EJMI

DOI: 10.14744/ejmi.2020.56831
EJMI 2020;4(3):332–340

Research Article

Clinical Significance of ERCC2, XPC, ERCC5 and XRCC3 Gene Polymorphisms in Diffuse Large B Cell Lymphoma

Aykut Bahceci,[1] Semra Paydas,[2] Melek Ergin,[3] Gulsah Seydaoglu,[4] Gulsum Ucar[5]

[1]Department of Medical Oncology, Dr. Ersin Arslan Training and Research Hospital, Gaziantep, Turkey
[2]Department of Medical Oncology, Cukurova University Faculty of Medicine, Adana, Turkey
[3]Department of Patology, Cukurova University Faculty of Medicine, Adana, Turkey
[4]Department of Biostatistics, Cukurova University Faculty of Medicine, Adana, Turkey
[5]Department of Pediatric Hematology, Cukurova University Faculty of Medicine, Adana, Turkey

Abstract

Objectives: DNA repair genes protects the genome from DNA damage both of endogenous and exogenous stress factors. Due to DNA repair gene polymorphisms, there are differences in the repair capacity between several cancer types. The aim of this study is to evaluate the association between some of the DNA repair gene polymorphisms and clinical outcome in Diffuse Large B-Cell Lymphoma (DLBCL).

Methods: The association between clinical factors including stage at diagnosis, extra-nodal involvement, tumor burden, bone marrow involvement, relapse status, disease-free/overall survival times and DNA repair gene polymorphisms including ERCC2 (Lys751Gln), XPC (Gln939Lys), ERCC5 (Asp1104His) and XRCC3 (Thr241Met) in 58 patients with DLBCL. T-Shift Real-Time PCR was used to detect these mutations.

Results: The median survival times were 60 months and 109 months in patients with CC genotype and CA/AA genotype of XPC gene polymorphism, respectively (p=0.017). More interestingly, median survival times were 9 months and 109 months in patients with CC (XPC)/CC (XRCC3) and CA/AA (XPC)/CT/TT (XRCC3) for both XPC and XRCC3 gene polymorphisms, respectively (p=0.004). Six of 18 patients with CC genotype for XPC (Gln939Lys) had bone marrow involvement while only one of 40 patients with CA and AA genotype of XPC (Gln939Lys) gene polymorphism had bone marrow involvement at diagnosis. Statistical analysis failed to show significant relationship between other gene polymorphisms and survival times. Cox Regression analysis standardized by age, stage and bone marrow involvement showed that IPI, XPC and XRCC3 gene polymorphisms were independent factors for OS.

Conclusion: XPC and XRCC3 gene polymorphisms may be important for clinical presentation and OS in DLBCL. However this study involves relatively low number of cases and these polymorphisms must be studied in larger studies to confirm our results.

Keywords: Diffuse large B cell lymphoma, gene polymorphism, survival

Cite This Article: *Bahceci A, Paydas S, Ergin M, Seydaoglu G, Ucar G. Clinical Significance of ERCC2, XPC, ERCC5 and XRCC3 Gene Polymorphisms in Diffuse Large B Cell Lymphoma. EJMI 2020;4(3):332–340.*

DNA repair mechanisms protects the genome from DNA damage both from endogenous and exogenous factors. Differences of repair capacity have been reported in many types of cancer. Mutations are genetic alterations observed in less than 1% in society but polymorphisms are genetic changes seen in more than 1% in population. [1] The most common type of genetic variation in the human genome is a single nucleotide polymorphism (SNP).[2]

Address for correspondence: Aykut Bahceci, MD. Ersin Arslan Egitim ve Arastirma Hastanesi, Onkoloji Klinigi, 27010 Gaziantep, Turkey
Phone: +90 342 221 07 00 **E-mail:** aykutbahceci@gmail.com

Submitted Date: March 15, 2020 **Accepted Date:** April 28, 2020 **Available Online Date:** June 05, 2020

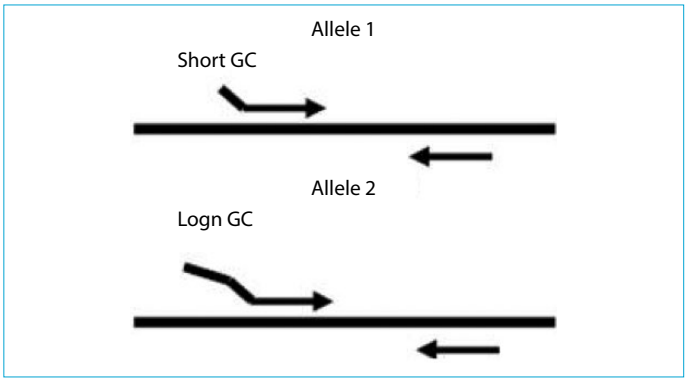

Figure 1. Tm Shift chemistry. Short and long tail added common allele-specific primers and reverse primers.

