The Problem of Hepatotoxicity of Antituberculosis Drugs and Polymorphism of *GSTT1* and *GSTM1* Glutathione Transferase Enzymes

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Abstract

Introduction: Tuberculosis is recognized as one of the most pressing problems of modern medicine all over the world. It is not only a medical problem, it is a social problem, which reflects the socio-economic condition of the country, the cultural and educational level and well-being of the population, the degree of healthcare development. Despite the downward trend in tuberculosis in Ukraine in recent years, in 2018 the incidence was 62.3 per 100,000 population. The highest incidence rates of all forms of tuberculosis are observed in the southeastern region, including the Odessa region, which requires improvement of treatment and prevention of the disease. Each tuberculosis patient undergoes long-term multicomponent chemotherapy drug therapy according to WHO-recommended regimens. Some of the most threatening organotoxic side effects are hepatotoxicity and nephrotoxicity caused by anti-TB drugs. Detoxification of anti-tuberculosis drugs occurs in the liver with the participation of a two-phase xenobiotic detoxification system. Phase I is aimed at changing the polarity of the xenobiotic molecule. Phase II enzymes convert intermediate metabolites to water-soluble compounds that are excreted in the body. One of the most important second phase enzymes is glutathione transferase (GST type T and M) conjugation enzymes. Known polymorphism of the *GSTT1* and *GSTM1* genes, which determines the presence or absence of functional activity of these enzymes. The influence of polymorphism of these genes on the development of hepatotoxicity is poorly understood, and inconsistent results have been obtained.

Aim of the Study: Detection of liver dysfunction in patients with pulmonary tuberculosis on the background of *GSTT1* and *GSTM1* gene polymorphism.

Materials and Methods: The study involved patients with pulmonary tuberculosis (first diagnosed pulmonary tuberculosis (FDPT) and chronic pulmonary tuberculosis (CPT)) who underwent standard anti-tuberculosis therapy. Analysis of hepatotoxic effects of antituberculosis drugs was carried out using blood biochemical studies. *GSTT1* and *GSTM1* gene polymorphism was determined by multiplex PCR in the study of DNA from blood samples.

Results and Conclusion: Two months after the start of treatment, no statistically significant differences were found between the AST and ALT levels in the patients with the absence or presence of *GSTT1* and *GSTM1* gene deletions. In addition, in the group of patients with no *GSTM1* gene, there was a significant increase in AST and ALT aminotransferases compared to the group with the presence of the enzyme. In patients with CPT with no *GSTT1* enzyme, unlike the group with the presence of the enzyme, showed a significant increase in total (12.0 ± 2.69 vs 9.9 ± 1.44, p = 0.03) and indirect (9, 25 ± 2.08 vs 7.4 ± 1.06, p = 0.02) bilirubin compared with patients with FDPT, indicating a more severe liver lesion than patients with enzyme.

Keywords: *Xenobiotic Detoxification Genes; Tuberculosis; First Diagnosed Pulmonary Tuberculosis (FDPT); Chronic Pulmonary Tuberculosis (CPT)*

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Polymorphism of xenobiotic detoxification genes in tuberculosis patients of residents of odessa region

Phase I of biotransformation is provided mainly by a large family of enzymes - cytochromes P450. There are tens of thousands of xenobiotics that are oxidized by cytochromes P450. The main functions of this phase are the formation of hydrophilic groups in the substrate molecule (xenobiotic), due to which they are detoxified by enzymes of the second phase. An important feature of the system of phase I enzymes is their selective localization and high power on the main routes of xenobiotics in the body - food (liver, digestive tract), respiratory (lungs, bronchi) and many metabolic pathways: hydroxylation, epoxidation, oxidation by sulfur and desulfurization, etc. Studies have shown a correlation between CYP1A1 and CYP2E1 polymorphism and susceptibility to lung disease. On the other hand, there are a number of drugs that can affect the activity of cytochrome CYP2C9, including anti-TB drugs rifampicin, isoniazid.

Enzymes of the 2nd phase of biotransformation, the main purpose of which is the neutralization (decontamination, detoxification) of hydrophilic and often toxic products of phase 1 with the help of various hydrolases and transferases, are present in all cells. They function in any way of xenobiotics, carry out or complete detoxification, and sometimes correct the errors of the first phase. This phase involves glutathione transferase, glucuronyltransferase, sulfotransferase, acetyltransferase, methyltransferase, which convert toxic intermediates of phase-1 metabolism into polar, water-soluble, non-toxic compounds to be excreted from the body.

