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Full Length Research Paper

Polymorphisms of the DNA repair gene XPD (751) and XRCC1 (399) correlates with risk of hematological malignancies in Turkish population

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Polymorphisms that occur in DNA repair genes affect DNA repair capacity and constitute a risk factor in hematological malignancies. This study, was aimed to investigate whether xeroderma pigmentosum complementation group D (XPD) and x-ray repair cross-complementing group 1 (XRCC1) gene polymorphisms were involved in the susceptibility to different hematological malignancies. The genotype and allele frequencies were obtained by analyzing XPD gene codon 751 in a total of 80 patients and XRCC1 gene codon 399 polymorphism in a total of 100 patients with hematological malignancies and 100 healthy controls. Mean age was 45 (range: 16 to 75) and 46 (range: 16 to 82) in the patients groups and 39.5 (range: 18 to 67) in the control group, respectively. Additionally, distribution of genotypes and alleles were compared in the patient and control groups. In the comparison of genotype and allele frequencies in hematological malignancies and healthy controls, XPD-751Gln variant was arranged and compared according to age and sex and Gln/Gln genotype was reported to be a protector, which was decreased significantly in acute myeloblastic leukemia (AML) (p = 0.042). No relationship was determined between allele frequencies (p = 0.054). In XRCC1-399, it was shown that Gln/Gln genotype was decreased significantly in AML (p = 0.014) plus all hematological malignancies (p = 0.033) and that Gln allele was present at a lower ratio in AML (p = 0.046). The distribution of polymorphism of both genes was not statistically significant in terms of age and sex. In leukemia with early relapse, XPD 751 Lys/Lys genotype was determined at a statistically higher ratio (p = 0.042). In the evaluation of both genes together, a decrease was noted in Gln/Gln + Lys/Gln haplotype frequency in hematological malignancies (p = 0.048). In this study, it was demonstrated that a decrease in Gln/Gln genotype and Gln allele acted as a protector in XPD codon 751 and XRCC1 codon 399 polymorphisms in acute myeloblastic leukemia (AML) and that an increase in Lys/Lys genotype in acute leukemia was associated with early relapse.

Key words: DNA repair, XPD gene, XRCC1 gene, DNA, PCR-RFLP.

INTRODUCTION

DNA repair mechanisms have an essential role in genome stability. The polymorphisms in DNA repair genomes resulting from the interaction between gene and the environment increase the tendency of cells to cancer by affecting DNA repair mechanisms. It has been shown in literature that these polymorphisms play an important role in mismatch repair (MMR), DNA repair, nucleotide excision repair (NER) and base excision repair (BER) mechanisms in hematological malignancies (Das-Gupta

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et al., 2000; Pedersen -Bjergaard et al., 2002).

XPD (Xeroderma pigmentosum complementation group D) gene participates in NER and it is in the 13.3th district of Q part in the 19th chromosome. Transcription factor II H is an inferior unit of the basal transcription complex (http://www.ncbi.nlm.nih.gov/gene?term=%20L47234). DNA repair includes a 5'→3' helicase activity dependant on ATP molecule. Several polymorphisms have been identified in the XPD repair gene and the most important of these have been determined in codons 156, 312 and 751. These polymorphisms lead to changes at the amino acid level. The polymorphism in codon 751 transforms into glutamine amino acid. The polymorphisms in XPD gene give information about the capacity of DNA repair and the risk of cancer. Studies have shown that these polymorphisms lead particularly to cancer, xeroderma pigmentosum, cockayne syndrome and various neurological defects (Taylor et al., 1997; Taylor and Lehman, 1998; Kumar et al., 2003). The polymorphisms in XPD-751 gene have been investigated in several diseases. XPD repair gene polymorphisms have been examined especially in colorectal glands and cancers (Yeh et al., 2005; Skjelbred et al., 2006, Artac et al., 2010), breast cancers (Metsola et al., 2005; Shi et al., 2004; Chacko et al., 2005), pancreas cancers (Jiao et al., 2007), bladder cancers (Shen et al., 2003), lung cancers (Hou et al., 2002; Xing et al., 2002; Park et al., 2002 a, b; Gao et al., 2003; Liang et al., 2003; Sreeja et al., 2007), esophageal carcinomas (Yu et al., 2004) and hematological malignancies (Allan et al., 2004; Mehta et al, 2006; Monzo et al., 2006).

