Original Article
The relationship of DNA repair gene XPD, XRCC1, OGG1, APE1, and WRN polymorphism with the risk of age-related cataract in Hani people from Mojiang region in Yunnan

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Abstract: Age-related cataract (ARC) is the leading cause of blindness in the elderly. This study investigated DNA repair genes, XPD, XRCC1, OGG1, APE1, and WRN single nucleotide polymorphisms (SNPs), to clarify their relationship with ARC in Hani patients from Mojiang region in Yunnan. Polymerase chain reaction-ligase detection reaction (PCR-LDR) was used to perform genotype analysis in ARC patients and healthy control. The genotype frequency distribution of XPD, XRCC1, OGG1, APE1, and WRN SNP in Hani accorded with Hardy-Weinberg equilibrium principle. OGG1 genotype analysis: the frequency of allele G was significantly higher than the control (P = 0.008; OR: 1.468; 95% CI: 1.106-1.949); the risk of allele G was 1.468 times of allele A; CC genotype may be associated with ARC (OR: 1.716; 95% CI: 1.460-2.018); the risk of this genotype was 1.716 times of CG and GG genotypes. GG genotype may have protective effect on ARC (OR: 0.684; 95% CI: 0.568-0.823). XRCC1 genotype analysis: AG genotype may be associated with ARC (OR: 1.464; 95% CI: 1.108-1.934); AG genotype frequency was higher than control (P = 0.007); the risk of this genotype was 1.464 times of GG and AA genotypes; Alleles A frequency was significantly higher than the control (P = 0.010; OR: 1.329; 95% CI: 1.131-1.561); Allele A risk was 1.329 times of allele G. XPD, APE1, and WRN genotypes showed no relationship with ARC risk. OGG1 and XRCC1 gene polymorphisms were associated with ARC risk in Hani from Mojiang region in Yunnan.

Keywords: DNA repair gene, XPD, XRCC1, OGG1, APE1, WRN, gene polymorphism, age-related cataract

Introduction

Age-related cataract (ARC), also known as senile cataract, is caused by lens opacity increased with the growth of age. ARC is the main cause of blindness around the world. According to the world health organization report, about 160 million people became blind because of ARC [1, 2]. Though multiple risk factors (aging, sunlight or ultraviolet radiation, diabetes, smoking, malnutrition, genetic defects, and oxidative stress, etc.) of ARC had been clarified, its pathogenesis was still not clear [3]. Genetic defects, oxidative stress, and ultraviolet radiation were once regarded as the three main pathogenic factors of ARC [4-7]. A lot of researches focused on the relationship

between lens epithelial cells DNA damage and lens opacity [8, 9]. Too much oxidation products can lead to lens epithelial cells damage, resulting in cell apoptosis and necrosis [10]. DNA damage of lens epithelial cells may be the primary cause of lens opacity. Genetic defects affect DNA repair efficacy, which is associated with ARC. With the rapid development of molecular biology technology and human genome project, a variety of genetic research about complex diseases had been carried out. Based on the result of genome-wide association study (GWAS), together with ARC related reports, we screened out five genes (XPD, XRCC1, OGG1, APE1, and WRN) and five corresponding single nucleotide polymorphisms (SNPs) loci lys751gln

Table 1. Primers of target genes used in the PCR

PCR length	Primer name		Sequence (5'-3')
rs1052133	CTTTGCTGGTGGCTCCTGA	CCCAGTGTACCCTCCTCCC	110
rs11574311	GGGAGGAAAGGAGGAAAATG	CTTTTTTCTCACCTTTCTC	71
rs1130409	CTATCTCTGCCCCACCTC	CAAATTCAGCCACAATCA	125
rs13181	CACCAGGAACCGTTTATG	TTCTCTGCAGGAGGATCA	139
rs25487	CCAACACCCCCAAGTAC	TCTGACTCCCCTCCAGAT	179

