Mol Biol Rep (2012) 39:6995–7001
DOI 10.1007/s11033-012-1529-8

DNA repair XRCC1 Arg399Gln polymorphism is associated with the risk of development of end-stage renal disease

Sinan Trabulus · Gulgun S. Guven · Mehmet R. Altiparmak · Bahadir Batar · Ozlem Tun · Ayse S. Yalin · Aydin Tunckale · Mehmet Guven

Received: 19 October 2011 / Accepted: 24 January 2012 / Published online: 3 February 2012

Abstract Patients with end-stage renal disease (ESRD) display enhanced genomic damage. DNA repair gene polymorphisms may affect DNA repair capacity and modulate susceptibility to ESRD. In this study, we aimed to determine the frequency of polymorphisms in two DNA repair enzyme genes, Xeroderma pigmentosum complementation group D (XPD) and X-ray cross-complementing group 1 (XRCC1), in patients with ESRD and to evaluate their association with ESRD development. By using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP), we genotyped four single nucleotide polymorphisms (SNPs) in *XPD* codons 312 and 751 and *XRCC1* codons 194 and 399 in 136 dialysis patients (71 patients undergoing hemodialysis and 65 subjected to peritoneal dialysis) and 147 healthy controls. Patients having *XRCC1* 399 *Arg/Gln* (OR:1.98; 95% CI: 1.21–3.25, $P = 0.007$) or *XRCC1*-399 *Gln/Gln* (OR: 3.95; 95% CI: 1.45–10.76, $P = 0.005$) genotype had a significantly higher risk of ESRD than those with *XRCC1* 399 *Arg/Arg* genotype. We also found a significantly higher frequency of the *XRCC1 399Gln* allele in patients with ESRD than in controls, with OR = 2.03 (95% CI = 1.08–3.81, $P = 0.03$). We further investigated the potential combined effect of these DNA repair variants on the risk of ESRD development. It was found that combination of the *Arg/Gln* or *Gln/Gln* genotypes of *XRCC1 Arg399Gln* polymorphism with the two possible genotypes of *XPD-Asp312Asn* or with the *Lys/Gln* or *Gln/Gln* genotypes of *XPD Lys751Gln* was significantly associated with the development of ESRD. This is the first report showing an association between DNA repair gene polymorphisms and ESRD development, and suggests that *XRCC1 Arg399Gln* polymorphism may confer increased risk for the development of the disease. Further larger studies should be conducted to confirm these results.

Keywords XPD · XRCC1 · Dialysis · Polymorphism

Introduction

Patients with end-stage renal disease (ESRD) display enhanced genomic damage [1]. If genomic damage is left unrepaired or is repaired with errors, mutations of critical genes may occur and may result in an enhanced cancer risk. Genomic damage may also be involved in initiation as well as progression of cardiovascular diseases [2]. End-stage renal disease is associated with a high incidence of cancers and cardiovascular diseases [3, 4]. Among the several pathogenic mechanisms suggested to explain these phenomena there are uremia per se, micro inflammation and oxidative stress [5, 6], which involves the whole cell structure (proteins, membrane lipids, carbohydrates and DNA) [7]. Oxidative stress is enhanced in patients with

S. Trabulus · M. R. Altiparmak
Department of Internal Medicine, Division of Nephrology, Istanbul University, Cerrahpasa Medical Faculty, Istanbul, Turkey

G. S. Guven
Department of Medical Genetics, Istanbul University, Cerrahpasa Medical Faculty, Istanbul, Turkey

B. Batar · O. Tun · M. Guven (✉)
Department of Medical Biology, Istanbul University, Cerrahpasa Medical Faculty, Istanbul, Turkey
e-mail: mgguven@istanbul.edu.tr; mguven66@gmail.com

A. S. Yalin · A. Tunckale
Department of Internal Medicine, Istanbul University, Cerrahpasa Medical Faculty, Istanbul, Turkey

ESRD [8]. It has been reported that oxidative stress can induce DNA damage, such as base modifications and strand breaks [9, 10].