XRCC1 (X-ray repair cross-complementing group 1) gene one is of the BER repair genes and is located at the 13.2 district of Q part in chromosome 19. This gene has 17 exons (Chacko et al., 2005) which is essential for the synthesis of DNA proteins including DNA polymerase beta and DNA ligase III and BER and single suture fractures. There are 3 common polymorphisms in XRCC1 DNA repair gene: codon 194 (Arg→Trp), codon 280 (Arg→His) and codon 399 (Arg→Gln) polymorphisms. XRCC1 codon 399 is considered to be protected in the process of evolution. The 399 poly (ADP-ribose) polymerase (PARP) and BRCT (BRCA1 C-end) on the XRCC codon are associated. On the way to BER and PARP is an enzyme in the form of zinc finger causing DNA suture fractures; it also has a great importance in the repair of endogen oxidative DNA damage (Duell et al., 2000; Lei et al., 2002). XRCC1 gene polymorphisms have been investigated in several diseases and tissues. Polymorphisms in XRCC1 repair gene have been examined especially in colorectal cancers (Artac et al., 2010), breast cancers (Duell et al., 2001; Moullan et al., 2003; and Smith et al, 2003a,b), pancreas cancers (Duell et al., 2002), bladder cancer (Stern et al., 2001; 2002), head and neck cancers (Tae et al., 2004), lung cancers (David-Beabes and London, 2001; Park et al., 2002a,b; Sreeja et al., 2007; Kalikaki et al., 2009), prostate cancers (Rybicki et al., 2004), skin cancers (Hemminki et al., 2001). leukocyte diseases (Duell et al., 2000; Qiao et al., 2002) and hematological malignancies (Seedhouse et al., 2002; 2004; Seedhouse and Russell, 2007).

The objective of this study was to compare the polymorphisms in XPD (codon 751) and XRCC1 (codon 399) DNA repair genes in patients with hematological malignancies and healthy individuals using the polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method and to determine other associated clinical parameters.

MATERIALS AND METHODS

Subjects

Ethics committee approval was obtained for the study. A total of 100 patients who had been diagnosed between the dates 1 July, 2004 and 1 June, 2005 by a hematologist with various hematological malignancies including Hodgkin-leukemia (HL), non-Hodgkin lymphoma (NHL), acute myeloblastic leukemia (AML), acute lymphoblastic leukemia (ALL) and multiple myeloma (MM), and 100 healthy individuals (controls) were involved in the study. The mean age was 45 (range: 16 to 75) and 46 (range: 16 to 82) in the patients groups, and 39.5 (range: 18 to 67) in the control group. Blood samples were obtained from all the individuals into tubes with EDTA and DNA extraction was performed in these samples.

Genotyping

DNA was extracted from peripheral blood samples using the Invisorb DNA isolation kit. PCR followed by enzymatic digestion analysis and was used for genotyping of XRCC1 Arg399Gln and XPD Lys751Gln polymorphisms. The XRCC1 Arg399Gln polymorphism, a A →G transversion and the XPD Lys751Gln polymorphism, a A →C transversion in exon 23 were amplified in a 403-bp fragment and in a 324-bp fragment using the following primers: XRCC1-399F 5'-AGTAGTCTGCTGGCT CTGG-3' and XRCC1-399R 5'-TCTCCCTTGGTCTCCAACCT-3'; XPD-751F 5'-ATCCTGTCCCTACTGGCCATTC-3' and XPD-751R 5'-TGTGGA CGTGACAGTGAGAAA-3' with 2 mM/l $MgCl_2$ (Butkiewicz et al., 2001; Yu et al., 2004; Baccaralli et al., 2004). The following thermal cycling conditions were used: PCR initiated by a 4 min denaturation step at 94°C followed by 35 cycles of 94°C for 30 s, 60°C for 30 s, 72°C for 45 s and a final elongation step of 72°C for 7 min. The PCR product was digested with 10 units/µl *MspI* (the restriction site is located at the XRCC1 Arg399Gln allele) and 10 units/µl *PstI* (the restriction site is located at the XPD Lys751Gln allele) at 37°C overnight. Next, the product was resolved using 2% agarose gels. XPD-751 PCR products contained an internal *PstI* site in the 751Lys allele, resulting in 104 and 220-bp long products. In addition, an extra *PstI* site was present in the Gln allele, resulting in 63, 104, and 157-bp long products. The agarose gel displayed results of these are shown in Figure 1. The XRCC1-399 PCR products contained an internal *MspI* site, resulting in 162-, 239-bp long products of 399Arg allele and 401-bp long product of 399Gln allele. The agarose gel display results of these are shown in Figure 2.

Arginine→Glutamine substation in codon 399 in XRCC1 gene polymorphism and Lysine→Glutamine substation in codon 751 of exon 23 in XPD gene polymorphism were genotyped using PCR-RFLP. The frequencies of XPD-751 genotypes Lys/Lys, Lys/Gln, Gln/Gln and XRCC1-399 genotypes Arg/Arg, Arg /Gln, Gln/Gln and allele frequencies in patients and healthy controls were compared.

