Association of SET8 rs16917496 polymorphism with cancer risk: a meta-analysis

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Abstract: Background: The association of the mir-502 binding site in the 3’untranslated region of SET8 rs16917496 polymorphism with cancer risk has been explored by previous studies, but the result is still uncertain. Materials and methods: We carried out an updated meta-analysis of fourteen articles (containing 2974 cases and 3142 controls) to obtain an assessment of the influence of the SET8 rs16917496 polymorphism with risk of cancer. Results: Overall, the results revealed that the SET8 rs16917496 polymorphism was statistically associated with the risk of cancer under heterozygous model (OR = 1.13, 95% CI: 1.01-1.27, P = 0.03), though no evidence of association was found of rs16917496 polymorphism with cancer risk in other four model (allele model: OR = 1.00, 95% CI: 0.85-1.18, P = 0.975; recessive model: OR = 0.85, 95% CI: 0.60-1.19, P = 0.346; dominant model: OR = 1.07, 95% CI: 0.87-1.32, P = 0.495; homozygous model: OR = 0.84, 95% CI: 0.56-1.26, P = 0.398). After stratifying the overall population into subgroup sorted by ethnicity, no significant correlation was observed of the rs16917496 with cancer risk among both Caucasian and Asian populations. Conclusion: These result indicated that the SET8 rs16917496 was a genetic susceptible risk factor for cancer, and rs16917496 could be used as a biomarker for estimating cancer risk in overall population.

Keywords: SET8, rs16917496, cancer risk, polymorphism

Introduction

MicroRNAs (miRNAs) are RNA molecules that are similar twenty-two nucleotides in length and act as post-transcriptional regulators of mRNA expression by forming base pairs with the thirty untranslated region (UTR) of a target mRNA to repress translation [1, 2]. More than seven hundred miRNAs have been found in humans, and these miRNAs are responsible for regulating at least thirty percent of protein-coding gene expression [3]. Specifically, miRNAs target nucleotides 2-8 at the 5’end, which is known as the ‘seed region’ of the 3’UTR of the target messenger RNA (mRNA). As a result of silence, the perfect complementarity of the miRNA and its target mRNA sequence can reduce the standards of protein [4, 5]. In human genome, single nucleotide polymorphism (SNP) is the most ordinary type of genetic variation.

SET8 (also known as SETD8, PR-SET7, KMT5A), situated in chromosome 12q24.31, is a special histone H4 lysine 20 methyltransferase (H4K20me1) [6]. Previous research results show that polymorphism rs16917496 C/T located in the binding site of miR-502 in SET8 3’UTR regulates SET8 expression and contributes to several cancers [7-11]. Hence, this locus might be associated with cancer and considered as a candidate-susceptible locus for cancer risk, but these studies displayed contradictory conclusions.

In our study, we comprehensively searched eligible researches and conducted a meta-analysis to explore the precise relationship of SET8 rs16917496 with cancer risk.

Materials and methods

The following retrieval expressions, Identification of eligible studies (“8q24” or “rs16917496” or “SET8”) and (cancer or carcinoma) and (genetic variant or polymorphism) were used to
search relevant studies in databases of PubMed, Science Direct, EMBase, Web of Science, CNKI and CBM up to December 2017 in any language.

Two investigators (Jiang and Zhu) were simultaneously identified title and abstract of each searched study to obtain relevant studies. Then, eligible study was carefully identified from relevant study by reading the full text.

Inclusion and exclusion criteria

A study was chosen to be included in this meta-analysis if it meet all of the following criteria: 1) studies assessing the correlation of rs16917496 polymorphism with cancer risk; 2) original case-control studies about the association of SET8 rs16917496 with cancer risk; 3) studies with abundant genotype distribution data for calculation of combined odds ratios (OR) and ninety-five percent confidence intervals (CI). When researches did not show the details regarding the genotype distribution in each group, the homologous authors of the research were touched for detailed data. Whereas, review, meta-analysis, letter, comment, communication, and single group-designed study, duplicative data published study or low quality score assessed study were excluded from our study.