Functional polymorphisms in DNA repair genes cause differences in the risk of various cancers.[3] DNA lesions that can not be repaired may cause a blockage of transcription and replication and also may cause mutagenesis and/or cellular toxicity. Therefore these genetic changes may cause genomic instability and hereditary diseases, aging and cancer.[4–7] Lymphomas are a group of clinically and biologically distinct heterogeneous family of cancer.[8] The aim of this study is to investigate the association between polymorphisms of some genes involved in DNA repair and clinical course in DLBCL. Here, the association was investigated between clinical outcome and ERCC2 (rs13181), XPC (rs2228001) and ERCC5 (rs17655) gene polymorphisms which are important in nucleotide excision repair and XRCC3 (rs861539) gene polymorphism which is important in the double helix repair.

Methods

Blood samples taken from 58 patients with DLBCL were used in this study at a single institution. Clinical factors including stage at diagnosis, extra-nodal involvement, tumor burden, bone marrow (BM) involvement, relapse status and survival data were analyzed and compared with gene polymorphisms. BM biopsy was taken from all patients at diagnosis.

Local ethics committee of Cukurova University approved the project, and informed consent was obtained from patients.

Method

Collection of samples

5 ml of whole blood enrolled into K3 EDTA tubes from patients and tubes were stored at -20°C.

DNA Isolation

Wizard Genomic Purification Kit (catalog No: A1120) (Promega, Madison, WI, USA) were used for DNA isolation. Tm

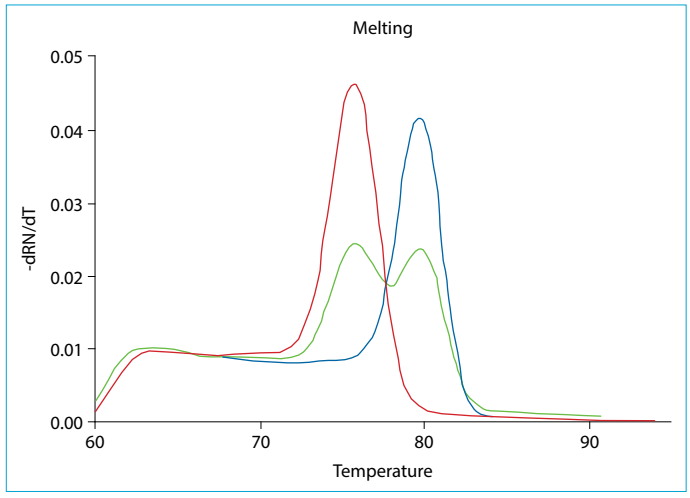

Figure 2. Short and long-tailed primers and amplified DNA samples melting curve analysis.

Shift chemistry, BioMark System (Fluidigm, South San Francisco, CA, USA) and Dynamic Array (Fluidigm, South San Francisco, CA, USA) chip was used to identify mutations. In the design phase of Tm shift chemistry, a short GC nucleotide tail (CGC) was added to one of the alleles and a longer nucleotide tail (TGCCGCCTGCCTGCG) was added to the other alleles. Also a single common reverse primer was designed (Fig. 1). After PCR performed with Melting Curve Analysis; PCR products amplified by the short-tailed primer give low melting point and PCR products amplified by the long-tailed primer give a higher melting point. With this principle, it is determined mutation of DNA samples (Fig. 2).

Statistical Analysis

Student's t test and Mann-Whitney-U tests were used for comparison between groups of continuous variables and Chi-square test was used for comparison of categorical variables. Survival curves were estimated according to the Kaplan-Meier method and log-rank tests and Cox Regression Analyses were used for univariate statistical comparisons. Data were summarized as mean, median, n and percentage. All data were analyzed using SPSS version 20.0 statistics and a p value of <0.05 was considered statistically significant.

