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ORIGINAL PAPER

Genetic polymorphisms of HSP70 in age-related cataract

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Abstract Polymorphisms have been identified in several HSP70 genes, which may affect HSP70 repair efficiency. We investigated the association of the polymorphisms in HSPA1A, HSPA1B, and HSPA1L genes in the HSPs repair pathway with the risk of cataract in a Chinese population. The study included 415 cataract patients and 386 controls. Genotyping was done by the polymerase chain reaction-restriction fragment length polymorphism method. HSPA1B 1267 A/A genotype seems to have a protective role against cataract (p=0.014, odds ratio (OR)=0.664, 95 % confidence intervals (CI)=0.480–0.919), and the G allele (p=0.057, OR=1.216, 95 % CI=0.999–1.479) does not seem to have a deleterious role in the development of cataract. Haplotypes with frequencies of GAT were significantly different than those of controls (p=0.005). In *HSPA1A G190C* and *HSPA1L T2437C* polymorphisms, there were no significant differences in frequencies of the variant homozygous in patients compared to controls. We conclude that the A/A genotype of *HSPA1B A1267G* polymorphism seem to have a protective role against age-related cataract.

Keywords Oxidative stress · Reactive oxygen species · Polymorphisms · Cataract · Heat shock proteins

Introduction

Cataract is a leading cause of blindness worldwide (Javitt et al. 1996). Oxidative stress is a major factor that often leads to cataract formation (Spector 1995; Rajkumar et al. 2008). Reactive oxygen species (ROS) are principally generated within the mitochondria in the lens epithelium and the superficial fiber cells, which are highly reactive. When ROS production exceeds the capacity of detoxification, they can cause oxidative damage to macromolecules in living cells, such as lipids, DNA, and proteins, causing mutagenesis and cell death (Bruner et al. 2000; Olinski et al. 2007). Oxidative stress has long been recognized as an important mediator of apoptosis in lens epithelial cells (LECs) and also plays a vital role in the pathogenesis of cataract (Ottonello et al. 2000; Truscott 2005).

Heat shock proteins (HSPs) are expressed in response to oxidative stress, extreme heat, ischemia, hypoxia, ultraviolet light, tissue damage, heavy metals, toxins, viruses, chemical poisons, and aging (Wang et al. 2010). They also play a major role during normal growth and differentiation of many cell types. ROS were the major substances responsible for DNA and protein damage leading to apoptosis, whereas HSPs played protective roles to prevent cell death (Milner and Campbell 1990). It has been proposed that the 70 kDa heat shock protein family (HSP70), one of the most conserved and well-known HSPs, plays an important role in controlling cellular responses to stress and apoptosis (Suemasu et al. 2009; Chiu et al. 2009). The HSP70 gene family is the most extensively investigated HSPs in humans. The human HSP70 gene family consists of HSPA1A, HSPA1B, and HSPA1L (Kampinga et al. 2009), and are located in the human leukocyte antigen class III region on the short arm of chromosome 6 (Milner and Campbell 1992). HSP70 proteins function as molecular chaperones and are essential for cell survival under stress conditions.

Evidence is accumulating to suggest the involvement of Hsp70 in the pathogenesis of many clinical diseases, for example, Parkinson's disease (Wu et al. 2004), high-altitude illness (Zhou et al. 2005), aging (Singh et al. 2006a, b), and uveitis (Spagnolo et al. 2007). Hsp70 are located in the lens epithelium and superficial cortical fibers of the human lens (Bagchi et al. 2001). It is suggested that the normal

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microenvironment of the lens is stressful, therefore requiring continuous expression of inducible Hsp70 (Bagchi et al. 2001; Dean et al. 1999). Studies using bovine lenses, mouse LECs, and rat lenses show that Hsp70 expression is upregulated under heat, oxidative, osmotic, and mechanical stresses (Banh et al. 2003; Yao et al. 2006).