Data extraction

The following baseline characteristics data were collected from eligible research: The first author’s name, published year, country, ethnicity, case and control group, genotyping method, genotype data as well as OR and 95% CI. Two investigators (Jiang and Zhu) independently assessed the quality score of eligible articles and collected the data. Any assessment results with disagreement were dealt with by discussion.

Statistics analysis

Meta-analysis was performed using Stata software (Version 11.0, College Station, TX, USA). The overall effect was established by Z test and the significantly difference was considered when P value was lower than 0.05. The crude OR and 95% CI were used as common measurements for evaluating the intensity of the correlation of rs16917496 polymorphism with cancer risk. The heterogeneity test was evaluated using Q test and estimated I²>50% was set up to consider significant difference [6]. The fixed model was used when the I²<50% [7], otherwise the random model was choose to evaluate the finally results [8]. Sensitivity analysis was performed to evaluate the stability of meta-analysis by omitting the relevant studies successively. The possible publication bias was evaluated by the Begg's funnel plot and P<0.05 was considered as the existence of publication bias [12].

Results

Figure 1 have list the detailed screening process. A total of 59 possible related studies were retrieved based on our inclusion criteria, of which 14 articles were excluded because of they are not related to cancer and SET8 rs16917496 polymorphism. Excluding the studies of other genes or other diseases, meta-analysis, studies lacking enough available data and failed to obtain related information from the homologous authors. Consequently, 14 articles including 14 case-control studies met our
rs16917496 polymorphism in SET8 gene

Table 1. Characteristics of eligible studies concerning rs16917496 and cancer risk in the present meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Cancer type</th>
<th>Case</th>
<th>Control</th>
<th>Genotyping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang</td>
<td>2012</td>
<td>China</td>
<td>Asian</td>
<td>Epithelial ovarian cancer</td>
<td>160</td>
<td>155</td>
<td>27</td>
</tr>
<tr>
<td>Guo</td>
<td>2011</td>
<td>China</td>
<td>Asian</td>
<td>Hepatocellular carcinoma</td>
<td>72</td>
<td>50</td>
<td>11</td>
</tr>
<tr>
<td>Ding</td>
<td>2012</td>
<td>China</td>
<td>Asian</td>
<td>Small-cell lung cancer</td>
<td>22</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Yang1</td>
<td>2014</td>
<td>China</td>
<td>Asian</td>
<td>Cervical Cancer</td>
<td>44</td>
<td>42</td>
<td>28</td>
</tr>
<tr>
<td>Hashemi</td>
<td>2014</td>
<td>Iran</td>
<td>Caucasian</td>
<td>Childhood acute lymphoblastic leukemia</td>
<td>3</td>
<td>59</td>
<td>13</td>
</tr>
<tr>
<td>Yang2</td>
<td>2014</td>
<td>China</td>
<td>Asian</td>
<td>Non-small cell lung cancer</td>
<td>95</td>
<td>57</td>
<td>12</td>
</tr>
<tr>
<td>Zhang</td>
<td>2017</td>
<td>China</td>
<td>Asian</td>
<td>Clear cell renal cell carcinoma</td>
<td>79</td>
<td>47</td>
<td>14</td>
</tr>
<tr>
<td>Mosallayi</td>
<td>2017</td>
<td>Iran</td>
<td>Caucasian</td>
<td>Colorectal Cancer</td>
<td>58</td>
<td>80</td>
<td>32</td>
</tr>
<tr>
<td>Zhao</td>
<td>2013</td>
<td>China</td>
<td>Asian</td>
<td>Esophageal cancer</td>
<td>32</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Song</td>
<td>2010</td>
<td>China</td>
<td>Asian</td>
<td>Breast cancer</td>
<td>504</td>
<td>491</td>
<td>115</td>
</tr>
<tr>
<td>Li</td>
<td>2017</td>
<td>China</td>
<td>Asian</td>
<td>Epithelial ovarian cancer</td>
<td>43</td>
<td>52</td>
<td>5</td>
</tr>
<tr>
<td>Gao</td>
<td>2017</td>
<td>China</td>
<td>Asian</td>
<td>Clear cell renal cell carcinoma</td>
<td>66</td>
<td>34</td>
<td>10</td>
</tr>
<tr>
<td>Barjui</td>
<td>2017</td>
<td>Iran</td>
<td>Caucasian</td>
<td>Breast cancer</td>
<td>38</td>
<td>183</td>
<td>19</td>
</tr>
<tr>
<td>Narouie</td>
<td>2017</td>
<td>Iran</td>
<td>Caucasian</td>
<td>Prostate cancer</td>
<td>29</td>
<td>94</td>
<td>46</td>
</tr>
</tbody>
</table>

selection criteria [9-11, 13-17, 23-26]. The baseline characteristics of each including article are shown in Table 1. While studies disagreeing with HWE containing three were shown in bold.