Results

The distribution of demographic and clinical characteristics of 58 patients were shown in Tables 1 and 2.

Genotype Frequencies

ERCC2 codon 751 gene: TT genotype was found in 24 cases (42.1%), TG genotype in 25 cases (43.9%) and GG genotype in 8 cases (14%). ERCC2 codon 751 gene mutation analysis could not be performed in 1 patient.

Table 1. Demographic and clinical characteristics of the patients included in the study

	Last status				Total	
	Alive		Exitus			
	n	%	n	%	n	%
Gender						
Male	18	60.0	12	40.0	30	51.7
Female	18	64.3	10	35.7	28	48.3
Smoking						
No	20	66.7	10	33.3	30	53.6
Yes	15	57.7	11	42.3	26	46.4
Stage						
Stage 1	11	73.3	4	26.7	15	27.8
Stage 2	7	58.3	5	41.7	12	22.2
Stage 3	11	64.7	6	35.3	17	31.5
Stage 4	4	40.0	6	60.0	10	18.5
Extranodal involvement						
No	21	61.8	13	38.2	34	58.6
Yes	15	62.5	9	37.5	24	41.4
Bone marrow involvement						
No	33	64.7	18	35.3	51	87.9
Yes	3	42.9	4	57.1	7	12.1
Multipl - Extranodal involvement						
No	33	60.0	22	40.0	55	94.8
Yes	3	100.0	0	0.0	3	5.2
B - symptom						
No	17	70.8	7	29.2	24	45.3
Yes	16	55.2	13	44.8	29	54.7
IPI						
0	12	85.7	2	14.3	14	24.1
1	11	61.1	7	38.9	18	31.0
2	10	50.0	10	50.0	20	34.5
3	3	60.0	2	40.0	5	8.6
5	0	0.0	1	100.0	1	1.7
IPI						
<=1	23	71.9	9	28.1	32	55.2
>1	13	50.0	13	50.0	26	44.8
IPI						
<=2	33	63.5	19	36.5	52	89.7
>2	3	50.0	3	50.0	6	10.3

ERCC5 codon 1104 gene: CC genotype was found in 38 cases (65.5%), CG genotype in 19 cases (32.8%) and GG genotype in 1 case (1.7%).

XPC codon 939 gene: CC genotype was found in 18 cases (31%), CA genotype in 30 cases (51.7%) and AA genotype in 10 cases (16.2%).

XRCC3 codon 241 gene: CC genotype was found in 10 cases (18.5%), CT genotype in 30 cases (55.6%) and TT genotype in 14 cases (23.3%). XRCC3 codon 241 gene mutation analysis could not be performed in 4 patients (Table 2).

The association between BM involvement, B symptoms and gene polymorphisms: Seven patients had BM involvement at diagnosis. There was significant association between ERCC5 and XPC gene polymorphism and BM involvement. Statistical analysis failed to show significant association between B symptoms and 4 DNA repair genes (Table 3).

Median survival rates according to risk factors have been shown in Table 4. XPC gene polymorphism and XPC + XRCC3 gene polymorphisms have been found to be associated with prognosis. The median survival time was 60

Table 2. Genotype distributions based on prognosis of patients included in the study

