Molecular Vision 2014; 20:661-669 <http://www.molvis.org/molvis/v20/661>
Received 30 January 2014 | Accepted 18 May 2014 | Published 21 May 2014

Polymorphisms of DNA repair genes *OGG1* and *XPD* and the risk of age-related cataract in Egyptians

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Purpose: To analyze the association of the polymorphisms of xeroderma pigmentosum complementation group D (*XPD*) and 8-oxoguanine glycosylase-1 (*OGG1*) genes with the risk of age-related cataract (ARC) in an Egyptian population.
Methods: This case-control study included 150 patients with ARC and 50 controls. Genotyping of *XPD* $Asp^{312}Asn$ was performed by amplification refractory mutation system PCR assay and genotyping of *OGG1* $Ser^{326}Cys$ was carried out by PCR including confronting two-pair primers.
Results: The Asn/Asn genotype of *XPD* gene was significantly associated with increased risk of ARC (odds ratio [OR] = 2.74, 95% confidence interval [CI] = 1.01–7.43, p = 0.04) and cortical cataract (OR = 5.06, 95% CI = 1.70–15.05, p = 0.002). The Asn^{312} allele was significantly associated with an increased risk of ARC (OR = 1.75, 95% CI 1.06–2.89, p = 0.03) and cortical cataract (OR = 2.81, 95% CI = 1.56–5.08, p<0.001). The *OGG1* Cys/Cys genotype frequency was significantly higher in ARC (OR = 4.13, 95% CI = 0.93–18.21, p = 0.04) and the Cys^{326} allele (OR = 1.85, 95% CI = 1.07–3.20, p = 0.03). Moreover, the Cys/Cys genotype of the *OGG1* gene was significantly higher in cortical cataract (OR = 6.00, 95% CI = 1.24–28.99, p = 0.01) and the Cys^{326} allele was also significantly associated with cortical cataract (OR = 2.45, 95% CI = 1.30–4.63, p = 0.005).
Conclusions: The results suggest that the Asn/Asn genotype and Asn^{312} allele of *XPD* polymorphism, as well as the Cys/Cys genotype and Cys^{326} allele of the *OGG1* polymorphism, may be associated with increased risk of the development of ARC, particularly the cortical type, in the Egyptian population.

The transparent crystalline lens of the eye is composed of fibers that come from the anterior subcapsular epithelia. The lens epithelia are essential for the growth, differentiation, and homeostasis of the lens. Epithelial cells near the lens equator divide and differentiate into lens fibers at a constant slow rate throughout life, resulting in a steady growth of the lens fiber mass. The mitotically quiescent central region of the epithelium is thought to protect the underlying fibers from injury and oxidative insult [1], to transport ions to and from the deeper layers of the lens [2], and perhaps to provide nutrients to elongating lens fibers [3]. Cataract develops with opacification of lens fibers. Age-related cataract (ARC) is a leading cause of blindness worldwide. Its etiology is multifactorial and not fully understood.

Oxidation may involve various biomolecules such as proteins, membrane lipids, and DNA. DNA base modifications resulting in mutations and genomic instability are a major consequence of oxidative stress. Oxidative DNA damage is processed by cellular DNA repair mechanisms, but their efficacy decreases with age [4]. Most oxidative DNA damage is repaired by both base excision repair (BER) and nucleotide excision repair (NER) pathways [5-7].

Reactive oxygen species generate a variety of modified bases in DNA, and 8-oxoguanine is one of the major and best-characterized products of oxidative DNA modifications [5,8]. It has been used as a biomarker for cellular oxidative stress [9], and can pair with adenine in double-stranded DNA during DNA replication. If this mispairing is not repaired, a G:C to T:A transversion mutation will occur. In mammalian cells, the major defense against the mutagenic effect of 8-oxoguanine is provided by the BER pathway. The 8-oxoguanine glycosylase-1 (*OGG1*) and mutY homolog genes initiate this repair pathway by recognizing and removing 8-oxoguanine and adenine paired with 8-oxoguanine, respectively [6,10,11].

