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ORIGINAL ARTICLE

Evaluation of Associations of *GSTM1/GSTT1* Null Genotypes with the Susceptibility to Age-Related Macular Degeneration, a Meta-Analysis

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Abstract

Background: The relationship between glutathione S-transferase M1 (*GSTM1*) and T1 (*GSTT1*) null genotypes (homozygotes for the null alleles) and the susceptibility to age-related macular degeneration (ARMD) have been reported and revealed inconsistent results. Therefore, the current meta-analysis was carried out.
Methods: Eligible published articles (before December 2020) were found by searching 8 databases. The data was extracted from articles. The heterogeneity across studies was estimated using Q and I^2 statistics and the odds ratios (ORs) and its 95 % confidence intervals (95 % CI) were estimated.
Results: In total, 6 independent studies including 1089 participants (634 controls and 455 patients) were used in the current study. There was no heterogeneity between studies for both polymorphisms. Statistical analysis showed that the null genotypes of the *GSTM1* (OR = 1.18, 95 % CI: 0.91 - 1.53, p = 0.191) and *GSTT1* (OR = 0.84, 95 % CI: 0.60 - 1.18, p = 0.328) loci were not correlated with the susceptibility to ARMD.
Conclusion: The *GSTT1* and *GSTM1* genetic polymorphisms did not associated with the risk of ARMD in Caucasian populations.

Keywords: *GSTM1*; *GSTT1*; Age-related macular degeneration; Meta-analysis.

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Introduction

Age-related macular degeneration (ARMD) is an extensively studied disease as a leading cause of visual disability in the aging population. It has been reported that both genetic and environmental elements have roles in the development of the disease.[1, 2] The heritability of ARMD seems to be about 15-65 %.[1] Retina has the highest oxygen-consuming among human tissues.[3] Based on the epidemiologic, genetic, and molecular pathologic studies it has been hypothesised that oxidative stress may play a key role in the aetiology of ARMD.[2, 4]

The members of glutathione S-transferases (GSTs, EC 2.5.1.18) superfamily belongs functionally to cellular detoxification system and they are classified to some classes, including theta (GSTT) and mu (GSTM) classes. The *GSTT1* (MIM: 600436) and *GSTM1* (MIM: 138350) genes are polymorphic. The null alleles of these loci have been reported in human populations. Several meta-analyses revealed that these polymorphisms were associated with numerous human complex diseases, such as cancer.[5-9] It should be noted that the risks of cataract and glaucoma are associated with *GSTM1/GSTT1* polymorphisms.[10-12]

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The relationship between the *GSTM1/GSTT1* null genotypes (homozygotes for the null alleles) and the risk of ARMD have been reported and revealed inconsistent results.[13-17] To evaluate the relationship between these genetic variations and the susceptibility to ARMD, the current meta-analysis was carried out.

Methods

Relevant published articles (before December 2020) were found by searching several databases, including PubMed, Scopus, Index Copernicus, DOAJ, Academic Journals Databases, SID, KoreaMed, and Google scholar. The following search terms were used: *GSTT1, GSTM1,* null genotype, age-related macular degeneration. Only articles published in English were included in the study. In addition, the bibliographies of the retrieved studies were screened to identify relevant articles.

The eligible studies had raw data on genotype distributions in both patient and control groups. The exclusion criteria were related to reviews, editorials, abstracts, comments and studies with same or overlapping data. The application of the above-mentioned criteria yielded five reports.[13-17] Study of Hunter et al[17] had been reported two case-control groups, therefore, considered as two studies. The following data were extracted: author's name, publication year, country, ethnicity of the participants and the frequencies of the genotypes for each polymorphism in ARMD patients and control subjects.

The heterogeneity across studies was estimated using Cochran's Q and I^2 statistics. If there was no heterogeneity between the studies (I^2 < 50 % and p > 0.10 for Q statistics), the fixed effects model[18] was used for estimation of the odds ratios (ORs) and its 95 % confidence intervals (95 % CI).

Results

Tables 1 and 2 summarised the extracted data from 6 studies which were including in the current study. The studies were published between 2006 and 2016. In total, 6 eligible independent studies with 1,089 participants (634 controls and 455 patients) were used. All of the studies were conducted in Caucasian populations.

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

Frist author	Total	Country	Ethnicity	Control group			Patient group		
				n	Age*	MP**	n	Age	MP
Oz	2006	Turkey	Caucasian	159	62.0 ± 8.6	0.566	35	63.0 ± 8.1	0.457
Guven	2011	Turkey	Caucasian	198	73.0 ± 10.0	0.450	120	75.0 ± 8.0	0.440
Liu	2011	USA	Caucasian	103	69.6 ± 9.8	0.408	131	79.4 ± 8.3	0.519
Othman	2012	Iran	Caucasian	112	63.2 ± 9.4	-***	112	69.5 ± 8.9	0.607
Hunter, 1	2016	USA	Caucasian	50	77.8 ± 8.4	0.460	37	80.9 ± 6.5	0.420
Hunter, 2	2016	USA	Caucasian	50	77.3 ± 10.5	0.438	48	79.4 ± 8.0	0.520