Statistical analysis

Genotype, allele frequency and haplotype distribution frequencies

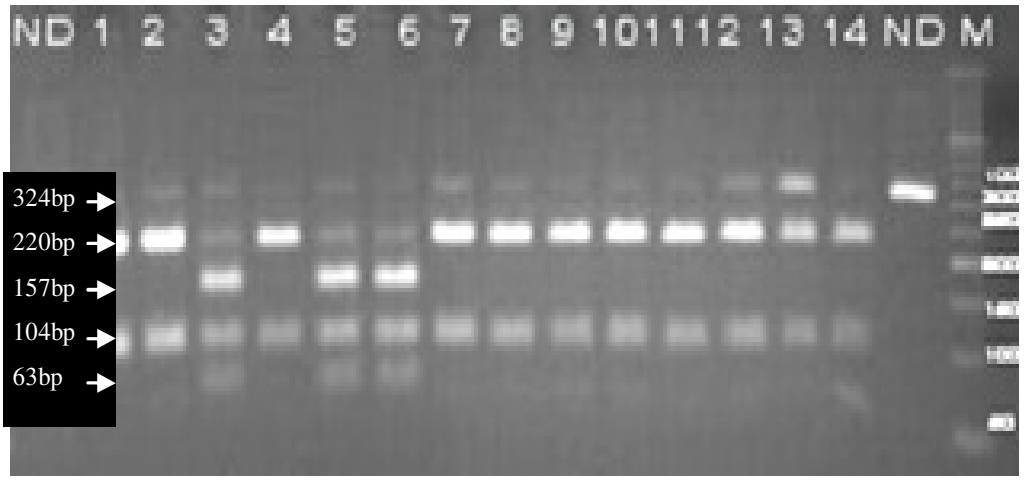

Figure 1. Pst I enzyme cutting of XPD gene codon 751 district. M, marker, ND; uncut PCR product is 1 to 2, 4, 7 to 12; 14 Lys/Lys genotype; 3, 5, 6, Gln/Gln genotype. 13th sample was separated to perform serial DNA analyses.

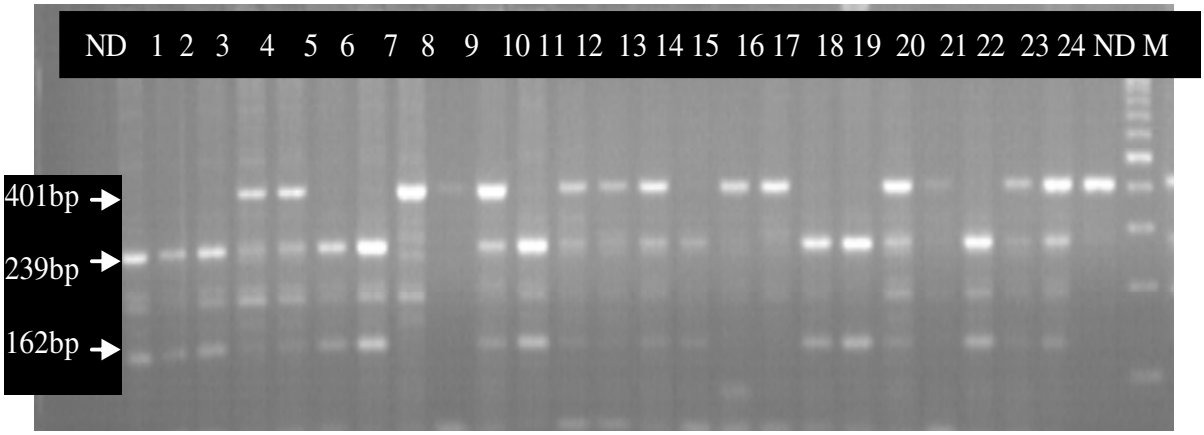

Figure 2. Msp I enzyme cutting of XRCC1-399 district. M, marker ND; uncut PCR product is 1-3, 6, 7, 11, 15, 18, 19, 22; Arg/Arg genotype, 4, 5, 8, 10, 12, 13, 14, 16, 17, 20, 21, 23, 24; Arg/Gln genotype, 9; Gln/Gln genotype.

of XRCC1-399 and XPD-751 polymorphisms were determined in healthy controls and patients with hematological malignancies and chi-square and logistic regression analysis tests (Odds ratios ORs) were performed using SPSS 11.0 statistical program. A confidence interval of 95% and P values < 0.05 were considered statistically significant.

RESULTS

In this study, DNA repair gene XPD-751 and XRCC1-399 polymorphisms were investigated using PCR-RFLP method in patients with hematological malignancies and healthy controls. Demographic features including age, gender and specific type of hematological malignancy are presented in Table 1.

Genotype and allele frequencies are shown in Table 2 according to the results of the analysis of XPD gene codon 751 Gln polymorphism in 80 patients with hematological malignancies including 35 subjects with acute myeloblastic leukemia (AML), 10 subjects with ALL, 15 subjects with acute lymphoblastic leukemia (MM), 4 subjects with Hodgkin-leukemia (HL) and 16 subjects with non-Hodgkin lymphoma (NHL), plus 100 healthy control individuals.

