



Effects of *GST* null genotypes on individual susceptibility to leukemia: A meta-analysis

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ABSTRACT

Background: Whether glutathione S-transferases (*GST*) null genotypes influence individual susceptibility to leukemia remains controversial. Thus, we performed this meta-analysis to better analyze potential influences of *GST* null genotypes on individual susceptibility to leukemia.

Methods: Literature retrieve was conducted in PubMed, Web of Science and Embase. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Results: Totally fifty-one studies were enrolled for analyses. Significant associations with elevated individual susceptibility to leukemia were detected for *GSTM1* ($p < .0001$, OR = 1.28, 95%CI 1.16–1.41), *GSTP1* ($p = .003$, OR = 1.22, 95%CI 1.07–1.40) and *GSTT1* ($p < .0001$, OR = 1.53, 95%CI 1.35–1.74) null genotypes in overall analyses. Further subgroup analyses by type of disease revealed that *GSTM1*, *GSTP1* and *GSTT1* null genotypes were all significantly associated with elevated individual susceptibility to acute lymphoblastic leukemia, *GSTM1* and *GSTT1* null genotypes were significantly associated with elevated individual susceptibility to acute myeloid leukemia, and *GSTT1* null genotype was also significantly associated with elevated individual susceptibility to chronic leukemia. When we stratified data according to ethnicity of participants, positive results were found for all investigated variants in Caucasians and West Asians. Additionally, *GSTM1* null genotype was also significantly correlated with elevated individual susceptibility to leukemia in East Asians.

Conclusions: Our findings indicated that *GSTM1*, *GSTT1* and *GSTP1* null genotypes might serve as potential genetic biomarkers of leukemia in certain ethnicities.

1. Introduction

Leukemia refers to malignancy that occurs in the hematopoietic system, and it is one of the leading causes of cancer-related morbidity and mortality all over the world (Siegel et al., 2014). Despite tremendous advances in early diagnosis and pharmacological treatment over the past few decades, the numbers of new leukemia cases and associated deaths continue to increase, making it one of the major threats to public health (Ferlay et al., 2015).

So far, the exact cause of leukemia is still unclear. Although chemicals, radiation and viral infection have been identified as potential pathogenic factors of leukemia by previous epidemiological investigations (Maia Rda and Wunsch Filho, 2013; Schüz and Erdmann, 2016), the fact that a great inter-individual variability in disease susceptibility existed in these exposed to above mentioned carcinogenic factors

suggests that genetic factors are also involved in its development.

Glutathione-S-transferases (GSTs) are a group of enzymes that play vital roles in regulating cellular detoxification of various exogenous carcinogens (Di Pietro et al., 2010). Moreover, it is believed that GSTs can also protect cells against oxidative stress and its associated DNA damage (Singh, 2015). Previous experimental studies demonstrated that *GST* null genotypes (entire deletion mutation of *GSTM1*, *GSTP1* or *GSTT1*) resulted in diminished gene expression and enzymatic activity (Hollman et al., 2016; Strange et al., 1998; Strange et al., 2001). Consequently, it is biologically plausible that subjects carrying these null genotypes may suffer a higher risk of developing multiple malignancies because their GST proteins do not function properly. Recently, associations between *GST* null genotypes and leukemia were intensively investigated, but the results of these studies were controversial. Therefore, we performed the present meta-analysis to better analyze

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potential influences of *GST* null genotypes on individual susceptibility to leukemia.

2. Materials and methods

2.1. Literature search and inclusion criteria

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist (Moher et al., 2009). Potentially related literatures (published before November 2018) were retrieved from PubMed, Web of Science and Embase using the following searching strategy: (glutathione S-transferases OR *GST*) AND (variant OR polymorphism OR mutation OR genotype OR allele OR genetic variation) AND leukemia. Furthermore, the references of retrieved articles were also screened for other potentially relevant studies.

To test the research hypothesis of this meta-analysis, included studies must meet all the following criteria: (1) case-control study on associations between *GST* null genotypes and leukemia; (2) providing genotypic frequency of investigated *GST* variants in cases and controls; (3) full text in English or Chinese available. Studies were excluded if one of the following criteria was fulfilled: (1) not relevant to *GST* null genotypes and leukemia; (2) case reports or case series; (3) abstracts, reviews, comments, letters and conference presentations. For duplicate publications, we only included the study with the largest sample size for analyses.

