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Research Article

XRCC1 Arg399Gln AND Arg194Trp POLYMORPHISMS IN WELDER OCCUPATIONALLY EXPOSED TO WELDING FUMES DWELLING IN INDUSTRIAL AREA OF HYDERABAD, TELANGANA

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ABSTRACT

Background: Welding is a common industrial process associated with various health hazards associated with increased reactive oxygen species (ROS) generation that inturn cause genotoxicity and damages the genetic material.
Objective: To investigate the inter individual variation of DNA damage and capacity of DNA repair proteins, genotoxic effects of welding workers associated with an occupational hazards in India.
Materials and Methods: A case-control study was conducted amongst 200 welder and 200 normal healthy controls in Hyderabad. Data with respect to demographic characteristics was collected using a questionnaire. Blood samples were collected from all the subjects, DNA was isolated and XRCC1 genotyping of rs1799782 and rs25487 was carried by PCR-RFLP.
Results and Discussion: Nearly 40% of the case are obese having BMI ≥23 Kg/m2. The percentage of smokers and alcoholics varied considerably between the groups. The genotype and the allele frequencies of rs1799782 and rs25487 differed significantly between the groups. Haplotype analysis revealed a correlation between four haplotypes of XRCC1 Arg194Trp and Arg399Gln polymorphisms with individuals exposed to welding fumes.
Conclusions: These findings suggest that XRCC1 rs1799782 Arg/Trp heterozygous genotype plays a protective role while Arg/Gln and Gln/Gln demonstrates a predisposing role towards genotoxicity in welder.

INTRODUCTION

Welding is ubiquitous method employed in all manufacturing industries, which pose potential, physical and chemical health hazards. Welder are exposed to a number of genotoxic metals, gases, fumes and radiations. The metal fumes produced are composed of almost 13 kinds of metal particulates, including ions of manganese (Mn), beryllium (Be), cadmium (Cd), chromium (Cr) cobalt (Cu), iron (Fe), lead (Pb), mercury (Hg), molybdenum (Mo), nickel (Ni), zinc (Zn), antimony (Sb), and vanadium (V) [OSHA., 1995] known to pose considerable health hazards. Nearly, 8,00,000 people worldwide are occupationally exposed to metal welding fumes that leads to increased reactive oxygen species (ROS) generation that inturn cause genotoxicity and damages genetic material [Singh *et al*., 2013a]. Emerging bodies evidence suggests that DNA damage in welder caused by welding-fumes, plays pivotal role in the development of several diseases like impaired pulmonary function, chronic bronchitis, interstitial lung disease, asthma, lung cancer, eye burns, short and long term skin injury and non-melanocytic skin cancer [Sultan A., 2003].

Exposure to occupational hazards which mainly contains chromium compounds especially hexavalent chromium has been known to promote damage of DNA The uncontrolled production of reactive oxygen species (ROS) can accelerate oxidative stress and DNA damage, thereby leading to genomic instability. Despite, the cellular insults DNA damage can be resurrected via respective DNA repair pathways to preserve a genomic stability. [Berm, 2005].

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The X-Ray Repair Cross-Complementation Group 1 (XRCC1) a prime gene mainly involved in BER pathway, is 33 kb long which is located on chromosome 19q13.2-13.3. XRCC1 gene repairs DNA damage induced by active oxygen, ionization radiation and alkylating agents. Alterations in the XRCC1 gene has been reported to have impaired functional consequence on sequence repairs of particular relevant nsSNP's like Arg399Gln, Arg194Trp and Arg280His have shown to influence the efficiency of DNA repair and form a risk factor for genomic instability [Iarmarcovai *et al*., 2005]. Therefore, our present study is pursued to investigate the inter individual variation of DNA damage and capacity of DNA repair proteins, genotoxic effects of welding workers associated with an occupational hazards in India.

