



HAL
open science

Association of the DNA repair genes polymorphism with the frequency of chromosomal mutations and health status of the population of the Almaty region

N. Altynova, A. Garshin, Matthieu Delannoy, A. Seisenbaeva, K. Bessalova, L. Skvortsova, I. Kiselev, G. Baratzhanova, A. Amyrgalieva, A. Tolebaeva, et al.

► To cite this version:

N. Altynova, A. Garshin, Matthieu Delannoy, A. Seisenbaeva, K. Bessalova, et al.. Association of the DNA repair genes polymorphism with the frequency of chromosomal mutations and health status of the population of the Almaty region. *International Journal of Biology and Chemistry*, 2021, 14 (1), pp.141. 10.26577/ijbch.2021.v14.i1.013 . hal-03600760

HAL Id: hal-03600760

<https://hal.univ-lorraine.fr/hal-03600760>

Submitted on 7 Mar 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

N.K. Altynova¹ , A.A. Garshin^{1*} , M. Delannoy² , A.S. Seisenbaeva¹ ,
 K.B. Bespalova¹ , L.A. Skvortsova¹ , I. Kiselev¹ , G.S. Baratzhanova¹ ,
 A.S. Amyrgaliev¹ , A.D. Tolebaeva¹ , G.S. Zhunussova¹ , O.K. Khamdiyeva¹ ,
 B.O. Bekmanov¹ , L.B. Djansugurova¹ 

¹Institute of General Genetics and Physiology, Almaty, Kazakhstan

²Universite de Lorraine, URAFPA, Nancy, France

*e-mail: garshin1511@gmail.com

Association of the DNA repair genes polymorphism with the frequency of chromosomal mutations and health status of the population of the Almaty region

Abstract. The study utilized molecular-genetic, cytogenetic, and statistical analyzes methods. A cytogenetic and molecular genetic analysis of the inhabitants of the villages of Amangeldy, Belbulak, in whose territory warehouses of unused pesticides are located, was carried out. Residents of the Basshi village, on the territory of which there are no products of disposal of pesticides, were taken as control. Cytogenetic analysis showed a high level of chromosomal aberrations for the inhabitants of the Belbulak village, an increased level for the inhabitants of the Amangeldy village and a low level in the Basshi cohort. Molecular genetic analysis did not reveal a significant correlation between the polymorphisms of the *XRCC1* Arg194Trp, *XRCC3* Thr241Met and *XPD* Lys751Gln genes and the frequency of chromosomal aberrations. However, study determined the associative relationship of the polymorphism of the DNA repair gene *XRCC1* Arg399Gln with the development of cardiovascular diseases in a population living near foci of pesticidal contamination.

Key words: Pesticides, POPs, chromosomal aberrations, genetic polymorphism, health status of the population.

Introduction

Intensive chemicalization of agriculture has led to increased productivity and, at the same time, environmental pollution of pesticides and other chemical compounds. The vast majority of pesticides are poisonous substances that strikes target organisms. Growth inhibitors and sterilizers, substances that cause infertility are also used. Under the action of pesticides, part of the biological reactions ceases to occur, and this gives the possibility to fight plant diseases, store food longer, and destroy pests [1; 2]. At the same time, a significant decrease in such qualities of the obtained products as microelement composition, usefulness and safety for the health of consumers is not taken into account. As a result, the destruction of biocenoses in areas where pesticides were used has also become a global problem [1; 3].

Unlike other pollutants (radionuclides, heavy metals, etc.), the real danger of pesticides is not fully

recognized. This is because pesticides are hundreds of active substances and tens of thousands of products. Lack of information on the ecotoxicological properties of pesticides is the main reason for their danger. The long-term environmental effects of pesticides have not been studied. An analysis of the results of studying the genetic activity of pesticides in model test systems showed that many of them are mutagens [4-6].

A genetic examination of people who have professional contact with pesticides has shown that many pesticides (tsira, kineb, TMTD, benomyl, polychloroprene, polychlorocamphene, cotoran, etc.) significantly increase the frequency of chromosomal aberrations in blood lymphocytes for people in contact with toxic chemicals [5; 7].

According to the World Health Organization (WHO), “hazardous pesticide” is defined as a pesticide that poses a risk of acute exposure to human health. In recent years, the term “especially hazardous

pesticides" (EHP) has been expanded to include not only pesticides with acute toxic effects, but also those pesticides that cause serious chronic effects on human health. Scientific evidence on the chronic effects of pesticides on human health is constantly updated by WHO/UNEP. The active substances of pesticides affect the endocrine system and have a carcinogenic effect.

Among chemical pollutants of the environment, persistent organic pollutants (POPs) are of particular danger [1-3; 8]. POPs are a group of toxic chemicals that pollute the environment, accumulate in the fatty tissues of living organisms and humans, causing irreparable damage to health. POPs are not decay in the environment for a long time, are transported by air and with water masses over long distances, far from the original source of pollution [8; 9].

Mutagenic activity of pesticides is one of the most dangerous manifestations of negative effects on human health and offspring. In the past 10 years, researches has been actively conducted on the effects of pesticides on human health [11-16]. It has been proven that some pesticides cause the development of cancer [12, 17]. Pesticides often cause allergies, diathesis, and respiratory diseases [18; 19]. Many pesticides are associated with the development of neurodegenerative diseases [12; 18-22], such as Alzheimer's, Parkinson's disease or adolescent suicidality. Endocrine diseases [12], problems of female and male reproductive systems [23-25], type 2 diabetes mellitus [12], metabolic syndromes and obesity [16], developmental disorders [26] are far from a complete list of the effects of pesticides on health.

