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LABORATORY STUDY

DNA repair genes XPD and XRCC1 polymorphisms and risk of end-stage renal disease in Egyptian population

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Abstract

DNA repair gene polymorphisms may affect DNA repair capacity and modulate susceptibility to end-stage renal disease (ESRD). We aimed to determine the association of polymorphisms in xeroderma pigmentosum complementation group D (*XPD*) and X-ray cross-complementing group 1 (*XRCC1*) with ESRD development. Polymorphisms in *XPD* codons 312 and 751 and *XRCC1* codon 399 were genotyped in 98 patients undergoing hemodialysis and 102 healthy controls using polymerase chain reaction and restriction fragment length polymorphism. Patients having XRCC1-399 Arg/Gln genotype or XRCC1-399 Gln/Gln genotype had a significantly higher risk of ESRD than those with XRCC1-399 Arg/Arg [odds ratio (OR): 2.48; 95% confidence intervals (CI): 1.36–4.52; $p = 0.004$ and OR: 4.05; 95% CI: 1.19–13.73; $p = 0.03$, respectively]. We also found a significantly higher frequency of the *XRCC1 399Gln* allele in patients with ESRD than in controls (OR: 2.22; 95% CI: 1.16–4.25; $p = 0.02$). Combination of the *Arg/Gln* or *Gln/Gln* genotypes of *XRCC1 Arg399Gln* polymorphism with *Asp/Asn* or *Asn/Asn* genotypes of *XPDAsp312Asn* or with the *Lys/Gln* or *Gln/Gln* genotypes of *XPD Lys751Gln* was significantly associated with the development of ESRD. Haplotypes association showed that association of Gln allele of *XRCC1 Arg399Gln* polymorphism with the Asn allele of *XPDAsp312Asn* polymorphism ($p = 0.004$) or Gln allele of *XRCC1 Arg399Gln* polymorphism with the Gln allele of *XPD Lys751Gln* polymorphism ($p = 0.003$) was highly significantly associated with the development of ESRD. This study revealed that *XRCC1 Arg399Gln* polymorphism may confer increased risk for the development of ESRD. Furthermore, larger studies should be conducted to confirm these results.

Keywords

Dialysis, end-stage renal disease, polymorphism, XPD, XRCC1

History

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Introduction

Worldwide, the increasing number of individuals in end-stage renal disease (ESRD) represents a serious health, social and economic problem. The causes of ESRD are heterogeneous, ranging from infectious diseases and metabolic multisystemic disease to congenital and genetic disorders. This variety of possible etiologies makes it difficult to identify the mechanisms involved in its pathogenesis. In many cases, the etiology remains unknown.[1] Traditional risk factors such as age, black race, male gender, smoking, hypertension, hyperlipidemia, diabetes and obesity cannot explain the complete individual susceptibility to development of ESRD and accompanying complications that essentially determine the clinical outcome. Because of clinically experienced inter-individual differences, an important role of genetic predisposition might be assumed.

Patients with ESRD display enhanced genomic damage.[2] 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.[3] ESRD is associated with a high incidence of cancers and cardiovascular diseases.[4] Among the several pathogenic mechanisms suggested to explain these phenomena, there are uremia *per se*, micro inflammation and oxidative stress,[5] which involves the whole cell structure (proteins, membrane lipids, carbohydrates and DNA).[6] Oxidative stress is enhanced in patients with ESRD.[7] It has been reported that oxidative stress can induce DNA damage, such as base modifications and strand breaks.[8] 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

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DNA damage and thereby lead to increased cancer or other disease susceptibility.[9]

Xeroderma pigmentosum complementation group D (*XPD*) encodes a helicase, which participates in both NER and basal transcription as part of the transcription factor IIH (TFIIH). As *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.[10] *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.[10,11] 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.[11,12] SNPs of *XPD* gene have been studied in relation to lung cancer[13] and colorectal cancer,[14,15] cataract and glaucoma development;[16,17] also, it has been investigated in different hematological malignancies, such as acute myeloid and lymphoblastic leukemia.[18–20]

