

Association of Arg194Trp, Arg280His and Arg399Gln Polymorphisms in X-ray Repair Cross-Complementing Group 1 Gene and Risk of Differentiated Thyroid Carcinoma in Iran

Pezhman Fard-Esfahani^{*1}, Armaghan Fard-Esfahani², Shima Fayaz¹, Bahareh Ghanbarzadeh³, Parinaz Saidi¹, Reyhaneh Mohabati¹, Seyed Kazem Bidoki³ and Mina Majidi²

¹Dept. of Biochemistry, Pasteur Institute of Iran, Tehran; ²Research Institute for Nuclear Medicine, Tehran University of Medical Sciences, Tehran; ³Dept. of Biochemistry and Genetics, Payam-e-Noor University of Tehran, Tehran, Iran

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ABSTRACT

Background: X-ray repair cross-complementing group 1 (*XRCC1*) gene is a DNA repair gene and its non-synonymous single nucleotide polymorphisms (SNP) may influence DNA repair capacity which has been considered as a modifying risk factor for cancer development. **Methods:** A case-control study was conducted to investigate impact of three frequently studied polymorphisms (*Arg194Trp*, *Arg280His* and *Arg399Gln*) on developing differentiated thyroid carcinoma (DTC). **Results:** Increased risks for DTC were shown in homozygous (odds ratio [OR]: 3.66, 95% confidence interval [CI]: 0.38-35.60) and in dominant trait (OR: 1.22, 95% CI: 1.64-2.32) of *Arg194Trp* genotype. Also, for *Arg280His* genotype, an increased risk for DTC was shown in dominant trait (OR: 1.42, 95% confidence interval [CI]: 0.76-2.68), while a mildly reduction of risk for DTC (OR: 0.77, 95% [CI]: 0.50-1.17) was estimated in dominant *Gln* genotype of *Arg399Gln*. Considering combinatory effects of *Arg194Trp* and *Arg280His* genotypes on DTC, the calculated OR and 95% CI for being heterozygous for one of *Arg194Trp* or *Arg280His* genotypes were 1.57 and 0.90-2.74, respectively. **Conclusion:** Genotyping of codons 194, 280 and 399 in *XRCC1* gene may use in risk assessment of DTC. *Iran. Biomed. J.* 15 (3): 73-78, 2011

Keywords: Endocrine related cancer, DNA repair gene, X-ray repair cross-complementing group 1 (*XRCC1*) gene, Differentiated thyroid carcinoma (DTC)

INTRODUCTION

Exogenous and endogenous mutagens damage DNA, which may result in uncontrolled cell proliferation or programmed cell death. To protect the integrity of genome, some DNA repair systems have been developed in variety of organisms from bacteria to mammals. A few pathways of DNA repair operate on specific types of damaged DNA. Among them, base excision repair (BER) operates on nil lesions [1] and more than 20 gene products are related to BER [2]. The X-ray repair cross-complementation group 1 (*XRCC1*) protein plays an important role in BER [3]. The *XRCC1* is a multi-domain protein, and is required for the efficient repair of single strand breaks and damaged bases in DNA [3, 4]. This protein is essential for mammalian viability because *XRCC1* deficiency in mice results in

embryonic lethality. As DNA damage may result in somatic mutations and subsequent stimulation of DNA repair processes, it can be considered that polymorphisms of DNA repair genes may alter cell repair function capacity and lead to carcinogenesis [5]. The *XRCC1* gene is located on chromosome 19q13.2 and 17 exons of this gene encode a protein with 633 amino acids [6]. A number of single nucleotide polymorphisms (SNP) have been reported in the Ensembl database. Among them, *Arg194Trp* (rs1799782), *Arg280His* (rs25489) and *Arg399Gln* (rs25487) are highly studied and caused non-conservative changes [7]. Some studies have shown a significant association between these variants and risk of different types of human cancer [8, 9]. These findings suggest that non-conservative changes may result in DNA repair capacity, although there are inconsistent reports in favor of cancer types and

*Corresponding Author; Tel.: (+98-21) 6695 3311; Fax: (+98-21) 6646 5132; E-mail: fard-esfahani@pasteur.ac.ir

different populations [10, 11]. Rationally, it seems non-conservative that *Arg194Trp*, *Arg280His* and *Arg399Gln* substitutions may attribute to cancer susceptibility.