The polymorphism of *the GSTT1* and *GSTM1* genes is due to the presence of two allele variants: functionally active and inactive «zero» allele, due to the delegation of the corresponding genes. In determining polymorphic variants of glutathione-S-transferase enzymes M1 and T1 by multiplex PCR, *GSTT1- (GSTT1-null)* and *GSTM1- (GSTM1-null)* variants correspond to homozygotic by mutation and complete lack of enzyme activity; *GSTT1+* and *GSTM1+* options include both homozygotic, and heterozygotic genotypes. The most common polymorphism of the *GSTP1* 105Ile/Val gene in the fifth exon is associated with a single nucleotide substitution of 313 A > G and concerns the hydrophobic site of binding to the substrate, which has a significant effect on the course of biochemical reactions.

Group	*GSTT1+*	*GSTT1-*	*GSTM1+*	*GSTM1-*
(No.129)	102 (79,1%)	27 (20,9%)	72 (55,9%)	57 (44,1%)
Patients with pulmonary tuberculosis (n = 191)	292 (80,5%)	71 (19,5%)	207 (55,5%)	156 (42,9%)
Reliability between patients and the control group according to the criterion χ^2	$x^2 = 1.3$ $p = 0.2$		$x^2 = 0.05$ $p = 0.81$	
GSTP1				
Genotypes	With/ With	Island/Val	Val/Val	
(No. 34)	18 (52,9%)	13 (38,3%)	3 (8,8%)	
Lung tuberculosis patients (n = 45)	23 (51,1%)	15 (33,3%)	7 (15,6%)	
x^2 (p)	0,02 (0,87)	0,20 (0,65)	0,79 (0,37)	
Distribution of frequencies of alleles of the studied polymorphism				
Allele	With105	105Val		
Lung tuberculosis patients (n = 45)	0,68	0,32		
(No.34)	0,72	0,28		
x^2 (p)	0.38 (p = 0.53)			

Table 1: *Distribution of polymorphic variants GSTT1, GSTM1 and GSTP1 in healthy individuals and patients with pulmonary tuberculosis.*

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The frequency of *genes GSTM1*, *GSTT1* and *GSTP1* in patients with tuberculosis of residents of the Odessa region is presented in table 1. Associations between increased risk of active tuberculosis and certain *GSTT1* polymorphism, *GSTM1,* and *GSTP1* have not been identified.

In the definition of the frequency of polymorphic variants of the *NAT2* gene was carried out among healthy residents of Odessa and Odessa region (n = 34) and among patients with pulmonary tuberculosis who were on inpatient treatment in the Odessa regional tuberculosis hospital (118 people with Newly diagnosed tuberculosis (NDT), 54 people with Chronic tuberculosis (CTB)). The percentage distribution of *NAT2* gene polymorphism among the inhabitants of the Odessa region corresponds to the frequency of alleles established for the European race is for *NAT 2*4* - 29.2%, *NAT 2*5* - 44.4%, *NAT 2*6* - 26.4%, *NAT 2*7* - 0%. The frequency of *NAT2*4* is significantly higher ($p < 0.01$) and *NAT 2*6* is reliably higher ($p < 0.05$) in the group of patients with tuberculosis against a group of practically healthy residents of Odessa and Odessa region.

Allele	Mutation rate (%)	Mutation rate (%)	
Surveyed groups	**Control Group (No = 34)**	**Lung tuberculosis patients, n = 172**	**P_1**
*NAT2*4*	21 (30,9%)	39 (11,3%)*	0,001
*NAT2*5*	32 (44,4%)	163 (47,4%)	0,96
*NAT2*6*	19 (27,9%)	127 (36,9%)	0,16
*NAT2*7*	0 (0%)	15 (4,4%)	0,08

***Table 2:** Distribution of allelic polymorphism of the NAT 2 gene in the group of patients with pulmonary tuberculosis.*

The frequency of homozygotes for the wild-type allele NAT 2 * 4 («fast» acetylators) in the group of patients with pulmonary tuberculosis is significantly lower than the control group (6.7 vs. 22.2%, $p < 0.05$). At the same time, homozygotes for the slow type of acetylation NAT 2 * 5/* 5, NAT 2 * 6/* 6, NAT 2 * 7/* 7 significantly higher among patients ($p < 0.05$) and the highest percentage of slow acetylators among patients on chronic tuberculosis ($p = 0.02$). The results obtained may indicate a possible role of slow acetylation in the body's lesser ability to resist tuberculosis infection.

