

Original Article

Glutathione S-transferase M1 polymorphism and age-related cataract risk in the Chinese population: a meta-analysis

Qian Zhang, Cong-Yi Wang, Zhuo-Lin Zhou, Feng-Zhi Li, Bo Ma

Department of Ophthalmology, Shaanxi Ophthalmic Medical Center, Xi'an No. 4 Hospital Affiliated to Guangren Hospital, Xi'an Jiaotong University, School of Medicine, Xi'an 710004, China

Received October 24, 2015; Accepted January 21, 2016; Epub February 15, 2016; Published February 29, 2016

Abstract: Backgrounds and Aims: Although a number of studies have been conducted on the association between GSTM1 polymorphism and age-related cataract (ARC), this association remains elusive and controversial. To assess the impact of GSTM1 polymorphism on the risk of ARC in the Chinese population, a meta-analysis was performed. Methods: Relevant studies were identified from PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) published through July 19, 2015. The strength of the association between the GSTM1 null allele and risk of ARC was estimated by calculating odds ratios (ORs) and 95% confidence intervals (CIs). Results: A total of 6 studies including 1062 ARC cases and 823 controls were involved in this meta-analysis. A non-significant association between GSTM1 null genotype and ARC was found among in overall and subgroup analyses stratified by geographical location. In subgroups stratified by ethnicity, significantly increased risk of ARC with the GSTM1 null genotype was found among Chinese not mentioned the ethnicity (OR = 2.05 95% CI: 1.45-2.90), but not among Chinese Han (OR = 0.80, 95% CI: 0.52-1.25). Conclusions: This meta-analysis showed that the GSTM1 null genotype may influence ARC risk in other ethnic Chinese, not Han people. Studies with larger sample sizes and wider spectrum of populations are warranted to verify this finding.

Keywords: GSTM1, polymorphism, age-related cataract, meta-analysis, Chinese

Introduction

Age-related cataract (ARC) is one of the leading causes of visual impairment and blindness among the elderly worldwide [1]. The global burden of blindness due to ARC is increasing as a result of a growing elderly population [2]. It was estimated that 8.2 million blind people lived in China in 2010, accounting for 20.9% of the total blind population in the world [3]. Data from the National Bureau of Statistics of China indicate that the proportion of persons aged 60 years and older will rise from 13.3% in 2010 to 34% in 2050 [4]. So the eye disease has become a major public health challenge in China, especially with regard to ARC.

ARC is a complex disease with a broad spectrum of risk factors including age, sex, smoking, exposure to sunlight, estrogen sufficiency or

deficiency, cardiovascular factors, and genetic background [5]. Various studies have indicated a significant genetic component to ARC risk [6, 7]. In recent years, several common low-penetrant genes have been identified as potential ARC susceptibility genes [8-11]. An important one is glutathione S-transferase (GST), which is one of the detoxification enzyme systems and plays important role in inactivating endogenous and exogenous toxic products under oxidative stress. The GST isoenzymes have been reported to express classes, mu, theta, and pi, in human lens tissue [12]. Located on the chromosome 1p13.3, the GSTM1 plays an important role in the xenobiotics' detoxification. The most common genotype of GSTM1 gene is homozygous deletion (null genotype), which has been suggested to be associated with the loss of enzyme activity, increased vulnerability to