			Last status					
			Alive		Exitus		Total	
			n	%	n	%	n	%
ERCC2	TT		14	58.3	10	41.7	24	42.1
	TG		16	64	9	36	25	43.9
	GG		5	62.5	3	37.5	8	14
ERCC2	TT		14	58.3	10	41.7	24	42.1
	TG + GG		21	63.6	12	36.4	33	57.9
ERCC5								
	CC		26	68.4	12	31.6	38	65.5
	CG		10	52.6	9	47.4	19	32.8
	GG		0	0	1	100	1	1.7
ERCC5	CC		26	68.4	12	31.6	38	65.5
	CG + GG		10	50	10	50	20	34.5
XPC	CC		8	44.4	10	55.6	18	31
	CA		22	73.3	8	26.7	30	51.7
	AA		6	60	4	40	10	17.2
XPC	CC		8	44.4	10	55.6	18	31
	CA + AA		28	70	12	30	40	69
XRCC3	CC		5	50	5	50	10	18.5
	CT		19	63.3	11	36.7	30	55.6
	TT		9	64.3	5	35.7	14	25.9
XRCC3	CC		5	50	5	50	10	18.5
	CT + TT		28	63.6	16	36.4	44	81.5
	ERCC2	ERCC5						
ERCC2 + ERCC5								
(TT–TG–GG) + (CC–CG–GG)	TT	CC	10	66.7	5	33.3	15	25.9
	TT	G allele	22	64.7	12	35.3	34	58.6
	G allele	CC						
	GG	GG	4	44.4	5	55.6	9	15.5
ERCC2 + ERCC5	TT	CC	10	66.7	5	33.3	15	25.9
	TT	G allele	26	60.5	17	39.5	43	74.1
	G allele	CC						
	GG	GG						
	XPC	XRCC3						
XPC + XRCC3								
(CC-CA-AA) + (CC-CT-TT)	CC	CC	1	20	4	80	5	8.6
	CA	T allele	14	66.7	7	33.3	21	36.2
	A allele	CC						
	AA	TT	21	65.6	11	34.4	32	55.2
XPC + XRCC3	CC	CC	1	20	4	80	5	8.6
	CA	T allele	35	66	18	34	53	91.4
	A allele	CC						
	AA	TT						
	XRCC3	ERCC2						
XRCC3 + ERCC2								
(CC-CT-TT) + (TT–TG–GG)	CC	TT	4	50	4	50	8	13.8
	CT	G allele	15	62.5	9	37.5	24	41.4
	T allele	TT						
	TT	GG	17	65.4	9	34.6	26	44.8
XRCC3 + ERCC2	CC	TT	4	50	4	50	8	13.8
	CT	G allele	32	64	18	36	50	86.2
	T allele	TT						
	TT	GG						
Last status	Live		31	100	0	0	31	53.4
	Live + Relapse		5	100	0	0	5	8.6
	Exitus		0	0	6	100	6	10.3
	Exitus + Relapse		0	0	16	100	16	27.6

Table 3. Distribution of gene polymorphisms of ERCC2, XPC, ERCC5 and XRCC3 according to Bone marrow involvement and B symptoms

	Bone marrow involvement					B Symptom				
	No	Yes		Total		No	Yes		Total	
	n	n	%	n	%	n	n	%	n	%
ERCC2										
TT	22	2	28.6	24	41.4	13	9	31.0	22	37.9
TG	21	4	57.1	25	43.1	8	14	48.3	22	37.9
GG	7	1	14.3	8	13.8	2	6	20.7	8	13.8
ERCC5										
CC	35	3	42.9	38	65.5	15	19	65.5	34	58.6
CG	16	3	42.9	19	32.8	9	9	31.0	18	31.0
GG	0	1	14.3*	1	1.7	0	1	3.4	1	1.7
XPC										
CC	12	6	85.7	18	31.0	6	9	31.0	15	25.9
CA	29	1	14.3	30	51.7	16	12	41.4	28	48.3
AA	10	0	0.0*	10	17.2	2	8	27.6	10	17.2
XRCC3										
CC	8	2	28.6	10	17.2	4	4	13.8	8	13.8
CT	28	2	28.6	30	51.7	11	19	65.5	30	51.7
TT	11	3	42.9	14	24.1	5	6	20.7	11	19.0

*p<0.05.

months in patients with CC genotype of XPC gene polymorphism while 109 months in patients with CA or AA genotype (p=0.017). When we evaluated XPC and XRCC3 gene co-polymorphisms we found that median survival time was only 9 months in patients with CC (XPC) and CC (XRCC3) gene polymorphism for two genes but 109 months in patients with CA/AA (XPC) and CT / TT (XRCC3) gene polymorphisms (p=0.004). Statistical analysis failed to show significant association between other gene polymorphisms and survival rates. According to the Cox Regression analysis standardized by age, stage and BM involvement we found that IPI, XPC and XRCC3 gene polymorphisms were found to be independent factors for OS.

Two Cox regression models were applied to determine independent factors for OS. In first model; XPC, XRCC3, ERCC2 and ERCC5 gene mutations were individually introduced to models. CA and AA genotype of the XPC gene was identified as a good prognostic factor and was found to be associated with longer OS (OR: 0.27, 95%CI: 0.08-0.86, p=0.027) (Table 5). CC genotype of XPC gene has been identified as a poor prognostic factor and was found to be associated with shorter OS (OR: 3.63, 95%CI: 1.15-11.41, p=0.027).

