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Associations of DNA-repair gene polymorphisms with a genetic susceptibility to ionizing radiation in residents of areas with high radon (^{222}Rn) concentration

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Abstract

Purpose: **To investigate the individual radiosensitivity of the human genome in long-term residents of areas with high radon concentration.**

Materials and methods: **The materials used for this investigation were venous blood samples extracted from children living in the boarding school of Tashtagol (Kemerovo Region, Russia). Cytogenetic damage assessment was performed using the cytokinesis-block micronucleus assay (CBMN) on peripheral blood lymphocytes. PCR, gel electrophoresis and product detection using a transilluminator were used to determine polymorphisms in the genes *ADPRT* (rs 1136410), h*OGG1* (rs 1052133), *NBS1* (rs 1805794), *XRCC1* (rs 25487), *XpC* (rs 2228001), *XpD* (rs 13181), and *XpG* (rs 17655). Statistical analysis was performed using nonparametric methods. To ensure accurate results, FDR-correction for multiple comparisons was performed.**

Results: **We discovered a significant increase in the frequency of binucleated lymphocytes with micronuclei (MN) in carriers of the His/His genotype of the *XpG* gene Asp1104His polymorphism in comparison to heterozygous and homozygous carriers of the Asp allele. In addition, the Ala/Ala genotype for the *ADPRT* gene Val762Ala polymorphism and the Glu/Gln genotype for the *NBS1* gene Glu185Gln polymorphism were associated with the elevated frequency of binucleated lymphocytes with nucleoplasmic bridges (NPB).**

Conclusions: **As a result of this study, the elevated frequency of cytogenetic damage in people with particular DNA-repair gene polymorphisms in response to chronic exposure to radon was demonstrated. It was shown that the genes and corresponding polymorphisms (the *XpG* gene Asp1104His polymorphism, the *ADPRT* gene Val762Ala polymorphism and the *NBS1* gene Glu185Gln polymorphism) can be used as molecular genetic markers of increased individual radiosensitivity in long-term residents of areas with high concentrations of radon.**

Keywords: Micronuclei, micronucleus test, DNA-repair, genetic susceptibility, ionizing radiation, radon

Introduction

During their lives humans are exposed to numerous environmental factors that have genotoxic and mutagenic effects. Every organism is unique and is characterized by a wide variety of specific features, including their individual susceptibility to genotoxic environmental factors. At the gene level, these inter-individual differences are determined by single nucleotide polymorphisms (SNP). The implementation and practice of high-throughput SNP genotyping technologies has led to great interest in extensive genetic association studies (Aldred and Eng 2006). SNP result in amino acid substitutions that alter protein function (Klein et al. 2005) or result in altered splicing (Valentonyte et al. 2005). Additionally, SNP can affect coding regions, including the disruption of exonic splicing enhancer sequences (Lamba et al. 2003) or exonic mRNA stability/instability sequences (Capon et al. 2004). When found in promoter regions, SNP may result in a variety of effects such as the alteration of transcription factor binding motifs, changes in the efficiency of enhancer or repressor elements (Thomas et al. 2006), or the introduction of an alternative translation initiation codon, leading to down-regulation of the wild-type transcript (Zysow et al. 1995).

One of the most important fields of modern ecogenetics is the study of the impact of hereditary differences on radiosensitivity (the organisms response to the influence of ionizing radiation) (Godon et al. 2008, Zharlyganova et al. 2008, Vellingiri et al. 2013, Forrester and Sprung 2014). Specifically, ecogenetic changes are due to the individual selection of genetic markers, including SNP (Detours et al. 2007, Yuan et al. 2009, Forrester et al. 2012, Alsbeih et al. 2013).

Radon (^{222}Rn) is a naturally radioactive noble gas. It is generated from uranium, a chemical element that is widespread in the Earth's crust. Despite the fact that radon is chemically inert, it is released into the atmosphere from rocks and soil along with trace amounts of uranium. The rate of radon seepage is variable and depends upon the amount of

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uranium present in the soil. The concentration of radon in the outside air is usually lower than that indoors. In addition, the concentration of radon in indoor air depends on the permeability of the ground, climatic factors, and the construction and ventilation of the house. Although radon is a physical agent that is present in the everyday environment of living organisms, it also plays a role in DNA damage. Radon, being electrically neutral, is not itself a potential health threat, but its decay daughter products, ^{218}Po, ^{214}Po, ^{214}Pb, and ^{214}Bi, are electrically charged and can affix themselves to tiny dust or smoke particles in indoor air. These particles can be inhaled into the lungs, where they may penetrate the epithelial cells that cover the bronchi and alveoli. These short-lived, unstable decay daughter products (especially ^{218}Po and ^{214}Po) emit alpha particles that can interact with biological tissues in the lungs and induce DNA damage (Rafique and Rahman 2010). According to the International Agency for Research on Cancer (IARC) assessment, radon is related to group I carcinogens (Rushton et al. 2010). It is important to note that for the majority of the population, radon exposure is limited by the amount that is present in their living spaces (Lubin 2010).

The cytokinesis-block micronucleus assay (CBMN) on peripheral blood lymphocytes is one of the most established cytogenetic assays in the field of genetic toxicology. Micronuclei (MN) are found in dividing cells that either contain chromosome breaks lacking centromeres (acentric fragments), and/or whole chromosomes that are unable to travel to the spindle poles during mitosis. By telophase, a nuclear envelope is formed around the lagging chromosomes and fragments, which then uncoil and gradually assume the morphology of an interphase nucleus, with the exception that they are smaller than the main nucleus in the cell; hence, they are called 'micronuclei.' MN therefore provide a convenient and reliable index of both chromosome breakage and chromosome loss. Because MN are expressed in cells that have completed nuclear division, they can be optimally scored during the binucleated stage of the cell cycle. Occasionally, nucleoplasmic bridges (NPB) are observed between the nuclei in a binucleated cell. These are most likely dicentric chromosomes in which the two centromeres have been pulled to opposite poles of the cell, and the DNA in the resulting bridge has been covered by a nuclear membrane. Thus, NPB in binucleated cells provide an additional and complementary measure of chromosome rearrangement, which can be scored together with the micronuclei count (Fenech 2000). In addition to MN and NPB, the CBMN assay detects nuclear buds (NBUD) or protrusions, which represent a mechanism by which cells remove amplified DNA; they are therefore considered markers of possible gene amplification (Fenech 2006).

It has been previously shown that the CBMN assay is applicable to the assessment of some negative effects from radon and its decay products by different contingents (Sinitsky 2014).

In this study, the CBMN assay was used to investigate the association between DNA-repair gene polymorphisms and susceptibility to radon. The amount of radon-induced mutations depends on the expression of the indicated genes and, as a result, impacts the efficiency of the DNA-repair protein synthesis and function. Therefore it is possible to use DNA-repair genes as candidate genetic markers for the estimation of radiosensitivity.

