Original Article

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Anatomy Section

Molecular Characterisation of X-ray Cross-complementing Group 1 (XRCC1) Gene and Risk Factors in Senile Cataract Patients attending a Tertiary Care Hospital, Uttar Pradesh, India

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ABSTRACT

Introduction: Cataract arises because of aging of the crystalline lens of the eye which prevents clear vision. X-ray Cross-complementing Group 1 (XRCC1) is a Deoxyribonucleic Acid (DNA) repair protein which is involved in Single-Strand Breaks (SSBs) and Base Excision Repair (BER) pathway which is responsible for the efficient repair of DNA damage is mainly responsible for cataract in patients.

Aim: To study the prevalence, risk factors and the molecular characterisation with its special association to XRCC1 gene in senile cataract patients.

Materials and Methods: This was a cross-sectional study carried out in the Department of Anatomy and Ophthalmology, Rama Medical College Hospital and Research Centre, Kanpur, Uttar Pradesh, India, from April 2021 to April 2022. A total of 500 clinical patients were included in which 250 patients were confirmed as cataract positive patients. Venous blood of 5 mL 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, which was further confirmed by Reverse Transcription-Polymerase Chain Reaction (RT-PCR).

Results: A total of 500 clinically suspected patients were included in which 250 cases were confirmed as cataract positive patients. The ratio of females was more (n=130, 52%) compared to males (n=120, 48%) with the mean age for females with 57.6% and for males with 61.13%. Hypertension (n=173, 69.2%) was the most common disease associated with the cataract patients. The ratio of males were more (n=91, 75.8%) compared to females (n=82, 63.07%). The mean age of males was 64.40 years and that of females were 62.45 years. The other co-morbidity included diabetes (48.8%), in which males constituted 67 (55.83%) participants compared to the females with 55 (42.3%) participants. The presence of XRCC1 gene was detected in all cataract positive patients, which was also confirmed by RT-PCR.

Conclusion: 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. The association of XRCC1 gene with age-related cataract susceptibility observed in the present study supports the view that XRCC1 gene plays an important role in susceptibility to age-related cataract, so early screening and its molecular profiling will help the clinician in the early diagnosis as well as early treatment.

Keywords: Aging, Crystalline lens, Molecular profiling, Repair protein, Single-strand breaks

INTRODUCTION

Cataract is an opacification of the lens that obscures the passage of light to the retina of the eye, causing low vision. It is the main cause of reversible blindness with an estimated 95 million people affected worldwide. Cataract has been documented to be the most significant cause of bilateral blindness in India where vision <20/200 in the better eye on presentation is defined as blindness [1].

The prevalence of cataract is higher in females than males in the developed and developing countries. In developing countries, cataract occurs at an earlier age [2]. Population-based studies have reported high prevalence rates of cataract in India compared with western populations [3,4]. Hypertension is linked to development of cataract and people with severe hypertension have a higher risk of cataract [5]. Lee H et al., observed that risk factors like diabetes mellitus, high myopia, occupational exposure to metal work, atopic dermatitis and smoking were responsible for presenile cataract [6]. As the age increases, the lenses of the eyes become less flexible, less transparent and thicker. Due to diabetes, high blood glucose levels over time can lead to structural changes in the lens of the eye that can accelerate the development of cataracts. There is also the association of cataract in patients with Diabetes Mellitus (DM) with age and duration of DM [7].

Deoxyribonucleic Acid (DNA) repair enzymes continuously monitor chromosomes to correct damaged nucleotide residues generated by exposure to carcinogens and cytotoxic compounds [8]. Studies have confirmed that 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) is one of the most crucial DNA repair pathways. As the key enzymes of the BER pathway, association between 8-oxoguanine Glycosylase-1 (OGG1), AP Endonuclease-1 (APE1) and X-ray Cross-complementing Group 1 (XRCC1) genes polymorphisms and Age-related Macular Degeneration (AMD), pterygium and onset primary open-angle glaucoma have been studied frequently and XRCC1 marks as a good biomarker of DNA damage [11,12]. In addition to ophthalmic disorders, malignancies, diabetes and neurological disorders such as Huntington's disease are also focuses of Single-nucleotide Polymorphism (SNP) researches [13,14].