In 2001, Kazakhstan conducted a preliminary inventory of obsolete pesticides in accordance with the Memorandum of Understanding between the Ministry of Natural Resources and Environmental Protection of the Republic of Kazakhstan and UNEP Chemicals dated January 8, 2001. The report contains data on inventory of pesticide stocks (including POPs pesticides) that are no longer used in Kazakhstan, and an analysis of collected information based on official data from the Republican Sanitary and Epidemiological Station of the Agency for Healthcare of the Republic of Kazakhstan. With the support of the Central Asian Regional Environmental Center, a project of the Environmental News Agency "Greenwomen" (Kazakhstan) was also implemented [29; 30].

Pesticides with the properties of POPs in Kazakhstan have never been produced; currently, they are not imported or exported. Export and import

of POPs pesticides is prohibited in accordance with the legislation of the Republic of Kazakhstan. But, significant quantities of POPs previously produced and used in the former USSR are accumulated in Kazakhstan. According to the Ministry of Agriculture, as of July 2012, about 6,931.4 tons of obsolete, banned and unusable pesticides are stored in warehouses of various regions of the republic [31]. As part of the international scientific program, in the inventory process in 2009-2010, in 64 districts of chemical plant protection products were discovered in 10 districts of Almaty region; 68,443 kg of obsolete and unusable pesticides were accumulated, of which 350 kg are prohibited (saifos, metaphos); 35543 kg of pesticides with a label and 32550 kg of a mixture of pesticides of unknown composition, i.e., 79% of their total number. These are pesticides: from the class of sym triazine (atrazine, protrazine, propazine, ziazine), organophosphorus (saifos, metaphos), chlorine-containing (nitrofen and illoxane), fluorine-containing (treflan), thiocarbamate (temik), as well as German and Chinese origin (50 % Thiram and Hataonyag). No inventory of POP pesticides was detected. However, when determining the content of organochlorine pesticides in the soil around the territories of 64 former pesticide storages in the Almaty region, it was found that the soil of 24 territories of the former storage facilities is contaminated with 2,4 DDD, 4,4 DDD, 4,4 DDD, 4,4 DDE metabolites and a-HCH, b-HCH and g-HCH isomers. The most polluted regions were the Eskildinsky, Talgar, Karasaysky, Enbekshikazakhsky districts. The main pollutants were lindane, the b-isomer of HCH and 4,4'DDE, 4,4'DDT metabolites. In addition to these metabolites in the soil, a-HCH, 4,4-DDD and 2,4-DDD, were present in many regions; their presence in the soil is unacceptable according to the regulatory documents of Kazakhstan [31-33].

The objectives of our study were as follows:

1. Assess the relative risk of the effects of pesticidal contamination on the induction of chromosomal mutations in humans
2. To analyze the association of polymorphisms of DNA repair genes with the frequency of chromosomal aberrations in people exposed to prolonged exposure to mutagenic factors

Materials and methods

Cytogenetic analysis. For humans, study was guided by the decision of the LEC of the Kazakh-Russian Medical University (KRMU), protocol No. 52 dated 09/05/2017. For the purpose of

cytogenetic and molecular-genetic analyzes, people, living in close proximity to the former pesticide warehouses, were examined in Belbulak (26 people) and Amangeldy (25 people). As control, 28 people living in the village of Basshi, on whose territory there are no waste material disposal products, were selected. Voluntary informed consent was obtained from the study volunteers, a survey was conducted, peripheral blood samples were collected in 2 types of tubes (heparinized and EDTA-treated). Samples of heparinized peripheral blood were used for the preparation of metaphase chromosome spreads and cytogenetic analysis. EDTA-treated blood samples were used for DNA extraction and molecular genetic analysis.

Blood was collected using a vacuum system for blood sampling and in heparinized tubes was transported from collection points using vehicles in closed refrigerated containers for 2-5 hours. Cultivation of lymphocytes and preparation of spreads was carried out according to the following procedure: to 0.5 ml of peripheral blood was added to 4.5 ml of culture medium consisting of 80% HAM medium with glutamine (2 mM), 20% cattle serum, penicillin 100 units/ml, streptomycin 100 units/ml. Lymphocyte division was stimulated with 2% PHA. Cells were incubated at 37 ° C for 48 hours. To accumulate metaphase plates, colchicine at a final concentration of 0.8 µg/ml was injected into the culture medium 2 hours before fixation. To obtain cytological preparations, the cells were hypotonized with 0.075 M KCl at 37 ° C for 15 minutes, fixed with a mixture of methyl alcohol/glacial acetic acid (3/1) and stained with 4% Giemsa stain solution.

Stained preparations of chromosomes were analyzed under microscopes from Leica and Zeiss (Germany), using oil immersion at a magnification of 10x100. All types of chromosomal aberrations detected during routine staining of chromosome spreads were taken into account. Microscopic examination of metaphase plates adhered to standard criteria for the selection and analysis of cytogenetic spreads [3].

Molecular genetic analysis. DNA was extracted from frozen (-20 °C) peripheral blood samples containing EDTA as an anticoagulation agent using the GeneJET Genomic DNA Purification Kit (Thermo Scientific, USA). DNA samples were stored at -20 °C. Quantitative and qualitative assessment of the isolated DNA was performed

using a DNA photometer (Biofotometer Plus, Eppendorf, Germany) and electrophoretic analysis. The polymorphism of the genes *XRCC1* Arg³⁹⁹Gln, *XRCC1* Arg¹⁹⁴Trp, *XRCC3* Thr²⁴¹Met, *XPD* Lys⁷⁵¹Gln was determined by polymerase chain reaction with analysis of restriction fragment length polymorphism (PCR-RFLP) in compliance with the generally accepted research scheme.

The results were processed using traditional methods of variation statistics [49].

The differences were regarded as significant at $p < 0.05$. Significance level (P) was determined using Chi2 (χ^2) and Student t-test.