Discussion

DNA repair system has important role in carcinogenesis. [6,9] Gene polymorphisms involved in DNA repair system lead to variation in DNA repair and they can change the sensitivity of individuals to cancer.[10,11] In previous studies it has been shown variable associations between polymorphisms in DNA repair genes and susceptibility to several types of cancer.[12–19] In this study, we aimed to evaluate to association between ERCC2, XPC, ERCC5 (involved in nucleotide excision repair) gene polymorphisms and XRCC3 (involved in the repair of double-stranded) gene polymorphism with presentation and clinical outcome of 58 patients with DLBCL.

Polymorphic alleles in genes involved in DNA repair are variable in different populations and in cancer types. The differences for prevalence in cancer types in different populations may be due to the polymorphisms in DNA repair genes. Similarly, changes in response to similar treatments in different ethnic groups may be related with polymorphisms in DNA repair genes.

XPC protein allows early recognition of damage and introduction of a nucleotide excision repair.[20,21] Polymorphism in DNA repair genes can change the capacity of organism in recognition of DNA damage and repair process. XPC Lys939Gln polymorphism results change in the glutamine instead of lysine at codon 939. XPC Lys939Gln polymorphism has been investigated in many cancers such as skin, lung, colorectal and bladder cancer and has been found to be associated with increased risk of cancer.[16,22–26] In our study, 18 of 58 patients had CC genotype for XPC Lys939Gln and 6 of these 18 patients had BM involvement

Table 4. The average overall survival and disease-free survival and median overall survival according to risk factors

	Exitus/Alive n/n	% of Alive	Overall survival (OS)			Desease free survival (DFS)		
			Mean (Month)	Medyan (Month)	p*	Mean (Month)	Medyan (Month)	p*
Stage								
Stage 1	4/11	73.3	85.8	–		84.5	–	
Stage 2 + 3	11/18	62.1	79.8	94.0		77.4	88.0	
Stage 4	6/4	40.0	49.6	60.0	0.150	38.5	33.0	0.150
Stage								
Stage 1 - 2	9/18	66.7	82.2	115.0		80.7	115.0	
Stage 3 - 4	12/15	55.6	63.4	70.0	0.238	58.6	87.0	0.454
Involvement								
Nodal	13/21	61.8	78.9	94.0		73.4	88.0	
Extranodal	9/15	62.5	77.4	73.0	0.748	74.3	115.0	0.782
Bone marrow involvement								
No	18/33	64.7	81.6	109.0		77.4	88.0	
Yes	4/3	42.9	49.8	56.0	0.069	74.3	115.0	0.782
IPI								
<=1	9/23	71.9	90.5	115.0		85.6	115.0	
>1	13/13	50.0	59.6	87.0	0.023	55.8	87.0	0.089
ERCC2								
TT	10/14	58.3	74.9	94.0		66.2	88.0	
TG	9/16	64.0	80.6	87.0	0.704	79.4	87.0	0.627
GG	3/5	62.5	59.5	73.0	0.921	54.1	–	0.022
ERCC2								
TT	10/14	58.3	74.9	94.0		66.2	88.0	
TG + GG	12/21	63.6	78.4	87.0	0.773	77.2	87.0	0.496
ERCC5								
CC	12/26	68.4	83.6	109.0		80.7	115.0	
CG	9/10	52.6	63.2	87.0	0.230	57.1	87.0	0.213
GG	1/0	0.0	56.0	56.0	0.133	16.0	16.0	0.109
ERCC5								
CC	12/26	68.4	83.6	109.0		80.7	115.0	
CG + GG	10/10	50.0	62.7	87.0	0.177	54.0	87.0	0.140
XPC								
CC	10/8	44.4	58.0	60.0		54.3	33,0	
CA	8/22	73.3	87.4	94.0	0.015	81.5	88.0	0.026
AA	4/6	60.0	93.9	109.0	0.218	85.3	115.0	0.283
XPC								
CC	10/8	44.4	58.0	60.0		54.3	33.0	
CA + AA	12/28	70.0	88.5	109.0	0.017	82.8	88.0	0.028
XRCC3								
CC	5/5	50.0	58.3	70.0		57.7	68.0	
CT	11/19	63.3	83.4	109.0	0.437	76.7	87.0	0.322
TT	5/9	64.3	70.5	94.0	0.420	63.9	88.0	0.381
XRCC3								
CC	5/5	50.0	58.3	70.0		57.7	68.0	
CT + TT	16/28	63.6	80.6	94.0	0.429	75.6	88.0	0.564
ERCC2 + ERCC5								
ERCC2 ERCC5								
TT CC	5/10	66.7	83.4	109.0		68.6	–	

