



Federal Medical-Biological Agency of Russia
**Urals Research Center For
Radiation Medicine**



Genetic markers associated with the development of stochastic effects

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In the late 1940s in the northern Chelyabinsk Oblast of Russia, the Mayak Production Association (Mayak) was created to produce weapons-grade plutonium. From 1949 to 1956 this plant conducted routine and accidental discharges of liquid radioactive waste into the Techa River.

The following radiation-induced effects were found in persons exposed as a result of radioactive contamination of the Techa River in the long-term period:

- increased level of chromosomal aberrations;
 - T-cell receptor (TCR) gene mutations;
 - increased level of apoptosis of lymphocytes and cells with cell cycle delay;
 - decrease in the number of neutrophils in blood;
 - increase in serum proinflammatory cytokine levels;
 - increased risk of malignant neoplasms.
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- The aim of study is investigation of the connection between SNP genes that regulate reparation, apoptosis, cell cycle, antioxidant and immune systems (28 polymorphic regions) and risk of malignant neoplasms development. Expression of mRNA of ATM, TP53, MDM2, CDKN1A, BAX, BCL-2, XPC, OGG1, STAT3, GATA3, MAPK8, NF-kB1 and PADI4 genes was also studied in chronically exposed individuals.

Description of the study group

The association of SNP with the risk of malignant neoplasm development was investigated in :

- 248 patients (median exposure dose to RBM was 0.87 Gy, dose range 0.002-4.6 Gy) with various types of solid cancers in the past history: breast cancer (49 people); skin cancer (46 people); GIT cancer (45 people); uterus cancer and cancer of ovaries (32 people); lung cancer (26 people).
- Comparison group consisted of 384 people without cancer (median exposure dose to RBM was 0.86 Gy, dose range 0.001-4.2 Gy).

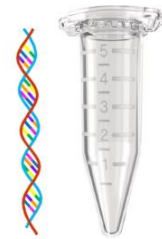
Transcriptional activity of the study genes were evaluated in 309 people.

- The group of exposed persons included 163 elderly people (median exposure dose to RBM was 0.72, dose range 0.08-3.51 Gy).
- The control group consisted of 146 people living in similar socio-economic conditions in the Southern Urals, the accumulated doses of which did not exceed 0.07 Gy.

The Research Scheme



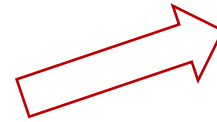
I. Blood sampling



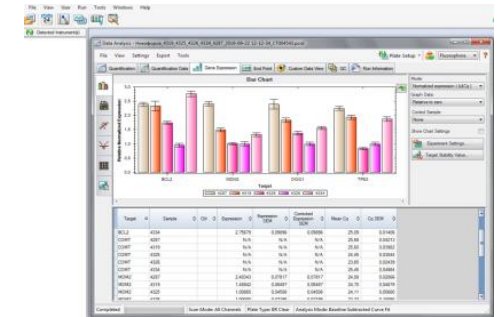
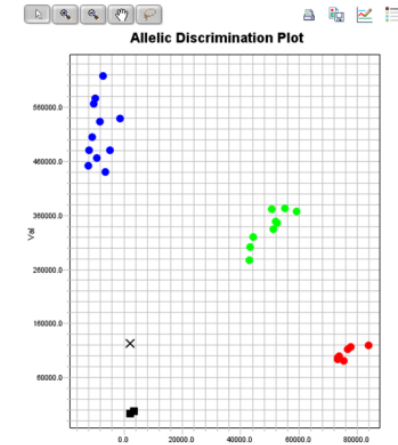
II. DNA/RNA extraction



III. Real-time PCR



IV. SNP analysis



IV. Expression analysis

Results

Table 1 . The relationship of SNP genes with the risk of cancer development

Gene/SNP	Model	Genotype	OR (95% CI)	p-value
<i>OGG1</i> rs1952133	Dominant	C/C C/G-G/G	1.00 1.99 (1.37-2.90)	0.0003
<i>MDM2</i> rs2279744	Dominant	A/A A/C-C/C	1.00 1.76 (1.16-2.67)	0.0069
<i>BCL2</i> rs2279115	Dominant	A/A C/A-C/C	1.00 1.54 (1.07-2.23)	0.02
<i>GPX1</i> rs1050450	Recessive	C/C-C/T T/T	1.00 2.12 (1.12-4.03)	0.02

Results

Table 2 . The relationship of SNP genes with the risk of cancer development

Gene/SNP	Model	Genotype	OR (95% CI)	p-value
<i>NBS1</i> rs13312840	Dominant	A/A-C/A C/C	0.60 (0.37-0.97) 1.00	0.032
<i>CDKN1A</i> rs1801270	Dominant	T/T-C/T C/C	0.66 (0.45-0.97) 1.00	0.036

Results

Relative mRNA genes levels in persons exposed as a result of radioactive contamination of the Techa River in the long-term period