There are more than 100 proteins that are encoded by these genes and participate in the processes of human DNA repair (López-Cima et al. 2007). The pathways of DNA repair can be divided into direct repair, nucleotide excision repair (NER), base excision repair (BER), double-strand break repair (DSBR) and mismatch repair (MMR) (Martin et al. 2008). Several key DNA repair genes include *ADPRT* (*PARP1*), h*OGG1*, *NBS1*, *XRCC1*, *XpC*, *XpD* and *XpG*.

The purpose of our study was to analyze possible associations between the *ADPRT* gene Val762Ala polymorphism, the h*OGG1* gene Ser326Cys polymorphism, the *NBS1* gene Glu185Gln polymorphism, the *XRCC1* gene Arg399Gln polymorphism, the *XpC* gene Lys939Gln polymorphism, the *XpD* polymorphism Lys751Gln, and the *XpG* gene Asp1104His polymorphism and individual susceptibility to radon exposure.

Materials and methods

Sample characteristics

The town of Tashtagol is situated in the mountain taiga district (Gornaya Shoria) on the south of the Kemerovo Region and is characterized by a low level of chemical pollution. Meanwhile, according to geophysical measurement results, the territory of Tashtagol is considered hazardous for radon pollution.

For the investigation, venous blood samples were extracted from children and teenagers living in the Tashtagol boarding school. For each individual examined, a protocol of agreement was signed by the parents or fiduciary. Samples were collected from 60 subjects aged 8–18 years (mean = 14.9 years). Blood samples from children living in the village Zarubino were used as a control (Table I).

Radiological investigations

Measures of the activity of radon per unit volume of air in living spaces and classrooms were performed with the radon radiometer PPA-01M-01 Alfarad set in measurement mode Air 1. The measurements were performed according to the standards of the Russian Health Department (2003) and the Federal Centre of Hygiene and Epidemiology of the Russian Federal Service on Customers' Rights Protection and Human Well-being Surveillance (2009). The results of the longitudinal monitoring of the radon concentration at the boarding school (Tashtagol) and in the village Zarubino are shown in Table II. Additionally, values of the exposure dose rate (EDR)

Table I. Gender and age characteristics of children/teenagers.

Person	Number	Age (m ± SD)	Age (min–max)
Exposed group			
Total	60	12.1 ± 2.32	8–17
Male	34	12.1 ± 2.30	8–16
Female	26	12.0 ± 2.41	8–17
Control group			
Total	60	14.9 ± 2.60	8–18
Male	27	14.8 ± 2.63	9–17
Female	33	15.0 ± 2.58	8–18

Table II. The unit volume activity of radon in rooms of the exposed and control groups.

Date of measurement	Number of measuring points	Average unit volume activity of radon, Bq/m^3, M ± m	Limit variation, (Bq/m^3)
Exposed group			
20 December 2007	11	235 ± 44	68–583
6 February 2008	6	415 ± 53	232–617
4 February 2009	7	730 ± 77	192–1285
11 February 2009	22	441 ± 88	110–1373
2 March 2010	10	905 ± 134	680–1143
2 March 2011	18	347 ± 101	74–749
Control group			
25 January 2011	10	64 ± 13	39–203
14 March 2011	10	118.7 ± 33	39–203
6 April 2011	17	119 ± 27	53–172

of gamma background radiation on the school premises were measured.

Cytogenetic investigations

Blood from the children was sampled using vacutainers with heparin and was stored at 4°C for 24 h before culturing. The blood (200 µl) was then transferred to flasks containing 3.8 ml of culture medium (3.0 ml RPMI-1640 + 0.8 ml inactivated bovine serum + 100 U/ml ampicillin). Phytohaemagglutinin (PHA) (30 mg/flask) was added to each culture, and the flasks were incubated for 44 h at 37°C. After a 44-h incubation period, 6 µg/ml of cytochalasin B was added to each culture and allowed to incubate another 24 h at 37°C. The cells were then resuspended in the flasks, poured into centrifuge tubes and centrifuged for 10 min at 1000 rev/min. The supernatant was removed, the pellet was disrupted, and 1 ml of cold, freshly prepared 0.125 M KCl was poured onto the wall of the tube. The pellet was gently resuspended in the KCl solution, and another 4 ml was added. The tube was then closed and inverted several times (for ~ 30 s). After the pellet was resuspended, 1 ml of cold, freshly prepared Carnoy's fixative (a compound of methanol and glacial acetic acid in a ratio of 3:1) was poured onto the wall of the tube and mixed. The samples were stored at − 20°C until the next centrifugation step. The suspension was centrifuged for 10 min at 1000 rev/min. The supernatant was removed and the pellet disrupted. Without inverting, another 5 ml of cold fixative was poured onto the pellet. This procedure was repeated several times until the pellet appeared clean and the cell suspension was clear.

After the last centrifugation step, the majority of the supernatant was removed, leaving a volume not exceeding 200 µl. Next, the suspension was gently transferred to a dry, cold glass slide using a pipette. Azure-eosin staining in a phosphate buffer was carried out for 15 min. The slides were analyzed using a Nikon Eclipse 80i microscope with transmitted light and a full filter at 1000 × magnification (oil immersion).

For each sample, 1000 binucleated cells were counted and different types of abnormalities (MN, NPB, NBUD) were registered within them. We used the suggestions from Fenech 2000 to identify the MN and other abnormalities.

DNA extraction

DNA extraction was performed using the routine phenol/chloroform method. 2 ml of blood was transferred to tubes and 12 ml of chilled sucrose buffer was added. The tubes were mixed and left for 1 h in the refrigerator. Thereafter, samples were centrifuged for 20 min at 4000 rev/min (cooled to + 3°C). The supernatant was removed, and 0.3 ml of SE-buffer was added to the pellet. The pellet was resuspended and transferred into Eppendorf tubes. A total of 30 µl of 10% SDS-buffer and 7.5 µl of proteinase K were added to each Eppendorf tube. The tubes were mixed and incubated for 24 h at 37°C. After incubation, 350 µl of phenol was added to each tube, which were then mixed and centrifuged for 6 min at 9000 rev/min.

The upper aqueous phase was transferred to another clean tube, and 300 µl of phenol/chloroform (1:1) was added. The tubes were stirred and centrifuged for 6 min at 9000 rev/min, and the previous step was repeated. DNA was precipitated with a mixture of 17 µl of 4 M NaCl and 700 µl of cold 90% ethanol.

PCR

SNP detection was performed using a reagent kit produced in the Lytech Company (Moscow, Russian Federation) by allele-specific End Point PCR. The amplification test tubes (0.5 ml) were prepared and numbered according to the sum of the sample analysis number and the negative controls. There were two test tubes for each sample: N (normal) and P (pathology). The reagents for PCR were removed from the freezer and thawed for 20–30 min before preparing the working mixture for amplification.

