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MDM2 309 T/ G Polymorphism Is Associated With Acute Myeloid Leukemia: A Meta-Analysis

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Abstract

Objective: The 309 T/G polymorphism of murine double minute 2 (*MDM2*) gene is associated with acute myeloid leukemia, but conflicting results have been reported. In this study, we performed a meta-analysis to estimate the association between *MDM2* 309 T/G polymorphism and acute myeloid leukemia risk.

Methods: Electronic search of PubMed was conducted to select case-control studies that contain available genotype frequencies of the *MDM2* 309 T/G polymorphism. Pooled Odds Ratio (OR) with 95% Confidence Interval (CI) was used to assess the strength of the association.

Results: Six case-control studies, which consist of 1121 cases and 3974 controls, were identified. After pooling all the eligible studies in the meta-analysis, we found that the *MDM2* 309 T/G polymorphism was significantly associated with risk of acute myeloid leukemia (Recessive model G/G versus T-carriers: OR=1.738, 95% CI: 1.424 – 2.122, *p= 0.000*; additive model G versus T: OR = 1.298, 95% CI: 1.159–1.453, *p= 0.000*). Symmetrical funnel plot derived from Egger's test *(P=0.970)* and Begg's test *(P=0.851)* indicated the lack of publication bias.

Discussion: This meta-analysis suggests that individuals with T/G or G/G genotype of *MDM2* SNP309 were significantly associated with increased acute myeloid leukemia risk. To draw comprehensive and true conclusions, well-designed studies with large sample sizes and representing different ethnicities are required.

Keywords: *MDM2* T309G; meta-analysis; acute myeloid leukemia

Introduction

Acute Myeloid Leukemia (AML) is a cancer that starts in the bone morrow and is characterized by rapid growth of abnormal blood cells, which ultimately replace healthy hematopoietic cells and blood elements [1]. Patients with AML show higher risks of infections and bleeding than healthy individuals [2]. The majority of patients with AML possess genetic alterations, which disturb the normal mechanisms of the growth and maturation of blood cells [3]. Thus far, well-designed studies on genes related to AML remain insufficient.

Susceptibility genes in AML have been studied. *MDM2*, a disease-susceptibility gene, is over expressed in many human cancers [4]. *MDM2*, as a ubiquity in E3 ligase, can negatively reduce the stability of p53 [5]. A single nucleotide polymorphism (T-G exchange at nucleotide 309 in the first intron) located in the core promoter of the *MDM2* gene can increase the affinity of the transcription factor *SP1* to the *MDM2* core promoter; this phenomenon up regulates *MDM2* expression, resulting in\attenuated *p53* stress responses and enhanced tumor transformation and resistance to apoptosis [6]. Previous studies suggested that over expression of *MDM2* is present in half of the total number of patients with AML [7]. Therefore, we hypothesize that the *MDM2* gene can be potentially used as a clinical biomarker in AML.

Several studies were conducted to investigate the potential association between the *MDM2* 309 T/G polymorphism and AML risk in humans [2,8,9]. However, published data show conflicting results. Therefore, we conducted this meta-analysis to quantitatively assess the effect of the *MDM2* 309 T/G polymorphism on the risk of AML.

Materials and Methods

Publication search

PubMed was searched using the terms '*MDM2 309*', 'polymorphism' and 'acute myeloid leukemia'. Case-control studies containing available genotype frequencies of *MDM2* 309 were chosen. Additional studies were identified by a manual search of the references of original studies.

Statistic analysis

For control group of each study, the observed genotype frequencies of the *MDM2* 309 T/G polymorphism were assessed for Hardy–Weinberg equilibrium using the $\chi 2$ test. The strength

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of association between309 T/G polymorphism of *MDM2* gene and acute myeloid leukemia was accessed by calculating crude odds ratios (ORs) with 95% Confidence Intervals (CIs). The pooled ORs were performed for dominant model (G/G+G/T vs. TT), and recessive model (G/G vs. G/T+T/T), additive genetic model (G vs. T) respectively. Heterogeneity assumption was checked by a chi-square based Q-test. A P-value of <0.05 for the Q-test indicated a lack of heterogeneity among the studies, the summary OR estimate of each study was calculated by the random effects model [10]. The potential for publication bias was examined by a Begg's test and Egger's linear regression test (P<0.05 considered representative of statistical significance) [11]. All statistical analyses were performed with Stata software (version9.0; Stata Corporation, College Station, TX).

Result

Eligible studies

We identified 6 case–control studies on the association between *MDM2* 309 T/G polymorphism and acute myeloid leukemia, which including 1121acute myeloid leukemia cases and 3974controls.These data were used in our meta-analysis (Table 1). The distribution of genotypes in the controls of all the studies was in agreement with Hardy-Weinberg equilibrium.