The xeroderma pigmentosum complementation group D (*XPD*) is one of the DNA repair genes. Transcription factor II Human (TFIIH), containing the *XPD* helicases, is involved in local opening of DNA around a site of damage, and mediates strand separation at the site of the lesion. *XPD* is considered an essential gene because TFIIH is required for all transcription by RNA polymerase II. *XPD* codes for a protein involved in transcriptional-coupled NER, which removes and corrects oligonucleotide fragments containing a variety of lesions, such as ultraviolet (UV)-induced lesions, chemical adducts, and crosslinks [7,12]. The aim of this work was to analyze

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the relationship between the *OGG1* Ser^{326}Cys gene in the BER pathway and *XPD* Asp^{312}Asn in the NER pathway with the risk of ARC in the Egyptian population for better understanding of the pathogenesis of cataract development, with the aim of preventing or delaying the onset of this disease.

METHODS

Patients: All participants were recruited from Zagazig University Hospital and Ophthalmology Department of Zagazig University. All subjects were of Egyptian nationality. A written informed consent form was signed by each participant before participation. The study design was approved by the Ethical Committee of Faculty of Medicine, Zagazig University.

This case-control study included 150 consecutive patients with ARC (50 nuclear, 50 cortical, 50 subcapsular type). ARC was defined as lens opacity accompanied by disturbance of vision in patients over 50 years of age who did not complain of any visual disturbance before this age and had no other eye abnormalities that could explain the vision loss. Cataract status was determined by lens examination using a slit-lamp biomicroscope (Haag-Streit BQ900, Switzerland). Lens opacities were determined using the Lens Opacities Classification System (LOCS) III [13]. Only patients with ARC who had a LOCS III score ≥3 were included in the study. Patients were excluded if they had secondary cataract arising due to a local cause such as trauma, myopia, glaucoma, action of toxins, inflammation, or degenerative ocular diseases; or it was associated with systemic disease (such as diabetes) or medications inducing cataract (like steroids). In addition, patients with total or mixed-type cataract and patients with a past history of intraocular surgery were excluded.

The control group included 50 sex-matched subjects of older ages than the patients. They were selected randomly from the same population as the patients, with normal ocular examination and a LOCS III score = 0.1. They presented to the outpatient department with nonspecific ocular complaints such as conjunctivitis, blepharitis, burning, itching, or presbyopia and no lens opacities, with a best corrected visual acuity of at least 6/6.

Blood sampling and DNA isolation: One ml of venous blood sample from each participant was collected into EDTA-treated tubes for genomic DNA extraction. Genomic DNA was extracted from whole blood using the commercially available G-spin ™ Total DNA Extraction Kit (iNtRON Biotechnology, Seongnam, Korea). 200 µl whole EDTA blood was added to a 1.5 ml microcentrifuge tube containing 20 µl proteinase K and 5 µl of RNase A solutions, and gently mixed. Then 200 µl of lysis buffer was added to each sample mixed thoroughly and incubated at 56 °C for 10 min. 200 µl of absolute ethanol was added to the lysate, inverted 5–6 times to mix. The mixture was poured to the spin column and centrifuged at 11,500 ×g for 1 min. The filtrate was discarded and the spin column was placed in a 2 ml collection tube. 700 µl of wash buffer A was added to the spin column, and centrifuged at 11,500 ×g for 1 min, the flow –through was discarded. 700 µl of wash buffer B was added to the spin column, centrifuged at 11,500 ×g for 1 min, the flow –through was discarded. The spin column was centrifuged at 11,500 ×g for 1 min to dry the membrane. The spin column was placed in a new 1.5 ml tube. 100 µl of elution buffer was directly added to the membrane, incubated for 1 min at room temperature and then centrifuged for 1 min at 11,500 ×g to elude the DNA. DNA purity and concentration were determined spectrophotometrically at 260 and 280 nm. The purified genomic DNA was stored at −20 °C until use.