2.2. Data extraction and quality assessment

The following data were extracted from included studies: (1) the name of the first author; (2) publication time; (3) country and ethnicity; (4) sample size; and (5) genotypic distribution of *GST* variants in cases and controls. When necessary, we wrote to the corresponding authors for extra details if the above mentioned data were not clearly stated in the manuscript. We used the Newcastle-Ottawa scale (NOS) to assess the quality of eligible studies (Stang, 2010). This scale has a score range of zero to nine, and studies with a score of more than seven were thought to be of high quality. Two reviewers (Jun Wang and Depei Wu) conducted data extraction and quality assessment independently. Any disagreement between two reviewers was solved by discussion with the third reviewer (Aining Sun) until a consensus was reached.

2.3. Statistical analyses

All statistical analyses were conducted using Review Manager Version 5.3.3 (The Cochrane Collaboration, Software Update, Oxford, United Kingdom). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate strength of associations between *GST* null genotypes and leukemia, and *p* values $\leq .05$ were considered to be statistically significant. Between-study heterogeneities were evaluated with I^2 statistic. If I^2 was $> 50\%$, random-effect models (REMs) would be used to pool the data. Otherwise, fixed-effect models (FEMs) would be employed for synthetic analyses. Subgroup analyses by type of disease and ethnicity of participants were subsequently performed. Sensitivity analyses were conducted to examine the stability of synthetic results. Funnel plots were used to evaluate possible publication biases.

3. Results

3.1. Characteristics of included studies

Totally 1431 potential relevant articles were identified by using our searching strategy. Among these articles, a total of 51 eligible studies were finally included for synthetic analyses (see Fig. 1 and Supplementary file 1). The NOS score of eligible articles ranged from 7 to 8,

which indicated that qualities of included studies were relatively good. Baseline characteristics of included studies were shown in Table 1.

3.2. Overall and subgroup analyses

To analyze potential correlations between *GST* null genotypes and leukemia, 45 studies about *GSTM1* null genotype (8475 cases and 15,453 controls), 21 studies about *GSTP1* null genotype (4057 cases and 7309 controls) and 42 studies about *GSTT1* null genotype (7886 cases and 13,985 controls) were enrolled for analyses.

Significant associations with elevated individual susceptibility to leukemia were detected for *GSTM1* ($p < .0001$, OR = 1.28, 95%CI 1.16–1.41), *GSTP1* ($p = .003$, OR = 1.22, 95%CI 1.07–1.40) and *GSTT1* ($p < .0001$, OR = 1.53, 95%CI 1.35–1.74) null genotypes in overall analyses.

Further subgroup analyses by type of disease revealed that *GSTM1*, *GSTP1* and *GSTT1* null genotypes were all significantly associated with elevated individual susceptibility to acute lymphoblastic leukemia, *GSTM1* and *GSTT1* null genotypes were significantly associated with elevated individual susceptibility to acute myeloid leukemia, and *GSTT1* null genotype was also significantly associated with elevated individual susceptibility to chronic leukemia. When we stratified data according to ethnicity of participants, positive results were found for all investigated variants in Caucasians and West Asians. Additionally, *GSTM1* null genotype was also significantly associated with elevated individual susceptibility to leukemia in East Asians (see Table 2).

3.3. Sensitivity analyses

We performed sensitivity analyses by removing one individual study each time. No alterations of results were detected in sensitivity analyses, which suggested that our findings were statistically reliable (see Supplementary file 2).

3.4. Publication biases

Publication biases were evaluated with funnel plots. We did not find obvious asymmetry of funnel plots in any comparisons, which indicated that our findings were unlikely to be influenced by severe publication biases (see Supplementary fig. 1).

4. Discussion

To the best of our knowledge, this is so far the most comprehensive meta-analysis on associations between *GST* null genotypes and leukemia. Our pooled analyses demonstrated that *GSTM1*, *GSTP1* and *GSTT1* null genotypes were all significantly associated with elevated individual susceptibility to certain types of acute leukemia, and *GSTT1* null genotype was also significantly associated with elevated individual susceptibility to chronic leukemia. Moreover, positive results were found for all investigated variants in Caucasians and West Asians. In addition, *GSTM1* null genotype was also significantly associated with elevated individual susceptibility to leukemia in East Asians.

