Short Communication

DNA Repair Polymorphisms in B-cell Chronic Lymphocytic Leukemia in Sufferers of Chernobyl Nuclear Power Plant Accident

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An association between DNA repair gene polymorphisms, environmental factors, and development of some types of cancer has been suggested by several studies. Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in the clean-up workers of the Chernobyl Nuclear Power Plant (NPP) accident and it has some specific features. Therefore, we have studied the possible differences in DNA repair gene polymorphisms in CLL patients depending on ionizing radiation (IR) exposure history and their clinical characterictics. Arg399Gln *XRCC1*, Thr241Met *XRCC3*, and Lys751Gln *XPD* polymorphisms were studied in 64 CLL patients, exposed to IR due to the Chernobyl NPP accident, 114 IR-non-exposed CLL patients, and 103 sex- and age-matched IR-exposed controls using polymerase chain reaction-restriction fragment-length polymorphism analysis. All investigated polymorphisms were equally distributed between two groups of CLL patients and IR-exposed controls, except that that there was a significant reduction of the common homozygous Lys/Lys *XPD* genotype among IR-exposed CLL patients (23.7%) compared with IR-exposed controls (45.6%), OR = 0.37; 95% CI = 0.18–0.75; (P = 0.005). The number of IR-non-exposed CLL patients (37.4%) with the Lys/Lys *XPD* genotype was also decreased compared to IR-exposed controls, although this difference was not significant (P = 0.223). These preliminary data suggest a possible modifying role of Lys751Gln *XPD* polymorphism for the development of CLL, expecially in radiation-exposed persons.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is one of the most common lymphoid malignancies in the Ukraine as well as in Western Europe and the USA.[1,2] The effect of ionizing radiation (IR) on CLL development is unclear,[3–8] making a study of CLL in patients exposed to IR due to the Chernobyl Nuclear Power Plant (NPP) accident especially relevant. CLL is the most common form of leukemia in clean-up workers of the Chernobyl NPP accident.[9] Preliminary results of the joint USA-Ukrainian epidemiological project for Study of Leukemia and Other Hematological Diseases Among Clean-up Workers at the Chernobyl Nuclear Plant (National Cancer Institute, USA and Research Center for Radiation Medicine, Academy of National Medical Science of Ukraine - RCRM, Kyiv, Ukraine) revealed a dose-response relationship between CLL and IR exposure (excess

relative risk was 4.09 per Gy).[10] Some differences in the course of disease in IR-exposed CLL patients were also found.[11] Specifically, the frequency of solid tumors (basal cell carcinoma and prostate cancer) was higher in CLL patients who were clean-up workers of the Chernobyl NPP accident than in IR non-exposed CLL patients.[12,13] Notably, increased incidence rates of secondary solid cancers were found among Japanese atomic bomb survivors already diagnosed with a primary cancer,[14] emphasizing the significance of genetic predisposition for the development of oncological disorders after IR exposure.[15]

Among the possible gene targets associated with radiosensitivity, our attention was drawn to the DNA repair genes. IR as a DNA damaging agent induces a range of lesions, such as base damage, single strand breaks, double strand breaks, and DNA cross links, and therefore, nearly all DNA repair pathways might be involved in their removal.[16] More than 130 human DNA repair genes are involved in different repair pathways.[17] Mutations in DNA repair genes are rare, resulting in embryonic death or serious genetic diseases; however, single nucleotide polymorphisms (SNPs), which alter the function or efficiency of DNA repair and are associated with cancer development, have been identified. Three of the best characterized DNA repair genes are the fol-

