The Possible Role of XRCC1 Gene Polymorphisms with Idiopathic Non-obstructive Azoospermia in Southeast Turkey

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Purpose: X-ray repair cross-complementing group 1 (XRCC1) plays a role in repairing DNA damage during spermatogenesis. We examined the effects the possible role of two single nucleotide polymorphisms of XRCC1 Arg-194Trp and Arg399Gln in DNA repair gene XRCC1 with risk of idiopathic non-obstructive azoospermia (INOA) in a south-east Turkey population.

Materials and Methods: The genotype and allele frequencies of two observed polymorphisms of XRCC1 Arg-194Trp and Arg399Gln were examined by polymerase chain reaction-restriction fragment length polymorphism in 102 infertile men with INOA and 102 fertile controls.

Result: In our study, all the observed genotype frequencies were in agreement with Hardy-Weinberg equilibrium. The genotype frequencies of the XRCC Arg194Trp were 84% (CC), 16% (CT) and 2% (TT) among the men with INOA, while the frequencies of those genotypes in the controls were found to be 88% (CC), 12% (CT) and 2% (TT) ($P < .05$). Similarly, the genotypes frequencies of GG, GA, and AA of the XRCC1 Arg399Gln were 44%, 39%, and 19% in the group of men with INOA, whereas these frequencies were 42%, 45%, and 15% in the control group, respectively. No significant difference between the control group and the men with INOA were found in the frequencies of genotypes and allele of XRCC1 Arg194Trp and Arg399Gln ($P > 0.05$).

Conclusion: Neither Arg194Trp nor Arg399Gln polymorphisms in the XRCC1 gene influenced risk of INOA in our study. However, these findings may be helpful in improving the understanding of the etiology of male infertility.

Keywords: DNA repair; idiopathic azoospermia; male infertility; single-nucleotide polymorphism; *XRCC1*.

INTRODUCTION

Male factor infertility is a multifactorial complex disorder that affects about 7% of male from the general population.[1,2] The most common cause of male infertility is impaired spermatogenesis, in which azoospermia is present in about 10%–15%.[3] Azoospermia is characterized by no spermatozoa in semen and can be caused by either a physical blockage in the genital track, known as obstructive azoospermia, or spermatogenic failure, known as non-obstructive azoospermia.[4] In about 50% of non-obstructive azoospermia, the causes of infertility are unknown and categorized as idiopathic.(5–8) In approximately 15% of idiopathic non-obstructive azoospermia cases (INOA), the etiology is related to known genetic disorders including chromosomal aberrations and single gene mutations, such as Y-chromosome microdeletions. However, approximately half of INOA has some unidentified genetic basis, and this suggests that polymorphism of genes in autosomal chromosomes may also play an important role in the spermatogenesis.[5–8]

Spermatogenesis is regulated by many infertility-related genes which is about 10% in the genome.[9] Up to the present, approximately 150 DNA repair genes have been identified, and most of them are known to have genetic variations in humans.[6] Among them, X-ray repair cross-complementing group 1 (XRCC1) is a well-studied DNA repair gene. It encodes a protein that interacts with several DNA repair proteins and plays a critical role in base excision repair (BER) pathway. XRCC1 is located on chromosome 19q13.2 and contains 17 exons.(5, 8) Many studies have been reported that the single-nucleotide polymorphisms (SNPs) in XRCC1 may be associated with the change of the DNA damage-repair response, which may be risk factor for various complex diseases such as cancer.[10] XRCC1 knockout in mice has shown that XRCC1 is the most abundant gene in pachytene spermatocytes as well as in round spermatids, and it is suggested that this might maintain spermatogenesis by repairing DNA damage during meiosis in germ cells. However, there have been only a few studies so far that examine the association between the XRCC1 polymorphisms and the risk of male infertility in human.[8] Therefore, in the current study, we aimed to investigate the possible association between

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Table 1. Primer sequences, annealing temperature, restriction enzyme and allele sizes used for Arg194Trp and Arg399Gln polymorphisms of XRCC1 gene.