The calculation of the percentage of cells with chromosome aberrations as a percentage of the total number of analyzed cells was calculated by the formula:

$$P = X/N \times 100 \%, \quad (3),$$

where X is the number of detected cells with aberrations, N is the number of metaphase cells studied.

The association of the polymorphism of the studied xenobiotic detoxification genes and DNA repair with cytogenetic disorders was evaluated using the *odds ratio (OR) method* [49]

Results and discussion

Cytogenetic analysis. To determine the impact of long-term pesticidal pollution of the environment on the genetic status of the population, we collected samples of peripheral blood of people living in the Almaty region of the Talgar region, the villages of Belbulak and Amangeldy, on the territory of which there are places of storage of old, unused and banned pesticides and farmland. As a control, an environmentally clean region was chosen – the Basshi village of the Kerbulak district of the Almaty region, on the territory of which there are no waste material disposal products.

Tables 1 and 2 show representative data for the studied cohorts. In the studied settlements, including control (Basshi), individuals with chronic diseases were detected (24-34%). The largest percentage of people (14-19%) have pathologies from the cardiovascular system (Table 1, 2).

7900 metaphase plates from 79 people were analyzed during the research. Table 3 shows the results of cytogenetic analysis.

Table 1 – Ethnic, age and gender composition of the studied groups

Village	Total number of people	Ethnicity, people (%)	Male, people (%)	Female, people (%)	Date of birth (average age)
Belbulak	26	Kazakhs – 14(54%) Russians-7 (27%) Others-5(19%)	5 (19%)	21(81%)	1942-2004 (49.5±3.58)
Amangeldy	25	Kazakhs -18 (84%) Russians – 4(72%) Others – 3 (16%)	14(56%)	11(44%)	1948-1997 (50.6±2.77)
Basshi	28	Kazakhs – 28(100%)	2 (7%)	26 (93%)	1949-1997 (42.7±2.16)

Table 2 – Medical status of representatives of the studied settlements

Village	Diagnosis, number of people (%)				
	CVD	Diabetes	anemia	AB	Total
Basshi (control, 2019)	4 (14%)	1 (3%)	3 (11%)	-	8 (28%)
Belbulak	5 (19%)	1 (4%)	-	3 (11%)	9 (34%)
Amangeldy	4 (16%)	-	-	2 (8%)	7 (24%)

Note: CVD – cardiovascular diseases, AB – asthmatic bronchitis

Table 3 – Frequency of chromosome aberrations of the studied villages residents

Frequency of aberrations, %	Belbulak	Amangeldy	Basshi (control)
Chromatid Breaks	0.69±0.16	0.24±0.09	0.25±0.09
Single fragments	1.03±0.19	0.72±0.17	0.36±0.11
Chromatid exchanges	-	-	-
<i>Chromatid type aberration frequency</i>	1.73±0.25	0.92±0.19	0.61±0.14
Chromosomal breaks	0.23±0.09	0.16±0.08	0
Paired fragments	0.81±0.17	0.60±0.15	0.14±0.07
Chromosomal exchanges	-	-	-
Translocation	-	-	-
Dicentrics	0.15±0.07	0.20±0.08	0
Rings	0.07±0.05	0.04±0.04	0
<i>Chromosome type aberration frequency</i>	1.27±0.22	1.12±0.21	0.14±0.07
Total aberrations	78	49	21
Frequency of aberrations	3.00±0.34	1.96±0.28	0.75±0.16
The number of cells studied	2600	2500	2800
The number of cells with aberrations	74	44	19

The highest frequency of CA is observed among the residents of Belbulak ($3.00 \pm 0.33\%$), while it significantly differs ($p \leq 0.001$) from residents of Basshi ($0.75 \pm 0.16\%$) and Amangeldy ($1.96 \pm 0.27\%$). As can be seen, the average frequency of

chromosome aberrations in residents of Belbulak settlement significantly exceeds the control group (Basshi village) by 3.7 times ($p \leq 0.001$). According to the analysis, Amangeldy is also distinguished by unfavorable cytogenetic indices. Statistical data

indicate an excess of the frequency of aberrations in this cohort by 2.3 times ($p \leq 0.1$) compared with the control group.

The obtained excess of frequency of chromosomal aberrations can be considered as a result of the negative influence of environmental pollutants on the structure of the genetic apparatus of cells of the inhabitants. As can be seen from table 1, the control and surveyed populations are completely consistent with each other by the age criterion. Since the group samples do not allow a more differentiated analysis of cytogenetic aberrations by age, and the average age of the examined in the three surveyed villages of Belbulak, Amangeldy and Basshi is within 50 years, an analysis of the age dependence of the frequency of chromosomal abnormalities in people under 50 years of age and older was carried

out. It was shown that in all the studied populations: 20–50-year-olds, and people over 60 years old – no significant statistical differences were found in the frequency of chromosomal aberrations due to age and gender.

Since the limit of fluctuations in the number of detected aberrations is quite high (0-6%), it was necessary to establish the level of frequency distribution of chromosomal aberrations in each of the groups. When systematizing the frequency of chromosomal aberrations in peripheral blood lymphocytes, the examined contingent was divided into three groups: individuals with chromosomal aberrations in peripheral blood lymphocytes up to 2% (spontaneous level), from 2 to 4% (increased) and more than 4% (high). The results of this distribution are presented in Figure 1.

