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ORIGINAL ARTICLE

Glutathione S-transferases variants as risk factors in Alzheimer's disease

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Abstract Glutathione S-transferase (GST) was suggested as an important contributor to Alzheimer's disease (AD). The *GSTs* polymorphisms have been investigated as candidate genetic risk factors for AD, yet results remained uncertain. Therefore, we performed a meta-analysis to clarify the relationship of *GSTs* polymorphisms with the occurrence of AD. PubMed, Embase, Cochrane library and Alzgene databases were searched and potential literatures were selected. Pooled analyses and subgroup analyses were conducted, and also publication bias tests and cumulative meta-analysis. This meta-analysis suggested null associations between polymorphisms of *GSTM1, GSTT1, GSTM3, GSTP1, GSTO1* and AD risk. *GSTs* variants may not have an impact on the morbidity of Alzheimer's disease. Further well designed researches are required to confirm these findings of the current study.

Keywords GSTM1 · GSTT1 · GSTM3 · GSTP1 · GSTO1 · Polymorphism · Alzheimer's disease · Meta-analysis

Introduction

Alzheimer's disease (AD) is becoming a heavy burden to the human society nowadays [1]. AD is a multifactorial disorder, involving genetic and environmental factors [1, 2]. One major contributor is the oxidative stress, which plays an important role in Alzheimer's diseases (see reviews: [3, 4]). However, the antioxidants, e.g., glutathione (GSH), could be potentially therapeutic [5]. As a group of the key antioxidant enzymes, the Glutathione S-transferases (GSTs) regulate the maintenance of GSH and cellular detoxification, and are involved in the activation of signals in cell apoptosis [6]. GST contains several subtypes, i.e., GST alpha (A, α), mu (M, μ), Pi (P, π), omega (O, ω), theta (T, θ), etc. [6]. The levels of GST and enzymatic activity are reduced in brain and ventricular fluid in AD [7, 8]. Genetic variations in these enzymes could impact the risk of diseases [9].

There were several studies to reveal associations between polymorphisms of *GSTs*' genes and AD. However, these findings were debated by other reports with inconsistent results. It was suggested that no pooled analysis concerning *GSTs* gene variants and risk of AD was documented. Therefore, we conducted the current meta-analysis to assess the effect of *GSTs* gene polymorphisms upon AD risk.

Materials and methods

Search strategy

To identify the relevant published articles based on the relationship of *GSTs* genetic polymorphisms and the risk of AD, we conducted a systematic literature search in PubMed, Embase, Cochrane library, and Alzgene

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databases up to March 2014. The following terms "genetic polymorphism or variants," "Glutathione S-transferase or GST," "Alzheimer's disease or AD or Alzheimer" were used and language was not restricted. A manual search of references in the retrieved articles was also performed to find additional potential studies.

Inclusion criteria and exclusion criteria

Inclusion criteria should be met: (1) studies evaluated *GSTs* gene polymorphisms and AD; (2) case–control or cohort studies design; (3) genotype distributions could be obtained from articles, authors, or other sources (i.e., Alzgene database); (4) the largest sample size or the latest studies were selected in case of overlapped publications. Accordingly, exclusion would be made under any of the conditions: nonclinical studies; abstracts, reviews or opinions, conference reports, and case reports; articles with insufficient genotypic data that could not be calculated or obtained from other resource.

Data extraction

After reviewing the relevant articles thoroughly, the following data for each single nucleotide polymorphism (SNP) on *GSTs* were extracted from studies that met the