In the comparison of XPD codon 751Gln variant genotype frequency between patients with hematological malignancies and healthy control groups, it was noted that Gln/Gln genotype was infrequent in AML, whereas, frequent in control groups (Table 2). The protective role of Gln/Gln genotype in AML has not been proven statistically. No statistically significant findings were obtained in other hematological malignancies either. No statistically significant relationship was determined between the allele frequencies of patients with hematological

Table 1. The distribution of age, gender and diagnosis in subjects with hematological malignancies and healthy controls.

Parameter	Hematological malignancy	Healthy control group
XPD-751	n=80	n=100
Age	45 (16-75)	39.5 (18-67)
Gender M/F	49/31 (61/39)	70/30
Diagnose		
AML	35	
ALL	10	
MM	15	
HL	4	
NHL	16	
XRCC1-399	N=100	n=100
Age	46 (16-82)	39.5 (18-67)
Gender M/F	54/46	74/26
Diagnose		
AML	36	
ALL	9	
MM	12	
HL	20	
NHL	23	

Table 2. The comparison of XPD variant gene frequency between subjects with hematological malignancies and healthy controls.

XPD	Codon 751	AML n=35 (%)	ALL n=10 (%)	HL n=4 (%)	MM n=15 (%)	NHL n=16 (%)	HMT n=80 (%)	Healthy control group n=100 (%)	P
Genotype	Lys/Lys	18 (51)	4 (40)	4 (100)	9 (60)	7 (44)	42 (52)	41 (41)	0.284 [a]
	Lys/Gln	16 (46)	4 (40)	0	4 (27)	6 (38)	30 (38)	41 (41)	0.627 [a]
	Gln/Gln	1 (2)	2 (20)	0	2 (13)	3 (18)	8 (10)	18 (18)	**0.027[a]**
Allele	Lys	52 (74)	12 (60)	8 (100)	22 (73)	20 (63)	114 (71)	123 (62)	0.071 [a]
	Gln	18 (26)	8 (40)	0 (0)	8 (27)	12 (37)	46 (29)	77 (38)	

A comparison of XPD variant gene frequencies between hematological malignancies and healthy control groups.
AML, Acute myeloid leukemia; ALL, acute lymphoid leukemia; HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; HMT, total of hematological malignancies and healthy controls.

malignancies and healthy control groups (p = 0.71) (Table 2). XPD-751 variant genotype (Gln/Gln) frequencies were 0.02, 0.20, 0.0, 0.13, 0.18, 0.10 for AML, ALL, HL, MM, NHL and HMT, respectively. In contrast, the frequency was 0.18 in the healthy control group. The frequency of normal genotype (Lys/Lys) was 0.51, 0.40, 1.0, 0.60, 0.44, 0.52 for AML, ALL, HL, MM, NHL and HMT, respectively and 0.41 in the control group (Table 2).

The genotype and allele frequencies obtained by analyzing XRCC1 gene codon 399 Gln polymorphism in a total of 100 patients with hematological malignancies and healthy controls are shown in Table 3. In this study, it was demonstrated that XRCC1 codon 399 Gln/Gln genotype was statistically significantly less frequent (p = 0.014; 0.047; 0.003) in AML, NHL and all other hematological malignancies compared with the control group. No significant relationship was determined in allele frequencies (p = 0.063) (Table 3).

Similarly, no statistically significant difference was determined in XPD-751 and XRCC1-399 genotype and allele frequencies in terms of age and gender (Table 4). In the comparison of patients with myeloid and lymphoid malignancies associated with XPD-751 and controls,

Table 3. The comparison of XRCC1 variant gene frequencies between subjects with hematological malignancies and healthy controls.

XRCC1	Codon 399	AML	ALL	HL	MM	NHL	HMT	Healthy control group	P
		n=36 (%)	n=9 (%)	n=20 (%)	n=12 (%)	n=23 (%)	n=100 (%)	n=100(%)	
Genotype	Arg/Arg	19 (53)	3 (33)	6 (30)	5 (42)	9 (39)	42 (42)	42 (42)	0.265 [a]
	Arg/Gln	17 (47)	5 (56)	14 (70)	5 (42)	14 (61)	55 (55)	43 (43)	0.662 [a]
	Gln/Gln	0 (0)	1 (11)	0 (0)	2 (16)	0 (0)	3 (3)	15 (15)	**0.014[a] 0.047[b] 0.003[c]**
Allele	Arg	55 (76)	11 (61)	26 (65)	15 (63)	32 (70)	139 (70)	127 (64)	0.063 [a]
	Gln	17 (24)	7 (39)	14 (35)	9 (37)	14 (30)	61 (30)	73 (36)	

AML: Acute myeloid leukemia, ALL: Acute lymphoid leukemia, HL: Hodgkin lymphoma, MM; Multiple myeloma, NHL: Non-Hodgkin lymphoma, HMT: Total Hematological malignancy and healthy control.
[a], Comparison of XRCC1 variant gene frequencies between hematological malignancies and healthy control groups; [b], comparison of XRCC1 variant gene frequencies between myeloid malignancies and healthy control groups; [c], comparison of XRCC1 variant gene frequencies between lymphoid malignancies and healthy control groups.