Analysis of the course of the disease depending on *GSTT1* gene polymorphism, *GSTM1* was performed in 148 patients with newly diagnosed pulmonary tuberculosis (NDPT) (Table 3).

The nature of the disease	GSTT1+ No. 125 (84,5%)	GSTT1- No.23 (15,5%)	GSTM1+ No. 77 (52,0%)	GSTM1- No. 71 (48,0%)
Clinical forms				
Disseminated	64 (51,2%)	13 (56,5%)	41 (53,2%)	35 (49,3%)
Infiltrative	52 (41,6%)	8 (34,8%)	30 (38,9%)	31 (43,7%)
Fibro-cavernous	2 (1,6%)	1 (4,3%)	-	3 (4,2%)
Local	5 (4,0%)	1 (4,3%)	4 (5,1%)	2 (2,8%)
Other	2 (1,6%)	-	2 (2,6%)	-
Presence of bacteriological discharge				
Mycobacterium MB+	88 (70,4%)	16 (69,6%)	51 (66,2%)	54 (76,0%)
By bacterioscopic method	72 (57,6%)	13 (56,5%)	41 (53,2%)	45 (63,4%)

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Duration of bacteriological discharge at the stationary stage	92,0 ± 50,9 Days	87,4 ± 30,1 Days	83,7 ± 33,2	107 ± 38,9[1]
Presence of destruction				
Presence	84 (67,2%)	16 (69,6%)	44 (57,1%)	56[1] (78,9%)
Lack	41 (32,8%)	7 (30,4%)	33 (42,9%)	15[1] (21,1%)
Prevalence of the process				
1 lung	41 (32,8%)	9 (39,1%)	24 (31,2%)	25 (35,2%)
1 lobe	23 (56,1%)	7 (77,8%)	14 (58,3%)	16 (64,0%)
2 lobes	15 (36,6%)	1 (11,1%)	7 (29,2%)	9 (36,0%)
3 lobes	2 (4,9%)	1 (11,1%)	3 (12,5%)	-
2 lungs	84 (67,2%)	14 (60,8%)	53 (68,8%)	46 (64,8%)
2 lobes	35 (41,7%)	5 (35,7%)	19 (35,8%)	22 (47,8%)
3 lobes	15 (17,9%)	1 (7,1%)	9 (16,9%)	7 (15,2%)
4 lobes	7 (8,3%)	-	2 (3,7%)	5 (10,8%)
5 lobes	27 (32,1)	8 (57,1%)	23 (43,4%)	12 (26,1%)
COPD	60 (48,0%)	9 (39,1%)	29 (37,6%)	40[1] (56,3%)

Table 3: Features of tuberculosis in patients with NDPT depending on GSTT1, GSTM1 gene polymorphism.
Note: 1: The differences are reliable, p < 0,05.

Statistically significant differences in the course of the disease were found only by *GSTM1* polymorphism and related to the duration of bacterial excretion at the inpatient stage, the presence of destructive processes in the lungs (57.1 vs. 78.9% of patients with *GSTM1*-null genotype, χ^2 7.96g = 0.005) and combination tuberculosis with chronic obstructive pulmonary disease with emphysema, pneumosclerosis and respiratory failure I - II degree (56.3% vs. 37.6% in patients with the enzyme, χ^2 = 6.14, p = 0.01). The more significant effect of the *GSTM1* gene polymorphism on the features of the tuberculosis process may be related to the different activity of glutathione transferase types in lung tissue, as the activity of *GSTT1* in lung tissue is not leading.

Characteristics of tuberculosis process			
Genotype	**With/ With**	**Island/Val**	**Val/Val**
Disseminated form	12 (31,6%)	24 (66,8%)[1]	4 (66,7%)
Infiltrative form	24 (63,2%)	8 (22,2%)[1]	2(33,3%)
Local form	2 (5,2%)	2 (5,5%)	-
Fibro-cavernous form	-	2 (5,5%)	-
Presence of bacteriological eating			
MBT+ by the cultural method	28 (73,7%)	30 (83,3%)	2 (33,3%)
MBT+ by the bacteroscopy method	24 (63,1%)	26 (72,2%)	2(33,3%)
Presence of destruction			
Presence	30 (78,9%)	28 (77,7%)	2(33,3%)
Lack	8 (21,1%)	8 (22,3%)	4 (66,7%)
Combination with COPD			
Presence	15 (39,5%)	23 (63,8%)[1]	4 (66,7%)

Table 4: Features of pulmonary tuberculosis in patients with newly diagnosed pulmonary tuberculosis (NDPT) depending on GST P1105Ile/Val polymorphism.