Table 2. Probes of target genes

Probe name	Sequence (5'-3')	LDR length
rs1130409_modify	P-TCGCCTATAGAAATGAAACATTTTTTTTTTTTTTTTTT-FAM	
rs1130409_A	TTTTTTTTTTTTTTTTTTCCTTCCTGATCATGCTCCTCT	77
rs1130409_G	TTTTTTTTTTTTTTTTTTTTCCTTCCTGATCATGCTCCTCC	79
rs1130409_T	TTTTTTTTTTTTTTTTTTTTTTCCTTCCTGATCATGCTCCTCA	81
rs13181_modify	P-AGAGGATAGAGCAGATTGCTTTTTTTTTTTTTTTTTTTTTT-FAM	
rs13181_A	TTTTTTTTTTTTTTTTTTTTTTTAGAATCAGAGGAGACGCTGT	84
rs13181_G	TTTTTTTTTTTTTTTTTTTTTTTTTAGAATCAGAGGAGACGCTGC	86
rs13181_T	TTTTTTTTTTTTTTTTTTTTTTTTTTTAGAATCAGAGGAGACGCTGA	88
rs25487_modify	P-GGGAGGGCAGCCGCCGACGCTTTTTTTTTTTTTTTTTTTTTTTTT-FAM	
rs25487_A	TTTTTTTTTTTTTTTTTTTTTTTTTGGCGTGTGAGGCCTTACCTCT	91
rs25487_G	TTTTTTTTTTTTTTTTTTTTTTTTTTTGGCGTGTGAGGCCTTACCTCC	93
rs1052133_modify	P-ATTGGCGCAGGTCGGCACTGTTTTTTTTTTTTTTTTTTTTTTTTTTT-FAM	
rs1052133_C	TTTTTTTTTTTTTTTTTTTTTTTTTTTGGTGGCTCCTGAGCATGGCGGG	96
rs1052133_G	TTTTTTTTTTTTTTTTTTTTTTTTTTTTTGGTGGCTCCTGAGCATGGCGGC	98
rs11574311_modify	P-AGTAAAAGAAAGTATGAGAATTTTTTTTTTTTTTTTTTTTTTTTTTTTTT-FAM	
rs11574311_C	TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTGGAAAGGAGGAAAATGCTGAGTG	101
rs11574311_T	TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTGGAAAGGAGGAAAATGCTGAGTA	103

Table 3. General information comparison

Index	Control	Case	P value
Gender (male/female)	224/176	234/164	> 0.05
Age (year)	72.1 ± 11.4	73.5 ± 10.8	> 0.05

(A/C), arg399gln (G/A), ser326cys, asp148glu, and rs11574311 (C/T) related to ARC. We performed correlation analysis on 400 cases of ARC patients in Hani from Mojiang region in Yunnan to investigate the relationship between regional DNA repair gene polymorphism and ARC.

Materials and methods

Research objects

Four hundred ARC patients of Hani diagnosed by the Second Affiliated Hospital of Kunming Medical University between February 2012 and June 2015 were enrolled. Inclusion criteria: no

cataract history, no other related diseases, except complicated cataract (diabetes, glaucoma, uvea related diseases, and trauma). The mean age of ARC group was 73.5 ± 10.8 years old, while it was 72.1 ± 11.4 years old in healthy control. 400 Hani people received healthy examination excluding cataract and other eye related diseases were selected as normal control. No difference of age composition was observed between two groups (P > 0.05).

The study protocol was approved by the Research Ethics Committee of the Second Affiliated Hospital of Kunming Medical University, and all patients gave their informed consent before study commencement.

Main instruments and reagents

Polymerase chain reaction (PCR) amplification (Gene Amp PCR system 9600), fluorescence

PCR amplification MJ PTC-200, and the 48-capillary 3730 DNA Analyzer was produced by Applied Biosystems (United States). DNA extraction and quantitative reagents bought from Shanghai Hanyu Biological Engineering co., LTD. Taq enzyme system was self-developed.

Primers and probes

Primers and probes used in the experiment were listed in **Tables 1** and **2**, and synthesized by Shanghai Hanyu Biological Engineering co., LTD.