The proven role of XRCC1 gene plays a very important role in patients associating the risk of cataract, would help the study in understanding the DNA repair mechanism. Hence, the present study was aimed to investigate the prevalence, its risk factors

and the presence of XRCC1 gene among senile cataract patients, as XRCC1 is a DNA repair gene that's emerging as an essential element in the repair of both damaged bases and Single-Strand Breaks (SSBs) marks as an important biomarker of DNA damage. Moreover, the present study will be helpful in understanding the precise mechanisms by which genetic polymorphisms of DNA repair genes influence the process of lens opacification.

MATERIALS AND METHODS

The present cross-sectional study carried out in the Department of Anatomy and Ophthalmology, Rama Medical College Hospital and Research Centre, Kanpur, Uttar Pradesh, India, from April 2021 to April 2022. A total of 500 clinical patients were included. Ethical clearance was taken from the Institutional Ethical Committee (RMCH/Pediatrics/2021/09).

Inclusion criteria: Patients affected with cataract and those who were ready to give their consent were included in the study.

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

Study Procedure

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. A 5 mL of venous blood was collected in Ethylenediamine Tetraacetic (EDTA) acid tubes. The DNA extraction for the detection of XRCC1gene was done using Qiagen DNA Extraction Kit as per manufactures guidelines, which was further confirmed by Reverse Transcription-Polymerase Chain Reaction (RT-PCR).

The presence of XRCC1 gene was detected using Rotor-Gene Q Software 2.3.1.49 by RT-PCR, and found that XRCC1, a DNA repair protein involved in SSBs and BER pathway, have been reported to be responsible for the efficient repair of DNA damage caused by active oxygen, ionisation and alkylating agents is mainly responsible for cataract in patients

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 presenting complaint, past eye history, general medical history, family eye history and allergy history along with examinations like slit-lamp examination and applanation tonometry test were recorded.

DNA extraction: For 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.

Polymerase chain reaction cycling: The amplified DNA was further confirmed by RT-PCR. Primers used for amplification of XRCC1 gene [Table/Fig-1] [15].

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

[Table/Fig-1]: The primer sequence used for the detection of XRCC1 genes.

Polymerase Chain Reaction (PCR) and its cycling conditions: After the DNA extraction, the RT-PCR was done. The sequences of the primers used in RT-PCR for detection of XRCC1 gene and its molecular weight are mentioned in the [Table/Fig-2,3].

The first step in a real-time PCR reaction was the conversion of RNA to complementary DNA (cDNA) known as reverse transcription. The next step uses fluorescent reporters and a PCR reaction to amplify and detect specific genes. The annealing allows the primers to connect to a specific spot on the single-stranded template DNA and extension step (20 seconds to one minute at 72°C), by which the DNA polymerase extends the primer sequences from the 3' of each primer to the end of the amplicon along with the suitable temperature and time, the time and temperature was adjusted according to the test. The SYBR Green dye emits its fluorescent signal simply by binding to the double-stranded DNA in solution [Table/Fig-4].

[Table/Fig-2]: Deoxyribose nucleic acid extraction kit.
[Table/Fig-3]: Primers for XRCC1 gene. (Images from left to right)

PCR protocol	Temperature	Time	Dye
Hold	98°C	2 minutes	Not acquiring
Cycling (Annealing/ Extension)	98°C	5 seconds	Not acquiring
	60°C	30 seconds	Acquiring Sybr Green
Melt	Ramp from 72°C to 95°C		
	Hold for 90s on the 1st step		
	Hold for 5s on the next steps, Melt A (Green)		

[Table/Fig-4]: No. 2 PCR cycling condition for XRCC1 gene.

