RESEARCH ARTICLE

Association between the MDM2 T309G Polymorphism and Leukemia Risk: a Meta-analysis

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Abstract

Several studies have suggested associations between MDM2 (mouse double minute 2 homolog) polymorphisms and leukemia risk, but they reported contradictory results. For better understanding of the effect of MDM2 T309G polymorphism on leukemia risk, we performed a meta-analysis. All eligible studies were identified through a search of PubMed, Web of Science, EMBASE, and Chinese Biomedical Literature (CBM) databases before May 2014. Assessment of associations between the MDM2 T309G polymorphism and leukemia risk was conducted by odds ratios (ORs) and 95% confidence intervals (95% CIs). Finally, a total of 11 publications covering 12 case-control studies with 2, 362 cases and 5, 562 controls concerning MDM2 T309G polymorphism with respect to leukemia were included in the meta-analysis. Significant associations were found between MDM2 T309G polymorphism and leukemia risk in four models in overall populations (G vs T: OR=1.29, 95% CI=1.11-1.49, *p*=0.001; GG vs TT: OR=1.67, 95% CI=1.21-2.30, *p*=0.002; GG vs TG/TT: OR=1.56, 95% CI=1.21-2.00, *p*=0.001; GG/TG vs TT: OR=1.28, 95% CI=1.05-1.57, *p*=0.015). In the sub-group analysis according to ethnicity, increased leukemia risks were observed in three genetic models among Asians but not Caucasians. In conclusion, the results of our meta-analysis suggest that the MDM2 T309G polymorphism can increase the risk of leukemia, especially among Asian populations.

Keywords: MDM2 - polymorphism - leukemia - meta-analysis

Asian Pac J Cancer Prev, **15 (16)**, 6767-6772

Introduction

Leukemia is a common malignant disease of hematopoietic systems, it is a malignant tumor of the hematopoietic system and cause by unbalanced hematopoietic cells proliferation and death, uncontrolled differentiation disorder, disruption and other mechanisms of apoptosis in the bone marrow and other hematopoietic tissues proliferate accumulation and infiltration of other tissues and organ (Estey, 2001; Jiang et al., 2014; Yan et al., 2014). Based on the speed of disease progression, leukemia can be divided into acute leukemia and chronic leukemia, while acute leukemia can be subdivided into acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL) according to cytogenetic analysis (Yan et al., 2014; Yan et al., 2014), then chronic leukemia can be divide into chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL) (Jiang et al., 2014). Although previous researches suggest that radiation, smoking, obesity and exposure to chemical carcinogens are considered to be risk factors (Finch, 2007; Bjork et al., 2009; Lichtman, 2010), the pathogenesis of leukemia is still not fully clarified (Yalcin et al., 2009). However, only a small proportion of people exposed to these environment and lifestyle risk factors developed leukemia, indicating that the host genetic factors might play an important role in the genesis of leukemia (Ross, 2008; Mullighan, 2010).

The mouse double minute 2 homolog (MDM2), which is a key negative regulator of the P53 tumor suppressor pathway, has been mapped to chromosome 12q13-14 (Picksley and Lane, 1993; Chen et al., 2014). The MDM2 protein plays a critical role in the regulation of p53 protein stability and functional, it regulates p53 activity through a negative feedback loop (Poyurovsky et al., 2010). A functional single nucleotide polymorphism (SNP) in the promoter region of MDM2, SNP T309G (rs2279744), was reported to affect MDM2 expression levels. Individuals who carrying the GG genotype of the MDM2 SNP309 polymorphism were found to increase MDM2 expression and thereby attenuates p53 activity (Bond et al., 2004; Qin et al., 2013). The polymorphism of MDM2 T309G is suggested to be associated with the risk of various human cancers (Peng et al., 2013; Chen et al., 2014; Chen et al., 2014; Gao et al., 2014; Tang et al., 2014; Wang et al., 2014). However, results concerning the relationship between MDM2 T309G polymorphism and leukemia risk were different or even contradictory (Ellis et al., 2008; Phang et al., 2008; Zenz et al., 2008; Chen et al., 2009;

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Do et al., 2009; Xiong et al., 2009; Phillips et al., 2010; Dong et al., 2012; Ebid et al., 2012; Chen et al., 2013; Liu et al., 2013). To derive a more precise estimation of the associations between the MDM2 T309G polymorphism and leukemia risk, we performed a meta-analysis of all available studies.