Methods

Genome DNA extraction: 5 ml peripheral blood was extracted from subjects under fasting statue to the tube containing 200 ml 2% EDTA anticoagulation. 200 µl sample was added with 200 µl buffer GB and 20 µl Proteinase K at 56°C for 10 min. Then 350 µl BD was added at 25°C for 2-5 min. The solution was added to adsorption column CG2 and centrifuged at 12000 rpm (~13400 g) for 30 s. After removing the liquid and adding 500 µl GDB, the solution was centrifuged at 12000 rpm (~13400 g) for 30 s. The solution was then centrifuged at 12000 rpm (~13400 g) for 30 s after removing the liquid and adding 600 µl PWB. And then, the solution was further centrifuged at 12000 rpm (~13400 g) for 2 min. After leaving the absorption column CG2 at 25°C for 2 min, the adsorption column CG2 was then put into a 1.5 ml centrifuge tube with 100 µl elution buffer TB at 25°C for 2 min. After centrifuged at 12000 rpm (~13400 g) for 2 min, the solution was collected to the centrifugal tube and stored at -80°C (According to the manual provided by TIANGEN).

PCR amplification: PCR amplification system included 10 mmol/L Tris-HCl (pH 8.3), 2.0 mmol/L $MgCl_2$, 50 mmol/L KCl, 200 µmol/L dNTP, 1.5 U Taq polymerase, 300 nmol/L primers, and 5 µl DNA template. The total volume of solution was 50 µl. PCR condition contained one cycle of 95°C for 2 min, followed by 40 cycles of 94°C for 30 s, 54°C for 30 s, and 65°C for 30 s, and extension at 65°C for 10 min at last.

Ligase detection reaction (LDR): LDR reaction system composition: 20 mmol/L Tris-HCl (pH 7.5), 10 mmol/L $MgCl_2$, 100 mmol/L KCl, 1 mmol/L EDTA, 1 mmol/L nicotinamide adenine dinucleotide (NAD^+), 10 mmol/L dithiothreitol (DTT), 3 µl PCR products, 12.5 nmol/L probes and primers, and 0.1 mmol/L DNA ligase. The total volume was 20 µl. LDR reaction condition: 95°C for 2 minutes, followed by 40 cycles of 94°C for 15 s and 50°C for 25 s. After amplification, 0.5 µl 0.5 mmol/L EDTA stop buffer was added to stop the reaction. 2.5 µl product was mixed with equal volume of buffer and degenerated at 94°C for 2 min. Then the product was moved to sequencer after cooling and electrophoresed for 30 min. Electrophoresis result was analyzed by Genemapper software.

Statistical analysis

Chi-square test was performed to analyze genotype distribution. Hardy-weinberg balance method was applied to determine genotype and allele frequencies. Odds ratios and 95% CI were used for comparison. P < 0.05 was considered as statistical difference. All the above mentioned statistical analyses were performed on SPSS 16.0.

Results

No significant difference about gender and age were observed between two groups (**Table 3**). For all gene polymorphism, common allele was considered to be the reference genotype, while uncommon allele was detected. Five genotypes OGG1-Ser326CYs, XRCC1-Arg399Gln, APE1-Asp148Glu, XPD-Lys751Gln, and WRN conformed to Hardye Weinberg equilibrium distribution in case group (P = 0.076, P = 0.261, P = 0.239, P = 0.239, and P = 0.198, respectively) and control group (P = 0.376, P = 0.663, P = 0.630, P = 0.445, and P = 0.521, respectively). The frequency of occurrence of the above mentioned five kinds of DNA repair gene polymorphisms in case group and control were listed in **Table 1**. OGG1 gene polymorphism analysis showed that the cases and frequency were CC 170 (42.5%), CG 82 (20.5%), and GG 121 (30.3%) in case group, whereas they were CC 134 (33.5%), CG 78 (19.5%), and GG 177 (44.3%) in control (P < 0.05). Statistical analysis presented that CC genotype of OGG1 may be associated with ARC (OR: 1.716; 95% CI: 1.460-2.018); the risk of this genotype was 1.716 times of CG and GG genotypes. GG genotype may have protective effect on ARC (OR:

Table 4. XPD, XRCC1, OGG1, APE1, and WRN genotype and allele frequency distribution