Meta-analysis

The results of the association between the *MDM2* 309 T/G polymorphism and acute myeloid leukemia and the heterogeneity test were shown in Table 2. As shown in Figure 1 and Figure 2, the recessive model (G/G vs. G/T+T/T) and additive model (G vs. T) showed a significant association with acute myeloid leukemia risk (Recessive model G/G vs. T - carriers: OR = 1.738, 95% CI: 1.424 ~ 2.122, *p= 0.000*; additive model G vs. T: OR=1.298, 95% CI: 1.159 ~ 1.453, *p= 0.000*, Table 2, Figure 1, Figure 2. As shown in Figure 3, there is no significant association was found in dominant model (G/G+G/T vs. T/T: OR = 1.285, 95% CI: 0.988 ~ 1.669, *p= 0.061*, Table 2, Figure 3

Publication bias

Funnel plot and Egger's test were done to estimate the publication bias of literatures. The results of Egger's test provided statistical evidence for funnel plot symmetry (for G vs. T: *P=0.128*, GG vs. G/T+T/T: *P = 0.970*) (Table 2), suggesting the absence of publication bias.

Discussion

The p53 pathway plays a significant role in the prevention of tumor formation, and *MDM2* is an ubiquitin E3 ligase that negatively regulates the stability of p53 [5]. The proper regulation of *MDM2* levels is vital for TP53 tumor suppression. Previous studies revealed that SNP309 G/G cell lines expressed higher levels of *MDM2* (eightfold mRNA and fourfold protein levels) than TT cell lines; moreover, intermediate protein levels (1.9-fold) were observed in heterozygous (T/G) cell lines [6]. Studies found that the *MDM2* 309 T/G polymorphism is associated with increased risk of many cancers [12]. Observed that patients with the *MDM2* 309 T/G polymorphism exhibit higher risk of esophageal squamous cell carcinoma compared with other genotype groups [13]. Found that the*MDM2* 309 T/G polymorphism is associated with increased risk of bladder cancer. Anuradh et al. [14] found that presence of *MDM2* 309 G/G genotype at promoter region increased *MDM2* gene expression, hence inhibiting the p53 stress response resulting in leukemic cell transformation. Further, their study indicated that the over expression of *MDM2* may lead to cell vulnerability to chemotherapy due to p53 degradation. Therefore, the *MDM2* 309 T/G polymorphism could be associated with AML risk, with the 309 G allele as the risk factor.

Previous studies on associations between *MDM2* SNP309 and AML risk provided inconsistent results, and most of these studies involved less than a few hundred AML cases [14,15,16,8,9], which is insufficient to reliably assess any genetic effects. As such, we performed this meta-analysis to provide up-to-date clinical evidence for adopting *MDM2* SNP309 as a prognostic biomarker in patients with AML. Based on six case-control studies on *MDM2* SNP309 and AML, the *MDM2* 309 G allele probably acts as an AML risk factor. We found that individuals with the *MDM2* 309G allele (G/G or T/G) showed significantly higher risk of AML compared with those with the reference *MDM2* 309T/T genotype.

All the results in this study should be considered prudently

Table 1: The distribution of the *MDM*2 309 T/G polymorphism for cases and controls

Author	year	Case			Control			P[a]
		TT	TG	GG	TT	TG	GG	
Nathan A. Ellis(study in UK)	2008	31	34	13	958	1027	286	0.676
Nathan A. Ellis(study in USA)	2008	35	40	14	330	303	88	0.156
Xiong, X	2009	32	123	76	35	68	25	0.435
Phillips, C. L	2010	176	178	78	194	229	62	0.661
Gamal T Ebid	2012	21	33	14	30	29	6	0.789
Anuradh Cingeetham	2015	50	76	97	73	150	81	0.828

a:p value for Hardy–Weinberg equilibrium in control group.