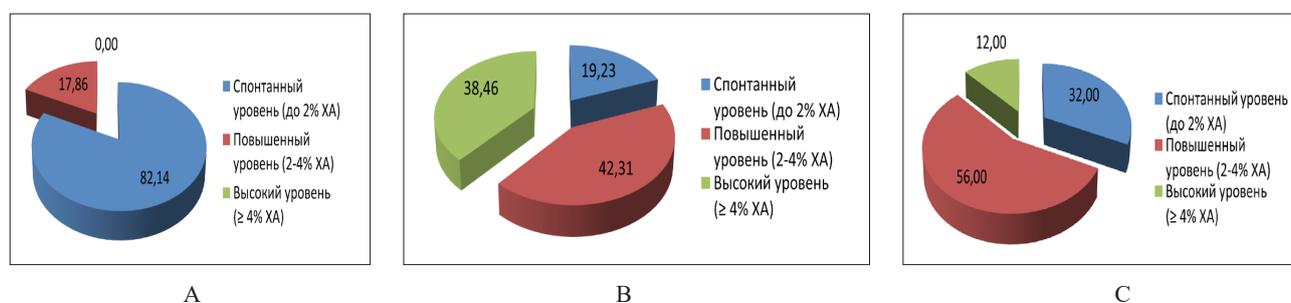


Figure 1 – Fractional distribution of the studied cohorts according to the level of chromosomal aberrations frequency.

Note: A – residents of Basshi village (% of people in group), B – residents of Belbulak village (% of people in group); C – residents of Amangeldy village (% of people in group).

Blue – spontaneous level (up to 2% chromosomal aberrations); red – increased level (2-4% chromosomal aberrations); green – high level (above 4% chromosomal aberrations)

The population-wide spontaneous mutation rate for the population of Kazakhstan was determined for 19% of the examined residents of Belbulak, 32% of residents of Amangeldy and 82% of residents of Basshi. An increased level of frequency of chromosome aberrations is characteristic of 43% of the Belbulak cohort, 56% of the Amangeldy cohort and 18% of the Basshi cohort. The highest level of chromosomal aberrations is discovered for the examined residents of Belbulak, the proportion of people with a high level of aberrations was 38%. Only 12% of the surveyed population of Amangeldy showed a high level of chromosomal aberrations. In the cohort of residents of Basshi, people with a high level of chromosomal aberrations were not detected.

Molecular genetic analysis. To analyze the state of the body's reparative systems of Basshi, Belbulak, and Amangeldy residents we studied single-

nucleotide gene polymorphisms of *XRCCI* Arg³⁹⁹Gln (rs25487), *XRCCI* Arg¹⁹⁴Trp (rs1799782), *XRCC3* Thr²⁴¹Met (rs861539), *XPD* Lys⁷⁵¹Gln (rs13181), genes, involved in DNA repair. The results of the study of the frequencies of polymorphic variants of the studied genes are presented in tables 4 and 5.

An analysis of the distribution of alleles and genotypes of polymorphisms of DNA repair genes among residents of the three studied settlements did not reveal statistically significant differences ($P > 0.05$). For the *XRCCI* Arg¹⁹⁴Trp, *XRCC3* Thr²⁴¹Met, *XPD* Lys⁷⁵¹Gln genes homozygous genotypes for normal alleles are predominate (Arg/Arg; Thr/Thr; Lys/Lys, respectively) in the studied cohorts of people from three settlements. The frequencies of normal alleles of the analyzed genes in all cohorts are higher than the frequencies of mutant alleles. Arg³⁹⁹Gln polymorphism of the *XRCCI* gene is the exception. For this polymorphism, an increase in the

frequency of occurrence of the mutant allele (399Gln) is almost 2 times in the studied samples of people from three settlements (tables 4 and 5). However, the differences obtained are not statistically significant.

An associative analysis was performed between the *XRCCI* Arg³⁹⁹Gln genotype and the presence of cardiovascular disease (CVD) in residents of the studied villages. When comparing the group of patients (CVD) with the control group, we did not find significant differences in the frequency of alleles and genotypes of *XRCCI* Arg³⁹⁹Gln ($P > 0,05$; Table 6). Arg399Gln (G>A) polymorphism is located at the 399 codon, at the site of interaction of XRCCI with poly- (ADP-ribose) -polymerase. The nucleotide substitution of G for A leads to the replacement

of arginine (Arg) with glutamine (Gln), however, there is still no data on the functional significance of this substitution. *XRCCI* gene polymorphism is associated with a decrease in the ability of a protein, a product of this gene, to repair DNA, an increase in the number of gene mutations and the risk of tumor formation [58]. However, data on the association between *XRCCI* gene polymorphism and the risk of developing cardiovascular pathologies are contradictory in the literature. Some researchers suggest that the Arg³⁹⁹Gln polymorphism of the *XRCCI* gene is associated with susceptibility to CVD [59-61], while other authors do not find a reliable association between the Arg399Gln polymorphism of the *XRCCI* gene and the risk of CVD [62].

Table 4 – Frequencies of genotypes and alleles of DNA repair genes for residents of Belbulak settlement and in the control

Gene	Genotype variants	Belbulak, % (people.)	Basshi, % (people)	χ^2	P	OR (95% CI)
		n=26people	n=28people			
<i>XRCCI</i> Arg ³⁹⁹ Gln	Arg/Arg	8% (2 people)	11% (3 people)	0.642	0.725	0.69 (0.11 – 4.53)
	Arg/Gln	46% (12 people)	53% (15 people)			0.74 (0.25 – 2.17)
	Gln/Gln	46% (12 people)	36% (10 people)			1.54 (0.52 – 4.60)
	Arg	0.308	0.375	0.542	0.461	0.74 (0.33 – 1.65)
	Gln	0.692	0.625			1.35 (0.61 – 3.00)
<i>XRCCI</i> Arg ¹⁹⁴ Trp	Arg/Arg	58% (15 people)	57% (16 people)	1.434	0.488	1.02 (0.35 – 3.01)
	Arg/Trp	31% (8 people)	39% (11 people)			0.69 (0.22 – 2.12)
	Trp/Trp	11% (3 people)	4% (1 people)			3.52 (0.34 – 36.22)
	Arg	0.731	0.768	0.198	0.657	0.82 (0.34 – 1.96)
	Trp	0.269	0.232			1.22 (0.51 – 2.91)
<i>XRCC3</i> Thr ²⁴¹ Met	Thr/Thr	58% (15people)	71% (20 people)	1.709	0.425	0.55 (0.18 – 1.69)
	Thr/Met	31% (8 people)	25% (7 people)			1.33 (0.40 – 4.40)
	Met/Met	11% (3 people)	4% (1 people)			3.52 (0.34 – 36.22)
	Thr	0.731	0.839	1.894	0.169	0.52 (0.20 – 1.33)
	Met	0.269	0.161			1.92 (0,75 – 4.93)
<i>XPB</i> Lys ⁷⁵¹ Gln	Lys/Lys	38% (10people)	54% (15 people)	1.294	0.524	0.54 (0.18 – 1.60)
	Lys/Gln	50% (13 people)	39% (11 people)			1.55 (0.52 – 4.55)
	Gln/Gln	12% (3 people)	7% (2 people)			1.70 (0.26 – 11.06)
	Lys	0.635	0.732	1.189	0.276	0.64 (0.28 – 1.44)
	Gln	0.365	0.268			1.57 (0.69 – 3.56)