MATERIALS & METHODS

Study population

A total of 400 study population which comprises of 200 welder and 200 healthy controls were recruited from Usha Company, Hyderabad, India and Industrial Area, Patancheru, Hyderabad, India. Written approval was obtained from the ethics committee of Osmania University and informed consent from all subjects before sampling. Information on demographics like BMI, smokers, dietary habits (Vegetarian and Non-vegetarians), were noted in a well designed proforma.

Genotyping

Five ml of blood sample was obtained from all the subjects, DNA was isolated and the polymorphisms rs1799782 and rs25487were amplified by PCR and products were confirmed using 2% agarose gel and then the amplicons were digested by treating with appropriate restriction enzymes (Fermentas, India) for 12 h at 37°C and then genotyped using 3% agarose gels.

Statistical analysis

Data was compiled and appropriate statistical analysis was carried out. Continuous data were expressed as mean ± SD. The demographic characteristics of patients and controls were compared by the Student's *t*-test for unpaired data. The association between genotypes and individuals exposed to welding fumes were evaluated by calculating the odds ratios (OR) at 95 % confidence interval. Allele and genotype frequencies were determined from observed genotype counts. Hardy Weinberg equilibrium was estimated by the χ^2 test. A two tailed p-value of <0.05 was considered to be statistically significant.

RESULTS

Demographic details

The present case-control study was conducted on a total of 200 case and 200 control subjects. The mean ages of case and controls are 35.10 ± 2.12 and 35.68 ± 2.49 years respectively. The demographic characteristics of the study population is represented in Table 1. The study subjects were classified based on demographic factors such as age, diet, addiction to smoking and alcoholism, etc. Majority of the subjects were >30years of age in both case and controls. Nearly 40% of the case are obese having BMI ≥23 Kg/m^2 while it was 28% in controls and differed significantly between the groups (p<0.05). When habits were taken into consideration, the percentage of smokers and alcoholics varied considerably between the groups.

Table 1 Demographic data of the case and control groups

		Controls	Case	Chi square(p-value)
Age	<30	7(3.5%)	12(6%)	1.38 (0.24)
	>30	193(96.5%)	188(94%)	
BMI	Obese	55(27.5%)	79(39.5%)	6.46 (0.01)*
	Non Obese	145(72.5%)	121(60.5%)	
Alcoholic	Yes	36(18%)	54(27%)	4.64(0.03)*
	No	164(82%)	146(73%)	
Smoking	Yes	33(16.5%)	61(30.5%)	10.9 (0.0009)*
	No	167(83.5%)	139(69.5%)	
Non-vegetarian	Yes	160(80%)	166(83%)	0.59(0.43)
	No	40(20%)	34(17%)	

rs1799782

Table 2 and Table 3 describes the percentage distribution of rs1799782 and rs25487 polymorphisms in patients and control groups. The overall genotype frequencies of CC, CT and TT of rs1799782 were 16 %, 51% and 33% in case while they were 9%, 67% and 24% in controls respectively. The distribution of genotypes differed significantly between the groups (p ≤0.05) while the alleles did not vary between the groups (p=1). The genotypic distributions of rs1799782 polymorphisms were in accordance with Hardy Weinberg equilibrium in case but not in controls (p < 0.01).

Table 2 Distribution of genotypes and allele frequencies of rs1799782 polymorphism in welder and control subjects.

Genotype/ Alleles	Controls	Case	Adjusted OR	p-value	AIC
Codominant					
T/T	48(24)	66(33)	1.00(Ref)		
C/T	134(67)	102(51)	0.55(0.35-0.87)	**0.003**	549.3
C/C	18(9)	32(16)	1.29(0.65-2.57)		
Dominant					
T/T	48(24)	66(33)	1.00(Ref)		
C/T-C/C	152(76)	134(67)	0.64(0.41-0.99)	**0.04**	554.5
Recessive					
T/T-C/T	182(91)	168(84)	1.00(Ref)		
C/C	18(9)	32(16)	1.93(1.04-3.56)	**0.03**	554
Overdominant					
T/T-C/C	66(33)	98(49)	1.00(Ref)		
C/T	134(67)	102(51)	0.51	**0.001**	547.9*
Allele					
C	0.43	0.42	1.00 (Ref)		
T	0.57	0.58	1.04(0.59-1.82)	1.00	

AIC Akaiki information criteria; OR Odds Ratio; CI Confidence interval; Ref Reference
*Log additive model value

Table 3 Distribution of genotypes and allele frequencies of rs25487polymorphism in welder and control subjects.