There are several points that need to be addressed about this meta-analysis. Firstly, previous experimental studies showed that null genotypes of investigated variants were associated with diminished enzymatic activity of *GST*, and this could result in decreased detoxifying capacity of carcinogens and inefficient metabolism of chemotherapeutic agents, which may partially explain the underlying mechanism of our positive findings (Board and Anders, 2011; Hayes and Strange, 2000; McIlwain et al., 2006). In addition, our results indicated that *GST* genotyping can be used to identify subjects at higher risk of developing leukemia, and patients carrying *GST* null genotypes may require more aggressive therapy. Secondly, the pathogenic mechanism of leukemia is highly complex, and hence it is unlikely that a single genetic variant can significantly contribute to its development. So to better illustrate

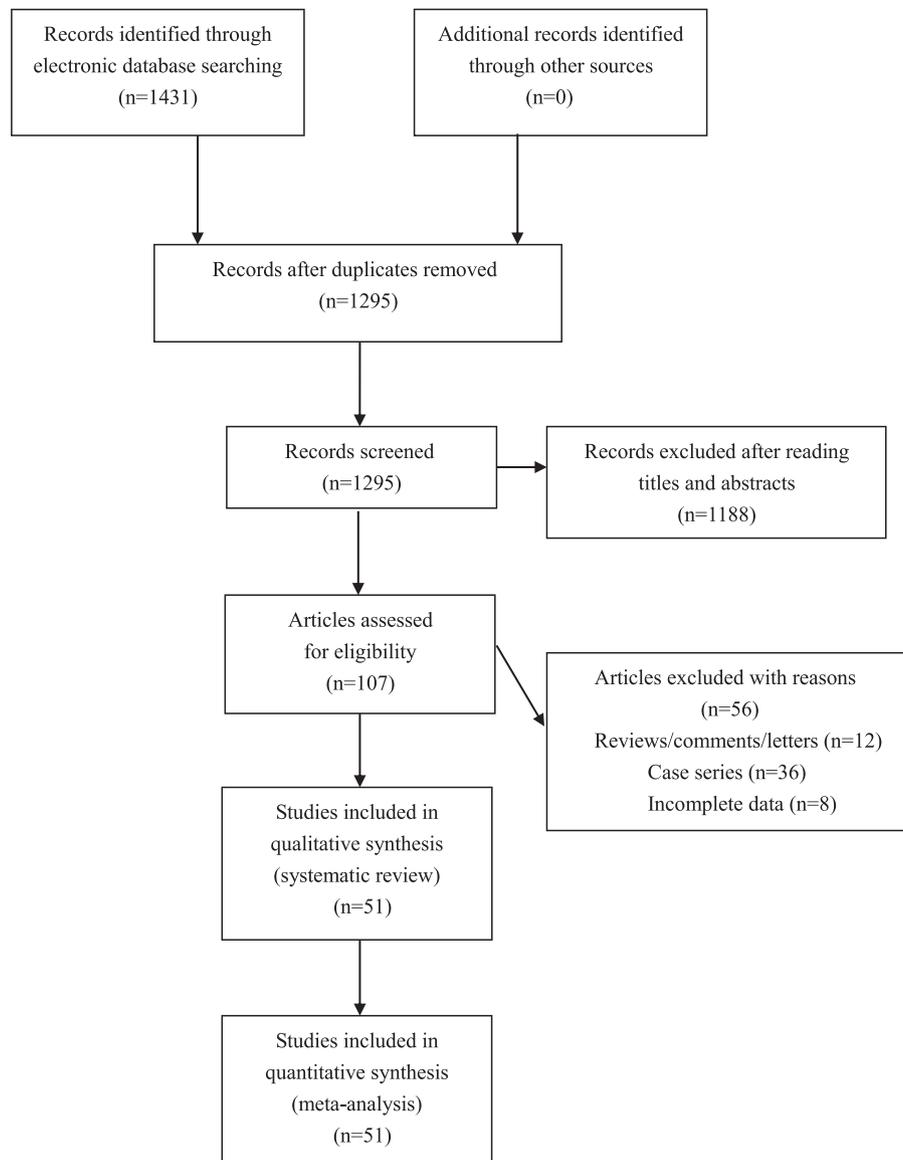


Fig. 1. Flowchart of study selection for the present study.

potential associations of certain genetic variants with leukemia, we strongly recommend further studies to perform haplotype analyses and explore potential gene-gene interactions.

As with all meta-analysis, this study certainly has some limitations. First, our results were derived from unadjusted analyses due to lack of raw data, and lack of further adjusted analyses for age, gender and comorbidity conditions may impact the reliability of our findings (Xie et al., 2017a; Shi et al., 2016). Second, obvious heterogeneities were found in several subgroups, which indicated that the controversial results of included studies could not be fully explained by differences in ethnic background and type of disease, and other baseline characteristics of participants may also contribute to between-study heterogeneities (Xie et al., 2017b; Zhu et al., 2018). Third, associations between *GST* variants and leukemia may also be influenced by gene-gene and gene-environmental interactions. However, most eligible studies ignore these potential interactions, which impeded us to perform relevant analyses accordingly (Sun et al., 2018; Dong et al., 2018). Fourth, grey literatures like abstracts and other research materials that were not formally published in academic journals were not considered to be eligible for analyses since it is hard to determine their quality. However, since grey literatures were not analyzed, although funnel

plots suggested that severe publication biases were unlikely to be existed in the current meta-analysis, it is still possible that our findings may be impacted by potential publication biases (Chen et al., 2013). Fifth, since our pooled analyses were based on case-control studies, despite our positive findings, future perspective studies are still needed to examine whether there is direct causal relationship between *GST* null genotypes and leukemia (Ma et al., 2018). To sum up, our findings should be cautiously interpreted on account of above mentioned limitations.