In the experimental set-up, all the required entries were entered in the RT-PCR like name of the run, the run time wherein accordingly to the finish run, operator method, the software name of the version and the serial number of the machine along with it the melt information for threshold was entered [Table/Fig-5].

Experiment Information	
Run name	Cataract three step with melt XRCC1 gene
Run start	3/3/2022 6:13:40 PM
Run finish	3/3/2022 7:18:26 PM
Operator	Cataract XRCC1 gene
Notes	
Run on software version	Rotor-Gene Q software 2.3.1.49
Run signature	The run signature is valid.
Gain green	9.67
Machine serial no.	0317145
Melt information	
Digital filter	Light
Imported analysis settings	
Sample page	Page 1
Temp. threshold	0°C
Threshold	0.07045

[Table/Fig-5]: The experiment information for run of XRCC1 gene [6].

Master mix prepration for XRCC 1 gene:

Evagreen master mix=10 uL

Forward primer=0.25 uL

Reverse primer=0.25 uL

Nuclease free water=4.50 uL

DNA template=5.00 uL

Total volume=20.00 uL

The above master mix, sometimes known as super mix or ready mix, is a batch mixture of PCR reagents at optimal concentrations that can be prepared and divided among many PCR tubes or 96-well PCR plates. The master mix usually includes DNA polymerase, Deoxynucleoside Triphosphates (dNTPs), Magnesium chloride ($MgCl_2$) and buffer. The quantity of the primers and master mix was already provided in the kit.

Primers was obtained from 'Saha gene' and was reconstituted with sterile double distilled water based on the manufacturer's instruction.

STATISTICAL ANALYSIS

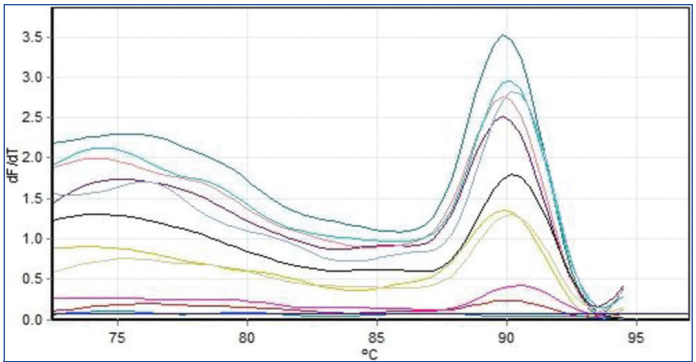
Descriptive data analysis was done. The data was analysed by descriptive statistics.

RESULTS

A total of 500 clinically suspected patients with cataract were included, in which 250 were confirmed to have cataract. There were more females (n=130) than males (n=120). The mean age of the population was 59.37 years. Hypertension was the most common (n=173, 69.2%) disease associated with the cataract patients. The number of males were more (n=91, 75.8%) compared to females (n=82, 63.07%). The mean age of males was 64.40 years and that of females was 62.45 years. The other co-morbidity included diabetes (48.8%), in which males constituted 67 (55.83%) participants compared to the females with 55 (42.3%) participants [Table/Fig-6]. The presence of XRCC1 gene was detected in all cataract positive patients, which was also confirmed by RT-PCR. From the [Table/Fig-7-21] Indicates the presence of XRCC1 gene along with its melting point and Cycle Threshold (CT) in sample 1 to 17, which were confirmed by RT-PCR. [Table/Fig-13,14] indicates the quantitation information for the run sample. The CT value more than 35 was considered negative for the XRCC1 gene.

Gender	Mean age (years)	Standard deviation
Male	61.136	8.56
Female	57.665	8.72
Whole population	59.37	9.99
Co-morbidities	**n (%)**	**Standard deviation**
Hypertension	173 (69.2)	8.58
Type 2 diabetes mellitus	122 (48.8)	8.66

[Table/Fig-6]: Age-wise distribution of cataract patients.



