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A case-control study on the polymorphism of DNA repair gene *XRCC1* (rs25487 and rs1799782) and its association with age related cataract (ARC)

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Abstract: **Age related cataract (ARC) is an ocular disorder which causes the blindness within age. However, the genes protect the DNA against mutations because they perform an important role during the DNA repair mechanism, but some polymorphic variations may increase the genetic susceptibility of ARC during the DNA repair process. We aimed to determine the frequency of polymorphisms in a DNA repair gene X-Ray complementing group 1 (*XRCC1)* codon399 (rs25487) and codon194 (rs1799782) in patients of ARC and to evaluate the association with the risk of age related cataract (ARC). In the present case-control study, we used polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) to analyze *XRCC1* codon399 and codon194 in 150 patients with ARC (cortical cataract (CC)- 27, nuclear cataract (NC)- 24, posterior sub-capsular (PSC)-64, and mixed type of cataract (MTC)-35) and in 150 age matched healthy controls. Our results revealed that polymorphism in *XRCC1* codon399 (rs25487), there was no statistically significant difference for genotype GG (p = 0.17) in both groups, but the data suggested that allele G (OR- 1.48, 95%CI-1.06-2.08, p = 0.02) may be associated with an increased risk of ARC. There was no statistically significant difference was found for genotypes TT (OR-0.88, 95%CI-0.53-1.45, p = 0.62), CT (OR- 1.31, 95%CI-0.69-2.51, p = 0.40) and in allelic (allele C-OR- 1.09, 95%CI- 0.79-1.51, p = 0.56) distribution of *XRCC1* codon194 (rs1799782) between ARC patients and controls.**

Keywords: **Age related cataract (ARC), single nucleotide polymorphism (SNP), DNA repair gene, Polymorphism of *XRCC1* gene.**

I. INTRODUCTION

Age related (or senile) cataract is one of the major problems of the eye lens characterized by loss of its transparency [1]. It is a multifactorial disease caused by interaction between environmental and genetic factors. There are various other risk factors which are responsible for its cause for instance: age, obesity, female gender, smoking and alcoholic consumption, steroids, sunlight, or exposure to UV light and, nutritional deficiencies has been influenced in development of cataract [2] but the etiology of age related cataract (ARC) is still unknown. Age related cataract causes damages in lens protein or cells and, it could be possible through some environmental insult on lens [3]. According to a study conducted by Global Burden of Diseases (GBD) in 2010, approximately 18.4% (35.1 million) people have moderately to severe visual impairment, whereas around 33.4% (10.9 million) people were diagnosed completely blind due to age related cataract [4]. Age related cataracts in older Indian population showed that the prevalence of both operated and un-operated cataract cases was similar in North India (73.8%) and South India (71.8%) [5].

The *XRCC1* (X-ray repair complementary group 1) protein plays a fundamental role in DNA base excision repair (BER), but it may also be involved in non-homologous end joining and the single-strand break repair pathway [6,7], has been reported to be responsible for the efficient repair of DNA damage caused by active oxygen, ionization, and alkylating agents [8].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 SSBs [8]. It was founded that DNA repair genes loses their ability to repair DNA damages which leads the susceptibility to age-related diseases like age related (or senile) cataract, glaucoma, and macular degeneration [9].

At presently, over 100 DNA repair genes have been identified and their polymorphic association has been reported in various diseases. X-ray complementing group 1 (*XRCC1*) is the only one gene who has been studied extensively [2].

II. MATERIAL AND METHODS

Study subjects: The present study included a total 300 subjects of both sexes with age between 40 to 84 years. Out of them, 150 subjects were clinically diagnosed with age related cataract (ARC). All cases were recruited from three districts of Punjab viz., Patiala, Barnala and Ludhiana and remaining subjects (n= 150) were sex and age matched healthy controls. The sampling of healthy controls was done from same regions of the state as cases. Written informed consent was taken from each subject before enrollment. Before sampling, all patients were diagnosed for different types of cataract by ophthalmologist following LOC-III classification with the help of slit lamp examination. Opacities were classified into cortical, nuclear, posterior sub-capsular and mixed type of cataract (CC, NC, PSC, MTC). The present study was approved by Institutional ethical committee of Punjabi University, Patiala.