Meta-analysis results assessed the correlation of rs16917496 polymorphism with cancer risk through analyzing data obtained from 14 articles, containing 2974 cases and 3142 controls. The results of the heterogeneity test and meta-analysis for overall and subgroups shown in Figures 2-6 are summarized in Table 2. As shown in Table 2, the random model was choose to evaluate the allele model, recessive model, dominant model, homozygous model, the fixed model was choose to evaluate the heterozygous model. Table 2 demonstrated no correlation was observed in rs16917496 polymorphism and risk of cancer among overall population using allele model, recessive model, dominant model, homozygous model (allele model: OR = 1.00, 95% CI: 0.85-1.18, P = 0.975; recessive model: OR = 0.85, 95% CI:
rs16917496 polymorphism in SET8 gene

0.60-1.19, $P = 0.346$; dominant model: $OR = 1.07$, 95% CI: 0.87-1.32, $P = 0.495$; homozygous model: $OR = 0.84$, 95% CI: 0.56-1.26, $P = 0.398$), whereas significance correlation of the SET8 rs16917496 polymorphism with cancer risk among overall population was found in heterozygous model ($OR = 1.13$, 95% CI: 1.01-1.27, $P = 0.03$), rs16917496 polymorphism had no connection with cancer risk among Caucasian population in five genetic models (allele model: $OR = 1.14$, 95% CI: 0.77-1.68, $P = 0.506$; recessive model: $OR = 1.14$, 95% CI: 0.57-2.29, $P = 0.715$; dominant model: $OR = 1.04$, 95% CI: 0.44-2.48, $P = 0.929$; homozygous model: $OR = 0.90$, 95% CI: 0.27-2.99, $P = 0.863$; heterozygous model: $OR = 1.24$, 95% CI: 0.93-1.66, $P = 0.136$) and Asian population in five genetic models (allele model: $OR = 0.95$, 95% CI: 0.79-1.15, $P = 0.589$; recessive model: $OR = 0.75$, 95% CI: 0.49-1.14, $P = 0.173$; dominant model: $OR = 1.04$, 95% CI: 0.88-1.22, $P = 0.641$; homozygous model: $OR = 0.79$, 95% CI: 0.52-1.22, $P = 0.288$; heterozygous model: $OR = 1.11$, 95% CI: 0.99-1.26, $P = 0.085$).

**Heterogeneity**

As was shown in the Table 2 that obvious heterogeneities existed in overall meta-analysis is about the rs16917496 polymorphism and cancer risk. Heterogeneity may be drive from ethnicity, cancer type, genotyping method, gene model, environment and sample capacity. In the subgroup analysis and analysis of different gene models, heterogeneity obvious different, which suggested that ethnicity and different gene model analysis may be were sources of heterogeneity.

**Sensitivity analysis**

When omitting each article, the $P$ values of overall effect and ORs in comparison of genotype were similar in overall population and each ethnicity subgroups, suggesting that the results were stable in these groups.
Publication bias

Using Begg's test and funnel plot to evaluate publication bias. As shown in Table 2 and Figures 7-11. These results indicated that no publication bias was found in comparison the association of the mir-502 binding site in the 3' untranslated region of SET8 gene rs16917496 polymorphisms with cancer risk.