Note: 1: The differences are reliable, p < 0,05.

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Analysis of the course of tuberculosis depending on the *GSTP1*105Ile/Val polymorphism (Table 4) showed that while in patients with the Ile/Ile genotype the disseminated form occurred only in 31.6%, in patients with the Ile/Val and Val/genotypes Val its frequency was 66.7% (p = 0.002; RR 0.47, 95% CI 0.28 - 0.79). At the same time, the infiltrative form is significantly more common in the group of patients with the genotype Ile/Ile (63.2 vs. 23.8%, p = 0.001; RR 2.65, 95% CI 1.47 - 4.80). Also, the combination of pulmonary tuberculosis with COPD is more common in the presence of the Val allele (64.3 vs. 39.5%, p = 0.03; RR 1.63, 95% CI 1.03 - 2.56). Thus, the presence of the Val allele increases the probability of formation of the disseminated form of pulmonary tuberculosis by 4 times (0R 4.33, 95% CI 1.70 - 11.07) and is associated with the combination of tuberculosis with COPD.

Characteristic of the course of pulmonary tuberculosis depending on the polymorphism of the gene of phase II biotransformation of the drug NAT2 were analyzed in 141 patients with pulmonary tuberculosis, which was first diagnosed by analysis of medical records. According to the NAT2 genotype, 92 patients had a genotype of slow acetylation (63.0%), 48 and 6 patients had a genotype of moderate and rapid acetylation, respectively (32.9% and 4.1%, respectively). At the beginning of treatment, the phenomena of destruction were observed somewhat more often in moderate and fast acetylators (52.2% and 50.0%, respectively) than in slow acetylators (40%, P > 0.05). Also, in fast and moderate acetylators at the beginning of treatment the phenomena of disintegration and contamination of lung tissue (50% in both groups) were observed more often than in slow acetylators (41.3%, P > 0.05). About half of the patients in all three groups at the time of treatment isolated the pathogen of tuberculosis according to microscopy. Also, in the initial study, among slow acetylators, 4 patients (4.3%) had monoresistant strains of M. tuberculosis (MBT) and 2 patients with primary multidrug resistance (2.2%). Among moderate acetylators, 12.5% of patients had MBT with primary polyresistance, and 8.3% - multidrug-resistant strains.

At the time of discharge, 100% of slow acetylators and about 96% of moderate/fast acetylators did not emit MBT under microscopy. Interestingly, among moderate/fast acetylators, the cessation of bacterial excretion according to microscopy took 60.1 days, while in slow acetylators - 55.7 days. According to the culture method, regardless of the NAT2 genotype, about 40% of TB patients isolated the Office. Regarding the resistance of MBT strains, fast/moderate acetylators at the time of discharge were 27.3% resistant strains, among slow acetylators this figure was 18.2%. Finally, 29.2% of patients with fast/moderate tuberculosis acetylators who were first diagnosed developed multidrug-resistant tuberculosis (MDR-TB), while such conversion occurred in only 15.0% of slow acetylators (χ^2 4,408; p = 0.036).). Thus, belonging to fast/moderate acetylators almost doubled the risk of developing multidrug-resistant pulmonary tuberculosis.

The effect of *GSTT1*, *GSTM1*, *GSTP1* and NAT2 polymorphism on the state of the liver and kidneys in patients with pulmonary tuberculosis on the background of anti-tuberculosis therapy.

To assess the functional state of the liver, an analysis of total, direct and indirect bilirubin, aminotransferases, ß-lipoproteins, thymol test in 76 patients. Patients with antisocial behavior and severe comorbidities were excluded from the study. In patients with NDT, the level of these indicators did not differ significantly from normal and remained at the same level after 2 months from the start of treatment, regardless of the variant for the genes *GSTT1*, GSTM. In patients with a long history of ineffective treatment with *GSTM1*-null genotype two months after the start of treatment, there was an increase in the level of AST (from 0.24 ± 0.13 to 0.33 ± 0.35) and ALT (from 0.32 ± 0, 11 to 0.41 ± 0.35), while in patients with the presence of the enzyme the level of ACT was almost unchanged (0.26 ± 0.11 to 0.25 ± 0.11), and ALT increased insignificantly (from 0, 27 ± 0.11 to 0.33 ± 0.35). In a certain group of patients with *GSTT1* deletion there was a significant increase (p = 0.02) in the level of total bilirubin (9.9 ± 1.44 vs. 12.0 ± 2.69) due to the fraction of indirect bilirubin (7.4 ± 1.06 against 9.25 ± 2.08) at the beginning of treatment.

