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ALLELIC POLYMORPHISMS OF DNA REPAIRING GENES AS MARKERS OF RESISTANCE TO ASBESTOS-CONTAINING AEROSOLS

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We studied the frequency distribution of DNA repairing genes allelic polymorphisms in the occupational group of asbestos-cement plants workers (n = 95). The aim of the work was to determine the probable molecular genetic markers of resistance to the development of bronchopulmonary pathology under the action of chrysotile-asbestos-containing dust. In 46 workers with chronic forms of bronchopulmonary pathology and 49 workers of the same professions without chronic diseases of the respiratory system, allelic polymorphisms XPD (rs13181, rs799793), ERCC1 (rs11615), XRCC3 (rs861539), XRCC1 (rs25487), ATM (rs664677), XRCC7 (rs7003908) and MLH1 (rs1799977) were determined using the real-time polymerase chain reaction. It was established that XRCC1•G/A (rs25487) (OR = 0.45; 95% CI: 0.18–1.10; P = 0.050; χ^2 = 3.73); MLH1•A/A (rs1799977) (OR = 0.28; 95% CI: 0.14 – 0.71; P = 0.003; χ^2 = 8.75) genotypes contribute to the resistance to bronchopulmonary pathology development, while XPD•Asn/Asn (rs799793) (OR = 2.20; 95% CI: 1.75–2.77; P = 0.001; χ^2 = 6.62); XRCC1•A/A (rs25487) (OR = 1.73; 95% CI: 1.23–2.43; P = 0.040; χ^2= 3.92); ATM•T/T (rs664677) (OR = 3.47; 95% CI: 1.01–12.51; P = 0.020; χ^2 = 4.98); MLH1•A/G (rs1799977) (OR = 2.95; 95% CI: 1.17–7.49; P = 0.010; χ^2 = 6.42) genotypes were found to be associated with the risk of respiratory disease development. The obtained results show interconnection between certain alleles of DNA repair genes and the risk of bronchopulmonary pathology development under the influence of industrial aerosols, including asbestos-containing ones.

K e y w o r d s: allelic polymorphisms of genes, bronchopulmonary pathology.

The type of the damage in the structure of a DNA molecule determines the way of repair and enzymes of repair provide restoration of the DNA molecule original structure. The main functions of the repair enzymes are the removal of short single-stranded DNA sequences with the false paired or damaged bases and their replacement with the complementary sequences. Single nucleotide polymorphism (SNP) of DNA repair genes can alter the structure and activity of enzymes that they encode [1, 2].

Exquisite repair is based on the identification of the modified base with glycosylases, which cleave the N-glycoside bond between the base and the sugar-phosphate core of the DNA molecule. SNP of glycosylases genes which is associated with the replacement of one of the nucleotides in the gene coding sequence is shown to be related to increased carcinogenesis risk [3]. The nucleotide excision repair (NER) is realized with the help of insertase and deoxyribonuclease I, which recognize DNA damage and cleave phosphodiester bonds near lesions. NER

enzymes include about 30 proteins, among them: XPB, XPC, XPD, etc. [4]. At the final repair stage, DNA-polymerase restores the cleaved section using the undamaged complementary DNA chain as a matrix and the polynucleotide ligase restores phosphodiester bonds [5]. The allelic polymorphism of genes encoding DNA polymerase or ligase III which are involved NER final stage significantly increases the cytotoxicity of adducts [4].

Double-strand DNA breaks appear during replication and under the action of damaging agents. Double-strand break repair (DSBR) errors cause mutations and chromosome rearrangements that induce genome instability and carcinogenesis [6, 7]. There are two mechanisms of DSBR repair: non-homologous end joining (NHEJ) and homologous recombination (HR) [6, 8]. NHEJ provides the ligation of DNA ends with minimal enzymatic treatment on the site of their combination. HR provides a complete restoration of the initial DNA sequence and homologues or sister chromatids are involved in the process. The main components of HR enzyme system are: RAD51, XRCC2, XRCC3 [1, 8, 9]. NHEJ is followed by formation of a new combination of genes and often leads to malignant transformation [9]. The mismatch repair (MMR) occurs when the modified base has not been removed from the DNA or when a non-canonical pair of nucleotides appears during replication. MMR enzymes MLH1, MSH2, MSH3, MSH6 recognize the damage in the structure of the duplex and cut the affected area at specific sites. It has been established that the carcinogenic activity of mutagens depends on the activity of MMR enzymes due to their involvement in apoptosis regulation [10].