[Table/Fig-7]: Graphical representation of melt data for XRCC1 GENE melt A. Green of sample 1-10; Sample 16.

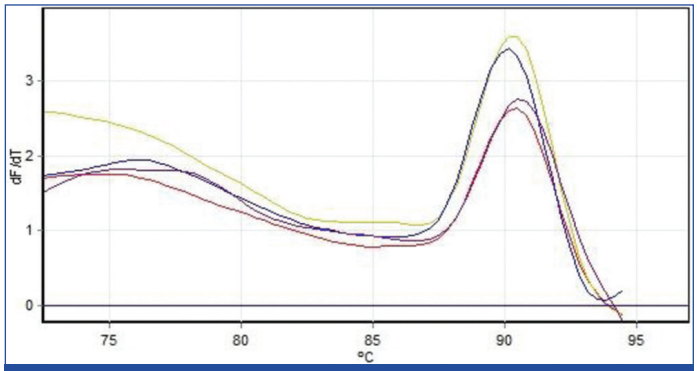
DISCUSSION

Cataract is one of the most common causes of visual impairment in the world cause of nearly half of the blind population. It is a vision impairing disease that occurs due to aging, and mainly affects elderly patients or people above the age of 50. This condition causes clouding in the eye lens or thickening of the lens, which leads to decrease in vision that gradually worsens with time. Senile

No.	Colour	Name	Type	Peak 2
1		Sample 1	Blood	90.0
2		Sample 2	Blood	89.8
3		Sample 3	Blood	88.9
4		Sample 4	Blood	89.8
5		Sample 5	Blood	90.0
6		Sample 6	Blood	89.8
7		Sample 7	Blood	89.0
8		Sample 8	Blood	89.0
9		Sample 9	Blood	90.0
10		Sample 10	Blood	90.2
11		Sample 16	Unknown	86.5

Bin name temperature sample number sample name peak

[Table/Fig-8]: List of samples with peak values.

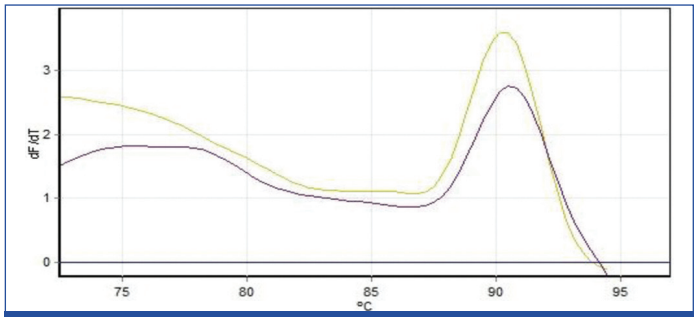


[Table/Fig-9]: Graphical representation of Melt data for XRCC1 gene melt. Green of samples No. 11-14.

No.	Colour	Name	Type	Peak 2
1		Sample 11	Blood	90.5
2		Sample 12	Blood	90.3
3		Sample 13	Blood	90.0
4		Sample 14	Blood	89.2

Bin name temperature sample no. sample name peak

[Table/Fig-10]: List of samples with peak values.



[Table/Fig-11]: Graphical representation of Melt data for XRCC1 GENE Melt A. Green of sample No. 15 and 17.

No.	Colour	Name	Type	Peak 2
1		Sample 15	Blood	89.9
2		Sample 17	Blood	86.6
Bin name temperature sample no. sample name peak				

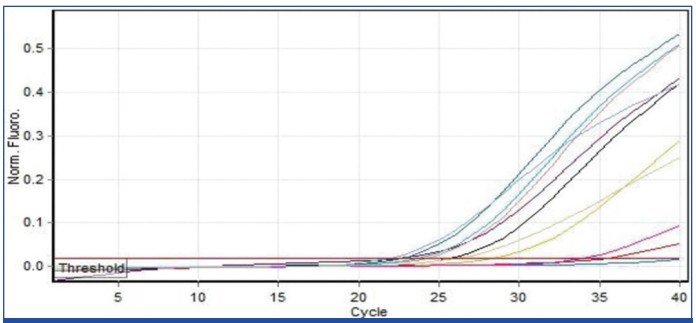
[Table/Fig-12]: List of samples with peak values.