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.[21] It is a multidomain protein that interacts with the nicked DNA and participates with at least three different enzymes, poly-ADP-ribose polymerase, DNA ligase III and DNA polymerase β, to repair single-strand breaks.[21] 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).[10] Although the functional effects of these polymorphisms in XRCC1 have not been well known, amino acid changes at evolutionary conserved regions may alter its function. The *XRCC1* polymorphisms have been extensively studied in relation to acute myeloid leukemia,[22,23] acute lymphoblastic leukemia,[24,25] chronic lymphocytic leukemia,[26] lymphoma,[27,28] chronic myeloid leukemia[29] and cardiovascular disease.[30] XRCC1 and XPD polymorphisms are also associated with increased risk of hepatocellular carcinoma.[31,32]

In this study, we aimed to examine the possible relationship between DNA repair enzymes (*XPD Asp312Asn* and *XPD Lys751Gln* and *XRCC1 Arg399Gln*) polymorphisms and the risk of developing ESRD in a sample from Egyptian cohort.

Methods

Study subjects

Ninety-eight patients with ESRD undergoing hemodialysis were enrolled in this controlled study (48 females and 50 males, mean age 47.8 ± 14.2 years, range: 20–80, median 50). All subjects were of Egyptian nationality. Time on dialysis of patients was 3.9 ± 3.7 years. Control group was formed by 102 healthy individuals (46 females and 56 males, mean age 46.3 ± 13.2 years, range: 21–76, median 48). The causes of ESRD were hypertension in 44 patients, diabetes mellitus (DM) in 11 patients, preeclampsia in 4 patients, drug induced in 3 patients, glomerulonephritis in 6 patients, obstructive uropathy in 5 patients, atrophic kidney in 3 patients, systemic lupus erythematosus in 5 patients, polycystic kidney in 2 patients, combined polycystic kidney and hypertension in 1 patient, combined DM and hypertension in 6 patients, amyloidosis and hypertension in 1 patient and unknown cause in 7 patients.

This study was approved by the ethical committee of the Faculty of Medicine, Menoufia University. All patients provided signed informed consent to provide a blood sample and to review the medical record for research purposes.

Genotyping

DNA was isolated from peripheral leucocytes using a GeneJET whole blood Genomic DNA Purification Kit (Thermo Scientific, Waltham, MA) according to the manufacturer's instructions.

XPD genotypes were detected using a polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) method. An *Asp* → *Asn* in exon 10 (codon 312) and a *Lys* → *Gln* in exon 23 (codon 751) were amplified to form an undigested fragments of 751 and 436 bp, respectively, using primers described by Batar et al.[33]: 5′-CTG TTG GTG GGT GCC CGT ATC TGT TGG TCT-3′ (forward) and 5′-TAA TAT CGG GGC TCA CCC TGC AGC ACT TCC T-3′ (reverse) for codon 312; and 5′-GCC CGC TCT GGA TTA TAC G-3′ (forward) and 5′-CTA TCA TCT CCT GGC CCC C-3′ (reverse) for codon 751. PCR conditions were 94 °C for 3 min, followed by 38 cycles of 94°C for 45 s, 60 °C for 45 s, 72 °C for 60 s and a final extension step at 72 °C for 7 min. PCR products were digested with StyI (for codon 312) and PstI (for codon 751) (Thermo Scientific) at 37 °C overnight and analyzed on 3% agarose gels. StyI digestion resulted in two fragments of 507 and 244 bp for the wild-type homozygous (*Asp*/*Asp*); three fragments of 474, 244, and 33 bp for the variant homozygous (*Asn*/*Asn*); and four fragments of 507, 474, 244 and 33 bp for the heterozygous (*Asp*/*Asn*) (Figure 1). PstI digestion resulted in two fragments of 290 and 146 bp for the wild-type homozygous (*Lys*/*Lys*); three fragments of 227, 146 and 63 bp for the variant homozygous (*Gln*/*Gln*); and four fragments at 290, 227, 146 and 63 bp for the heterozygous (*Lys*/*Gln*) (Figure 2).