Table 5 – Frequencies of genotypes and alleles of DNA repair genes for residents of Amangeldy and in control

Gene	Genotype variants	Amangeldy, % (people)	Basshi, % (people)	χ^2	P	OR (95% CI)
		n=25people	n=28people			
XRCC1 Arg399Gln	Arg/Arg	16% (4 people)	11% (3 people)	1.024	0.599	1.59 (0.32 – 7.91)
	Arg/Gln	40% (10 people)	53% (15 people)			0.58 (0.19 – 1.72)
	Gln/Gln	44% (11 people)	36% (10 people)			1.41 (0.47 – 4.27)
	Arg	0.360	0.375	0.026	0.873	0.94 (0.42 – 2.07)
	Gln	0.640	0.625			1.07 (0.48 – 2.35)
XRCC1 Arg194Trp	Arg/Arg	64% (16 people)	57% (16 people)	0.305	0.859	1.33 (0.44 – 4.04)
	Arg/Trp	32% (8 people)	39% (11 people)			0.73 (0.23 – 2.26)
	Trp/Trp	4% (1 people)	4% (1 people)			1.13 (0.07 – 18.99)
	Arg	0.800	0.768	0.161	0.689	1.21 (0.48 – 3.07)
	Trp	0.200	0.232			0.83 (0.33 – 2.10)
XRCC3 Thr241Met	Thr/Thr	48% (12 people)	71% (20 people)	3.062	0.216	0.37 (0.12 – 1.15)
	Thr/Met	44% (11 people)	25% (7 people)			2.36 (0.74 – 7.55)
	Met/Met	8% (2 people)	4% (1 people)			2.35 (0.20 – 27.59)
	Thr	0.700	0.839	2.926	0.087	0.45 (0.18 – 1.14)
	Met	0.300	0.161			2.24 (0.88 – 5.70)
XPB Lys751Gln	Lys/Lys	68% (17 people)	54% (15 people)	2.437	0.296	1.84 (0.60 – 5.65)
	Lys/Gln	32% (8 people)	39% (11 people)			0.73 (0.23 – 2.26)
	Gln/Gln	0% (0 people)	7% (2 people)			-
	Lys	0.840	0.732	1.809	0.179	1.92 (0.74 – 5.02)
	Gln	0.160	0.268			0.52 (0.20 – 1.36)

Table 6 – Effect of genetic polymorphism *XRCC1* Arg399Gln on the development of cardiovascular diseases

Basshi						
Gene	Genotype variants	CVD, % (people)	healthy, % (people)	χ^2	P	OR (95% CI)
		n=4people	n=24people			
XRCC1 Arg399Gln	Arg/Arg	25% (1 people)	8% (2 people)	1.050	0.592	3.67 (0.25- 53.83)
	Arg/Gln	50% (2 people)	54% (13 people)			0.85 (0.10 – 7.04)
	Gln/Gln	25% (1 people)	38% (9 people)			0.56 (0.05 – 6.18)
	Arg	0.500	0.354	0.622	0.430	1.82 (0.40 – 8.23)
	Gln	0.500	0.646			0.55 (0.12 – 2.47)

Belbulak						
Gene	Genotype variants	CVD, % (people)	healthy, % (people)	χ^2	P	OR (95% CI)
		n=5 people	n=21 people			
XRCC1 Arg399Gln	Arg/Arg	0% (0 people)	10% (2 people)	2.930	0.231	-
	Arg/Gln	20% (1 people)	52% (11 people)			0.23 (0.02 – 2.39)
	Gln/Gln	80% (4 people)	38% (8 people)			6.50 (0.61 – 68.96)
	Arg	0.100	0.357	2.507	0,113	0.20 (0.02 – 1.73)
	Gln	0.900	0.643			5.00 (0.58 – 43.37)
Amangeldy						
Gene	Genotype variants	CVD, % (people)	healthy, % (people)	χ^2	P	OR (95% CI)
		n=4 people	n=21 people			
XRCC1 Arg399Gln	Arg/Arg	0% (0 people)	19% (4 people)	0.920	0.631	-
	Arg/Gln	50% (2 people)	38% (8 people)			1.63 (0.19-13.93)
	Gln/Gln	50% (2 people)	43% (9 people)			1.33 (0.16 – 11.36)
	Arg	0.250	0.381	0.500	0.479	0.54 (0.10 – 3.02)
	Gln	0.750	0.619			1.85 (0.33 – 10.28)

There is evidence that mutations in the genes for DNA repair and detoxification of xenobiotics are directly proportional to the number of chromosomal aberrations in lymphocytes, and genetic polymorphisms in these genes can affect individual sensitivity to the effects of certain pesticides [63].