Table 2: ORs and 95% CI for acute myeloid leukemia risk and the *MDM2* 309 T/G polymorphism under different genetic models.

genetic model	pooled OR [95% CI] p	Heterogeneity	Begg's Test	Egger's Test
		p-value	p-value	p-value
Additive (G vs. T)	1.298[1.159~1.453]<0.001	0.111	0.573	0.128
Recessive (G/Gvs. T-carriers)	1.738[1.424~2.122]<0.001	0.577	0.851	0.97
Dominant (G-carriers vs. T/T)	1.285[0.988~1.669]0.061	0.062	0.039	0.004

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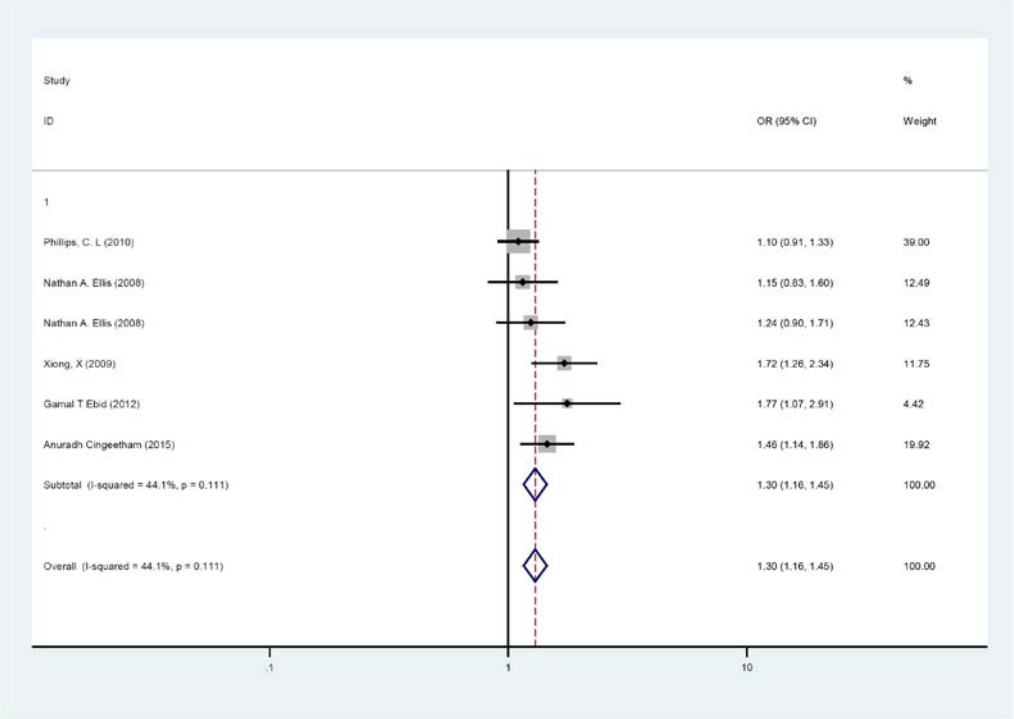

Figure 1: Forest plot of ORs of AMLG allele when compared to the T allele (Additive model) .The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI.

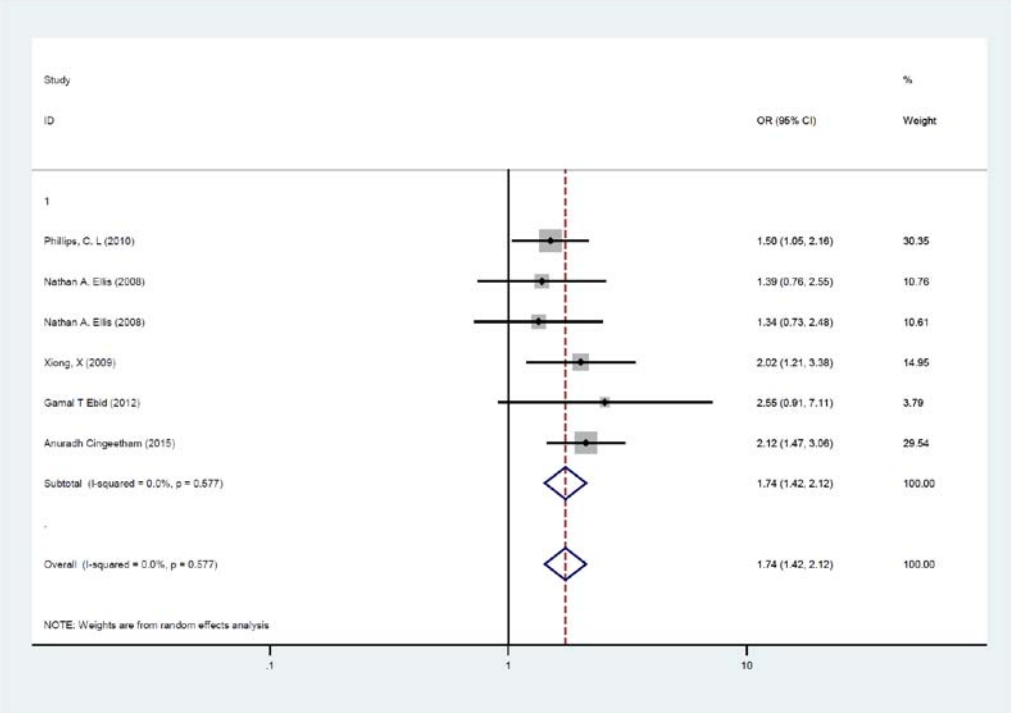

Figure 2: Forest plot of ORs of AMLG/G genotype when compared to the T allele carriers (G/T + T / T) (Recessive model). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and95% CI.

