Introduction

Acute Myeloid Leukemia (AML) is a cancer that starts in the bone marrow 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 χ2 test. The strength
of association between 309 T/G polymorphism of MDM2 gene and acute myeloid leukemia was assessed 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 1121 acute myeloid leukemia cases and 3974 controls. 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<0.001; 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

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Table 1: The distribution of the MDM2 309T/G polymorphism for cases and controls

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Case</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nathan A. Ellis</td>
<td>2008</td>
<td>31</td>
<td>13</td>
<td>0.676</td>
</tr>
<tr>
<td>Nathan A. Ellis</td>
<td>2008</td>
<td>35</td>
<td>14</td>
<td>0.156</td>
</tr>
<tr>
<td>Xiong, X</td>
<td>2009</td>
<td>32</td>
<td>76</td>
<td>0.435</td>
</tr>
<tr>
<td>Phillips, C. L</td>
<td>2010</td>
<td>176</td>
<td>78</td>
<td>0.661</td>
</tr>
<tr>
<td>Gamal T Ebid</td>
<td>2012</td>
<td>21</td>
<td>30</td>
<td>0.789</td>
</tr>
<tr>
<td>Anuradh Cingeetham</td>
<td>2015</td>
<td>50</td>
<td>76</td>
<td>0.828</td>
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</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Genetic model</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>p-value</th>
<th>p-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additive</td>
<td>G vs. T</td>
<td>1.298 [1.159 ~ 1.453]</td>
<td>&lt;0.001</td>
<td>0.573</td>
<td>0.128</td>
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<tr>
<td>Recessive</td>
<td>G/G vs. T - carriers</td>
<td>1.738 [1.424 ~ 2.122]</td>
<td>&lt;0.001</td>
<td>0.851</td>
<td>0.97</td>
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<tr>
<td>Dominant</td>
<td>G-carriers vs. T/T</td>
<td>1.285 [0.988 ~ 1.669]</td>
<td>0.061</td>
<td>0.039</td>
<td>0.004</td>
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</table>
MDM2 309 T/G Polymorphism Is Associated With Acute Myeloid Leukemia: A Meta-Analysis

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 and 95% 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 \textit{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 \textit{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 \textit{MDM2}309 T/G polymorphism and AML.

**Acknowledgements**

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**Conflict of interest**

The authors declare no competing financial interests.

**References**


