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"TO STUDY THE MOLECULAR CHARACTERIZATION OF X-RAY CROSS-COMPLEMENTING GROUP 1 (XRCC1) GENE AND ITS ASSOCIATED RISK FACTORS IN SENILE CATARACT PATIENTS"

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ABSTRACT

Introduction: Cataracts are caused by the ageing of the crystalline lens of the eye, which prevents clear vision. X-ray cross-complementing group 1 (XRCC1), a DNA repair protein involved in single-strand breaks (SSBs) and BER pathway, has been reported to be responsible for the efficient repair of DNA damage caused by active oxygen, ionization, and alkylating agents is mainly responsible for cataract in patients.

Aim and Objective: To study the molecular characterization with its special reference to XRCC1 gene in Senile Cataract Patients.

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Material and Methods: This was a cross sectional study carried out in the Department of Biochemistry for a period of 12 month i.e, from June 2023 to June 2024. A total of 500 clinical patients were included in the study out of which 250 patients were confirmed as cataract-positive patients. The 5ml of venous blood was collected in Ethylene diamine tetra-acetic acid tubes. The DNA extraction for the detection of XRCC1gene was done using Qiagen DNA Extraction Kit as per manufactures guidelines, and the confirmation of the gene was performed by PCR.

Results: In the current study a total of 500 clinically suspected patients were included out of which 250 cases were confirmed as cataract positive patients. The ratio of females was more (130, 52%) as compared to the males (120, 48%)with the mean age for females with 57.6% and for males with 61.13%.Hypertension (173, 69.2%) was the most common disease associated with the cataract patients. The ratio of males were more(91, 75.8%) compared to females (82 ,63.07%). The other comorbidity included diabetes (48.8%), in which males constituted(67) 55.83% compared to the females (55)with 42.30%.The presence of XRCC1 gene was detected in all cataract positive patients, which was confirmed by conventional PCR

Conclusion: The XRCC1 gene plays an very important role in patients associating the risk of cataract in understanding the DNA Repair mechanism

Keywords: Seline, Crystalline lens, Molecular characterization, XRCC1, DNA, PCR

INTRODUCTION

The opacity of the natural human lens, known as cataract, can be caused by acquired, developmental, or congenital factors. It is one of the most prevalent causes of vision impairment worldwide and has been linked to about half of the blind population [1]. The most common cause of bilateral blindness in India is a slow buildup of yellow-brown pigment in the lens with aging, which decreases light transmission [2].

When compared to populations in the West, cataract prevalence is higher in India [3, 4]. People with severe hypertension are more likely to acquire cataracts, and hypertension is associated to cataract formation [5]. Presenile cataract was caused by risk factors such as smoking, atopic dermatitis, high myopia, diabetes mellitus, and occupational metal job exposure [6]. In people with diabetes mellitus (DM), cataracts are also linked to the age and duration of DM [7].

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The DNA repair enzymes plays an important role in continuously monitor chromosomes to correct damaged nucleotide residues generated by exposure to carcinogensand cytotoxic compounds [8] . The polymorphisms of DNA repair genes decreased their ability to repair DNA damage, leaving human body a greatly increased susceptibility to cancer or age-related diseases [9,10]. Base excision repair (BER) pathway plays one of the most crucial role in the DNA repair pathways.

X-ray repair cross-complementing protein 1(XRCC1) is DNA repair protein. In human this protein is encoded by XRCC1 gene. Wherever DNA repair is complexes with DNA ligase III XRCC1 also involved. The XRCC1 marks a good biomarker and the association between 8-oxoguanine glycosylase-1(OGG1), AP endonuclease-1 (APE1) and X-ray repair cross-complementing-1 (XRCC1) genes polymorphisms and age-related macular degeneration, pterygium and onset primaryopen-angle glaucoma have been studied [11,12].

Patients' cataracts are primarily caused by the X-ray cross-complementing group 1 (XRCC1), a DNA repair protein involved in single-strand breaks (SSBs) and the BER pathway. It has been reported that this protein effectively repairs DNA damage brought on by active oxygen, ionization, and alkylating agents [13]. To fix SSBs found at codons 194 (Arg-Trp), 280 (Arg-His), and 399 (Arg-Gln), three primary enzymes are needed: DNA ligase III, DNA polymerase β, and poly-ADP-ribose polymerase (PARP). The most prevalent XRCC1 gene polymorphism was discovered at codon Arg399Gln, which is caused by a nucleotide alteration from guanine to adenine in the PARP binding domain. This substitution may have an impact on the effectiveness of complex formation or repair.