Materials and Methods

Search strategy

We conducted an extensive search to identify all available studies on the association between the MDM2 SNP309 polymorphism and leukemia risk in PubMed, Web of Science, EMBASE, and Chinese Biomedical Literature (CBM) databases up to May 01, 2014, using the following search strategy: ("leukemia" or "hematology" or "malignancy" or "neoplasm" or "cancer") and ("MDM2" or "Murine double minute 2") and ("polymorphism" or "polymorphisms" or "mutation" or "mutations" or "SNP"). There was no restriction on time period, sample size, population, language, or type of report. All eligible studies were retrieved and their references were manual checked to find more relevant articles.

Inclusion and exclusion criteria

Studies included in the meta-analysis were required to match the following criteria: (1) case-control study; (2) study evaluating the association between MDM2 SNP309 polymorphism and leukemia risk; (3) article provided sufficient data to estimate an odds ratio (OR) and 95% confidence interval (95% CI); (4) the control population did not contain malignant tumor patients. The following exclusion criteria were used for excluding studies: (1) not a case-control study; (2) the source of cases and controls, and other essential information were not provided; (3) reviews or reports; (4) only recruited the latest study if more than one studies from the same group occurred.

Data extraction

All the data were carefully extracted by two authors independently from all eligible publications according to the inclusion and exclusion criteria listed above. When encountered the conflicting evaluations, an agreement was reached following a discussion, if could not reached agreement, then a third author was consulted to resolve the debate. The following information was extracted from the included studies: name of first author; year of publication; country of origin; ethnicity of the population; genotyping methods; source of the control group; the types of leukemia and the distribution of genotypes of cases and controls. Different ethnicities were categorized as Asian and Caucasians, while different types of leukemia were categorized as AML, ALL, CML and CLL.

Statistical analysis

The Hardy-Weinberg equilibrium of controls for each study was tested by using a professional web-based program, $p>0.05$ suggests the controls was followed HWE balance. The pooled odds ratios (OR) with 95% confidence intervals (95% CI) were calculated to assess the strength of the association between the MDM2 T309G polymorphism and leukemia risk according to allele contrast (G vs T), homozygote (GG vs TT), heterozygote (TG vs TT), recessive (GG vs TG/TT), and dominant (GG/TG vs TT) models. The significance of the summary OR was determined with a Z-test and $p<0.05$ was considered as statistically significant.

The between-study heterogeneity was texted by using a Chi-square based Q statistic test. Heterogeneity was considered significant when $p<0.10$, and the random effects model was used to pool the results (DerSimonian and Laird method) (DerSimonian and Laird, 1986). Otherwise, the fixed-effects model (the Mantel-Haenszel method) was used (Mantel and Haenszel, 1959). Moreover, we also used I^2 value to test the effect of heterogeneity (Higgins and Thompson, 2002). If obvious heterogeneity was existed (I^2 value >50% or $p<0.10$), the overall estimate of risk was calculated by the random-effects model; If obvious heterogeneity was absent (I^2 value <50% or $p>0.10$), then the fixed-effects model was used. Publication bias was estimated by Egger's test ($p<0.05$ was considered representative of statistically significant publication bias) (Egger et al., 1997) and visual observation of funnel plot (Begg and Mazumdar, 1994), $p<0.05$ or an asymmetric plot suggested possible publication bias. All statistical manipulations were undertaken using the program STATA version 12.0 (Stata Corporation, College Station, TX), a p value <0.05 was considered statistically significant, except where otherwise specified.