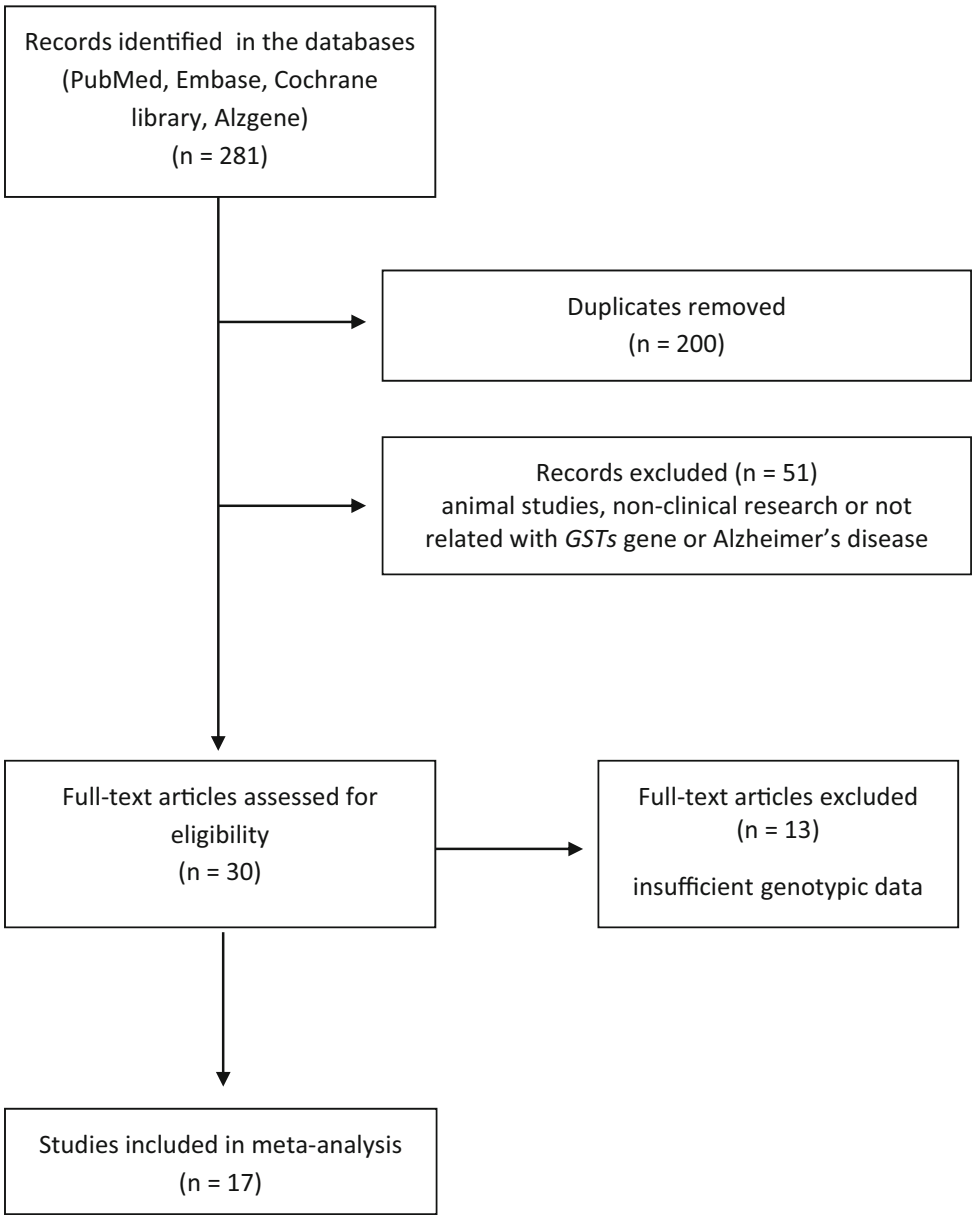

Fig. 1 Flow diagram of article selection concerning *GST*s polymorphisms in AD studies

