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Research article

POLYMORPHISM OF *TP53* (RS1042522) GENE AND PECULIARITIES OF THE IMMUNE PROFILE IN CHILDREN EXPOSED TO AIRBORNE BENZO(A)PYRENE

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Examining peculiarities of an immune profile and genetic polymorphisms is especially relevant when identifying markers of effect and sensitivity to exposure to benzo(a)pyrene in northern areas.

We examined 1253 children who lived in industrial centers and on conditionally clean territories in the north and south of Eastern Siberia. Levels of benzo(a)pyrene in ambient air and in children's blood were determined by using HPLC. TP53 (rs1042522) polymorphism was examined by using real-time PCR; p53 levels were identified with flow cytofluorometry; IgG to benzo(a)pyrene, by the radioallergosorbent tests.

Exposure of children in Northern Siberia to airborne benzo(a)pyrene at the dose of $7.11 \cdot 10^{-3}$ μg/(kg·day) causes benzo(a)pyrene contamination in blood, activates apoptosis (p53) and stimulates occurrence of specific sensitization (IgG to benzo(a)pyrene) ($p < 0.05$). Similar disorders were established in children in Southern Siberia under exposure to airborne benzo(a)pyrene at the dose of $86.46 \cdot 10^{-3}$ μg/(kg·day). The detected changes in immune profiles of children living in Northern Siberia are associated with G-allele and GG-genotype (rs1042522) of the TP53 gene (OR = 1.37–1.83, $p < 0.05$); children in Southern Siberia, C-allele and CC-genotype of the said gene (OR = 1.55–2.38, $p < 0.05$).

Therefore, the immune profile of children exposed to airborne benzo(a)pyrene at the dose of $7.11 \cdot 10^{-3}$ μg/(kg·day) in Northern Siberia bears some signs of activated apoptosis (p53) and specific sensitization (IgG to benzo(a)pyrene) associated with G-allele and GG-genotype of the TP53 gene (rs1042522) (OR = 1.37–1.83, $p < 0.05$). These identified changes in the immune profile are comparable with effects produced by exposure to airborne benzo(a)pyrene at the dose of $86.46 \cdot 10^{-3}$ μg/(kg·day) in Southern Siberia, which are associated with C-allele and CC-genotype of the same gene (OR = 1.55–2.38, $p < 0.05$). This confirms a hypothesis that effects of technogenic chemical factors can be modulated by specific climatic conditions in northern areas and a contribution made by genetic predisposition. Their combined effect creates a serious risk of developing impairments in an immune profile (OR = 1.37–1.83, $p < 0.05$; RR = 1.17; 95 % CI: 1.07–1.27) even under low-dose exposure to airborne benzo(a)pyrene.

Keywords: *benzo(a)pyrene, airborne exposure, children, immune profile, genetic polymorphism, apoptosis, p53, sensitization.*

Benzo(a)pyrene is a polycyclic aromatic hydrocarbon (PAH) of hazard degree I able to produce mutagenic, carcinogenic (IARC's group A carcinogen) and immunosuppressing effects [1, 2].

Impacts of technogenic chemical factors on human health in an actual industrially developed area are not isolated. A combination of climatic conditions and peculiar light regime typical for a given territory can modulate adverse effects produced by technogenic chemical exposures [3]. In particular, combined influence of subarctic climatic conditions and photoperiodic seasonal asymmetry in northern areas induces deadaptation-like changes in the immune regulation even under low-dose chemical exposures [4, 5].

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It should be noted that polymorphisms of candidate genes responsible for the immune regulation make a significant contribution to formation of a specific immune profile, which plays an important role in adaptation to changed environmental conditions [6, 7]. Changes in an immune profile associated with polymorphisms of the tumor suppressing gene p53 *TP53* (rs1042522) can be related to dysregulation of the cell cycle, DNA repair and apoptosis and growing risks of oncoproliferative states. This is especially relevant under exposure to benzo(a)pyrene as a well-known chemical carcinogen [8, 9].

Hence, it is quite relevant to accomplish a comparative assessment of peculiarities of an immune profile associated with the *TP53* (rs1042522) gene polymorphisms in children exposed to airborne benzo(a)pyrene in the south and north of Eastern Siberia for further development and substantiation of markers of effects and sensitivity to exposure to technogenic chemical factors in northern areas with specific climatic conditions and light regime.