Discussion

In this study, according to 14 studies about the correlation of SET8 rs16917496 polymorphism with cancer risk, this meta-analysis offered strong evidence of connection of SET8 rs16917496 polymorphism with cancer risk. The results showed that the rs16917496 polymorphism was not statistically correlation with the risk of cancer under 4 genetic model (allele model, recessive model, dominant model, homozygous model), whereas rs16917496 was associated with increased susceptibility to cancer under heterozygous model. In subgroups analyses, and no correlation was found of rs16917496 with cancer risk in Caucasian and Asian populations under 5 genetic model. The influence of SET8 rs16917496 polymorphism on various types of cancer has been considered. Ding et al. [11] indicated no correlation of SET8 rs16917496 polymorphism with small-cell lung cancer risk, In contrast, Yang et al. [15] found that SET8 rs16917496 was associated with an increased risk of non-small cell lung cancer. The SET8 rs16917496 is not only associated with lung cancer, but also related to other cancers, such as epithelial ovarian cancer, hepatocellular carcinoma, Cervical Cancer and acute lymphoblastic leukemia. Mosallayi et al. [17] found that SET8 rs16917496 polymorphism was no connection with an increased risk of Colorectal Cancer. Wang et al. [9] showed that SET8 rs16917496 polymorphism was correlated with epithelial ovarian cancer risk. Guo et al.
rs16917496 polymorphism with cancer risk and found that SET8 rs16917496 polymorphism was correlation with an increased cancer risk, which was in line with the previous meta analysis. In the subgroups analysis, no significant correlation was observed of the polymorphism of rs16917496 with cancer risk among both Caucasian and Asian populations.

SET8 encodes a histone H4 lysine 20 monomethyltransferase that is implicated in normal cell cycle progression, the SET8 is regulated by miR-502 via the binding site in the 3'-UTR of the SET8 mRNA [19-21]. That histone H4 methyltransferase encoded by SET8 gene is crucial for omnifarious biological processes, such as transcriptional regulation, heterochromatin formation, DNA replication, cell-cycle arrest, and maintenance of genome integrity [19, 20]. SET8 methyltransferase activity modifies p53 protein function by monomethylation of p53 at lysine 382 [22]. In cellular stresses including DNA damage, p53-dependent cell cycle arrest or apoptosis activated for which depletion of cellular SET8 is an essential prerequisite as seen that p53K382me1 levels decrease with DNA damage [8, 22]. Given, the importance of SET8-P53 interaction in cell-cycle and apoptosis control, deregulation of SET8 under influence of SNP rs16917496 T>C within the miR-502 binding site in the 3'-UTR of the SET8 gene would adversely affect this vital axis in the cell [10]. Thus, SET8 may be a critical element in the development of cancer, and inhibit SET8 may restrain tumorigenesis and progression. Previous studies have suggested that the SNP rs16917496 adjusts SET8 expression and
rs16917496 polymorphism in SET8 gene

leads to cancer risk and the early development of cancer [7, 23].

The meta-analysis, to our knowledge, is the first time to comprehensively estimate the correlation of SET8 rs16917496 polymorphism with cancer risk in Caucasian and Asian population, and it is more reliable than previous single case-control study because it includes the largest of sample size. Although some puzzles have been made more unambiguous by this meta-analysis, along with previous studies, several limitations should also be noted. First, the controls for three studies didn’t conform Hardy-Weinberg equilibrium, which may affect the results. Second, the coverage of the clinical data (sex, age group, etc.) of the case and control groups was not all-sided. Third, we limited capacity to analyze the interaction of all gene-to-environment and gene-to-gene. Fourth, no enough case-control studies on cancer type studies could be collected in the meta-analysis, restraining further analysis of the correlation of SET8 rs16917496 with cancer among more cancer type. Finally, number of samples was not enough big, which may effect validity and reliability of the meta-analysis result.

In summary, this meta-analysis demonstrated that rs16917496 is a genetic susceptible locus for cancer risk in overall population. Considering the limitations of this study, the more studies and larger scales of control-cases is essential to verify the correlation of SET8 rs16917496 polymorphisms with cancer risk.

Figure 8. Begg’s funnel plot of recessive model (CC vs TC+TT) of rs61764370 with cancer risk.

Figure 9. Begg’s funnel plot of dominant model (CC+TC vs TT) of rs61764370 with cancer risk.
rs16917496 polymorphism in SET8 gene

**Disclosure of conflict of interest**

None.

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