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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.

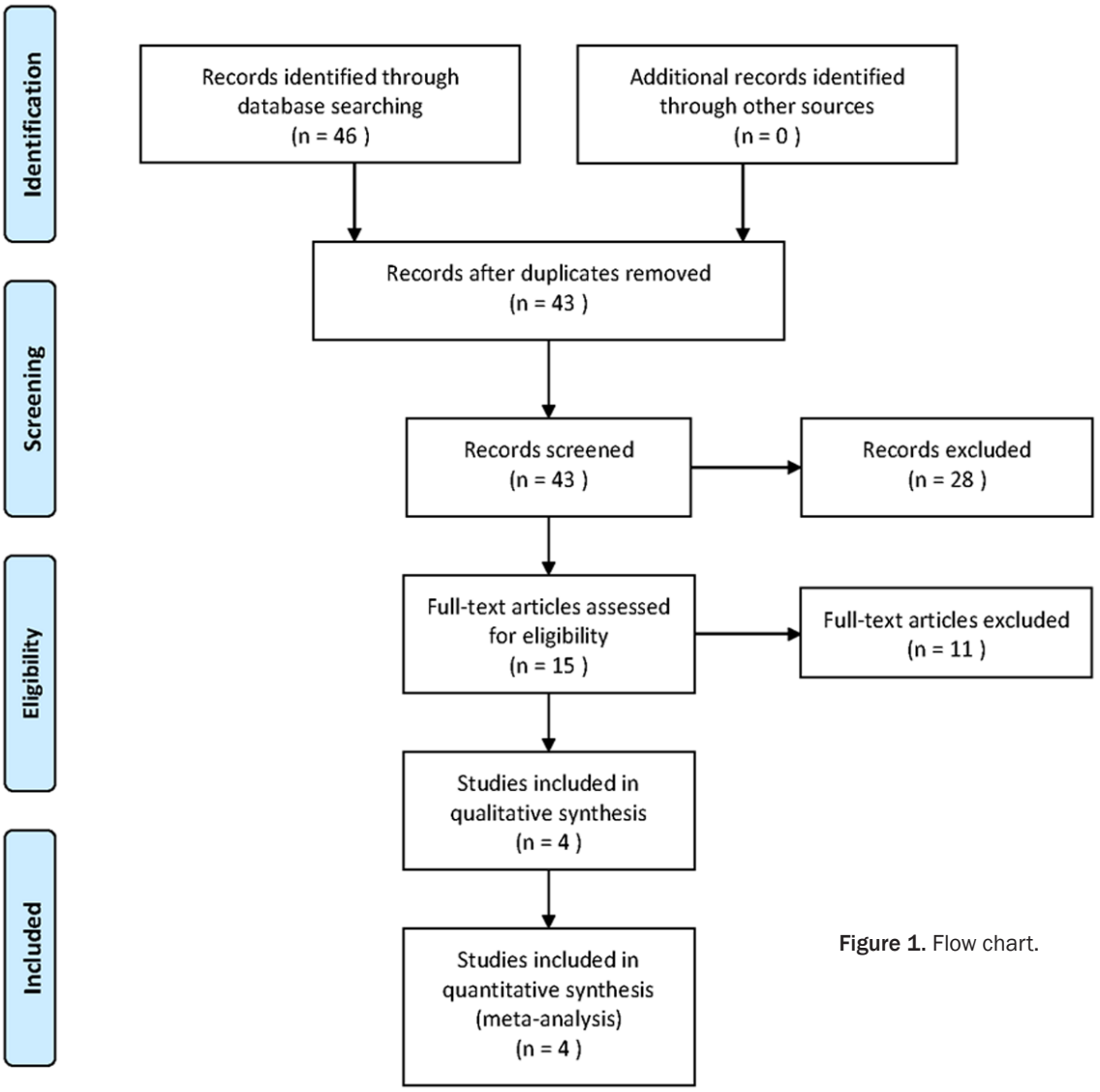

Figure 1. Flow chart.

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.