Run name	Cataract three step with melt XRCC1 gene 2022-08-13
Run start	3/3/2022 6:13:40 PM
Run finish	3/3/2022 7:18:26 PM
Operator	Cataract XRCC1 gene
Notes	
Run on software version	Rotor-Gene Q software 2.3.1.49
Run signature	The run signature is valid
Gain green	9.67
Machine serial no.	0317145

[Table/Fig-13]: Experimental information (Quantitation report).

Quantitation information	
Threshold	0.0202
Left threshold	1.000
Standard curve imported	No
Standard curve (1)	N/A
Standard curve (2)	N/A
Start normalising from cycle	1
Noise slope correction	No
No template control threshold	% 0
Reaction efficiency threshold	Disabled
Normalisation method	Dynamic tube normalisation
Digital filter	Light
Sample page	Page 1
Imported analysis settings	

[Table/Fig-14]: Quantitation information.



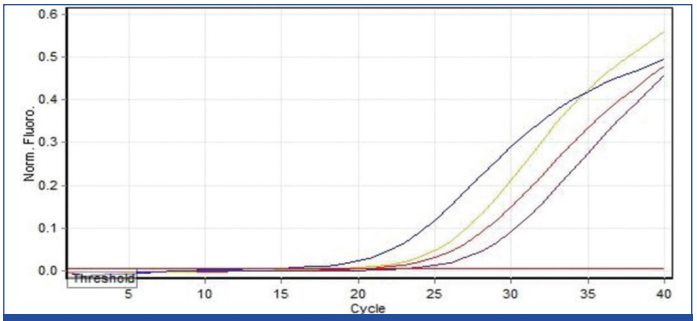
[Table/Fig-15]: Graphical representation of Quantitation data for Cycling A. Green of sample No. 1-10; Sample 16.

cataract has high probability of causing partial or total blindness if left untreated. In fact, it is one of the leading causes of blindness worldwide [16]. The oxidative stress is supposed to be an important factor in the development of Age-related Macular Degeneration (AMD). XRCC1 gene locates on chromosome 19q13.2. The protein encoded by this gene is involved in the efficient repair of DNA SSBs [17]. Genome instability caused by the great variety of DNA damaging agents would be an overwhelming problem for cells and organisms if it were not for DNA repair.

Deoxyribose nucleic acid repair enzyme X-ray repair cross-complementing-1 plays an important role in continuously monitoring chromosomes to correct damaged nucleotide residues generated by exposure to carcinogens and cytotoxic compounds. Studies have confirmed that polymorphisms of DNA repair genes decreased

No.	Colour	Name	Type	CT	CT Comment	Given Conc (Copies)	Calc Conc (Copies)
1		Sample 1	Blood	33.66			
2		Sample 2	Blood	28.47			
3		Sample 3	Blood	22.89			
4		Sample 4	Blood	24.38			
5		Sample 5	Blood	22.77			
6		Sample 6	Blood	24.31			
7		Sample 7	Blood	34.15			
8		Sample 8	Blood	25.81			
9		Sample 9	Blood	23.94			
10		Sample 10	Blood	26.32			
11		Sample 16	Blood	22.03			