DNA repair enzymes continuously monitor chromosomes to correct damaged nucleotide residues generated by exposure to cytotoxic compounds or carcinogens. Repair of oxidative DNA damage is mediated by both base excision repair (BER) and nucleotide excision repair (NER) mechanisms. It has been hypothesized in many studies that polymorphisms in DNA repair genes reduce their capacity to repair DNA damage and thereby lead to increased cancer or other disease susceptibility [11, 12]. Although hundreds of polymorphisms in DNA repair genes have been identified, their effects on repair function have not been well characterized.

Xeroderma pigmentosum complementation group D (XPD) encodes a helicase, which participates in both NER and basal transcription as part of the transcription factor IIH. Because XPD is important in multiple cellular tasks and rare *XPD* mutations result in genetic diseases, *XPD* polymorphisms may operate as genetic susceptibility factors. Several single nucleotide polymorphisms (SNPs) in *XPD* gene exons have been identified, of them *Asp312Asn* and *Lys751Gln* polymorphisms are the most common [13]. *XPD Asp312Asn* in exon 10 causes an amino acid substitution in a conserved region of XPD. *XPD Lys751Gln* in exon 23 also causes an amino acid substitution in the C-terminal part of the protein [13, 14]. These polymorphisms may produce the most relevant change in XPD function and affect different protein interactions, diminish the activity of TFIIH complexes, influence DNA repair capacity, and alter the genetic susceptibility for diseases [14, 15].

X-ray cross-complementing group 1 (XRCC1), a DNA repair protein involved in single-strand breaks and BER pathway, has been reported to be responsible for the efficient repair of DNA damage caused by active oxygen, ionization, and alkylating agents [16]. It is a multidomain protein that interacts with the nicked DNA and participates with at least three different enzymes, poly-ADP-ribose polymerase (PARP), DNA ligase III, and DNA polymerase β, to repair single-strand breaks [16]. Three coding polymorphisms were identified in the *XRCC1* gene at the codons 194 (Arg to Trp), 280 (Arg to His), and 399 (Arg to Gln) [13]. Whereas the functional effects of these polymorphisms in *XRCC1* have not been well known, amino acid changes at evolutionary conserved regions may alter its function. Two polymorphisms: *Arg194Trp* and *Arg399Gln* have been widely studied in the literature.

No studies have examined the possible relationship between DNA repair enzymes polymorphisms and the risk of development ESRD. As the *XPD Asp312Asn* and *XPD Lys751Gln* and *XRCC1 Arg194Trp* and *XRCC1 Arg399Gln* polymorphisms have immediate functional significance and are very common in the population, we initiated this case control study to determine the possible association with these polymorphisms and the development ESRD.

Materials and methods

Subjects

Between October 2006 and November 2007, 136 patients with ESRD (85 females and 51 males, mean age 47 ± 13) were recruited consecutively to this controlled study in our out-patient clinic. All subjects were of Turkish nationality belonging to the Turkish ethnic group. Of these 136 patients, 71 were undergoing chronic hemodialysis (HD) and 65 were undergoing peritoneal dialysis (PD). Patients who had been undergoing HD or PD more than 6 months were enrolled in this study. Time on dialysis of patients was 49.9 ± 45.0 months. Control group was formed by 147 healthy individuals who do not smoke regularly (92 females and 55 males, mean age 48 ± 15).

The causes of ESRD were chronic glomerulonephritis in 61 patients (45%), diabetes mellitus in 23 patients (17%), hypertensive nephrosclerosis in 17 patients (12%), chronic interstitial nephritis in eight patients (6%), polycystic kidney disease in eight patients (6%), amyloidosis in five patients (4%), multiple myeloma in two patients (1%), and unknown in 12 patients (9%). In eight of 136 patients, there were different types of malignancy: multiple myeloma in one patient, colon cancer in one patient, colon cancer with multiple myeloma in one patient, breast cancer in two patients, lymphoma in one patients, cervix cancer in one patient, and larynx cancer in one patient. Seven patients were receiving immunosuppressive drugs.

The study was approved by the Ethics Committee of Istanbul University Cerrahpasa Medical Faculty and conducted in accordance with the current version of the Declaration of Helsinki. All participants gave their written informed consent prior to participation in the study.