The DNA sequence variations in the HSP70 genes have been characterized by a number of single nucleotide polymorphisms (SNPs; Milner and Campbell 1992). Many recent studies have focused on the association of these HSP70 gene polymorphisms with glaucoma (Humaira et al. 2010), uveitis (Tosaka et al. 2007), and longevity (Li et al. 1995). The selected SNPs were chosen based on previously published research (Wu et al. 2004; Singh et al. 2006a, b). Polymorphisms in *HSPA1A G190C*, *HSPA1B A1267G*, and *HSPA1L T2437C* were determined using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP)-based assay with the primers described in previous studies (Milner and Campbell 1992; Ishihara et al. 1995). These SNPs could affect Hsp70 expression or function, and further contribute to disease susceptibility and stress tolerance (Favatier et al. 1997). Hsp70 repair mechanisms are in place to protect against oxidative damage and imply a role for Hsp70 genes in the response of the lens to oxidative stress. Therefore, Hsp70 genes are potential candidate genes for further exploration.

No experimental or clinical data with regard to the effect of hsp70 gene polymorphisms on cataract are available. The purpose of the study presented here was to evaluate the possible association between these Hsp70 genes and risk of age-related cataract in Chinese population. We analyzed *HSPA1A G190C*, *HSPA1B A1267G*, and *HSPA1L T2437C* polymorphisms in 415 patients with age-related cataract and in an otherwise healthy control group of 386 patients of similar age. This is the first study to report the interactive association of Hsp70 gene variants with cataract in a Chinese population. We hope that our results will contribute to a better understanding of the disease's causative agents.

Patients and methods

Patients

Patients with senile cataract were recruited from the Eye Hospital, the First Affiliated Hospital, Harbin Medical University, Harbin, China. This case–control study included total of 415 patients with age-related cataract and 386 disease-free controls. All 415 subjects with cataract had severe visual disturbances and their corrected visual acuities were under 0.3 (less than about 20/60). They had an age-related cataract in at least one eye and had no other eye abnormalities that could explain the vision loss. Cataract status was determined by lens examination using a slit-lamp biomicroscope. Lens opacities were classified into cortical, nuclear, posterior subcapsular, and mixed type using Lens Opacities Classification System II (Chylack et al. 1989). We excluded patients with secondary cataract due to diabetes, trauma, steroid administration, and other causes. The sex- and age-matched control subjects were collected from unrelated volunteers in the same clinic. Both groups belonged to the same ethnic group. The mean ages for the cataract patients and the controls were 67.17±6.92 and 65.77±6.49 years; of them, 53.0 and 52.3 % were men, respectively (Table 1). Informed consent was obtained from each subject before the study. The study was approved by the Bioethics Committee of Harbin Medical University and each patient gave written informed consent.

Blood samples and DNA isolation

We collected 5 ml of venous blood into ethylene diamine tetraacetic acid tubes from all patients and controls. Immediately after collection, whole blood was stored in aliquots at −80 °C until use. Genomic DNA was extracted from leukocytes using a Roche DNA purification kit (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions.

Genotyping of *HSPA1A* codons 190

HSPA1A genotypes were detected using a PCR-RFLP method. The biallelic polymorphism at position 190 in the HSPA1A gene was detected by BsrBI restriction enzyme digestion of the fragment 325 bp DNA, which was previously amplified by using the primers given in Table 2. PCR conditions were 94 °C for 4 min, followed by 35 cycles of 94 °C for 30s, 62 °C for 40s, 72 °C for 40s, and a final extension step at 72 °C for 7 min. The 325 bp PCR products were digested with BsrBI (MBI Fermentas, Burlington, CA, USA) 37 °C for 5 h and analyzed with 2 % agarose gels. BsrBI digestion resulted in three fragments of 171, 84, and 70 bp for wild-type (G/G); four fragments of 241, 171, 84, and 70 bp for heterozygous (G/C); and two fragments of 241 and 84 bp for variant homozygous (C/C).

Genotyping of *HSPA1B* codons 1267

HSPA1B genotypes were detected using a PCR-RFLP method. The biallelic polymorphism at position 1267 in the HSPA1B gene was detected by PstI restriction enzyme digestion of the fragment 1,117 bp DNA, which was previously amplified by using the primers given in Table 2. PCR conditions were 94 °C for 4 min, followed by 35 cycles of