Table 4. The comparison of XPD-751 and XRCC1-399 genotypes in terms of age and gender in patients with hematological malignancies, (χ^2), P<0.05.

Parameter	Patients with hematological malignancy					
	Age <40	Age ≥40	P	Male	Female	P
XPD – 751	n=38 (%)	n=42 (%)		n=49 (%)	n=31 (%)	
Lys/Lys	21 (55)	21 (50)	0.638 [x2]	25 (51)	17 (55)	0.739
Lys/Gln	13 (34)	17 (40)	0.563 [x2]	19 (39)	11 (35)	0.767
Gln/Gln	4 (11)	4 (10)	0.881 [x2]	5 (10)	3 (10)	0.939
XRCC1-399	n=62 (%)	n=38 (%)		n=54 (%)	N=46 (%)	
Arg/Arg	25 (40)	16 (42)	0.847 [x2]	19 (35)	23 (50)	0.135
Arg/Gln	35 (56)	20 (53)	0.884 [x2]	32 (59)	22 (48)	0.354
Gln/Gln	2 (4)	2 (5)	0.583 [x2]	3 (6)	1 (2)	0.390

individuals with Gln/Gln genotype were found to be significantly less in number (OR = 0.115[b]; 95% CI = 0.014 to 0.928[b]; p = 0.042[b*]). In other words, it was concluded that the protective Gln/Gln genotype was not present in these individuals (Table 5).

In the comparison of patients with myeloid and lymphoid malignancies associated with XRCC1-399 amino acid changes and controls, it was shown that individuals with heterozygote (Arg/Gln) and homozygote (Gln/Gln) genotype were significantly decreased in number in each one of the malignancies. Parallel to that, it was concluded that Gln/Gln genotype did not have any protective role in these individuals (Arg/Gln, OR = 2.310[c*]; 95% CI= 1.154 to 4.623 [c*]; p = 0.018 [c*]), (Gln/Gln, OR = 0.275[a*]; 95% CI = 0.084 to 0.898 [a*] p = 0.033 [a*]; OR = 0.850[b]; 95% CI = 0.783 to 0.923 [b]; p = 0.014 [b]). In addition, it was found that Gln allele frequency was significantly less in the group of patients with myeloid malignancies (OR = 1.860[b]; 95% CI = 0.749 to 0.788 [b]; p = 0.046 [b]) (Table 6).

Leukemia in early relapse was found to be significantly more frequent in subjects with XPD-751 Lys/Lys genotype in the first 12 months (OR = 13.122*; 95% CI = 1.091 to 157.761*; p = 0.042*) (Table 7).

In the comparison of subjects with haploid XRCC1-399 and XPD-751 genes and controls, a statistically significant relationship was determined between disease and the decrease in the frequency of haploid Gln/Gln + Lys/Lys. It was shown that, the risk of developing a hematological malignancy increased with the number of Gln alleles (OR = 0.932[a]; 95% CI = 0.881 to 0.986[a]; p = 0.048 [a]) (Table 8). No significant difference was determined in other haploids.

DISCUSSION

The mechanisms of BER and NER have been studied in a very detailed manner in breast cancer (Mechanic et al.,

Table 5. The comparison of XPD-751 variant gene genotype and allele frequency between subjects with hematological malignancies, myeloid malignancies, lymphoid malignancies and healthy controls.

XPD-751	Hematological malignancy	Myeloid malignancy (AML)	Lymphoid malignancy (ALL, HL, MM and NHL)	Healthy control group	OR*	95% CI*	p
	n=80 (%)	n=35 (%)	n=45 (%)	n=100 (%)			
Genotype							
Lys/Lys	42 (52)	18 (51)	24 (53)	41 (41)	1.513[a]*	0.830-2.758 [a]*	0.177 [a]*
					1.466[b]*	0.664-3.239 [b]*	0.344 [b]*
					1.513[c]*	0.736-3.111 [c]*	0.261 [c]*
Lys/Gln	30 (38)	16 (46)	14 (31)	41 (41)	0.875[a]*	0.476-1.608 [a]*	0.666 [a]*
					1.317[b]*	0.596-2.912 [b]*	0.496 [b]*
					0.643[c]*	0.302-1.369 [c]*	0.252 [c]*
Gln/Gln	8 (10)	1 (2)	7 (16)	18 (18)	0.543[a]*	0.219-1.346 [a]*	0.188 [a]*
					0.115[b]*	0.014-0.928 [b]*	0.042 [b]*
					1.002[c]*	0.375-2.676 [c]*	0.996 [c]*
Allele							
Lys	114 (71)	52 (74)	62 (69)	123 (62)	0.551[a]	0.994-2.422 [a]	0.053 [a]
Gln	46 (29)	18 (26)	28 (31)	77 (38)	1.808[b]	0.986-3.318 [b]	0.054 [b]
					1.386[c]	0.816-2.354 [c]	0.226 [c]

