

THE DISTRIBUTION OF *TP53* GENE POLYMORPHISMS IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS, SUFFERERS OF CHORNOBYL NUCLEAR POWER PLANT ACCIDENT

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Previous analyses in a cohort of Chernobyl cleanup workers revealed significantly increased radiation-related risk for all leukemia types, including chronic lymphocytic leukemia (CLL). Numerous investigations emphasized the significance of genetic susceptibility to the radiation carcinogenesis. The aim of the work was to study the distribution of *TP53* single nucleotide polymorphisms (SNPs) in CLL patients exposed to ionizing radiation (IR) due to Chernobyl nuclear power plant accident and estimate their impact on disease development. **Materials and Methods:** The *TP53* exonic and intronic SNPs were analyzed in 236 CLL patients by polymerase chain reaction and direct sequencing. The main group included 106 IR exposed CLL patients and the control group was composed of 130 IR non-exposed CLL patients. **Results:** Nineteen *TP53* SNPs were found in the observed CLL cohort. No significant differences were found between the main and the control groups, but increased frequencies of T/T rs12947788 + G/G rs12951053 homozygotes and rs146340390 C/T variants were found among IR-exposed CLL patients compared with healthy Europeans (data from the 1000 Genomes Project). Rare nucleotide substitution rs146340390 (c.665C>T) was found only in the main group. These features were primarily typical for the most affected group of IR-exposed patients, namely, cleanup workers engaged in emergency works in the 2nd quarter of 1986. **Conclusion:** These preliminary findings don't contradict the assumption on possible influence of IR on CLL development via the p53-dependent pathway. This article is a part of a Special Issue entitled “The Chernobyl Nuclear Accident: Thirty Years After”.

Key Words: chronic lymphocytic leukemia, *TP53* gene, polymorphism.

Previous analyses in the cohort of Chernobyl cleanup workers revealed significant radiation-related increased risk for all leukemia types, including chronic lymphocytic leukemia (CLL) [1–3]. Further study did not find additional effects of occupational and lifestyle factors on CLL risk in this radiation-exposed cohort [4]. Numerous investigations emphasized the significance of genetic susceptibility to the development of tumors after exposure to carcinogens [5–7]. Considering the role of *TP53* as a key tumor suppressor, intensive search of its cancer susceptibility allelic variants have been conducted. The *TP53* codon 72 G/C (Arg72Pro) polymorphism (rs1042522) is the most studied single nucleotide polymorphism (SNP) that might be associated with the risk of acute lymphoblastic leukemia [8], breast cancer [9], cervical cancer and papillary thyroid carcinoma (in combination with pri-miR-34b/c rs4938723) [10, 11], digestive tract cancers in Asians [12], etc. Another studied *TP53* SNPs included rs78378222 (associated with basal cell carcinoma, prostate cancer, glioma, and colorectal adenoma [13]), rs12947788 and rs12951053 (associated with asbestos-exposed non-small cell lung cancer [14]), rs1042522,

rs17878362, and rs1625895 (associated with diffuse large B-cell lymphoma [15]), rs17878362 (associated with breast and colorectal cancer [16]). Only two *TP53* SNPs (rs1042522 and rs17878362) were analyzed in CLL patients up-to-date [17–19]. Thus, the aim of the work was to study the distribution of *TP53* SNPs in CLL patients exposed to ionizing radiation (IR) due to Chernobyl nuclear power plant accident and clarify their impact on the disease development.

MATERIALS AND METHODS

The *TP53* exonic and intronic polymorphisms were analyzed in 236 CLL patients, 196 males (83.1%) and 40 females (16.9%), with median age of 58 years at the moment of CLL diagnosis, referred to the State Institution “National Research Centre for Radiation Medicine of the National Academy of Medical Sciences of Ukraine”, Kyiv, Ukraine. All patients were Caucasians from the central part of Ukraine. The study was approved by the local Ethics Review Committee, and all patients signed an informed consent form prior to participation in the study. CLL was diagnosed on the basis of clinical history, lymphocyte morphology, and immunophenotypic criteria. The stage of the disease was assessed by Binet [20] and Rai classification [21].