Genotype/ Alleles	Controls	Case	Adjusted OR	p-value	AIC
Co-dominant					
G/G	82(41)	50(25)	1.00(Ref)		
A/G	98(49)	76(38)	1.27(0.80-2.02)	<0.0001	516.8
A/A	20(10)	74(37)	6.07(3.31-11.13)	<0.0001	
Dominant					
G/G-G/A	82(41)	150(25)	1.00(Ref)		
G/A-A/A	118(59)	150(75)	2.08(1.36-3.19)	<0.0001	554.8
Recessive					
G/G-G/A	180(90)	126(63)	1.00(Ref)		
A/A	20(10)	73(37)	5.29(3.07-9.11)	<0.0001	515.9*

Overdominant					
G/G-A/A	102(51)	124(62)	1.00(Ref)		
A/G	98(49)	76(38)	0.64(0.43-0.95)	0.02	553.6
Allele					
G	0.66	0.44	1.00 (Ref)		
A	0.34	0.56	2.47(1.39 -4.37	0.002	557.1

AIC Akaiki information criteria; OR Odds Ratio; CI Confidence interval; Ref Reference
*Log additive model value

There was a statistical difference in the distribution of genotypic and allelic frequencies between the case and control groups in different inheritance models: codominant model: TT vs CC(OR=1.29 95% CI=0.65 - 2.57); dominant model: TT vs. CT+CC (OR=0.64, 95 % CI=0.41-0.99); overdominant model: CT vs. CC+TT (OR=0.51, 95 % CI=0.34-0.77); recessive model: CC vs CT+TT (OR=1.93 95% CI =1.04 - 3.6); and T allele vs.C allele (OR=1.04, 95 % CI=0.59-1.82).

rs25487

The genotype frequencies of AA, AG and GG of rs25487polymorphism were 25%, 38% and 37% in patients and 41%, 49% and 10% in controls correspondingly. The genotypic distributions of rs25487 polymorphisms were in accordance with Hardy Weinberg equilibrium in controls but not in case ($p < 0.01$). The genotypic and allelic frequencies between the patient and control groups differed significantly when compared with different models: codominant model: GG vs. AA (OR=6.07, 95 % CI=3.31-11.13); dominant model: GG vs. GG+AG (OR=2.08, 95 % CI=1.36-3.19); over dominant model: AG vs. GG+AA (OR=0.64, 95 % CI=0.43-0.95); recessive model: AA vs. GG+AG (OR= 5.29, 95 % CI=3.07-9.11); and G allele vs. A (OR=2.47, 95 % CI=1.39-4.37).

Haplotype Analysis

The haplotype analysis for rs1799782 and rs25487 polymorphisms using SNPstat software (http://bioinfo.iconcologia.net/ snpstats/start.htm) generated four haplotypes; T-A, T-G, C-A and C-G that differed significantly between the groups ($p<0.0001$). Individuals with G allele demonstrated an OR value of 1.99; CI: 1.28-3.07 ($p=0.0022$) while individuals with mutant alleles at both loci showed an OR of 3.18; CI: 1.84 - 5.48 ($p<0.0001$). The four haplotypes of the *XRCC1* gene consisting of two alleles of each polymorphism are shown in Table 4.