Table 1 Demographic data of the patients and controls

	Cataract group (%)	Control group (%)	*p* value
Number of patients	415	386	
Gender			
Male, *n* (%)	220 (53.0)	202 (52.3)	0.887
Female, *n* (%)	195 (47.0)	184 (47.7)	
Age (years)			
Mean±SD	67.17±6.92	65.77±6.49	0.134
Family history of congenital cataract	0 (0.0)	0 (0.0)	
Smokers	87 (21.0)	65 (16.8)	0.149
Nonsmokers	328 (79.0)	321 (83.2)	

SD standard deviation

94 °C for 30s, 60 °C for 1 min, 72 °C for 1 min, and a final extension step at 72 °C for 7 min. The 1,117 bp PCR products were digested with PstI (MBI Fermentas) 37 °C for 5 h and analyzed with 1.5 % agarose gels. PstI digestion resulted in one fragment of 1,117 bp for wild-type (A/A); three fragments of 1,117, 936, and181 bp for heterozygous (A/G); and two fragments of 936 and 181 bp for variant homozygous (G/G).

Genotyping of *HSPA1L* codons 2437

HSPA1L genotypes were detected using a PCR-RFLP method. The biallelic polymorphism at position 190 in the HSPA1L gene was detected by NcoI restriction enzyme digestion of the fragment 878 bp DNA, which was previously amplified by using the primers given in Table 2. PCR conditions were 94 °C for 4 min, followed by 35 cycles of 94 °C for 30s, 62 °C for 50s, 72 °C for 50s, and a final extension step at 72 °C for 7 min. The 325 bp PCR products were digested with NcoI (MBI Fermentas) 37 °C for 5 h and analyzed with 1.5 % agarose gels. NcoI digestion resulted in two fragments of 551 and 327 bp for wild-type (T/T); three fragments of 878, 551, and 327 bp for heterozygous (T/C); and one fragment of 878 bp for variant homozygous (C/C).

Table 2 Primers for polymerase chain reaction amplification

HSPA1A G190C primers
5-TCC GGC GTC CGG AAG GAC C-3 (forward)
5-TGC GGC CAA TCA GGC GCT T-3 (reverse)
HSPA1B A1267G primers
5-CAT CGA CTT CTA CAC GTC CA-3 (forward)
5-CAA AGT CCT TGA GTC CCA AC-3 (reverse)
HSPA1L T2437C primers
5-GGA CAA GTC TGA GAA GGT ACA C-3 (forward)
5-GTA ACT TAG ATT CAG GTC TGG-3 (reverse)

Statistical analysis

Statistical analyses were performed with SPSS for Windows (version 17.0; SPSS Inc., Chicago, IL, USA). Differences between the means of the two continuous variables were evaluated by the Student's *t* test. Chi-square (χ^2) or Fischer's exact test (two-sided) were used to compare 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. The odds ratio (OR) and their 95 % confidence intervals (CI) were calculated to estimate the strength of the association between polymorphism genotype alleles of patients and controls. Mean±standard deviation are presented for continuous variables and a p value<0.05 was considered statistically significant.

Results

Three genotypes were determined for all cataract cases and controls. For all polymorphisms, the more common allele was considered as the reference genotype, whereas the less common allele was examined as the variant. There were no significant differences in sex, age, smoking habits, ethnicity, and family history of congenital cataract, which suggested that cataract patients' data are comparable with controls in Table 1. The distributions of the *HSPA1A G190C*, *HSPA1B A1267G*, and *HSPA1L T2437C* genotypes were in accordance with the Hardy–Weinberg equilibrium among the patients (p=0.058, p=0.775, p=0.913, respectively) and the controls (p=0.708, p=0.054, p=0.923, respectively). The frequencies of the genotypes and alleles of HSP70-1 G190C, *HSPA1B A1267G*, and *HSPA1L T2437C* polymorphisms in the cataract group and control group are shown in Table 3.