Patients were distributed into two groups according to IR exposure. The main group included 106 IR exposed CLL patients and the control group included 130 IR non-exposed CLL patients. The group of IR-exposed CLL patients included 83 cleanup workers (in particular, 72 cleanup workers of 1986), 16 inhabit-

Submitted: August 1, 2016.

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Abbreviations used: CLL – chronic lymphocytic leukemia; d – differences between expected and observed allele frequencies; *IGHV* – immunoglobulin heavy chain; HWE – Hardy – Weinberg equilibrium; IR – ionizing radiation; MAF – minor allele frequency; SNP – single nucleotide polymorphism.

ants of radionuclide contaminated areas, and 7 evacuees. Patients of the two groups were of comparable age, CLL stage at diagnosis, mutational status of immunoglobulin heavy chain (*IGHV*) genes (Table 1).

Table 1. Baseline clinical characteristics of observed CLL patients

Characteristics	IR-exposed patients, n = 106*	Control group, n = 130*	p value
Median age, years (range)	57 (39–76)	58 (33–77)	0.714
Sex, n (%)			0.015
Male	95 (89.6)	101 (77.7)	
Female	11 (10.4)	29 (22.3)	
Rai stage at diagnosis, n (%)			0.532
0	13 (12.3)	18 (13.8)	
I	35 (33.0)	47 (36.2)	
II	48 (45.3)	49 (37.7)	
III	5 (4.7)	12 (9.2)	
IV	5 (4.7)	4 (3.1)	
Binet stage at diagnosis, n (%)			0.259
A	50 (47.2)	66 (50.8)	
B	49 (46.2)	49 (37.7)	
C	7 (6.6)	15 (11.5)	
<i>IGHV</i> mutational status, n (%)			0.345
Mutated	36 (34.6)	36 (28.8)	
Unmutated	68 (65.4)	89 (71.2)	

Note: **IGHV* mutational status was evaluated in 104 and 125 patients of IR-exposed and control groups, respectively.

Genomic DNA was extracted from peripheral whole blood samples with the QIAamp Blood Mini Kit (Qiagen, Crawley, UK) according to the manufacturer’s protocol. *TP53* genotyping was performed for 3–10 exons and adjacent introns by PCR amplification followed by direct sequencing as described earlier [22]. Obtained data were validated using the IARC *TP53* Mutation Database (<http://p53.iarc.fr/>) and dbSNP database (<http://www.ncbi.nlm.nih.gov/SNP>). The Hardy — Weinberg equilibrium (HWE) was evaluated using the chi-square (χ^2) test for all revealed SNPs. The frequencies of SNPs in the main and the control groups were compared by χ^2 test. The SNP frequencies obtained in the analysis were compared by Brandt — Snedecor method or χ^2 test with the data from the 1000 Genomes Project (<http://www.1000genomes.org/>). Linkage disequilibrium of SNPs was determined based on *d* estimates (differences between expected and observed allele frequencies) using CubeX online program (<http://www.oege.org/software/cubex/>). All tests were two-sided and considered to be statistically significant with a p value of ≤ 0.05 . Statistical analysis was performed using the SPSS 16.0 software package (SPSS, Chicago, IL).

RESULTS AND DISCUSSION

Nineteen *TP53* SNPs were found in the observed CLL cohort. The distribution of SNPs, minor allele frequency (MAF) and concordance with HWE are presented in Table 2. No significant differences were found between the main and the control groups.