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lowing: *XRCC1* (X-ray Repair Cross-Complementing protein 1 gene), a component of base excision repair and the repair of single-strand breaks; *XRCC3* (X-ray Repair Cross-Complementing protein 3 gene), a member of the RecA/Rad51-related protein family that participates in the homologous recombination of double-strand breaks; and *XPD* (Xeroderma Pigmentosum group D-complementing protein gene), an important component of nucleotide excision repair. Several variants of these genes have been described, including SNP rs25487 in *XRCC1*, which affects codon 399 in exon 10 resulting in an arginine (Arg) to glutamine (Gln) substitution. The *XRCC1* Arg399Gln polymorphism was associated with decreased radiation-specific DNA repair rates in healthy individuals[18] and an increased risk of lung cancer (among light smokers),[19] colorectal cancer,[20] hepatitis-related hepatocellular carcinoma,[21] and breast carcinoma.[22] The threonine (Thr) to methionine (Met) polymorphism at codon 241 of *XRCC3* (SNP rs862539) was associated with a higher level of chromosomal DNA damage (as determined by micronucleus assay) in interventional cardiologists and industrial radiographers with low-dose radiation exposure[23,24] and an increased risk of colorectal cancer,[25] lung cancer,[26] and bladder cancer.[27] The *XPD* lysine (Lys) 751 to Gln polymorphism (SNP rs13181) was associated with reduced nucleotide repair capacity,[28] an increased risk of esophageal squamous cell carcinoma,[29] hepatocellular carcinoma,[30] lung cancer in smokers,[31] bladder cancer,[32] and female breast cancer in radiologic technologists.[33]

There are only a few studies investigating DNA repair gene polymorphisms in CLL patients. For example, Ganster et al. found differences between cytogenetically high-risk CLL patients (17p and/or 11q deletion) and healthy age- and sex-matched controls for the SNPs rs13181 in *XPD* and rs25487 in *XRCC1*.[34] However, there have been no studies of DNA repair gene polymorphisms in CLL patients exposed to IR. Thus, the aim of this study was to evaluate the possible differences in DNA repair gene polymorphisms (Arg399Gln *XRCC1*, Thr241Met *XRCC3*, and Lys751Gln *XPD*) in CLL patients depending on their IR exposure history and clinical characteristics.

MATERIALS AND METHODS

Patients

The study of DNA repair gene polymorphisms was conducted in 178 consecutive patients with CLL and 103 IR-exposed persons without oncological pathology (IR-exposed controls) observed in the RCRM. 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 or Rai classifica-

tion,[35,36] and treatment was initiated in accordance with National Cancer Institute of the USA (NCI) criteria.[37] Secondary solid tumors had developed in 32 (17.9%) CLL patients, and Richter transformation was observed in 20 (11.2%) patients. Richter transformation was diagnosed according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL)-NCI guidelines.[38]

CLL patients were divided into two groups according to IR exposure. The group of 64 IR-exposed CLL patients (57 male and 7 female; median age 57.5 years) included 50 clean-up workers, 10 inhabitants of radionuclide-contaminated areas, and 4 evacuees from Prypiyat.

Information about the radiation doses of 4 clean-up workers (employees of the Ministry of Internal Affairs) was available from the State Registry of Chernobyl Catastrophe Sufferers of Ukraine. Individual doses for another 13 clean-up workers were reconstructed using the RADRUE (Realistic Analytical Dose Reconstruction and Uncertainty Analysis) method.[10,39] Among clean-up workers, 41 were clean-up workers from 1986 (estimated doses were available for 13 persons – 0.14, 2.2, 2.7, 5.7, 8.4, 8.9, 20.15, 21.0, 25.0, 26.0, 27.8, 100, and 120 cSv), 4 were clean-up workers from 1987 (estimated doses were available for 2 patients – 9.85 and 9.9 cSv), and 5 were clean-up workers from 1988–1989 (estimated doses were available for 2 patients – 2.8 and 4.9 cSv). Accumulated doses (since 1986 to the diagnosis of CLL) in 10 residents of contaminated areas (0.23, 0.39, 0.47, 0.54, 0.73, 0.73, 1.24, 1.62, 1.67, and 2.12 cSv) were calculated based on ^{137}Cs soil contamination density (mean age dose typical for a given level of local contamination) and levels of radioactive cesium in the body at the time of CLL diagnosis (if available). Absorbed doses for the 4 evacuees from Prypiyat (3.74, 3.87, 4.9, and 5.23 cSv) were reconstructed taking into account date and route of evacuation, date of removal from contaminated territory, and the administration of iodine as a precautionary measure.[40]

The group of 114 IR non-exposed CLL patients consisted of 99 males and 15 females with a median age of 57 years.