Table 1 Basic characteristics of the related studies in this meta-analysis

Author	Year	Country/area	Genotypes distribution		Ethnicity
GSTM1			Case (present/null)	Control (present/null)	
Green	1995	USA	43/36	49/72	Other
Stroombergen	1999	UK	20/23	111/114	Caucasian
Nicholl	1999	UK	13/10	7/16	Caucasian
Bernadini	2005	Italy	98/112	104/124	Caucasian
Pinhel	2008	Brazil	19/22	12/12	Other
Ghosh	2012	India	33/17	69/31	Asian
Piacentini	2012	Italy	56/112	76/67	Caucasian
GSTT1			Case (present/null)	Control (present/null)	
De Sousa	1998	USA	57/14	100/16	Other
Stroombergen	1999	UK	20/23	160/65	Caucasian
Bernadini	2005	Italy	166/44	174/53	Caucasian
Pinhel	2008	Brazil	22/19	19/5	Other
Ghosh	2012	India	34/16	84/16	Asian
Piacentini	2012	Italy	117/51	96/47	Caucasian
GSTM3 rs7483			Case (GG/GA/AA)	Control (GG/GA/AA)	
Hong	2009	Germany	167/169/28	167/159/32	Caucasian
Maes	2010	USA	142/160/45	82/55/9	Other
Bullock	2013 (1)	Bonn	117/104/25	103/93/25	Caucasian
Bullock	2013 (2)	Bristol	87/70/16	20/26/5	Caucasian
Bullock	2013 (3)	Nottingham	53/22/2	45/34/11	Caucasian
Bullock	2013 (4)	Oxford	116/100/22	124/97/23	Caucasian
Bullock	2013 (5)	Oviedo	114/62/15	63/50/6	Caucasian
Bullock	2013 (6)	Rotterdam	199/157/35	2643/2008/459	Caucasian
Bullock	2013 (7)	Santander	185/117/23	213/146/30	Caucasian
GSTP1 rs1695			Case (AA/AG/GG)	Control (AA/AG/GG)	
Zuntar	2004	Croatia	32/17/7	114/102/15	Caucasian
Bernadini	2005	Italy	18/95/97	16/95/117	Caucasian
Pinhel	2008	Brazil	14/25/2	15/9/0	Other
Giedraitis	2009	Sweden	43/38/3	160/168/54	Caucasian
Piacentini	2012	Italy	77/74/17	62/67/14	Caucasian
GSTO1 rs4925			Case (CC/CA/AA)	Control (CC/CA/AA)	
Kolsch	2004	Germany	99/124/21	126/129/25	Caucasian
Ozturk	2005	USA	449/441/100	319/315/93	Other
Capurso	2010	Italy	48/38/17	122/31/4	Caucasian
Piacentini	2012 (2)	Italy	56/48/15	51/53/10	Caucasian

Bullock (2013) (1–7) represent each subgroup study in the Ref. [23]; Piacentini 2012 (2) represents Ref. [19]

inclusion criteria: first author, year of publication, country of participants, ethnicity of the population, and allele distributions in cases and controls.

Statistical analysis

We performed the combined analysis for the SNPs that had more than three studies involved. The association between *GSTs* genetic variants and risk of AD was measured by the odds ratio (OR) with 95 % confidence intervals (CI) according to our previous method [10]. The Cochran's Q test and I^2 test were used to estimate heterogeneity across studies. If a significant heterogeneity (assigned as p value <0.1 and $I^2 > 50$ %) existed, the random effect Mantel–Haenszel model was chosen. To determine the statistical significance of the pooled OR, Z test was used with $p < 0.05$ as statistically significant. Pooled analysis was performed under different genetic models [10] (i.e., codominant model, dominant model, recessive model, additive model, and allele model) when necessary. Begg's test and Egger's test were applied to evaluate the evidence of publication bias; p value <0.05 in both tests was considered

Table 2 Pooled measures of the relevant *GST*s polymorphisms in Alzheimer's disease