In this study, we aimed to comparatively assess polymorphisms of the *TP53* (rs1042522) gene and peculiarities of an immune profile in preschoolers exposed to airborne benzo(a)pyrene in the north and south of Eastern Siberia.

Materials and methods. We comparatively assessed polymorphisms of the *TP53* (rs1042522) gene and immune profile indicators in preschoolers who lived in Eastern Siberia (n = 1253). The observation group 1 (n = 526) and the observation group 2 (n = 376) were made of children living in industrially developed areas in the north and south of the region respectively. The reference group 1 (n = 180) and the reference group 2 (n = 171) included children who lived on conditionally clean territories in the north and south of the region.

The study was accomplished in conformity with the fundamentals stated in the Declaration of Helsinki by the World Medical Association and approved by the Local Ethics Committee of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies (The meeting report No. 2 dated January 17, 2022).

Benzo(a)pyrene levels in ambient air and contamination with this PAH in the examined children's blood were identified by using high-performance liquid chromatography on an Agilent 1200 (USA) in conformity with the Methodical Guidelines MUK 4.1.3040-12[1] and MUK 4.1.1273-03[2].

The intracellular transcription factor p53 was determined by using flow-cytometric analysis on a FACSCalibur (USA). Production of IgG specific to benzo(a)pyrene was established by the radioallergosorbent tests.

SNP of the *TP53* (rs1042522) gene responsible for the transcription factor p53 were identified by real-time polymerase chain reaction (PCR-RT) on a CFX96 amplifier (Singapore). DNA was extracted from buccal epithelium by the sorbent method. A genotype of each participant was determined by allelic discrimination in TaqMan.

Data were statistically analyzed in StatSoft Statistica 10.0 by using ANOVA one-factor dispersion analysis. Data distribu-

[1] MUK 4.1.3040-12. Izmerenie massovoi kontsentratsii benz(a)pirena v krovi metodom vysokoeffektivnoi zhidkostnoi khromatografii [Measurements of mass concentration of benzo(a)pyrene in blood by high-performance liquid chromatography]: Methodical guidelines, approved by G.G. Onishchenko, the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, the RF Chief Sanitary Inspector on September 07, 2012. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200103098 (January 17, 2024) (in Russian).

[2] MUK 4.1.1273-03. Izmerenie massovoi kontsentratsii benz(a)pirena v atmosfernom vozdukhe i v vozdukhe rabochei zony metodom vysokoeffektivnoi zhidkostnoi khromatografii s fluorimetricheskim detektirovaniem [Measurements of mass concentration of benzo(a)pyrene in ambient air and workplace air by high-performance liquid chromatography with fluorometric detection]: Methodical guidelines, approved and enacted by G.G. Onishchenko, the RF Chief Sanitary Inspector and Deputy to the RF Minister of Health on April 01, 2003. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200034301 (January 17, 2024) (in Russian).

tion was checked for normality with the one-sample Kolmogorov – Smirnov test. The Tukey – Kramer test was applied to check authenticity of differences in multiple comparisons. The statistical significance for rejecting the null hypothesis (that is, absence of differences) was taken at $p < 0.05$. We calculated distribution of frequencies of the *TP53* (rs1042522) gene alleles and genotypes, odds ratio *OR*, relative risk *RR* and their 95 % confidence intervals (*CI*) for further analysis of relations between changes in immune regulation indicators and variant genotypes of this gene in Gen-Expert online calculator and Microsoft Office Excel 2010.

Results and discussion. Average annual benzo(a)pyrene levels equaled 0.62 average daily MPL in ambient air in an industrially developed area in the north and 0.014 average daily MPL in a conditionally clean area in the same region; they equaled 7.27 average daily MPL in ambient air in an industrially developed area in the south and 0.74 average daily MPL in a conditionally clean area in the same region[3].

An average daily exposure to airborne benzo(a)pyrene was 0.0071 μg/(kg·day) for children living in an industrially developed area in the north and was higher than that for children living in a conditionally clean northern area (0.0001 μg/(kg·day)) ($p = 0.001$). In its turn, an average daily exposure to airborne benzo(a)pyrene for children living in an industrially developed area in the south (0.0865 μg/(kg·day)) was not only authentically higher than that for children living in a conditionally clean southern area (0.0083 μg/(kg·day)) but also higher than that for children living in an industrially developed area in the north ($p = 0.001$).