[a], Comparison of XPD variant gene frequencies between hematological malignancies and healthy control groups; [b], comparison of XPD variant gene frequencies between myeloid malignancies and healthy control groups; [c], comparison of XPD variant gene frequencies between lymphoid malignancies and healthy control groups; * adjusted by age and sex. And adjusted OR (odds ratio) at 95% confidence interval (CI) and $P < 0.05$.

2006), nasopharynx cancer (Yang et al., 2007), gastric cancer (Ruzzo et al., 2007), skin cancers (McCarty et al., 2007), esophageal cancer (Ye et al., 2006), leukemia (Rzeszowska-Wolny et al., 2005), multiple myeloma (Hsieh et al., 2008) and cataract disease (Unal et al., 2007). In this study, the polymorphisms of XPD Lys751 Gln and XRCC1 Arg399Gln genes were analyzed which are nucleotide excision repair and base excision repair genes, respectively, with regard to their protective roles against the development of hematological malignancies.

In hematological malignancies, XPD gene responsible for AML is determined as the allele that encodes glutamine in codon 751 (Smith et al., 2007). Functional disorder in DNA helicase responsible for the NER function results from chemotherapy that leads to DNA defects and replacement of Lys amino acid with glutamine amino acid in XPD gene codon 751. In a study carried out after chemotherapy On AML, it was found that the rate of individuals that recovered from the disease were 44% Lys homozygote subjects (Lys/Lys), 36% heterozygote subjects (Lys/Gln) and 16% glutamine homozygote subjects (Gln/Gln) in one year. Similarly, subjects who died in one year were 38% Lys homozygotes, 35% hete-rozygotes and 23% glutamine homozygotes. Accor-ding to these results, XPD codon-751 glutamine variant significantly increases the risk of development of AML after chemotherapy and it tends to prevent myeloid cell death (Allan et al., 2004). In this study, comparison of myeloid and lymphoid malignancies associated XPD-751 with the control proved that individuals with homozygote Gln/Gln genotype were presented with significantly less myeloid malignancies. In other words, it was suggested that the absence of Gln/Gln genotype had a protective role in these individuals.

There are studies suggesting that Gln/Gln genotype poses a great risk for cancer (Seker et al., 2001). Studies on lung cancer had demonstrated that cancer is higher in individuals with XPD Gln/Gln genotype compared with individuals with XPD-751 Lys/Lys genotype; that is, XPD-751 Gln allele is the risk allele (Hu et al., 2004; De Las Peñas et al., 2006). According to Allan et al. (2004), XPD codon 751 genotype frequencies were recorded as 0.39 for Lys/Lys, 0.48 for Lys/Gln and 0.13 for Gln/Gln in AML patients in the post-chemotherapy period ($p = 0.008$). According to this, it might be suggested that, the presence of at least one Gln variant allele increases the risk of the disease in AML patients. The comparison of XPD codon 751Gln variant genotype frequencies bet-ween subjects with hematological malignancies and healthy individuals showed that Gln/Gln genotype was

Table 6. The comparison of XRCC1-399 variant gene genotype and allele frequency between subjects with hematological malignancies, myeloid malignancies, lymphoid malignancies and healthy controls.

XRCC1-399	Hematological malignancy	Myeloid malignancy (AML)	Lymphoid malignancy (ALL, HL, MM and NHL)	Healthy control group	OR*	95% CI*	p
	n=100 (%)	n=36 (%)	n=64 (%)	n=100 (%)			
Genotype							
Arg/Arg	42 (42)	19 (53)	23 (36)	42 (42)	0.909[a*]	0.504-1.639[a*]	0.752[a*]
					1.496[b*]	0.679-3.293[b*]	0.317[b*]
					0.632[c*]	0.315-1.271[c*]	0.198[c*]
Arg/Gln	55 (55)	17 (47)	38 (59)	43 (43)	1.690[a*]	0.941-3.034[a*]	0.079[a*]
					1.119[b*]	0.509-2.460[b*]	0.780[b*]
					2.310[c*]	1.154-4.623[c*]	0.018[c*]
Gln/Gln	3 (3)	0 (0)	3 (5)	15 (15)	0.275[a*]	0.084-0.898[a*]	0.033[a*]
					0.850[b]	0.783-0.923[b]	0.014[b]
					0.425[c*]	0.126-1.436[c*]	0.168[c*]
Allele							
Arg	139 (70)	55 (76)	84 (66)	127 (64)	1.310[a]	0.864-1.987[a]	0.204[a]
Gln	61 (30)	17 (24)	44 (34)	73 (36)	1.860[b]	0.749-0.788[b]	0.046[b]
					0.967[c]	0.849-1.207[c]	0.888[c]

a, Comparison of XRCC1 variant gene frequencies between hematological malignancies and healthy control groups; b, comparison of XRCC1variant gene frequencies between myeloid malignancies and healthy control groups; c, comparison of XRCC1variant gene frequencies between lymphoid malignancies and healthy control groups. * Adjusted by age and sex, and adjusted OR (odds ratio) at 95 % Confidence interval (CI), $P < 0.05$.