GST and age-related cataract

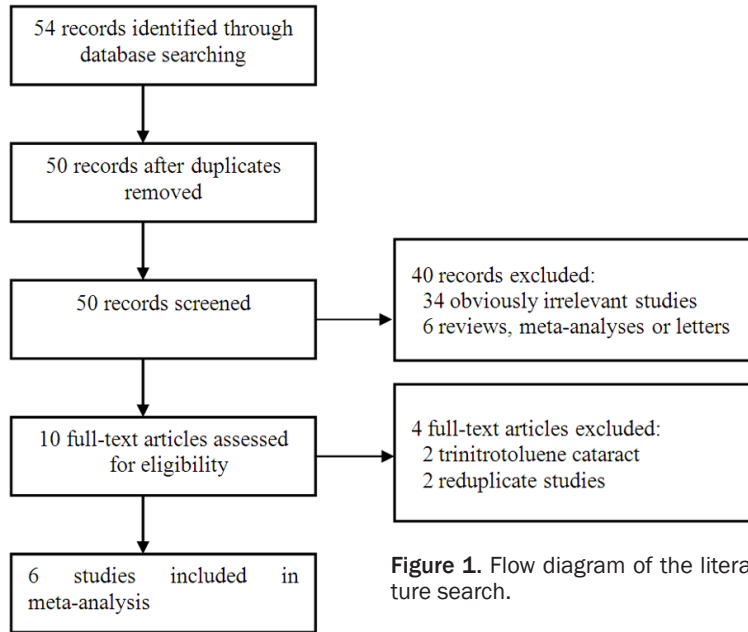


Figure 1. Flow diagram of the literature search.

cytogenetic damage and resulted in the increased susceptibility to many diseases, including ARC [13, 14]. An association between the GSTM1 polymorphism and ARC was first reported by Sekine et al. in Japanese [15]. Consequently, many studies sought to analyze the influence of the GSTM1 polymorphism on the risk for ARC, but no clear consensus has yet been reached. In order to lessen the influence of differing genetic backgrounds, we performed this meta-analysis to assess the relationship between the GSTM1 polymorphism and the risk for ARC in the Chinese population. We also performed subgroup analyses, stratified by geographic location and ethnicity, to explore the possible effects of gene-environment interactions with respect to the risk for ARC.

Materials and methods

Search strategy and selection criteria

We systematically searched PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) for studies published before July 15, 2015. The search was performed without any restrictions on language and focused on studies conducted in humans. Besides, we also reviewed the reference lists of the relevant articles and performed searching based on

Google scholar and Baidu scholar to identify additional studies. The following search keywords were used: (cataract or age-related cataract or senile cataract or ARC) and (glutathione S-transferase or GST or GSTM1) and (Chinese or China or Taiwan). The criteria used to select studies for this meta-analysis were as follows: (1) independent cohort or case-control studies for human, (2) the outcome had to be ARC, (3) there had to be at least two comparison groups (ARC group vs control group), (4) provides the distribution of GSTM1 polymorphism in patients and controls, (5) all participants were Chinese. The reasons for

exclusion of studies were: (1) duplicate publications, (2) incomplete data, (3) no control, (4) meta-analyses, letters, reviews, or editorial articles.

Data extraction

The title and abstract of all potentially relevant articles were screened to determine their relevance. Full articles were also scrutinized if the title and abstract were ambiguous. Information from all eligible publications was independently extracted by two authors. Discrepancies between the two authors were resolved by discussion, and if a consensus was not achieved, a decision was made by all the reviewers. The following data were extracted: the first author, publication year, source of controls, geographic area, ethnicity of study population, sample size, and GSTM1 polymorphism in cases and controls. If data from any category were not reported in the primary study, we did not contact the author to request the information. The categorization of ethnicity comprised Han and other ethnic Chinese.

Statistical analysis

The strength of the association between the GSTM1 null allele and risk of ARC was measured by odds ratios (ORs) with 95% confidence intervals (95% CIs). The significance of the pooled OR was determined by the Z test. Given

GST and age-related cataract

Table 1. Characteristics of studies included in the meta-analysis

References	Source of controls	Geographic location	Ethnicity	Cases number	Controls number	Cases		Controls	
						Null genotype	Non-null	Null genotype	Non-null
Pi 1996 [20]	PB	Liaoning	not stated	59	112	41	18	57	55
Hao 1999 [21]	PB	Beijing	Han	77	76	41	36	35	41
Xu 2007 [22]	PB	Jiangxi	not stated	120	118	81	39	60	58
Zhou 2010 [23]	PB	Jiangsu	Han	279	145	171	108	95	50
Jiang 2012 [24]	PB	Anhui	Han	422	312	176	246	173	139
Yan 2014 [25]	PB	Liaoning	not stated	105	60	68	37	29	31

PB: population-based.