Levels of contamination in blood of the children from the observation group in the north (0.00224 ± 0.00030 μg/dm^3) were higher than in the children from the reference group (0.00112 ± 0.00034 μg/dm^3) and the reference level ($p < 0.05$). Benzo(a)pyrene levels in blood of the children from the observation group in the south (0.00225 ± 0.00035 μg/dm^3) were also higher than those in blood of the children from the relevant reference group (0.00109 ± 0.00024 μg/dm^3) and the reference level ($p = 0.006$). However, benzo(a)pyrene levels did not differ authentically in blood of the children under low-dose exposure to airborne benzo(a)pyrene in an industrially developed area in the north and in blood of the children under high-dose exposure to airborne benzo(a)pyrene in the south ($p = 0.98$).

The immune profile of the examined children living in highly urbanized territories in the north and south of Eastern Siberia bears some signs of activated programmed cell death combined with developing specific hyper-sensitization to benzo(a)pyrene (Table 1).

Some signs of hyperexpression of the onco-suppressor protein p53 were identified in 43.9 % (231) of the children from the northern observation group against their peers in the corresponding reference group and the reference level as well ($p < 0.05$). Elevated p53 levels in the northern observation group were authentically associated with the G-allele and GG-genotype of the *TP53* gene (rs1042522) (*OR* = 1.37–1.83, $p < 0.05$) (Table 2).

[3] Ob utverzhdenii Programmy kompleksnogo razvitiya transportnoi infrastruktury munitsipal'nogo obrazovaniya «Gorod Dudinka»: reshenie Dudinskogo gorodskogo soveta deputatov ot 14.09.2017 № 10-0358 [On Approval of the program for complex development of the transport infrastructure in Dudinka municipal settlement: the Decision of the Dudinka Town Council of Deputies dated September 14, 2017 No. 10-0358]. *The official web-site with legal information on town Dudinka*. Available at: http://www.pravo-dudinka.ru/download/rgs/rgs_2017-09-14_10-0358.pdf (February 21, 2024) (in Russian); O sostoyanii i ob okhrane okruzhayushchei sredy Rossiiskoi Federatsii v 2018 godu [On the state and protection of the environment in the Russian Federation in 2018]: the state report. Moscow, Ministry of Natural Resources and Environment of the Russian Federation; NPP Kadastr, 2019 (in Russian); Sostoyanie zagryazneniya atmosfery v gorodakh na territorii Rossii za 2017 g. [Ambient air pollution in cities in Russia in 2017]: Annual data collection. St. Petersburg, 2018 (in Russian).

Table 1

Peculiarities of the immune profile of the children living in the north and south of Eastern Siberia under exposure to airborne benzo(a)pyrene

Reference level[4]	Observation group 1 – northern Siberia (n = 526)	Reference group 1 – northern Siberia (n = 180)	p_1	Observation group 2 – southern Siberia (n = 376)	Reference group 2 – southern Siberia (n = 171)	p_2
p53, % / p53,%						
1.2 –1.8	5.42 ± 0.47*	4.27 ± 0.29*	0.038	7.75 ± 0.89*	1.87 ± 0.10	0.001
IgG to benzo(a)pyrene, arb.un.						
0–0.3	0.208 ± 0.014	0.080 ± 0.02	0.001	0.212 ± 0.011	0.074 ± 0.009	0.001

N o t e: p_1 is authenticity of differences between the observation and reference group in the north; p_2 is authenticity of differences between the observation and reference group in the south; * means authentic difference from the reference level ($p < 0.05$).

Table 2

Frequencies of alleles and genotypes of the *TP53* (rs1042522) gene in the examined children in the north and south of Eastern Siberia, %

SNP	Genotype / allele	v_{obs}	v_{ref}	χ^2	p	*OR* (95 % *CI*)
TP53 (rs1042522)	Observation group 1 (n = 526) / Reference group 1 (n = 180)					
	CC	36.1	36.7	3.82	0.049	0.98 (0.69–1.39)
	CG	11.2	25.6			0.37 (0.24–0.57)
	GG	52.7	37.7			1.83 (1.30–2.59)
	C	41.7	49.4	6.49	0.01	0.73 (0.58–0.93)
	G	58.3	50.6			1.37 (1.07–1.74)
	Observation group 2 (n = 376) / Reference group 2 (n = 171)					
	CC	49.5	29.1	9.94	0.002	2.38 (1.59–3.57)
	CG	34.3	54.3			0.44 (0.30–0.65)
	GG	16.2	16.6			0.98 (0.59–1.62)
	C	66.6	56.3	8.76	0.003	1.55 (1.18–2.04)
	G	33.4	43.7			0.65 (0.49–0.85)

N o t e: v_{obs} is frequencies of alleles and genotypes in the observation groups 1 and 2; v_{ref} is frequencies of alleles and genotypes in the reference groups 1 and 2.