Table 7. The relationship between polymorphisms of XPD-751 and XRCC1-399 in early relapse in leukemia.

Parameter	Early relapse in leukemia in the first 12 months				p
	Present	Absent	OR*	95% CI*	
XPD - 751	n=21 (%)	n=8 (%)			
Lys/Lys	12 (57)	1 (13)	13.122*	1.091-157.761*	0.042*
Lys/Gln	7 (33)	6 (75)	0.090*	0.008-1.054*	0.055*
Gln/Gln	2 (10)	1 (12)	0.508*	0.033-7.841*	0.627*
XRCC-399	n=19 (%)	n=8 (%)			
Arg/Arg	10 (53)	2 (25)	3.607*	0.419-31.034*	0.243*
Arg/Gln	9 (47)	5 (63)	0.277*	0.032-2.385*	0.243*
Gln/Gln	0 (0)	1 (12)	0.857	0.633-1.160	0.093

* Adjusted by age and sex; and adjusted OR (odds ratio) at 95 % confidence interval (CI) and $P < 0.05$.

less frequent in AML, but more frequent in the healthy controls. It was proven that the protective role of Gln/Gln genotype in AML was statistically significant. No other statistically significant findings were determined in sub-groups of the hematological malignancies. It was suggested that, ^{399}Asp and ^{751}Gln haploids possess a 6.9% risk of developing pancreas cancer; similarly, it was found that ^{399}Asp and ^{751}Gln haploids determined in breast cancer and basal cell carcinomas were more com-mon in the patients compared with the healthy controls. Gln/Gln+Lys/Lys haploids were noted in 63.3% of patients with pancreas cancer and 61.5% of healthy controls (Jiao et al., 2007). In this study, a statistically significant relationship was determined between the decrease in the

Table 8. The comparison of XRCC1-399 and XPD-751 haploid analysis; the comparison of genotype and allele frequencies between subjects with hematological malignancies, myeloid malignancies, lymphoid malignancies and healthy controls.

XRCC1-399 + XPD-751	Hematological malignancy	Myeloid malignancy (AML)	Lymphoid malignancy (ALL, HL, MM and NHL)	Healthy control group	OR*	95% CI*	p
	n=55 (%)	n=31 (%)	n=24 (%)	n=88 (%)			
Genotype							
Arg/Arg + Lys/Lys	11 (20)	9 (29)	2 (8)	17 (19)	0.897[a*]	0.371-2.168 [a*]	0.809 [a*]
					1.431[b*]	0.530-3.864 [b*]	0.480 [b*]
					0.373[c*]	0.079-1.749 [c*]	0.211 [c*]
Arg/Arg + Lys/Gln	8 (15)	5 (16)	3 (13)	16 (18)	0.799[a*]	0.313-2.040 [a*]	0.638 [a*]
					1.010[b*]	0.327-3.115 [b*]	0.987 [b*]
					0.618[c*]	0.163-2.353 [c*]	0.481 [c*]
Arg/Arg + Gln/Gln	3 (5)	1 (3)	2 (8)	6 (7)	0.856[a*]	0.203-3.611 [a*]	0.832 [a*]
					0.467[b*]	0.052-4.188 [b*]	0.496 [b*]
					1.272[c*]	0.238-6.784 [c*]	0.779 [c*]
Arg/Gln + Lys/Lys	14 (25)	7 (23)	7 (30)	14 (16)	1.718[a*]	0.743-3.960 [a*]	0.206 [a*]
					1.243[b*]	0.420-3.682 [b*]	0.694 [b*]
					2.177[c*]	0.751-6.308 [c*]	0.152 [c*]
Arg/Gln + Lys/Gln	14 (25)	8 (26)	6 (25)	15 (17)	0.516[a*]	0.101-2.636 [a*]	0.427 [a*]
					1.844[b*]	0.672-5.068 [b*]	0.234 [b*]
					1.571[c*]	0.532-4.644 [c*]	0.414 [c*]
Arg/Gln + Gln/Gln	2 (4)	0 (0)	2 (8)	7 (8)	0.938[a*]	0.161-5.473 [a*]	0.943 [a*]
					0.920[b]	0.866-0.979 [b]	0.106 [b]
					1.188[c*]	0.224-6.304 [c*]	0.840 [c*]
Gln/Gln + Lys/Lys	2 (4)	1 (3)	1 (4)	4 (5)	0.909[a*]	0.504-1.639 [a*]	0.752 [a*]
					0.999[b*]	0.103-9.700 [b*]	0.999 [b*]
					0.934[c*]	0.097-9.018 [c*]	0.953 [c*]
Gln/Gln + Lys/Gln	0 (0)	0 (0)	0 (0)	6 (7)	0.932[a]	0.881-0.986 [a]	0.048 [a]
					0.932[b]	0.881-0.986 [b]	0.136 [b]
					0.932[c]	0.881-0.986 [c]	0.189 [c]
Gln/Gln + Gln/Gln	1 (2)	0 (0)	1 (4)	1 (2)	0.658[a*]	0.064-6.777 [a*]	0.725 [a*]
					0.966[b]	0.929-1.005 [b]	0.298 [b]
					1.542[c*]	0.144-16.558 [c*]	0.721 [c*]