Extraction of DNA and genotyping analysis

We collected 3 ml of venous blood from patients and controls. Immediately after collection, whole blood was stored in aliquots at −20°C until use. Genomic DNA was extracted from leukocytes using Roche DNA purification kit (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions.

XPD genotypes were detected using a polymerase chain reaction-restriction fragment lenght polymorphism (PCR–RFLP) method. An *Asp* → *Asn* in exon 10 (codon 312; rs.1799793) and a *Lys* → *Gln* in exon 23 (codon 751; rs.13181) were amplified to form an undigested fragments

of 751 and 436 bp, respectively, using primers described by Yu et al. [17] and Spitz et al. [18] respectively.

XRCC1 genotypes were detected using a multiplex PCR–RFLP method. An *Arg* → *Trp* in exon 6 (codon 194; rs.1799782) and *Arg* → *Gln* in exon 10 (codon 399; rs.25487) were amplified to form an undigested fragments of 491 and 615 bp, respectively, using primers described by Lunn et al. [14].

Statistical analysis

Mean and standard deviations (SD) are presented in case of continuous variables. Chi-square analysis (χ^2 tests) and Fisher's exact test were used to compare the gender distribution and test the association between the genotypes and alleles in relation to the cases and controls and test for deviation of genotype distribution from Hardy Weinberg equilibrium (HWE). The odds ratio (OR) and their 95% confidence intervals (CI) were calculated to estimate the strength of the association between polymorphism genotype alleles and patients and controls. Bonferroni adjustments were made for p value for the results of any SNP by multiplying the number of SNPs tested for the gene. Differences between the means of the two continuous variables were evaluated by the Student's *t*-test. A value of $P < 0.05$ was considered statistically significant. Analysis was performed with SPSS 11.5 statistical software.

Results

The patient and control groups were not statistically different with respect to age ($P = 0.47$) and gender ($P = 0.80$). Clinical characteristics of patients with ESRD are outlined in Table 1.

Table 2 shows the genotypic and allelic distributions of the polymorphisms in *XPD* and *XRCC1* genes for both patients and controls. The distributions of the *XPD-Asp312Asn*, *XPD-Lys751Gln*, *XRCC1-Arg194Gln* and *XRCC1-Arg399Gln* genotypes were in accordance with the HWE among the cases and controls. There were a significant difference between frequencies for *XRCC1-399 Arg/Gln* genotype and *XRCC1-399 Gln/Gln* genotype in patients and controls ($P = 0.007$ and $P = 0.005$, respectively). We found that the patients with *XRCC1-399 Arg/Gln* (OR:1.98; 95% CI: 1.21–3.25) or *XRCC1-399 Gln/Gln* (OR: 3.95; 95% CI: 1.45–10.76) genotype had a significantly higher risk of ESRD than those with *XRCC1-399 Arg/Arg* genotype. After Bonferroni correction for multiple testing, these associations remained significant ($P = 0.028$ and $P = 0.02$, respectively). In addition, the *Gln* allele of this polymorphism was associated with increased risk of ESRD (OR:2.03; 95% CI: 1.08–3.81, $P = 0.03$). No statistically significant differences were observed in the alleles or in the genotype frequencies of the *XRCC1-Arg194Trp*, *XPD-Asp312Asn* and *XPD-Lys751Gln* gene polymorphisms between the control group and the patients group.

Regarding the effect of combined polymorphisms of *XPD Asp312Asn*, *XPD Lys751Gln*, *XRCC1 Arg194Trp* and *XRCC1 Arg399Gln* on the risk of ESRD development, the wild type genotypes for each gene were taken as references (Table 3). The analysis showed that combination of *Arg/Gln* or *Gln/Gln* genotypes of *XRCC1 Arg399Gln* polymorphism with the two possible genotypes of *XPD-Asp312Asn* polymorphism (*Asp/Asn* and *Asn/Asn* or *Asp/Asp*) was significantly associated with the development of ESRD (p values <0.05 for both). Combination of *Arg/Gln* or *Gln/Gln* genotypes of *XRCC1 Arg399Gln* polymorphism with *Lys/Gln* or *Gln/Gln* genotypes of *XPD Lys751Gln* polymorphism was also found to increase the risk of ESRD development ($P < 0.05$). However, no significant association was found between other compound polymorphisms and the risk of development ESRD.

