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*Original Article*

# The effect of GSTT1, GSTM1 and GSTP1 gene polymorphisms on the susceptibility of age-related cataract in Chinese Han population

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**Abstract:** Objective: Age-related cataract (ARC) is one of the most common eye diseases in the elderly worldwide, especially in China. The genetic polymorphisms of many glutathione S-transferases coding genes are likely to be closely related to the development of ARC, especially the GSTT1, the GSTM1 and the GSTP1. This investigation is aimed to determine the possible associations of GSTT1, GSTM1 and GSTP1 polymorphisms with the susceptibility of ARC in Chinese Han Population. Methods: A case-control study including ARC cases (n = 312) and controls (n = 256) in Chinese Han Population was performed. GSTT1 and GSTM1 polymorphisms were detected by duplex polymerase chain reaction (PCR), and two SNPs (rs1695, A/G and rs1138272, C/T) in GSTP1 gene were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method, all the results were verified by sequencing method. Results: The *GSTT1* null genotype carriers had a much higher risk of ARC compared with non-null genotype ($\chi^2$ = 14.091, P<0.001), and the allele *G* carriers also had a increased risk over the allele *A* carriers in the SNP (*rs1695*, A/G) in *GSTP1* gene ($\chi^2$ = 7.696, P = 0.006), while the GSTM1 polymorphism and the SNP (rs1138272, C/T) in GSTP1 gene seem had no association with the susceptibility of ARC in Chinese Han Population. Conclusions: These preliminary results indicated carriage of null GSTT1 and GSTP1 Val/Val genotypes may contribute to genetic susceptibility to ARC in Chinese Han Population, and these genetic polymorphisms might be used as molecular markers for detecting ARC susceptibility.

**Keywords:** ARC, *GSTT1*, *GSTM1*, *GSTP1*, SNP, Chinese

## Introduction

Age-related cataract (ARC), also known as senile cataract, is a very common visual impairment disease that cloudy deposits gradually accumulate on the crystalline lens of the eye in people aged 50 years and over [1]. As the population aging speed up, the incidence and mortality rate of ARC accelerated sharply, which ranks as the leading cause of visual impairment among the elderly worldwide [2-4]. Cataracts extraction is an very effective treatment, however, this treatment option may not be feasibly available to a large proportion of patients in developing countries due to the inadequate surgical services and high surgery costs [5, 6]. Although ARC has its own characteristic clinical features and distinctive pathogenesis, the detailed underlying etiology of ARC is far from been fully elucidated, many demographic, environmental, life style-associated, disease-related and miscellaneous factors, such as dietary carbohydrate intake, age, smoking, alcohol consumption and ultraviolet radiation, are clearly related to the development of ARC [7-9]. Linkage analyses have verified some evidence of a genetic component to ARC, such as the family history was found to be a risk factor for cataract [10]. Identification of candidate genes involved in the occurrence and development of ARC could contribute to further understanding of the underlying mechanisms, and event a very important additional appropriate prevention strategies and targeted treatments for reducing this polygenic disease.

Oxidative stress appears to be a critical event in the pathogenesis of ARC, oxidative damage

**Table 1.** Primer pairs and reaction conditions used for *GSTM1*, *GSTT1* and *GSTP1* gene polymorphisms detecting

| Genes | Specific primer sequences (5' to 3') | Annealing temperature | Type of polymorphism | Genotype (bp) |
|---|---|---|---|---|
| *GSM1* | 5'-GAACTCCCTGAAAAGCTAAAGC-3' | 60°C | Gene deletion | -: Null |
| | 5'-GTTGGGCTCAAATATACGGTGG-3' | | | +: 215 |
| *GSTT1* | 5'-TTCCTTACTGGTCCTCACATCTC-3' | 60°C | Gene deletion | -: Null |
| | 5'-TCACCGGATCATGGCCAGCA-3' | | | +: 480 |
| *GSTP1* (*rs1695*) | 5'-AATACCATCCTGCGTCACCT-3' | 59°C | *Bsm*AI RFLP | A: 308, 258 |
| | 5'-TGAGGGCACAAGAAGCCCCTT-3' | | | G: 258, 219, 89 |
| *GSTP1* (*rs1138272*) | 5'-ACAGGATTTGGTACTAGCCT-3' | 50°C | AciI RFLP | C: 143, 27 |
| | 5'-AGTGCCTTCACATAGTCATCCTTG-3' | | | T: 170 |