Subgroups	Significance test		OR (95 % CI)	% Weight	Heterogeneity test	
	Z test	*p* value			I^2 (%)	*p* value
GSTM1						
Caucasian	0.31	0.757	0.909 (0.495, 1.668)	60.17	76.9	0.005
Asian	0.37	0.71	0.872 (0.423, 1.796)	13.73	NA	NA
Other	1.01	0.313	1.397 (0.730, 2.674)	26.09	30.4	0.231
Overall	0.06	0.955	0.988 (0.647, 1.509)	100	68.1	0.004
GSTT1						
Caucasian	0.65	0.515	0.803 (0.414, 1.555)	59.12	79	0.008
Asian	2.22	0.027	0.405 (0.182, 0.900)	15.16	NA	NA
Other	1.9	0.057	0.504 (0.249, 1.020)	25.73	11.5	0.288
Overall	1.84	0.066	0.635 (0.392, 1.030)	100	68.3	0.008
GSTM3 rs7483						
A vs. G						
Caucasian	1.13	0.258	0.935 (0.831, 1.051)	88.99	30	0.188
Other	3.35	0.001	1.689 (1.243, 2.296)	11.01	NA	NA
Overall	0.35	0.728	0.972 (0.830, 1.139)	100	64.1	0.004
AA vs. GG						
Caucasian	0.73	0.466	0.922 (0.740, 1.148)	89.92	0	0.507
Other	2.71	0.007	2.887 (1.343, 6.208)	10.08	NA	NA
Overall	0	0.997	1.001 (0.738, 1.357)	100	43.5	0.078
GA vs. GG						
Caucasian	0.76	0.445	0.949 (0.830, 1.086)	89.44	9.9	0.354
Other	2.48	0.013	1.680 (1.115, 2.530)	10.56	NA	NA
Overall	0.24	0.814	0.980 (0.826, 1.162)	100	44.5	0.072
GA + AA vs. GG						
Caucasian	1.03	0.305	0.928 (0.804, 1.070)	89.05	23.8	0.239
Other	3.09	0.002	1.850 (1.251, 2.734)	10.95	NA	NA
Overall	0.33	0.741	0.968 (0.801, 1.171)	100	59	0.012
AA vs. GG + GA						
Caucasian	0.65	0.515	0.932 (0.754, 1.152)	90.93	0	0.591
Other	2.16	0.031	2.268 (1.078, 4.771)	9.07	NA	NA
Overall	0	0.997	1.001 (0.780, 1.284)	100	24.8	0.0346
GSTP1 rs1695						
G vs. A						
Caucasian	1.95	0.051	0.835 (0.696, 1.001)	92.05	5.8	0.364
Other	1.98	0.048	2.371 (1.009, 5.573)	7.95	NA	NA
Overall	0.72	0.472	0.906 (0.692, 1.186)	100	53.9	0.07
GG vs. AA						
Caucasian	0.76	0.446	0.758 (0.372, 1.545)	95.49	60	0.057
Other	1.05	0.292	5.345 (0.236, 121.000)	4.51	NA	NA
Overall	0.53	0.597	0.827 (0.409, 1.671)	100	54.7	0.065
AG vs. AA						
Caucasian	1.48	0.138	0.881 (0.614, 1.07)	90.45	0	0.771
Other	2.03	0.043	2.976 (1.037, 8.539)	9.55	NA	NA
Overall	0.52	0.603	0.909 (0.634, 1.303)	100	39.3	0.159
AG + GG vs. AA						
Caucasian	1.82	0.069	0.783 (0.601, 1.019)	90.48	0	0.862
Other	2.18	0.029	3.214 (1.126, 9.173)	9.52	NA	NA