Only two SNPs (rs12947788, and rs12951053) showed evidence ($p < 0.05$) of deviation from HWE due to increased number of minor homozygotes (T/T and G/G, respectively), especially in the main group (Fig. 1). The frequencies of T/T rs12947788, and G/G rs12951053 genotypes in the main group were higher than these among healthy Caucasians (Table 3). Similar results were reported by Andujar et al. [14] for

Table 2. Distribution of exonic and intronic *TP53* SNPs among observed CLL patients

rs number, localization	Genotypes	All CLL patients			The main group, n (%)	The control group, n (%)	p
		n (%)	MAF	ρ HWE			
rs1042522, 17:7676154, p.P72R	Arg/Arg Arg/Pro Pro/Pro	115 (48.7) 97 (41.1) 24 (10.2)	0.31	0.575	49 (46.2) 48 (45.3) 9 (8.5)	66 (50.8) 49 (37.7) 15 (11.5)	0.368
rs1642785, 17:7676483, 2–3 intron	G/G G/C C/C	119 (50.4) 89 (37.7) 28 (11.9)	0.31	0.117	56 (52.8) 38 (35.9) 12 (11.3)	63 (48.5) 51 (39.2) 16 (12.3)	0.567
rs17878362, 3–4 intron	A1/A1 A1/A2 A2/A2	167 (70.8) 61 (25.8) 8 (3.4)	0.17	0.402	77 (72.7) 26 (24.5) 3 (2.8)	90 (69.2) 72 (26.9) 5 (3.9)	0.683
rs2909430, 17:7675327, 4–5 intron	A/A A/G G/G	178 (75.4) 50 (21.2) 8 (3.4)	0.15	0.069	80 (75.5) 23 (21.7) 3 (2.8)	98 (75.4) 27 (20.8) 5 (4.8)	0.427
rs12947788, 17:7674109, 7–8 intron	C/C C/T T/T	195 (82.6) 33 (14.0) 8 (3.4)	0.11	0.001	86 (81.2) 15 (14.1) 5 (4.7)	109 (83.8) 18 (13.9) 3 (2.3)	0.267
rs12951053, 17:7674089, 7–8 intron	T/T T/G G/G	195 (82.6) 33 (14.0) 8 (3.4)	0.11	0.001	86 (81.2) 15 (14.1) 5 (4.7)	109 (83.8) 18 (13.9) 3 (2.3)	0.267
rs17883323, 17:7676301, 3–4 intron	C/C C/A A/A	215 (91.1) 20 (8.5) 1 (0.4)	0.05	0.479	100 (94.3) 6 (5.7) 0	115 (88.5) 14 (10.8) 1 (0.7)	0.121
rs17880847, 17:7670579, 10–11 intron	T/T T/A	230 (97.5) 6 (2.5)	0.014	0.751	103 (97.2) 3 (2.8)	127 (97.7) 3 (2.3)	0.867
rs1800372, 17:7674892, c.639A>G (p.R213R)	A/A A/G	231 (97.9) 5 (2.1)	0.011	0.751	103 (97.2) 3 (2.8)	128 (98.5) 2 (1.5)	0.386
rs17880604, 17:7674326, 5–6 intron	C/C C/G	231 (97.9) 5 (2.1)	0.011	0.751	103 (97.2) 3 (2.8)	128 (98.5) 2 (1.5)	0.286
rs1800370, 17:7676261, c.108G>A (p.P36P)	G/G G/A	234 (99.2) 2 (0.8)	0.004	0.999	106 (100.0) 0	128 (98.5) 2 (1.5)	0.205
rs150293825, 17:7670695, c.1014C>T (p.F338F)	C/C C/T	234 (99.2) 2 (0.8)	0.004	0.999	106 (100.0) 0	128 (98.5) 2 (1.5)	0.205
rs146340390, 17:7674866, c.665C>T (p.P222L)	C/C T/T	234 (99.2) 2 (0.8)	0.004	0.999	106 (100.0) 0	130 (100.0) 0	0.127
rs113530090, 17:7675322, 4–5 intron	T/T T/C	245 (99.2) 2 (0.8)	0.004	0.751	105 (99.0) 1 (1.0)	129 (99.2) 1 (0.8)	0.965
rs145153611, 17:7675337, 4–5 intron	T/T T/C	245 (99.2) 2 (0.8)	0.004	0.751	105 (99.0) 1 (1.0)	129 (99.2) 1 (0.8)	0.965
rs539224556, 17:7670632, c.1077A>G (p.P359P)	A/A A/G	235 (96.6) 1 (0.4)	0.002	0.751	106 (100.0) 0	129 (99.2) 1 (0.8)	0.236
rs570110128, 17:7674354, 6–7 intron	C/C C/T	235 (96.6) 1 (0.4)	0.002	0.751	106 (100.0) 0	129 (99.2) 1 (0.8)	0.236
rs373232559, 17:7670453, 10–11 intron	G/G G/A	235 (96.6) 1 (0.4)	0.002	0.751	106 (100.0) 0	129 (99.2) 1 (0.8)	0.236
rs45599946, 17:7670455, 10–11 intron	C/C C/G	235 (96.6) 1 (0.4)	0.002	0.751	106 (100.0) 0	129 (99.2) 1 (0.8)	0.236