IR-exposed controls included 81 clean-up workers of the Chernobyl NPP accident and 22 acute radiation syndrome (ARS) convalescents, 91 males and 12 females with a median age of 59 years. Estimated doses (reconstructed using the abovementioned RADRUE method) were available for 58 clean-up workers (0.10–95.0 cSv, mean 23.59 ± 3.25 cSv, median 16 cSv). Among the ARS convalescents, 14 patients were ARS grade I (estimated doses 100.0–194.0 cSv), 7 were ARS grade II (estimated doses 230.0–390.0 cSv), and one patient was ARS grade III (estimated dose 590 cSv). ARS grades were assigned based on estimated irradiation doses according to the classification system established by Gus'kova and Baisogolov.[41]

Polymorphisms analysis

Blood samples from all study participants were collected

in EDTA-containing tubes. Genomic DNA was extracted from peripheral whole blood with the QIAamp Blood Mini Kit (Qiagen, Crawley, United Kingdom) according to the manufacturer's protocol.

Genotypes were determined using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method according to Seedhouse et al.[42] PCR was performed using 50 ng of genomic DNA in a 30-μL reaction mixture containing 20 mM of MgCl$_2$, 0.2 mM of each dNTP, 1 μM of each primer, and 1 U of Taq DNA polymerase (Applied Biosystems, Foster City, CA, USA) in to the manufacturer's buffer. Primers, annealing temperature, length of amplified fragments, restriction pattern, and restriction enzymes used are listed in Table 1.

After an initial heat-activation step at 95°C for 10 min., the amplification was performed in a 2720 thermal cycler (Applied Biosystems) under the following conditions: denaturation at 95°C for 1 min., annealing at 95°C for 1 min., and elongation at 72°C for 1 min. for a total of 30 cycles, and final extension at 72°C for 10 min. The amplified fragments were digested with appropriate restriction endonucleases. The digested PCR products were resolved on 4% agarose gels containing ethidium bromide and visualized under UV light.

Statistical analysis

Statistical calculations were performed with SPSS for Windows (version 13.0; SPSS Inc., Chicago, IL, USA). Each polymorphism was tested for deviation from the Hardy-Weinberg equilibrium by comparing the observed and expected genotype frequencies using the χ^2 test with one degree of freedom. Differences in distribution of genotypes were tested by the χ^2 or Fisher's exact test as appropriate. All tests were two-sided and considered to be statistically significant with a P-value of ≤ 0.05. Progression-free survival (PFS) was measured from the diagnosis of CLL to disease progression, and overall survival (OS) was measured from the diagnosis of CLL to death or last follow-up visit. PFS and OS were estimated by the Kaplan-Meier method and assessed by the log-rank test.

RESULTS AND DISCUSSION

Several studies suggest an association between DNA repair gene polymorphisms, environmental factors, and the development of several types of cancer. Although one study of survivors of the Hiroshima and Nagasaki nuclear bombings did not reveal an increased risk of CLL, a rare disease in Japan and the Far East,[43] other studies suggest that radiation may contribute to CLL development.[8,10,44–46] For this reason, we were interested in studying CLL in sufferers of the Chernobyl NPP accident. To analyze individual sensitivity to IR, we investigated the distribution of polymorphisms of three DNA repair genes in CLL patients depending on their IR exposure history.

All CLL patients and IR-exposed controls were compared by gender and age, and two groups of CLL patients were also compared by clinical data at diagnosis (Table 2).

Table 3 summarizes the distributions of the selected *XRCC1*, *XRCC3*, and *XPD* polymorphisms in CLL patients and IR-exposed controls. Genotype frequencies in all groups did not differ significantly from those predicted by Hardy-Weinberg equilibrium (P > 0.05) except for the distribution of SNP rs861539 in *XRCC3* in IR-exposed CLL patients (P = 0.04). Our results showed that the *XRCC1*-399Gln, *XRCC3*-241Met, and *XPD*-751Gln variant alleles occurred in IR-exposed controls at a frequency of 0.38, 0.36, and 0.33, respectively. These rates are comparable to those found in other Caucasian populations.[18,47–49]

In IR-exposed controls, the frequencies of the three polymorphisms were not significantly different in clean-up workers and ARS convalescents: for *XRCC1*, P = 0.190; for *XPD*, P = 0.423; and for *XRCC3*, P = 0.111. In IR-exposed CLL

Table 1. Primer sequences, conditions for amplification, restriction pattern, and restriction enzymes used.