Table 1 Clinical characteristics of patients with ESRD

Characteristics	HD group ($n = 71$)	PD group ($n = 65$)
Age (years)	52.1 ± 16.5	44.5 ± 12.6
Male/female	27/44	23/42
Etiology of chronic renal failure (diabetic/non-diabetic)	19/52	4/61
Time on dialysis (months)	39.8 ± 30.1	60.5 ± 53.8
Malignancy	7	1
Immunosuppressive therapy	6	1
Smoking	11	14

Discussion

Various studies have shown the existence of a large interindividual variation in repair of DNA damage induced by endogenous and exogenous insults and the individuals with less dramatic reduction in the capacity to repair DNA are observed at polymorphic frequency [19]. Such individuals with repair capacity below the population mean can be at increased risk of developing several chronic diseases. In our study, all the examined subjects were genotyped for two repair genes, *XRCC1* and *XPD* in order to analyze the possible influence of the genetically determined variations on susceptibility to ESRD. We found that the *XRCC1* codon 399 polymorphism was associated with

Table 2 Distribution of genotype and allele frequencies of *XPD* and *XRCC1* polymorphisms in patients and controls

Genotype/allele	Controls *n* (%)	Patients *n* (%)	*P* value	OR (95% CI)
XPD 312				
Asp/Asp	53 (36)	42 (31)		Reference
Asp/Asn	70 (48)	63 (46)	0.64	1.14 (0.67–1.93)
Asn/Asn	24 (16)	31 (23)	0.15	1.63 (0.84–3.18)
Asp allele frequency	0.60	0.54		Reference
Asn allele frequency	0.40	0.46	0.39	1.28 (0.73–2.24)
XPD 751				
Lys/Lys	47 (32)	44 (32)		Reference
Lys/Gln	74 (50)	66 (49)	0.86	0.95 (0.56–1.62)
Gln/Gln	26 (18)	26 (19)	0.85	1.07 (0.54–2.11)
Lys allele frequency	0.57	0.57		Reference
Gln allele frequency	0.43	0.43	1.00	1.00 (0.57–1.75)
XRCC1 194				
Arg/Arg	132 (90)	120 (88)		Reference
Arg/Trp	15 (10)	16 (12)	0.67	1.17 (0.56–2.48)
Trp/Trp	0 (0)	0 (0)	0.99[a]	
Arg allele frequency	0.95	0.94		Reference
Trp allele frequency	0.05	0.06	0.76	1.21 (0.36–4.11)
XRCC1 399				
Arg/Arg	90 (61)	57 (42)		Reference
Arg/Gln	51 (35)	64 (47)	0.007	1.98 (1.21–3.25)
Gln/Gln	6 (4)	15 (11)	0.005	3.95 (1.45–10.76)
Arg allele frequency	0.79	0.65		Reference
Gln allele frequency	0.21	0.35	0.03	2.03 (1.08–3.81)

[a] Fisher's exact test

susceptibility to ESRD. However, the *XRCC1* codon 194, XPD codon 312 and 751 polymorphisms were not associated with ESRD.

To our knowledge this is the first study to examine the effect of DNA repair gene polymorphisms on risk of ESRD. The major finding of this study is that the presence of a common genetic polymorphism of *XRCC1* codon 399, the *399Gln* variant, is associated with ESRD. Our finding is consistent with the published functional studies that reported some associations between *XRCC1 Arg399Gln* polymorphism and markers of DNA damage. In these studies it has shown that the *XRCC1 399Gln* polymorphic variant is associated with higher levels of DNA adducts, somatic mutations, micronuclei, sister chromatid exchanges and chromosomal damages.