Conclusion

Cytogenetic analysis showed a high level of chromosomal aberrations for residents of Belbulak and increased for residents of Amangeldy.

Molecular genetic analysis did not reveal a significant correlation between the polymorphisms of the *XRCC1* Arg¹⁹⁴Trp, *XRCC3* Thr²⁴¹Met and *XPB* Lys⁷⁵¹Gln genes and the frequency of chromosomal aberrations. However, the associative relationship of the polymorphism of the DNA repair gene *XRCC1* Arg³⁹⁹Gln with the development of cardiovascular diseases in a population living near foci of pesticidal contamination was determined.

Our further studies are aimed at analyzing the association between the number of chromosomal aberrations in human lymphocytes and the polymorphism of DNA repair and xenobiotic

detoxification genes in order to assess their role as determinants of pesticide toxicity.

Acknowledgments

These studies were carried out in the framework of the Ministry of Education and Science of the Republic of Kazakhstan projects “Comprehensive assessment of unutilized and banned pesticides impact on genetic status and health of population of Almaty region” State registration number 0118PK00749, and “Study of gene polymorphisms responsible for antioxidant protection and immune response in individuals exposed by pesticides for a long time” IRN AP09260631.

References

- 1 Fedorov L.A., Jablovkov A.V. (1999) Pesticidy – toksicheskiy udar po biosfere i cheloveku [Pesticides – a toxic blow to the biosphere and humans]. M.: Nauka, 462 p.
- 2 What Are Pesticides and How Do They Work? // NSW EPA. – 2013. <http://www.epa.nsw.gov.au/pesticides/pestwhatrhow.htm>

- 3 Zhumakanov M.O. (2016) Zagryaznenie okruzhajushhej sredy stojkimi organicheskimi zagryazniteljami [Environmental pollution with persistent organic pollutants]. G-Global. <http://group-global.org/ru/publication/31197-zagryaznenie-okruzhayushchey-sredy-stoykimi-organicheskimi-zagryaznitelyami>
- 4 Kurinnyj A.I., Pilinskaja M.A. (1974) Pesticidy kak mutagennyj faktor okruzhajushhej sredy [Pesticides as a mutagenic factor in the environment]. *Citologija i genetika*, vol.8, no. 4, pp. 342-374.
- 5 Pilinskaja M.A. (1986) Mutagennoe dejstvie pesticidov [Mutagenic effects of pesticides]. *Itogi nauki i tehniki. Obshhaja genetika*. M.: VINITI, vol.9. *Himicheskij mutagenез*, pp. 97-152.
- 6 Michael D.W. (2012) Application of short-term bioassays in the fractionation and analysis of complex environmental mixtures, Springer Science & Business Media, 588 p.
- 7 Pilinskaja M.A., L'vova T.S. (1979) Rezul'taty citogeneticheskogo obsledovanija grupp naselenija pri intensivnom i ogranichenom ispol'zovanii pesticidov [Results of cytogenetic examination of population groups with intensive and limited use of pesticides], *Citologija i genetika*, vol. 13, no. 3, pp.228-231.
- 8 Kaur R., Kaur M.G., Raghav Sh. Pesticides Classification and its Impact on Environment // *International Journal of Current Microbiology and Applied Sciences*. – 2019. – V. 8(3). P. 1889-1897.
- 9 Wanga R., Yuan Y., Yen H., Grieneisen M., Arnold J., Wang D., Wang Ch., Zhanga M. A review of pesticide fate and transport simulation at watershed level using SWAT: Current status and research concerns // *Science of The Total Environment*. – 2019. – Vol. 669. P. 512-526. <https://doi.org/10.1016/j.scitotenv.2019.03.141>
- 10 UNEP. The hazardous Chemicals and Waste Conventions. WHO/ UNEP/ FAO. – 20134 p. Available at: <http://www.pops.int/documents/background/hcwc>.
- 11 Witzak A., Abdel-Gawad H. Assessment of health risk from organochlorine pesticides residues in high-fat spreadable foods produced in Poland // *J. Environ. Sci. Health*. – 2014. – V.49. – P.917–928.
- 12 Philip J., Landrigan M.D., and Benbrook Ch. Perspective GMOs, Herbicides, and Public Health // *The New England Journal of Medicine*. – 2015. – V.373. – P.693-695.
- 13 Weber R., Schlumpf M., Nakano T., Vijgen J. The need for better management and control of POPs stockpiles // *Environmental Science and Pollution Research*. – 2015. – V. 22(19). – P. 14385-14390
- 14 Zikankuba V.L., Mwanyika G., Ntwenya J.E., James A., Yildiz F. Pesticide regulations and their malpractice implications on food and environment safety // *Cogent Food & Agriculture*. – 2019. – Vol. 5. <https://doi.org/10.1080/23311932.2019.1601544>
- 15 Sexton K. Cumulative risk assessment: an overview of methodological approaches for evaluating combined health effects from exposure to multiple environmental stressors // *Int. J. Environ. Res. Public Health*. – 2012. – V.9. – P.370–390.
- 16 Mostafalou S., Abdollahi M. Pesticides and human chronic diseases: evidences, mechanisms, and perspectives // *Toxicol. Appl. Pharmacol.* – 2013. – V.268. – P.157–177.
- 17 Bassil K.L. et al. Cancer health effects of pesticides. Systematic review // *Can. Fam. Physician*. – 2007. – V.53. – P.1704–17 24.
- 18 Salameh P. et all. Respiratory diseases and pesticide exposure: a case-control study in Lebanon // *J. Epidemiol. Community Health*. – 2006. – V.60. – P.256–261.
- 19 Hoppin J.A. et al. Pesticides and atopic and nonatopic asthma among farm women in the agricultural health study // *Am. J. Respir. Crit. Care Med*. – 2008. – V.177. – P.11–18.
- 20 Bjorling-Poulsen M., Andersen H.R., Grandjean P. Potential developmental neurotoxicity of pesticides used in Europe // *Environ Health*. – 2008. – V.7. – P.50.
- 21 Ahmed H. et al. Parkinson's disease and pesticides: A meta-analysis of disease connection and genetic alterations // *Biomed Pharmacother*. – 2017. – V.90. – P.638-649.
- 22 Sagiv S.K., Bruno J.L., Baker J.M., Palzes V., Kogut K., Rauch S., Gunier R., Mora A.M., Reiss A.L., and Eskenazi B. Prenatal exposure to organophosphate pesticides and functional neuroimaging in adolescents living in proximity to pesticide application // *PNAS*. – 2019. – Vol. 116, N. 37. – P. 18347-18356. <https://doi.org/10.1073/pnas.1903940116>
- 23 García A.M. Pesticide exposure and women's health//*Am.J.Ind.Med*. – 2003. – V.44. – P.584–594.
- 24 Roeleveld N., Bretveld R. The impact of pesticides on male fertility // *Curr. Opin. Obstet. Gynecol*. – 2008. – V.20. – P. 229–233.
- 25 Kaur R.P., Gupta V., Christopher A.F., Bansal P. Potential pathways of pesticide action on erectile function – A contributory factor in male infertility // *Asian Pacific Journal of Reproduction*. – 2015. – Vol. 4, Is. 4. – P. 322-330. <https://doi.org/10.1016/j.apjr.2015.07.012>