Levels of p53 were also higher in 54.5 % (205) of the children in the southern industrial area than in the children from the relevant reference group ($p < 0.05$), which, on the contrary, was associated with the C-allele and CC-genotype of the *TP53* (rs1042522) gene (*OR* = 2.17–2.83, $p < 0.05$).

Levels of the protein p53 expression in the children under high-dose exposure to airborne benzo(a)pyrene in the south were authentically 1.4 times higher than the same indicator in the children under low-dose exposure to airborne benzo(a)pyrene in the north ($p < 0.05$). Levels of the p53 protein were also higher in the children who lived in a conditionally clean northern area than in the children who lived in a conditionally clean area in the south ($p = 0.001$).

We established higher production of IgG specific to benzo(a)pyrene in 73.4 % (386) of

[4] Tietz' clinical guide to laboratory tests, 4th ed. In: A. Wu ed.; V.V. Menshikov translation. Moscow, Labora Publ., 2013, 1280 p. (in Russian).

the children from the observation group 1 and 63.1 % (237) of the children in the observation group 2 against the reference level and corresponding reference groups ($p < 0.05$). However, levels of this marker identified in the children under low-dose exposure to airborne benzo(a)pyrene in the north were comparable with those identified under high-dose exposure to airborne benzo(a)pyrene in the south ($p = 0.822$).

Benzo(a)pyrene is a highly toxic polycyclic aromatic hydrocarbon (PAH) able to produce strong cytotoxic, mutagenic, carcinogenic and neurotoxic effects [10]. Mutagenic and carcinogenic effects of benzo(a)pyrene occur due to covalent linking of its metabolite BaP-7,8-dihydrodiol-9,10-epoxide (BPDE) to nucleotide bases and the subsequent formation of cys- and trans-DNA adducts. This damages a nucleotide sequence, breaks DNA repair and replication and cell transformation and, consequently, results in cell death and / or carcinogenesis [11, 12].

Climatic and natural conditions in polar areas, in particular, in the north of Eastern Siberia are harsh and unstable as they are characterized with a long period of low temperatures, drastic changes in the atmospheric pressure, elevated electromagnetic activity and radiation as well as a changed light regime, namely, photoperiodic seasonal asymmetry. Extreme living conditions in northern areas make high demands of the immune and nervous systems as those maintaining homeostasis in the human body under unstable environmental conditions. Adaptation of the body to such harsh conditions becomes more complex and this leads to a decrease in adaptation potential and, consequently, facilitates occurrence of prenosological changes in an immune profile [13, 14].

The p53 protein is a transcription factor and tumor growth suppressor. It plays an important role in DNA repair, cell cycle regulation and apoptosis or programmed cell death. Activation of p53 by various DNA-damaging agents and carcinogens, benzo(a)pyrene included, stops the cell cycle in its G1 phase and induces Nucleotide Excision Repair (NER), an important pathway of DNA repair. It is put into effect by activating inhibitors of the cyclin-dependent kinase c21 (CDK-21) as well as the *GADD45* (Growth arrest and DNA damage) gene. However, a growing dose of a carcinogen as well as longer exposure to it creates higher risks of mutations of the tumor suppressor gene p53. DNA damage in a mutated cell does not stop the cell cycle or DNA repair due to disrupted p53-dpendent formation of the cyclin-dependent kinase inhibitor 1A p21, which results in its proliferation and transformation into a malignant neoplasm [15, 16].