NCBI SNP*	Primer sequences	Annealing temperature (°C)	Restriction enzyme	Allele size
rs 1799782; Arg194Trp (580C>T)	F: 5´- GCCAGGGCCCCTCCTTCAA-3´ R: 5´- TACCCTCAGACCCACGAGT-3´	57	PvuII	C:485 T:396+89
rs25487; Arg399Gln (1196G>A)	F: 5´-TTG TGC TTT CTC TGT GTC CA-3´ R: 5´-TCC TCC AGC CTT TTC TGA TA-3´	68	MspI	A: 615 G:374+221

*www.ncbi.nlm.nih.gov/gene

two known SNPs of Arg194Trp and Arg399Gln of the XRCC1 gene and INOA in a south-east Turkey population. Understanding the molecular mechanism of abnormal spermatogenesis and the genes involved are important in developing both diagnostic tools and treatment strategies for male infertility.[9]

PATIENTS AND METHODS

Study population

The total 102 infertile men aged between 22 and 39 were included in this study. All infertile men are diagnosed with INOA, with at least one year of infertility. All men underwent at least two semen analyses. The semen analysis for sperm concentration, motility and morphology was performed according to the World Health Organization criteria.[11] Inclusion criteria for the INOA group were primary infertility; absence of any known causes of infertility; clinical eugonadism; azoospermia and normal karyotype. Individuals with known causes of infertility, including genetic factors (e.g. karyotyping, and Y-chromosome microdeletion screening), lifestyle factors (e.g. alcoholism and occupation), clinical factors affecting the fertility (varicocele, cryptorchidism and infections, etc.) and men whose partner had factors involved in infertility were excluded from this study. The control group was consisted of 102 fertile controls with their ages ranging from 24 to 41 years. The controls were selected from fertile men who had at least one child without assisted reproductive technologies and had normal semen sperm parameters, and all the control cases had the normal karyotype. Both the infertile men and the fertile controls were recruited within the same geographical region in the Southeastern Anatolia Region of Turkey.

All studied men were referred from the Urology Department to the Medical Biology and Genetics Department at Dicle University Hospital. The study was approved by the Ethics Review Board of Dicle University's Faculty of Medicine (reference number 87/26.02.2016).

SNPs selection and genotyping of XRCC1 gene polymorphisms

In the present study, for genotyping, we selected two known SNPs of the XRCC1 gene; Arg194Trp in exon 6 (rs1799782, NG_033799.1:g.27157C>T, NM_006297.2:c.580C>T) and Arg399Gln in exon 10 (rs25487, NG_033799.1:g.29005A>G, NM_006297.2:c.1196A>G), which can alter DNA repair capacity. SNPs were selected from the HapMap project and PubMed (http://www.ncbi.nlm.nih.gov/pubmed). The SNP ID number and detailed sequence information are available in the public SNP database[6]. After informed consent from each subject, 2 mL heparinised peripheral venous blood was collected using a vacuum tube containing ethylenediaminetetra acetic (EDTA) to prevent coagulation. All samples were stored in tubes at -20°C until the DNA extraction. Genomic DNA was extracted from whole blood using whole blood genomic DNA purification kit (Thermo Scientific, St. Leon-Rot, Germany) explained in our previous study,[12] then was stored at −80°C until using