Inclusion and Exclusion criteria for cases and controls: The present study included patients having primary cataract only. The others with secondary cataract due to hypertension, thyroid, diabetes, trauma, steroid administration, and other ocular diseases were excluded. For controls, subjects without any family history of cataract, diabetes, hypertension, thyroid, and any other ocular diseases were selected.

Methods: The demographic details along with clinical and physical profiles such as sex, height, weight, age, age on set, duration of disease, type of cataract, dietary habits, smoking and alcohol consumption and, patient's family history were recorded from both cases and controls using Specific Performa.

Blood sampling: 3ml of intra venous blood samples were collected from study subjects into EDTA vacutainer. The samples were transported to Molecular laboratory of Human Genetics department of Punjabi University, Patiala. Genomic DNA was isolated from both cases and controls using salting out method [10].

Statistical Analysis: The distribution of demographical characteristics among cases and control groups were compared using the $\chi 2$ test. The risk for cases was estimated using odds ratio (OR) and 95% confidence interval (CI). The association between SNPs and ARC risk were evaluated by using logistic regression analysis after adjusting for age and gender through SNPstats. SNPs frequencies for allele and genotypes of cases and controls were also compared by $\chi 2$ test. Therefore, Multiple inheritance models (Codominant, dominant, recessive and log-additives were also estimated by SNPstats online tools software (https://www.snpstats.net/start.htm). All the tests were two-sided and p value <0.05 was considered as statistically significant.

***Genotyping of XRCC1 codon399 and codon194*:** *XRCC1* genotypes were determined by PCR-RFLP method. An Arg399Gln (A>G) substitution in exon 10 (codon399) and Arg194Trp (C > T) substitution in exon 6 (codon194) were amplified from undigested fragments of 615bp and 491bp respectively, using primers described by Hameed et al. [11].

III. RESULTS

The present study included 150 patients of age related cataract (68 males and 82 females) and 150 healthy controls (75 males and 75 females). The age of the cases and control was 59.6±8 and 54.9±8 years, respectively. Table 1 has shown the different demographic characteristics of ARC patients and healthy controls. The frequency of ARC female patients (55%) was higher in in cases as compare to males (45%) and it was indicating that females have higher risk as compare to male for developing age related cataract especially in PSC type of cataract. Therefore, the mean ages observed as 59.6±8 (CC-60.6±8, NC-59.5±8, PSC-59.7±8 and MTC-58.6±8) for cases and 54.9±8 for controls, respectively. On the other hand, the mean age at onset of the age related cataract was observed as 57.8±8 in general for cases but in the patients of CC-58.8±8, NC-58.2±8, PSC-57.8±8 and MTC-56.9±8 while the mean age at onset of disease was not observed in healthy controls. The family history was not observed in the controls but in 60% of the cases have positive family history while 40% of the patients have negative family history with ARC.

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Moreover, based on the types of cataract the highest positive family history observed in PSC-23.3% as compare to MTC-14.7%, NC-11.3% and CC-10.7%. In general, the incidence of vegetarian patients was observed higher in cases 70.7% (PSC-27.4%, MTC-16.7%, NC-14% and CC-14%) than controls 51.4%. The frequency of smokers reported higher in the controls (10.7%) as compared to cases (2.7%), but the highest frequency of smoker was found in PSC (2%) type of cataract as compared to MTC (0.7%) while that was found negligible in case of CC (0%) and NC (0%) types of cataract. 27.3% of cases was observed as alcoholic and 26.7% in controls. Based on types of cataract, frequency of alcoholic cases was observed higher in PSC (12.6%) and MTC (8%) in contrast to CC (4%) and NC (2.7%) as represented in Table 1.

Table 1: The distribution of demographic characteristics based on types of cataract observed in the subjects with ARC and controls