Results

Study characteristics

According to the inclusion criteria defined above, a total of 11 publications (Ellis et al., 2008; Phang et al., 2008; Zenz et al., 2008; Chen et al., 2009; Do et al., 2009; Xiong et al., 2009; Phillips et al., 2010; Dong et al., 2012; Ebid et al., 2012; Chen et al., 2013; Liu et al., 2013) containing 12 case-control studies with 2362 cases and 5562 controls concerning MDM2 T309G polymorphism with respect to leukemia were included in the meta-analysis. The studies were published between 2008 and 2013, all of these studies were written in English. The study characteristics of the included in the meta-analysis were presented in Table 1, distribution of MDM2 T309G

Table 1. General Characteristics of Studies Included in The Meta-Analysis

First Author	Year	Country	Ethnicity	Method of Genotyping	Source of Control	Types of leukemia
Liu	2013	China	Asian	PCR-RFLP	PB	CML
Chen	2012	China	Asian	PCR–RFLP	PB	ALL
Ebid	2012	Egypt	Caucasus	PCR–RFLP	PB	AML
Dong	2011	China	Asian	PCR–RFLP	PB	CLL
Phillips	2010	USA	Caucasian	TaqMan	PB	AML
Do	2009	Wales	Caucasian	PCR–RFLP	PB	ALL
Xiong	2009	China	Asian	PCR	PB	AML
Chen	2009	China	Asian	PCR	PB	CML
Ellis	2008	USA	Caucasian	PCR–RFLP	PB	AML
Ellis	2008	UK	Caucasian	PCR–RFLP	PB	AML
Phang	2008	Singapore	Asian	PCR	PB	AML
Zenz	2008	Germany	Caucasian	DHPLC	PB	CLL

PCR-RFLP, PCR-restriction fragment length polymorphism; DHPLC, denaturing high performance liquid chromatography; PB, population based

genotypes among leukemia cases and controls were shown in Table 2. The 12 case-control studies consist of 6 Caucasians and 6 Asians, and 12 case-control studies comprised 2 ALL studies, 6 AML studies, 2 CLL studies and 2 CML studies.

Table 2. Distribution of MDM2 T309G Genotypes Among Leukemia Cases and Controls Included in The Meta-Analysis

First	cases			controls			HWE	
Author	TT	TG	GG	TT	TG	GG	P	X^2
Liu	25	58	33	44	89	29	0.17	1.9
Chen	37	81	56	119	173	64	0.93	0.01
Ebid	21	33	14	30	29	6	0.07	0.79
Dong	39	84	50	82	141	37	0.06	3.63
Phillips	176	178	78	194	229	62	0.19	0.66
Do	46	55	13	187	167	60	0.03	4.96
Xiong	32	123	76	35	68	25	0.43	0.61
Chen	6	20	17	29	83	26	0.02	5.71
Ellis	31	34	13	958	1027	286	0.68	0.17
Ellis	35	40	14	330	303	88	0.16	2.01
Phang	17	13	14	30	80	50	0.84	0.04
Zenz	239	299	79	445	470	150	0.15	2.06

HWE, Hardy – Weinberg equilibrium

Quantitative synthesis of data

Table 3 listed the main results of the meta-analysis of MDM2 T309G polymorphism and leukemia risk. Significant association were found between MDM2 T309G polymorphism and leukemia risk in four models in overall populations (G vs T: OR=1.29, 95% CI=1.11-1.49, *p*=0.001; GG vs TT: OR=1.67, 95% CI=1.21-2.30, P=0.002; Figure 1; GG vs TG/TT: OR=1.56, 95% CI=1.21-2.00, *p*=0.001; GG/TG vs TT: OR=1.28, 95% CI=1.05-1.57, *p*=0.015), indicating that individuals carrying a homozygous GG genotype may have an increased leukemia risk compared with those bearing a wild-type T allele.