The working reagent mixture for amplification was prepared immediately before the experiment. One sample consisted of 17.5 µl of diluent, 2.5 µl of the reaction mixture, and 0.2 µl of Taq-polymerase. There were two working mixtures: The mixture for the reaction N (normal) and the mixture for reaction P (pathology). After that, 1 drop (25 µl) of mineral oil was added to all the test tubes. Next, 5 µl of the samples for analysis were deposited into the test tubes with the working mixtures for amplification N (normal) and P (pathology) under the layer of oil. A total of 5 µl of the diluent was also placed in both types of mixtures for the negative control. The test tubes were centrifuged for 3–5 sec at 1500–3000 rev/min at 25°C on a microcentrifuge-vortex. The test tubes were then placed into a thermocycler at + 94°C, and the amplification was performed according to a special program (Table III).

Detection of amplification products

The detection of amplification products was performed using separation by horizontal electrophoresis in a 3% agarose gel.

Table III. Amplification program for the DNA sample analysis.

Temperature,°C	Time	Number of cycles
94°	Pause	
93°	1 min	1
93°	10 sec	35
64°	10 sec	
72°	20 sec	
72°	1 min	1
10°	Storage	

TAE (Tris, Acetate, EDTA) was used as both the gel and electrode buffer. Ten microlitres of a 1% solution of ethidium bromide was added to 100 ml of melted agarose and mixed. The melted agarose was cooled to 50–60°C and poured into the plate for hardening.

Next, 8–10 µl of the amplified PCR product was placed into the gel pockets according to a sequence that corresponded to the sample numeration. The electrophoretic chamber was connected to a power supply at the voltage corresponding to an intensity of the electric field at 10–15 V per cm of gel. Electrophoretic separation of amplification products was carried out in the direction from the cathode (−) to anode (+). The control for electrophoretic separation was visual.

Following electrophoresis, the gel was removed from the casting and placed on the glass of a UV-transilluminator. Image capture was performed by a photo camera and the computer software GelImager.

Statistical methods

Statistical analysis was carried out using STATISTICA 7.0 (StatSoft Software). Because the variances within distinct groups were not equal and the distribution of many characteristics deviated from normal distribution, we decided to calculate the median and 95% confidence interval (CI) for the median. Significance differences between groups was defined with the Mann-Whitney U-test. To avoid the effect of multiple comparisons, FDR correction was applied. The differences were statistically significant if $p < 0.05$.

Results

In our previous study (Sinitsky and Druzhinin 2014), we observed a significant two-fold excess in the frequency of binucleated lymphocytes with MN (0.6% / 1000 binucleated cells) in long-term residents of areas with high radon and decay product concentrations in comparison with control samples (0.3% / 1000 binucleated cells). These results indicated the genotoxic influence on the genome. Measurements of gamma background radiation showed no sign of exceeding the permissible level of radiation. These data confirm the assumption of radon's leading role in the radiation load. Children in the control group were enrolled from a residential district not characterized by radiation and chemical contaminations.

In this work, 60 DNA samples from children living in radon exposure conditions and characterized by an increased rate of cytogenetic damage and 60 DNA samples of children from the control group were genotyped. As potential markers, polymorphisms in excision repair genes, such as the *ADPRT* gene Val762Ala polymorphism, the h*OGG1* gene Ser326Cys polymorphism, the *NBS1* gene Glu185Gln polymorphism, the *XRCC1* gene Arg399Gln polymorphism, the *XpC* gene Lys939Gln polymorphism, the *XpD* polymorphism Lys751-Gln, and the *XpG* gene Asp1104His polymorphism were assessed.

The frequency distribution of genotypes observed did not differ from Hardy-Weinberg equilibrium.

Analysis of the associations between polymorphisms of DNA-repair genes and the frequency of cytogenetic damage in the exposed group showed that the His/His genotype for the *XpG* gene Asp1104His polymorphism was characterized by an increased (0.80% [95% CI = 0.53–1.07]) frequency of binucleated lymphocytes with MN in comparison with heterozygous (Asp/His) and homozygous carriers of the Asp allele (Asp/Asp) (0.69% [CI = 0.60–0.79] and 0.56% [CI = 0.49–0.63], respectively). In addition, carriers of the Ala/Ala genotype for the *ADPRT* gene Val762Ala polymorphism, the Glu/Gln genotype for the *NBS1* gene Glu185Gln polymorphism and the Lys/Lys genotype for the *XpD* gene Lys751Gln polymorphism were characterized by an increased frequency of binucleated lymphocytes with NPB (0.66% [CI = 0.20–1.12], 0.49% [CI = 0.28–0.71] and 0.36% [CI = 0.16–0.56]). After performing the FDR-correction for multiple comparisons, significant differences were only observed for the following genes: The *XpG* gene Asp1104His polymorphism, the *ADPRT* gene Val762Ala polymorphism and the *NBS1* gene Glu185Gln polymorphism.

Furthermore, carriers of the dominant model of *XpG* gene showed a decreased frequency of binucleated lymphocytes with MN (0.56% vs. 0.72% by carriers of Asp/His-His/His). Recessive model of *NBS1* gene was characterized by a decreased frequency of binucleated lymphocytes with NPB (0.05% vs. 0.43% by carriers of Glu/Glu-Glu/Gln) and recessive model of *ADPRT* gene was characterized by an increased frequency of binucleated lymphocytes with NPB (0.66% vs. 0.27% by carriers of Val/Val-Val/Ala).

Detailed results are presented in Table IV. No significant associations between cytogenetic markers and DNA-repair gene polymorphisms were observed in the control group.

Discussion

As follows from the presented data, the radon concentration in the indoor air from the boarding school in winter exceeded the permissible level (200 Bq/m^3) for residential buildings. Declines in the volume activity of radon in the spring were measured, but in this case, even if ventilation was improved, the radon concentrations remained relatively high (Table II). The average volume activity of radon in the living conditions of the exposed group ranged from 235–905 Bq/m^3 in winter and from 200–347 Bq/m^3 in spring. The average volume activity of radon for the past 5 years has been 463 ± 98 Bq/m^3, which greatly exceeds the values detected in the control spaces. Individual effective dose inhalation exposure due to radon isotopes and its short-lived decay products was ~ 27 mZv/year.

Thus, the living and education conditions of children and adolescents in this boarding school (Tashtagol) do not

Table IV. Association of polymorphisms of the genes *ADPRT*, h*OGG1*, *NBS1*, *XRCC1*, *XpC*, *XpD*, and *XpG* with some cytogenetic indicators in the conditions of exposure to radon.