Due to the exposure to ionizing radiation and alkylating agents, DNA single-strand breaks and those are efficiently repair by XRCC1. XRCC1 protein participates in the base excision repair pathway due to interaction with DNA ligase III, polymerase beta and poly (ADP-ribose) polymerase. It has a important work in DNA processing during recombination in germ cells and meiogenesis . The XRCC1 protein acts as a scaffolding protein in process, so that it interacts with multiple repair enzymes and act accordingly. Due to scaffolding, repair enzymes (XRCC1) carry out their enzymatic steps in repairing DNA. XRCC1 has a crucial role in single-strand break repair, base excision repair and nucleotide excision repair.

The XRCC1 gene has been shown to play a significant impact in patients' associations with cataract risk, which would aid research into the mechanism of DNA repair. Therefore, the goal of the current study was to look into the prevalence, risk factors, and existence of the XRCC1 gene in individuals with senile cataracts. One crucial component for repairing broken bases and SSBsmarks is the DNA repair gene

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XRCC1, which also serves as a significant indicator of DNA damage. In order to comprehend the precise mechanisms by which genetic variants in DNA repair genes impact the process of lens opacification, the current study was conducted.

MATERIAL AND METHODS

This was a cross -sectional study carried out in the Department of Biochemistry for a period of 12 month i.e, from June 2023 to June 2024. A total of 500 clinical patients were included in the study out of which 250 patients were confirmed as cataract-positive patients. The 5ml of venous blood was collected in Ethylene diamine tetra-acetic acid tubes. The DNA extraction for the detection of XRCC1gene was done using Qiagen DNA Extraction Kit as per manufactures guidelines, and the confirmation of the gene was performed by PCR.

Inclusion criteria- The Patients with cataract and those who were ready to give their consent were included.

Exclusion criteria- Patients suffering from any immunocompromised disease, patients with type1 diabetes mellitus, those with any thyroid disorder, tuberculosis and cancer, pregnantand lactating females were excluded.

The demographic details and clinical history along with the relevant clinical investigations like visual acuity test, slit-lamp examination, retinal exam and applanation tonometry were recorded. 5ml of venous blood was drawn in Ethylene diamine tetraacetic acid tubes. The DNAextraction for the detection of XRCC1 gene was done using Qiagen DNA Extraction Kit as per manufactures guidelines, which was further confirmed by PCR.

GENOTYPIC METHOD

The Molecular Detection of DNA extraction was done to detect the presence of XRCC1 gene in clinically positive cataract positive patients with the history like personal and demographic data, reason for visit or with the presenting complaint, past history of the eye, allergy, general medical history, family eye history along with examinations like slit lamp examination and applanation tonometry test were recorded.

DNA Extraction: the detection of XRCC1 gene, chromosomal DNA from the clinical positive cataract patients was done . DNA extraction was carried out using a commercial available the DNA Extraction kit (Qiagen DNA Extraction Kit) as indicated by manufacturer’s instructions.

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PCR Cycling: The amplified DNA was further confirmed by PCR. Primers used for amplification of XRCC1 gene..

Gene	Primer Sequence (5' to 3')	Size (base pair)
XRCC1	F5'-TTGTGCTTTCTCTGTGTCCA-3' R3'-TCCTCCAGCCTTTCTGATA-5'	278 bp

Table no. 1: The Primer sequence used for the detection of XRCC1 genes

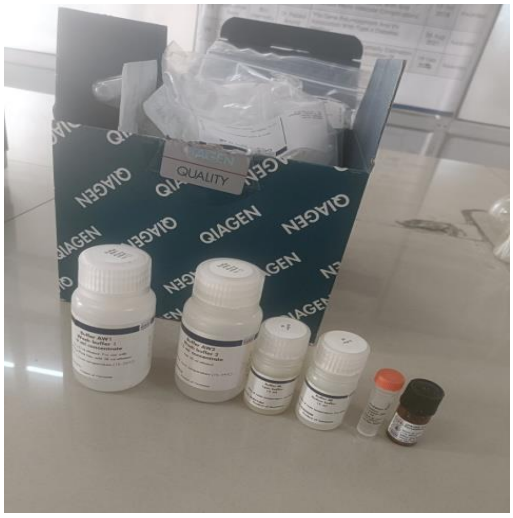

Figure no. -1: DNA Extraction Kit

Figure no. 2: Primers for XRCC1

Polymerase Chain Reaction (PCR) and its Cycling Conditions: After the DNA Extraction, the PCR was performed. The sequences of the primers used in PCR for detection of XRCC1 gene and its molecular weight are mentioned in the Table 1.

The Primers was obtained from "**Saha gene'** laboratory and reconstituted with sterile distilled water following the manufacturer's guidelines.