In the sub-group analysis according to ethnicity, the results suggested that increased leukemia risks were observed in three genetic models among Asians (G vs T: OR=1.46, 95% CI=1.16-1.83, *p*=0.001; GG vs TT: OR=2.15, 95% CI=1.30-3.54, *p*=0.003; GG vs TG/TT: OR=2.03, 95% CI=1.63-2.53, *p*=0.001; GG/TG vs TT: OR=1.28, 95% CI=1.05-1.57, *p*=0.015) but not Caucasians (Figure 2). In the sub-group analysis according to type of leukemia, significantly association was found

Table 3. Results of meta-analysis for MDM2 T309G polymorphism and Leukemia risk

Comparison	Population	N	Test of association			Model	Test of heterogeneity	
			OR	95% CI	*P*		*P*	I2
G vs T	Overall	12	1.29	1.11-1.49	0.001	R	0.001	66.3
	Asian	6	1.46	1.16-1.83	0.001	R	0.021	62.4
	Caucasians	6	1.15	1.00-1.21	0.047	F	0.454	0
	CML	2	1.49	1.13-1.98	0.005	F	0.428	0
	ALL	2	1.34	0.83-2.12	0.237	R	0.016	82.8
	AML	6	1.22	0.98-1.53	0.079	R	0.016	64.2
	CLL	2	1.27	0.83-1.96	0.27	R	0.006	66.3
GG vs TT	Overall	12	1.67	1.21-2.30	0.002	R	0	70.2
	Asian	6	2.15	1.30-3.54	0.003	R	0.008	68.2
	Caucasians	6	1.2	0.98-1.46	0.082	F	0.234	26.7
	CML	2	2.31	1.29-4.14	0.005	F	0.484	0
	ALL	2	1.61	0.52-5.02	0.412	R	0.008	86
	AML	6	1.56	0.98-2.48	0.064	R	0.013	65.5
	CLL	2	1.62	0.57-4.60	0.362	R	0	90.2
TG vs TT	Overall	12	1.16	0.96-1.40	0.129	R	0.029	48.8
	Asian	6	1.14	0.74-1.75	0.567	R	0.009	67.2
	Caucasians	6	1.11	0.96-1.28	0.15	F	0.349	10.4
	CML	2	1.15	0.69-1.92	0.588	F	0.979	0
	ALL	2	1.42	1.03-1.95	0.03	F	0.717	0
	AML	6	1.04	0.68-1.55	0.849	R	0.003	71.9
	CLL	2	1.2	0.99-1.45	0.071	F	0.831	0
GG vs TG/TT	Overall	12	1.56	1.21-2.00	0.001	R	0.002	63.3
	Asian	6	2.03	1.63-2.53	0	F	0.412	0.7
	Caucasians	6	1.14	0.94-1.37	0.207	R	0.092	47.1
	CML	2	2.12	1.35-3.34	0.001	F	0.363	0
	ALL	2	1.32	0.47-3.69	0.596	R	0.007	86.2
	AML	6	1.54	1.23-1.93	0	F	0.617	0
	CLL	2	1.45	0.54-3.90	0.456	R	0	91.9
GG/TG vs TT	Overall	12	1.28	1.05-1.57	0.015	R	0.005	59.3
	Asian	6	1.38	0.89-2.16	0.153	R	0.003	72.7
	Caucasians	6	1.13	0.99-1.29	0.072	F	0.558	0
	CML	2	1.43	0.88-2.32	0.147	F	0.737	0
	ALL	2	1.51	1.12-2.03	0.007	F	0.166	48
	AML	6	1.17	0.79-1.73	0.447	R	0.001	75.1
	CLL	2	1.2	1.00-1.45	0.048	F	0.18	44.3

OR, odds ratio; CI, confidence interval; F, fixed effects model; R, random effects model

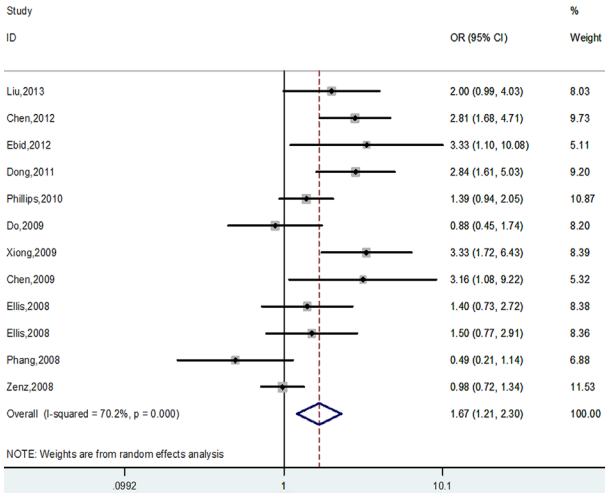

Figure 1. The Forest Plot Describing The Meta-Analysis under homozygous Model for The Association between MDM2 T309G Polymorphism and Leukemia Risk in Overall Populations (GG vs TT)