Thyroid carcinomas are the most frequent endocrine malignancies which among these thyroid carcinomas, more than 90 percent are differentiated thyroid carcinomas (DTC). Pathologically, DTC include papillary, follicular, and Hürthle cell carcinoma [12]. To date, exposure to ionizing radiation is the only known risk factor for thyroid cancer [13]. However, there are evidences that some gene variants including DNA repair genes influence on DTC susceptibility. *XRCCI* is one of the candidate genes which its variant relationship with thyroid cancer has not been extensively studied [14].

In the present case-control study, the genotype frequency distributions of three common *XRCCI* SNP (*Arg194Trp*, *Arg280His* and *Arg399Gln*) are compared in DTC patients and thyroid cancer-free controls using usual statistical methods.

MATERIALS AND METHODS

Cases and controls. The cases were thyroid cancer patients with DTC pathologic diagnosis after surgical excision. The controls were individuals who were thyroid cancer free. The sample volumes are indicated in Table 1. Both cases and control groups were admitted to Research Institute for Nuclear Medicine of Shariati Hospital during the period of September 2008-2009 and signed a consent form for genetic tests. Individuals with cervical lymph node involvement, any other cancer history, heavy smokers, radiation exposure history and alcohol users were excluded from the research. Controls were frequency matched to cases based on age and sex.

Genotype analysis. Peripheral blood was collected in tubes containing EDTA and genomic DNA was extracted from leukocytes by previously described method in literature. *XRCCI* codons 194 and 399 were determined using PCR-RFLP as described previously [11, 15]. Briefly, the primers used for *XRCCI* codon 194 were GCCAGGGCCCCTCCTTCAA and TACC CTCAGACCCACGAG; and for codon 399 were TCCTCCACCTGTGCTTTCT and AGTAGTCTGC TGGCTCTGGG. The PCR reactions for two polymorphisms were the same. Each 25 µl reaction contained 10 pmol of each primer, 2.0 mM MgCl₂, 200 mM each dNTP, 1 unit of *Taq* DNA polymerase (CinnaGen Smart *Taq*, Iran) and 50-250 ng of genomic DNA. The PCR conditions for codon 194 were 95°C

Table 1. Arg194Trp (A), Arg280His (B) and Arg399Gln (C): demographic and genotype frequencies of case and control subjects.

(A)

Variable	DTC (n = 157)			Controls (n = 187)	
	n	%	P ^a	n	%
Sex			0.596		
Male	34	21.7		45	24.1
Female	123	78.3		142	75.9
Age			0.137		
≤ 50	131	83.4		144	77.0
> 50	26	16.6		43	23.0
Arg194Trp			0.477		
Arg/Arg	136	86.6		166	88.8
Arg/Trp	18	11.5		20	10.7
Trp/Trp	3	1.9		1	0.5
Trp allele frequency		7.6	0.357		5.9

(B)

Variable	DTC (n = 170)			Controls (n = 193)	
	n	%	P ^a	n	%
Sex			0.826		
Male	38	22.4		45	23.3
Female	132	77.6		148	76.7
Age			0.173		
≤ 50	141	82.9		149	77.2
> 50	29	17.1		44	22.8
Arg280His			0.411		
Arg/Arg	146	85.88		173	89.64
Arg/His	23	13.53		18	9.33
His/His	1	0.59		2	1.04
His allele frequency		30.3	0.366		33.4

(C)

Variable	DTC (n = 155)			Controls (n = 190)	
	n	%	P ^a	n	%
Sex			0.700		
Male	34	22		45	23.7
Female	121	78		145	76.3
Age			0.131		
≤ 50	130	83.9		147	77.4
> 50	25	16.1		43	22.6
Arg280His			0.401		
Arg/Arg	78	50.3		83	43.7
Arg/Gln	60	38.7		87	45.8
Gln/Gln	17	11		20	10.5
Gln allele frequency		30.3	0.385		33.4