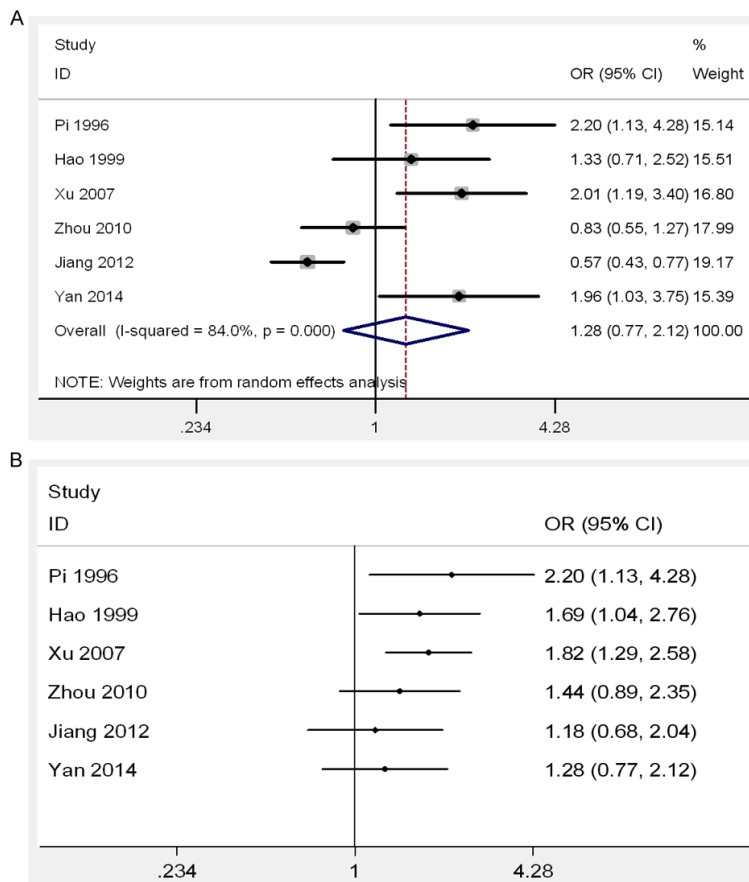


Figure 2. The forest plots of all selected studies on the association between GSTM1 polymorphism and ARC risk in Chinese (A: Meta-analysis; B: Cumulative meta-analysis). Note: Weights are from random-effects analysis. Abbreviations: CI, confidence interval; OR, odds ratio.

that there was distribution of null/present heterozygote in only one study selected, the Hardy-Weinberg equilibrium (HWE) test could not be conducted. Cochran's Q-statistic was used to assess heterogeneity, indicated by a $P < 0.10$. The random-effects model was chosen to pool the ORs when significant heterogeneity was

observed; otherwise the fixed-effects model was used. Subgroup analyses were performed to test whether the effect size varied by the geographic area and ethnicity. A sensitivity analysis was performed to illustrate the accuracy and stability of the analytic results. Sensitivity analyses were conducted by deleting a single study each time involved in the meta-analysis. All statistical analyses were conducted using Stata version 10.0 (Stata Corp, College Station, Texas, United States). A two-sided $P < 0.05$ was considered statistically significant.

Results

Description of included studies

A total of 54 articles that examined the association between GSTM1 polymorphism and risk of ARC were identified. After screening the titles and abstracts of these articles, 44 were excluded. Of the remaining 10 potentially relevant articles [16-25], two articles [16, 17] were excluded due to trinitrotoluene cataract, and three [18, 19] articles were excluded because they concerned subjects included in an expanded series [23]. The flow chart of study selection is shown in **Figure 1**. Finally, 6 case-control studies [20-25] published between

GST and age-related cataract

Table 2. Main results in the total and subgroup analyses

Subgroups	n	Random-effect model	Fixed-effect model	Heterogeneity	
		OR (95% CI)	OR (95% CI)	χ^2	P
Total analysis	6	1.28 (0.77-2.12)	0.98 (0.81-1.18)	31.26	0.000
Geographic location					
North China	4	1.30 (0.62-2.73)	0.89 (0.71-1.12)	22.82	0.000
South China	2	1.27 (0.54-3.02)	1.17 (0.85-1.62)	6.58	0.010
Ethnicity					
Han	3	0.80 (0.52-1.25)	0.71 (0.57-0.89)	6.31	0.043
Not stated	3	2.04 (1.44-2.90)	2.05 (1.45-2.90)	0.06	0.968

OR: Odds ratio; CI: Confidence interval; North China includes Beijing, Liaoning Anhui; South China includes Jiangsu, Jiangxi.