Table 4 (cont). The average overall survival and disease-free survival and median overall survival according to risk factors

		Exitus/Alive n/n	% of Alive	Overall survival (OS)			Desease free survival (DFS)		
				Mean (Month)	Medyan (Month)	p*	Mean (Month)	Medyan (Month)	p*
TT	G allele	12/22	64.7	80.1	94.0	0.848	78.8	88.0	0.720
G allele	CC								
GG	GG	5/4	44.4	53.6	56.0	0.172	46.1	16.0	0.520
ERCC2 + ERCC5									
TT	CC	5/10	66.7	83.4	109.0		68.6	–	
TT	G allele	17/26	60.5	75.5	87.0	0.588	73.5	88.0	0.926
G allele	CC								
GG	GG								
XPC + XRCC3									
XPC	XRCC3								
CC	CC	4/1	20.0	31.0	9.0		30.2	9.0	
CA	T allele	7/14	66.7	79.8	.	0.077	78.9	–	0.093
A allele	CC								
AA	TT	11/21	65.6	84.9	94.0	0.001	78.9	88.0	0.007
XPC + XRCC3									
CC	CC	4/1	20.0	31.0	9.0		30.2	9.0	
CA	T allele	18/35	66.0	82.7	109.0	0.004	78.2	88.0	0.013
A allele	CC								
AA	TT								
XRCC3 + ERCC2									
CC	TT	4/4	50.0	60.1	9.0		60.1	9.0	
CT	G allele	9/15	62.5	77.2	94.0	0.650	61.9	68.0	0.453
T allele	TT								
TT	GG	9/17	65.4	82.2	87.0	0.397	80.8	115.0	0.308
XRCC3 + ERCC2									
CC	TT	4/4	50.0	60.1	9.0		60.1	9.0	
CT	G allele	18/32	64.0	79.7	94.0	0.591	75.1	88.0	0.372
T allele	TT								
TT	GG								

P *Log Rank Test.

Table 5. Results of two cox regression models

Model 1			Model 2		
	OR (95% CI)	p		OR (95% CI)	p
Age	0.99 (0.95–1.03)	0.665	Age	0.99 (0.96–1.03)	0.968
Stage (3 or 4)	1.43 (0.43–4.78)	0.555	Stage (3 or 4)	1.14 (0.36–3.52)	0.820
Bone marrow involvement (+)	1.02 (0.20–5.19)	0.977	Bone marrow involvement (+)	1.34 (0.30–5.89)	0.699
IPI (>1)	2.16 (0.68–6.81)	0.187	IPI (>1)	4.43 (1.32–14.84)	0.016
XPC (AA)	0.27 (0.08–0.86)	0.027	Co-expression of XPC and XRCC3 (At least one mutant)	0.13 (0.29–0.58)	0.008
XRCC3 (TT)	0.67 (0.21–2.11)	0.508			
ERCC2 (GG)	0.77 (0.29–2.06)	0.615	Co-expression of ERCC2 and ERCC5 (At least one mutant)	0.89 (0.30–2.84)	0.896
ERCC5 (GG)	1.40 (0.48–4.12)	0.539			

OR: Odds ratios; CI: Confidence interval.

while only one of 40 patients with CA and AA genotype of XPC gene had BM involvement in first presentation. This finding suggests that XPC gene polymorphism may have a protective effect against BM involvement. Two Cox regression models were applied to determine independent factors affecting total survival and this model showed that AA genotype of the XPC gene is an independent factor that is associated with longer overall survival (OR:0.27, 95%CI: 0.08-0.86, p=0.027).