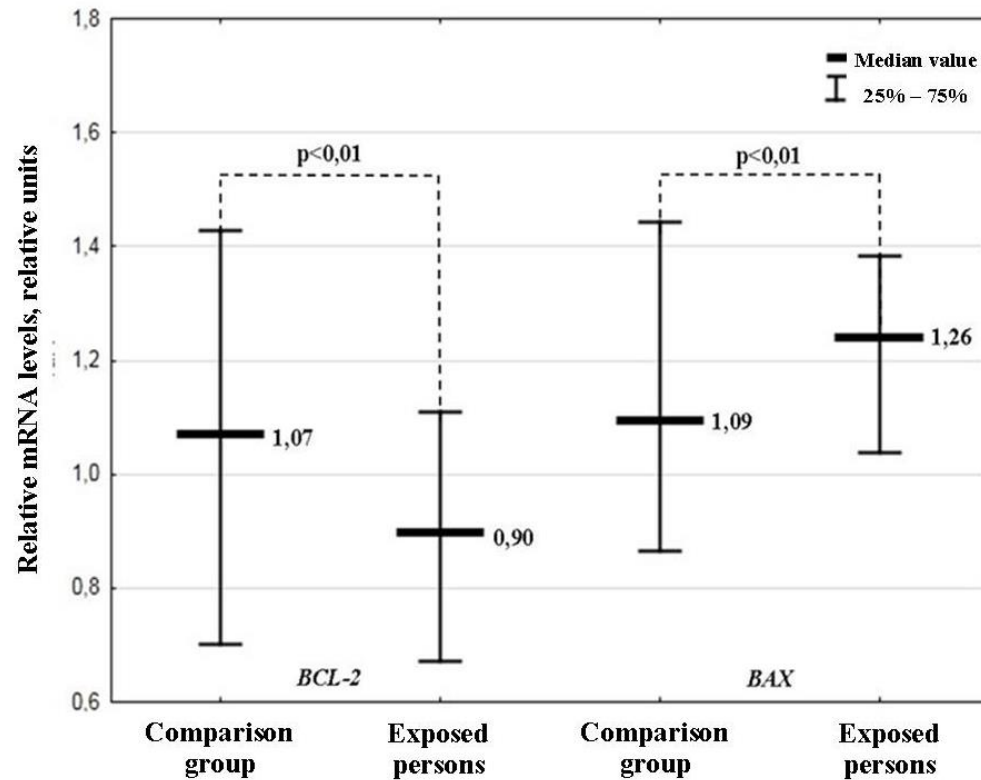


Figure 1 - Distribution of the relative levels of mRNA *BCL-2* and *BAX* genes in the comparison group and the group of exposed people.

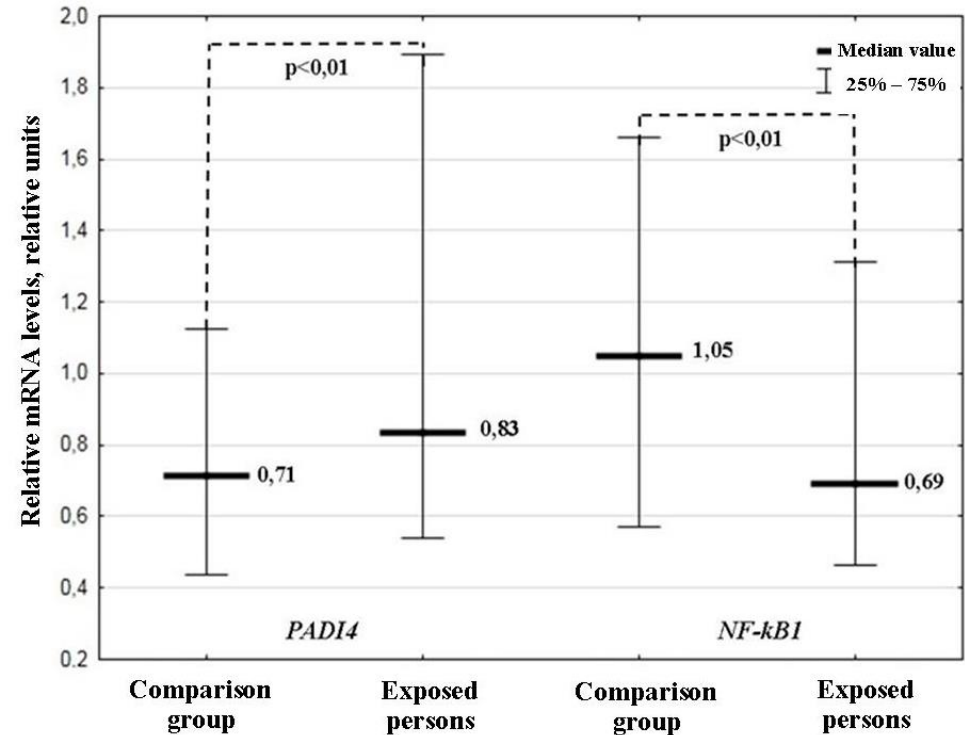


Figure 2 - Distribution of the relative levels of mRNA *PADI4* and *NF-kB1* genes in the comparison group and the group of exposed people.

Conclusion

- The preformed study revealed the connection between polymorphic region rs1952133 of the *OGG1* gene, rs2279744 of the *MDM* gene, rs2279115 of the *BCL2* gene and rs1050450 of the *GPX1* gene and increased risk of cancer development; and association between polymorphic region rs13312840 of the *NBS1* gene and rs1801270 of the *CDKN1A* gene with decreased risk of cancer development.
- The most pronounced changes of the transcriptome in exposed persons were noted in genes that regulate apoptosis of *BCL-2*, *BAX*, *NF-kB1* and *PADI4*.
- The genes that we have studied play the key role in the system of cell protection from radiation exposure. Radiation-induced changes in the transcription activity as well as the presence of tumor-associated allelic variants of genes may impede effective work of protective mechanisms of a cell, which in its turn results in the development of late effects of radiation exposure.

Thank you for your attention

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