As shown in Table 3, the analysis of the polymorphisms located at HSPA1B codon 1267 in the cataract group showed that 109 (28.2 %) were homozygous for the A/A genotype, 103 (26.7 %) were variant homozygous for the G/G genotype, and 174 (45.1 %) were heterozygous for the A/G genotype. There was a significant difference between the study and control groups in the HSPA1B A/A genotype (p=0.014), even after Bonferroni correction (Bonferroni-corrected p<0.017). The statistical analysis revealed a possibly protective effect of HSPA1B 1267 A/A genotype (OR=0.664, 95 % CI=0.480–0.919) in controls and there was a significant association based on the recessive models (OR=0.664, 95 % CI=0.48–0.919, p=0.014). When compared to healthy controls, the G allele frequency of *HSPA1B A1267G* was not significantly different in the cataract group (p=0.057, OR=1.216, 95 % CI=0.999–1.479). However, no statistically

Table 3 Polymorphisms in *HSPA1A G190C*, *HSPA1B A1267G*, and *HSPA1L T2437C* genes and risk of cataract development

	Controls (%)	Patients (%)	*p* value	OR (95 % CI)
HSPA1A G190C	386	415		
G/G	223 (57.8)	226 (54.5)	0.355	DM=0.639(0.377–1.084), $p>0.05$
G/C	139 (36.0)	150 (38.9)	0.968	
C/C	24 (6.2)	39 (6.6)	0.115	RM=0.874 (0.661–1.156), $p>0.05$
G allele frequency	0.758	0.725		
C allele frequency	0.242	0.275	0.154	1.185 (0.947–1.483)
HSPA1B A1267G				
A/A	109 (28.2)	86 (20.7)	0.014	DM=0.895 (0.656–1.220), $p>0.05$
A/G	174 (45.1)	209 (50.4)	0.138	
G/G	103 (26.7)	120 (28.9)	0.528	RM=0.664 (0.480–0.919), $p=0.014$
A allele frequency	0.508	0.459		
G allele frequency	0.492	0.541	0.057	1.216 (0.999–1.479)
HSPA1L T2437C				
T/T	163 (42.2)	163 (39.3)	0.429	DM=0.892 (0.591–1.346), $p>0.05$
T/C	175 (45.4)	195 (47.0)	0.671	
C/C	48 (12.4)	57 (13.7)	0.602	RM=0.885 (0.667–1.173), $p>0.05$
T allele frequency	0.649	0.628		
C allele frequency	0.351	0.372	0.405	1.096 (0.894–1.345)

OR odds ratio, *CI* confidence intervals, *DM* dominant model, *RM* recessive model

significant differences were observed in the alleles or in the genotype frequencies of *HSPA1A G190C* and *HSPA1L T2437C* gene polymorphisms between the control group and the patients with age-related cataract (Table 3).

Table 4 shows the association between these genes genotypes and the development of cataract according to sex both in the patients and in the controls. Stratification by sex of the subjects revealed that there was no significant association with the development of cataract in female or male subjects.

Table 5 shows the distribution of genotype frequencies of *HSPA1A G190C*, *HSPA1B A1267G*, and *HSPA1L T2437C* polymorphisms in healthy controls and cataract patients after stratifying by cataract subtypes. When compared to healthy controls, the genotype frequency of the A/A of *HSPA1B A1267G* was significantly different in the cortical-type cataract group ($p=0.012$, OR=0.503, 95 % CI=0.297–0.854). However, the results for cortical cataract were no longer significant after Bonferroni correction (Bonferroni-corrected $p<0.0083$).

Investigation of the genotype frequencies both in patients and controls revealed that there was a significant difference between frequencies of HSPA1B 1267 A/A genotype in patients with cortical (16.5 %) cataract and healthy controls (28.2 %). Statistical analysis revealed that HSPA1B 1267 A/A genotype may have a protective effect against the development of cataract.

Table 4 Polymorphisms in *HSPA1A G190C*, *HSPA1B A1267G*, and *HSPA1L T2437C* genes and risk of cataract development

	Sex	Patients	Controls	*p* value
HSPA1A G190C		415	386	
G/G	Females	106	106	0.925
	Males	120	117	
G/C	Females	65	65	0.636
	Males	85	74	
C/C	Females	24	13	0.606
	Males	15	11	
HSPA1B A1267G				
A/A	Females	40	53	0.775
	Males	46	56	
A/G	Females	100	85	0.918
	Males	109	89	
G/G	Females	55	46	0.893
	Males	65	57	
HSPA1L T2437C				
T/T	Females	77	80	0.825
	Males	86	83	
T/C	Females	100	85	0.677
	Males	95	90	
C/C	Females	18	19	0.419
	Males	39	29	

Table 5 Distribution of genotype frequencies of *HSPA1A G190C*, *HSPA1B A1267G*, and *HSPA1L T2437C* polymorphisms in controls and patients with different cataract subtypes

