Original Article
Zinc finger and BTB domain containing 20 rs9841504 polymorphism might decrease gastric cancer risk: a meta-analysis

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Abstract: Background: The association between ZBTB20 rs9841504 polymorphism and gastric cancer is inconclusive and contradictory. Therefore, we performed a meta-analysis. Methods: Online electronic databases (PubMed, EMBASE, and Cochrane database) were searched. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. Results: Four publications containing 6 case-control studies with a total of 7810 cases and 7840 controls were enrolled in this meta-analysis. We found that ZBTB20 rs9841504 polymorphism significantly associated with decreased gastric cancer risk (OR = 0.78; 95% CI 0.67-0.91; P = 0.001). In the subgroup analysis by race, Asian with ZBTB20 rs9841504 polymorphism showed decreased gastric cancer risk (OR = 0.78; 95% CI 0.66-0.91; P = 0.002). But Hispanic with ZBTB20 rs9841504 polymorphism did not show decreased gastric cancer risk (OR = 0.91; 95% CI 0.54-1.53; P = 0.72). When the studies with adjusted by age, gender, and smoking were included, ZBTB20 rs9841504 polymorphism also significantly associated with decreased gastric cancer risk (OR = 0.75; 95% CI 0.67-0.87; P<0.001). Even when the studies adjusted by age, gender, smoking and drinking, the result was also significant (OR = 0.74; 95% CI 0.63-0.87; P = 0.0002). Conclusions: In conclusion, our meta-analysis study confirmed that ZBTB20 rs9841504 polymorphism might decrease to the risk for gastric cancer.

Keywords: ZBTB20, polymorphism, gastric cancer, meta-analysis

Introduction
Gastric cancer is the fifth most common malignancy in the world [1]. In 2012, 952000 new cases were diagnosed and 723000 people died of the disease worldwide [1]. The management of gastric cancer is complex and requires a multidisciplinary approach [2]. Gastric cancer has been considered to be the result of environmental and genetic factors. However, the specific mechanism remains obscure.

Zinc finger and BTB domain containing 20 (ZBTB20) is developmentally regulated in liver, and acts as a key repressor of AFP gene transcription in liver, the specific ablation of which in liver leads to thousands-fold increase in AFP mRNA levels in adulthood [3]. More interestingly, ZBTB20 is implicated in the reactivation of AFP in hepatocellular carcinoma [4]. Several studies suggested that ZBTB20 rs9841504 polymorphism was associated with the risk of gastric cancer. However, other studies did not confirm the result [5-8]. Therefore, in order to derive a more comprehensive estimation of the association between ZBTB20 rs9841504 polymorphism and gastric cancer risk, we conducted this meta-analysis.

Materials and methods

Literature search
Online electronic databases (PubMed, EMBASE, and Cochrane database) were searched using the search terms: ZBTB20 or Zinc finger and BTB domain containing 20 and gastric cancer. Additional studies were identified by a hand search from reference of original studies or review articles on this topic. There was no language restriction.
Inclusion and exclusion criteria

The following inclusion criteria were used: (1) the study should have evaluated the association between the ZBTB20 rs9841504 polymorphism and gastric cancer risk; (2) the study should have a case-control or cohort design; (3) sufficient data should have been provided in order to calculate odds ratios (OR) and 95% confidence interval (CI). Studies were excluded if any of the following conditions applied: (1) only abstracts or reviews were available, without sufficient data; (2) animal studies; (3) studies were repeated or publications overlapped.

Data extraction

The following data were recorded from each article: first author, years of publication, ethnicity, gender, age, numbers of case and control, and adjustment. The data were extracted by two of the authors independently. Discrepancies between these two authors were resolved by discussion.

Quality assessment

The included studies were assessed independently by the two reviewers using the Newcastle-Ottawa Scale (NOS). The NOS employs a star rating system to assess quality from 3 broad perspectives of the study: (1) selection of the study groups, (2) comparability of the groups, and (3) identification of the exposure (for case-control studies) or outcome of interest (for cohort studies). Scores ranged from 0 to 9 stars.
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**Table 1. Characteristics of the studies**