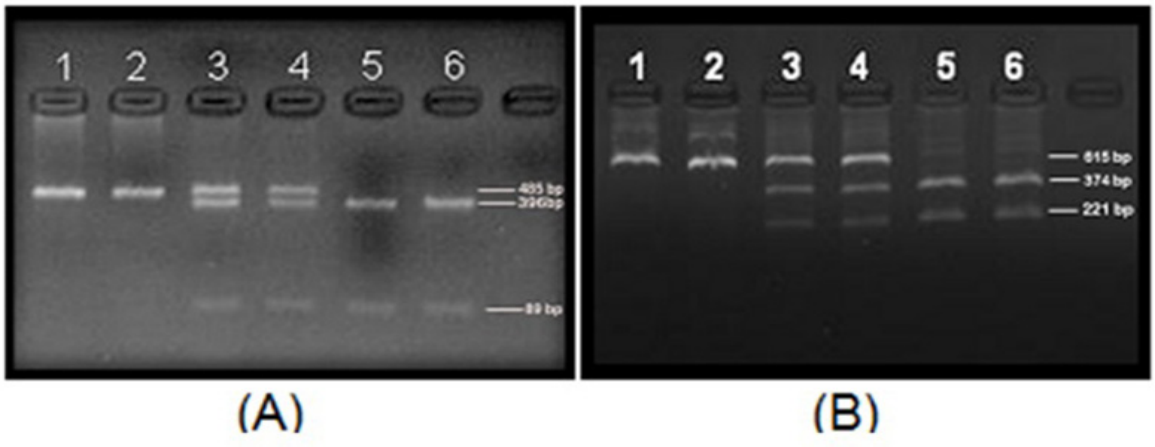

Figure 1. PCR-RFLP products of XRCC1 gene Arg194Trp and Arg399Gln polymorphisms obtained by 3% agarose gel electrophoresis. **(A)** Arg194Trp polymorphism; lanes 1,2: homozygous CC alleles; lanes 3,4: heterozygous CT alleles; Lanes 5,6: homozygous TT alleles. **(B)** Arg399Gln polymorphisms; lanes 1,2: homozygous AA alleles; lanes 3,4: heterozygous GA alleles; Lanes 5,6: homozygous AA alleles.

Table 2. Genotype distributions and allele frequencies of XRCC1 Arg194Trp (C>T) and Arg399Gln (G>A) polymorphisms in infertile men with idiopathic nonobstructive azoospermia (INOA) and fertile controls.

	Infertile men N = 102 (%)	Controls N = 102 (%)	OR	95% CI	*P*-value
XRCC1 580C>T (Arg194Trp)					
Genotype					
CC	84 (82%)	88 (86%)	Reference		
CT	16 (16%)	12 (12%)	1.39	0.62-3.12	.41
TT	2 (2%)	2 (2%)	1.04	0.14-7.60	.96
Allele					
C	184 (90%)	188 (92%)	Reference		
T	20 (10%)	16 (8%)	1.27	0.64-2.54	.48
XRCC1 1196G>A (Arg399Gln)					
Genotype					
GG	44 (43%)	42 (41%)	Reference		
GA	39 (38%)	45 (44%)	0.82	0.45-1.51	.53
AA	19 (19%)	15 (15%)	1.20	0.54-2.68	.64
Allele					
G	127 (62%)	129 (63%)	Reference		
A	77 (38%)	75 (37%)	1.04	0.69-1.55	.83

The distribution of the genotypes among the control subjects was in agreement with that predicted under the conditions of Hardy-Weinberg equilibrium (χ^2 test: $P = .060$ for the Arg194Trp polymorphism and $P = .605$ for the Arg399Gln polymorphism).

it for genotyping.

Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used to genotype two SNPs of XRCC1, Arg194Trp and Arg399Gln, with the use of appropriate primer sets and restriction enzyme as previously described.[13,14] The primer sets and enzymes were used in this study are shown in **Table 1**.

The PCR reaction was performed in a 20 µL reaction volume containing 1xPCR buffer, 80 ng of DNA, 2 mmol/L MgCl2,0.2 mmol/L of each dNTP (Fermentas, St. Leon-Rot, Germany), 1 unit of Taq DNA Polymerase (Fermentas) and 0.2 mmol/L of primer for codon 194 or 0.8 µM primer for codon 399 (Bio Basic Inc., Markham, Canada).

A thermal cycler (Senso-Quest labcycler, SensoQuest GmbH, Göttingen,Germany) was used with the following conditions: 4 min of initial denaturation at 94°C, followed by 30 amplification cycles. Each cycle was consisted of denaturation at 94°C for 30s, annealing at 57°C and 68°C (for codon 194 and codon399, respectively) for 30 sand extension at 72°C for 30 s, with a final extension step of incubation at 72°C for 5 min.

For genotyping of the Arg194Trp and Arg399Gln SNPs of XRCC1 gene, RFLP analysis was carried out by using the restriction enzymes PvuII and MspI (New England Biolabs, Beverly, MA, USA). PCR products were digested by PvuII and MspI restriction enzymes, respectively, at 37°C overnight. The digested products were then separated on a 3% agarose gels (FMC Bioproducts) along with a 100–1500 bp DNA ladder (BioBasic Inc., Markham, Canada) and stained with ethidium bromide. Ethidium bromide- stained gels were analysed using the AlphaImager Imaging System (AlphaInnotech, San Leandro, CA, USA).

The 485 bp fragment of codon 194 yielded a 396 + 89 bp band, acting as an indicator of complete digestion. XRCC1 Arg194Trp genotypes CC (Arg/Arg), CT (Arg/Trp), and TT (Trp/Trp) generated 485 bp, 485 + 396 bp and 396 bp DNA bands, respectively (**Figure 1.A**). XRCC1 codon 399 Arg allele generated 2 DNA bands (221 and 374 bp), whereas the variant Gln allele has a single 615 bp uncut band, and the heterozygote (Arg/Gln) displays all 3 bands (615, 374 and 221 bp) (**Figure 1.B**).