5. Conclusion

The present meta-analysis aimed to better analyze potential influences of *GST* null genotypes on individual susceptibility to leukemia, and we found that *GST* null genotypes were associated with elevated susceptibility to leukemia in certain ethnicities. However, taking the above mentioned limitations into consideration, further prospective studies with larger sample sizes are still warranted to confirm our findings.

Table 1
The characteristics of included studies for *GST* variants and leukemia.

First author, year	Country	Ethnicity	Type of disease	Sample size (case/control)	Null genotype [n (%)]		NOS score
					Cases	Controls	
<i>GSTM1</i>							
Al-Achkar 2014	Syria	West Asian	Chronic myelogenous leukemia (CML)	126/172	54 (42.8%)	39 (22.7%)	7
Allan 2001	UK	Caucasian	Acute myeloid leukemia (AML)	417/1019	229 (55.0%)	496 (48.7%)	8
Arruda 2001	Brazil	African	Acute myeloid leukemia (AML)	38/276	28 (73.6%)	102 (36.9%)	7
Bajpai 2007	India	West Asian	Chronic myelogenous leukemia (CML)	80/105	24 (30.0%)	26 (24.7%)	7
Balta 2003	Turkey	Caucasian	Acute lymphoblastic leukemia (ALL)	139/185	77 (55.4%)	101 (54.6%)	7
Bhat 2012	India	West Asian	Chronic myelogenous leukemia (CML)	75/124	31 (41.3%)	43 (35.0%)	8
Bolufer 2007	Spain	Caucasian	Acute myeloid leukemia (AML)	295/451	143 (48.5%)	232 (51.4%)	7
Bolufer 2007	Spain	Caucasian	Acute lymphoblastic leukemia (ALL)	140/451	64 (45.7%)	232 (51.4%)	7
Chen 1997	USA	Caucasian	Acute lymphoblastic leukemia (ALL)	163/213	90 (55.2%)	114 (53.5%)	7
Chen 1997	USA	African	Acute lymphoblastic leukemia (ALL)	34/203	14 (41.2%)	56 (27.6%)	7
Chen 2008	China	East Asian	Acute myeloid leukemia (AML)	120/204	72 (60.0%)	113 (55.4%)	8
Chen 2008	China	East Asian	Acute myeloid leukemia (AML)	120/204	82 (68.3%)	113 (55.4%)	8
Chen 2008	China	East Asian	Chronic myelogenous leukemia (CML)	108/204	58 (53.7%)	113 (55.4%)	8
Crump 2000	USA	Mixed	Acute myeloid leukemia (AML)	297/152	159 (53.5%)	75 (49.3%)	8
D'Alò 2004	Italy	Caucasian	Acute myeloid leukemia (AML)	193/273	82 (42.5%)	128 (46.9%)	7
Davies 2002	USA	Caucasian	Acute lymphoblastic leukemia (ALL)	616/532	331 (53.7%)	286 (53.8%)	7
Davies 2002	USA	African	Acute lymphoblastic leukemia (ALL)	35/201	14 (40.0%)	64 (31.8%)	7
Dunna 2013	India	West Asian	Acute lymphoblastic leukemia (ALL)	152/251	89 (58.6%)	94 (37.5%)	7
Dunna 2013	India	West Asian	Acute myeloid leukemia (AML)	142/251	90 (63.4%)	94 (37.5%)	7
Gra 2008	Russia	Caucasian	Acute lymphoblastic leukemia (ALL)	332/490	181 (54.5%)	238 (48.6%)	7
Gra 2008	Russia	Caucasian	Acute myeloid leukemia (AML)	71/490	38 (53.5%)	238 (48.6%)	7
Güven 2015	Turkey	Caucasian	Acute lymphoblastic leukemia (ALL)	95/190	45 (47.4%)	99 (52.1%)	8
Haase 2002	Germany	Caucasian	Acute myeloid leukemia (AML)	213/239	107 (50.2%)	122 (51.0%)	7
Hishida 2005	Japan	East Asian	Chronic myelogenous leukemia (CML)	51/476	26 (51.0%)	249 (52.3%)	7
Kassogue 2015	Morocco	Caucasian	Chronic myelogenous leukemia (CML)	92/93	45 (48.9%)	38 (40.9%)	7
Kim 2012	Korea	East Asian	Acute myeloid leukemia (AML)	398/1700	230 (57.8%)	923 (54.3%)	7
Krajcinovic 2002	Canada	Caucasian	Acute lymphoblastic leukemia (ALL)	269/301	151 (56.1%)	141 (46.8%)	7
Lemos 1999	Portugal	Caucasian	Acute lymphoblastic leukemia (ALL)	22/128	14 (63.6%)	74 (57.8%)	7
Lemos 1999	Portugal	Caucasian	Chronic lymphoblastic leukemia (CLL)	13/128	5 (38.5%)	74 (57.8%)	7
Lemos 1999	Portugal	Caucasian	Acute myeloid leukemia (AML)	18/128	10 (55.6%)	74 (57.8%)	7
Lemos 1999	Portugal	Caucasian	Chronic myelogenous leukemia (CML)	11/128	9 (81.8%)	74 (57.8%)	7