- 26 Buscail C. et al. Prenatal pesticide exposure and otitis media during early childhood in the PELAGIE mother-child cohort // *Occup. Environ. Med.* – 2015. – V.72(12). – P.837–844.
- 27 Bajak A. The Developing World is awash in pesticides. Does it have to be? Accessed on January 17, 2017. Available at: <https://ensia.com/features/developing-world-pesticides/>
- 28 Hou B., Wu L. Safety impact and farmer awareness of pesticide residues // *Food and Agricultural Immunology.* – 2010. – Vol. 21, No. 3. – P. 191-200.
- 29 Review on the implementation of the obligations of the Republic of Kazakhstan under the Stockholm Convention on POPs. Analytical Environmental Agency “Greenwomen”, 2018, 131 p.
- 30 Current projects on the problem of POPs in Kazakhstan: Report program 001 «Supporting the activities of the authorized body in the field of environmental protection» <http://kzdocs.docdat.com>
- 31 Nurzhanova A., Kalugin S., Zhambakin K. Obsolete pesticides and application of colonizing plant species for remediation of contaminated soil in Kazakhstan // *Environmental Science and Pollution Research.* – 2013. – Vol 20(4). – P. 2054-2063.
- 32 Nurzhanova A., Kulakow P.A., Rubin E., Rakhimbayev I., Sedlovshik A., Zhambakin K., Kalugin S., Kolyshva E., Erickson L.E. Obsolete Pesticide Pollution and Phytoremediation of Contaminated Soil in Kazakhstan // *In Application of Phytotechnologies for Cleanup of Industrial, Agricultural, and Wastewater Contamination.* – 2009. Springer, Dordrecht, The Netherlands. – P. 87-112.
- 33 Nurzhanova A.A. i dr. (2008) Jekologicheski opasnye ochagi zagryazneniya pochvy hlrorganicheskimi pesticidami v Kazahstane [Environmentally hazardous foci of soil pollution with organochlorine pesticides in Kazakhstan], *Agromeridian. Teoreticheskij i nauchno-prakticheskij sel'skohozyajstvennyj zhurnal*, vol. 1, no.7, pp. 31-34.
- 34 Teodoro M., Briguglio G., Fenga C., Costab C. Genetic polymorphisms as determinants of pesticide toxicity: Recent advances // *Toxicology Reports.* – 2019. – Vol. 6. P. 564-570.
- 35 Vasilenko N. L., Nevinsky G. A. Enzymes of direct, excision and mismatch DNA repair in pro-and eukaryotes and their biological role // *Molecular Biology.* – 2003. – Vol. 37, N. 6. – P. 803-817
- 36 Catana A. et al. Genetic polymorphism of DNA repair gene ERCC2/XPD (Arg 156 Arg) (A22541C) and lung cancer risk in Northern Romania // *Revista Română de Medicină de Laborator.* – 2012. – Vol. 20, N. 2. – P. 157-161.
- 37 Akhmadishina L.Z. et. al. DNA Repair XPCC1 and XPD Genes Polymorphism as Associated with the Development of Bladder Cancer and Renal Cell Carcinoma // *Russian journal of Genetics.* – 2014. – Vol. 50, N. 4. – P. 481-490.
- 38 Guo S., Li X., Gao M., Li Y., Song B., Niu W. The relationship between XRCC1 and XRCC3 gene polymorphisms and lung cancer risk in northeastern Chinese // *PLoS One.* – 2013. -Vol.8, N. 2.- P. 1-5.
- 39 Wang Y.D., Zhai W.L., Wang H.Y., Xia X.Q. An updated meta-analysis on the association of X-ray repair cross complementing group 1 codon 399 polymorphism with hepatocellular carcinoma risk // *Asian Pac J Cancer Prev.* – 2014. – Vol.15, N. 11. – P. 4443-4448.
- 40 Yang H.Y., Yang S.Y., Shao F.Y., Wang H.Y., Wang Y.D. Updated assessment of the association of the XRCC1 Arg399Gln polymorphism with lung cancer risk in the Chinese population // *Asian Pac J Cancer Prev.* – 2015. – Vol.16, N. 2. – P. 495-500.
- 41 Huang Z.H., Hua D., Du X. Polymorphisms in p53, GSTP1 and XRCC1 predict relapse and survival of gastric cancer patients treated with oxaliplatin-based adjuvant chemotherapy // *Cancer ChemotherPharmacol.* – 2009. – Vol. 64, N. 5. – P. 1001-1007.
- 42 Singh S. Cytoprotective and regulatory functions of glutathione S-transferases in cancer cell proliferation and cell death // *Cancer Chemother Pharmacol.* – 2015. – Vol. 75, N. 1. – P. 1-15.
- 43 Klusek J, Głuszek S, Klusek J. GST gene polymorphisms and the risk of colorectal cancer development // *ContempOncol (Pozn).* – 2014. – Vol. 18(4). – P. 219-221.
- 44 Gong M, Dong W, Shi Z, Xu Y, Ni W, An R. Genetic polymorphism of GSTM1, GSTT1 and GSTP1 with prostate cancer risk: a meta-analysis of 57 studies // *PLoS One.* – 2012. – Vol. 7. – e50587.
- 45 Jaramillo-Rangel G, Ortega-Martínez M, Cerda-Flores RM, Barrera-Saldaña HA. Polymorphisms in GSTM1, GSTT1, GSTP1, and GSTM3 genes and breast cancer risk in northeastern Mexico // *Genet Mol Res.* – 2015. – Vol.14, N. 2. – P. 6465-6471.
- 46 da Silva C.N., da Silva D.N., Moraes K.L., Cordeiro J.A., Brasil V.V., Saddy V.A., Silva A.M. GSTM1 and GSTT1 genes null polymorphisms in kidney cancer susceptibility: evidence based on a meta-analysis // *J Bras Nefrol.* – 2015. – Vol.37, N. 2. – P. 248-254.
- 47 Parrón T., Requena M., Hernández A.F., Alarcón R. Environmental exposure to pesticides and cancer risk in multiple human organ systems //