Types of Cataract	CC(27)	NC(24)	PSC(64)	MTC(35)	Total(150)	Control(150)
Cohorts	**N (%)**	**N(%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Male	10(6.7%)	9(6%)	32(21.3%)	17(11.3%)	6 (45%)	75(50%)
Female	17(11.3%)	15(10%)	32(21.3%)	18(12%)	82(55%)	75(50%)
Familial	16(10.7%)	17(11.3%)	35(23.3%)	22(14.7%)	90(60%)	0(0%)
Non-Familial	11(7.3%)	7(4.7%)	29(19.3%)	13(8.6%)	60(40%)	0 0%)
Vegetarian	21(14%)	19(12.6%)	41(27.4%)	25(16.7%)	106(70.7%)	77(51.4%)
Non-Vegetarian	6(4%)	5(3.4%)	23(15.3%)	10(6.6%)	44(29.3%)	73(48.6%)
Alcoholic	6(4%)	4(2.7%)	19(12.6%)	12(8%)	41(27.3%)	40(26.7%)
Non-Alcoholic	21(14%)	20(13.4%)	45(30%)	23(15.3%)	109(72.7%)	110(73.3%)
Smoker	0(0%)	0(0%)	3(2%)	1(0.7%)	4(2.7%)	16(10.7%)
Non-Smoker	27(18%)	24(16%)	61(40.7%)	34(22.6%)	146(97.3%)	134(89.3%)
Mean (age)	60.6±8	59.5±8	59.7±8	58.6±8	59.6±8	54.9±8
Mean age at onset +SEM	58.8±8	58.2±8	57.8±8	56.9±8	57.8±8	-

The frequency distribution of genotypes and alleles of a variable rs25487 (Arg399Gln) of gene *XRCC1* in both patients of age related cataract and in healthy controls after analysis with Hardy-Weinberg equilibrium. The genotype frequencies of homozygous wild (AA), heterozygous (GA), and homozygous mutant (GG) were 13%, 35% and 52% in patients with ARC while 15%,50% and 35% in controls, respectively. The frequency of G (mutant) allele was 69% in ARC patients and 60% in controls. However, that difference did not show any statistically significant difference for genotype GG ($p = 0.17$) among the patients of ARC and in controls, but the data suggested that allele G (OR- 1.48, 95%CI-1.06-2.08, $p = 0.02$) was significantly associated with an increased risk of ARC. Therefore, the genotypes homozygous GG (OR- 1.61, 95%CI- 0.80-3.25, $p = 0.17$) and heterozygous GA (OR-0.76, 95%CI-0.37-1.53, $p = 0.44$) in contrast with homozygous AA (reference) did not show significant difference and association among ARC patients and controls as represented in Table 2.

The genotype and allelic frequencies of second variable in rs1799782 (Arg194Trp) of gene *XRCC1* were observed in homozygous wild (CC), heterozygous (CT), and homozygous mutant (TT) as 46%, 19.3% and 34.7% in ARC patients and 46%, 14.7% and 39.3% in sex and age matched healthy controls, respectively. The frequency of allele C was observed as 56% in cases and 53% in controls. The present data suggest that mutant genotype TT (OR-0.88, 95%CI-0.53-1.45, $p = 0.62$) did not show significant difference between ARC patients and controls in comparison with CC. Whereas, the genotype CT (OR- 1.31, 95%CI-0.69-2.51, $p = 0.40$) and allele C (OR- 1.09, 95%CI- 0.79-1.51, $p = 0.56$) also did not show any association with ARC patients and in controls as represented in Table 3.

Table 2: The frequency distribution of genotypes and alleles of *XRCC1* gene in SNP rs25487 (Arg399Gln) of cases and controls.

Genotype	Cases n (%) N = 150	Controls n (%) N =150	OR (95% CI)	p-value
XRCC1-rs 25487				
Gln/Gln	20 (13%)	22 (15%)	Ref	--
Arg/Gln	52 (35%)	75 (50%)	0.76 (0.37-1.53)	0.44
Arg/Arg	78 (52%)	53 (35%)	1.61 (0.80-3.25)	0.17
G (Arg)	208 (69%)	181(60%)	1.48 (1.06-2.08)	0.02*
A (Gln)	92 (31%)	119 (40%)	Ref	--

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Table 3: The frequency distribution of genotypes and alleles of *XRCC1* gene in SNP rs1799782 (Arg194Trp) of cases and controls.

Genotype	Cases n (%) N = 150	Controls n (%) N =150	OR (95% CI)	p-value
XRCC1-rs1799782				
Arg/Arg	69 (46%)	69 (46%)	Ref	--
Arg/Trp	29 (19.3%)	22 (14.7%)	1.31 (0.69 -2.51)	0.40
Trp/ Trp	52 (34.7%)	59 (39.3%)	0.88 (0.53-1.45)	0.62
C (Arg)	167 (56%)	160 (53%)	1.09 (0.79-1.51)	0.56
T (Trp)	133 (44%)	140 (47%)	Ref	--

Table 4: The distribution of genotypes and allele frequencies of two SNPs of a gene *XRCC1* polymorphism in both Age related cataract patients and controls based on the types of cataract.