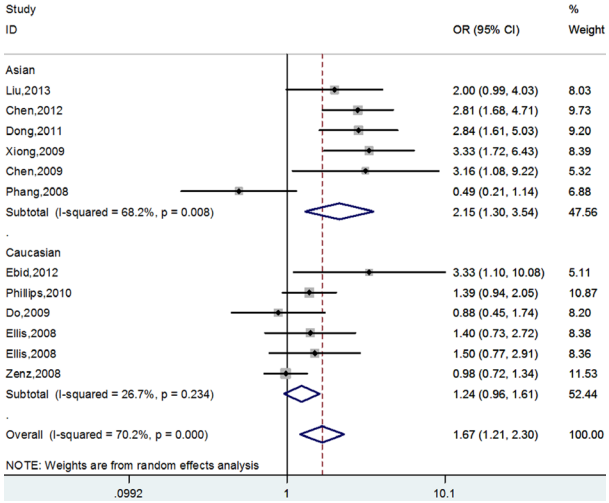

Figure 2. The Forest Plot Describing The Meta-Analysis Sub-Group Analysis Base on Ethnicity under Homozygous Model for The Association between MDM2 T309G Polymorphism and Leukemia Risk (GG vs TT)

between MDM2 T309G polymorphism and CML (G vs T: OR=1.49, 95% CI=1.13-1.98, p=0.005; GG vs TT: OR=2.31, 95% CI=1.29-4.14, p=0.005; GG vs TG/TT: OR=2.12, 95% CI=1.35-3.34, p=0.001), ALL (TG vs TT: OR=1.42, 95% CI=1.03-1.95, p=0.030), AML (GG vs TG/TT: OR=1.54, 95% CI=1.23-1.93, p=0.000) and CLL (GG/TG vs TT: OR=1.20, 95% CI=1.00-1.45, p=0.048) (Figure 3 and Figure 4).

Heterogeneity analysis and sensitive analysis

As shown in Table 3, there was significant between-study heterogeneity in overall populations. Therefore, the random effect model was utilized to evaluate the relationship of MDM2 T309G polymorphism and leukemia risk. Since the substantial heterogeneity among these studies in overall comparisons, we assessed the source of heterogeneity by ethnicity, subsequently, heterogeneity disappeared in subgroups of Caucasian subjects (I^2<50%, p>0.1).

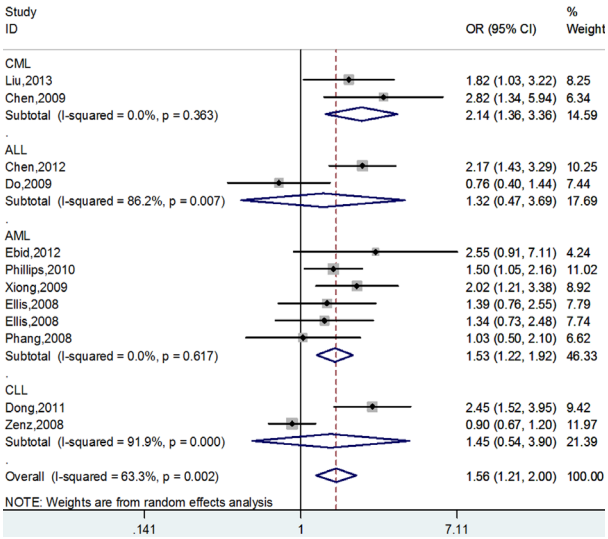

Figure 3. The Forest Plot Describing The Meta-Analysis Sub-Group Analysis Base on Type of Leukemia under Recessive Model for The Association between MDM2 T309G Polymorphism and Leukemia Risk (GG vs GT/TT)