**mean ± SD of age (Years); **Male proportion, ***Sex-matched controls*

Table 2: Genotypes of the studied polymorphisms in age-related macular degeneration patients and controls

Frist author/ Polymorphisms	Control group		Patient group	
GSTM1 Genotypes	Positive genotype	Null genotype	Positive genotype	Null genotype
Oz	18	17	96	63
Guven	102	96	45	75
Liu	33	47	40	48
Othman	71	41	72	40
Hunter, 1	28	22	22	15
Hunter, 2	36	14	32	16
GSTT1 Genotypes	Positive genotype	Null genotype	Positive genotype	Null genotype
Oz	25	10	118	41
Guven	157	41	100	20
Liu	63	17	71	15
Othman	81	31	85	27

The associations of the null genotypes of the *GSTM1* (Figure 1A) and *GSTT1* (Figure 1B) with the risk of ARMD were investigated. There was no heterogeneity across studies for any of the polymorphisms (For *GSTM1*: Q statistics = 5.84, df = 5, p = 0.322, I^2 = 14.3 %; For *GSTT1*: Q statistics = 0.70, df = 3, p = 0.873, I^2 = 0.00). Statistical analysis showed that *GSTM1* (OR = 1.18, 95 % CI: 0.91 - 1.53, p = 0.191) and *GSTT1* (OR = 0.84, 95 % CI: 0.60 - 1.18, p = 0.328) polymorphisms were not associated with the susceptibility to ARMD.

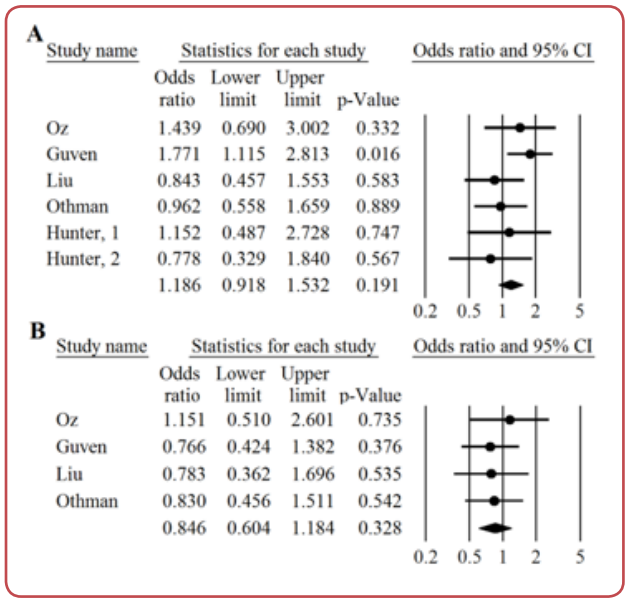

Figure 1: Forest plots of the relationship between the null genotypes versus active genotypes of the GSTM1 (A) and GSTT1 (B) and the susceptibility to age-related macular degeneration

For evaluation of the publication bias, the funnel plot and Egger's test were used. There was no evidence for publication bias (p > 0.320, data not shown). The stability of the findings was evaluated by removing of individual studies sequentially. Sensitivity tests indicated that the present findings were stable.

Discussion

Numerous studies indicated that ARMD has many risk factors. High oxidative stress level is one of the most important risk factors for development of ARMD.[23] Many reactive oxygen species (ROS) such as superoxide, hydrogen peroxide etc, are generated in the retina during transformation of light into vision.[23] The GST superfamily plays a key roles in defence against ROS and oxidative stress. Considering that the null genotypes of *GSTT1* and *GSTM1* were associated with several multifactorial human complex diseases.[5-12]

There were studies investigated the relationship between these polymorphisms and the risk of ARMD,[13-17] the results were inconsistent. Considering that association studies usually were done on a relatively small samples size, in order to increase the sample size and aid the generalisation of the results to larger populations, the present meta-analysis was carried out. To the best of author's knowledge, the current study is the first meta-analysis undertaken to investigate the relationship between the susceptibility to ARMD and null-genotypes of *GSTT1/GSTM1* loci. Overall, the present findings indicated that there was no association between the study null genotypes and the risk of ARMD. Due to some limitations of this study, which are described below, the present results should be interpreted with caution.

Study Limitations

A number of limitations of the current study should be acknowledged. All of the studies used for the present meta-analysis were conducted in Caucasian participants. Therefore, there was no data from Asian and African populations. Considering that the risk of other multifactorial complex traits (such as diabetes mellitus and gastric cancer) with polymorphisms (such as the *GSTT1* and *GSTM1*) were not similar between the ethnic groups[10, 11, 19-22] further association studies from African and Asian populations are required. Considering that environmental factors in the pathogenesis of the ARMD is involved[1, 2] and reports which were included in the analysis did not report the environmental factors, further studies are necessary to examine the interaction between genes and environments, as well as the combinations of polymorphisms.

Conclusion

The current study suggests that the *GSTM1/GSTT1* null genotypes are not significantly associated with the susceptibility to age-related macular degeneration.

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None.

Conflict of interest

None.

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