The *GSTP1*105Ile/Val, NAT2 polymorphism at the beginning of treatment had no significant effect on the level of biochemical parameters characterizing the liver condition. Significantly lower ALT level of 0.25 ± 0.11 (p 0.02) in patients with the Val allele at the beginning of treatment was interesting. An increase in AST and ALT after 2 months is observed only in the group of heterozygotes Ile/Val, but does not reach statistical significance. Almost unchanged level of these indicators indicates the absence of pronounced hepatotoxicity of short-term treatment on the background of the studied genetic polymorphism. However, in patients with a long history of treatment, the level of biochemical parameters at the beginning of inpatient treatment is significantly higher in the group of patients with slow metabolism of NAT2 (Table 5). Thus, this group needs more careful monitoring of the functional state of the liver for timely prevention of adverse reactions.

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Acetylation by genotype	Total bilirubin	Direct bilirubin	Indirect bilirubin	ALT	AST	Thymol test	B-lipoprotein
Patients with NDPT							
Fast	8,30 ± 0,57	2,00 ± 0,00	6,30 ± 0,57	0,27 ± 0,01	0,27 ± 0,01	2,86 ± 0,70	42,70 ± 4,61
Moderate	8,12 ± 0,64	2,16 ± 0,53	6,12 ± 0,35	0,26 ± 0,01	0,28 ± 0,01	2,02 ± 0,81	36,10 ± 3,39
Slow	8,26 ± 0,68	2,25 ± 0,67	6,01 ± 0,37	0,35 ± 0,09	0,30 ± 0,11	2,58 ± 1,69	37,41 ± 4,10
P_1	0,63	0,90	0,47	0,56	0,54	0,15	0,02
P_2	0,61	0,32	0,37	0,24	0,39	0,36	0,41
Patients with a long history of treatment							
Fast	8,00 ± 0,00	2,00 ± 0,00	6,00 ± 0,00	0,27 ± 0,01	0,25 ± 0,01	3,60 ± 0,70	40,70 ± 3,60
Moderate	8,00 ± 0,00	2,00 ± 0,00	6,00 ± 0,00	0,27 ± 0,01	0,27 ± 0,03	2,74 ± 1,49	37,00 ± 2,83
Slow	9,23 ± 1,01	3,23 ± 1,01	6,00 ± 0,00	0,43 ± 0,12	0,30 ± 0,11	3,23 ± 1,79	44,76 ± 4,10
P_3	0,0003	0,0002	0,97	0,0004	0,0001	0,0003	0,0003

***Table 5:** Biochemical indicators that characterize the condition of the liver in patients at the beginning of treatment depending on the status of acetylation and the history of treatment.*

Notes:

1. P1 - level of significance, a statistical criterion for comparing fast acetylators with moderate ones;

2. P2 - level of significance, statistical criterion for comparing fast acetylators with slow ones;

3. P3 - level of significance, statistical criterion for comparison of slow acetylators with NDT and long history of treatment.

In order to analyze the role of polymorphisms in the GST and NAT2 genes in impaired renal function on the background of anti-TB therapy, 100 patients were examined for pulmonary tuberculosis without severe comorbidities. At the beginning of treatment, elevated levels of total urinary protein were found in 48% of patients with pulmonary tuberculosis, and the level of microalbuminuria was elevated in 81% of patients. The percentage of patients with total protein in the urine increased after 3 months of treatment in patients who are slow acetylators for NAT2, del *GSTT1*, *GSTM1* and heterozygotes for NAT2 * 5, NAT2 * 6 (p < 0,05) (Table 6).