Statistical analysis

A goodness-of-fit Chi-square test was used to determine the Hardy-Weinberg equilibrium of the observed genotype frequencies. Statistical significance was defined as $P < .05$ and all statistical tests were two-tailed. The results were expressed as means with standard deviation (± SD) if the variables were continuous and as percentage if the variables were categorical. All statistical data were obtained using SPSS software (SPSS 11.5 for Windows, SPSS Inc., Chicago, IL, USA).

RESULTS

In this study, we analyzed the distribution of XRCC1 Arg194Trp and Arg399Gln polymorphisms in a sample of 102 men with INOA and 102 fertile controls in a Turkish population and investigated their possible associations with INOA.

The genotype and allele frequencies of the XRCC Arg194Trp and Arg399Gln polymorphisms for the cases and controls and their associations with the risk of INOA are shown in **Table 2**. All observed SNPs were in agreement with HWE (χ^2 test: $P = .060$ and .605, respectively).

The genotype frequencies of the XRCC Arg194Trp were 84% (CC), 16% (CT) and 2% (TT) among the men with INOA, while the frequencies of those genotypes in the controls were found to be 88% (CC), 12% (CT) and 2% (TT) (χ^2 test: $P < .05$). Similarly, the genotypes frequencies of GG, GA, and AA of the XRCC1 Arg399Gln were 44%, 39%, and 19% in the group of men with INOA, whereas these frequencies were 42%, 45%, and 15% in the control group, respectively. However, these differences were not statistically significant among the cases and controls using the $P < .05$ threshold ($P = .611$ for Arg194Trp, and $P = .064$ for Arg399Gln).

Table 3 shows comparison of mean values (± SEM) of semen analysis parameters, such as ejaculated volume, sperm count, total motility and normal morphology between fertile (control) and azoospermic group. Semen volume was significantly lower in azoospermic group ($P < .001$).

Table 3. Semen analysis parameters of fertile (control) and infertile men with idiopathic nonobstructive azoospermia (INOA).

Parameters	Fertile (control) (n = 102)	Azoospermic (n = 102)
Volume (mL)	3.25 ± 1.37	2.15 ± 1.37
Sperm count (million/mL)	80.35 ± 44.23	0
Total motility (%)	71.16 ± 18.26	0
Normal morphology (%)	63.25 ± 5.49	0

All values are expressed as mean ± SEM.

DISCUSSION

Several single nucleotide polymorphisms have previously been identified as responsible for male infertility. For example; in a case-control study, the possible association of SNPs in the follicle-stimulating hormone receptor (FSHR) gene and male infertility have been investigated in south-east Turkey, and the results showed that the FSHR haplotype is not associated with different serum FSH levels. However, it has been showed a different distribution between fertile and infertile men.[15] In another study, the association of the methylenetetrahydrofolate reductase (MTHFR), methionine synthase reductase (MTRR) and methylenetetrahydrofolate dehydrogenase (MTHFD1) genes polymorphisms have been investigated in INOA among a population in south-east Turkey. There has been found a synergistic interaction between some polymorphisms. Therefore, this suggested that there has been no individual, but interactive association between four prominent folate metabolism pathway markers and male infertility.[2] Furthermore, Balkan et al.[16] have investigated the association of the SNPs of FAS/FASLG genes in male infertility. Their results suggested that the AA-GG binary genotype for FAS-670A/G SNP might be a genetic predisposing factor of INOA among south-eastern Anatolian men. In a recent study, the possible association of the microRNA-related genes and male infertility have been investigated in a population of south-east Turkey[17], and the results have showed a significant difference between patients and control groups for the individual AA genotype frequency of the GEMIN3 (rs197388) gene. It has indicated that the AA genotype may be considered as indicative of a high predisposition to INOA. Recently, the potential role of the ICAM-1 gene polymorphism has been investigated in male infertility with INOA in a Turkish population. It has been found that the E469K polymorphism of ICAM-1 is not posing a risk for INOA.[3]