The main important factors of the carcinogenic risk are factors of high penetrance, which include carcinogen dose, imbalance of detoxifying enzymes system and impaired DNA repair [11]. A useful model for studying the influence of genes polymorphism of the factors of high penetrance on human carcinogenesis is tobacco smoking, since the multicomponent composition of tobacco smoke causes all possible damages of DNA and even infrequent variants of SNP and their protein products involved in DNA repair has been established [12]. In particular, smokers with a high level of CYP1A1 and CYP2D6 induction, which was detected in lymphocytes treated with polycyclic aromatic hydrocarbons, had significantly higher incidences of lung cancer [12, 13]. And if smoking was combined with pneumoconiosis induced by asbestos dust, an 18-fold increase of the risk of lung cancer developing was observed [14].

Previously we studied the frequency of allelic variants of DNA repair genes polymorphisms in two independent groups of workers of hazardous and harmful industries in Ukraine [6]. To confirm the prognostic importance of the distribution of DNA repair genes allelic polymorphisms, it is necessary to standardize the results obtained and to prove that in workers of different harmful industries the frequencies of minor and dominant homozygotes and heterozygotes deviate significantly from the theoretically expected values.

The aim of the present study was to estimate the frequency and distribution of DNA repair genes allelic polymorphism in the occupational group of asbestic cement plants workers and to identify the possible genetic markers of resistance to bronchopulmonary pathology (BPP) development under the action of asbestos-containing aerosols.

Materials and Methods

Characteristics of the research respondents. The workers of the main occupations of the asbestos-cement plants (ACP) Kramatorsk Slate Ltd (n = 55) and “Balakliysky Slate” Ltd (n = 40) at the age from 20 to 62 years were included in the study. According to the results of the workplaces certification, the mean variation of chrysotile-asbestos maximum permissible concentration (MPC, which is 0.5 mg/m^3) in the air of the working area exceeded the average-shift of the MPC by 3.4-10.2 times.

For the comparative analysis, respondents were divided into two groups: “without obvious signs of BPP” (control), (n = 49) and a group of the workers “with signs of BPP” (study) (n = 46). BPP for nosology included: chronic bronchitis, chronic obstructive pulmonary disease, pneumoconiosis.

The verification of the BPP diagnosis was made in the clinic of occupational diseases at Kundiiev Institute of Occupational Health of the National Academy of Medical Sciences of Ukraine by estimating the function of external respiration and the diffusing capacity of the lung for carbon monoxide (DLCo). The general characteristics of respondents are presented in Table 1.

Genotyping. The blood samples were taken in sterile conditions into the medium, containing 11.7 mM EDTA (Sarstedt, Germany) , frozen and stored at -20 °C. DNA for genotyping was isolated from peripheral blood leukocytes using the Neo-

Table 1. General characteristics of the examined groups

Indication	Control, (n = 49)	Group with BBP, (n = 46)
Age, years	41.6 ± 7.0	44.3 ± 7.3
Experience of work in harmful conditions, years	14.1 ± 4.9	17.6 ± 5.6
Age at the beginning of the work in harmful conditions, years	24.2 ± 6.1	25.1 ± 6.4
Smoking, %	30.0 ± 6.5	24.0 ± 6.3

Prep100DNA and NEOGENE (Ukraine) kits in accordance with the manufacturer's instructions. Polymerase chain reaction (PCR) in real time was used to determine genes SNP: *XPD* (rs13181, rs799793), *ERCC1* (rs11615), *XRCC3* (rs861539), *XRCC1* (rs25487), *ATM* (rs664677), *XRCC7* (rs7003908) and *MLH1* (rs1799977) with the use of 7500 Fast Real-Time PCR System Appliter (Applied Biosystems, USA) and TaqMan Assays [6, 7].