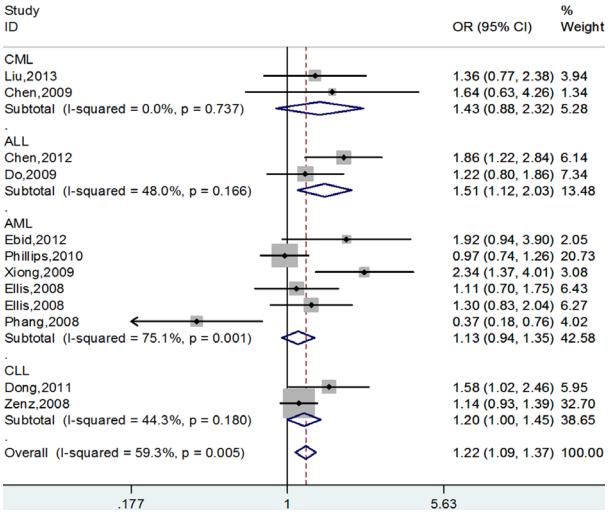

Figure 4. The Forest Plot Describing The Meta-Analysis Sub-Group Analysis Base on Type of Leukemia under Dominant Model for The Association between MDM2 T309G Polymorphism and Leukemia Risk (GG/TG vs. TT)

We selected two articles whose genetic distributions in controls exhibited significant failure to follow HWE, but the deviation might contribute to any bias, and the significances of data in all genetic models were also not statistically changed. We also evaluate the stability of the overall results by sequential remove individual studies. The result of sensitive analysis shows that no single study could influence the overall results qualitative (data not shown), indicating robustness and reliability of our results.

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias. The shape of the funnel plot did not suggest any evidence of obvious asymmetry (Figure 5). Similarly, the results revealed the absence of publication bias (p>0.05, data not shown).

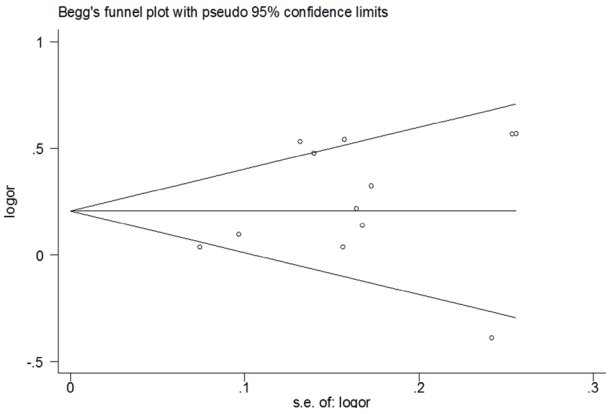

Figure 5. Begg Funnel Plot for Publication Bias Test for The Association between MDM2 T309G Polymorphism and Leukemia Risk under Homozygous Model for The Association between MDM2 T309G Polymorphism and Leukemia Risk (GG vs TT). Each point represents a separate study for the indicated association. Log [OR], natural logarithm of OR. Horizontal line means effect size.

Discussion

Leukemia is a type of malignant clonal hematopoietic stem cell disorders with a bad prognosis (Estey, 2001). According to the speed of onset, leukemia can be divided into acute leukemia and chronic leukemia (Vardiman et al., 2009). Acute leukaemia is an extremely heterogeneous malignant disease, and acute leukemia can be subdivided into acute lymphoid leukemia (ALL) and acute myeloid leukemia (AML) according to cytogenic analysis (Vardiman et al., 2009). Acute lymphoblastic leukemia (ALL) is more common in children, which comprises over 80% of all the acute leukemia. It is estimated that approximately 33.6 in every 1, 000, 000 children under 15 years old will develop ALL. While acute myeloid leukemia (AML) is the most common form of acute leukemia in adults as well as in children (Gamazon et al., 2013), it causing immature myeloid precursors to accumulate, and resulting in an estimated 13, 330 cases and an estimated 8, 950 deaths in the United States in 2010 (Wang et al., 2013). But unfortunately, the exact pathological mechanism of leukemia is still unclear recently. There are several studies published to assess the associations of MDM2 T309G polymorphism with the risk of leukemia, but they reported contradictory results and failed to confirm a strong and consistent association (Ellis et al., 2008; Phang et al., 2008; Zenz et al., 2008; Chen et al., 2009; Do et al., 2009; Xiong et al., 2009; Phillips et al., 2010; Dong et al., 2012; Ebid et al., 2012; Chen et al., 2013; Liu et al., 2013). In order to evaluate the evidence between the associations of MDM2 T309G polymorphisms with leukemia risk, we conducted this meta-analysis.