Gene, SNP	Primers (forward and reverse)	PCR product, bp; restriction enzyme; restriction pattern, bp
XRCC1, rs25487	5'-TTGTGCTTTCTCTGTGTCCA-3' 5'-TCCTCCAGCCTTTTCTGATA-3'	616; MspI Arg/Arg: 376, 240; Arg/Gln: 616, 376, 240; Gln/Gln: 616
XPD, rs13181	5'-TCAAACATCCTGTCCCTACT-3' 5'-CTGCGATTAAAGGCTGTGGA-3'	344; PstI Lys/Lys: 110, 234; Lys/Gln: 63, 110, 171, 234; Gln/Gln: 63, 110, 171
XRCC3, rs861539	5'-GGTCGAGTGACAGTCCAAAC-3' 5'-CTACCCGCAGGAGCCGGAGG-3'	415; NlaIII Thr/Thr: 141, 274; Thr/Met: 104, 141, 170, 274; Met/Met: 104, 141, 170

Table 2. Baseline characteristics of observed CLL patients and IR-exposed controls.

Characteristics	IR-exposed CLL patients, n = 64	IR non-exposed CLL patients, n = 114	IR-exposed controls, n = 103	P value
Male, n (%)	57 (89.1)	99 (86.8)	91 (88.3)	$P_1 = 0.666$
Female, n (%)	7 (10.9)	15 (13.2)	12 (11.7)	$P_2 = 0.998$
				$P_3 = 0.751$
Age, years, mean ± Std error	57.78 ± 1.09	56.63 ± 0.83	58.16 ± 0.91	$P_1 = 0.408$
				$P_2 = 0.219$
				$P_3 = 0.068$
Binet stage at diagnosis, n (%)				
A	29 (45.3)	46 (40.4)	–	
B	27 (42.2)	45 (39.5)	–	$P_1 = 0.427$
C	8 (12.5)	23 (20.2)	–	
Rai stage at diagnosis, n (%)				
0	9 (14.1)	6 (5.3)	–	
I	18 (28.1)	39 (34.2)	–	
II	27 (42.2)	45 (39.5)	–	$P_1 = 0.109$
III	5 (7.8)	19 (16.7)	–	
IV	5 (7.8)	5 (4.4)	–	

Notes: P_1 - differences between IR-exposed and IR non-exposed CLL patients; P_2 - differences between IR-exposed CLL patients and IR-exposed controls; P_3 - differences between IR non-exposed CLL patients and IR-exposed controls.

Table 3. SNP genotype distribution in CLL patients and IR-exposed controls.

Gene, SNP		IR-exposed controls	All CLL patients		IR-exposed CLL patients		IR non-exposed CLL patients		IR-exposed vs. IR non-exposed CLL patients
		N (%)	N (%)	P value*	N (%)	P value*	N (%)	P value*	P value
XPD, rs13181 (Lys751Gln)	Lys/Lys	47 (45.6)	54 (32.5)	0.097	14 (23.7)	0.018	40 (37.4)	0.431	0.137
	Lys/Gln	44 (42.7)	89 (53.6)		34 (57.6)		55 (51.4)		
	Gln/Gln	12 (11.7)	23 (13.9)		11 (18.6)		12 (11.2)		
	frequency of the polymorphic allele	0.33	0.41	0.074	0.47	0.012	0.37	0.402	0.061
XRCC1, rs25487 (Arg399Gln)	Arg/Arg	38 (40.4)	67 (39.6)	0.541	27 (42.9)	0.881	40 (37.7)	0.496	0.693
	Arg/Gln	41 (43.6)	82 (48.5)		28 (44.4)		54 (50.9)		
	Gln/Gln	15 (16.0)	20 (11.8)		8 (12.7)		12 (11.3)		
	frequency of the polymorphic allele	0.38	0.36	0.751	0.35	0.632	0.37	0.997	0.751
XRCC3, rs861539 (Thr241Met)	Thr/Thr	30 (41.1)	74 (46.5)	0.559	28 (53.8)	0.254	46 (43.0)	0.841	0.312
	Thr/Met	33 (45.2)	60 (37.7)		16 (30.8)		44 (41.1)		
	Met/Met	10 (13.7)	25 (15.7)		8 (15.4)		17 (15.9)		
	frequency of the polymorphic allele	0.36	0.34	0.720	0.31	0.362	0.37	0.974	0.317

*, Comparison with IR-exposed controls.

patients, doses of irradiation did not differ for carriers of different genotypes: for *XRCC1*, P = 0.396; for *XPD*, P = 0.614; and for *XRCC3*, P = 0.692.