Li 2012	China	East Asian	Acute lymphoblastic leukemia (ALL)	106/100	56 (52.8%)	49 (49.0%)	8
Liu 2017	Australia	Caucasian	Leukemia	424/420	248 (58.5%)	227 (54.0%)	8
Lordelo 2012	Brazil	African	Chronic myelogenous leukemia (CML)	105/273	55 (52.4%)	176 (64.5%)	8
Majumdar 2008	India	West Asian	Acute myeloid leukemia (AML)	110/144	57 (51.8%)	34 (24.8%)	8
Mandegary 2011	Iran	West Asian	Acute myeloid leukemia (AML)	114/99	64 (56.2%)	48 (48.5%)	8
Mondal 2005	India	West Asian	Chronic myelogenous leukemia (CML)	81/123	23 (28.4%)	34 (27.7%)	8
Moulik 2014	India	West Asian	Acute lymphoblastic leukemia (ALL)	100/300	35 (35.0%)	84 (28.0%)	8
Naoe 2000	Japan	East Asian	Acute myeloid leukemia (AML)	411/150	227 (55.2%)	77 (51.3%)	7
Nasr 2015	Egypt	Caucasian	Acute myeloid leukemia (AML)	50/50	24 (48.0%)	7 (14.0%)	8
Ossepian 2010	Russia	Caucasian	Chronic myelogenous leukemia (CML)	83/205	44 (53.0%)	94 (45.9%)	7
Özten 2012	Turkey	Caucasian	Chronic myelogenous leukemia (CML)	106/190	48 (45.3%)	81 (42.6%)	8
Rollinson 2000	UK	Caucasian	Acute myeloid leukemia (AML)	479/827	258 (53.9%)	407 (49.2%)	8
Rollinson 2000	UK	Caucasian	Acute lymphoblastic leukemia (ALL)	71/114	35 (49.3%)	55 (48.2%)	7
Sasai 1999	Japan	East Asian	Acute myeloid leukemia (AML)	43/43	22 (51.2%)	23 (53.5%)	8
Suneetha 2008	India	West Asian	Acute lymphoblastic leukemia (ALL)	92/150	36 (39.1%)	37 (24.7%)	8
Taspinar 2008	Turkey	Caucasian	Chronic myelogenous leukemia (CML)	107/135	48 (44.9%)	55 (42.3%)	7
Wang 2002	China	East Asian	Leukemia	34/34	25 (73.5%)	12 (35.3%)	7
Wang 2004	China	East Asian	Acute lymphoblastic leukemia (ALL)	67/146	51 (76.1%)	77 (52.7%)	7
Weich 2015	Argentina	Caucasian	Leukemia	36/133	6 (16.7%)	48 (37.6%)	7
Weich 2016	Argentina	Caucasian	Chronic myelogenous leukemia (CML)	141/141	56 (39.7%)	57 (40.4%)	8
Yuille 2002	UK	Caucasian	Chronic lymphoblastic leukemia (CLL)	138/270	77 (55.8%)	135 (50.0%)	7
Zehra 2018	Pakistan	West Asian	Acute lymphoblastic leukemia (ALL)	62/62	29 (46.8%)	28 (45.2%)	7
Zhou 2013	China	East Asian	Acute myeloid leukemia (AML)	163/204	86 (52.5%)	97 (47.6%)	8
Zi 2014	China	East Asian	Acute myeloid leukemia (AML)	206/231	114 (55.3%)	107 (46.3%)	7
Zou 2004	China	East Asian	Leukemia	61/183	40 (66.6%)	99 (54.1%)	7
<i>GSTP1</i>							
Allan 2001	UK	Caucasian	Acute myeloid leukemia (AML)	414/1015	212 (51.2%)	496 (51.0%)	8
Balta 2003	Turkey	Caucasian	Acute lymphoblastic leukemia (ALL)	136/185	60 (44.1%)	82 (44.3%)	7
Dunna 2013	India	West Asian	Acute lymphoblastic leukemia (ALL)	147/248	91 (61.9%)	108 (43.5%)	7
Dunna 2013	India	West Asian	Acute myeloid leukemia (AML)	143/248	91 (63.6%)	108 (43.5%)	7
Güven 2015	Turkey	Caucasian	Acute lymphoblastic leukemia (ALL)	95/190	47 (49.5%)	109 (57.4%)	8
Karkucak 2012	Turkey	Caucasian	Chronic myelogenous leukemia (CML)	71/67	26 (36.6%)	31 (46.3%)	7
Kim 2012	Korea	East Asian	Acute myeloid leukemia (AML)	406/1696	132 (32.5%)	619 (36.5%)	7
Krajcinovic 2002	Canada	Caucasian	Acute lymphoblastic leukemia (ALL)	269/301	151 (56.1%)	141 (46.8%)	7
Liu 2017	Australia	Caucasian	Leukemia	422/420	134 (31.8%)	118 (28.1%)	8
Mandegary 2011	Iran	West Asian	Acute myeloid leukemia (AML)	110/105	54 (49.1%)	51 (48.6%)	8
Moulik 2014	India	West Asian	Acute lymphoblastic leukemia (ALL)	100/300	43 (43.0%)	105 (35.0%)	8
Nasr 2015	Egypt	Caucasian	Acute myeloid leukemia (AML)	50/50	30 (60.0%)	18 (36.0%)	8
Rollinson 2000	UK	Caucasian	Acute myeloid leukemia (AML)	472/823	242 (51.3%)	420 (51.0%)	8
Rollinson 2000	UK	Caucasian	Acute lymphoblastic leukemia (ALL)	66/112	30 (45.5%)	50 (44.6%)	8