Statistical analysis. The clinical data were analyzed for the normality of distribution using the Shapiro-Vilka test, as well as by the Levine Leuven test. Student's statistical criterion was used to determine the differences between the groups. A value of $P < 0.05$ was considered statistically significant. All calculations were made on the basis of SPSS ver.17.0, ver.23. The frequency of genotype distribution was analyzed using the Pearson Chi-square test. The SNP Analyzer program was used to verify the Hardy-Weinberg equilibrium.

The studies have been performed in accordance with the ethical standards, all patients participating in the study gave their consent and signed an informational agreement approved by the Bioethics Commission of the State Institution "Institute of Occupational Health of the National Academy of Medical Sciences of Ukraine", February 29, 2016.

Results and Discussion

The frequency distribution of genotypes of different DNA repair systems genes in the control and BPP group of ACP workers was studied. It should be noted that the obtained values of the frequencies of genotypes of DNA repair genes in both studied groups were close to that in the population of the European race (Table 2).

No significant differences in the frequency of allele gene polymorphisms *XPD* (rs13181), *ERCC1* (rs11615), *XRCC3* (rs861539) and *XRCC7* (rs7003908) in experimental and control groups were found ($P > 0.05$)

It was established that heterozygotes *XRCC1•G/A* and dominant homozygotes *MLH1•A/A* were significantly more frequent among respondents of the control group. Thus, the heterozygote *XRCC1•G/A* frequency in the control group was 61.2%, while in the group with BPP it was 41.3%. The frequency of dominant homozygotes *MLH1•A/A*, in the control group was 65.3% and in the group with BPP – 34.8%, indicating the interconnection

Table 2. Frequency distribution of genotypes of DNA repair genes in European race

Polymorphisms	Dominant homozygotes, %	Heterozygotes,%	Minor homozygotes, %	Reference
XPD (rs13181)	*A/A* – 35.4	*A/C* – 52.4	*C*/C– 12.2	15
XPD (rs799793)	*Asp/Asp* – up to 43	*Asp/Asn* 50-53	*Asn/Asn* – 17	16
ERCC1 (rs11615)	*C/C* – up to 50	*C/T* – 30	*T/T* – 17	17
XRCC3 (rs861539)	*C/C* – 53.1	*C*/T – 30.1	*T/T*– 16.8	18
XRCC1 (rs25487)	*G/G* – 33	*G/A* – 50	*A/A* – 17	6
ATM (rs664677)	*A/A* – 30-35	*A/T* – 50	*T/T* – 13	19
XRCC7 (rs7003908)	*C/C* – 33	*C/T* – 50	*T/T* – 17	20
MLH1 (rs1799977)	*A/A* – 25-45	*A/G* – 35-45	*G/G* – to 10	21

Table 3. Frequency distribution of genotypes of DNA repair genes in the occupational groups of workers of the asbestos-cement plants

Gene polymorphisms	Genotypes						*P*
	Dominant homozygotes, %		Heterozygotes, %		Minor homozygotes, %		
	Control	BPP	Control	BPP	Control	BPP	
XPD (rs13181)	26.5	41.3	59.2	43.5	14.3	15.2	0.20
XPD (rs799793)	42.9	39.1	57.1	47.8	0	13.1	0.03
ERCC1 (rs11615)	38.8	45.7	44.9	36.9	16.3	17.4	0.70
XRCC3 (rs861539)	34.7	39.1	55.1	50.0	10.2	10.9	0.80
XRCC1 (rs25487)	36.7	43.5	61.2	41.3	2.1	15.2	0.03
XRCC7 (rs7003908)	46.9	43.5	32.7	47.8	20.4	8.7	0.10
ATM (rs664677)	34.7	26.1	55.1	45.6	10.2	28.3	0.07
MLH1 (rs1799977)	65.3	34.8	30.6	56.5	4.1	8.7	0.01

Table 4. Analysis of associations of genotypes of DNA repair genes in the study groups