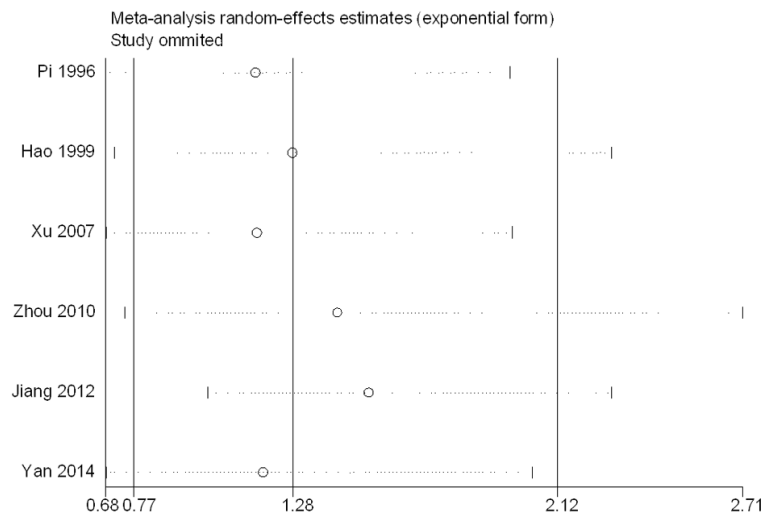


Figure 3. Sensitivity analysis on the association between GSTM1 polymorphism and ARC risk in Chinese.

1996 and 2014 comprising 1062 ARC cases and 823 controls met the inclusion criteria. Four studies [20, 21, 24, 25] were performed in North China, and two studies [22, 23] were conducted in South China. Three studies [21, 23, 24] reported the same race (Chinese Han) and three studies [20, 22, 25] did not mention the ethnicity. The characteristics of the included studies are summarized in **Table 1**.

Quantitative data synthesis

Overall analysis: There was evidence of between-study heterogeneity among all included studies ($\chi^2 = 31.26$; $P = 0.000$). Therefore, the random-effects model was used in the overall analysis. The results showed that the pooled OR for ARC was 1.28 (95% CI: 0.77-

2.12) in Chinese patients with GSTM1 null genotype (**Figure 2A**). In addition, a cumulative meta-analysis showed a trend for a non-association between the GSTM1 null genotype and risk of ARC in Chinese as data accumulated by publication year (**Figure 2B**).

Subgroup and sensitivity analyses: In the subgroup analyses based on ethnicity, the results showed that the association between the GSTM1 null genotype and risk for ARC is statistically significant among Chinese not mentioned the ethnicity (OR = 2.05 95% CI: 1.45-2.90), but not among Chinese Han (OR = 0.80, 95% CI: 0.52-1.25) (**Table 2**).

Subgroup analyses by geographic location did not reveal any significant association between GSTM1 polymorphism and risk for ARC (**Table 2**). A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data-set to the pooled OR. For the overall analysis, the corresponding pooled ORs were

not materially altered (**Figure 3**). Hence, the conclusion of this meta-analysis is relatively stable and credible for the overall analysis.

Discussion

This meta-analysis aimed to systematically summarize the epidemiological evidence for the association between GSTM1 null genotype and risk of ARC in Chinese. Six case-control studies with 1062 ARC cases and 823 controls were finally included in the meta-analysis. The results showed a non-significant association between GSTM1 polymorphism and ARC in overall and subgroup analyses stratified by geographical location. The finding from cumulative meta-analysis also showed that there was not a trend of more obvious association between

GSTM1 null genotype and risk of ARC in Chinese as data accumulated by publication year. Therefore, GSTM1 null genotype is not significantly associated with increased risk of ARC in China. The findings from this meta-analysis provide new and strong epidemiological evidence for the association between GSTM1 null genotype and risk of ARC. Till date, two meta-analyses were published to assess the association between the polymorphism of GSTM1 and ARC risk, but the existing evidence was still weak due to limited sample size in Chinese, ethnic difference or disagreements among the published studies [26, 27]. To our knowledge, our study represented the first meta-analysis with a large sample size on the interaction of GSTM1 variant with ARC in the Chinese population. Therefore, the present meta-analysis of all available case-control studies was conducted to shed some light on those inconsistent results.