XRCC1 codon 399 genotype was detected using a PCR–RFLP method. An *Arg* → *Gln* in exon 10 (codon 399) were amplified to form an undigested fragments of 615 bp, using primers described by Batar et al.[33]: 5′-TTG TGC TTT CTC TGT GTC CA-3′ (forward) and 5′-TCC TCC AGC CTT TTC TGA TA-3′ (reverse). PCR conditions were 94 °C for 3 min, followed by 30 cycles of 94 °C for 30 s, 56 °C for 1 min, 72 °C for 45 s and a final extension step at 72 °C for 10 min. The 615 bp PCR products were digested with MspI (Thermo Scientific) at 37 °C overnight and analyzed on 3% agarose gel. MspI digestion resulted in two fragments of 374 and 221 bp for wild-type homozygous (*Arg*/*Arg*); one fragment of 615 bp for variant homozygous (*Gln*/*Gln*); and three fragments of 615, 374 and 221 bp for variant heterozygous (*Arg*/*Gln*) (Figure 3).

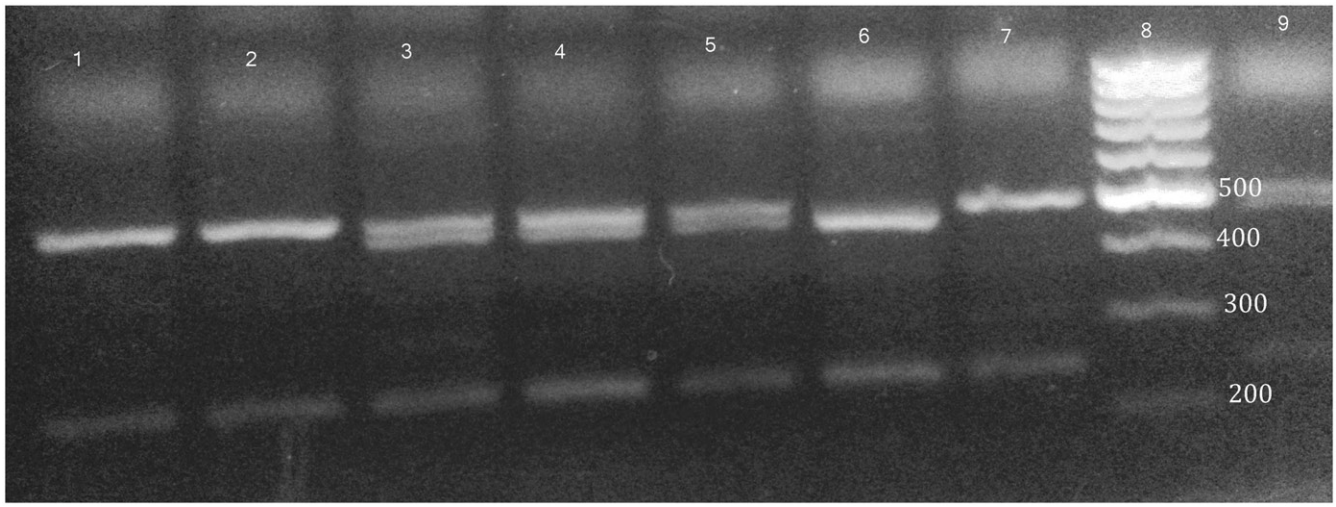

Figure 1. XPD 312 genotypes on ethidium bromide stained 3% agarose gel. Lanes 1, 2 and 7 are homozygous Asp/Asp genotype. Lanes 3, 4, 5 and 9 are heterozygous Asp/Asn genotype. Lane 6 is homozygous Asn/Asn genotype. Lane 8 is 100 bp ladder.