Gene polymorphisms	Genotypes	OR, 95% CI; *P*, χ^2
XPD (rs13181)	*A/A*	1.95 (0.75-5.07); *P* = 0.100
	A/C	0.53 (0.22-1.30); *P* = 0.100
	C/C	1.08 (0.30-3.82); *P* = 0.900
XPD (rs799793)	*Asp/Asp*	0.86 (0.35-2.11); *P* = 0.700
	Asp/Asn	0.65 (0.27-1.60); *P* = 0.300
	Asn/Asn	2.20 (1.75-2.77); *P* = 0.001; χ^2 = 6.62
ERCC1 (rs11615)	*T/T*	1.33 (0.54-3.26); *P* = 0.400
	T/C	0.72 (0.29-1.77); *P* = 0.400
	C/C	1.08 (0.33-3.57); *P* = 0.900
XRCC3 (rs861539)	*C/C*	1.21 (0.48-3.03); *P* = 0.600
	C/T	0.81 (0.34-1.97); *P* = 0.600
	T/T	1.07 (0.25-4.70); *P* = 0.900
XRCC1 (rs25487)	*G/G*	1.32 (0.54-3.28); *P* = 0.500
	G/A	0.45 (0.18-1.10); *P* = 0.050; χ^2 = 3.73
	A/A	1.73 (1.23-2.43); *P* = 0.040; χ^2 = 3.92
ATM (rs664677)	*A/A*	0.66 (0.25-1.75); *P* = 0.300
	A/T	0.68 (0.28-1.66); *P* = 0.300
	T/T	3.47 (1.01-12.51); *P* = 0.020; χ^2 = 4.98
XRCC7 (rs7003908)	*C/C*	0.87 (0.36-2.11); *P* = 0.700
	C/T	1.89 (0.76-4.73); *P* = 0.100
	T/T	0.37 (0.09-1.44); *P* = 0.100
MLH1 (rs1799977)	*A/A*	0.28 (0.14-0.71); *P* = 0.003; χ^2 = 8.75
	A/G	2.95 (1.17-7.49); *P* = 0.010; χ^2 = 6.42
	G/G	2.24 (0.33-18.68); *P* = 0.300

Note: OR – Odd Ratio (Odds Ratio); CI – confidential interval (confidence interval); χ^2 – (Pearson Xi square)

between these distinctions and resistance to BPP development (Table 3, 4).

The study showed that the frequency of minor homozygotes of the genes: *XPD* (rs799793), *XRCC1* (rs25487), *ATM* (rs664677) and the heterozygote *MLH1* (rs1799977) was significantly more common in the BPP group than in the control group. The study of the frequency of *XPD* (rs799793) polymorphism showed that the frequency of minor homozygotes XPD•Asn/Asn in the BPP group was 13.1% and in the control group they were absent. The frequency of minor homozygotes *XRCC1•A/A* in the BPP group was 15.2% and in the control group 2.1%. Correspondingly, the frequency of *ATM* gene minor homozygotes in the BPP group was found to be 28.3%, in the control group – 10.2%. The frequency of *MLH1•A/G* heterozygotes in the BPP group was also significantly higher (56.5%) as compared with the control group (30.6%) (Table 3, 4) indicating the association with the risk of the BPP development.

As a result of the analysis of the frequency of genotypes of DNA repair genes SNP, a certain genotypes, that promote resistance to development of BPP have been found: *XRCC1•G/A* (rs25487) (OR = 0.45; 95% CI: 0.18-1.10; $P = 0.050$; $\chi^2 = 3.73$); *MLH1•A/A* (rs1799977) (OR = 0.28; 95% CI: 0.14-0.71; $P = .003$; $\chi^2 = 8.75$). Also, genotypes with the risk of BPP development have been established: *XPD•Asn/Asn* (rs799793) (OR = 2.20; 95% CI: 1.75-2.77; $P = 0.001$; $\chi^2 = 6.62$); *XRCC1•A/A* (rs25487) (OR = 1.73; 95% CI: 1.23-2.43; $P = 0.040$; $\chi^2 = 3.92$); *ATM•T/T* (rs664677) (OR = 3.47; 95% CI: 1.01-12.51; $P = 0.020$; $\chi^2 = 4.98$); *MLH1•A/G* (rs1799977) (OR = 2.95; 95% CI: 1.17-7.49; $P = 0.010$; $\chi^2 = 6.42$).