SNP	Genotype/ Allele	Control	Case	OR (95% CI)	P value
OGG1	CC	134 (33.5)	170 (42.5)	1.716 (1.460~2.018)	< 0.001
	CG	78 (19.5)	82 (20.5)	1.065 (0.753~1.505)	0.724
	GG	177 (44.3)	121 (30.3)	0.684 (0.568~0.823)	0.001
	C	122 (30.5)	131 (32.8)	1.110 (0.824~1.495)	0.494
	G	145 (36.3)	182 (45.5)	1.468 (1.106~1.949)	0.008
XRCC1	AA	102 (25.5)	111 (27.8)	1.122 (0.820~1.536)	0.472
	AG	177 (44.3)	215 (53.8)	1.464 (1.108~1.934)	0.007
	GG	77 (19.3)	69 (17.3)	0.874 (0.611~1.252)	0.464
	A	149 (37.3)	198 (49.5)	1.329 (1.131~1.561)	0.010
	G	66 (16.5)	59 (14.8)	0.878 (0.597~1.283)	0.495
APE1	GG	76 (19.0)	83 (20.8)	1.116 (0.789~1.580)	0.535
	GT	83 (20.8)	78 (19.5)	0.925 (0.655~1.307)	0.659
	TT	56 (14.0)	61 (15.3)	1.105 (0.747~1.637)	0.617
	G	69 (17.3)	63 (15.8)	0.897 (0.617~1.303)	0.568
	T	87 (21.8)	79 (19.8)	0.885 (0.629~1.247)	0.485
XPD	GG	69 (17.3)	72 (18.0)	1.053 (0.732~1.515)	0.781
	GT	67 (16.8)	69 (17.3)	1.036 (0.716~1.498)	0.851
	TT	56 (14.0)	66 (16.5)	1.214 (0.825~1.787)	0.325
	G	61 (15.3)	58 (14.5)	0.942 (0.638~1.391)	0.766
	T	76 (19.0)	71 (17.8)	0.920 (0.643~1.316)	0.648
WRN	CC	72 (18.0)	78 (19.5)	1.104 (0.774~1.574)	0.587
	CT	83 (20.8)	77 (19.3)	0.922 (0.651~1.305)	0.645
	TT	79 (19.8)	85 (21.3)	1.096 (0.778~1.546)	0.599
	C	102 (25.5)	112 (28.0)	1.136 (0.831~1.554)	0.474
	T	113 (28.3)	107 (26.8)	0.928 (0.680~1.265)	0.635

P < 0.05 was considered with statistical difference.

Table 5. Logistic regression analysis

Variable	B	Wald	Sig.	Exp (B)
Age	0.113	177.182	0.000	1.120
Nationality	-0.555	13.701	0.000	0.574
Constant	-6.440	111.536	0.000	0.002

0.684; 95% CI: 0.568-0.823). The frequency of allele G was significantly higher than the control (P = 0.008; OR: 1.468; 95% CI: 1.106-1.949), and the risk of allele G was 1.468 times of allele A. XRCC1 genotype analysis revealed that the cases and frequency were AA 111 (27.8%), AG 215 (53.8%), and GG 69 (17.3%) in case group, whereas they were AA 102 (25.5%), AG 177 (44.3%), and GG 77 (19.3%) in control. AG genotype may be associated with ARC (OR: 1.464; 95% CI: 1.108-1.934). AG genotype frequency was higher in case group (P = 0.007). The risk of this genotype was 1.464 times of

GG and AA genotypes. Alleles A frequency was significantly higher than the control (P = 0.010; OR: 1.329; 95% CI: 1.131-1.561). Allele A risk was 1.329 times of allele G.

XPD, APE1, and WRN genotypes showed no statistical difference between case group and control (**Table 4**).

We conducted multivariate stepwise Logistic regression analysis (Backward: LR) for identification of risk factors including age, gender and nationality. Regression equation: Logit (p) = -6.440 + 0.113 × Age-0.555 × Nationality. We found that gender was not included in the regression equation, while factors of age and nationality were significant as the level of a = 0.05. Age played a protective role; Nationality was the risk factor (**Table 5**).

Discussion

Lens gradually became opacity with the growth of age, also increased the risk of cataracts. ARC is the most common type of cataract in our country with unclarified pathogenesis. Current study believed that age, gender, genetic and environmental factors changed the physical and chemical properties of lens [11, 12]. Studies showed that long-term ultraviolet radiation can cause lens epithelial cells DNA damage. However, not all impaired patients appeared cataract, which may be associated with genetic characteristics [13]. In order to maintain normal physiological function, DNA repair system can make the damaged structure and function gradually recover to normal. In recent years, researches showed that some genes involved in DNA damage repair have SNP, while DNA repair ability had close relationship with SNP [14]. As a common genetic variation, SNP occurs at the genome level that leads to DNA sequence polymorphism. Some SNP had protective effect on dis-

ease, while the others may directly lead to disease occurrence [10]. DNA repair has an important role in maintaining genetic integrity, a growing number of DNA repair processes were discovered to be associated with disease.