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Polymerase Chain Reaction (PCR)

For the PCR amplification, 2 µl of template DNA was added to 18 µl reaction containing 10 µl of Qiagen master mix, 2 µl of primer mix (1 µl each of the respective forward and reverse primers) and 6 µl of molecular-grade water.

The PCR cycling conditions

The cyclic conditions for genes, initial denaturation at 95 °C for 15 min, 30 cycles of 94 °C for 30 s, 52 °C for 1 min 30 s and 72 °C for 1 min 30 s were followed by extension of 72 °C for 10 min.

Step	**Program** **XRCC1** **Time** **Temperature**	**Cycles**
Initial denaturation	15 min 95 ºC	
Denaturation	30 s 94 ºC	
Annealing	1min 30 s 52 ºC	30
Extension	1 min 30 s 72º C	
Final extension	1 min 30 s 72º C	

Table no. 2 : The PCR cycling conditions to amplify XRCC1 gene fragments

The Agarose gel preparation and visualized by Gel Doc™ EZ Gel Documentation System

The Agarose Gel Electrophoresis was performed in order to identify the Purified PCR Product which was previously identified by its amplified DNA fragments. The resulting PCR product was subjected to 1 % agarose

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gel electrophoresis and visualized by Gel Doc™ EZ Gel Documentation System (Bio-Rad Laboratories Inc., Hercules, CA, USA). A 1 kb DNA Ladder (Thermo Fisher Scientific ™, Waltham, MA, USA) was used as the marker to evaluate the PCR product of the sample [14].

Statistical Anlaysis: The data was entered in the Ms Excel and a suitable Descriptive data analysis was done.

RESULTS

In the present study a total of 500 patients were screened which came for treatment of eye related problem in ophthalmology OPD of a tertiary care centre. Among those 50% were cataract patients and remaining 50% came with eye related problem, belonging to the age group 50 to 91 years. Many risk factors related to development of cataract i.e. age, gender, BMI, diabetes mellitus, hypertension, smoking, alcohol and genetic factors.

S.No.	Gender	Frequency	Percentage
1	Male	120	48 %
2	Female	130	52 %

Table no. 3: Gender wise distribution of Number of Patients with Cataract

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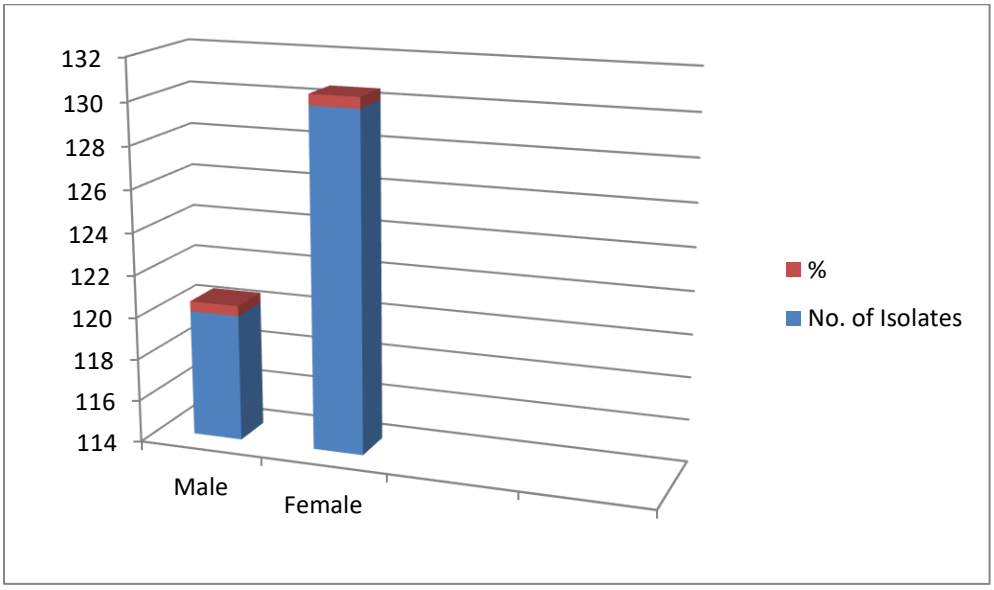

Graph no. 1: Gender wise distribution of Number of Patients with Cataract

Samples were processed as soon as received in laboratory. In cases where a delay was expected, the sample was refrigerated for up to 4 hours at 4°C. A total of 500 clinical patients was included in the study in which 250 patients was confirmed as cataract positive. The gender wise distribution was also studied where, Males was found with 48% and Females with 52% which stated the dominancy of Females to be more in the present study.