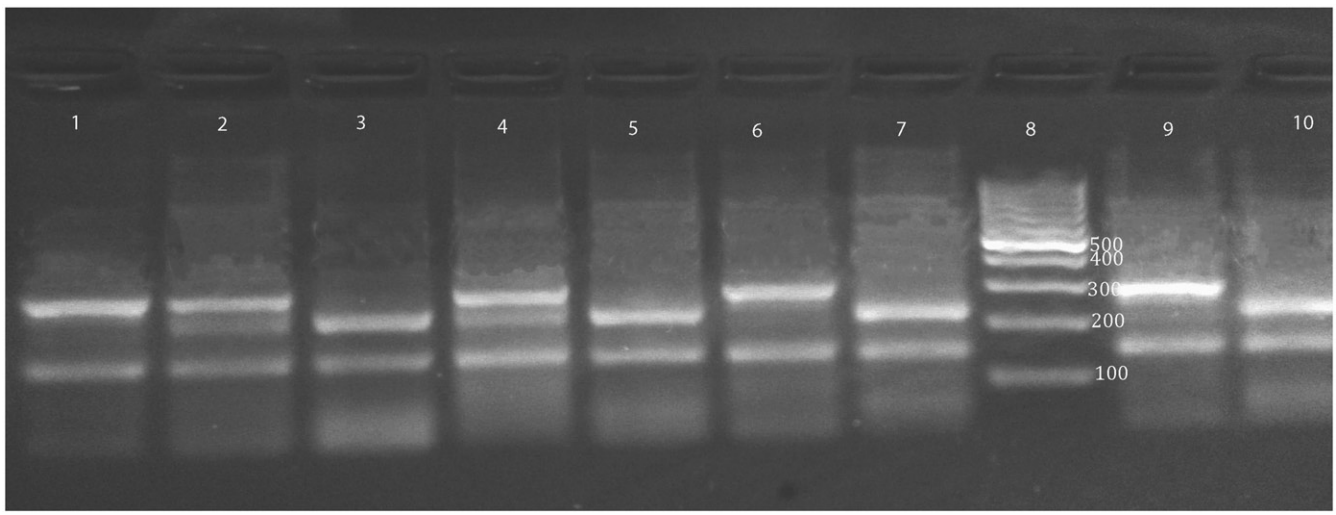

Figure 2. XPD 751 genotypes on ethidium bromide stained 3% agarose gel. Lanes 1, 6 and 9 are homozygous Lys/Lys genotype. Lanes 2 and 4 are heterozygous Lys/Gln genotype. Lanes 3, 5, 7 and 10 are homozygous Gln/Gln genotype. Lane 8 is 100 bp ladder.