Genotype	Control *n* (%)	Cataract subtypes			
		Cortical *n* (%) *n*=121	Nuclear *n* (%) *n*=109	PSCC *n* (%) *n*=59	Mixed *n* (%) *n*=126
HSPA1A G190C					
G/G	223 (57.8)	61 (50.4)	61 (56.0)	34 (57.6)	70 (55.6)
G/C	139 (36.0)	50 (41.3)	38 (34.9)	17 (28.8)	45 (35.7)
C/C	24 (6.2)	10 (8.3)	10 (9.1)	8 (13.6)	11 (8.7)
HSPA1B A1267G					
A/A	109 (28.2)	20 (16.5)*	26 (23.9)	13 (22.1)	27 (21.4)
A/G	175 (45.3)	59 (48.8)	54 (49.5)	30 (50.8)	66 (52.4)
G/G	102 (26.5)	42 (34.7)	29 (26.6)	16 (27.1)	33 (26.2)
HSPA1L T2437C					
T/T	163 (42.2)	49 (40.5)	42 (38.5)	25 (42.4)	47 (37.3)
T/C	175 (45.4)	59 (48.8)	54 (49.5)	26 (44.1)	56 (44.4)
C/C	48 (12.4)	13 (10.7)	13 (12.0)	8 (13.5)	23 (18.3)

PSCC posterior subcapsular cataract

*p=0.012; OR, 0.503; 95 % CI, 0.297–0.854

Haplotypes with frequencies are shown in Table 6. In age-related cataract patients, the frequencies of GAT were significantly different than those of controls (p=0.005), and the frequencies of GAC, GGT, GGC, CAT, CAC, CGT, and CGC were not significantly different than those of control (p=0.678, p=0.235, p=0.219, p=0.238, p=0.063, p=0.248, and p=0.139, respectively).

No statistically significant difference was found for the genotypic and allelic distributions of the polymorphisms in *HSPA1A G190C* and *HSPA1L T2437C* between controls and patients even after stratifying by the cataract subtypes.

Discussion

In this study, we analyzed the association between *HSPA1A G190C*, *HSPA1B A1267G*, and *HSPA1L T2437C* polymorphisms and the risk of cataract in a Chinese population. Since these polymorphisms may alter HSP70 repair capacity and subsequently lead to synergistic effects with cataract induced by oxidative damage. In our experiments, we did not find that the *HSPA1A G190C*, *HSPA1B A1267G*, and *HSPA1L T2437C* polymorphisms increased the risk of cataract, but we found that there was a possibly protective effect of HSPA1B 1267A/A genotype in controls.

Table 6 Haplotype frequencies of *HSPA1A G190C*, *HSPA1B A1267G*, and *HSPA1L T2437C* in controls and patients

HSPA1A G190C	HSPA1B A1267G	HSPA1L T2437C	Frequency	Patients	Controls	*p* value	OR (95 % CI)
G	A	T	0.350	0.304	0.398	0.005	0.657 (0.490–0.880)
G	A	C	0.069	0.065	0.073	0.678	0.890 (0.514–1.539)
G	G	T	0.184	0.201	0.166	0.235	1.258 (0.877–1.803)
G	G	C	0.139	0.155	0.122	0.219	1.315 (0.877–1.972)
C	A	T	0.022	0.030	0.016	0.238	1.886 (0.701–5.075)
C	A	C	0.046	0.060	0.032	0.063	1.998 (0.989–4.034)
C	G	T	0.082	0.093	0.070	0.248	1.379 (0.827–2.300)
C	G	C	0.107	0.092	0.124	0.139	0.710 (0.452–1.113)

HSPs are well known in helping cells to deal with stress-induced damage to polypeptides (Parsell and Lindquist 1993). Moreover, their expression is enhanced during stress conditions, suggesting that they are associated with cell repair (Hendrick and Hartl 1993). Accordingly, HSPs are putative regulators of the pathophysiology of a number of degenerative disorders such as diabetes, cancer, aging, and heart-related diseases (Atalay et al. 2009; Soo et al. 2008; Brundel et al. 2008). HSP70 is involved in cell cycle regulation, DNA damage reparation, and apoptosis. However, some sequence changes, such as single nucleotide variations appeared during long-term evolution (Milner and Campbell 1992). Genetic study has helped to explain the molecular mechanisms of various diseases. Regulatory SNPs and coding SNPs are able to cause some alteration of qualitative or quantitative protein that is necessary for life activity. As a crucial chaperone molecule, HSP70 sequence variations can alter protein expression or functions, leading to variation in tolerance to stress and susceptibility to certain diseases (Favatier et al. 1997).