S.No.	Age	Male	Female	Total	Percentage
1.	50-60	53	73	126	50.4%
2.	61-70	45	38	83	33.2%
3	71-80	19	17	36	14.4%
4.	81-90	03	01	04	1.6%
5.	91-100	00	01	01	0.4%
		120	**130**	**250**	**100%**

Table no. 4 :Age wise Distribution of Cataract patients

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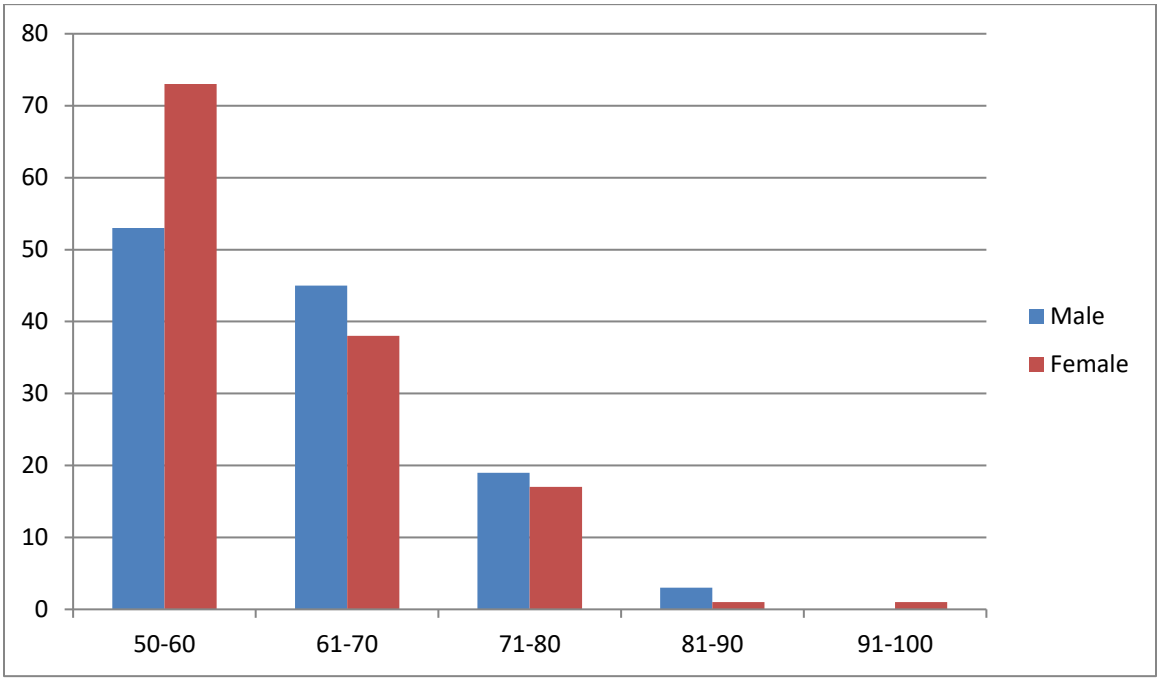

Graph no. 2: Age wise Distribution of Cataract patients

The maximum number of cases was reported in the age group of 50-60 years of age that was 50.4 % followed by 61-70 years of age that was 33.2% followed by 71-80 years of age that was 14.4% followed by 81-90 years of age that was 1.6% and the minimum in the age group of 91-100 years of age that was 0.4 %. It was also noted that there was no cases found in the age above or 100 years in OPD patients.

S. No.	Diseases	Male	Female	Total (n=500)
1	Cataract	120	130	250
2	Glaucoma	05	04	09
3	Chalazion	10	04	14
4	Refraction Error	35	41	76
5	Pterygium	01	01	02
6	Presbyopia	04	08	12
7	Stye	03	03	06

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8	Concretion	01	00	01
9	Squint	04	12	16
10	ARMD	08	06	14
11	Foreign Body	07	05	12
12	Corneal Ulcer	04	07	11
13	Corneal Opacity	02	03	05
14	MGD	02	01	03
15	Entropion	01	01	02
16	Ectropion	02	00	02
17	PACG	02	06	08
18	Esotropia	01	02	03
19	CDC	02	04	06
20	NPDR	07	02	09
21	Other diseases	20	19	39
		241	259	500

Table no. 5: Disease wise Distribution of patients

Out of the total number of disease there were 250 patients affected with cataract and other 250 with other disease such as Glaucoma, Chalazion,, Refraction Error and others.