a, Comparison of XRCC1-399 and XPD-751 haplotype frequencies between hematological malignancies and healthy control groups; b, comparison of XRCC1-399 and XPD-751 haplotype frequencies between myeloid malignancies and healthy control groups; **c**, comparison of XRCC1-399 and XPD-751 haplotype frequencies between lymphoid malignancies and healthy control groups.* Adjusted by age and sex, adjusted OR (odds ratio) at 95 % confidence interval (CI) and $P < 0.05$.

frequency of Gln/Gln+Lys/Gln haploids and the increase in the number of Gln allele as well as the risk of developing disease.

Seedhouse et al. (2002) showed that the frequency of Arg homozygote genotype in AML patients was higher compared with healthy controls. They found that Arg homozygotes were in equal proportion; however, Arg/Gln heterozygotes were higher in number in AML group compared with healthy individuals.

XRCC1 Arg399Gln genotype has a protective role in hematological malignancies, especially against the development of AML (Allan et al., 2004). The same effect has also been shown in bladder and skin cancer (Andrew et al., 2008). This important effect has been determined in all XRCC1-399 hematological malignancies and AML. In this study, XRCC1 codon-399 Gln/Gln genotype was found to be statistically significantly less frequent in AML, NHL and the other hematological malignancies compared with the controls. It was concluded that, there was no significant difference in allele frequencies. Moreover, no statistically significant difference was determined between XPD-751 and XRCC1-399 genotype and allele frequencies when compared in terms of age and gender. In terms of XRCC1-399 amino acid changes, subjects with myeloid and lymphoid malignancies were compared with the controls and individuals with heterozygote

(Arg/Gln) and homozygote (Gln/Gln) genotype were significantly less in number in both malignancies. The protective role of Gln/Gln genotype faded with the decrease in the number of Gln/Gln genotypes. Meanwhile, a significant decrease was observed in the number of myeloid malignancies with Gln allele. A considerable difference was determined in the feature of being Gln homozygote in between XRCC1-399 NHL patients and healthy controls. It was thus concluded that, Gln homozygote genotype had a protective role in AML and NHL. The reduction in the disease intensity and the risk of relapse was found to be 70% in the newly diagnosed AML patients after the administration of chemotherapy. Leukemia in early relapse was found to be statistically more common in subjects with XPD-751 Lys/Lys genotype in the first 12 months. Hence, it was demonstrated that individuals with Lys/Lys genotype were at risk of the disease relapse. Comparison of the haploid analysis of subjects with XRCC1-399 and XPD-751 genes with the control group showed that there was no significant difference between the frequency of Gln/Gln+Lys/Lys haploids and the development of the disease. It has been shown that in hematological malignancies, disease risk increased in parallel to the number of Gln allele increases. No statistically significant differences were determined in the other haploids.

In conclusion, relying on the data obtained in this study it can be suggested that XPD variant allele Gln/Gln is associated with a reduced DNA repair capacity and increased leukomogenic risk. At the same time, the protective role of the Gln/Gln genotype in XPD and XRCC1 genes was confirmed. The XRCC1 gene codon 399 and the XPD gene codon 751 polymorphisms were declared to have protective roles in Gln/Gln genotypes in AML. These are possibly associated with the reduced frequency of Gln allele and with early relapse in acute leukemia subjects with Lys/Lys genotype. However, due to the small sample size of this study, further studies are needed to evaluate these associations within acute leukemia and in other populations. XPD and XRCC1 DNA repair genes was studied in terms of their association with the risk of leukemia and disease outcome. Polymorphisms in XPD, a member of nucleotide excision repair pathway and XRCC1 base excision repair pathway, was associated with the development of treatment-related AML and with poor outcome of AML in elderly patients. It can be suggested that, XPD Lys751Gln and XRCC1 Arg399Gln polymorphisms might have a role in the etiology of AML in children as well as in adults which may affect the outcome of childhood AML therapy.

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