Table 2 continued

Subgroups	Significance test		OR (95 % CI)	% Weight	Heterogeneity test	
	Z test	*p* value			I^2 (%)	*p* value
Overall	0.62	0.537	0.892 (0.620, 1.283)	100	45.3	0.121
GG vs. AA + AG						
Caucasian	0.49	0.622	0.851 (0.448, 1.618)	96.4	65.4	0.034
Other	0.72	0.471	3.101 (0.143, 67.338)	3.6	NA	NA
Overall	0.36	0.718	0.893 (0.485, 1.647)	100	57.1	0.054
GSTO1 rs4925						
A vs. C						
Caucasian	1.26	0.207	1.603 (0.770, 3.339)	72.58	92.1	0
Other	1.28	0.201	0.911 (0.789, 1.051)	27.42	NA	NA
Overall	1.26	0.209	1.364 (0.841, 2.212)	100	91.8	0
AA vs. CC						
Caucasian	1.32	0.186	2.332 (0.664, 8.184)	70.24	84	0.002
Other	1.67	0.096	0.764 (0.557, 1.049)	29.76	NA	NA
Overall	1.11	0.267	1.636 (0.686, 3.902)	100	85.1	0
CA vs. CC						
Caucasian	1.07	0.287	1.444 (0.734, 2.839)	69.2	82.5	0.003
Other	0.05	0.959	0.995 (0.811, 1.219)	30.8	NA	NA
Overall	1.12	0.264	1.279 (0.831, 1.968)	100	79.6	0.002
CA + AA vs. CC						
Caucasian	1.18	0.24	1.614 (0.727, 3.586)	71.7	88.8	0
Other	0.61	0.544	0.942 (0.777, 1.142)	28.3	NA	NA
Overall	1.18	0.236	1.379 (0.810, 2.346)	100	88.1	0
AA vs. CC + CA						
Caucasian	1.28	0.202	2.036 (0.683, 6.069)	68.98	80.3	0.006
Other	1.74	0.082	0.766 (0.567, 1.034)	31.02	NA	NA
Overall	1	0.318	1.467 (0.691, 3.116)	100	81.7	0.001

NA could not be calculated

statistically significant. Further, subjects were stratified by ethnicity to perform subgroup analyses. And cumulative meta-analysis was conducted to evaluate the trend of pooled results from studies that subsequently accumulated until the recent year of publications [11]. Statistical analyses were performed using STATA software (SE 11.0 version, Stata Corporation, College Station, TX, USA).

Results

Screening and characteristics of related studies

The initial search yielded 281 potential papers (239 from PubMed, 10 from Embase, 0 from Cochrane library, and 32 from Alzgene database). There were 200 repeated literatures, 51 records of animal studies, and nonclinical research or not related with *GSTs* gene or Alzheimer's disease among these articles. 13 documents were excluded because of insufficient genotypic data among cases and controls. According to the inclusion criteria, 17 articles [12–28], were finally selected for further analysis (see Fig. 1, literature selections in each stage). Among these articles, genetic polymorphisms of *GSTM1*, *GSTM3*, *GSTT1, GSTP1*, and *GSTO1* were studied in more than three researches. Most of the related studies only provided the distributions of present (+/+ and +/−) and null (−/−) alleles in *GSTM1* and *GSTT1* genes. The basic characteristics of all the included studies are shown in Table 1.

Results of heterogeneity tests

Evidence of heterogeneity was observed among studies within the included *GSTs* SNPs(see Table 2, heterogeneity results of I^2 and *p* value). Therefore, random effects pooling model was used to calculate the combined ORs for all SNPs in AD.