Gender	Expressed	Expressed %	Non Expressed	Non Expressed %
Male (120)	74	61.67 %	46	38.33 %
Female (130)	83	63.85 %	47	36.15 %

Table no. 6: Gender wise XRCC1 gene expression in Cataract patients

Expressed	Expressed %	Non Expressed	Non Expressed %
157	62.8 %	93	37.2 %

Table no. 7: XRCC1 gene expression in Cataract patients

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Gender	Expressed	Expressed %	Non Expressed	Non Expressed %
Male (119)	35	29.41 %	84	70.59 %
Female (131)	41	31.30 %	90	68.70 %

Table no. 8: Gender wise XRCC1 gene in Control patients

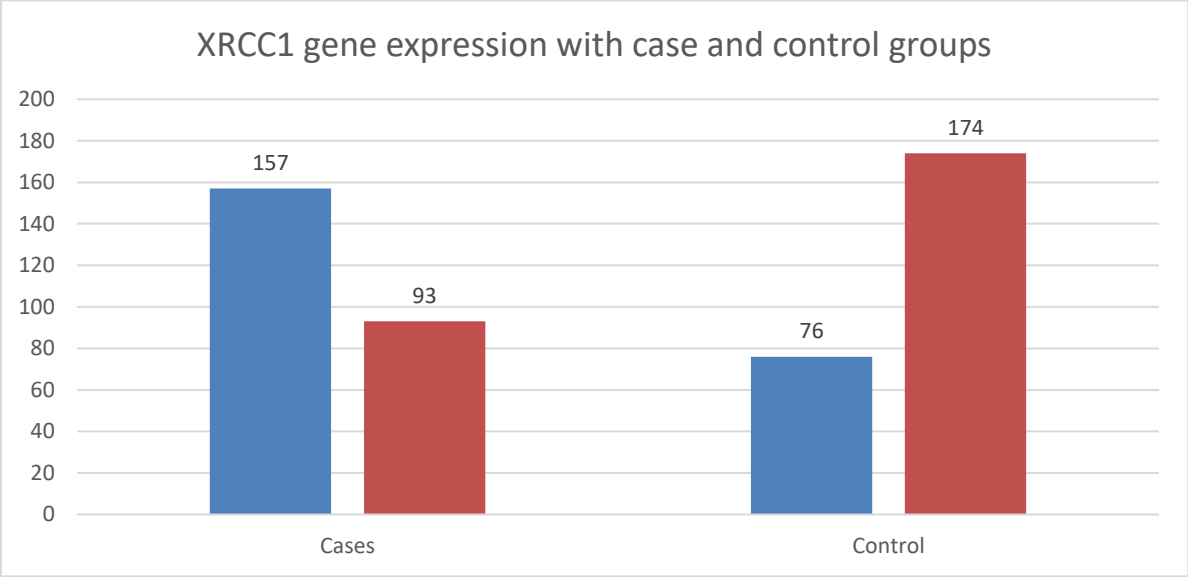
Expressed	Expressed %	Non Expressed	Non Expressed %
76	30.4 %	174	69.6 %

Table no.9: XRCC1 gene expression in Control patients (250)

Expression of XRCC1 gene results:

In the current study study it was observed that XRCC1 gene was slightly more affected in Females (63.8%) than with Males (61.6%). Whereas, the expression of XRCC1 was 62.8% and 37.2% was not expressed.

In the control group also the Females expression for XRCC1 gene was more with 31.3% and Males being 29.4%. The expression for XRCC1 gene was 30.4% and None expressed were 69.6% in the control group.



Graph no. 3: XRCC1 gene expression with case and control groups

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S.No.	Gender	Smokers (No.)	Smokers (%)	Nonsmokers (No.)	Nonsmokers (%)
1.	Male (120)	37	30.83%	83	69.16 %
2.	Female (130)	18	13.84%	112	86.15 %

Table no. 10: Smokers and Nonsmokers among Cataract patients

Gender	Smokers (No.)	Smokers %	Nonsmokers (No.)	Nonsmokers %
Male (119)	30	25.21 %	89	74.79 %
Female (131)	13	9.9 %	118	90.1 %

Table no. 11: Smokers and Nonsmokers in Control patients

It was also noted that the no. of cases of smokers was more in Males (30.83) as compared to the Females (13.84%). In the control group the rate of Male smokers was more with 25.21%.

S.No.	Gender	Alcohol drinkers	Alcohol drinkers (%)	Non Alcohol drinkers	Non Alcohol drinkers (%)
1.	Male (120)	30	25 %	90	75 %
2.	Female (130)	6	4.6 %	124	95.3 %

Table no.12: Alcohol Drinkers and Non Alcohol drinkers in Cataract patients

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Gender	Alcohol drinkers	Alcohol drinkers %	Non Alcohol drinkers	Non Alcohol drinkers %
Male (119)	16	13.4 %	103	86.6 %
Female (131)	5	3.8 %	126	96.2 %

Table no. 13: Alcohol Drinkers and Non Alcohol drinkers in Control patients

In this study it was observed that the ratio of Alcohol drinkers was less as compared to the Non alcoholic drinkers (75%) with Males (25%) dietary habits been affected more as compared to the Females (4.6%) . It was also noted that the Male alcohol drinkers was more 13.4% as compared to the female (3.8%) in the control group.