The exact mechanism for the ethnic discrepancy is uncertain but differences in underlying genetic backgrounds and social factors among different populations studied may be important. Ethnically diverse subjects may have unique cultures and lifestyles that can contribute to different genetic characteristics and susceptibility to specific cataract. In this meta-analysis stratified by ethnicity, significantly increased risk of ARC with the GSTM1 null genotype was found in Chinese not mentioned the ethnicity. Therefore, the relationship between GSTM1 polymorphism and ARC might be susceptible in different ethnicity. We didn't perform subgroup analysis on other ethnicity history, because of the lack of sufficient data.

This study has some limitations. First was the small sample size, especially with regard to subgroup analyses, which increased the limitation of statistical power. Hence, studies with larger sample sizes and with sufficient large subgroups would be warranted to verify our findings. Secondly, due to the limitations of funnel plotting, which requires a range of studies, we did not evaluate publication bias in this meta-analysis. Third, the present meta-analysis was based primarily on unadjusted effect estimates and confidence intervals and the confounding factors were not controlled. In spite of these limitations, our meta-analysis also had some advantages. First, we have fol-

lowed the inclusion and exclusion criteria strictly to reduce possible selection bias. Second, our inclusion of non-English language reports, were important in minimizing a major potential threat to the validity of any meta-analysis-publication bias and the related threat of a language bias. Third, the sensitivity analysis had been performed to confirm the reliability and stability of this meta-analysis. Most of the important, impact of different genetic background was minimized by including the studies performed in the Chinese population only, which suggested that there was almost no significantly different genetic background among the subjects. Therefore, the 6 studies would appear to be comparable in all respects relevant to our meta-analysis.

In conclusion, this meta-analysis indicated no significant association of GSTM1 polymorphism with ARC among the Chinese Han population. However, GSTM1 null genotype might contribute to individual susceptibility to ARC in other ethnic Chinese. To further evaluate gene-gene and gene-environment interactions on GSTM1 polymorphism and ARC, larger studies in specific population with different environmental background or other risk factors are required. Such studies may eventually lead to have a better, comprehensive understanding of the association between the GSTM1 polymorphism and ARC risk.

Disclosure of conflict of interest

None.

Address correspondence to: Bo Ma, Department of Ophthalmology, Shaanxi Ophthalmic Medical Center, Xi'an No. 4 Hospital Affiliated to Guangren Hospital, Xi'an Jiaotong University, School of Medicine, No. 21, Jiefang Road, Xi'an 710004, China. Tel: +86 029 87480906; E-mail: shanx-mb72@126.com

References

- [1] Foster A, Resnikoff S. The impact of Vision 2020 on global blindness. *Eye* 2005; 19: 1133-1135.
- [2] Asbell PA, Dualan I, Mindel J, Brocks D, Ahmad M, Epstein S. Age-related cataract. *Lancet* 2005; 365: 599-609.
- [3] Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. *Br J Ophthalmol* 2012; 96: 614-8.