^aP<0.05 is significant

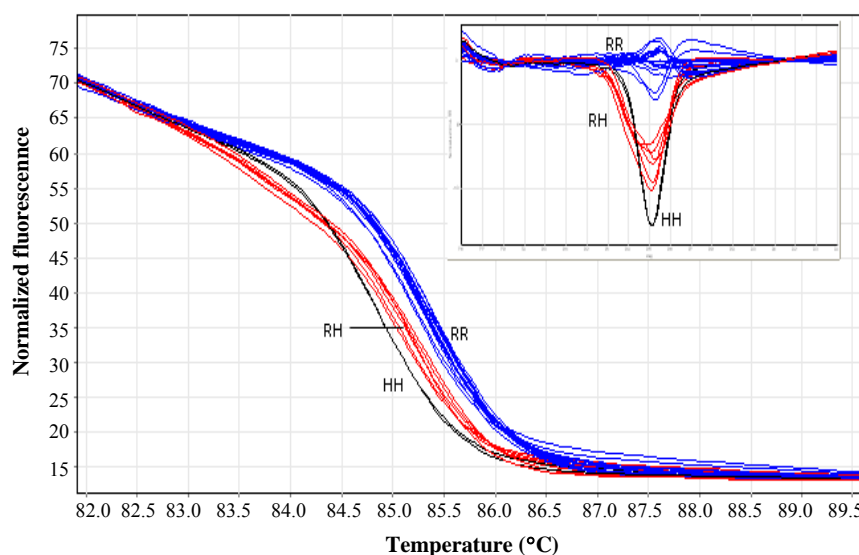


Fig. 1. High resolution melting of *XRCC1* gene in 25 samples. RR-, RH- and HH-type curves are shown as RR, RH and HH, respectively. Small box shows difference graphs.

for 2 min; 35× (95°C for 30 s, 57°C for 30 s and 72°C for 45 s); 72°C for 7 min and for codon 399 were 95°C for 2 min; 35× (95°C for 30 s, 61°C for 30 s and 72°C for 45 s); 72°C for 7 min. PCR products of codon 194 (485 bp) and codon 399 (517 bp) were digested by *PvuII* and *BclI* restriction enzymes (Fermentas, Switzerland), respectively. Using submarine electrophoresis, the DNA fragments were separated in 2% agarose gel and visualized by ethidium bromide. The expected fragments for codon 194 were 485 bp (194Arg) and 396 plus 89 bp (194Trp) as well as for codon 399 were 384 and 133 bp (399Arg) and 517 bp (399Gln).

For *Arg280His* genotyping, we developed a high resolution melting (HRM) technique and confirmed the 280His alleles by RLFP. A 125-bp fragment of *XRCC1* gene containing codon 280 was proliferated using CCC CAG TGG TGC TAA CCT AAT and CTT CTC CTC GGG GTT TGC C primers. The PCR-HRM reactions carried out in 10- μ l reactions using Type-it HRM PCR Kit (Qiagen, Germany) contained 10 pmol of each primers and 20-50 ng genomic DNA. The thermocycling program was 95°C for 5 min; 45× (95°C for 30 s, 60°C for 30 s and 72°C for 10 s); 72°C for 4 min, followed by Pre-HRM heteroduplex enrichment (95°C for 10 s; 65°C for 5 min) and HRM protocol was ramp from 75°C to 95°C, rising by 0.05°C each step and waiting for 2 s in each step. As it was the first time that PCR-HRM used for genotyping of *Arg280His* change in *XRCC1* gene, for confirmation, all samples showed 280His allele were subjected to *RsaI* restriction enzyme treatment.

Statistical analysis. The relationship between the

XRCC1 codons 194, 280 and 399 genotypes and DTC risk was analyzed by two-sided Chi-squared tests. In each codon we calculated the relative risk of the homozygous patients (*Trp/Trp* for codon 194, *His/His* for codon 280 and *Gln/Gln* for codon 399), heterozygous patients (*Arg/Trp* for codon 194, *Arg/His* for codon 280 and *Arg/Gln* for codon 399) compared with the wild type *Arg/Arg* genotypes (all three codons) for amino acid substitutions. Moreover, the recessive and dominant effects of the mentioned substitutions were estimated (codon 194: *Trp/Trp* versus *Arg/Trp* + *Arg/Arg* and *Trp/Trp* + *Arg/Trp* versus *Arg/Arg*, respectively; codon 280: *His/His* versus *Arg/His* + *Arg/Arg* and *His/His* + *Arg/His* versus *Arg/Arg*, respectively; codon 399: *Gln/Gln* versus *Arg/Gln* + *Arg/Arg* and *Gln/Gln* + *Arg/Gln* versus *Arg/Arg*, respectively). In addition, relative risks of having combinatory heterozygous form of three codons were calculated. The relative risk was expressed as odds ratio (OR) with 95% CI using logistic regression analyses.