Toxicology Letters. – 2014. – Vol. 30. – P. 157–165. <https://doi.org/10.1016/j.toxlet.2013.11.009>.

48 Bacton K., Evans G. Methods for the analysis of chromosomal aberrations in humans (methodological guide), Geneva: WHO edition, 1975. – 64 p.

49 Jedrychowski, W., Maugeri, U., Epidemiologic Methods in Studing Chronic Diseases Teaching Manual // A handbook sponsored by the International Center for Studies and research in Biomedicine in Luxembourg. – 2000. – P. 245-247.

50 Ficová, I., Galdíková, M. Testing the potential clastogenic/ cytotoxic effects of pesticide // Calypso. Scfolia veterinaria. – 2017. – V. 61(3). – P. 47–51.

51 Health of the population of the Republic of Kazakhstan and the activities of healthcare organizations in 2011-Statistical collection, Astana-Almaty, 2012.- 320 p.

52 The health of the population of the Republic of Kazakhstan and the activities of health care organizations in 2013 – Statistical collection, Astana-Almaty, 2014.- 356 p.

53 Health of the population of the Republic of Kazakhstan and the activities of healthcare organizations in 2016-Statistical collection.-Astana, 2017. – 356 p.

54 Order of the Minister of Health No. 128 from March 6, 2013 “On the collection of administrative data from organizations providing outpatient care in accordance with the Code of the Republic of Kazakhstan” On people’s health and the health care system (with amendments and additions as of 13.05.2019), Appendix 18.- 2013.

55 Omarova Z.M. (2010) Influence of pesticides on children’s health. Russian Bulletin of Erinatology and Pediatrics, no. 1, pp. 59-64.

56 Nogaeva M.G., Tuleutaeva S.A. (2014) The prevalence of diseases of the circulatory system in

the Republic of Kazakhstan, Medicine, no. 10, pp. 13-16.

57 Karthikeyan R. et al. Potential of plant-based remediation of pesticide contaminated soil and water using non-target plants such as trees, shrubs and grasses // Plant Sciences. – 2004. – Vol. 23, N.1. – P.1-11.

58 Ruey-Hong Wong, Shu-Yuan Chang, Shu-Wei Ho, Pei-Lin Huang, Yi-Jie Liu, Yu-Ching Chen, Yu-Hsuan Yeh, Hong-Shen Lee. Polymorphisms in metabolic GSTP1 and DNA-repair XRCC1 genes with an increased risk of DNA damage in pesticide-exposed fruit growers // Mutation Research. – 2008. – Vol. 654. – P. 168–175.

59 Hameed H., Faryal M., Aslam M.A., Akbar A., Saad A.B., Pasha M.B., Latif M., Rehan Sadiq Shaikh R.R., Ali M., Iqbal F. Association of polymorphisms (rs 1799782, rs25489 and rs25487) in XRCC1 and (rs 13181) XPD genes with acute coronary artery syndrome in subjects from Multan, Pakistan // Pak. J. Pharm. Sci. – 2016. – Vol. 29. – P. 869-876.

60 Guo S.J., Zhou Y.T., Liu W.Y., Zuo Q.N., Li X.H. The polymorphism of XRCC1 and coronary artery disease risk: a meta-analysis // Eur. Rev. Med. Pharmacol. Sci. – 2017. – Vol.21. – P.1559-1567.

61 Ma W.Q., Han X.Q., Wang X., Wang Y., Zhu Y. Associations between XRCC1 gene polymorphisms and coronary artery disease: a meta-analysis // PLoS One. – 2016. – Vol.11. – e0166961.

62 Ying-Nan Wang, De-Wei Wang, Lei Gao, Shi-Yong Wu, Dong-Yin Zhang and Shu Qin. XRCC1 gene rs25487, rs1799782 polymorphisms do not influence the susceptibility of CAD // Biomedical Research. – 2017. – Vol. 28, Issue 18.

63 Teodoro M., Briguglio G., Fenga C., Costa Ch. Genetic polymorphisms as determinants of pesticide toxicity: Recent advances // Toxicology Reports. – 2019. – Vol.6. – P.564-5