GST and age-related cataract

- [4] Wang L, Huang W, He M, Zheng Y, Huang S, Liu B, Jin L, Congdon NG, He M. Causes and five-year incidence of blindness and visual impairment in urban Southern China: the Liwan Eye Study. *Invest Ophthalmol Vis Sci* 2013; 54: 4117-21.
- [5] Livingston PM, Carson CA, Taylor HR. The epidemiology of cataract: a review of the literature. *Ophthalmic Epidemiol* 1995; 2: 151-164.
- [6] Reddy MA, Francis PJ, Berry V, Bhattacharya SS, Moore AT. Molecular genetic basis of inherited cataract and associated phenotypes. *Surv Ophthalmol* 2004; 49: 300-315.
- [7] Hejtmancik JF, Kantorow M. Molecular genetics of age-related cataract. *Exp Eye Res* 2004; 79: 3-9.
- [8] Chen Y, Wu Q, Miao A, Jiang Y, Wu X, Wang Z, Wu F, Lu Y. Effect of HSF4b on age related cataract may through its novel downstream target Hif1 α . *Biochem Biophys Res Commun* 2014; 453: 674-8.
- [9] Zhou Z, Wang B, Hu S, Zhang C, Ma X, Qi Y. Genetic variations in GJA3, GJA8, LIM2, and age-related cataract in the Chinese population: a mutation screening study. *Mol Vis* 2011; 17: 621-6.
- [10] Yang J, Luo J, Zhou P, Fan Q, Luo Y, Lu Y. Association of the ephreceptor tyrosinekinase-type A2 (EPHA2) gene polymorphism rs3754334 with age-related cataract risk: a meta-analysis. *PLoS One* 2013; 8: e71003.
- [11] Çelîk SK, Aras N, Yildirim Ö, Turan F, Görür A, Yildirim H, Tamer L. Glutathione S-transferase GSTM 1, null genotype may be associated with susceptibility to age-related cataract. *Adv Clin Exp Med* 2015; 24: 113-9.
- [12] Hayes JD, Flanagan JU, Jowsey IR. Glutathione transferases. *Annu Rev Pharmacol Toxicol* 2005; 45: 51-88.
- [13] Hayes JD, Strange RC. Glutathione S-transferase polymorphisms and their biological consequences. *Pharmacology* 2000; 61: 154-166.
- [14] Sireesha R, Laxmi SG, Mamata M, Reddy PY, Goud PU, Rao PV, Reddy GB, Vishnupriya S, Padma T. Total activity of glutathione-S-transferase (GST) and polymorphisms of GSTM1 and GSTT1 genes conferring risk for the development of age related cataracts. *Exp Eye Res* 2012; 98: 67-74.
- [15] Sekine Y, Hommura S, Harada S. Frequency of glutathione-S-transferase 1 gene deletion and its possible correlation with cataract formation. *Exp Eye Res* 1995; 60: 159-163.
- [16] Xu J, Li C, Long Y, Zhan C, Wang W. Study on GSTs activity in trinitrotoluene cataract. *Hua Xi Yi Ke Da Xue Xue Bao* 2002; 33: 98-100.
- [17] Xu J, LC, Long Y, Zhan C, Wang W, Qiao J, et al. A study on relationship between glutathione S-transferase μ gene deletion and trinitrotoluene cataract susceptibility. *Chinese J Ind Med* 2001; 14: 129-132.
- [18] Zhou J, Guan H. Detection of copy number variations of GSTM1 and GSTT1 gene in age-related cataract by real-time quantitative PCR. *Rec Adv Ophthalmol* 2014; 34: 838-841.
- [19] Zhou J. The association of GSTT1 and GSTM1 copy number variations with age-related cataract in Han Chinese. Master Thesis of Nantong University China 2009.
- [20] Pi J, Bai Y, Zheng Q. A study on relationship between glutathione S-transferase mu gene deletion and senile cataract susceptibility. *Zhonghua Yan Ke Za Zhi* 1996; 32: 224-226.
- [21] Hao Y, He S, Gu Z, Zhao Y, Li X, Wang C, Li Q, Liu T. Relationship between GSTM1 genotype and susceptibility to senile cataract. *Zhonghua Yan Ke Za Zhi* 1999; 35: 104-106.
- [22] Xu MF, Fu SH, Zhang LH. Relationship between GSTM1 gene deletion and susceptibility to senile cataract. *Acta Academiae Medicinae Jiangxi* 2007; 47: 33-38.
- [23] Zhou J, Hu J, Guan H. The association between copy number variations in glutathione S-transferase M1 and T1 and age-related cataract in a Han Chinese population. *Invest Ophthalmol Vis Sci* 2010; 51: 3924-8.
- [24] Jiang Z, Liang K, Zhang Q, Tao L. Glutathione S-transferases polymorphisms confer susceptibility to senile cortical cataract in the Han Chinese population. *Mol Vis* 2012; 18: 1247-52.
- [25] Yan J, Tian J. The study of the relationship between GSTM1 gene deletion and the onset of senile cataract. *China & Foreign Medical Treatment* 2014; 27: 53-54.
- [26] Liao RF, Ye MJ, Liu CY, Ye DQ. An Updated Meta-Analysis: Risk Conferred by Glutathione S-Transferases (GSTM1 and GSTT1) Polymorphisms to Age-Related Cataract. *J Ophthalmol* 2015; 2015: 103950.
- [27] Sun L, Xi B, Yu L, Gao XC, Shi DJ, Yan YK, Xu DJ, Han Q, Wang C. Association of glutathione S-transferases polymorphisms (GSTM1 and GSTT1) with senile cataract: a meta-analysis. *Invest Ophthalmol Vis Sci* 2010; 51: 6381-6.