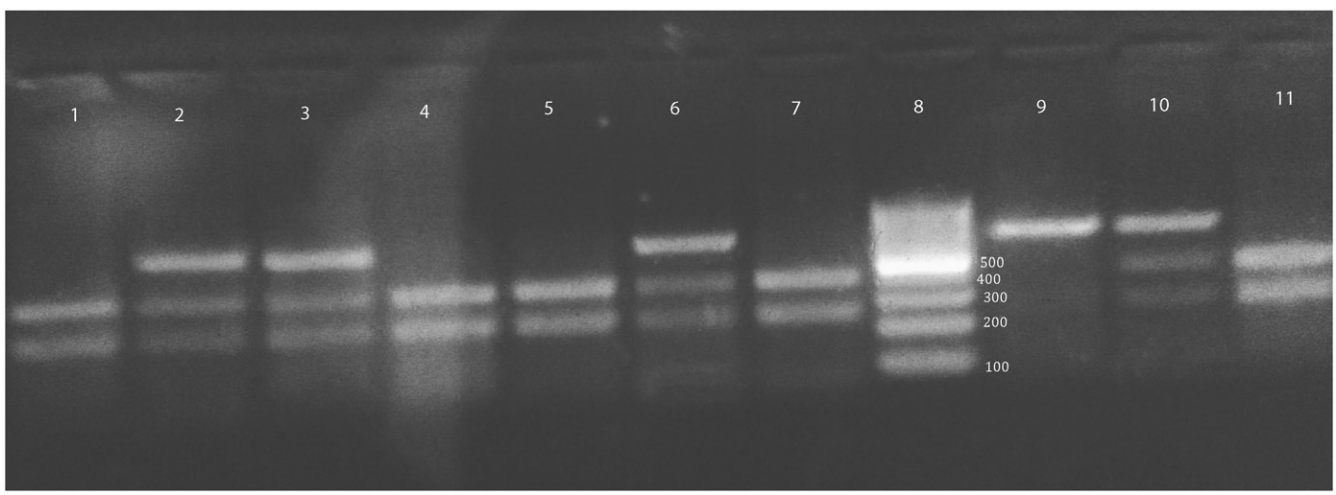

Figure 3. XRCC1 399 genotypes on ethidium bromide stained 3% agarose gel. Lanes 1, 4, 5, 7 and 11 are homozygous Arg/Arg genotype. Lanes 2, 3, 6 and 10 are heterozygous Arg/Gln genotype. Lane 9 is homozygous Gln/Gln genotype. Lane 8 is 100 bp ladder.

Statistical analysis

Data were processed using the Statistical Package for Social Science version 16 (SPSS, Chicago, IL). The ages of the patients and the controls were compared by the Student *t* test. The chi-square test was used to compare the gender distribution and to test the association between the genotypes and alleles in relation to the cases and controls. Deviation of genotype distribution from the Hardy–Weinberg equilibrium and haplotype association analysis were carried out using the web tool SNPStats. The odds ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated to estimate the strength of the association between polymorphism genotype alleles of patients and controls. A value of $p < 0.05$ was considered statistically significant.

Results

The distributions of the *XPDAsp312Asn*, *XPD-Lys751Gln* and *XRCC1-Arg399Gln* genotypes did not display significant deviation from the Hardy–Weinberg equilibrium between patients and healthy individuals. There were no significant age and sex differences between patients and controls ($p = 0.4$).

There were a significant difference between frequencies for *XRCC1-399 Arg/Gln* genotype and *XRCC1-399 Gln/Gln* genotype in patients and controls ($p = 0.004$ and $p = 0.03$, respectively). We found that patients with *XRCC1-399 Arg/Gln* (OR: 2.48; 95% CI: 1.36–4.52) or *XRCC1-399 Gln/Gln* (OR: 4.05; 95% CI: 1.19–13.73) genotype had a significantly higher risk of ESRD than those with *XRCC1-399 Arg/Arg* genotype (Table 1). The Gln allele of this polymorphism was associated with increased risk of ESRD (OR: 2.22; 95% CI: 1.16–4.25; $p = 0.02$).

No statistically significant differences were observed in the alleles or in the genotype frequencies of the *XPD-Asp312Asn* and *XPD-Lys751Gln* gene polymorphisms between the control group and the patients group (Table 1).

Regarding the effect of combined polymorphisms of *XPD Asp312Asn*, *XPD Lys751Gln* and *XRCC1 Arg399Gln* on the risk of ESRD development, the wild type genotypes for each gene were taken as references (Table 2). The analysis showed that combination of *Arg/Gln* or *Gln/Gln* genotypes of *XRCC1 Arg399Gln* polymorphism with *Asp/Asn* or *Asn/Asn* of *XPDAsp312Asn* polymorphism was significantly associated with the development of ESRD ($p = 0.05$). Furthermore, combination of *Arg/Gln* or *Gln/Gln* genotypes of *XRCC1 Arg399Gln* polymorphism with *Lys/Gln* or *Gln/Gln* genotypes of *XPD Lys751Gln* polymorphism was found to increase the risk of ESRD development ($p = 0.01$). However, no significant association was found between other compound polymorphisms and the risk of developing ESRD.