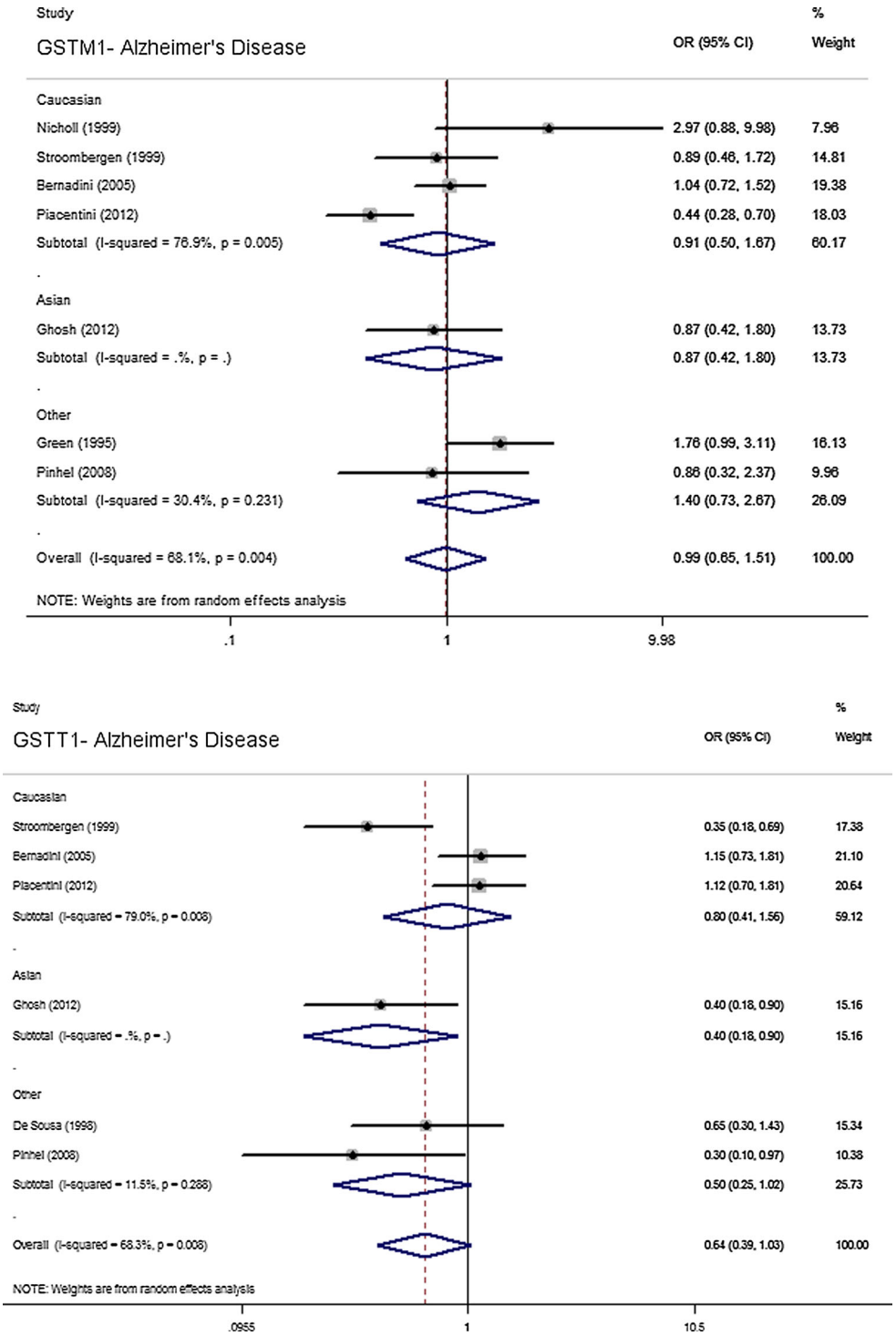

Fig. 2 Forest plot about the effect of *GSTM1*, *GSTT1* alleles upon Alzheimer's disease risk

GSTM1 (present versus null) alleles

In summary, results of meta-analysis failed to show any influence of *GSTM1* on the risk of AD among either overall population (OR = 0.988, 95 % CI 0.647–1.509; $z = 0.06$, $p = 0.955$), or Caucasians, Asians, or other populations (see Fig. 2; Table 2).

GSTT1 (present versus null) alleles

A null association of *GSTT1* in AD samples was found by the meta-analysis among overall population or Caucasians. A potential relationship was revealed in Asians for AD (OR = 0.405, 95 % CI 0.182–0.900; $z = 2.22$, $p = 0.027$); however, with only one study involved, this

needs to be confirmed in the future (see Fig. 2; Table 2).

GSTM3 rs7483 (G/A)

Summary ORs and 95 % CIs were evaluated under different inherited models to estimate the correlation of *GSTM3* rs7483 with AD risk. The results did not show any significant effect of *GSTM3* rs7483 within each genetic model. Further subgroup analyses also found significant impact of *GSTM3* rs7483 on AD risk in other population (one study was involved), but not in overall and Caucasian populations (see Table 2).