(continued on next page)

Table 1 (continued)

First author, year	Country	Ethnicity	Type of disease	Sample size (case/control)	Null genotype [n (%)]		NOS score
					Cases	Controls	
Sailaja 2010	India	West Asian	Chronic myelogenous leukemia (CML)	260/248	119 (45.8%)	108 (43.5%)	8
Suneetha 2008	India	West Asian	Acute lymphoblastic leukemia (ALL)	92/150	49 (53.3%)	69 (46.0%)	8
Weich 2015	Argentina	Caucasian	Leukemia	36/133	29 (80.6%)	80 (60.2%)	7
Weich 2016	Argentina	Caucasian	Chronic myelogenous leukemia (CML)	141/141	79 (56.0%)	74 (52.5%)	8
Yuan 2003	China	East Asian	Acute lymphoblastic leukemia (ALL)	80/85	43 (53.8%)	27 (31.8%)	7
Yuan 2003	China	East Asian	Acute myeloid leukemia (AML)	40/85	14 (35.0%)	27 (31.8%)	7
Yuille 2002	UK	Caucasian	Chronic lymphoblastic leukemia (CLL)	138/273	79 (57.2%)	133 (48.7%)	7
Zhou 2013	China	East Asian	Acute myeloid leukemia (AML)	163/203	90 (55.2%)	109 (53.7%)	8
Zi 2014	China	East Asian	Acute myeloid leukemia (AML)	206/231	116 (56.3%)	127 (55.0%)	7
<i>GSST1</i>							
Al-Achkar 2014	Syria	West Asian	Chronic myelogenous leukemia (CML)	126/172	34 (27.0%)	27 (16.7%)	7
Allan 2001	UK	Caucasian	Acute myeloid leukemia (AML)	417/1019	79 (19.0%)	140 (13.7%)	8
Arruda 2001	Brazil	African	Acute myeloid leukemia (AML)	38/276	13 (24.3%)	44 (18.1%)	7
Bajpai 2007	India	West Asian	Chronic myelogenous leukemia (CML)	80/105	16 (20.0%)	9 (8.5%)	7
Balta 2003	Turkey	Caucasian	Acute lymphoblastic leukemia (ALL)	139/185	29 (20.9%)	42 (22.7%)	7
Bhat 2012	India	West Asian	Chronic myelogenous leukemia (CML)	75/124	27 (36.0%)	26 (21.0%)	8
Bolufier 2007	Spain	Caucasian	Acute myeloid leukemia (AML)	289/455	74 (25.6%)	61 (13.7%)	7
Bolufier 2007	Spain	Caucasian	Acute lymphoblastic leukemia (ALL)	141/455	36 (25.5%)	61 (13.7%)	7
Chen 1997	USA	Caucasian	Acute lymphoblastic leukemia (ALL)	163/213	23 (14.1%)	32 (15.0%)	7
Chen 1997	USA	African	Acute lymphoblastic leukemia (ALL)	34/203	12 (35.3%)	49 (24.1%)	7
Chen 2008	China	East Asian	Acute lymphoblastic leukemia (ALL)	120/204	61 (50.8%)	100 (49.0%)	8
Chen 2008	China	East Asian	Acute myeloid leukemia (AML)	120/204	66 (55.0%)	100 (49.0%)	8
Chen 2008	China	East Asian	Chronic myelogenous leukemia (CML)	108/204	51 (47.2%)	100 (49.0%)	8
Crump 2000	USA	Mixed	Acute myeloid leukemia (AML)	297/152	48 (16.2%)	26 (17.1%)	8
D'Alò 2004	Italy	Caucasian	Acute myeloid leukemia (AML)	193/273	56 (29.0%)	52 (19.0%)	7
Davies 2002	USA	Caucasian	Acute lymphoblastic leukemia (ALL)	616/532	96 (15.6%)	87 (16.4%)	7
Davies 2002	USA	African	Acute lymphoblastic leukemia (ALL)	35/201	6 (17.1%)	56 (27.9%)	7
Dunna 2013	India	West Asian	Acute lymphoblastic leukemia (ALL)	152/251	38 (25.0%)	39 (15.5%)	7
Dunna 2013	India	West Asian	Acute myeloid leukemia (AML)	142/251	57 (40.1%)	39 (15.5%)	7