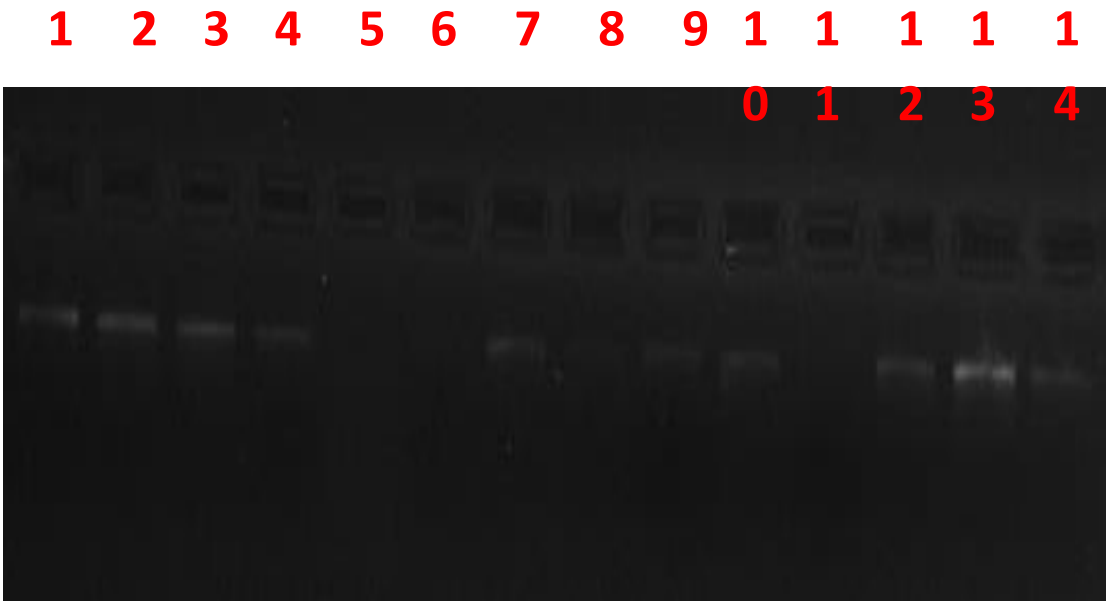

Figure no. 3: DNA visualization under gel documentation system

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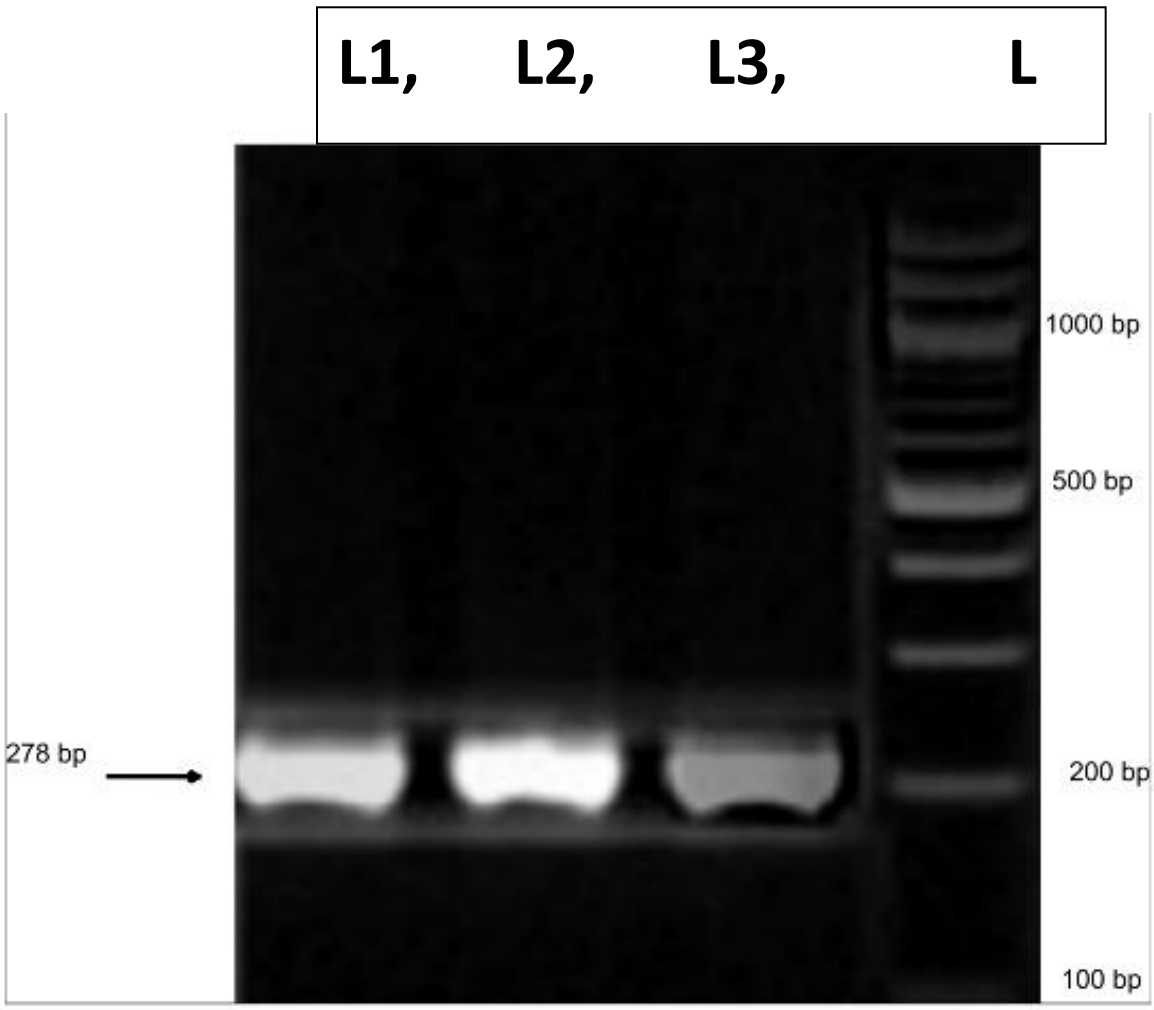