Genotyping of XPD (rs1799793) polymorphism: Amplification refractory mutation system polymerase chain reaction (ARMS-PCR) assay was used for detection of *XPD* (rs1799793; Asp^{312}Asn) polymorphism as described by Rybicki et al. [14]. An internal control primer pair was included in each reaction at a 1:5 dilution relative to the allele-specific primers (ARMS-A: 5′-CCC ACC TTC CCC TCT CTC CAG GCA AAT GGG-3′ and ARMS-B: 5′-GGG CCT CAG TCC CAA CAT GGC TAA GAG GTG-3′). A 150 bp PCR fragment was generated with the following primers: reverse primer: 5′-CAG GAT CAA AGA GAC AGA CGA GCA GCG C-3′ ; Asp (G) allele forward specific primer: 5′-GTC GGG GCT CAC CCT GCA GCA CTT CGG C-3′; Asn (A) allele forward specific primer: 5′-GTC GGG GCT CAC CCT GCA GCA CTT CGA T-3′. Each sample was amplified twice by different pairs of primers.

The PCR was performed in a final volume of 25 µl containing 100 ng of template DNA, 0.1 µM of internal control primer and 0.5 µM of the allele-specific primers (Biosearch Technologies, Novato, CA) and 12.5 µl of 2X *i*-Taq™ PCR Master Mix (iNtRON Biotechnology).

Cycling conditions were initial denaturation of 94 °C for 2 min, followed by 38 cycles of 94 °C for 30 s, 66 °C (wild allele) or 62 °C (mutant allele) for 50 s and 72 °C for 1 min, and finally 72 °C for 7 min. Negative controls (without DNA) were included in each round of amplification to check for contamination. Genotypes were typed as Asp/Asp and Asn/Asn depending on the development of bands when primers specific for allele Asp^{312} or allele Asn^{312} were used respectively. Samples were typed as heterozygotes (Asp/Asn) when bands were seen with both primers.

Table 1. Demographic data of age-related cataract patients (n=150) versus controls (n=50).

Parameters	Controls	Cataract patients	P value
	Age (years)		
Range:	60–78	50–78	
Mean ± SD:	67.83±5.54	60.33±6.22	<0.001*
	Sex		
Male:	22 (44)	56 (37.3)	
Female:	28 (56)	94 (62.7)	0.40**

* Two tailed *t* test **Chi-square (χ^2) test

Genotyping of OGG1 (rs1052133) polymorphism: Genotyping of the *OGG1* (rs1052133, Ser^{326}Cys) polymorphism was performed by PCR with confronting two-pair primers following Niwa et al. [15]. The extracted DNA was amplified with the four primers: for the C (Ser) allele: 5′-CAG CCC AGA CCC AGT GGA CTC-3′ (F1) and 5′-TGG CTC CTG AGC ATG GCG GG-3′ (R1); for the G (Cys) allele: 5′-CAG TGC CGA CCT GCG CCA ATG-3′ (F2), 5′-GGT AGT CAC AGG GAG GCC CC-3′ (R2). Where the bases affected by the polymorphism are underlined.

The PCR was performed in a final volume of 25 µl containing 100 ng of template DNA, 0.5 µM of each primer (Biosearch Technologies), and 12.5 µl of 2X *i*-Taq™ PCR Master Mix (iNtRON Biotechnology).

The amplification protocol was as follows: 95 °C for 10 min followed by 30 cycles of 95 °C for 1 min, 64 °C for 1 min, and 72 °C for 1 min, and a final extension 72 °C for 5 min using a thermal cycler PTC-100 machine (MJ Research, Inc., Watertown, MA). The *OGG1* Ser^{326}Cys polymorphism was genotyped as a 252 bp band for the C (Ser^{326}) allele, a 194 bp band for the G (Cys^{326}) allele, and a 406 bp common band.

The PCR products of both genes were separated in a 3% agarose electrophoresis system (Maxicell, EC 360 M-E-C Apparatus Corporation, St. Petersburg, FL), then visualized with ethidium bromide staining under UV transillumination with 100-bp SiZer™ DNA marker (iNtRON Biotechnology).