Genotypes	**CC (27)**	**NC (24)**	**PSC (64)**	**MTC (35)**	**Controls (150)**
rs25487 (Arg399Gln)					
Gln/Gln	1(3.7%)	3(12.5%)	7(10.9%)	9(25.7%)	22(15%)
Arg/Gln	12(44.5%)	9(37.5%)	19(29.7%)	12(34.3%)	75(50%)
Arg/Arg	14(51.8%)	12(50%)	38(59.4%)	14(40%)	53(35%)
G (Arg)	14(25.9%)	15(31.3%)	33(25.8%)	30(42.8%)	181(60%)
A (Gln)	40(74.1%)	33(68.7%)	95(74.2%)	40(57.2%)	119(40%)
rs1799782 (Arg194Trp)					
Arg/Arg	14(51.8%)	12(50%)	28(43.7%)	15(42.8%)	69(46%)
Arg/Trp	5(18.5%)	3(12.5%)	14(21.8%)	7(20%)	22(14.7%)
Trp/ Trp	8(29.7%)	9(37.5%)	22(34.5%)	13(37.2%)	59(39.3%)
C (Arg)	33(61.1%)	27(56.3%)	70(54.7%)	37(52.8%)	160(53%)
T (Trp)	21(38.9%)	21(43.7%)	58(45.3%)	33(47.2%)	140(47%)

On the basis of types of cataract, the frequency distribution of both variables rs25487 (Arg399Gln) and rs1799782 (Arg194Trp) of *XRCC1* gene polymorphism among ARC patients and in controls was observed and indicating possible association with ARC. It was observed that in SNP rs25487 (Arg399Gln) the frequency of genotype GG (CC-51.8%, NC-50%, PSC-59.4% and MTC-40%) was higher in each type of cataract as compared to heterozygous GA (CC-44.5%, NC-37.5%, PSC-29.7% and MTC-34.3%) and genotype AA (CC-3.7%, NC-12.5%,PSC-10.9% and MTC-25.7%). However, the frequency of genotype GA was higher in the controls (50%) as compare to the cases (35%) as represented in Table 2.

On the other hand, in SNP rs1799782 (Arg194Trp) the frequency of genotype CC (CC-51.8%, NC-50%, PSC-43.7% and MTC-42.8%) was higher in each type of cataract as compare to the genotype CT (CC-18.5%, NC-12.5%, PSC-21.8% and MTC-20%) and TT (CC-29.7%, NC-37.5%, PSC-34.5% and MTC-37.2%).

However, the frequency of genotype CC was similar in both patients of ARC (46%) and in controls (46%) as mentioned in Table 3. Therefore, data shows that allele G (OR- 1.48, 95%CI-1.06-2.08, p = 0.02) was significantly associated with an increased risk of ARC. It may be due to higher frequency of genotype GG in SNP rs25487 (Arg399Gln) as represented in Table 4.

In the present study, we have calculated the association between SNPs and risk of age related cataract (ARC) under different inheritance models such as codominant, dominant, recessive and log-additive etc. by using logistic regression adjusted for gender and age. We have observed that SNPs rs25487 (Arg399Gln) and rs1799782 (Arg194Trp) of *XRCC1* gene polymorphisms were not showing any significant association with ARC. However, in SNP rs25487 allele G (OR-1.48, 95%CI-1.06-2.08, p = 0.02) was significantly associated with an increased risk of ARC as represented in Table 2. Therefore, both SNPs rs25487 (OR-1.26, 95%CI- 0.86-1.84,p = 0.24) and rs1799782 (OR-1.16, 95%CI-0.87-1.56,p = 0.32) of gene *XRCC1* were not associated with the development of ARC under the log-additive model. However, there was no significant association observed between both SNPs of *XRCC1* gene and no susceptibility was observed with ARC as represented in Table 5.

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Table 5: Relationships of two variable rs25487 and rs1799782 of *XRCC1* gene polymorphism and their risk susceptibility among ARC patients and in controls after adjusted by age and gender.