asbestos-exposed non-small cell lung cancer and malignant pleural mesothelioma (asbestos-related cancer). Association between rs12951053 and ovarian cancer risk was found, and it was suggested that rs12951053 is in weak linkage disequilibrium with SNPs affecting transcription factor binding sites [23].

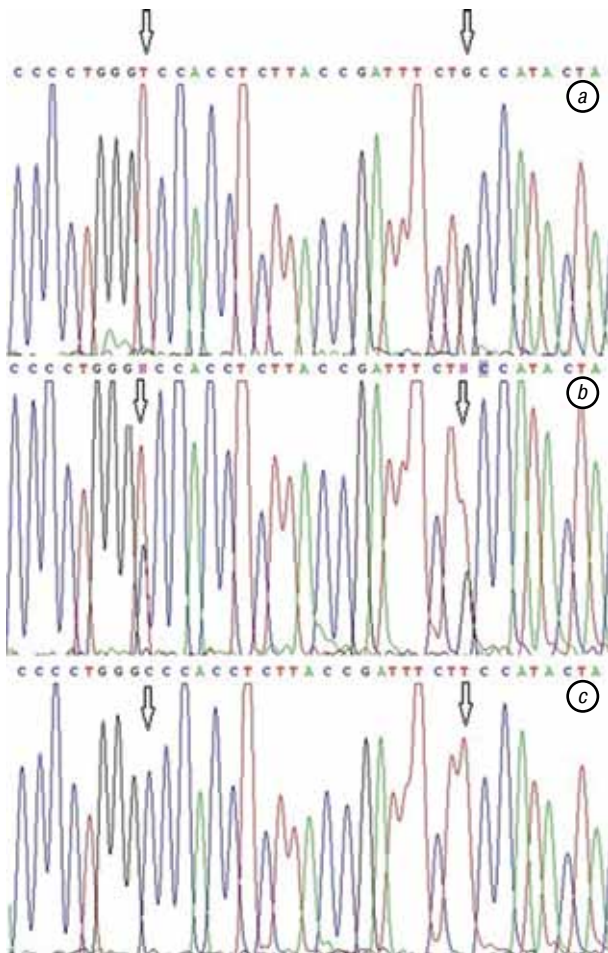


Fig. 1. Sanger sequencing raw data for rs12947788 (C/T) and rs12951053 (T/G) *TP53* polymorphisms: a) T/T, G/G; b) C/T, T/G; c) C/C, T/T genotypes. The positions of polymorphisms are indicated by arrows

Table 3. Distribution of rs12947788, rs12951053, and rs146340390 *TP53* SNPs among observed CLL patients comparing with healthy Caucasians (data from the 1000 Genomes Project)