Figure no. 4: DNA Amplified with PCR for XRCC1 gene with patient suffering from cataract (case group). Lane L is DNA ladder; Lane L1 and L3 are sample positive for XRCC1 gene (278bp); Lane L2 is the positive control for XRCC1 gene (278 bp).

DISCUSSION

Cataracts are the primary cause of visual impairment globally, accounting for roughly half of the blind population. It is a vision-impairing condition that comes with ageing and primarily affects elderly individuals or people over the age of fifty. This condition involves clouding or thickness of the eye lens, resulting in a loss in vision that gradually worsens over time. If left untreated, senile cataracts are likely to

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cause partial or total blindness [16]. Oxidative stress has a significant role in the progression of age-related macular degeneration (AMD). In the present study a total of 500 patients were screened which came for treatment of eye related problem in ophthalmology OPD of a tertiary care centre. Among those 50% were cataract patients and remaining 50% came with eye related problem, belonging to the age group 50 to 91 years. Many risk factors related to development of cataract i.e. age, gender, BMI, diabetes mellitus, hypertension, smoking, alcohol and genetic factors.

In present study it was observed that the prevalence of cataract to be 50% among male and female both, which was similar to the study by Singh Sumeer [17] et al (43.62 in Urban and 44.68 in Rural)in their study found the monotype subtype cataract. Study by Vashist P [18] et al. observed the prevalence rate with (58% in North India and 53% in South India). There was another study by Nirmalan PK [19] et al where the prevalence was observed to be (47.5 % in rural area). There was a study which was in constrast to the current study where Murthy GVS [20] et al reported 17.6% prevalence.

Prevalence of cataract in male and female was different in present study, and various studies support to it ,Female prevalence of cataract was 52 % which is lesser than Murthy GV [20] (55.8 %), Padma G [21]. (56.3 %), Sobit [22] et al.(56.6 %). Male prevalence of cataract in the present study was 48 % which was higher than Murthy GV [20] (44.1%), Padma G. [21] (43.8 %), Sobit [22] et al.(43.2 %) but Singh Sumeer [17] study did not support present study because he could not find any significant difference in the prevalence of cataract among male and female.

In the present study it was observed that the prevalence of diabetes mellitus in case group was 48.8 %, which is higher than Kapoor [23] et al. (4.4 %), followed by Barath [24] et al. (7.2 %), it indicates the prevalence of diabetes increases with time and diabetes mellitus became the risk factor for development of cataract in patients. It was found that the prevalence of hypertension in case group was 69.2 % which was higher than Bharath [24] et al. (21.9 %),followed by Kapoor [23] et al. (24.2 %), it indicates the prevalence of hypertension also became the risk factor for development of cataract in patients. In the present study prevalence of habit of smoking tobacco was 34.8 % and it varies with study of Padma G [21] study that found the prevalence of tobacco smoking was 28.4 % in their sample of study and present study found higher prevalence of tobacco smoking compare to Padma G study. study I found that the habit of alcohol consumption was 21.6 % and it varies with Padma G [21] study that was 17.8 % and present study shows the higher prevalence of alcohol consumption among the case group compare to Padma G study.The DNA

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repair enzyme X-ray repair cross-complementing-1 plays a vital function in repairing damaged nucleotide residues caused by carcinogens and cytotoxic chemicals. [17] XRCC1 is a crucial enzyme in the base excision repair pathway (BER) and plays a critical role in DNA excision repair [18].