Based on observed genotypes, the haplotype analysis was performed using PHASE program [16] for reconstruction of haplotypes. The frequencies of haplotypes were compared by chi-squared tests and the relative risks were estimated.

RESULTS

Sex distributions of case and control subjects in addition to detailed genotype analysis results for the 194Trp, 280His and 399Gln are demonstrated in Table 1.

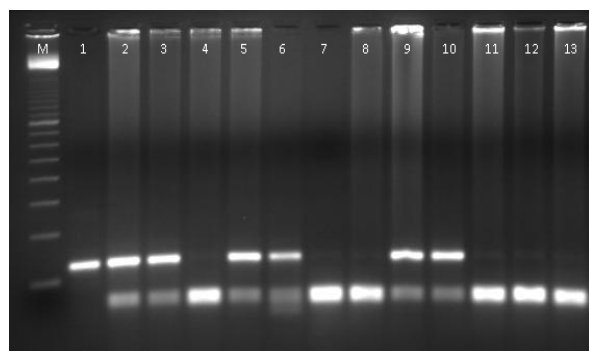


Fig. 2. RFLP of samples treated by *RsaI* restriction enzyme. Lane 1, untreated; lanes 2, 3, 5, 6, 9 and 10, 280RH; lanes 4, 7, 8, 11, 12 and 13, 280RR; M, 100 bp DNA ladder. Gel: agarose 3.5%.

Genotyping of *194Trp* and *399Gln* was done by PCR-RFLP method (Fig. 1), while PCR-HRM and PCR-RFLP was used for *280His* codon (Fig. 2).

According to the Hardy-Weinberg equilibrium model, the frequencies of observed genotypes of the controls did not deviate significantly from those expected (*194Trp*: $\chi^2 = 0.217$, $df = 1$, $P > 0.05$; *280His*: $\chi^2 = 3.382$, $df = 1$, $P > 0.05$; *399Gln*: $\chi^2 = 0.159$, $df = 1$, $P > 0.05$).

In *Arg194Trp*, *Arg280His* and *Arg399Gln* genotypes, the differences in genotype frequency distributions between DTC cases and controls were not significant ($P = 0.477$, $P = 0.411$ and $P = 0.401$, respectively). Calculated OR are presented in Table 2. For the *Arg194Trp* change, a 3.6-fold increase in risk for DTC was estimated in homozygous *Trp* genotype. Also, when considering *Trp* as recessive trait, the risk was in concordance with it (3.62 fold). By separating *Arg194Trp* genotypes into groups with and without the *Trp* allele, the OR was calculated as 1.32 in favor of having DTC. In case of *Arg280His* change, the dominant *His* genotype was associated with increased DTC (OR: 1.42, 95% [CI] 0.76-2.68). Finally, in

Arg399Gln change, the dominant *Gln* genotype was borderline associated with reduction of DTC. Sex and age adjusted OR showed the same trend as the crude OR for all alleles.

Association between carrying different combinatory forms of heterozygous alleles and DTC were estimated and stated as OR. Considering combination of *Arg194Trp* and *Arg280His* heterozygous genotypes, the association between "being heterozygous in only one site" was borderline significant (OR 1.57, 95% [CI] 0.90-2.74, $P = 0.111$). The other data were not significant and not shown.

The retrieved haplotype frequencies and OR are shown in Table 3. The OR were calculated by comparison of each haplotype with the most frequent one (CGG) in controls. No significant risk association between *XRCC1* haplotypes and DTC cases was found.

DISCUSSION

For the first time in Iran, the role of *XRCC1* gene polymorphisms in relation with DTC was examined in a case-control study.

The impact of changes in DNA repair genes including *XRCC1* gene has been studying in growing studies to elucidate possible susceptibility to various types of cancers [17, 18]. There are significant heterogeneities among studies due to cancer type, population and site of SNP [19-21]. There are only few studies which assessed *XRCC1* gene polymorphism relations with thyroid carcinomas. In a case-control study [22], a significant increased risk of DTC for the *Arg194Trp* homozygous polymorphic genotype was calculated ([OR: 10.4, 95% CI: (1.0-105.5), while for *Arg194Trp* heterozygous polymorphic genotype, the OR was estimated as: 1.4, 95% [CI] (0.9-2.1). These results are in concordance with those of our survey

Table 2. Crude and adjusted odd ratio (OR) and confidence interval (CI) of case and control subjects for *Arg194Trp*, *Arg280His* and *Arg399Gln* alleles.