Statistical analysis: Data were processed using the Statistical Package for Social Science version 13 (SPSS Inc., Chicago, IL). The ages of the patients and the controls were compared by the Student *t* test. The chi-square test was used to compare the gender distribution, to test the association between the genotypes and alleles in relation to the cases and controls, and to test for deviation of genotype distribution from the Hardy–Weinberg equilibrium (HWE). The odds ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated to estimate the strength of the association between polymorphism genotype alleles of patients and controls. A value of p<0.05 was considered statistically significant.

RESULTS

The ages of the controls ranged from 60 to 78 years, with a mean of 67.83±5.54 years. There were 22 males and 28 females. The ages of the cataract patients ranged from 50 to 78 years with a mean of 60.33±6.22 years. There were 56 males and 94 females. There was a statistically significant increase in the age of controls compared to cataract patients (p<0.001), but no significant difference was found as regard sex (p = 0.40). The demographic data for the study groups are shown in Table 1.

XPD (rs1799793) polymorphism analysis and age-related cataract risk: The genotype frequencies were in accordance with the HWE among the controls (p = 0.33), but not among the patients (p<0.001). In patients with ARC, the frequencies of Asp/Asp, Asp/Asn, and Asn/Asn genotypes were 44.7, 32.0, and 23.3%, respectively; in controls, the frequencies were 56.0, 34.0, and 10.0%, respectively. The frequencies of Asp and Asn alleles in cataract patients were 60.7 and 39.3%, while in controls, they were 73.0 and 27.0%, respectively. Regarding the risk of development of ARC, the Asp/Asp genotype and Asp wild allele were taken as references; the Asn/Asn genotype was significantly associated with an increased risk of ARC (OR = 2.74, 95% CI = 1.01–7.43, p = 0.04). The Asn allele was significantly associated with an increased risk of ARC (OR = 1.75, 95% CI = 1.06–2.89, p = 0.03); Table 2.

Table 3 shows the distribution of allele and genotype frequencies of *XPD* Asp^{312}Asn polymorphism in controls and cataract subtypes. The genotype frequency of the Asn/Asn of *XPD* Asp^{312}Asn was significantly higher in the cortical cataract (OR = 5.06, 95% CI = 1.70–15.05, p = 0.002), but not in other types. The Asn allele was significantly associated with cortical cataract (OR = 2.81, 95% CI = 1.56–5.08, p<0.001).

Table 2. Genotype distributions and allelic frequencies of *XPD* Asp[312]Asn (rs1799793) polymorphism in age-related cataract patients (n=150) and controls (n=50).

XPD Asp [312]Asn polymorphism	Cataract patients, n (%)	Controls, n (%)	Odds ratio (95% confidence interval)	P value*
		Genotype		
Asp/Asp	67 (44.7)	28 (56.0)	1 (reference)	––
Asp/Asn	48 (32.0)	17 (34.0)	0.91 (0.46–1.80)	0.79
Asn/Asn	35 (23.3)	5 (10.0)	2.74 (1.01–7.43)	0.04
		Alleles		
Asp	182 (60.7)	73 (73.0)	1 (reference)	––
Asn	118 (39.3)	27 (27.0)	1.75 (1.06–2.89)	0.03

* Chi-square (χ^2) test

OGG1 (rs1052133) polymorphism analysis and age-related cataract risk: The distribution of *OGG1* Ser[326]Cys genotypes was consistent with HWE in controls (p = 1.00), but not in patients (p = 0.009). Table 4 shows the analysis of polymorphism located at *OGG1* in cataract patients. Seventy-seven patients (51.3%) were homozygous for the Ser/Ser genotype, 51 (34.0%) were heterozygous for the Ser/Cys genotype, and 22 (14.7%) were homozygous for the Cys/Cys genotype. In the control group, the frequencies of Ser/Ser, Ser/Cys, and Cys/Cys genotypes were 64.0, 32.0, and 4.0%, respectively. The frequencies of Ser and Cys alleles in cataract patients were 68.3 and 31.7%, and in controls they were 80.0 and 20.0%, respectively. Regarding the risk of development of ARC, the Ser/Ser genotype and Ser[326] allele were taken as references. The occurrence of the *OGG1* Cys/Cys genotype was significantly higher in cataract patients than controls (OR = 4.13, 95% CI = 0.93–18.21, p = 0.04), and the Cys[326] allele was also significantly higher in cataract patients than controls (OR = 1.85, 95% CI = 1.07–3.20, p = 0.03).

