads to the accumulation of acetylhydrazine, which is oxidized with the participation of the cytochrome P450 CYP2E1 isoenzyme into toxic reactive metabolites [8]. Potentially dangerous electrophilic metabolites of isoniazid formed with the participation of the CYP2E1 enzyme can be neutralized by the GST enzyme by conjugation of the sulfhydryl group of glutathione with metabolites [12] Conjugation with glutathione of dangerous metabolites facilitates their excretion from the body and, thus, reduces the likelihood of toxicity.

In the human body, there are 7 classes of cytosolic GST enzymes (α, μ, π, θ, σ, ω, ζ), which include 17 isoforms of the enzyme, each encoded by a separate gene or a group of genes located on different chromosomes. GST isoenzymes are characterized by a wide substrate specificity, often their specificity overlaps. For example, GSTA-class isoenzymes are mainly bound to cumene hydroperoxide, GSTM-class – epoxides, GSTP-class – ethacric acid [19], etc.

The most studied genes are *GSTM1* and *GSTT1*, since their extensive deletion polymorphisms of 16kb and 54-kb, respectively, are known, which lead to the complete absence of protein products. Deficiency of GST enzyme activity due to homozygous null mutations at the *GSTM1* and *GSTT1* loci modulates susceptibility to hepatotoxicity caused by drugs and xenobiotics.

Each organ has a unique set of GST isoenzymes. Thus, the *GSTM1* gene is expressed in 116 tissues and cells, and the expression of the *GSTT1* gene is found only in 9 human tissues, according to the database of the UniProt consortium [https://www.uniprot.org]. Basically, both genes are expressed mainly in the liver, occupying a key position in the detoxification and metabolism of a large number of xenobiotics.

Some researchers have presented evidence that homozygous deletion mutations of these genes increase the risk of liver damage caused by drugs such as troglitazone [22; 48], takrin [39], carbamazepine [46], etc. However, it is still unclear whether the null genotypes of *GSTM1* and *GSTT1* are genetic predictors of liver damage when using anti-tuberculosis drugs.

The available research on this problem is very contradictory. Thus, it has been established that homozygous zero polymorphism *GSTT1* may be a risk factor for hepatotoxicity caused by anti-tuberculosis drugs in representatives of the Caucasian race [25]. At the same time, the presence of at least one functional allele of *GSTM1* was significantly more common among groups with a higher degree of hepatotoxicity of anti-tuberculosis drugs in Brazilians [32]. In contrast, *GSTT1* and *GSTM1* were not associated with increased liver damage caused by anti-tuberculosis drugs in the populations of India, Korea [15; 24] and China [44]. It has been shown that the null genotype of the *GSTT1* gene increases the risk of drug damage to the liver, in particular, due to the use of isoniazid [34].

It is likely that the contradictory data are associated with a high degree of heterogeneity in the frequencies of deletion genotypes of the *GSTM1* and *GSTT1* genes among different ethnic populations in the world [35]. Deletion of *GSTT1* was found in 20% of Caucasians and 80% of Asians. While the zero genotype of *GSTM1* is detected in 38-67% of representatives of the Caucasian race, in 33-63% of East Asians and in 22-35% of Africans and African Americans [36].

Table 1

Frequencies of polymorphic deletion genotypes *GSTM1* and *GSTT1* in patients with respiratory tuberculosis and conditionally healthy volunteers

Polymorphic variants	Group 1, (n=53), n (%)	Group 2, (n=74), n (%)	χ^2	Significance level
GSTM1 (del)	22 (41)	29 (39)	0.07	0.79
GSTT1 (del)	27 (51)	32 (43)	0.73	0.39
GSTM1(del) / GSTT1 (del)	11 (21)	13 (17)	0.20	0.65
GSTM1(+) / GSTT1 (+)	15 (28)	26 (35)	0.20	0.65
GSTM1(+) / GSTT1 (del)	16 (30)	19 (26)	0.31	0.57
GSTM1(del) / GSTT1 (+)	11 (21)	16 (22)	0.01	0.90

Table 2

ALT and AST activity in blood serum of patients receiving anti-tuberculosis therapy and healthy volunteers according to deletion genotypes *GSTM1* and *GSTT1*

Polymorphic variants	Group 1 (n=53)		Group 2 (n=74)		ALT	AST
	ALT, units/l	AST, units/l	ALT, units/l	AST, units/l	Significance level	Significance level
GSTM1 (del)	69.22±33.29	38.04±6.97	27.88±2.79	29.69±4.52	0.18	0.52
GSTT1 (del)	60.61±23.87	41.74±10.28	31.41±4.37	31.91±5.09	0.51	0.51
GSTM1(del)/GSTT1 (del)	92.45±52.64*	42.86±10.35	24.83±4.56	23.83±1.84	**0.04**	0.54
GSTM1(+)/GSTT1 (+)	19.95±2.52	21.66±2.10	29.38±3.88	27.25±2.09	0.65	0.13
GSTM1(+)/GSTT1 (del)	36.12±11.64	40.89±16.76	34.42±6.50	29.28±3.31	0.68	0.21
GSTM1(del)/GSTT1 (+)	30.50±8.70	30.00±6.89	28.65±3.60	26.04±1.24	1.00	0.98

*p <0.05.

Finally, a meta-analysis conducted by Li et al. (2013) showed that *GSTM1* polymorphism is associated with an increased risk of hepatotoxicity associated with taking anti-tuberculosis drugs in the entire population, especially among East Asians. At the same time, there was no statistically significant association between *GSTT1* polymorphism and the risk of hepatotoxicity. The authors of this work suggested that detoxification of antitubercular drugs takes place to a greater extent with the participation of the *GSTM1* enzyme, and the *GSTT1* enzyme is only able to partially compensate for the absence of *GSTM1*. Researchers Tang et al. (2013), Yang et al. (2019) in their works came to similar conclusions.

Unlike previous studies, our work has not established a clear relationship between the increase in ALT and AST levels in carriers of the deletion genotype *GSTM1* and/or *GSTT1*. However, in the group of patients with a recent diagnosis of pulmonary tuberculosis, the carrier of the double deletion genotype *GSTM1(del)/GSTT1(del)* led to a significant increase in the activity of ALT and AST against the background of anti-tuberculosis therapy, compared with carriers of genotypes without deletions.

Probably, in the Yakut population, the *GSTM1 and GSTT1* genes are equally capable of participating in the detoxification of drugs used in the treatment of tuberculosis. That is, in the absence of one enzyme, the other is fully capable of compensating for its absence. Since our study is preliminary, performed on a small set and needs further research.

In addition, the results obtained in a group of healthy volunteers were interesting. We observed a tendency to increase the levels of transaminases in the body of carriers of the deletion genotype of the *GSTT1* gene, as well as in combination with *GSTM1(+)/GSTT1(del)*. This is probably evidence that the *GSTT1* gene has a greater affinity in detoxification of endogenous metabolites in contrast to the *GSTM1* gene.

Thus, the preliminary results of our study showed that the carriage of a combination of deletion genotypes in the *GSTM1* and *GSTT1* genes statistically significantly increases the activity of ALT and AST in tuberculosis therapy in patients of Yakut nationality. An increase in ALT and AST levels in the blood indicates the likelihood of hepatocellular liver damage during anti-tuberculosis therapy in carriers of a combination of deletion genotypes (*GSTM1(del)/GSTT1(del)*) of the enzyme glutathione-S transferase.

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