may contribute in the development of cataracts by resulting in many molecular changes, such as degradation, cross-linking, and aggregation of lens proteins [11, 12]. As to keep the crystallins and other proteins in lens fiber cells serving the lens for a lifetime, the lens must develop efficient reducing and detoxification systems, such as catalase system, superoxide dismutase system, glutathione peroxidase system and glutathione S-transferase (GST) system [13, 14]. As a supergene family of phase II detoxifying enzymes catalyze a variety of reduced glutathione-dependent reactions, the GST provides important protection in the metabolism of a wide range of chemicals including environmental carcinogens, reactive oxygen species, and chemotherapeutic agents [15]. The members of the GST family include various isoforms, including GSTA, GSTM, GSTP, GSTK, GSTT, and GSTZ, and GSTM, GSTT and GSTP are the three major GST isoenzymes with highly polymorphic in human [16-18]. Individuals with GSTM1, GSTT1 and GSTP1 genes homozygous deletions have reduced the enzyme detoxification function. Fox example, the two common deletion in the GSTM1 and GSTT1 genes resulting in lack of the corresponding active protein [19-21]; two SNPs in the GSTP1 gene, resulting in amino acid substitutions at codons 105 (Ile→Val) and 114 (Val→Ala), have diminished GST enzyme activity for several classes of substrates [22, 23].

Although Zhou *et al* have studied the association between copy number variations in glutathione S-transferase M1 and T1 and age-related cataract in a Han Chinese population [14], the potential association analysis of the SNP (*rs1695*, A/G) in *GSTP1* gene with age-related cataract in Chinese has not been studied, and the potential associations of *GSTT*1, the *GSTM1* and the *GSTP1* polymorphisms with the risk of ARC in Chinese Han population are still poorly uncovered. Thus, in this study, we focused on investigating the possible associations of *GSTT*1, *GSTM1* and *GSTP1* polymorphisms with the susceptibility of ARC in Chinese Han Population, and result indicated that carriage of null GSTT1 and GSTP1 Val/Val genotypes may contribute to genetic susceptibility to ARC in Chinese Han Population.

## Materials and methods

### *Clinical samples*

All the 312 ARC patient specimens were consecutive obtained from Chinese adults diagnosed and/or treated with ARC in our hospital, during July 1 2010 to June 30, 2013, and all the patients were >50 years old, were ethnic Chinese Han population. Accordingly, 256 age-, sex- and ethnically-matched healthy Chinese people who had no history of any eye diseases were enrolled as controls in this study. All participants' data about risk factors were obtained from questionnaires, including living environment conditions, occupation, ages, life style-associated dietary habit and family history of eye diseases. There was no significant difference regarding age and gender between case and control groups (P>0.05). This study was approved by the local ethics committee, and the informed consent form was obtained by each subject.

### *PCR amplification and genotyping*

Genomic DNA was extracted from peripheral venous blood by the Axygen DNA isolation kit

**Table 2.** Characteristics of the ARC group and the healthy control group in this study

| Characteristics | The ARC group (n = 312) | The healthy control group (n = 256) | *P*-value |
|---|---|---|---|
| Age mean (Range) (years) | 67.12±12.35 (50-87) | S | NS[a] |
| Gender (male/female) | 150/162 | 123/133 | NS[a] |
| Historical eye diseases (Y/N)[b] | 47/265 | 0/256 | P<0.001* |
| Cortical Cataract | 109 | 0 | P<0.001* |
| Nuclear Cataract | 78 | 0 | P<0.001* |
| Other Cataract | 125 | 0 | P<0.001* |

Abbreviations: NS, Not significant; Y/N, Has historical eye diseases/Not has historical eye diseases; *Represents statistically significant.

**Table 3.** Genotype distribution of *GSTM1*, *GSTT1* and *GSTP1* gene polymorphisms in the ARC patients and the healthy controls

| Genotypes | ARC group (n = 312) | Control group (n = 256) | OR (95% CI) | $\chi^2$ and *P*-value |
|---|---|---|---|---|
| *GSTM1* | | | | |
| + | 108 (34.62%) | 91 (35.55%) | 1 | $\chi^2$ = 0.054 |
| - | 204 (65.38%) | 165 (64.45%) | 0.960 (0.679-1.357) | P = 1.000 |
| *GSTT1* | | | | |
| + | 131 (41.99%) | 148 (57.81%) | 1 | $\chi^2$ = 14.091 |
| - | 181 (58.01%) | 108 (42.19%) | 0.528 (0.378-0.738) | P<0.001 |
| *GSTP1 rs1695* A>G | | | | |
| AA[a] | 122 (39.10%) | 115 (44.92%) | | |
| AG | 119 (38.14%) | 109 (42.58%) | 0.972 (0.675-1.398) | $\chi^2$ = 9.988 |
| GG | 71 (22.76%) | 32 (12.50%) | 0.478 (0.293-0.780) | P = 0.007 |
| A[a] | 363 (58.17%) | 339 (66.21%) | 1 | $\chi^2$ = 7.696 |
| G | 261 (41.83%) | 173 (33.79%) | 0.710 (0.557-0.905) | P = 0.006 |
| *GSTP1 rs1138272 C>T* | | | | |
| CC[a] | 280 (89.74%) | 230 (89.84%) | | |
| CT | 31 (9.94%) | 25 (9.77%) | 0.982 (0.564-1.710) | $\chi^2$ = 0.024 |
| TT | 1 (0.32%) | 1 (0.39%) | 1.000 (0.020-50.397) | P = 0.988 |
| C[a] | 591 (94.71%) | 485 (94.73%) | | $\chi^2$<0.001 |
| T | 33 (5.29%) | 27 (5.27%) | 0.997 (0.591-1.681) | P = 0.991 |