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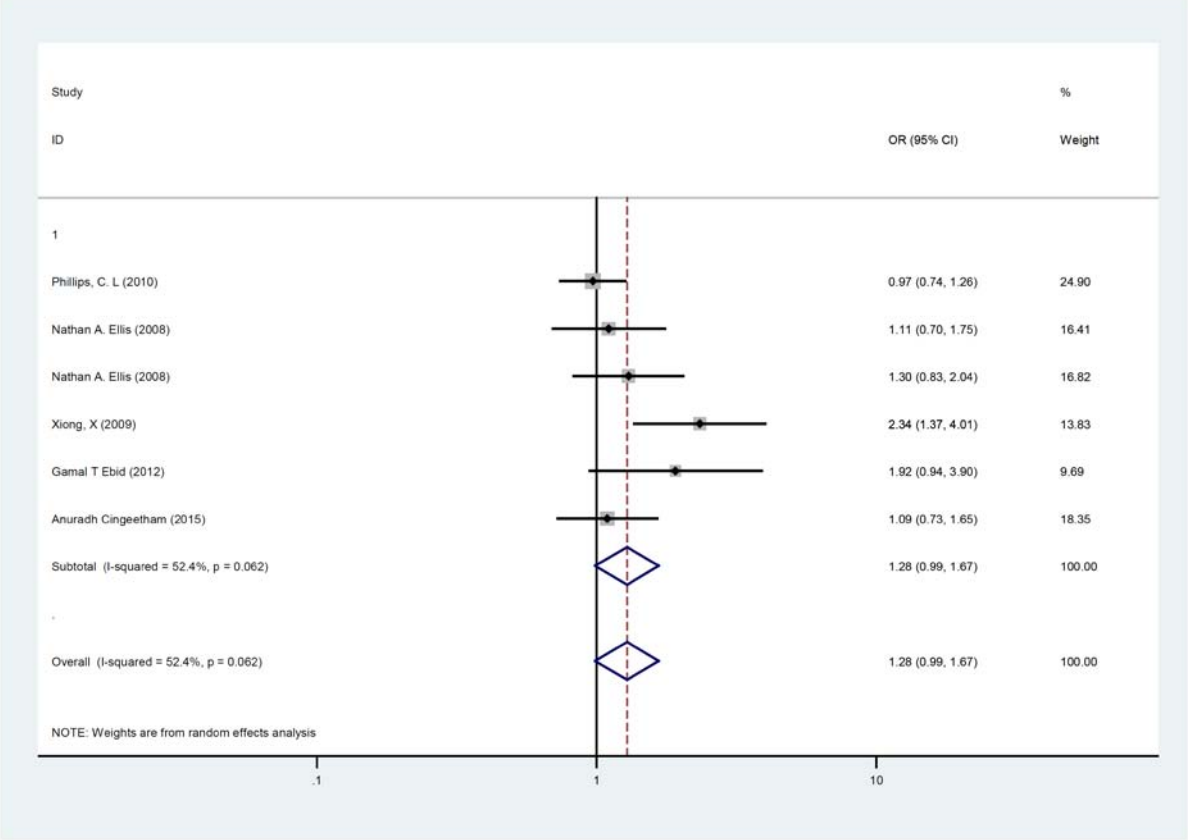

Figure 3: Forest plot of ORs of AMLG allele carriers (G/G +G/T) when compared to the T/T genotype (Dominant model). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and95% CI.

because of several limitations. The first limitation is the lack of adjustment according to detailed individual data, such as age, sex, and lifestyle. Second, the total sample size used in our meta-analysis is insufficient to draw a conclusion of the relationship between the *MDM2* 309 T/G polymorphism and AML risk. To achieve a more reliable conclusion, further analysis must be performed using adjusted individual data and a large sample size without significant publication bias.

In conclusion, this meta-analysis, which consists of six eligible studies (1121 cases and 3974 controls in all), indicates that *MDM2*309 G/G and T/G may act as an AML risk factor. Although some limitations exist, our meta-analysis can provide valuable information for studying the relationship between *MDM2*309 T/G polymorphism and AML.

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Conflict of interest

The authors declare no competing financial interests.

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