SNP	Genotypes	The main group, n (%)	The control group, n (%)	Healthy Caucasians, n (%)	IR-exposed CLL patients vs healthy Caucasians	IR non-exposed CLL patients vs healthy Caucasians
rs12947788	C/C	86 (81.2)	109 (83.8)	412 (81.9)	0.01	0.05
	C/T	15 (14.1)	18 (13.9)	83 (16.5)		
	T/T	5 (4.7)	3 (2.3)	8 (1.6)		
Minor homozygotes					0.042	0.583
rs12951053	T/T	86 (81.2)	109 (83.8)	412 (81.9)	0.01	0.05
	T/G	15 (14.1)	18 (13.9)	83 (16.5)		
	G/G	5 (4.7)	3 (2.3)	8 (1.6)		
Minor homozygotes					0.042	0.583
rs146340390	C/C	104 (98.1)	130 (100.0)	4298 (99.95)	0.0001	0.996
	C/T	2 (1.9)	0	2 (0.05)		

Another nucleotide substitution, c.665C>T (rs146340390), was found only in the main group (Fig. 2). This substitution was identified as an extremely rare mutation in different solid tumors — 8 of 29,893 cases, 0.026% (IARC *TP53* database), and also as a very rare SNP — 2 of 4300 cases among Americans

of European descent, 0.047% (GO-ESP project; <https://esp.gs.washington.edu/drupal>). We considered c.665C>T substitution as SNP in our cases since in one patient it was found in DNA from the buccal mucosa as well as in tumor DNA (germline DNA sample was not available for the second patient). The frequency of rs146340390 was higher in comparison with healthy persons (data of GO-ESP project). c.665C>T results in substitution of proline to leucine in position 222 (p.Pro222Leu) and significantly impaired p53 activity (23.96% compared to wild type *TP53*).

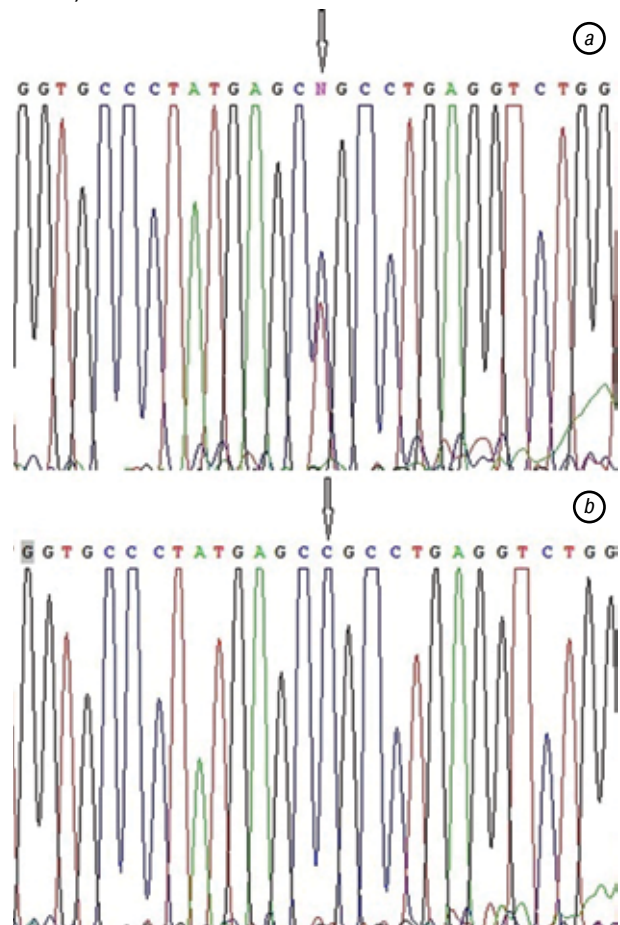


Fig. 2. Sanger sequencing raw data for rs146340390 (substitution c.665C>T) of *TP53*: a) C/T genotype; b) C/C genotype