Table 4 Haplotype Analysis

Haplotypes	Patients	Controls	Comparison of groups	OR(95% CI)	p-value
T G	0.25	0.41	T vs. A	1.00	-
T A	0.33	0.16	T vs. G	3.18(1.84-5.48)	<0.0001
C G	0.19	0.24	A vs. A	1.34(0.74-2.40)	0.33
C A	0.22	0.18	A vs. G	1.99(1.28-3.07)	0.0022

DISCUSSION

Welding work is an indispensable occupation in India associated with health hazards (Anuradha *et al*., 2014) and welder are often exposed to fumes consisting of concoction of metals and its oxides which can cause genetic damage (Zorawar Singh *et al*., 2016). Zhang *et al*., in the year 2012 reported that any alteration in XRCC1 Arg399Gln could induce DNA damage associated with hexavalent chromium (Zhang *et al*., 2012). Till date, there are several studies correlating XRCC1 (Arg194Trp) with various diseases such as prostate cancer (Zhu *et al*., 2015) and lung cancer (Jing Zhang *et al*., 2014). However, there were no reports pertaining to these polymorphisms in Indian context, thus the present study was aimed to screen for XRCC1 rs1799782 and rs25487 polymorphisms in welder exposed to welding fumes in industrial area of Hyderabad, Telangana.

XRCC1 is a key factor involved in base excision repair. The XRCC1 protein interacts with repair enzymes and does not allow the rejoining of DNA strand breaks and repair gaps left unrepaired during BER (Horton *et al*., 2008). The inter-individual variations of DNA repair processes are also influenced by variants that arise genetic polymorphismsin the repair genes. The important findings of our study was the protective role of AT genotype and the predisposing role of recessive model, indicating a possible association of rs1799782 polymorphism towards welding fumes. Contrary to this, the GG and GA genotypes of rs25487 also demonstrated a significant association of this SNP with welding fumes. To the best of our knowledge, the present study was the first attempt to evaluate the role of XRCC1 rs1799782 and rs25487 polymorphisms in individuals exposed to welding fumes. Our findings were similar to the observations of Salimi *et al*., who reported a significant association of rs1799782 polymorphism with systemic lupus erythomatus (SLE) in Iranian population [Salimi]. It could be due to the significant increase of DNA damage in XRCC1 194 trp variant as reported by Marco *et al*., (2014). The XRCC1 variant allele coding Gln amino acid at position 399 is associated with cancers of the head and neck, breast, lung and colon/rectum [Goode, 2002].

Animal studies by Thacker *et al*., 2003 demonstrated the role of XRCC1 genes in mammalian double strand break repair and any defect in the gene makes the embryo lethal to alkylating agents and various other DNA damaging agents (Thacker *et al*., 2003).

In a study by Cornetta *et al*., (2006) confirmed that individuals with Gly/Gly had fewer breaks compared to Gly/Arg and Arg/Arg indicating reduced repair capacity in these individuals. Our findings were in accordance with his findings while contradictory to the observations of Wang *et al*., which demonstrated an increased tail length in healthy individuals with Gly variant. Recently Gal *et al*. (2005) have shown that XRCC1 399Gln allele was associated with a decreased risk of mortality in patients with oral cancer. Aka *et al*., 2004 illustrated that there is a change in residual DNA values due to rs25487 polymorphism and was confirmed by comet assay. The haplotypes with mutant allele at one loci (1.99 fold) as well as on both (3.18) conferred genotoxicity risk towards welding fumes.

In conclusion, our findings suggest the association of rs1799782 and rs25487 polymorphisms with DNA damage in individuals exposed to welding fumes. Furthermore, other factors such as obesity (BMI), diet, alcohol and smoking were also involved in causing genotoxicity along with SNPs. Haplotype analysis demonstrated that the mutant alleles of both SNPs confers around 1.9 fold and three fold risk towards welding fumes when the Gln allele present at one loci and Trp/Gln present at both loci. Further extensive studies with XRCC1 polymorphisms and occupational exposure of welding in different ethnic groups may help us to identify the

potentiality of these markers and inturn may help the clinician for better management of the condition.

Conflict of interest

None

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