We did not find any difference in the distribution of *XRCC1* and *XRCC3* polymorphisms between CLL patients and IR-exposed controls. However, a significant difference was observed for rs13181 in *XPD* between IR-exposed controls and IR-exposed CLL patients; the proportion of the common homozygous Lys/Lys genotype was lower (odds ratio (OR) = 0.37; 95% confidence interval (CI) = 0.18 –

0.75; P = 0.005), and the frequency of carriers of the polymorphic allele was higher (OR = 1.83; 95% CI = 1.15 – 2.91; P = 0.012) in IR-exposed CLL patients. In IR-exposed CLL patients, the number of Lys/Lys *XPD* homozygotes was similar among clean-up workers (23.9%; mean irradiation dose = 23.26 ± 8.01 cSv) and other IR-exposed CLL patients (23.1%; mean irradiation dose = 1.96 ± 0.44 cSv, P = 0.967). There was also a decreased frequency of the common homozygous Lys/Lys *XPD* genotype in IR-exposed CLL patients compared with IR non-exposed CLL patients (23.7% vs 37.4%, P = 0.071). The number of IR-non-exposed CLL patients (37.4%) with the Lys/Lys *XPD* genotype was also decreased compared to IR-exposed controls, although this difference was not significant (P = 0.223).

We have compared the distribution of DNA repair gene polymorphisms to some characteristics of CLL patients, such as the clinical data at the time of diagnosis (stage, initial white blood cell count, size of lymph nodes), response to treatment, OS, PFS, development of autoimmune complications, secondary tumors, and Richter transformation. Only a few associations were revealed. Namely, in CLL patients, there was an increased frequency of Richter transformation in Gln/Gln *XRCC1* homozygotes after the application of 2 or more lines of therapy (Table 4), regardless of whether they had been exposed to radiation.

Disease progression was less severe in CLL patients with the Gln/Gln *XPD* genotype. Gln/Gln *XPD* homozygotes had a longer PFS (medians 96 and 53 months; P = 0.035), a longer response duration after second line therapy (medians 17 and 13 months; P = 0.034), and a tendency to higher rates of OS (medians 137 and 75 months; P = 0.131) compared to other *XPD* genotypes.

Secondary solid tumors were diagnosed in 15 (23.4%) IR-exposed CLL patients compared with 17 (14.9%) IR non-exposed CLL patients (P = 0.155). Among IR-exposed CLL patients, these tumors included basal cell carcinoma (7), prostate cancer (4), urethra cancer (1), melanoma (1), colon cancer (1), and a malignant tumor of the soft tissue of the jaw (1). The spectrum of tumors among IR non-exposed CLL patients included prostate cancer (4), colon cancer (3),

renal cancer (3), stomach cancer (2), basal cell carcinoma (2), lung cancer (1), thyroid cancer (1), and a brain tumor (1). Only the frequency of basal cell carcinoma was different between the two groups of CLL patients (10.9% vs. 2.6%; P = 0.021). Among carriers of the polymorphic 751Gln *XPD* allele, a higher frequency of basal cell carcinoma was found in IR-exposed compared with IR non-exposed CLL patients (15.5% vs 1.5%; P = 0.021) (Table 5).

So, the genotype distribution in IR non-exposed CLL patients was consistent with data from Ganster *et al.*[34] There was a weak tendency towards a decreased number of Lys/Lys *XPD* homozygotes in this group. However, we found a significant reduction in the number of Lys/Lys *XPD* homozygotes (23.7%) and an increase in carriers of the polymorphic 751Gln *XPD* allele (76.3%) among IR-exposed CLL patients compared with IR-exposed controls. The number of Lys/Lys *XPD* homozygotes among IR-exposed CLL patients was also lower in comparison with healthy controls in other studies, for example, 42.6% in Hou *et al.*,[49] and 43.5% in David-Beabes *et al.*[48] Furthermore, IR-exposed CLL patients had an increased frequency of basal cell carcinoma,

Table 4. The frequency of Richter transformation in CLL patients according to *XRCC1* genotypes and treatment.