Various studies have shown that the single nucleotide polymorphisms in DNA repair genes affect DNA repair capacity, and the absence or decrease of DNA repair ability may increase the risk of several syndromes, such as renal disease, cancer, coronary artery disease and other diseases.[18,19] However, very few studies have reported the associations between these polymorphisms in male infertility. In our study, we investigate the associations of two well-characterized polymorphisms (Arg194Trp and Arg399Gln) of XRCC1 gene with risk of INOA in a south-east Turkey population to reveal the possible role of genetic polymorphisms in XRCC1 gene during spermatogenesis. We did not identify any association between Arg194Trp and Arg399Gln polymorphisms and the risk of INOA. Although the association of the XRCC1 Arg194Trp and Arg399Gln polymorphisms in male infertility has been shown previously,[5–8] as yet, there has been no final conclusion about the association of those polymorphisms in male infertility. For example, Gu et al.[6] has explored the possible role of the XRCC1 Arg399Gln polymorphism in the susceptibility to risk of INOA in a Chinese population and found that the AA genotype of Arg399Gln showed a significant association with a increased risk of INOA. These results are consistent with the study of Zheng et al.[8], which indicated that Arg399Gln SNP of XRCC1 gene could be a marker for genetic susceptibility to INOA and the A allele might be a risk gene of INOA in Northern Chinese Han population. However, Ghasemi et al.[20] has reported a conflicting result, which indicated that there has been no significant association between XRCC1 Arg399Gln polymorphism and risk of male infertility. In addition, another study investigated the associations of three polymorphisms (T-77C, Arg-194Trp, and Arg399Gln) in XRCC1 gene with risk of INOA in a Chinese population. They do not have any evidence of involvement of XRCC1 T-77C and Arg-194Trp polymorphisms in INOA.(7) In another study, the effects of the XRCC1 polymorphisms (T-77C, Arg194Trp, Arg280His, Arg399Gln) on male infertility have been explored in a Chinese population. They do not have any evidence of involvement of XRCC1 T-77C, Arg194Trp, and Arg280His polymorphisms in INOA.[5] In another report, XRCC1 polymorphisms (Arg194Trp, Arg399Gln) and xerodermapigmentosum group D (XPD) polymorphism (Lys751Gln) are investigated whether there was a risk of developing INOA in a Chinese population. They founded that the XPD 751Gln allele was seemed to be a risk allele for azoospermia. When combined the XPD 751 Lys/ Gln+Gln/ Gln genotype with the XRCC1 194 Arg/Arg or 399 Arg/Arg genotype, the risk of azoospermia increased. In conclusion, their study showed that the XPD and XRCC1 polymorphisms have contributed to the risk of

Table 4. The XRCC1 Arg194Trp and Arg399Gln allele frequencies among control groups of various populations.

Population	Arg194Trp		Arg399Gln		References
	Arg399 (%)	399Gln (%)	Arg194 (%)	194Trp (%)	
Chinese	79	21	88	12	[10]
Korean	75	25	67	33	[19]
Thai	75	25	70	30	[26]
Indian	78	22	87	13	[27]
German	68	32	93	7	[24]
Italian	72	28	92	8	[25]
Turkish	66	34	91	9	[21]
Turkish	69	31	89	11	[22]
Turkish	65	35	94	6	[23]
Turkish	63	37	92	8	This study

developing INOA.[6,7] It is speculated that the results of these studies might be attributed to differences in sample size, ethnic background and geographic variations. There is much evidence in the literature that the frequencies of genetic polymorphisms vary among different populations. In our study, 102 fertile controls were within the same geographical region in the Southeastern Anatolia Region of Turkey. The allele frequencies for the Arg399Gln and Arg194Trp variants of XRCC1 gene among various control populations are presented in Table 4. In the present study, the frequencies of these variant alleles were similar to the frequencies reported for other Turkish studies.[21–23] Besides, allele frequencies for these variants that found in the present study for Turkish population were quite similar to the frequencies reported for other Caucasian population (German and Italian).[24,25]

CONCLUSIONS

Our data suggests that the genotype of Arg399Gln and Arg194Trp polymorphisms are not associated with INOA in a Turkish population. Therefore, this does not appear to be responsible for spermatogenic failure in male infertility. Since sample size is a significant factor affecting the result of case–control association studies, more works with large sample size and more various populations are needed to further explore the pathophysiology of these functional SNPs in INOA. In addition, it may be far better to investigate the role of XRCC1 Arg194Trp and Arg399Gln SNPs and their relationship to the sperm DNA damage levels in the etiopathogenesis of INOA.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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