[a] homozygous genotypes were used asreference group OR, odds ratio and CI, confidence interval.

(Axygen, CA) according to the recommended protocol, and then stored at -80°C for analyzing. GSTM1 and GSTT1 genotype polymorphisms were detected by duplex polymerase chain reaction (PCR) referenced to previously described methods [24], and the two SNPs (*rs1695*, A/G and *rs1138272*, C/T) in *GSTP1* gene, resulting in amino acid substitutions at codons 105 (Ile→Val) and 114 (Val→Ala), were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. All polymerase chain reaction (PCR) primers were synthesized by TaKaRa Biotechnology Co., Ltd (Dalian, China) as references [25] listed in **Table 1**, and the corresponding theoretical annealing temperature and PCR amplified fragment lengths were also listed in **Table 1**. All PCRs were carried out in 50 μL of reaction mixture containing 100 ng template DNA, 1× buffer (Tris-HCl 100 mmol/L, pH 8.3; KCl 500 mmol/L), 0.25 μmol/L primers, 2.0 mmol/L $MgCl_2$, 0.25 mmol/L dNTPs and 1.0 U rTaq DNA polymerase (Promega, Madison, WI, USA). The PCRs were performed on 94°C for 5 min, followed by 35 cycles of 94°C for 30 s, annealing at the corresponding temperature (shown in **Table 1**) for 30 s and 72°C for 30 s, and a final extension at 72°C for 7 min. All amplified PCR products were preliminary checked by electrophoresis on 2.0% agarose

gel and then analyzed under UV light. The two SNPs of *GSTP1* gene were genotyped by the created restriction site-polymerase chain (CRS-PCR) method. Aliquots of 10 μL amplified PCR products were digested with 4 U corresponding selected restriction enzymes (MBI Fermentas, St. Leon-Rot, Germany, **Table 1**) at the corresponding temperatures for 10h following the recommended supplier's manual. Digested products were separated by 2.5% agarose gel electrophoresis and analyzed under UV light. As a quality control, about 10% of randomly selected samples were re-analyzed by DNA sequencing method (ABI3730xl DNA Analyzer, Applied Biosystems, Foster City, CA, USA) to make sure concordance with the genotyping results from PCR-RFLP.

*Statistical analysis*

All statistical analyses were performed by using the Statistical Package for Social Sciences software (SPSS, Windows version release 17.0; SPSS Inc.; Chicago, IL, USA). The chi-squared ($\chi^2$) test was utilized to evaluate the Hardy-Weinberg equilibrium in genotypic distributions and clinical characteristics. A level of $P<0.05$ was considered statistically significant.

## Results

*Population characteristics*

The demographic and clinical characteristics of the study population are summarized in **Table 2**. There are no significant statistical different of age and gender between the ARC group and the healthy control group. The age range is 50 to 87 years for the ARC group, and 51 to 84 years for the healthy control group. The percentage of those who have historical eye diseases is 15.06% in the ARC group, and 0% in the healthy control group. As for the ARC group patients, the percentages of the different subtypes are 34.94% (cortical cataract), 25.00% (nuclear cataract) and 40.06% (other cataract).

*Genotyping*

Genotype frequencies of *GSTM1*, *GSTT1*, and *GSTP1* polymorphisms between the ARC group and the healthy control group were detected by duplex polymerase chain reaction or polymerase chain reaction-restriction fragment length polymorphism, and compared by the chi-squared ($\chi^2$) test method, and the results were listed in **Table 3**. For the *GSTM1* gene, the genotype frequencies of null and no-null were 65.38% and 34.62% in the ARC group, and the corresponding values were 64.45% and 35.55% in the control group, no significant differences in genotype distribution of *GSTM1* were observed between the ARC patients and the healthy controls ($\chi^2 = 0.054$, $P = 1.000$). For the *GSTT1* gene, the genotype frequencies of null and no-null were 58.01% and 41.99% in the ARC group, and the corresponding values were 42.19% and 57.81% in the control group, statically significant differences in genotype distribution of *GSTT1* were observed between the ARC patients and the healthy controls ($\chi^2 = 14.091$, $P<0.001$).