In this study, elevated p53 levels were identified in children under isolated exposure to a technogenic factor (benzo(a)pyrene) (the observation group 2), in children living in harsh climatic conditions in a northern area (the reference group 1), and in children under combined exposure to both adverse factors, technogenic and climatic one (the observation group 1). This, probably, indicates that programmed cell death was activated for cells with DNA damage under exposure to various stress factors. We established that high-dose exposure to airborne benzo(a)pyrene, 0.0865 μg/(kg·day), associated with the C-allele and wild CC-genotype of the *TP53* (rs1042522) gene caused the greatest growth in the p53 expression, namely, by 4.1 times against the reference group 2. A less significant increase in p53 levels in the children who lived in an industrially developed area in the north of Eastern Siberia, namely, by 1.3 times, was probably associated with exposure to low doses of benzo(a)pyrene, 0.0071 μg/(kg·day), as well as such genetic determinants as a prevailing minor G-allele and GG-genotype of the *TP53* (rs1042522) gene. Frequency of the G-allele of the *TP53* (rs1042522) gene was 58.3 % in the children living in an industrially developed area in the north of Eastern Siberia. This is authentically higher than average frequencies in the global

(28.6 %), European (26.3 %) and Asian (41.5 %) populations[5]. According to literature data, the G-allele of the *TP53* (rs1042522) gene is associated with lower expression of the p53 protein, inhibited DNA repair and apoptosis [17]. It is also a known fact that isolated exposure to benzo(a)pyrene as well as combined exposure to benzo(a)pyrene and a vaccine SARS-CoV-2 antigen activates expression of the *TP53* (rs1042522) gene in CG-heterozygotes and, on the contrary, inhibits its expression in GG-homozygotes in *in vitro* experiments [18]. In addition to that, the GG-genotype of the *TP53* (rs1042522) gene might be associated with an elevated risk of developing oncoproliferative processes [19, 20], which is especially important under exposure to benzo(a)pyrene in the environment as an obvious carcinogen.

Conclusion. Benzo(a)pyrene levels identified in blood of children exposed to airborne benzo(a)pyrene at the dose of 0.0071 μg/(kg·day) were higher in an industrially developed area in the north of Eastern Siberia than in a conditionally clean area in the same region ($p < 0.05$) and did not differ from levels identified in blood of children exposed to airborne benzo(a)pyrene at the dose of 0.0865 μg/(kg·day) in the south of Eastern Siberia ($p > 0.05$). The same trend was revealed for immune regulation indicators. Thus, production of p53 and IgG specific to benzo(a)-pyrene was higher in children under low-dose exposure to benzo(a)pyrene in the north than in children living in a conditionally clean area in the north and was comparable with that identified in children under high-dose exposure to benzo(a)pyrene in the south of Eastern Siberia ($p < 0.05$). Changes in the immune regulation identified in children living in an urbanized area in the north were associated with the minor G-allele and GG-genotype of the *TP53* (rs1042522) gene (*OR* = 1.37–1.83, $p < 0.05$; *RR* = 1.17; 95 % *CI*: 1.07–1.27) and with the wild C-allele and CC-genotype of the same gene in children living in an industrially developed area in the south (*OR* = 1.55–2.38, $p < 0.05$). The phylogenetic aspect of the *TP53* (rs1042522) gene has an emphasis on the maximum duration of the cell cycle under 'northern stress' (limited functional of the tumor suppressor p53). An association between changes in immune profiles of children living in an industrially developed area in the north and the minor G-allele and GG-genotype of the said gene indicates that genetic predisposition makes an additional background contribution to occurrence of more intensive adverse effects produced by exposure to benzo(a)pyrene in a northern area with a specific climatic background and light regime. Therefore, these identified changes in the immune regulation in children living in an industrially developed area in the north (elevated levels of p53 and IgG specific to benzo(a)pyrene), which are associated with the G-allele and GG-genotype of the *TP53* (rs1042522) gene, describe peculiar adaptation reactions of the immune system under combined exposure to benzo(a)pyrene, sub-Arctic climatic conditions and photoperiodic asymmetry in the presence of relevant genetic determinants. Hence, they can be used as indicators of health risks (*OR* = 1.37–1.83, $p < 0.05$; *RR* = 1.17; 95 % *CI*: 1.07–1.27) for children exposed to airborne technogenic chemical factors in northern areas.

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[5] ALFA Allele Frequency of TP53 (rs1042522). *National Library of Medicine*. Available at: https://www.ncbi.nlm.nih.gov/snp/rs1042522#frequency_tab (February 11, 2024).

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