Variable	Crude OR (95% CI), P value ^a	Sex-adjusted OR (95% CI), P value ^a	Age-adjusted OR (95% CI), P value ^a
<i>Arg194Trp</i>			
Trp/Trp vs Arg/Arg	3.66 (0.38-35.60), 0.226	3.52 (0.37-34.46), 0.437	3.34 (0.34-32.54), 0.137
Trp/Trp + Arg/Trp vs Arg/Arg ^b	1.22 (0.64-2.33), 0.545	1.21 (0.64-2.31), 0.732	1.21 (0.64-2.33), 0.276
Trp/Trp vs (Arg/Arg + Arg/Trp) ^c	3.62 (0.37-35.19), 0.229	3.53 (0.36-34.28), 0.416	3.35 (0.34-32.58), 0.131
<i>Arg280His</i>			
His/His vs Arg/Arg	0.59 (0.05-6.60), 0.12	0.58 (0.05-6.43), 0.82	0.55 (0.05-6.18), 0.44
His/His + Arg/His vs Arg/Arg ^b	1.42 (0.76-2.68), 0.275	1.42 (0.75-2.68), 0.547	1.42 (0.76-2.69), 0.214
His/His vs (Arg/Arg + Arg/His) ^c	0.57 (0.05-6.29), 0.634	0.56 (0.05-6.22), 0.87	0.53 (0.05-5.85), 0.34
<i>Arg399Gln</i>			
Gln/Gln vs Arg/Arg	0.90 (0.44-1.85), 0.784	0.90 (0.44-1.85), 0.951	0.89 (0.43-1.83), 0.270
(Gln/Gln + Arg/Gln) vs Arg/Arg ^b	0.77 (0.50-1.17), 0.219	0.76 (0.50-1.17), 0.419	0.77 (0.50-1.18), 0.154
Gln/Gln vs (Arg/Arg + Arg/Gln) ^c	1.05 (0.53-2.08), 0.895	1.05 (0.53-2.08), 0.920	1.03 (0.52-2.09), 0.314

^a $P < 0.05$ is significant, ^bdominant T allele, ^crecessive T allele

Table 3. XRCC1 haplotype frequency and risk association.

Haplotype ^a	Frequency (%)		DTC	
	DTC	Control	OR (95% CI)	P value
CGG	43.6	38.4	1.0 (Ref)	
CAG	19.9	22.3	0.79 (0.37-1.65)	0.526
CAA	15.5	20.7	0.66 (0.30-1.45)	0.308
CGA	13.1	12.4	0.93 (0.38-2.26)	0.874
TGG	5.6	4.7	1.05 (0.29-3.85)	0.942
TGA + TAG + TAA	2.3	1.5	1.35 (0.17-11.05)	0.779

^a Haplotypes follow the SNP: XRCC1 Arg194Trp, Arg280His and Arg399Gln

(Table 4). In the same research, the calculated OR for *Arg399Gln* homozygous and heterozygous were 0.5, 95% [CI] (0.3-0.8) and 0.8, 95% [CI] (0.6-1.0), respectively, demonstrating a decreased risk of DTC for *Arg399Gln* genotypes. Again, the data is in the same direction with our results. Increased risk for DTC is also shown with *Arg194Trp* [23] and *Arg399Gln* genotypes in another case-control study [24]. For *Arg280His* genotype, we found a trend toward having DTC in dominant trait (OR: 1.42, 95% [CI] (0.76-2.68) which is in opposite side of the results from both mentioned studies.

Although the haplotype analysis showed no significant results, the combined relative genetic risk of dominant trait of SNP showed some trends toward having DTC: OR $_{Arg194Trp}$ X OR $_{Arg280His}$ X OR $_{Arg399Gln}$ = 1.22 X 1.42 X 0.77 = 1.33.

All mentioned SNP studied here were missense mutations and we expected impaired function of protein. Although we found an increased risk effect of *Arg194Trp* and *Arg280His* alleles for developing DTC, a minor protective effect of *Arg399Gln* genotype was found for this type of carcinoma. The latter result is in contrast with our hypothesis.

The results are not significant, s are not conclusive, probably because of small sample size or other unknown phenomena in developing thyroid carcinomas. Clearly, larger population samples from different populations and following meta-analysis assays will give better estimation of above SNP' association with DTC.

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