Surveyed groups	Prior to treatment		After 3 months of treatment	
	Part of patients with micro-albuminuria %	Protein content (± m$\overline{X}_x$)	Part of patients with micro-albuminuria%	Protein content (± m$\overline{X}_x$)
Patients with NDPT, del *GSTM1*	83,3[1]	0,15 ± 0,02	100,0	0,24 ± 0,04
Patients with NDPT, del *GSTT1*	100,0	0,2 ± 0,02	100,0	0,29 ± 0,04
Patients with NDPT, *NAT2* homozygotes (fast acetylators)	60,0[1]	0,17 ± 0,08	100,0	0,3 ± 0,16
Patients with NDPT, *NAT2* homozygotes (slow acetylators)	87,9[1]	0,18 ± 0,02	100,0	0,24 ± 0,04

***Table 7:** The level of microalbuminuria in patients with pulmonary tuberculosis with different genotypes GSTT1, GSTM1 and NAT2.*

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After 1 and 3 months of hospitalization, there is an increase in total urine protein in patients with NAT2 genotypes homozygotes for slow acetylation genes, del *GSTT1*, del *GSTM1* (among patients with pulmonary tuberculosis with a long history of treatment) and in the presence of alleles NAT2 * 5, NAT2 * 6 (p < 0.05).

Regardless of gene polymorphism, all patients with pulmonary tuberculosis had significant changes in microalbuminuria 1 and 3 months after the start of ATD (anti tuberculosis drugs) treatment. These changes indicate the beginning of the destruction and increased permeability of the cell membranes of the glomeruli.

In the groups of patients homozygous for NAT2 genes determining slow acetylation and *GSTM1* deletion, the number of patients with high levels of microalbuminuria before treatment was slightly lower than in the groups of patients with other GST and NAT2 genotypes (p < 0.05) (Table 7). Among all examined patients with deletion of the *GSTT1* gene found 100% incidence of renal excretory dysfunction at the stage of seeking medical attention. In view of this, it can be assumed that the null allele *GSTT1* may be a risk factor for damage to the basement membranes of the glomeruli of the kidneys during the primary immune response to *M. tuberculosis*.

Three months after the start of treatment, the content of urinary albumins in slow acetylators (homozygotes by alleles NAT 2 * 5, NAT 2 * 6) was 0.07 mg/l ± 0.01 mg/l compared with 0.009 mg/l ± 0.001 mg/l in fast acetylators (NAT2 * 4/* 4).

The percentage of patients with total protein in the urine increased significantly from 42% at the beginning of treatment to 77.8% three months after treatment in patients with NAT2 alleles, which determine slow acetylation, but most significantly - in homozygotes NAT2 * 5 (p < 0.05), which may indicate a more pronounced damage to kidney tissue by toxic isoniazid derivatives.

These results indicate the role of polymorphic variants of xenobiotic detoxification enzyme genes as a factor in protecting renal tissues from the toxic effects of anti-TB drugs, changes in which in the preclinical stage can be more likely to be suspected by determining microalbuminuria [1-10].

Conclusion

1. *GSTM1-null* genotype in patients with newly diagnosed pulmonary tuberculosis is associated with a longer duration of bacterial excretion, pulmonary destruction (57.1 vs. 78.9% of patients with *GSTM1-null* genotype, χ^2 7.96 g = 0.005) and a combination of tuberculosis with chronic obstructive pulmonary disease with emphysema, pneumosclerosis and respiratory failure of I - II degree (56.3% vs. 37.6% in patients with the presence of the enzyme, $\chi^2 = 6.14$, p = 0.01). The presence of the *Val* allele of the *GSTP1* gene increases the probability of formation of the disseminated form of pulmonary tuberculosis 4 times (0R 4.33, 95% CI 1.70 - 11.07) and is associated with the combination of tuberculosis with COPD (64.3 vs. 39.5%, p = 0.03, RR 1.63, 95% CI 1.03 - 2.56).

2. The development of multidrug-resistant tuberculosis during treatment was observed significantly more often in fast/moderate acetylators with newly diagnosed tuberculosis compared with slow acetylators in *NAT* 2 (29.2 vs. 15.0%, χ^2 4.408; p = 0.036).

3. Deletion of *GSTM1*, del *GSTT1* and the presence of alleles of slow acetylation of NAT2 may be an endogenous risk factor for impaired renal filtration and reabsorption system under the toxic effects of anti-TB drugs. Determining the level of microalbuminuria is a more sensitive method of assessing the condition of the kidneys. The most significant changes in the indicators characterizing the condition of the liver and kidneys are observed in the group of patients with a long history of ineffective treatment in the presence of deletions of the *GSTT1* and *GSTM1* genes.

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