The haplotype association analysis showed that the association of Gln allele of *XRCC1 Arg399Gln* polymorphism with the Asn allele of *XPDAsp312Asn* polymorphism ($p = 0.004$, OR: 8.35; 95% CI: 1.94–35.85; Table 3) or Gln allele of *XRCC1 Arg399Gln* polymorphism with the Gln allele of *XPD Lys751Gln* polymorphism ($p = 0.003$, OR: 9.22; 95% CI: 2.14–39.71; Table 4) was highly significantly associated with the development of ESRD. Furthermore, haplotypes association of the three codons revealed that association of Gln allele of *XRCC1 399* with the Asn allele of *XPD 312* and Gln allele of *XPD 751* ($p < 0.0001$) was significantly associated with the development of ESRD (Table 5).

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.[34] Such individuals with repair capacity below the population mean can be at increased risk of developing several chronic diseases. Data regarding

Table 1. Distribution of *XPD* and *XRCC1* genotype polymorphisms in patients and controls.

Polymorphism	Controls ($n = 102$) *N* (%)	Patients ($n = 98$) *N* (%)	χ^2	*p* Value	OR (95% CI)
XPD 312					
Asp/Asp	42 (41.2)	42 (42.9)			Reference
Asp/Asn	46 (45.1)	44 (44.9)	0.00	0.99	0.96 (0.53–1.73)
Asn/Asn	14 (13.7)	12 (12.2)	0.01	0.90	0.86 (0.35–2.07)
Both (Asp/Asn-Asn/Asn)	60 (58.8)	56 (57.1)	0.01	0.92	0.93 (0.53–1.64)
Asp allele frequency	0.64	0.65			Reference
Asn allele frequency	0.36	0.35	0.01	0.93	0.93 (0.52–1.67)
XPD 751					
Lys/Lys	43 (42.2)	40 (40.8)			Reference
Lys/Gln	43 (42.2)	44 (44.9)	0.02	0.87	1.10 (0.60–2.01)
Gln/Gln	16 (15.7)	14 (14.3)	0.00	0.94	0.94 (0.41–2.17)
Both (Lys/Gln-Gln/Gln)	59 (57.8)	58 (59.2)	0.00	0.96	1.06 (0.60–1.86)
Lys allele frequency	0.63	0.63			Reference
Gln allele frequency	0.37	0.37	0.00	0.94	0.98 (0.55–1.74)
XRCC1 399					
Arg/Arg	68 (66.7)	42 (42.9)			Reference
Arg/Gln	30 (29.4)	46 (46.9)	8.13	0.004	2.48 (1.36–4.52)
Gln/Gln	4 (3.9)	10 (10.2)	4.36	0.03	4.05 (1.19–13.73)
Both (Arg/Gln-Gln/Gln)	34 (33.3)	56 (57.1)	10.51	0.001	2.67 (1.50–4.73)
Arg allele frequency	0.81	0.66			Reference
Gln allele frequency	0.19	0.34	5.12	0.02	2.22 (1.16–4.25)

Note: Data are expressed as number (%).

Table 2. Distribution of combined *XPD* and *XRCC1* genotypes among ESRD patients and control.

Genotype combinations	Controls ($n = 102$)	Patients ($n = 98$)	χ^2	p Value	OR (95% CI)
XPD 312 and XRCC1 399					
Asp/Asp and Arg/Arg	24 (23.5)	22 (22.4)			Reference
Asp/Asn or Asn/Asn and Arg/Gln or Gln/Gln	16 (15.6)	36 (36.7)	3.79	0.05	2.45 (1.08–5.60)
Asp/Asp and Arg/Gln or Gln/Gln	18 (17.6)	20 (20.4)	0.05	0.82	1.21(0.51–2.87)
Asp/Asn or Asn/Asn and Arg/Arg	44 (43.1)	20 (20.4)	2.45	0.11	0.50(0.23–1.09)
XPD 751 and XRCC1 399					
Lys/Lys and Arg/Arg	23 (22.5)	18 (18.3)			Reference
Lys/Gln or Gln/Gln and Arg/Gln or Gln/Gln	14 (23.5)	34 (34.7)	5.54	0.01	3.10 (1.29–7.45)
Lys/Lys and Arg/Gln or Gln/Gln	20 (19.6)	22 (22.4)	0.31	0.58	1.41 (0.59–3.34)
Lys/Gln or Gln/Gln and Arg/Arg	45 (44.1)	24 (24.5)	0.56	0.45	0.68 (0.31–1.50)

Note: Data are expressed as number (%).