Characteristic/genotype	Binucleated cells with MN, %	Binucleated cells with NPB, %	Binucleated cells with NBUD, %	Proliferation index
ADPRT Val762Ala				
Val/Val ($n = 29$)	0.60 [0.01–0.11]	0.22 [0.06–0.37]*	0.97 [0.62–1.32]	1.83 [1.77–1.88]
Val/Ala ($n = 21$)	0.65 [0.07–0.18]	0.35 [0.13–0.56]	0.81 [0.44–1.18]	1.78 [1.72–1.84]
Ala/Ala ($n = 10$)	0.78 [0.02–0.34]	0.66 [0.20–1.12]* **	1.13 [0.19–2.06]	1.74 [1.66–1.81]
Val/Ala-Ala/Ala ($n = 31$)	0.69 [0.04–0.34]	0.45 [0.01–0.48]	0.91 [0.27–0.42]	1.76 [0.98–1.15]
Val/Val-Val/Ala ($n = 50$)	0.62 [0.02–0.18]	0.27 [0.06–0.34]**	0.90 [0.43–0.87]	1.81 [1.15–1.65]
h*OGG1* Ser326Cys				
Ser/Ser ($n = 23$)	0.66 [0.57–0.76]	0.42 [0.17–0.68]	0.94 [0.46–1.43]	1.80 [1.73–1.86]
Ser/Cys ($n = 28$)	0.64 [0.56–0.72]	0.34 [0.17–0.52]	0.95 [0.65–1.26]	1.79 [1.75–1.84]
Cys/Cys ($n = 9$)	0.63 [0.38–0.88]	0.09 [0.06–0.30]	0.90 [0.69–1.71]	1.80 [1.66–1.94]
Ser/Cys-Cys/Cys ($n = 37$)	0.64 [0.47–0.68]	0.28 [0.11–0.40]	0.94 [0.26–1.22]	1.79 [1.54–1.84]
Ser/Ser-Ser/Cys ($n = 51$)	0.65 [0.51–0.68]	0.38 [0.11–0.44]	0.95 [0.31–1.12]	1.79 [1.55–1.86]
NBS1 Glu185Gln				
Glu/Glu ($n = 17$)	0.61 [0.51–0.71]	0.32 [0.09–0.56]	0.96 [0.40–1.51]	1.77 [1.70–1.84]
Glu/Gln ($n = 28$)	0.65 [0.56–0.74]	0.49 [0.28–0.71]*	0.94 [0.60–1.27]	1.79 [1.74–1.83]
Gln/Gln ($n = 15$)	0.68 [0.54–0.82]	0.05 [0.02–0.17]* **	0.94 [0.31–1.34]	1.84 [1.74–1.94]
Glu/Gln-Gln/Gln ($n = 43$)	0.66 [0.50–0.68]	0.02 [0.01–0.12]	0.94 [0.36–1.51]	1.80 [1.59–1.91]
Glu/Glu-Glu/Gln ($n = 45$)	0.64 [0.41–0.68]	0.43 [0.19–0.56]**	0.94 [0.35–1.49]	1.78 [1.65–1.80]
XRCC1 Arg399Gln				
Arg/Arg ($n = 31$)	0.67 [0.58–0.76]	0.39 [0.21–0.57]	0.76 [0.44–1.82]	1.77 [1.72–1.82]
Arg/Gln ($n = 21$)	0.60 [0.50–0.70]	0.31 [0.06–0.57]	1.00 [0.63–1.37]	1.85 [1.79–1.91]
Gln/Gln ($n = 8$)	0.68 [0.49–0.86]	0.18 [0.10–0.46]	1.48 [0.32–2.64]	1.74 [1.64–1.84]
Arg/Gln-Gln/Gln ($n = 29$)	0.62 [0.52–0.74]	0.28 [0.09–0.31]	1.13 [0.71–1.53]	1.82 [1.26–1.97]
Arg/Arg-Arg/Gln ($n = 52$)	0.64 [0.49–0.71]	0.36 [0.17–0.44]	0.86 [0.52–1.04]	1.80 [1.64–1.90]
XpC Lys939Gln				
Lys/Lys ($n = 27$)	0.67 [0.58–0.77]	0.26 [0.07–0.45]	0.82 [0.47–1.18]	1.80 [1.75–1.86]
Lys/Gln ($n = 25$)	0.61 [0.53–0.69]	0.38 [0.18–0.59]	1.09 [0.66–1.52]	1.80 [1.74–1.85]
Gln/Gln ($n = 8$)	0.69 [0.47–0.91]	0.50 [0.02–0.97]	0.93 [0.08–1.85]	1.75 [1.64–1.85]
Lys/Gln-Gln/Gln ($n = 33$)	0.65 [0.36–0.83]	0.41 [0.25–0.62]	0.98 [0.32–1.29]	1.74 [1.53–1.89]
Lys/Lys-Lys/Gln ($n = 52$)	0.62 [0.49–0.76]	0.53 [0.12–0.64]	1.04 [0.61–1.13]	1.79 [1.67–1.86]
XpD Lys751Gln				
Lys/Lys ($n = 24$)	0.65 [0.55–0.76]	0.36 [0.16–0.56]*	1.18 [0.75–1.60]	1.80 [1.74–1.85]
Lys/Gln ($n = 27$)	0.63 [0.54–0.71]	0.32 [0.12–0.52]	0.84 [0.50–1.18]	1.79 [1.73–1.84]
Gln/Gln ($n = 9$)	0.72 [0.51–0.92]	0.31 [0.20–0.84]*	0.40 [0.06–0.85]	1.83 [1.64–2.02]
Lys/Gln-Gln/Gln ($n = 36$)	0.64 [0.50–0.87]	0.32 [0.22–0.56]	0.76 [0.41–0.98]	1.79 [1.68–1.92]
Lys/Lys-Lys/Gln ($n = 51$)	0.64 [0.51–0.91]	0.34 [0.15–0.45]	1.00 [0.56–1.37]	1.79 [1.61–1.88]
XpG Asp1104His				
Asp/Asp ($n = 27$)	0.56 [0.49–0.63]* **	0.37 [0.16–0.58]	1.00 [0.60–1.41]	1.80 [1.75–1.84]
Asp/His ($n = 26$)	0.69 [0.60–0.79]*	0.34 [0.07–0.40]	0.95 [0.61–1.28]	1.80 [1.75–1.86]
His/His ($n = 7$)	0.80 [0.53–1.07]*	0.58 [0.05–1.12]	0.68 [0.42–1.78]	1.76 [1.58–1.93]
Asp/His-His/His ($n = 33$)	0.72 [0.61–0.85]**	0.31 [0.13–0.53]	0.89 [0.71–1.02]	1.79 [1.57–1.99]
Asp/Asp-Asp/His ($n = 53$)	0.63 [0.42–0.77]	0.30 [0.12–0.44]	0.98 [0.77–1.14]	1.80 [1.66–1.92]

*, **p < 0.05.

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comply with the standards and parameters of radiation safety; this group is chronically exposed to excessive doses of radon, which promotes some genotoxic effects associated with the increase in frequency of various cytogenetic markers.

The extent of genetic damage caused by the action of some genotoxic substances (including radon) on the human genome depends on the activity of the enzymes involved in DNA-repair processes. It is known that different polymorphic variants of DNA-repair genes are associated with the activity of the resultant, synthesized proteins and therefore directly impact the efficiency of the repair process and the level of cytogenetic markers induced by the genotoxic substance. The estimate of DNA-repair gene polymorphisms allows for the evaluation of differential allele expression and individual susceptibility to genotoxic stress.