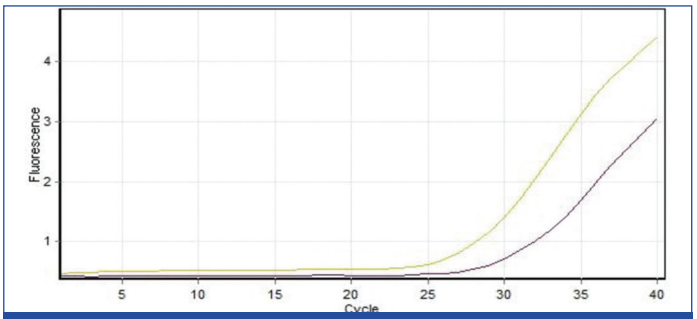
[Table/Fig-16]: List of samples with Cycle Threshold (CT) values.
The NEG {No Template Control (NTC)}: Sample cancelled due to NTC Threshold
The NEG {Reaction Efficiency (R. Eff)}: Sample cancelled as efficiency less than reaction efficiency threshold



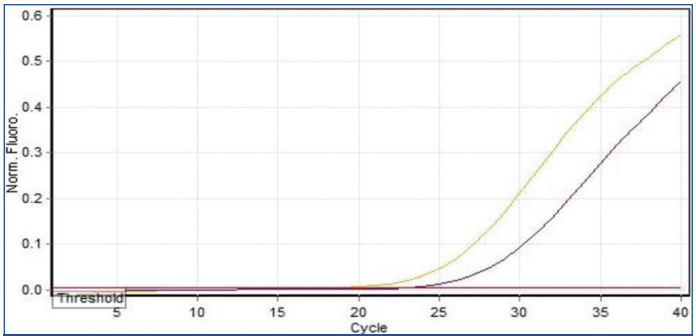
[Table/Fig-17]: Graphical representation of quantitation data for cycling A. Green of Sample No. 11-14.
Standard Curve

No.	Colour	Name	Type	CT	CT Comment	Given Conc (Copies)	Calc Conc (Copies)
1		Sample 11	Blood	20.43			
2		Sample 12	Blood	18.89			
3		Sample 13	Blood	13.64			
4		Sample 14	Blood	23.42			

[Table/Fig-18]: List of samples with CT values.
NEG {No Template Control (NTC)}: Sample cancelled due to NTC threshold
NEG {Reaction Efficiency (R. Eff)}: Sample cancelled as efficiency less than reaction efficiency threshold



[Table/Fig-19]: Graphical representation of raw data for Absorbance (Cycling Absorbance Green) of sample No. 15 and 17 (Flurosence).



[Table/Fig-20]: Graphical representation of quantitation data for cycling A. Green of sample No. 15 and 17 (Flurosence).

No.	Colour	Name	Type	CT	CT Comment	Given Conc (Copies)	Calc Conc (Copies)
1		Sample 15	Blood	18.83			
2		Sample 17	Blood	23.38			

[Table/Fig-21]: List of samples with ct values.
CT: Cycle threshold; The NEG (NTC): Sample cancelled due to NTC threshold
The NEG (R. Eff): Sample cancelled as efficiency less than reaction efficiency threshold
The report was generated by Rotor-Gene Q Series Software 2.3.1 (Build 49)

their ability to repair DNA damage, leaving human body a greatly increased susceptibility to cancer or age-related diseases [17]. BER is of great importance in DNA excision repair pathway as XRCC1 the key enzymes in BER pathway [18].

Hypertension is linked to senile cataract development and people with severe hypertension have a higher risk of cataract [5]. The oxidative stress which is associated with diabetes mellitus, might play an important role in the initiation and progression of diabetic complications, it has been suggested that free oxygen radical trigger cataract, kind of the degenerative manifestations of diabetes mellitus [19].

The human XRCC1, a DNA repair protein, in human is encoded by XRCC1 gene. It is a most well-known DNA repair protein, complexing with atleast three different enzymes, Poly-Adipose Diphosphate (ADP)-ribose Polymerase (PARP), DNA ligase III, and DNA polymerase β. The human XRCC1 gene (Gene ID 37414; OMIM 21171001 and 21174504) is 33 kb long and located on chromosome 19q13.2-13.3, consists of 17 exons, and encodes a 2.2 kb transcript, which corresponds to a putative protein of 633 amino acids.