In patients with ESRD, DNA damage has been shown by numerous biomarkers, such as the analysis of sister chromatid exchange and chromosomal aberrations [20, 21], micronucleus frequency [22–24], comet assay (single-cell gel electrophoresis) in peripheral lymphocytes [16, 25], 8-hydroxy 2-deoxyguanosine content in leukocytes [26, 27], and mitochondrial DNA deletions in skeletal muscle tissue and hair follicles [28].

Moreover, the *XRCC1 399Gln* gene variant has been associated with artherosclerotic coronary artery disease, schizophrenia, pterygium, cataracts and systemic lupus erythematosus [2, 29–32] as well as various cancer types such as breast, lung, prostate, renal, carcinomas of head and neck, stomach, colon and acute lymphoblastic leukemia [33–40].

Combinations of common genetic polymorphisms may increase or decrease the susceptibility to certain diseases [41]. To investigate the presence of such an effect we also made an association analysis between genotype combinations and ESRD. It was found that combination of *Arg/Gln* or *Gln/Gln* genotypes of *XRCC1 Arg399Gln* polymorphism (at least one *Gln* carriers) with all genotypes of *XPD-Asp312Asn* polymorphism and *XPD Lys751Gln* polymorphism (except *Lys/Lys* genotype) may increase the risk of ESRD development. The only exception was the combination with *Lys/Lys* genotype of *XPD Lys751Gln* polymorphism, which has been reported previously to have an protective effect against certain diseases [42, 43]. It may be hypothesized that increased risk associated with *Gln* allele at *XRCC1* codon 399 was decreased with *Lys/Lys* genotype of *XPD Lys751Gln* polymorphism.

Table 3 Distribution of combined *XPD* and *XRCC1* genotypes among ESRD patients and control

Genotype combinations	Patients $n = 136$ (%)	Control $n = 147$ (%)	OR (95% CI)	P value
XPD 312 and *XRCC1 399*				
Asp/Asp and *Arg/Arg*	16 (12)	38 (26)	Reference	
Asp/Asn or *Asn/Asn* and *Arg/Gln* or *Gln/Gln*	53 (39)	42 (29)	3.00 (1.47–6.10)	0.002
Asp/Asp and *Arg/Gln* or *Gln/Gln*	26 (19)	15 (10)	4.12 (1.74–9.76)	0.001
Asp/Asn or *Asn/Asn* and *Arg/Arg*	41 (30)	52 (35)	1.87 (0.92–3.82)	0.08
XPD 312 and *XRCC1 194*				
Asp/Asp and *Arg/Arg*	39 (29)	43 (29)	Reference	
Asp/Asn or *Asn/Asn* and *Arg/Trp* or *Trp/Trp*	13 (10)	6 (4)	2.39 (0.83–6.90)	0.10
Asp/Asp and *Arg/Trp* or *Trp/Trp*	3 (2)	9 (6)	0.37 (0.09–1.46)	0.14
Asp/Asn or *Asn/Asn* and *Arg/Arg*	81 (59)	89 (61)	1.00 (0.59–1.70)	0.99
XPD 751 and *XRCC1 399*				
Lys/Lys and *Arg/Arg*	17 (13)	26 (18)	Reference	
Lys/Gln or *Gln/Gln* and *Arg/Gln* or *Gln/Gln*	52 (38)	36 (24)	2.21 (1.05–4.65)	0.04
Lys/Lys and *Arg/Gln* or *Gln/Gln*	27 (20)	21 (14)	1.97 (0.85–4.54)	0.11
Lys/Gln or *Gln/Gln* and *Arg/Arg*	40 (29)	64 (44)	0.96 (0.46–1.98)	0.90
XPD 751 and *XRCC1 194*				
Lys/Lys and *Arg/Arg*	40 (29)	43 (29)	Reference	
Lys/Gln or *Gln/Gln* and *Arg/Trp* or *Trp/Trp*	12 (9)	11 (7)	1.17 (0.47–2.96)	0.74
Lys/Lys and *Arg/Trp* or *Trp/Trp*	4 (3)	4 (3)	1.08 (0.25–4.59)	1.00
Lys/Gln or *Gln/Gln* and *Arg/Arg*	80 (59)	89 (61)	0.97 (0.57–1.64)	0.90