PARP1 (*ADPRT*) is the gene that encodes the chromatin-associated protein poly(ADP-ribose)polymerase-1, which participates in nuclear protein modification through poly ADP-ribosylation. This type of modification is involved in the regulation of various cell processes such as differentiation, proliferation, malignant transformation and DNA repair. These processes are critical for genomic stability (Lilyestrom et al. 2010). PARP-1 protein alterations play a role in the aethiopathogenesis of type 1 diabetes (Charron and Bonner-Weir 1999) and Fanconi anaemia (Ramirez et al. 2003). It is known that the Val762Ala polymorphism of the *PARP1* gene is associated with prostate cancer risk (Lockett et al. 2004).

The human *OGG1* (h*OGG1*) (8-oxoguanine glycosylase 1) gene is located on chromosome 3p26 and encodes two isoenzymes, namely α-hOGG1 and β-hOGG1, which are products of alternative splicing. The α-hOGG1 protein is located in the nucleus, while the β-hOGG1 is located in the mitochondria. The hOGG1 protein catalyses the cleavage of glycoside bonds between nitrogenous bases and deoxyribose, leaving abasic apurinic/apyrimidinic sites in the DNA strand. These spaces are then removed, and DNA repair completes the strand with the participation of phosphodiesterase, DNA-polymerases

and DNA-ligases. The hOGG1 protein is extremely important for cell survival in the conditions of oxidative DNA damage. Mutations in the h*OGG1* gene may also increase the risk of cancer (Li et al. 2008). According to Wang et al. (2006), the Ser326Cys polymorphism in this gene can be associated with the suppression of DNA-repair. Significant defects in the repair of oxidation-induced DNA alterations are also related to variant alleles of the h*OGG1* gene Ser326Cys polymorphism.

The *NBS1* gene encodes a nuclear protein of the same name, which forms a trimeric complex with MRE11 and RAD50. This complex is involved in DNA double-strand break (DSB) signalling processes. NBS1 can also interact with the helicase WRN, which activates BER. Among many polymorphisms of the *NBS1* gene, the most studied is Glu185Gln, which may be associated with an increased risk of cancer, particularly breast cancer (Lu et al. 2006, 2009).

XRCC1 (X-ray cross-complementing gene 1) is the major gene involved in BER (Vidal et al. 2001). The XRCC1 protein also regulates the activity of DNA polymerase β, DNA ligase III, PARP-1 and polynucleotide kinase. The three most commonly observed SNP in the *XRCC1* gene are Arg194Trp, Arg280His, and Arg399Gln. It seems to be that these polymorphisms affect gene expression and are connected with an increased risk of cancer, including breast cancer (Lohman et al. 2003), pancreatic cancer (Duell et al. 2002) and lung cancer (Ratnasinghe et al. 2001, Ito et al. 2004, Pachouri et al. 2007).

The *XpC* gene (xeroderma pigmentosum C) encodes the XpC protein, which plays a role in the early steps of global genome repair (GGR), particularly in the detection of DNA damage. It is proposed that XpC is also involved in DSBR. *XpC* mutations may lead to xeroderma pigmentosum, which is a rare autosomal-recessive disease characterized by high photosensitivity and increased risk of skin cancer (Bernardes de Jesus et al. 2008). The *XpC* gene Lys939Gln polymorphism, in combination with the *XRCC1* gene Arg399Gln polymorphism, significantly increases the risk of Hodgkin's lymphoma (El-Zein et al. 2009) and other malignancies (Francisco et al. 2008).

The *XpD* gene encodes the XpD protein, which is one of the subunits forming transcription factor IIH (TFIIH) and plays an important role in NER as part of the core incision machinery. Mutations in the *XpD* gene lead to defects in DNA repair and transcription (Evans et al. 1997) and cause three syndromes in humans, namely xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome, along with other disorders such as skin hyperpigmentation induced by sunlight, neuronal degeneration and mental deficiency. At present, there are 17 known polymorphisms of the *XpD* gene, and some of them may be associated with an increased risk of cancer (Goode et al. 2002). According to Au et al. (2003), the *XpD* gene Lys751Gln polymorphism results in certain defects in NER.

The *XpG* gene is located on chromosome 13q32–33, and the XpG protein plays a key role in global genome repair and transcription-coupled repair, which are two distinct pathways of NER. It has also been shown that XpG stimulates the activity of the DNA glycosylase NTH1, involved in BER. Mutations in XpG may lead to xeroderma pigmentosum and Cockayne syndrome (Vermeulen et al. 1993). The *XpG* gene Asp1104His polymorphism may also be related to laryngeal and hypolaryngeal carcinomas (Wen et al. 2006), as well as breast cancer (Kumar et al. 2003).

In this study, significant associations with the main cytogenetic parameters examined – frequency of binucleated lymphocytes with MN – were obtained only with the *XpG* gene Asp1104His polymorphism. Homozygotes for the His allele were associated with an increase in this indicator compared with heterozygous and homozygous carriers of the major allele (Figure 1). This fact may be interpreted as being due to the decreased functional activity of the XpG protein, which reduces the efficiency of repair and increases the frequency of acentric fragments which are realized in MN. Available data from the literature on this polymorphism are quite contradictory.

In work from Chinese researchers, significant associations were not observed between polymorphisms in this gene and the level of MN in vinyl chloride-exposed workers (Qiu et al. 2011 , Wang et al. 2013). This may be due to genetic differences between the Chinese and Russian population or different responses of reparative systems to the influence of either chemical agents or ionizing radiation. Additionally, the research of Mušák et al. (2009) in which samples from residents of Slovakia were studied demonstrated that carriers of the Asp allele showed a significant decrease in the frequency of chromatid-type chromosome aberrations (CA). This finding corresponds to the trend in the frequency of cells with MN that we observed in our investigation. In a recent study, an increased risk of cancer in carriers of the His/His genotype (Li et al. 2014) was demonstrated. However, in the work of Sanyal et al. (2004), data regarding the protective effect of His/His variants of the *XpG* gene Asp1104His polymorphism were seen for the case of bladder cancer, and the study by Vodicka et al. (2004) showed a slight increase in repair activity of this allele. Yet, in the research of Jeon et al. (2003) the risk of developing lung cancer was seen for the Asp/His genotype, and a protective effect was observed for the Asp/Asp genotype. On the contrary, according to Rajaraman et al. (2008) who studied the risks of long-term exposure to radiation in radiology

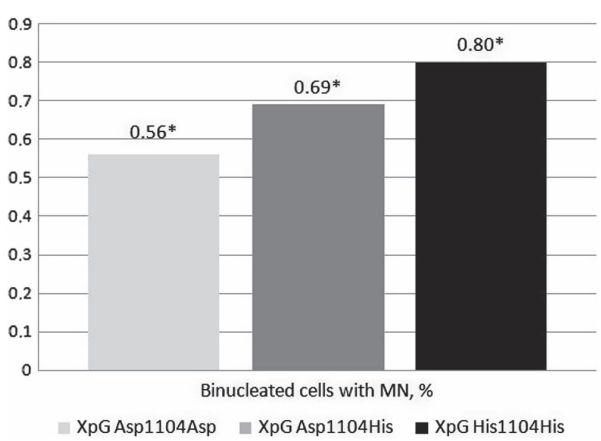

Figure 1. Associations between the frequency of binucleated cells with micronuclei (MN) (%) and polymorphisms of the *XpG* gene Asp1104His polymorphism (*significant at $p < 0.05$).

technicians, an association exists between the risk of breast cancer and the wild-type allele. It should be noted that at present, no studies describing the association of cytogenetic parameters and of the *XpG* gene Asp1104His polymorphism in the case of exposure to low doses of ionizing radiation have been performed.