Gra 2008	Russia	Caucasian	Acute lymphoblastic leukemia (ALL)	332/490	104 (31.3%)	94 (19.2%)	7
Gra 2008	Russia	Caucasian	Acute myeloid leukemia (AML)	71/490	21 (29.6%)	94 (19.2%)	7
Guvén 2015	Turkey	Caucasian	Acute lymphoblastic leukemia (ALL)	95/190	24 (25.3%)	52 (27.4)	8
Haase 2002	Germany	Caucasian	Acute myeloid leukemia (AML)	213/239	72 (33.8%)	59 (24.8%)	7
Hishida 2005	Japan	East Asian	Chronic myelogenous leukemia (CML)	51/476	29 (56.9%)	238 (50.0%)	7
Kassogue 2015	Morocco	Caucasian	Chronic myelogenous leukemia (CML)	92/93	45 (48.9%)	38 (40.9%)	7
Kim 2012	Korea	East Asian	Acute myeloid leukemia (AML)	398/1700	214 (53.8%)	859 (50.5%)	7
Li 2012	China	East Asian	Acute lymphoblastic leukemia (ALL)	106/100	67 (63.2%)	44 (44.0%)	8
Liu 2017	Australia	Caucasian	Leukemia	424/420	154 (36.3%)	114 (27.1%)	8
Lordelo 2012	Brazil	African	Chronic myelogenous leukemia (CML)	105/273	21 (20.0%)	65 (23.8%)	8
Majumdar 2008	India	West Asian	Acute myeloid leukemia (AML)	110/144	16 (14.5%)	11 (7.6%)	8
Mandegary 2011	Iran	West Asian	Acute myeloid leukemia (AML)	114/99	45 (39.5%)	23 (33.3%)	8
Mondal 2005	India	West Asian	Chronic myelogenous leukemia (CML)	81/123	16 (19.8%)	9 (7.3%)	8
Moulik 2014	India	West Asian	Acute lymphoblastic leukemia (ALL)	100/300	31 (31.0%)	45 (15.0%)	8
Naoe 2000	Japan	East Asian	Acute myeloid leukemia (AML)	411/150	197 (47.9%)	81 (54.0%)	7
Nasr 2015	Egypt	Caucasian	Acute myeloid leukemia (AML)	50/50	30 (60.0%)	4 (8%)	8
Ovsepian 2010	Russia	Caucasian	Chronic myelogenous leukemia (CML)	83/205	20 (24.1%)	27 (13.2%)	7
Özten 2012	Turkey	Caucasian	Chronic myelogenous leukemia (CML)	106/190	47 (44.3%)	35 (18.4%)	8
Rollinson 2000	UK	Caucasian	Acute myeloid leukemia (AML)	479/827	89 (18.6%)	125 (15.1%)	8
Rollinson 2000	UK	Caucasian	Acute lymphoblastic leukemia (ALL)	71/114	15 (21.1%)	9 (7.9%)	8
Sasai 1999	Japan	East Asian	Acute myeloid leukemia (AML)	43/43	26 (60.5%)	13 (30.2%)	7
Suneetha 2008	India	West Asian	Acute lymphoblastic leukemia (ALL)	92/150	11 (10.9%)	20 (13.3%)	8
Taspinar 2008	Turkey	Caucasian	Chronic myelogenous leukemia (CML)	107/135	43 (40.2%)	25 (19.2%)	7
Wang 2004	China	East Asian	Acute lymphoblastic leukemia (ALL)	67/146	41 (61.2%)	72 (49.3%)	7
Weich 2015	Argentina	Caucasian	Leukemia	36/133	3 (8.3%)	14 (10.5%)	7
Weich 2016	Argentina	Caucasian	Chronic myelogenous leukemia (CML)	141/141	20 (14.2%)	24 (17.0%)	8
Yuille 2002	UK	Caucasian	Chronic lymphoblastic leukemia (CLL)	138/270	41 (29.7%)	66 (24.4%)	7
Zehra 2018	Pakistan	West Asian	Acute lymphoblastic leukemia (ALL)	62/62	7 (11.3%)	4 (6.4%)	7
Zhou 2013	China	East Asian	Acute myeloid leukemia (AML)	163/204	61 (37.4%)	55 (27.0%)	8
Zi 2014	China	East Asian	Acute myeloid leukemia (AML)	206/231	73 (35.5%)	55 (23.7%)	7
Zou 2004	China	East Asian	Leukemia	61/183	39 (63.9%)	89 (48.6%)	7