Treatment	The frequency of Richter transformation, number (%)		P value
	Arg/Arg + Arg/Gln *XRCC1* genotypes	Gln/Gln *XRCC1* genotype	
Non treated, n = 31	0 of 28	0 of 3	–
Applied 1st line therapy, n = 46	1 of 39	0 of 7	–
Applied 2nd line therapy, n = 92	15 of 82 (18.3)	4 of 10 (40.0)	0.109

Table 5. The distribution of secondary solid tumors and SNP genotypes in CLL patients.

Gene, SNP		IR-exposed CLL patients, number			IR non-exposed CLL patients, number			P value
		Basal cell carcinoma	Other solid tumors	Without solid tumors	Basal cell carcinoma	Other solid tumors	Without solid tumors	
XPD, rs13181 (Lys751Gln)	Lys/Lys	0	2	12	1	4	35	0.739
	Lys/Gln + Gln/Gln	7	6	32	1	11	55	0.021
XRCC1, rs25487 (Arg399Gln)	Arg/Arg	4	2	21	1	5	33	0.347
	Arg/Gln + Gln/Gln	3	6	27	1	10	55	0.227
XRCC3, rs861539 (Thr241Met)	Thr/Thr	3	3	22	1	4	41	0.265
	Thr/Met + Met/Met	4	2	18	1	6	54	0.091

and all cases of this tumor arose in carriers of the polymorphic 751Gln *XPD* allele. Ganster *et al.* reported similar results in a subgroup of CLL patients with acquired unfavorable cytogenetic aberrations; the frequency of dominant Lys/Lys *XPD* homozygotes was 23.2% and the frequency of carriers of the polymorphic allele was 76.8% in their study.[34] They concluded that rs13181 in *XPD* and rs25487 in *XRCC1* are associated with reduced DNA repair capacity, which may lead to genetic instability and increase susceptibility to CLL. They further suggested that the impact of these two polymorphisms on disease development could be enforced by environmental factors. Our data are in agreement with this supposition. Based on our preliminary data, it is possible to conclude that persons with altered DNA repair capacity are more sensitive to genotoxic agents and have an increased risk of cancer development, including CLL, and that the role of *XPD* gene polymorphism is intensified under the influence of IR.

The associations of rs25487 in *XRCC1* and rs13181 in *XPD* with unfavorable cytogenetic aberrations (17p and/or 11q deletion) revealed by Ganster *et al.*[34] assume more severe behavior of CLL in carriers with these genotypes. Deletions of 17p and 11q are associated with rapid progression of disease, poor response to therapy, and short survival.[50] Acquisition of *TP53* mutations and/or 17p deletion is a frequent molecular event in Richter transformation.[51] Richter transformation is also associated with microsatellite instability and hypermethylation of the promoter of *hMLH1*, a gene that takes part in the repair of double-strand breaks.[52] Our data concerning the weak association of the Gln/Gln *XRCC1* genotype with Richter transformation in previously treated patients also confirms the role of DNA repair in the development of this CLL complication.

However, we did not find signs of more aggressive CLL behavior in carriers of the polymorphic 751Gln *XPD* allele. Furthermore, some parameters of disease were less severe in Gln/Gln *XPD* homozygotes compared with carriers of other *XPD* genotypes. Similar results were shown by Kuptsova *et al.* in acute myeloid leukemia; patients with the Gln751C/Asp312G *XPD* haplotype were more likely to have a complete response to treatment and less likely to have a resistant disease than patients with other haplotypes.[53]

In summary, we observed a lower frequency of homozygous Lys/Lys *XPD* genotype and an increased number of carriers of the polymorphic 751Gln *XPD* allele in IR-exposed CLL patients compared with IR-exposed controls. Basal cell carcinoma was found mainly in IR-exposed CLL patients who were carriers of the polymorphic 751Gln *XPD* allele. Further studies are required to investigate a possible modifying role of rs13181 in *XPD* for the development of CLL in radiation-exposed persons.

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