Gene (SNP ID)	Model	Genotype	Cases	Control	OR (95% CI)	p-value	AIC	BIC
XRCC1-rs25487 (Arg399Gln)	Codominant	G/G G/A A/A	78 (52%) 52 (34.7%) 20 (13.3%)	53 (35.3%) 75 (50%) 22 (14.7%)	1.00 1.87 (1.05-3.33) 1.20 (0.53-2.71)	0.1	424.2	587.1
	Dominant	G/G G/A-A/A	78 (52%) 72 (48%)	53 (35.3%) 97 (64.7%)	1.00 1.67 (0.97-2.86)	0.061	423.3	582.5
	Recessive	G/G-G/A A/A	130 (86.7%) 20 (13.3%)	128 (85.3%) 22(14.7%)	1.00 0.89 (0.41-1.91)	0.76	426.7	585.9
	Log-additive	--	--	--	1.26 (0.86-1.84)	0.24	425.4	584.7
XRCC1-rs1799782 (Arg194Trp)	Codominant	C/C C/T T/T	69 (46%) 29 (19.3%) 52 (34.7%)	69 (46%) 22 (14.7%) 59 (39.3%)	1.00 0.78 (0.35-1.72) 1.36 (0.75-2.46)	0.34	426.6	589.6
	Dominant	C/C C/T-T/T	69 (46%) 81 (54%)	69 (46%) 81 (54%)	1.00 1.16 (0.68-1.99)	0.59	426.5	585.8
	Recessive	C/C-C/T T/T	98 (65.3%) 52 (34.7%)	91 (60.7%) 59 (39.3%)	1.00 1.45 (0.83-2.53)	0.19	425	584.3
	Log-additive	--	--	--	1.16 (0.87-1.56)	0.32	425.8	585

OR- odds ratio; 95% CI- 95% Confidence Interval; AIC-Akaike information criterion; BIC- Bayesian information criterion; p-values were calculated through unconditional logistic regression analysis with adjustments for age and gender; * the data is statistically significant at $p < 0.05$.

IV. DISCUSSION

Age related cataract occurs when there is denaturation of proteins in the lens resulting cloudiness which prevents light from passing clearly through the lens and causing loss of vision. Age related cataract is multifactorial in origin and it increases in incidence with aging. It is usually bilateral and begins either in superficial cortex or close to the nucleus of the lens. It can be divided into Nuclear (NC), Cortical (CC) and Posterior sub-capsular cataracts (PSC) but pure forms of cataract (only one type of opacity present) usually found in the early stages of the disease more frequently. It becomes more severe when several types of opacities co-exist in the same lens in resultant it produces the Mixed type of cataract (MTC) [12]. It could be caused by interaction between the gene and environmental factors. There are various risk factors such as diabetes, sunlight or exposure to UV light or nutritional deficiencies have been implicated in the development of cataract [13]. Endogenous oxidative damage to proteins, lipids, and DNA have been hypothesized to be important etiologic factors in aging and development of chronic diseases like cancer and ocular disorders including glaucoma, uveitis and age related macular degeneration and age related cataract [9]. Therefore, Ultraviolet (UV) light, one of the contributing factors to cataractgenesis that was showing the cause of DNA damage in lens epithelium [14-16] and chromosomal abnormalities as evidence for such damage had been reported in lens epithelia from patients of cataract [17] which is a major cause of loss of lens transparency in aging population [13].

Therefore, many previous studies have focused on polymorphisms in DNA repair genes. These studies have showed that *XRCC1* codon399 polymorphism caused more marker DNA damage in older subjects as compare to younger [18]. Luo et al. suggested that polymorphism in *XRCC1* codon 399 have association with development of age related cataract in Han Chinese population [1]. Padma et al. found that polymorphism in *XRCC1* codon399 have no association with development of ARC [2]. Chiang et al. reported that *XRCC1* codon399 polymorphism increased with the risk of pterygium but codon194 was associated with decreased risk of developing cornea disease named pterygium [19].

V. CONCLUSION

This is the first study to evaluate the possible association of *XRCC1* codon399 and codon194 with ARC development in North Punjab population. We have found a possible risk for *XRCC1*-rs25487 in allele G only in contrast with genotype AA but there was no association found in genotype GG. Our results suggested that **t**he polymorphisms in *XRCC1* codon 399 (rs25487) and codon 194 (rs1799782) were not associated with the risk of ARC in the North Punjab population but in codon399 (rs25487) allele G may be associated with an increased risk of ARC.

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