Studies showing gene polymorphism and clinical outcome is relatively limited in lymphomas. In our previous study we showed the protective effect of ERCC5 Asp1104His polymorphism in B cell lymphomas and this effect was found to be more prominent in the male sex. Also, AA genotype of XPC gene in non-smoker group was found to be protective from the disease.[27]

It has been shown that glutathione S-transferase (GST) variant genotypes are unsuccessfull in detoxifying the carcinogenes and drug metabolites and these patients are more susceptible to the development of some cancers. [28] GST polymorphisms in breast cancer has been studied and GG genotype and G allele for GSTP1 rs1695 gene have been found to be associated with poor response to chemotherapy and longer OS in patients with G allele compared to patients who had not G allele.[28]

The presence of GSTM1 / GSTT1 genotype has been found to be associated with poor response to chemotherapy.[29] Whereas in a trial from India failed to show relationship between GST and response to chemotherapy.[30] In another trial from China it has been found an association between GSTP1 Val/Val genotypes, absence of GSTM1 genotype and response to chemotherapy and survival time in breast cancer.[31] In these trials, inconsistent and contradictory data may be associated with ethnic differences, cancer type, stage of disease, variable exposure to carcinogenes in various populations, the combination of sensitivity variants or most importantly the number of patients in these studies.

The limitations of our study is the relatively small number of patients and also the retrospective nature of study.

In conclusion; DNA repair gene polymorphisms change the function of proteins and this may cause to some diseases and also different response to therapy and clinical outcome in these diseases. DNA repair gene polymorphisms may be a prognostic and may be helpful in the design of individualized treatment. Therefore more studies are needed in order to better determine the relationship between polymorphisms of these genes and diseases.

Disclosures

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the committee of Cukurova University (meeting number: 7-30.06.2009).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that they have no conflict of interest.

Authorship Contributions: Concept – A.B., S.P.; Design – A.B., S.P.; Supervision – A.B., S.P.; Materials – A.B., S.P.; Data collection and/or processing – A.B., S.P., M.E., G.S., G.U.; Analysis and/or interpretation – A.B., S.P., G.S.; Literature search – A.B.; S.P.; Writing – A.B., S.P.; Critical review – A.B., S.P.

Financial Disclosure: This work was supported by the Cukurova University Research Fund (TF2010LTP24) and Turkish Medical Oncology Society.

References

1. Risch NJ. Searching for genetic determinants in the new millennium. Nature 2000;405:847–56.
2. Carlson CS, Eberle MA, Rieder MJ, Smith JD, Kruglyak L, Nickerson DA. Additional SNPs and linkage-disequilibrium analyses are necessary for whole-genome association studies in humans. Nature genetics 2003;33:518–21.
3. Hu JJ, Mohrenweiser HW, Bell DA, Leadon SA, Miller MS. Symposium overview: genetic polymorphisms in DNA repair and cancer risk. Toxicology and applied pharmacology. 2002;185:64–73.
4. Peltomaki P. DNA mismatch repair and cancer. Mutation research 2001;488:77–85.
5. Friedberg EC. DNA damage and repair. Nature 2003; 421:436–40.
6. Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. Nature 2001;411:366–74.
7. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature 2000;408:239–47.
8. Testoni M, Zucca E, Young KH, Bertoni F. Genetic lesions in diffuse large B-cell lymphomas. Annals of oncology: official journal of the European Society for Medical Oncology / ESMO. 2015.
9. Papaefthymiou MA, Giaginis CT, Theocharis SE. DNA repair alterations in common pediatric malignancies. Medical science monitor: international medical journal of experimental and clinical research 2008;14:RA8–15.
10. Krajinovic M, Labuda D, Mathonnet G, et al. Polymorphisms in genes encoding drugs and xenobiotic metabolizing enzymes, DNA repair enzymes, and response to treatment of childhood acute lymphoblastic leukemia. Clinical cancer research: an official journal of the American Association for Cancer Research