Table 3. Haplotype association of *XPD 312* and *XRCC1 399* with ESRD.

		Frequency				
XPD 312	*XRCC1 399*	Total ($n = 200$)	Controls ($n = 102$)	Patients ($n = 98$)	OR (95% CI)	p Value
Asp	Arg	0.4726	0.47	0.4762	Reference	–
Asn	Arg	0.2674	0.3437	0.1871	0.58 (0.34–1.00)	0.051
Asp	Gln	0.1724	0.1672	0.1769	1.03 (0.52–2.04)	0.92
Asn	Gln	0.0876	0.0191	0.1599	8.35 (1.94–35.85)	0.0048

Table 4. Haplotype association of *XPD 751* and *XRCC1 399* with ESRD.

		Frequency				
XPD 751	*XRCC1 399*	Total ($n = 200$)	Controls ($n = 102$)	Patients ($n = 98$)	OR (95% CI)	p Value
Lys	Arg	0.4546	0.4625	0.4463	Reference	–
Gln	Arg	0.2854	0.3512	0.2169	0.63 (0.37–1.08)	0.094
Lys	Gln	0.1779	0.1698	0.1863	1.17 (0.63–2.19)	0.61
Gln	Gln	0.0821	0.0165	0.1504	9.22 (2.14–39.71)	0.0032

the relationship between DNA repair enzymes *XRCC1* and *XPD* polymorphisms and ESRD are limited.

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.

Our study provides no evidence of a role of *XPDAsp312Asn* and *Lys751Gln* polymorphisms, both homozygous variant (Asn/Asn and Gln/Gln) and combined heterozygous + homozygous variant genotypes (Asp/Asn-Asn/Asn and Lys/Gln-Gln/Gln) in susceptibility to ESRD. We also found no significant association between the *XPD 312Asn* and *751Gln* alleles and ESRD risk. Our findings are in agreement with the results reported by Trabulus et al.[35] in Turkish population. The frequencies of *XPD 312Asn* and *751Gln* alleles in our ESRD patients were 0.35 and 0.37, whereas in controls they were 0.36 and 0.37, respectively. Trabulus et al.[35] analyzed the *XPDAsp312Asn* and *Lys751Gln* polymorphism on a cohort which included 136 dialysis patients and 147 controls from Turkey. The frequency of the variant *XPD 312Asn* and *751Gln* alleles were 0.46 and 0.43 in cases and 0.40 and 0.43 in controls.

There may be some explanations regarding the results indicating no relationship between the polymorphisms of *XPDAsp312Asn* and *Lys751Gln* and the risk of ESRD in this study. First, the exposure and interaction of other genes participating in DNA damage recognition, repair and cell cycle regulation may have altered the effect of *XPD* and *XRCC1* polymorphisms.[36] Second, ethnic, genetic and environmental differences in allele frequency for the investigated polymorphisms might also affect the results in genetic studies. Third, different levels of exposure of certain oxidative stimuli in different individuals may have also contributed to the association between the polymorphisms of the DNA repair genes and the risk of diseases. Fourth, DNA repair capacity among individuals is variable and it is genetically determined. Everyone has a unique combination of polymorphic traits that modify susceptibility and response to drugs, exogenous and endogenous chemical toxins and carcinogenic exposures.