Hypertension has been associated to senile cataract formation, and persons with severe hypertension are more likely to develop a cataract [5].The oxidative stress associated with diabetes mellitus plays an essential role in the onset and progression of diabetic problems, as free oxygen radicals cause cataracts, which are one of the degenerative symptoms of diabetes [12]. Wherever DNA repair occurs, XRCC1 binds with DNA ligase III. [20].

The XRCC1 protein acts as a scaffolding protein in interacting with the multiple repair enzymes, because of which the repair enzymes carry out their enzymatic steps in the repair of the damaged DNA. XRCC1 has a crucial role in the single-strand break repair, base excision repair as well as nucleotide excision repair. In the present study the presence of XRCC1 gene as a DNA repair gene was detected. This finding was parallel to many other studies where XRCC1 gene was detected in senile cataract patients [21,22]. The DNA damage of lens epithelial cells may be the primary cause of lens opacity [23].

XRCC1 is involved in single-strand breaks (SSBs) along with the base excision repair (BER) pathway and has been reported to be responsible for the efficient repair of DNA damage caused by the ionization, oxygen, and alkylating agents [24].

There were many polymorphisms investigated for the *XRCC1* gene coding for polymorphism resulting in amino acid substitutions where codon 399 (Arg-Gln) receiving the most attention [25] . The *XRCC1* gene is located on chromosome 19q13.2. The protein encoded by this gene is involved in the efficient repair of DNA single-strand breaks induced by exposure to ionizing radiation and alkylating agents [26].

The genetic polymorphisms of *XRCC1* have also been frequently reported in many human age-related cataract cases [27]. The development of lens opacities and oxidative stress or UV light-induced DNA damage have an association in the lens epithelium [26]. The oxidative stress is involved in cataractogenesis, by which the role of antioxidants could be considered as a potential cataract preventive agent . The active oxygen radicals damage the lens epithelial cells, and large conformational changes in proteins may be found as protein–protein cross-links, causing an increase in concentration [28-30]. The XRCC1 genetic polymorphisms may be very useful in the identification of age-related cataract patients at an early stage [30].

XRCC1 is involved in the single-strand breaks and the BER pathway, one of the most important pathways involved in the repair of oxidative and UV-related DNA damage [31,32]. In the present study it was observed

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that the prevalence of XRCC1 was observed to be 30.4% and 62.8 % in case of control and cases respectively. This study was in support to the study performed by the other research investigators where Chen Wang [33] observed the prevalence of XRCC1 in control with 53.1 % and 55.2% in cases. There was another study which was similar to the current study by Xu Zha [34] where 25.5% and 27.8% prevalence was recorded for control and case respectively. Padma G.[21] studied the prevalence with 49.7% and 43.3% respectively for control and cases. Although the pathophysiology of cataract is still not fully understood, as it's a multifactorial disease caused by interaction between the genetic and environmental factors, epidemiological investigations also prompt many risk factors such as diabetes, gender, sunlight or ultraviolet radiation, smoking and nutritional deficiencies which may relate to the formation of cataract [35,36] . It has been well accepted that oxidative stress plays a critical role in the pathogenesis of senile cataract [37-39]. The XRCC1 plays a crucial role in the elevated susceptibility to age-related cataracts revealing that this mutation been regarded as one of the potential mechanisms for the increasing risk of age-related cataracts.

Screening for the possible relationship between polymorphisms of DNA repair genes and cataract may contribute to understanding the pathogenesis of cataract development and may be useful in the prevention of this disease [40,41].

CONCLUSION

The X-ray repair cross-complementing-1 DNA repair gene is essential for fixing damaged nucleotide residues caused by exposure to cytotoxic and carcinogenic substances. It is also essential for fixing single-strand breaks, base excisions, and nucleotide excisions that contribute to age-related cataract susceptibility. Therefore, XRCC1 genetic polymorphism discovery and early screening may be helpful in early age-related cataract patient identification.

Current evidence suggests that DNA repair gene polymorphism is important in senile cataract; nevertheless, more research is required to validate the obtained results and fully investigate any potential link between DNA repair gene polymorphism and cataract.

Declarations:

Conflicts of interest: There is not any conflict of interest associated with this study

Consent to participate: There is consent to participate.

Consent for publication: There is consent for the publication of this paper.

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Author's contributions: Author equally contributed the work.

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