Abbreviations: HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa scale; NA, Not available.

Authors' contributions

Jun Wang and Aining Sun conceived of the study, participated in its design. Jun Wang and Depei Wu conducted the systematic literature review. Depei Wu performed data analyses. Jun Wang and Aining Sun drafted the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Conflict of interest

The authors declare that they have no conflict of interest.

Table 2
Pooled analyses for GST variants and leukemia.

Polymorphisms	Population	Sample size (cases/controls)	Null genotype vs. present genotype		
			P value	OR (95%CI)	I ² statistic
<i>GSTM1</i>	Overall	8475/15453	< 0.0001	1.28 (1.16–1.41)	61%
	AML	3778/6931	0.0002	1.39 (1.17–1.66)	73%
	ALL	2735/4425	< 0.0001	1.25 (1.13–1.38)	49%
	CML	1166/2369	0.07	1.15 (0.99–1.33)	45%
	CLL	151/398	0.55	1.12 (0.76–1.65)	61%
	Caucasian	4932/8881	0.001	1.13 (1.05–1.21)	46%
	East Asian	1949/3672	0.0004	1.25 (1.10–1.41)	29%
<i>GSTP1</i>	West Asian	1346/2388	< 0.0001	1.79 (1.38–2.34)	69%
	Overall	4057/7309	0.003	1.22 (1.07–1.40)	57%
	AML	2004/4456	0.16	1.16 (0.94–1.42)	63%
	ALL	985/1571	0.03	1.34 (1.03–1.74)	58%
	CML	472/456	0.79	1.04 (0.80–1.34)	0%
	Caucasian	2310/3710	0.02	1.13 (1.02–1.26)	40%
	East Asian	895/2300	0.45	1.13 (0.82–1.55)	62%
<i>GSTT1</i>	West Asian	852/1299	0.005	1.48 (1.12–1.95)	57%
	Overall	7886/13985	< 0.0001	1.53 (1.35–1.74)	67%
	AML	3640/6708	< 0.0001	1.70 (1.37–2.11)	75%
	ALL	2325/3796	0.003	1.41 (1.13–1.77)	62%
	CML	1155/2241	0.0008	1.71 (1.25–2.33)	68%
	Caucasian	4204/6946	< 0.0001	1.59 (1.33–1.90)	66%
	East Asian	1915/3638	0.07	1.24 (0.99–1.56)	63%
West Asian	1258/2296	< 0.0001	1.99 (1.68–2.37)	42%	

Abbreviations: OR, Odds ratio; CI, Confidence interval; NA, Not available; AML, Acute myeloid leukemia; ALL, Acute lymphoblastic leukemia; CML, Chronic myelogenous leukemia; CLL, Chronic lymphoblastic leukemia.

The values in bold represent there is statistically significant differences between cases and controls.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yexmp.2019.01.004>.

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