Homozygous carriers of the Ala allele for the *ADPRT* gene Val762Ala polymorphism are characterized by a three-fold excess of the frequency of binucleated lymphocytes with NPB, compared with the homozygous carriers of the Val allele (0.66% vs. 0.22%) (Figure 2). NPB are due to the presence of dicentric chromosomes in the cell, which are specific markers of radiation exposure. It is known that the Ala/Ala genotype is associated with decreased activity of the enzyme poly(ADP-ribose)polymerase-1 (Lockett at al. 2004), which reduced the effectiveness of DNA-repair and resulted in an increase in genome instability in carriers of this genotype, a specific response seen in conditions of chronic radon exposure. [AQ7] Minina et al. (2011) found that the excess of CA in carriers of the minor allele of this gene was associated with conditions of radon exposure. Our work obtained a similar association with another cytogenetic indicator – the level of NPB – suggesting that the *ADPRT* gene Val762Ala polymorphism is a good marker of individual radiosensitivity to radon and its decay products. Moreover, Wray et al. (2103) found that inhibition or repression of PARP1 protein expression strongly repressed chromosomal translocations, implying that PARP1 is essential for this process. Finally, PARP1 inhibition also reduced both ionizing radiation-generated and VP16-generated translocations in two cell lines (Wray et al. 2013) [AQ8] . On the other hand, the research of Coelho et al. (2013) [AQ9] , who investigated the effects of metal(loid)s in the mining districts of central Portugal, showed that there was no significant association of this gene with MN and CA. We can suggest that such conflicting results are due to a low genotoxic effect of metal(loid)s in comparison with radon radiation and the lack of a pronounced adaptive response to such influences.

The carriers of the Gln/Gln genotype for the *NBS1* gene Glu185Gln polymorphism were characterized by a low level of binucleated lymphocytes with NPB (Figure 3) compared to heterozygotes (0.05% vs. 0.49%), which may indicate a reduced sensitivity to low doses of ionizing radiation. Currently, there are no data regarding the associations between gene polymorphisms and some indicators of micronucleus tests. According to Angelini et al. (2012), there were no significant correlations with the level of MN and polymorphisms of several genes, including the *NBS1* gene Glu185Gln polymorphism. A recent meta-analysis of 48 studies found no significant association between the *NBS1* gene Glu185Gln polymorphism and the overall risk of developing cancer (He et al. 2014). However, it has been found that this polymorphism may increase the risk of certain cancers, such as leukaemia and nasopharyngeal cancer. In particular, there is an association with an increased risk of urinary cancer but a reduction in the risk for cancers of the digestive system. There have also been no previous studies about associations of this gene with individual radiosensitivity. [AQ10]

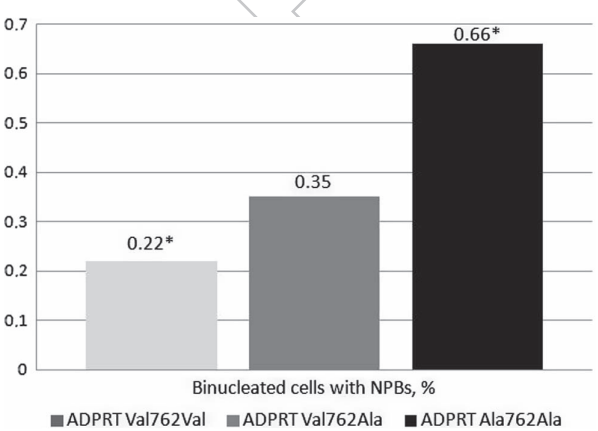

Figure 2. Associations between the frequency of binucleated cells with nucleoplasmic bridges (NPB) (%) and polymorphisms of the *ADPRT* gene Val762Ala polymorphism (*significant at $p < 0.05$).

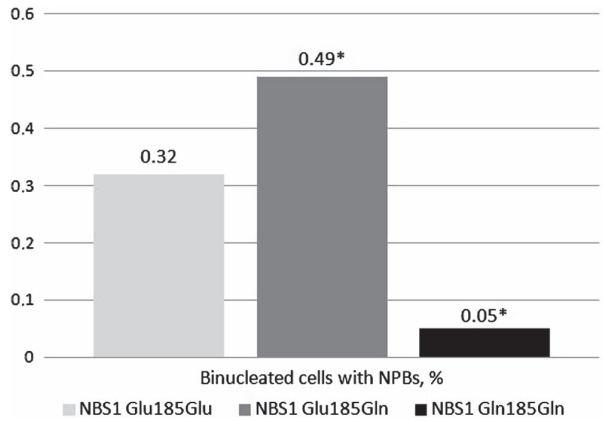

Figure 3. Associations between the frequency of binucleated cells with nucleoplasmic bridges (NPB) (%) and polymorphisms of the *NBS1* gene Glu185Gln polymorphism (*significant at $p < 0.05$).

Conclusions

This study demonstrated an excess in the frequency of some cytogenetic damage (MN, NPB) in people with certain DNA-repair gene polymorphisms in response to chronic exposure to radon. It was discovered that the *XpG* gene Asp1104His polymorphism, the *ADPRT* gene Val762Ala polymorphism and the *NBS1* gene Glu185Gln polymorphisms can be used as molecular genetic markers of increased individual radiosensitivity in long-term residents of areas with high radon and decay product concentrations.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

Aldred MA, Eng C. 2006. SNP'ing at nasopharyngeal cancer susceptibility: For whom the bell tolls. Cancer Biol Ther 10:1292–1293.