The XRCC1 protein plays an important role in the BER pathway. XRCC1 is thought to act as a scaffold protein, play a coordinating role for consecutive stages of the BER system [44], interact with several proteins of BER and single-strand break repair machinery including OGG1, NEIL1, NEIL2, ANPG, NTH1, as well as APE1, PNK, TDP1, PARP1, PARP2, POLβ, LIG3a, and exert function in recognizing and binding to single-strand breaks. The *XRCC1 Arg399Gln* polymorphism is located within the XRCC1 BRCA1 carboxyl-terminal domain (BRCT I) and is hypothesized to have functional significance because it is located within a well-conserved region and encodes a nonconservative amino acid change. Chinese hamster ovary cells with no functional XRCC1 protein are hypersensitive to a broad range of DNA damage, such as that induced by alkylating agents, ROS, or ionizing radiation, suggesting an essential role for XRCC1 in DNA repair [16].

In conclusion, our current study demonstrated that XRCC1 Arg399Gln polymorphism may contribute to individual susceptibility to ESRD. In accordance with our knowledge, this is the first report showing an association between DNA repair gene polymorphisms and ESRD susceptibility. Thus, BER genes are suggested to be used as a predictive factor for ESRD. However, further studies are needed to evaluate the influence of their polymorphisms on the risk of ESRD.

Acknowledgments This work was supported by the Research Fund of The University of Istanbul. Project numbers: 453/27122005, UDP-3522 and UDP-3555.

Conflict of interest statement The authors declare that there are no conflicts of interest.

References

1. Schupp N, Stopper H, Rutkowski P, Kobras K, Nebel M, Bahner U, Vienken J, Heidland A (2006) Effect of different hemodialysis regimens on genomic damage in end-stage renal failure. Semin Nephrol 26:28–32
2. Guven M, Guven GS, Oz E, Ozaydin A, Batar B, Ulutin T, Hacihanefioglu S, Domanic N (2007) DNA repair gene XRCC1 and XPD polymorphisms and their association with coronary artery disease risks and micronucleus frequency. Heart Vessels 22:355–360
3. Maisonneuve P, Agodoa L, Gellert R et al (1999) Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. Lancet 354:93–99
4. Herzog C, Ma J, Collins A (1998) Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. N Engl J Med 339:799–805
5. Tepel M, Echelmeyer M, Orie NN, Zidek W (2000) Increased intracellular reactive oxygen species in patients with end-stage renal failure: effect of hemodialysis. Kidney Int 58:867–872
6. Miyata T, Kurokawa K, Van Ypersele De Strihou C (2000) Advanced glycation and lipoxidation end products: role of reactive carbonyl compounds generated during carbohydrate and lipid metabolism. J Am Soc Nephrol 11:1744–1752