GSTP1 rs1695 (Ile105Val, A/G)

A meta-analysis was carried out for *GSTP1* rs1695 in AD under different genetic models, and we did not find associations between *GSTP1* rs1695 and AD risks among overall and Caucasian populations (see Table 2).

GSTO1 rs4925 (C/A), rs1804834 (A/G)

According to the pooling analysis and subgroup analysis, lack of significant effect of *GSTO1* rs4925 on AD morbidity was concluded. The combined ORs and 95 % CI values under related inherited models are shown in Table 2.

Table 3 Results of Begg's test and Egger's test in the association between *GST*s variants and AD risk

Subgroups	Begg's test *p* value	Egger's test *p* value
GSTM1	1	0.462
GSTT1	0.26	0.037
GSTM3 rs7483		
A vs. G	0.175	0.326
AA vs. GG	0.917	0.596
GA vs. GG	0.175	0.204
GA + AA vs. GG	0.118	0.26
AA vs. GG + GA	1	0.753
GSTP1 rs1695		
G vs. A	0.462	0.2
GG vs. AA	0.806	0.796
AG vs. AA	0.806	0.271
AG + GG vs. AA	0.462	0.149
GG vs. AA + AG	0.806	0.825
GSTO1 rs4925		
A vs. C	0.308	0.242
AA vs. CC	0.089	0.14
CA vs. CC	0.308	0.435
CA + AA vs. CC	0.308	0.341
AA vs. CC + CA	0.089	0.113

Publication bias and cumulative analysis

Begg's and Egger's tests indicated no evidence of significant asymmetry for most of the related *GSTs* SNPs within Alzheimer's disease (see Table 3).

In the cumulative meta-analyses, the evidences were observed to support the pooling analyses regarding relevant *GSTs* SNPs and AD (see Fig S1).

Discussion

Effects of *GSTs* genetic polymorphisms and ethnicity in neurodegenerative diseases [29] are of our interest. Combined analyses concerning *GSTs* SNPs in Alzheimer's disease have not been reported yet. To the best of our knowledge, this is the first meta-analysis discussing *GSTs* polymorphisms among AD subjects. In this study, a total of 17 articles regarding SNPs of *GSTM1*, *GSTT1*, *GSTM3*, *GSTP1*, and *GSTO1* genes were evaluated in AD. No significant effect of *GSTM1* or *GSTT1* present polymorphism was observed in Alzheimer's disease in the pooled analyses. We used several genetic models to assess the roles of *GSTM3, GSTP1,* and *GSTO1* genetic variants in AD; however, we found null associations between these *GSTs* SNPs and AD risk.

rs1332018 (C/A), rs1799735 (del/AGG) of *GSTM3* [21]; *GSTP1* Ala114Val (*GSTP1*A/*B/*C/*D*) [15, 24, 30]; *GSTP1* C341T [24] and *GSTO1* rs1804834 [27, 31] were also reported in AD. We did not perform any pooled analysis on these SNPs in AD because the relevant studies were limited.

Some potential limitations should be taken into consideration. First, the relative small global sample size and the number of cases in some ethnic subgroups were shortcomings, considering small or inadequate samples could lead to misleading results. Moreover, other *GSTs* genes, e.g., *GSTA1*, *GSTO2*, may also play a role in the development of Alzheimer's disease. One research [18] suggested that *GSTA1* rs3957356 was associated with the increased AD in Dominant model. Positive effect of rs156697 on *GSTO2* was also found [32] among older (>80 years old) AD patients. Third, there was an evidence of heterogeneity in the current meta-analysis. One potential explanation to the heterogeneity is the influence of ethnic background or environment [2] in the correlation of gene variants with AD. Heterogeneity could also come from individual clinical study.

In conclusion, our meta-analysis suggested that SNPs of the relevant *GSTs* (*GSTM1*, *GSTT1*, *GSTM3*, *GSTP1*, and

GSTO1) did not confer risk for AD. Further well-designed researches are needed to confirm these findings, especially in the subsets with limited studies involved in the current study.

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Conflict of interest None declared.

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