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Ethnicity</th>
<th>Age group</th>
<th>Gender</th>
<th>Adjustment</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shi 1</td>
<td>2011</td>
<td>Asian</td>
<td>Adult</td>
<td>Mixed</td>
<td>Age, gender, and smoking and drinking status.</td>
<td>828</td>
<td>169 4</td>
</tr>
<tr>
<td>Shi 2</td>
<td>2011</td>
<td>Asian</td>
<td>Adult</td>
<td>Mixed</td>
<td>Age, gender, and smoking and drinking status.</td>
<td>1423</td>
<td>425 24</td>
</tr>
<tr>
<td>Shi 3</td>
<td>2011</td>
<td>Asian</td>
<td>Adult</td>
<td>Mixed</td>
<td>Age, gender, and smoking and drinking status.</td>
<td>1096</td>
<td>283 15</td>
</tr>
<tr>
<td>Song</td>
<td>2013</td>
<td>Asian</td>
<td>Adult</td>
<td>Mixed</td>
<td>Age, gender</td>
<td>2172</td>
<td>960 113</td>
</tr>
<tr>
<td>Sun</td>
<td>2014</td>
<td>Hispanic</td>
<td>Adult</td>
<td>Mixed</td>
<td>Age, gender, smoking status, and body mass index</td>
<td>95</td>
<td>31 5</td>
</tr>
<tr>
<td>Dong</td>
<td>2015</td>
<td>Asian</td>
<td>Adult</td>
<td>Mixed</td>
<td>Age, gender, family history of cancer, smoking and drinking status.</td>
<td>133 2 2</td>
<td>142 40 4</td>
</tr>
</tbody>
</table>

HWE: Hardy-Weinberg equilibrium.

**Table 2. Quality scores of the studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shi 1</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Shi 2</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Shi 3</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Song</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Sun</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Dong</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

Statistical analysis

The strength of association between ZBTB20 rs9841504 polymorphism and gastric cancer risk was assessed by calculating OR with 95% CI. A statistical test for heterogeneity was performed based on the Q statistic. The P > 0.10 of the Q-test indicated a lack of heterogeneity among studies. The summary OR estimate of each study was calculated by the random-effects model. Stratified analysis was performed by race. Potential publication bias was examined by funnel plot and Egger’s test. All statistical tests were performed with the software Reviewer Manager version 5.1 and STATA 12.0. A P value <0.05 was considered statistically significant.

Results

Characteristics of the studies

As shown in Figure 1, a total of 43 records were initially identified. When the full-texts were examined, we excluded 39 articles. Finally, 4 publications containing 6 case-control studies with a total of 7810 cases and 7840 controls were enrolled in this meta-analysis. The characteristics of the included studies were listed in Table 1.

To determine the stableness of the result, we performed the sensitivity analysis by omitting one study at a time. We found that single study did not impact the pooled OR, indicating that the results of our research were statistically robust (Figure 3).

Funnel plot and Begg’s test were conducted to assess the publication bias. The shape of fun-
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We found that ZBTB20 rs9841504 polymorphism significantly associated with decreased gastric cancer risk. In the subgroup analysis by race, Asian with ZBTB20 rs9841504 polymorphism showed decreased gastric cancer risk. But Hispanic with ZBTB20 rs9841504 polymorphism did not show decreased gastric cancer risk.

The association between ZBTB20 and other diseases were reported. Zhang et al. reported that a cognate ZBTB20 site in AFP promoter which mediates the postnatal repression of AFP gene in the liver [9]. Zhou et al. indicated that ZBTB20 as a crucial regulator governing the terminal differentiation of hypertrophic chondrocytes at least partially through repression of Sox9 [10]. Jiang and colleagues suggested that though specific deletion of transcription factor Zbtb20 in Sertoli cells has no apparent influence on spermatogenesis, its specific localization in Sertoli cells makes Zbtb20 a useful marker for the identification of Sertoli cells in seminiferous tubules [11]. Ren et al. indicated that ZBTB20 as a critical regulator of nociception and pain sensation by modu-

Figure 2. Meta-analysis of the association between ZBTB20 rs9841504 polymorphism gastric cancer risk.

Figure 3. Sensitivity analysis of the association between ZBTB20 rs9841504 polymorphism gastric cancer risk.

Table 3. Meta-analysis results

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>$P_{\text{heterogeneity}}$</th>
<th>Model</th>
<th>OR (95% CI)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.04</td>
<td>R</td>
<td>0.78 (0.67-0.91)</td>
<td>0.001</td>
</tr>
<tr>
<td>Asian</td>
<td>0.03</td>
<td>R</td>
<td>0.78 (0.66-0.91)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hispanic</td>
<td>-</td>
<td>R</td>
<td>0.91 (0.54-1.53)</td>
<td>0.72</td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, gender, and smoking</td>
<td>0.09</td>
<td>R</td>
<td>0.75 (0.67-0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, gender, smoking and drinking</td>
<td>0.06</td>
<td>R</td>
<td>0.74 (0.63-0.87)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

R, random effects model.

Discussion

This present meta-analysis of 6 case-control studies evaluated the association between ZB-
ZBTB20 and gastric cancer

In conclusion, our meta-analysis study confirmed that ZBTB20 rs9841504 polymorphism might reduce the risk for gastric cancer.

Disclosure of conflict of interest

None.

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References

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