Table 5 shows the distribution of allele and genotype frequencies of *OGG1* Ser[326]Cys polymorphism in controls and cataract subtypes. When compared with controls, the genotype frequency of the Cys/Cys of *OGG1* Ser[326]Cys was significantly increased in the cortical cataract (OR = 6.00, 95% CI = 1.24–28.99, p = 0.01), but not in other types. The Cys[326] allele was significantly associated with cortical cataract (OR = 2.45, 95% CI = 1.30–4.63, p = 0.005).

DISCUSSION

Age-related cataract has been a focus of investigators attempting to identify the causes and the pathogenesis of the disease and hoping to decrease the incidence or delay its onset. Agents such as UV light and hydrogen peroxide, to which the lens is exposed throughout life, have been suggested to compromise genomic integrity and are harmful to lens epithelial cells [16,17]. It is possible that accumulated damage from these and other agents may lead to a decrease in lens epithelial cell density, as observed by some investigators [18-20]. Accumulated damage could impair the ability

Table 3. Genotype distributions and allelic frequencies of *XPD* Asp[312]Asn (rs1799793) polymorphism in controls (n=50) versus in different subtypes of age-related cataract patients (n=150).

XPD Asp[312]Asn polymorphism	Controls, n (%)	Cataract patients, n (%)		
		cortical cataract, n=50	nuclear cataract, n=50	posterior subcapsular cataract, n=50
		Genotype		
Asp/Asp	28 (56)	17 (34)	24 (48)	26 (52)
Asp/Asn	17 (34)	15 (30)*	18 (36)*	15 (30)*
Asn/Asn	5 (10)	18 (36)[a]	8 (16)*	9 (18)*
		Alleles		
Asp (G)	73 (73)	49 (49)	66 (66)	67 (67)
Asn (A)	27 (27)	51 (51)[b]	34 (34)*	33 (33)*

*not significant [a]p=0.002; odds ratio=5.06; 95% confidence interval (1.70–15.05). [b] p<0.001; odds ratio=2.81; 95% confidence interval (1.56–5.08).

Table 4. Genotype distributions and allelic frequencies of *OGG1* Ser[326]Cys (rs1052133) polymorphism in age-related cataract patients (n=150) and controls (n=50).

OGG1 Ser[326]Cys polymorphism	Cataract patients, n (%)	Controls, n (%)	Odds ratio(95% confidence interval)	P value*
		Genotype		
Ser/Ser	77 (51.3)	32 (64.0)	1 (reference)	––
Ser/Cys	51 (34.0)	16 (32.0)	1.09 (0.55–2.17)	0.8
Cys/Cys	22 (14.7)	2 (4.0)	4.13 (0.93–18.21)	0.04
		Alleles		
Ser	205 (68.3)	80 (80.0)	1 (reference)	––
Cys	95 (31.7)	20 (20.0)	1.85 (1.07–3.20)	0.03

* Chi-square test

of the lens epithelial cells to protect underlying fibers, or the reduced epithelial cell density could diminish the protection afforded by the epithelium. Lens epithelium DNA may also be affected by different insults. Many studies have indicated the association between the oxidative or UV light DNA damage and cataract development [21-26]. Spector reported that, in most cases, photochemically induced oxidative stress in rat lenses may cause irreversible changes in the lens epithelia. The earliest detectable changes in lens cell biology are observed in the epithelial cell redox set point and at the DNA level in terms of DNA integrity and 3H-thymidine incorporation followed by decreased membrane transport and changes in gene expression. Significant modification in classical cataract parameters such as hydration and transparency occur at later times [22].