To the best of our knowledge, no studies have investigated the role of *HSPA1A G190C*, *HSPA1B A1267G*, and *HSPA1L T2437C* polymorphisms for patients suffering from cataract, but these polymorphisms have been studied in patients suffering from glaucoma in a Pakistani population. In our study, we chose these key HSP70 genes because they play a vital role in the HSPs repair pathway. We found a possibly protective effect of HSPA1B 1267A/A genotype in the development of cataract, but we did not find that the HSPA1B 1267G/G genotype increased the risk of cataract.

ROS can cause oxidative damage to lipids, DNA, and proteins (Babizhayer and Costa 1994; Manuguerra et al. 2006). Oxidative damage to the lens epithelium accumulates throughout a lifetime, leading to apoptosis and the inevitable reduction of lens epithelium density. A previous study noted that young lenses have a relatively uniform covering of LECs, whereas old lenses have a lower density of surface LECs with frequent gaps (Pendergrass et al. 2005). Moreover, numerous studies suggest that apoptosis and death of LECs plays an important role in the pathogenesis of cataracts (Ottonello et al. 2000; Charakidas et al. 2005), and blocking apoptosis may prevent cataract formation (Li et al. 1995).

HSP70 can be expressed in response to a variety of stress stimuli, including reactive oxygen species and DNA damage, and plays an important role in the maintenance of cellular integrity and viability (Kiang and Tsokos 1998; Lixia et al. 2006). HSP70 plays a protective role in the visual system (Yu et al. 2001; Weinreb et al. 2001). The lens expresses HSP70 in normal unstressed conditions, which suggests that the normal microenvironment of the lens is stressful and HSP70 is continuously needed (Bagchi et al. 2002; Dean et al. 1999). Therefore, according to our research, HSPA1B 1267A/A may be one possibly protective mechanism to maintain a normal microenvironment in the lens. We think the possibly protective mechanism is that HSPA1B can maintain a normal microenvironment in the lens, protect LECs from oxidative injury and DNA damage, and also block LECs apoptosis, which may prevent the development of cataract. We also came to the conclusion that *HSPA1B A1267G* polymorphisms did not increase the risk of cataract, although these polymorphisms decreased their repair capacity. The exposure and interaction of other genes participating in repair recognition, and cell cycle regulation may have altered the effect of HSPA1B polymorphisms. Further investigations of the role of HSP70 in the lens could clarify the mechanism by which the lens deals with stress stimuli.

Most studies have suggested that the *HSPA1A G190C*, *HSPA1B A1267G*, and *HSPA1L T2437C* polymorphisms are risk factors for different kinds of diseases, but in our study we did not find these gene polymorphisms increased the risk of cataract. We would like to propose possible reasons why we did not find a significant relationship between the aforementioned three genes with cataract. First, cataract is a multifactorial disease and the pathogenesis is complicated. The lens is exposed throughout life to a large number of possibly injurious agents such as hydrogen peroxide, oxygen, and UV light which result in oxidative damage as shown in studies in lenses of several mammalian species (Wolf et al. 2008; Shui et al. 2006). Second, the interaction of other genes participating in DNA damage reparation, apoptosis, and cell cycle regulation may have altered the effect of HSP70 gene polymorphisms. Third, ethnic differences may be an important factor that may affect genetic studies of this type. Finally, of course, there may not be a relationship.

In conclusion, this is the first study to evaluate the possible association between the HSP70 genes and cataract in a Chinese population. However, there is a need for studies in other ethnicities and nationalities to confirm our findings to examine more completely the possible relationship between HSP70 gene polymorphisms and cataract. There is also a need for further studies to investigate how the precise mechanisms of HSP70 gene polymorphisms affect the development of age-related cataract. Manipulating these targets may provide a strategy to prevent or slow the progression of age-related cataract.

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