We analyzed the relationship of DNA repair genes OGG1, XRCC1, APE1, XPD, and WRN polymorphism with ARC risk in Hani from Yunnan. The above mentioned gene polymorphism may change the DNA repair ability and produce synergy on oxidative damage causing cataract. Our results showed that OGG1 and XRCC1 gene polymorphisms increased the risk of cataract, whereas the rest genes had no significant association with ARC. It was reported that XPD gene polymorphism was related to ARC [15], whereas our study failed to find its relevance in Hani. WRN gene belongs to RecQ helicase family that can maintain gene stability after DNA damage repair. This gene received more investigation in tumor [16].

OGG1 gene is an important gene in BER repair pathway that locates on chromosome 3p26.2. It can remove modified bases 8-oxygen guanine with mutation potential after oxide attack. APE1 is an AP endonuclease that can enhance OGG1 flip and for a gap on DNA chain for repair [17]. DNA ligase III/XRCC1 complex may close the gap. APE1 inserted from the locus without purine or pyrimidine, and completed repair process together with DNA polymerase, DNA ligase III, and XRCC1 [18]. XPD has a critical role in NER repair pathway by participating in DNA uncoiling to excise DNA damage fragment [19]. OGG1-CC genotype increased the risk of ARC, GG genotype had certain protective effect, and C/G sequence occurred serine transforming to cysteine. Patients carrying allele G showed higher risk of ARC. OGG1-CC genotype weakened DNA repair ability of BER enzyme [20] and enhanced oxygen-induced DNA damage [21], leading to ARC.

XRCC1 gene located on chromosome 19 q13.2. It participated in BER repair pathway together with DNA ligase III, poly A DP ribose, and DNA polymerase B. Study found that XRCC1 gene encoding region contains three SNPs loci that may appear amino acid transformation: G28152A (Arg399Gln), G27466A (Arg280His), and C263047T (Arg194Trp) [22]. XRCC1 gene had various SNPs. G→A gene mutation occurred on exon 10, leading to 399 codon

arginine transform to glutamate. It was often thought to cause DNA repair dysfunction [23]. Meta-analysis showed that XRCC1 gene polymorphisms had been widely studied in cancer. There was no correlation of Arg399Gln, Arg280His, and Arg194Trp gene polymorphism with head and neck cancer [24]. Chinese Arg399Gln and Arg194Trp gene polymorphisms elevated the risk of esophageal squamous cell carcinoma [25]. Multiple studies focused on the correlation between XRCC1 gene polymorphism and ARC, but the result was not consistent. Luo YF et al. [26] showed that XRCC1 (Arg399Gln) gene polymorphism increased ARC risk in Han, whereas Zhang Y [10] got the opposite result. Indian scholar showed that XRCC1 (Arg399Gln) loci SNP was not correlated with ARC in the Indian population [15]. XRCC1 gene mutation loci 28152 G→ A changed the codon, affected the repair function, and improved the individual susceptibility to cataract. XRCC1-AG phenotype presented correlation with ARC, and individuals carrying allele A had higher ARC risk.

Several studies showed that APE1, XPD, and WRN gene polymorphism were associated with multiple diseases, while our study did not find their correlation with ARC risk. The reason may be as follows: firstly, cataract had various pathogenic factors and complex pathogenesis. Lens was always exposed to damage factors, such as hydrogen peroxide, oxygen, and ultraviolet radiation [21]. Secondly, racial differences may affect gene polymorphism research [26]. Finally, other genes may influence APE1, XPD, and WRN function in the DNA repair process [27]. Also, these genes may of course have no relevance to ARC.

This study aimed to investigate DNA repair genes and ARC risk in Hani. More experimental data need to compare with other nationalities to clarify the relationship between DNA repair gene polymorphism and cataract. At present, our results showed the importance of SNP in DNA repair process. DNA repair gene polymorphism targets can promote DNA repair and maintain gene stability. More in-depth research is needed to use these target genes to prevent or delay ARC occurrence and development.

Disclosure of conflict of interest

None.

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