7. Floccari F, Aloisi C, Crascì E, Sofi T, Campo S, Tripodo D, Criseo M, Frisina N, Buemi M (2005) Oxidative stress and uremia. Med Res Rev 25:473–486
8. Locatelli F, Canaud B, Eckardt KU, Stenvinkel P, Wanner C, Zoccali C (2003) Oxidative stress in end-stage renal disease: an emerging threat to patient outcome. Nephrol Dial Transplant 18:1272–1280
9. Cadet J, Douki T, Ravanat JL (2011) Measurement of oxidatively generated base damage in cellular DNA. Mutat Res 711:3–12
10. Wiseman H, Halliwell B (1996) Damage to DNA by reactive oxygen and nitrogen species : role in inflammatory disease and progression to cancer. Biochem J 313:17–29
11. Ladiges W, Wiley J, MacAuley A (2003) Polymorphisms in the DNA repair gene XRCC1 and age-related disease. Mech Ageing Dev 124:27–32
12. Stern MC, Siegmund KD, Conti DV, Corral R, Haile RW (2006) XRCC1, XRCC3, and XPD polymorphisms as modifiers of the effect of smoking and alcohol on colorectal adenoma risk. Cancer Epidemiol Biomarkers Prev 15:2384–2390
13. Shen MR, Jones IM, Mohrenweiser H (1998) Nonconservative amino acid substitution variants exist at polymorphic frequency in DNA repair genes in healthy humans. Cancer Res 58:604–608
14. Lunn RM, Langlois RG, Hsieh LL, Thompson CL, Bell DA (1999) XRCC1 polymorphisms: effects on aflatoxin B1-DNA adducts and glycophorin A variant frequency. Cancer Res 59:2557–2561
15. Benhamou S, Sarasin A (2002) ERCC2/XPD gene polymorphisms and cancer risk. Mutagenesis 17:463–469
16. Caldecott KW (2003) XRCC1 and DNA strand break repair. DNA Repair (Amst) 2:955–969
17. Yu HP, Wang XL, Sun X, Su YH, Wang YJ, Lu B, Shi LY, Xiong CL, Li YY, Li F, Xu SQ (2004) Polymorphisms in the DNA repair gene XPD and susceptibility to esophageal squamous cell carcinoma. Cancer Genet Cytogenet 154:10–15
18. Spitz MR, Wu X, Wang Y, Wang LE, Shete S, Amos CI, Guo Z, Lei L, Mohrenweiser H, Wei Q (2001) Modulation of nucleotide excision repair capacity by XPD plymorphisms in lung cancer patients. Cancer Res 61:1354–1357
19. Benhamou S, Sarasin A (2000) Variability in nucleotide excision repair and cancer risk: a review. Mutat Res 462:149–158
20. Duell EJ, Wiencke JK, Cheng TJ, Varkonyi A, Zuo ZF, Ashok TD, Mark EJ, Wain JC, Christiani DC, Kelsey KT (2000) Polymorphisms in the DNA repair genes XRCC1 and ERCC2 and biomarkers of DNA damage in human blood mononuclear cells. Carcinogenesis 21:965–971
21. Nazarkina ZK, Khodyreva SN, Marsin S, Lavrik OI, Radicella JP (2007) XRCC1 interactions with base excision repair DNA intermediates. DNA Repair (Amst) 6:254–264
22. Zhu SM, Xia ZL, Wang AH, Ren XF, Jiao J, Zhao NQ, Qian J, Jin L, Christiani DC (2008) Polymorphisms and haplotypes of DNA repair and xenobiotic metabolism genes and risk of DNA damage in Chinese vinyl chloride monomer (VCM)-exposed workers. Toxicol Lett 178:88–94
23. Zhang Z, Wan J, Jin X, Jin T, Shen H, Lu D, Xia Z (2005) Genetic polymorphisms in XRCC1, APE1, ADPRT, XRCC2, and XRCC3 and risk of chronic benzene poisoning in a Chinese occupational population. Cancer Epidemiol Biomarkers Prev 14:2614–2617
24. Qu T, Morii E, Oboki K, Lu Y, Morimoto K (2005) Micronuclei in EM9 cells expressing polymorphic forms of human XRCC1. Cancer Lett 221:91–95
25. Mateuca RA, Roelants M, Iarmarcovai G et al (2008) hOGG1326, XRCC1399 and XRCC3241 polymorphisms influence micronucleus frequencies in human lymphocytes in vivo. Mutagenesis 23:35–41
26. Battershill JM, Burnett K, Bull S (2008) Factors affecting the incidence of genotoxicity biomarkers in peripheral blood lymphocytes: impact on design of biomonitoring studies. Mutagenesis 23:423–437
27. Ishikawa H, Tian Y, Yamauchi T (2003) Influence of gender, age and lifestyle factors on micronuclei frequency in healthy Japanese populations. J Occup Health 45:179–181