2002;8:802–10.
11. Goode EL, Ulrich CM, Potter JD. Polymorphisms in DNA repair genes and associations with cancer risk. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2002;11:1513–30.
12. De Ruyck K, Szaumkessel M, De Rudder I, et al. Polymorphisms in base-excision repair and nucleotide-excision repair genes in relation to lung cancer risk. Mutation research 2007;631:101–10.
13. Shen M, Purdue MP, Kricker A, et al. Polymorphisms in DNA repair genes and risk of non-Hodgkin's lymphoma in New South Wales, Australia. Haematologica 2007;92:1180–5.
14. Joseph T, Kusumakumary P, Chacko P, Abraham A, Pillai MR. DNA repair gene XRCC1 polymorphisms in childhood acute lymphoblastic leukemia. Cancer letters 2005;217:17–24.
15. Pakakasama S, Sirirat T, Kanchanachumpol S, et al. Genetic polymorphisms and haplotypes of DNA repair genes in childhood acute lymphoblastic leukemia. Pediatric blood & cancer 2007;48:16–20.
16. Rouissi K, Bahria IB, Bougatef K, et al. The effect of tobacco, XPC, ERCC2 and ERCC5 genetic variants in bladder cancer development. BMC cancer 2011;11:101.
17. Ritchey JD, Huang WY, Chokkalingam AP, et al. Genetic variants of DNA repair genes and prostate cancer: a population-based study. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2005;14:1703–9.
18. Sobti RC, Singh J, Kaur P, Pachouri SS, Siddiqui EA, Bindra HS. XRCC1 codon 399 and ERCC2 codon 751 polymorphism, smoking, and drinking and risk of esophageal squamous cell carcinoma in a North Indian population. Cancer genetics and cytogenetics 2007;175:91–7.
19. Duell EJ, Millikan RC, Pittman GS, et al. Polymorphisms in the DNA repair gene XRCC1 and breast cancer. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2001;10:217–22.
20. Thoma BS, Vasquez KM. Critical DNA damage recognition functions of XPC-hHR23B and XPA-RPA in nucleotide excision repair. Molecular carcinogenesis 2003;38:1–13.
21. de Laat WL, Jaspers NG, Hoeijmakers JH. Molecular mechanism of nucleotide excision repair. Genes & development 1999;13:768–85.
22. Blankenburg S, Konig IR, Moessner R, et al. Assessment of 3 xeroderma pigmentosum group C gene polymorphisms and risk of cutaneous melanoma: a case-control study. Carcinogenesis 2005;26:1085–90.
23. Vogel U, Overvad K, Wallin H, Tjonneland A, Nexo BA, Raaschou-Nielsen O. Combinations of polymorphisms in XPD, XPC and XPA in relation to risk of lung cancer. Cancer letters 2005;222:67–74.
24. Jin B, Dong Y, Zhang X, Wang H, Han B. Association of XPC polymorphisms and lung cancer risk: a meta-analysis. PloS one 2014;9:e93937.
25. Wu Y, Jin M, Liu B, et al. The association of XPC polymorphisms and tea drinking with colorectal cancer risk in a Chinese population. Molecular carcinogenesis 2011;50:189–98.
26. Dou K, Xu Q, Han X. The association between XPC Lys939Gln gene polymorphism and urinary bladder cancer susceptibility: a systematic review and meta-analysis. Diagnostic pathology 2013;8:112.
27. Bahceci A, Paydas S, Tanriverdi K, Ergin M, Seydaoglu G, Ucar G. DNA repair gene polymorphisms in B cell non-Hodgkin's lymphoma. Tumour biology: the journal of the International Society for Oncodevelopmental Biology and Medicine. 2014.
28. Liu J, Luo J, Wang Y, Li L, Yang S. Predictive potential role of glutathione S-transferases polymorphisms on prognosis of breast cancer. International journal of clinical and experimental pathology 2014;7:8935–40.
29. Tulsyan S, Chaturvedi P, Agarwal G, et al. Pharmacogenetic influence of GST polymorphisms on anthracycline-based chemotherapy responses and toxicity in breast cancer patients: a multi-analytical approach. Molecular diagnosis & therapy 2013;17:371–9.
30. Mishra A, Chandra R, Mehrotra PK, Bajpai P, Agrawal D. Glutathione S-transferase M1 and T1 polymorphism and response to neoadjuvant chemotherapy (CAF) in breast cancer patients. Surgery today. 2011;41:471–6.
31. Bai YL, Zhou B, Jing XY, et al. Predictive role of GSTs on the prognosis of breast cancer patients with neoadjuvant chemotherapy. Asian Pacific journal of cancer prevention: APJCP 2012;13:5019–22.