The DNA repair capacity has an important role in protecting the genome against DNA damage. The proteins involved in the DNA repair pathway function directly with damaged DNA and are involved with the genes and proteins that regulate DNA replication and progression through the cell cycle [27,28]. There is also interindividual variation in DNA repair capacity, which is likely attributable to genetic variation in DNA repair genes [29,30]. Decreased activity of repair enzymes with age may decrease the capacity to repair damaged DNA molecules. Defective antioxidant enzymes and functional variants of DNA replication and repair genes might be expected to be highly significant to cancer and aging [31,32]. We analyzed the association between two DNA repair genes, *XPD* Asp[312]Asn and *OGG1* Ser[326]Cys polymorphisms, and the risk of ARC in the Egyptian population because these polymorphisms may alter DNA repair capacity. In addition, these enzymes play a vital role in the NER and BER pathways [33-37], and may subsequently lead to synergistic effects with other insults resulting in ARC.

We chose control subjects with higher ages than the patients. Recruiting subjects from this age group had the merit of maximizing the probability that they were unaffected by cataract, that is, to avoid including younger subjects who might develop cataract in later life. The distributions of genotypes of *XPD* and *OGG1* were in accordance with the

Table 5. Genotype distributions and allelic frequencies of *OGG1* Ser[326]Cys (rs1052133) polymorphism in controls (n=50) and in cataract patients (n=150) with different cataract subtypes.

OGG1 Ser[326]Cys polymorphism	Controls, n (%)	Cataract patients, n (%)		
		cortical, n=50	nuclear, n=50	posterior subcapsular, n=50
		Genotype		
Ser/Ser	32 (64)	22 (44)	27 (54)	28 (56)
Ser/Cys	16 (32)	18 (36)*	17 (34)*	16 (32)*
Cys/Cys	2 (4)	10 (20)[a]	6 (12)*	6 (12)*
		Alleles		
Ser	80 (80)	62 (62)	71 (71)	72 (72)
Cys	20 (20)	38 (38)[b]	29 (29)*	28 (28)*

*not significant [a] p=0.01; odds ratio, 6.00; 95% confidence interval, 1.24–28.99. [b] p=0.005; odds ratio, 2.45; 95% confidence interval, 1.30–4.63.

HWE among controls, but not among patients, indicating the possible association of these polymorphisms with the disease. The absence of deviation from the controls indicates absence of selection bias. Deviation from HWE in patients with ARC was also found in the Indian population [38].

In this study, the frequency of variant allele Asn^{312} of *XPD* gene was 27%, while in the Indian population it has been reported to be 36% [38]. We found a possible risk for *XPD* Asn/Asn genotype and cataract development. There was a significant increase in the frequencies of *XPD* Asn/Asn genotype in cataract patients as compared to controls (OR = 2.74). In addition, there was a significant increase in the frequencies of *XPD* Asn^{312} variant allele in cataract patients as compared to controls (OR = 1.75). Regarding cataract subtypes, there were significant increases in the frequencies of the Asn/Asn genotype and Asn^{312} in cortical cataract only, but not in other subtypes. Padma et al. were the first to report the association of *XPD* Asp^{312}Asn polymorphism and ARC. They found a significant increase in the frequencies of the *XPD* Asn/Asn genotype in cataract patients as compared to controls, but they did not find a significant difference related to the Asn^{312} allele [38]. They also observed a significant increase in the frequencies of *XPD* Asn/Asn genotype in cortical cataract, but not in other subtypes. These results can possibly be explained by the decreased activity of the enzyme of *XPD* Asn^{312} allele in DNA repair with age, promoting cataract development.

Hou et al. reported that the *XPD* Asn^{312} variant allele may be associated with the reduced repair of aromatic DNA adducts [39]. Different *XPD* alleles have been associated with chromosomal aberrations, frequency of sister chromatid exchanges, DNA adducts, and reduced efficiency of DNA repair as measured by the host cell reactivation assay and increased UV-induced DNA strand breaks detected by the alkaline comet assay [40,41].