For the *rs1695* A>G of *GSTP1*, the genotypic frequencies of AA, AG and GG were 39.10%, 38.14% and 22.76% in the ARC group, and 44.92%, 42.58% and 12.50% in the control group, significant differences in genotype distribution of *GSTP1* were observed between the ARC patients and the healthy controls ($\chi^2 = 9.988$, $P = 0.007$). The corresponding allelic frequencies in the ARC group and control group were 58.17% and 66.21% for A allele, and 41.83% and 33.79% for G allele, respectively, implying the G-allele was associated with a much higher ARC risk than the A-allele ($\chi2 = 7.696$, $P = 0.006$). For the *rs1138272* C>T of *GSTP1*, the genotypic frequencies of CC, CT and TT were 89.74%, 9.94% and 0.32% in the ARC group, and 89.84%, 9.77% and 0.39% in the control group, no significant differences in genotype distribution of *GSTP1* were observed between the ARC patients and the healthy controls ($\chi^2 = 0.024$, $P = 0.988$). The corresponding allelic frequencies in ARC group and control group were 94.71% and 94.73% for C allele, and 5.29% and 5.27% for T allele, respectively, indicating the SNP (*rs1138272* C>T) of *GSTP1* may not associated with the risk of ARC in Chinese Han population ($\chi^2<0.001$, $P = 0.991$).

## Discussion

As a common but serious opacities and visual impairment disease, the age-related cataract (ARC) often happens in the aged people and develops slowly as a consequence of aging. In the previous studies, many factors has been shown to association with the susceptibility of ARC, such as body mass index (BMI) [26], environment [27], vitamin [28], apolipoprotein [29] and so on. Genetics has been demonstrated to be a kind of important factors associated with the development of ARC, including cortical cat-

aract, nuclear cataract, posterior subcapsular and other cataracts in numerous clinical studies [10, 13, 30, 31]. In this case-control study, we analyzed the distribution of genetic polymorphisms of glutathione S-transferases coding genes *GSTT*1, *GSTM1* and *GSTP1* in ARC patients and healthy controls in Chinese Han Population, in order to investigate the possible associations of *GSTT*1, *GSTM1* and *GSTP1* polymorphisms with the susceptibility of ARC in Chinese Han Population.

Our data indicated that the distribution of genotype frequencies of *GSTT1* and the *rs1695* A>G of *GSTP1* in ARC patients were statistical different from healthy controls. For *GSTT1*, the frequency of null genotype was 42.19% in the healthy control people, while the percentage was about 1.37 fold in the ARC patients, suggesting the *GSTT1* null genotype was significantly associated with the risk of ARC ($\chi^2$ = 14.091, P<0.001) as reported by previous study [14]. For the *rs1695* A>G of *GSTP1*, the frequency of G allele was 33.79% in the healthy control people, while the percentage was about 1.24 fold in the ARC patients, suggesting the *rs1695* A>G of *GSTP1* was associated with the risk of ARC ($\chi^2$ = 9.988, P = 0.007), and the G allele carriers may be have a higher risk of ARC than the A allele carriers ($\chi^2$ = 7.696, P = 0.006). While unlike many previous studies, there were no statistical differences about the genotype frequencies of the previously hypothesized risk factors *GSTM1* and the SNP (*rs1138272* C>T) of *GSTP1* between the ARC patient group and the healthy group, suggesting they may not associated with the risk of ARC in Chinese Han Population.

Although many studies showed that oxidative damage may contribute in the development of cataracts, many reducing and detoxification systems, such as catalase system, superoxide dismutase system, glutathione peroxidase system and glutathione S-transferas (GST) system may play a role in inhibiting the pathogenesis of ARC as it protect cells from oxidative damage, and the genotype polymorphisms of *GSTT1* and the *rs1695* A>G of *GSTP1* were indicated to associate with the risk of ARC, while the genotype polymorphisms of *GSTM1* and the *rs11-38272* C>T of *GSTP1* may not associate with the risk of ARC, implying there maybe other underlying mechanisms which have not been revealed. Results from this study may provide a framework for further analyze the role of GST genes polymorphisms, even genotype variants of many reducing and detoxification genes for the susceptibility to ARC. However, larger prospective studies about evaluating the association between the genotype polymorphisms of *GSTT1* and *GSTP1* on ARC risk are also needed to confirm these findings in larger different populations and to elucidate the underlying molecular mechanisms.

## Disclosure of conflict of interest

None.

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