Alsbeih G, El-Sebaie M, Al-Harbi N, Al-Hadyan K, Shoukri M, Al-Rajhi N. 2013. SNPs in genes implicated in radiation response are

associated with radiotoxicity and evoke roles as predictive and prognostic biomarkers. Radiat Oncol 8:125.
Au WW, Salama SA, Sierra-Torres CH. 2003. Functional characterization of polymorphisms in DNA repair genes using cytogenetic challenge assays. Toxicogenomics 111:1843–1850.
Bernardes de Jesus BM, Bjuıres M, Coin F, Egly JM. 2008. Dissection of the molecular defects caused by pathogenic mutations in the DNA repair factor XPC. Mol Cell Biol 28:7225–7235.
Capon F, Allen MH, Ameen M, Burden AD, Tillman D, Barker JN, Trembath RC. 2004. A synonymous SNP of the corneodesmosin gene leads to increased mRNA stability and demonstrates association with psoriasis across diverse ethnic groups. Hum Mol Genet 13:2361–2368.
Charron MJ, Bonner-Weir S. 1999. Implicating PARP and NAD+ depletion in type I diabetes. Nat Med 5:269–270.
Detours V, Delys L, Libert F, Weiss Solís D, Bogdanova T, Dumont JE, Franc B, Thomas G, Maenhaut C. 2007. Genome-wide gene expression profiling suggests distinct radiation susceptibilities in sporadic and post-Chernobyl papillary thyroid cancers. Br J Cancer 97: 818–825.
Duell EJ, Holly EA, Bracci PM, Wiencke JK, Kelsey KT. 2002. A population-based study of the Arg399Gln polymorphism in X-ray repair cross-complementing group 1 (XRCC1) and risk of pancreatic adenocarcinoma. Cancer Res 62:4630–4636.
El-Zein R, Monroy CM, Etzel CJ, Cortes AC, Xing Y, Collier AL, Strom SS. 2009. Genetic polymorphisms in DNA repair genes as modulators of Hodgkin disease risk. Cancer 115:1651–1659.
Evans E, Moggs JG, Hwang JR, Egly JM, Wood RD. 1997. Mechanism of open complex and dual incision formation by human nucleotide excision repair factors. EMBO J 21:6559–6573.
Fenech M. 2000. The in vitro micronucleus technique. Mutat Res 455:81–95.
Fenech M. 2006. Cytokinesis-block micronucleus assay evolves into a 'cytome' assay of chromosomal instability, mitotic dysfunction and cell death. Mutat Res 600:58–66.
Forrester HB, Li J, Hovan D, Ivashkevich AN, Sprung CN. 2012. DNA repair genes: Alternative transcription and gene expression at the exon level in response to the DNA damaging agent, ionizing radiation. PLoS One 12:1–13.
Forrester HB, Sprung CN. 2014. Intragenic controls utilizing radiation-induced alternative transcript regions improves gene expression biodosimetry. Radiat Res 181:314–323.
Francisco G, Menezes PR, Eluf-Neto J, Chammas R. 2008. XPC polymorphisms play a role in tissue-specific carcinogenesis: A meta-analysis. Eur J Hum Genet 16:724–374.
Godon C, Cordelières FP, Biard D, Giocanti N, Mégnin-Chanet F, Hall J, Favaudon V. 2008. PARP inhibition versus PARP-1 silencing: Different outcomes in terms of single-strand break repair and radiation susceptibility. Nucleic Acids Res 36:4454–4464.
Goode EL, Ulrich CM, Potter JD. 2002. Polymorphisms in DNA repair genes and associations with cancer risk. Cancer Epidemiol Biomarkers Prev 12:1513–1530.
He YZ, Chi XS, Zhang YC, Deng XB, Wang JR, Lv WY, Zhou YH, Wang ZQ. 2014. *NBS1* Glu185Gln polymorphism and cancer risk: Update on current evidence. Tumour Biol 35:4659–4665.
Ito H, Matsuo K, Hamajima N, Mitsudomi T, Sugiura T, Saito T, Yasue T, Lee KM, Kang D, Yoo KY, Sato S, Ueda R, Tajima K. 2004. Gene-environment interactions between the smoking habit and polymorphisms in the DNA repair genes, APE1 Asp148Glu and XRCC1 Arg399Gln, in Japanese lung cancer risk. Carcinogenesis 25:1395–1401.
Jeon HS, Kim KM, Park SH, Lee SY, Choi JE, Lee GY, Kam S, Park RW, Kim IS, Kim CH, Jung TH, Park JY. 2003. Relationship between XPG codon 1104 polymorphism and risk of primary lung cancer. Carcinogenesis 24:1677–1681.
Klein RJ, Zeiss C, Chew EY, Tsai JY, Sackler RS, Haynes C, Henning AK, San Giovanni JP, Mane SM, Mayne ST, Bracken MB, Ferris FL, Ott J, Barnstable C, Hoh J. 2005. Complement factor H polymorphism in age-related macular degeneration. Science 308:385–389.
Kumar R, Hoglund L, Zhao C, Forsti A, Snellman E, Hemminki K. 2003. Single nucleotide polymorphisms in the *XPG* gene: Determination of role in DNA repair and breast cancer risk. Int J Cancer 103:671–675.
Lamba V, Lamba J, Yasuda K, Strom S, Davila J, Hancock ML, Fackenthal JD, Rogan PK, Ring B, Wrighton SA, Schuetz EG. 2003. Hepatic CYP2B6 expression: Gender and ethnic differences and relationship to CYP2B6 genotype and CAR (constitutive androstane receptor) expression. J Pharmacol Exp Ther 307:906–922.
Li H, Hao X, Zhang W, Wei Q, Chen K. 2008. The hOGG1 Ser326Cys polymorphism and lung cancer risk: A meta-analysis. Cancer Epidemiol Biomarkers Prev 17:1739–1745.
Li X, Xu J, Yang X, Wu Y, Cheng B, Chen D, Bai B. 2014. Association of single nucleotide polymorphisms of nucleotide excision repair genes with laryngeal cancer risk and interaction with cigarette smoking and alcohol drinking. Tumour Biol 35:4659–4665.
Lilyestrom W, van der Woerd MJ, Clark N, Luger K. 2010. Structural and biophysical studies of human PARP-1 in complex with damaged DNA. J Mol Biol 395:983–994.
Lockett K-L, Hall M-C, Xu J, et al. 2004. The *ADPRT* V762A genetic variant contributes to prostate cancer susceptibility and deficient enzyme function. Cancer Res 64:6344–6348. [AQ11]
Lockett KL, Hall MC, Xu J, et al. 2004. The *ADPRT* V762A genetic variant contributes to prostate cancer susceptibility and deficient enzyme function. Cancer Res 64:6344–6348. [AQ12]
Lohman K, Lange EM, Case LD, Mohrenweiser HW, Hu JJ. 2003. Polymorphisms of XRCC1 and XRCC3 genes and susceptibility to breast cancer. Cancer Lett 190:183–190.
López-Cima MF, González-Arriaga P, García-Castro L, Pascual T, Marrón MG, Puente XS, Tardón A. 2007. Polymorphisms in XPC, XPD, XRCC1, and XRCC3 DNA repair genes and lung cancer risk in a population of northern Spain. BMC Cancer 7:162.
Lu J, Wei Q, Bondy ML, Li D, Brewster A, Shete S, Yu TK, Sahin A, Meric-Bernstam F, Hunt KK, Singletary SE, Ross MI, Wang LE. 2006. Polymorphisms and haplotypes of the *NBS1* gene are associated with risk of sporadic breast cancer in non-Hispanic white women < or = 55 years. Carcinogenesis 27:2209–2216.
Lu M, Lu J, Yang X, Yang M, Tan H, Yun B, Shi L. 2009. Association between the *NBS1* E185Q polymorphism and cancer risk: A meta-analysis. BMC Cancer 9:124.
Lubin JH. 2010. Environmental factors in cancer: Radon. Rev Environ Health 25:23–31.
Martin LP, Hamilton TC, Schilder RJ. 2008. Platinum resistance: The role of DNA repair pathways. Clin Cancer Res 14:1291–1295.
Pachouri SS, Sobti RC, Kaur P, Singh J. 2007. Contrasting impact of DNA repair gene XRCC1 polymorphisms Arg399Gln and Arg194Trp on the risk of lung cancer in the north-Indian population. DNA Cell Biol 26:186–191.
Rafique M, Rahman SU, et al. 2010. Assessment of indoor radon doses received by the students in the Azad Kashmir Schools, Pakistan. Radiat Protect Dosimetry 142:339–346.
Rajaraman P, Bhatti P, Doody MM, Simon SL, Weinstock RM, Linet MS, Rosenstein M, Stovall M, Alexander BH, Preston DL, Sigurdson AJ. 2008. Nucleotide excision repair polymorphisms may modify ionizing radiation-related breast cancer risk in US radiologic technologists. Int J Cancer 123:2713–2716.
Ramirez MH, Adelfalk C, Kontou M, Hirsch-Kauffmann M, Schweiger M. 2003. The cellular control enzyme polyADP ribosyl transferase is eliminated in cultured Fanconi anemia fibroblasts at confluency. Biol Chem 384:169–174.
Ratnasinghe D, Yao SX, Tangrea JA, Qiao YL, Andersen MR, Barrett MJ, Giffen CA, Erozan Y, Tockman MS, Taylor PR. 2001. Polymorphisms of the DNA repair gene XRCC1 and lung cancer risk. Cancer Epidemiol Biomarkers Prev 10:119–123.
Rushton L, Bagga S, Bevan R, Brown TP, Cherrie JW, Holmes P, Fortunato L, Slack R, Van Tongeren M, Young C, Hutchings SJ. 2010. Occupation and cancer in Britain. Br J Cancer 102:1428–1437.
Sanyal S, Festa F, Sakano S, Zhang Z, Steineck G, Norming U, Wijkström H, Larsson P, Kumar R, Hemminki K. 2004. Polymorphisms in DNA repair and metabolic genes in bladder cancer. Carcinogenesis 25:729–734.
Sinitsky MY. 2014. The cytokinesis-block micronucleus assay on peripheral blood lymphocytes as a prospective biological test-system to estimate the influence of radon on the human organism: Recent progress and future prospects. Open J Genetics 4:1–7.
Sinitsky MY, Druzhinin VG. 2014. The application of the cytokinesis-block micronucleus assay on peripheral blood lymphocytes for the assessment of genome damage in long-term residents of areas with high radon concentration. J Radiat Res 55:61–66.
Thomas KH, Meyn P, Suttorp N. 2006. Single nucleotide polymorphism in 5′-flanking region reduces transcription of surfactant protein B gene in H441 cells. Am J Physiol Lung Cell Mol Physiol 291:386–590; Tumor Biol 35:675–687.
Valentonyte R, Hampe J, Huse K, Rosenstiel P, Albrecht M, Stenzel A, Nagy M, Gaede KI, Franke A, Haesler R, Koch A, Lengauer T, Seegert D, Reiling N, Ehlers S, Schwinger E, Platzer M, Krawczak M, Muller-Quernheim J, Schurmann M, Schreiber S. 2005. Sarcoidosis is