28. Andreassi MG (2003) Coronary atherosclerosis and somatic mutations: an overview of the contributive factors for oxidative DNA damage. Mutat Res 543:67–86
29. Saadat M, Pakyari N, Farrashbandi H (2008) Genetic polymorphism in the DNA repair gene XRCC1 and susceptibility to schizophrenia. Psychiatry Res 157:241–245
30. Chiang CC, Tsai YY, Bau DT, Cheng YW, Tseng SH, Wang RF, Tsai FJ (2010) Pterygium and genetic polymorphisms of the DNA repair enzymes XRCC1, XPA, and XPD. Mol Vis 16:698–704
31. Padma G, Mamata M, Reddy KR, Padma T (2011) Polymorphisms in two DNA repair genes (XPD and XRCC1)–association with age related cataracts. Mol Vis 17:127–133
32. Warchoł T, Mostowska A, Lianeri M, Lącki JK, Jagodziński PP (2012) XRCC1 Arg399Gln Gene Polymorphism and the risk of systemic lupus erythematosus in the polish population. DNA Cell Biol 31:50–56
33. Silva SN, Moita R, Azevedo AP, Gouveia R, Manita I, Pina JE, Rueff J, Gaspar J (2007) Menopausal age and XRCC1 gene polymorphisms: role in breast cancer risk. Cancer Detect Prev 31:303–309
34. Butkiewicz D, Rusin M, Sikora B, Lach A, Chorąży M (2011) An association between DNA repair gene polymorphisms and survival in patients with resected non-small cell lung cancer. Mol Biol Rep 38:5231–5241
35. Berhane N, Sobti RC, Mahdi. SA (2011) DNA repair genes polymorphism (XPG and XRCC1) and association of prostate cancer in a north Indian population. Mol Biol Rep doi: 10.1007/s11033-011-0998-5
36. Sturgis EM, Castilli EJ, Li L, Zheng R, Eicher SA, Clayman GL, Strom SS, Spitz MR, Wei Q (1999) Polymorphisms of DNA repair gene XRCC1 in squamous cell carcinoma of the head and the neck. Carcinogenesis 20:2125–2129
37. Duarte MC, Colombo J, Rossit AR, Caetano A, Borim AA, Wornrath D, Silva AE (2005) Polymorphisms of DNA repair genes XRCC1 and XRCC3, interaction with environmental exposure and risk of chronic gastritis and gastric cancer. World J Gastroenterol 11:6593–6600
38. Abdel-Rahman S, Soliman AS, Bondy ML, Omar S, El-Badawy SA, Khaled HM, Seifeldin IA, Levin B (2000) Inheritance of the 194Trp and the 399Gln variant alleles of the DNA repair gene XRCC1 are associated with increased risk of early-onset colorectal carcinoma in Egypt. Cancer Lett 159:79–86
39. Tumer TB, Yilmaz D, Tanrikut C, Sahin G, Ulusoy G, Arinç E (2010) DNA repair XRCC1 Arg399Gln polymorphism alone, and in combination with CYP2E1 polymorphisms significantly contribute to the risk of development of childhood acute lymphoblastic leukemia. Leuk Res 34:1275–1281
40. Hirata H, Hinoda Y, Matsuyama H, Tanaka Y, Okayama N, Suehiro Y, Zhao H, Urakami S, Kawamoto K, Kawakami T, Igawa M, Naito K, Dahiya R (2006) Polymorphisms of DNA repair genes are associated with renal cell carcinoma. Biochem Biophys Res Commun 342:1058–1062
41. Görgün E, Güven M, Unal M, Batar B, Güven GS, Yenerel M, Tatlipinar S, Seven M, Yüksel A (2010) Polymorphisms of the DNA repair genes XPD and XRCC1 and the risk of age-related macular degeneration. Invest Ophthalmol Vis Sci 51:4732–4737
42. Gao W, Romkes M, Zhong S, Nukui T, Persad RA, Smith PJ, Branch R, Keohavong P (2010) Genetic polymorphisms in the DNA repair genes XPD and XRCC1, p53 gene mutations and bladder cancer risk. Oncol Rep 24:257–262

43. Huang CG, Iv GD, Liu T, Liu Q, Feng JG, Lu XM (2011) Polymorphisms of COMT and XPD and risk of esophageal squamous cell carcinoma in a population of Yili Prefecture, in Xinjiang, China. Biomarkers 16:37–41
44. Moller P, Wallin H, Dybdahl M, Frentz G, Nexo BA (2000) Psoriasis patients with basal cell carcinoma have more repair-mediated DNA strand-breaks after UVC damage in lymphocytes than soriasis patients without basal cell carcinoma. Cancer Lett 151:87–92