These polymorphisms were previously considered as the markers of carcinogenesis of various types and localizations, including lung cancer but were studied predominately in smokers. A fibrous natural material asbestos is recognized as a carcinogen. In our study for the first time the interconnection between allelic polymorphisms of DNA repair genes and predisposition or resistance of ACP workers to the development of BPP under the influence of industrial asbestos-containing aerosols was shown. The data obtained allow to identify genotypes that promote resistance to respiratory diseases: *XRCC1•G/A* (rs25487) (OR = 0.45; 95% CI: 0.18-1.10; $P = 0.050$; $\chi^2 = 3.73$); *MLH1•A/A* (rs1799977) (OR = 0.28; 95% CI: 0.14-0.71; $P = 0.003$; $\chi^2 = 8.75$). The genotypes associated with the risk of BPP developing were also identified: *XPD•Asn/Asn* (rs799793) (OR = 2.20; 95% CI: 1.75-2.77; $P = 0.001$; $\chi^2 = 6.62$); *XRCC1•A/A* (rs25487) (OR = 1.73; 95% CI: 1.23-2.43; $P = 0.040$; $\chi^2 = 3.92$); *ATM•T/T* (rs664677) (OR = 3.47; 95% CI: 1.01-12.51; $P = 0.020$; $\chi^2 = 4.98$); *MLH1•A/G* (rs1799977) (OR = 2.95; 95% CI: 1.17-7.49; $P = 0.010$; $\chi^2 = 6.42$).

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Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

АЛЕЛЬНІ ПОЛІМОРФІЗМИ ГЕНІВ РЕПАРАЦІЇ ДНК ЯК МАРКЕРИ РЕЗИСТЕНТНОСТІ ДО ДІЇ АЗБЕСТОВМІСНИХ АЕРОЗОЛІВ

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Вивчали розподіл частот алельних поліморфізмів генів репарації ДНК в професійній групі працівників азбестоцементних заводів ($n = 95$). Метою роботи було встановити можливі молекулярно-генетичні маркери резистентності до розвитку бронхолегеневої патології за дії азбестовмісного пилу. У 46 осіб з хронічними формами бронхолегеневої патології та в 49 осіб – працівників тих самих професій, але без захворювань дихальної системи, методом полімеразної ланцюгової реакції в реальному часі визначено алельні поліморфізми генів: *XPD* (rs13181, rs799793), *ERCC1* (rs11615), *XRCC3* (rs861539), *XRCC1* (rs25487), *ATM* (rs664677), *XRCC*7 (rs7003908) і *MLH*1 (rs1799977). Встановлено, що генотипи *XRCC1•G/A* (rs25487) (OR = 0,45; 95%CI: 0,18-1,10; $P = 0,050$; $\chi^2 = 3,73$);

MLH1•A/A (rs1799977) (OR = 0,28; 95%CI: 0,14-0,71; *P* = 0,003; χ^2 = 8,75) сприяють резистентності до розвитку бронхолегеневої патології, а генотипи: *XPD•Asn/Asn* (rs799793) (OR = 2,20; 95%CI: 1,75-2,77; *P* = 0,001; χ^2 = 6,62); *XRCC1•A/A* (rs25487) (OR = 1,73; 95%CI: 1,23-2,43; *P* = 0,040; χ^2 = 3,92); *ATM•T/T* (rs664677) (OR = 3,47; 95%CI: 1,01-12,51; *P* = 0,020; χ^2 = 4,98); *MLH1•A/G* (rs1799977) (OR = 2,95; 95%CI: 1,17-7,49; *P* = 0,010; χ^2 = 6,42) асоційовані з ризиком розвитку захворювань дихальної системи. Одержані результати свідчать про наявність зв'язку між певними алелями генів репарації ДНК із ризиком розвитку бронхолегеневої патології за впливу промислових аерозолів, включно азбестовмісних.

Ключові слова: алельний поліморфізм генів, бронхолегенева патологія.

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