Wherever, DNA repair complexes with DNA ligase III XRCC1 is also involved. Due to the exposure to ionising radiation and alkylating agents, DNA SSBs occur and these can be efficiently repaired by XRCC1. XRCC1 protein participates in the BER pathway due to interaction with DNA ligase III, polymerase beta and poly (ADP-ribose) polymerase [20].

It also plays a role in DNA processing during meiogenesis and recombination in germ cells. The XRCC1 protein acts as a scaffolding protein, so that it interacts with multiple repair enzymes. Due to scaffolding, repair enzymes carry out their enzymatic steps in repairing DNA. XRCC1 has a crucial role in SSB repair, BER and 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. DNA repair efficacy affected by genetic defect, which is associated with Age-related Cataract (ARC) [23].

Evidence has shown that XRCC1 is implicated in SSBs and the BER pathway and has been reported to be responsible for the efficient repair of DNA damage caused by ionisation, oxygen and alkylating agents [24]. Several polymorphisms were investigated in the XRCC1 gene with the coding polymorphism resulting in amino acid substitutions detected at codon 399 (Arg-Gln) receiving the most attention [25]. The XRCC1 may have a strong association with the ability to repair Deoxyribonucleic Acid (DNA); they could potentially influence many age-related diseases including cancers, atherosclerosis, and eye problems such as glaucoma, Age-related Macular Degeneration (AMD), and pterygium [26]. More importantly, genetic polymorphisms of XRCC1 have also been frequently documented in many human age-related cataract cases [27]. In this regard, it states that the genetic polymorphisms of XRCC1 may be related to the development and progression of age-related cataract.

An association between the development of lens opacities and oxidative stress or Ultraviolet (UV) light-induced DNA damage in the lens epithelium has been reported, and the effects of DNA repair in lens epithelial cells have also been proved [28]. Specifically, oxidative stress is involved in cataractogenesis, in this regard, the role of antioxidants could be considered as a potential cataract preventive agent. A potential explanation is that the active oxygen radicals damage the lens epithelial cells, and large conformational changes in proteins may be found as protein-protein cross-links, which causes a corresponding increase in concentration [29]. The XRCC1 genetic polymorphisms may be useful for identifying age-related cataract patients at an early stage [30].

It is noteworthy that XRCC1 was demonstrated to be implicated in SSBs and the BER pathway, which is one of the most important pathways involved in the repair of oxidative and UV-related DNA damage [31,32]. However, the variants of XRCC1 may contribute to disturbing single-base damage repair and single-strand DNA breaks resulting from endogenous oxidative radiation and inflammatory DNA damaging processes [33]. Although the pathophysiology of cataract is still not fully understood, as a multifactorial disease caused by interaction between genetic and environmental factors, epidemiological investigations prompt many risk factors such as diabetes, gender, sunlight or ultraviolet radiation, smoking and nutritional deficiencies, etc., may relate to cataract formation. It has been well accepted that oxidative stress plays a critical role in the pathogenesis of senile cataract. The association of XRCC1 plays a critical role in the elevated susceptibility to age-related cataracts revealing that this mutation was also regarded as one of the potential mechanisms increasing the risk of age-related cataracts.

Limitation(s)

The present study was limited by its small sample size. More insights about the aetiology and modifiable risk factors for cataract would have been generated by a large sample size. Also, the present study was self supported so there was a lack of financial help because of which the other genes responsible for DNA repair damage could not be targeted.

CONCLUSION(S)

The XRCC1 protein participates in the BER pathway due to interaction with DNA ligase III, polymerase beta and poly (ADP-ribose) polymerase. XRCC1 has a crucial role in SSB repair, BER and nucleotide excision repair. The association of XRCC1 polymorphisms with age-related cataract susceptibility observed in the present meta-analyses supports the view that XRCC1 plays an important role in susceptibility to age-related cataract. Thus, early screening and detection of XRCC1 genetic polymorphisms may be useful for identifying age-related cataract patients at an early stage.

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