It is noteworthy that from 5 T/T rs12947788 and G/G rs12951053 homozygotes 3 cases were found in cleanup workers engaged in emergency works in 2nd quarter (April–May) of 1986, one case in cleanup worker of 1987, and one — in evacuee. Both patients with rs146340390 (substitution c.665C>T) were cleanup workers engaged in emergency works in 2nd quarter of 1986. Doses of irradiation were not known in these patients, but the data on irradiation doses were available for other 18 cleanup workers engaged in emergency works in 2nd quarter of 1986 (35.68 ± 8.53 cSv), 10 cleanup workers engaged in emergency works in other periods of 1986 (9.57 ± 3.43 cSv), 7 cleanup workers of 1987–1989 (5.73 ± 1.09 cSv), 4 evacuees (4.76 ± 0.35 cSv), and 7 inhabitants of radionuclide contaminated areas (1.01 ± 0.26 cSv). These data are in accordance with the data of International Program on the

Health Effects of the Chernobyl Accident (IPHECA) [24]. According to them, the majority of cleanup workers of 1986 received the doses higher than 10 cSv (80.0%), and absorbed dose for cleanup workers of 1986 averaged 31 cSv (41 cSv for cleanup workers engaged in emergency works in 26–30.04.1986, and 9.7 cSv for those working in May–December, 1986). Thus, we may conclude that the frequencies of rs12947788, rs12951053, and rs146340390 SNPs were the highest in the group of CLL patients who received the largest irradiation doses during Chernobyl nuclear power plant accident.

The frequency of the others SNPs in the main and the control groups did not differ from that in healthy European population (data not shown).

Exonic rs1042522 was in linkage disequilibrium with intronic rs1642785 ($d = 0.908$; $r^2 = 0.8236$; $p < 0.001$), rs17878362 ($d = 0.733$; $r^2 = 0.2444$; $p < 0.001$), rs2909430 ($d = 0.972$; $r^2 = 0.3698$; $p < 0.001$), rs12951053 ($d = 0.85$; $r^2 = 0.1967$; $p < 0.001$), and rs12947788 ($d = 0.85$; $r^2 = 0.1967$; $p < 0.001$). Strong association was found between rs12951053 and rs12947788 ($d = 0.793$; $r^2 = 0.40$; $p < 0.001$), and only 3 combinations of rs12951053 and rs12947788 genotypes were found (82.0% CC/TT; 14.6% CT/CG, and 3.4% TT/GG). These data were in accordance with previously reported results [15, 25–27].

A total of 17 different combinations of associated SNPs were found among observed CLL patients. The most CLL cases were homozygous for the major alleles of rs1042522, rs1642785, rs17878362, rs17883323, rs2909430, rs12951053, and rs12947788 (100 cases; 46.6%). Previously it has been shown that combined G/G rs1642785 and A1/A1 rs17878362 alleles are associated with the highest basal and radiation-induced levels of fully spliced *TP53* transcript and incompletely spliced transcript retaining intron 2 (p53I2) [25]. The second most common combination (42 cases; 17.7%) was Arg/Pro-G/C-A1/A2-C/C-A/G-C/C-T/T (indicated genotypes of listed above SNPs), and the third common combination was Arg/Pro-G/C-A1/A1-C/C-A/A-C/T-T/G (38 cases; 16.1%). The other haplotype frequencies ranged from 0.4 to 3.0%. No differences were found between the main and the control groups ($p = 0.811$).

In summary, increased frequencies of T/T rs12947788+G/G rs12951053 homozygotes and rs146340390 were found among IR-exposed CLL patients compared with healthy Europeans. These features were primarily typical for the most affected group of IR-exposed patients, namely, cleanup workers engaged in action in the 2nd quarter of 1986. These preliminary findings don't contradict the assumption on possible influence of IR on CLL development, and are in accordance with the data evidencing that cellular responses on IR are realized mainly through the p53-dependent pathway [28].

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