In this study, the frequency of variant allele Cys^{326} in controls was 20%. The Cys^{326} allele frequency ranges from 23% to 41% in Caucasians and 40% to 60% in Asians [42]. We found that *OGG1* Ser^{326}Cys polymorphism may be associated with an increased risk of ARC. The statistical analysis revealed a possible deleterious effect of the *OGG1* Cys/Cys genotype (OR = 4.13) and Cys^{326} allele (OR = 1.85) in the development of cataract. Moreover, the genotype frequency of the Cys/Cys of *OGG1* gene was significantly increased in the cortical cataract (OR = 6.00). The Cys^{326} allele was significantly associated with cortical cataract (OR = 2.45). It has been hypothesized that this could be due to the *OGG1* Cys^{326} protein having an impaired repair activity, allowing 8-oxoguanine to accumulate in the DNA with a consequent increase in mutation rates. Our results are consistent with the results of Zhang et al., who first reported comparable findings in Harbin, China [43].

The *OGG1* Ser^{326}Cys polymorphism has been shown to diminish the 8-oxoguanine glycosylase-1 DNA (hOgg1) activity in vitro, suggesting that the Cys^{326} allele may pose a higher risk of 8-oxoguanine formation in DNA [44,45]. The effect of endogenous hOgg1 activity in human cells by the 326 allele status remains controversial. No allele-specific differences due to gender or smoking behavior have been found by Janssen et al. [46], whereas Chen and colleagues found a significant age-dependent decrease in hOgg1 activity in the lymphocytes of homozygous Cys^{326} allele carriers [47]. Several hypotheses have been proposed for the mechanism underlying a potential deficiency in the DNA repair capacity of the *OGG1* Cys^{326} allele form. This variant, or its mRNA, could be less stable, causing the steady-state level of the hOgg1 enzyme in the cell to decrease [48]. Following this, subnuclear localization may be brought about by a phosphorylation of the Ser^{326}, which is important for the localization of the protein and has potential catalytic efficiency [49]. Bravard et al. supported the idea that individuals homozygous for the *OGG1* Cys^{326} variant could more readily accumulate mutations under conditions of oxidative stress [48]. Their results established that the intrinsic hOgg1 activity, and therefore repair capacity, of cells carrying the *OGG1* Cys^{326} variant is particularly sensitive to the cellular redox status.

The association of *XPD* Asp^{312}Asn and *OGG1* Ser^{326}Cys polymorphisms with cortical cataract observed in the present study may be supported by results of some epidemiological studies. Family epidemiological investigations have shown that hereditary factors play an important role in the occurrence of ARC [50-54]. Moreover, it is known that cortical cataract is highly heritable among other subtypes of ARC [53,54]. Previous studies have already reported an association between the UV light exposure and the development of cortical cataract. A review of 22 epidemiologic studies by McCarty and Taylor revealed that there is a well-documented risk for the development cortical cataract and UV-B exposure [55].

The results of this study cannot be generalized for several reasons. First, ARC is a multifactorial disease and its pathogenesis is complicated. The lens is exposed throughout life to a large number of possibly injurious agents that come through the aqueous humor, such as hydrogen peroxide and UV light, which result in oxidative damage. Second, ethnic differences may be an important factor that may affect genetic studies of this type. Third, the interaction of other genes participating in

DNA damage recognition repair and cell cycle regulation may have altered the effect of *OGG1* and *XPD* polymorphisms.

As with other candidate gene studies, there are some limitations in our study. First, as the power to detect disease susceptibility genes is influenced by the number of sample size, the size of the sample in our study seems to be relatively small. Second, the patients were recruited only from the town of Zagazig, and not from other areas in Egypt.

In conclusion, this is the first study to identify a possible association between the *XPD* $Asp^{312}Asn$ and *OGG1* $Ser^{326}Cys$ polymorphisms of the DNA repair enzyme genes and ARC in an Egyptian population. The present data support the importance of DNA repair gene polymorphisms and DNA repair genes as potential pharmacologic targets to promote DNA repair and maintain genome stability. Manipulating these targets may provide a strategy to prevent, delay the age at onset, or slow the progression of ARC. However, larger studies in multiple ethnic groups would be required to establish such relationships.

ACKNOWLEDGMENTS

We gratefully thank to Prof. Bahaa-Eldin H. Abdulhalim, MD, for his useful advices and guidance.

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Articles are provided courtesy of Emory University and the Zhongshan Ophthalmic Center, Sun Yat-sen University, P.R. China. The print version of this article was created on 21 May 2014. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.