associated with a truncating splice site mutation in BTNL2. Nat Genet 37:357–364.

Vellingiri B, Shanmugam S, Subramaniam MD, Balasubramanian B, Meyyazhagan A, Alagamuthu K, Prakash V, Shafiahammedkhan M, Kathannan S, Pappuswamy M, Raviganesh B, Anand S, Shahnaz N D, Cho SG, Keshavarao S. 2013. Cytogenetic endpoints and Xenobiotic gene polymorphism in lymphocytes of hospital workers chronically exposed to ionizing radiation in cardiology, radiology and orthopedic laboratories. Ecotoxicol Environ Saf 100:266–274.

Vermeulen W, Jaeken J, Jaspers NG, Bootsma D, Hoeijmakers JH. 1993. Xeroderma pigmentosum complementation group G associated with Cockayne syndrome. Am J Hum Genet 53:185–192.

Vidal AE, Boiteux S, Hickson ID, Radicella JP. 2001. XRCC1 coordinates the initial and late stages of DNA abasic site repair through protein-protein interactions. EMBO J 20:6530–6539.

Vodicka P, Kumar R, Stetina R, Sanyal S, Soucek P, Haufroid V, Dusinska M, Kuricova M, Zamecnikova M, Musak L, Buchancova J, Norppa H, Hirvonen A, Vodickova L, Naccarati A, Matousu Z, Hemminki K. 2004. Genetic polymorphisms in DNA repair genes and possible links with DNA repair rates, chromosomal aberrations and single-strand breaks in DNA. Carcinogenesis 25:757–763.

Wang CL, Hsieh MC, Hsin SC, Lin HY, Lin KD, Lo CS, Chen ZH, Shin SJ. 2006. The hOGG1Ser326Cys gene polymorphism is associated with decreased insulin sensitivity in subjects with normal glucose tolerance. J Hum Genet 51:124–128.

Wen SX, Tang PZ, Zhang XM, Zhao D, Guo YL, Tan W, Lin DX. 2006. Association between genetic polymorphism in xeroderma pigmentosum G gene and risks of laryngeal and hypopharyngeal carcinomas. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 28:703–706.

Yuan X, Liao Z, Liu Z, Wang LE, Tucker SL, Mao L, Wang XS, Martel M, Komaki R, Cox JD, Milas L, Wei Q. 2009. Single nucleotide polymorphism at rs1982073:T869C of the TGFbeta 1 gene is associated with the risk of radiation pneumonitis in patients with non-small-cell lung cancer treated with definitive radiotherapy. J Clin Oncol 27:3370–3378.

Zharlyganova D, Harada H, Harada Y, Shinkarev S, Zhumadilov Z, Zhunusova A, Tchaizhunusova NJ, Apsalikov KN, Kemaikin V, Zhumadilov K, Kawano N, Kimura A, Hoshi M. 2008. High frequency of AML1/RUNX1 point mutations in radiation-associated myelodysplastic syndrome around Semipalatinsk nuclear test site. J Radiat Res 49:549–555.

Zysow BR, Lindahl GE, Wade DP, Knight BL, Lawn RM. 1995. C/T polymorphism in the 5'untranslated region of the apolipoprotein(a) gene introduces an upstream ATG and reduces in vitro translation. Arterioscler Thromb Vasc Biol 15:58–64.