Total of 11 publications (Ellis et al., 2008; Phang et al., 2008; Zenz et al., 2008; Chen et al., 2009; Do et al., 2009; Xiong et al., 2009; Phillips et al., 2010; Dong et al., 2012; Ebid et al., 2012; Chen et al., 2013; Liu et al., 2013) containing 12 case-control studies with 7924 individuals (2362 cases and 5562 controls) were included in our meta-analysis. The results showed that MDM2 T309G polymorphism was associated with increased risk of leukemia (Table 3). There were several reports suggest that the polymorphism of MDM2 T309G is associated with the risk of sarcoma and endometrial, hepatocellular, colorectal cancer, breast cancer, malignant bone tumor, osteosarcoma and gastric cancer (Peng et al., 2013; Chen et al., 2014; Chen et al., 2014; Gao et al., 2014; Tang et al., 2014; Wang et al., 2014). By contrast, there was a study reported that the MDM2 SNP309 G allele probably acts as an important HNSCC protective factor in Caucasians, no association exists in Asians (Liu et al., 2011). This shows that MDM2 T309G variation might play different roles in different cancers.

Ebid's article entitled "MDM2 T309G has a synergistic effect with P21 ser31arg single nucleotide polymorphisms on the risk of acute myeloid leukemia" hat published on APJCP in 2012, the article through analysis 77 diagnosed AML patients by PCR experiments, the results is high reliability, and the electrophoresis is intuitive, the results of Ebid's article suggested that MDM2 T309G polymorphism might be genetic susceptibility factors in the pathogenesis of AML, which consistent with our conclusions.

Subgroup analysis based on ethnicity indicated that MDM2 T309G polymorphism was a risk factor for leukemia in Asians but not for Caucasians, suggest ethnic different in the occurrence of leukemia is exist, gene polymorphisms could result in ethnic-specific susceptibility to leukemia. In addition, environmental factors like birthplace and socioeconomic status may play important roles in leukemogenesis, this is the possible reason of exist of racial disparities.

The heterogeneity plays an important role in a meta-analysis. Significant heterogeneity was observed in our meta-analysis in overall populations. To finding the source of heterogeneity, we used subgroup analysis. In the subgroup analysis by ethnicity, we found heterogeneity was disappeared in Caucasians. This may explain by that different ethnicity has different life style, exposed to different risk factors and the levels of exposed to risk factors is also differ, this may cause the heterogeneity.

Publication bias is also an important aspect which may have a negative effect on a meta-analysis. In our meta-analysis, both Funnel plot and Egger's test were used to test the publication bias of the included studies. As a result, both the shape of funnel plot and statistical results show no obvious publication bias, this suggests that the publication bias have little effect on the results in our study and the results of our meta-analysis are relatively stable.

There are some limitations of this meta-analysis should be pointed. First, the number of studies and the number of samples included in the meta-analysis were relatively small. Secondly, only published and English studies were included in this work, thus, publication and potential English language bias may have occurred. Thirdly, subgroup analyses according to age, gender, radiation exposure, histological types and other elements haven't been performed in the study because no sufficient relevant data available in the primary studies. So, more studies with larger sample size and providing detailed information should be performed to assess the effect of MDM2 T309G polymorphism on leukemia risk.

In summary, the results of our meta-analysis suggest that the MDM2 T309G polymorphism can increase the risk of leukemia, especially among Asian populations. Considering the limited sample size and ethnicities included in the meta-analysis, further large scaled and well-designed studies are needed to confirm our results.

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