Regarding *XRCC1 codon 399*, our results revealed a positive association between the *XRCC1 399 Gln* variant both homozygous (*Gln/Gln*) and combined heterozygous + homozygous variant genotypes (*Arg/Gln + Gln/Gln*) and the risk of ESRD. We also observed an association between variant *XRCC1 399 Gln* allele and the risk of ESRD. These results suggest that the *XRCC1 Arg399Gln* polymorphism may contribute to ESRD development. Our findings are in agreement with the study conducted by Trabulus et al.[35] who reported similar finding in Turkish population. It is also consistent with the published functional studies that reported some association between *XRCC1 Arg399Gln* polymorphism and markers of DNA damage. In these studies, it has been 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,[37] comet assay (single-cell gel electrophoresis) in peripheral lymphocytes,[21] 8-hydroxy 2-deoxyguanosine content in leukocytes[38] and mitochondrial DNA deletions in skeletal muscle. Moreover, the *XRCC1 399Gln* gene variant has been associated with arthrosclerotic coronary artery disease, schizophrenia, pterygium, cataracts and systemic lupus erythematosus[3,39–41] as well as various cancer types such as breast, lung, prostate, renal, carcinomas of head and neck, stomach, colon and acute lymphoblastic leukemia.[42–49]

Table 5. Haplotype association of *XPD 312*, *XPD 751* and *XRCC1 399* with ESRD.

			Frequency				
XPD 312	*XPD 751*	*XRCC1 399*	Total ($n=200$)	Controls ($n=102$)	Patients ($n=98$)	OR (95% CI)	p Value
Asp	Lys	Arg	0.3923	0.408	0.3821	Reference	–
Asp	Lys	Gln	0.1512	0.1454	0.1487	1.19 (0.56–2.52)	0.65
Asp	Gln	Arg	0.0797	0.0638	0.1038	1.60 (0.63–4.03)	0.32
Asn	Lys	Arg	0.0613	0.0581	0.0725	1.32 (0.50–3.48)	0.57
Asn	Gln	Gln	0.0593	0	0.1404	–	<0.0001
Asn	Lys	Gln	0.0277	0.0208	0.0292	1.35 (0.33–5.54)	0.68
Asp	Gln	Gln	0.0218	0.02	0.0184	–	0.89

Combinations of common genetic polymorphisms may increase or decrease the susceptibility to certain diseases.[50] 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 *Asp/Asn* or *Asn/Asn* genotypes of *XPDAsp312Asn* polymorphism or *Lys/Gln* or *Gln/Gln* genotypes of *XPD Lys751Gln* polymorphism may increase the risk of ESRD development. These results are in agreement with Trabulus et al. study.[35] We did not find any association between combination of *Asp/Asp* genotype of *XPDAsp312Asn* polymorphism with *Arg/Gln or Gln/Gln* genotypes of *XRCC1 Arg399Gln* polymorphism and ESRD risk. This is in contrast to the Trabulus et al.[35] findings, who reported a positive association between these combined genotypes and ESRD in Turkish population. Furthermore, our results revealed that the combined *Lys/Lys* genotype of *XPD Lys751Gln* and Arg/Gln or Gln/Gln genotypes of *XRCC1 Arg399Gln* did not increase with the risk of ESRD. *Lys/Lys* genotype of *XPD Lys751Gln* polymorphism has been reported previously to have a protective effect against certain diseases.[51,52]

Haplotype association of *Gln* allele of *XRCC1 Arg399Gln* with either Asn allele of *XPDAsp312Asn* or *Gln* allele of *XPD Lys751Gln* polymorphism may also increase the risk of ESRD development. Furthermore, haplotypes association of the three codons revealed that association of Gln allele of *XRCC1 399* with the Asn allele of *XPD 312* and Gln allele of *XPD 751* was significantly associated with the development of ESRD.

The limitations of this study are the small population size. The study measured only the genetic variants of *XPD* and *XRCC1*. Other risk factors of ESRD were not determined and hence multivariate regression analysis was not done.

In conclusion, our study demonstrated that *XRCC1 Arg399Gln* polymorphism may contribute to individual susceptibility to ESRD. 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.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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