Table 1. Characteristics of the studies

First Author	Year	Ethnicity	Age group	Gender	Adjustment	Case			Control			
						CC	CG	GG	CC	CG	GG	HWE
Shi 1	2011	Asian	Adult	Mixed	Age, gender, and smoking and drinking status.	828	169	4	1637	563	43	Yes
Shi 2	2011	Asian	Adult	Mixed	Age, gender, and smoking and drinking status.	1423	425	24	1483	549	37	Yes
Shi 3	2011	Asian	Adult	Mixed	Age, gender, and smoking and drinking status.	1096	283	15	1112	373	34	Yes
Song	2013	Asian	Adult	Mixed	Age, gender	2172	960	113	1174	466	60	Yes
Sun	2014	Hispanic	Adult	Mixed	Age, gender, smoking status, and body mass index	95	31	5	83	36	4	Yes
Dong	2015	Asian	Adult	Mixed	Age, gender, family history of cancer, smoking and drinking status.	133	32	2	142	40	4	Yes

HWE: Hardy-Weinberg equilibrium.

Table 2. Quality scores of the studies

Study	Selection	Comparability	Outcome	Overall quality
Shi 1	4	3	2	9
Shi 2	4	3	2	9
Shi 3	4	3	2	9
Song	4	2	2	8
Sun	4	2	3	9
Dong	4	2	3	9

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**. The NOS scores were listed in **Table 2**.

Quantitative data synthesis

As shown in **Figure 2**, we found that ZBTB-20 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). All the results are listed in **Table 3**.

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-

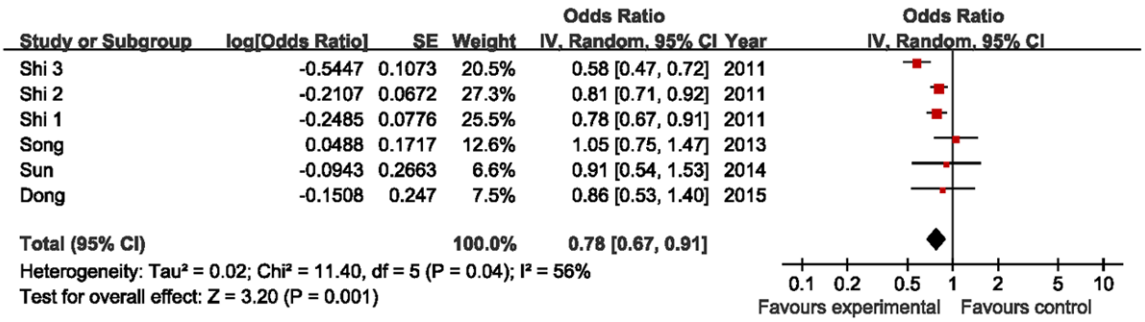

Figure 2. Meta-analysis of the association between ZBTB20 rs9841504 polymorphism gastric cancer risk.

Table 3. Meta-analysis results

	$P_{heterogeneity}$	Model	OR (95% CI)	*P* value
Overall	0.04	R	0.78 (0.67-0.91)	0.001
Asian	0.03	R	0.78 (0.66-0.91)	0.002
Hispanic	-	R	0.91 (0.54-1.53)	0.72
Adjust				
Age, gender, and smoking	0.09	R	0.75 (0.67-0.87)	<0.001
Age, gender, smoking and drinking	0.06	R	0.74 (0.63-0.87)	0.0002

R, random effects model.

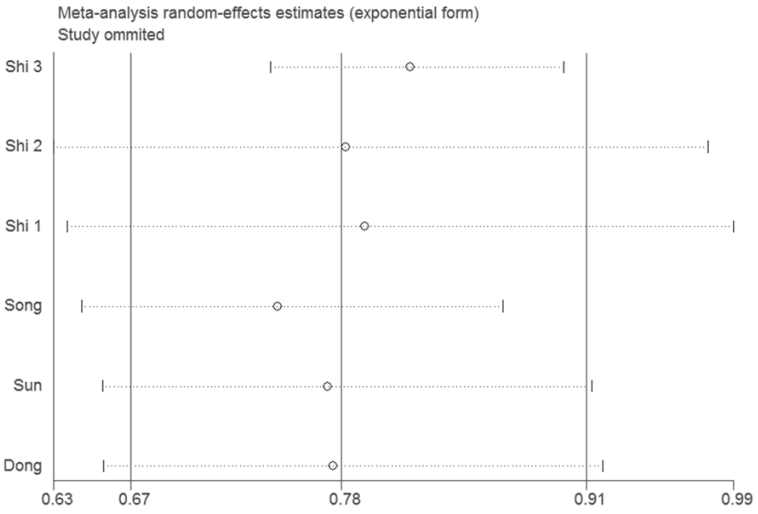

Figure 3. Sensitivity analysis of the association between ZBTB20 rs9841504 polymorphism gastric cancer risk.

nel plot was symmetry (**Figure 4**). Egger's test did not detect obvious publication bias (P = 0.99).

Discussion

This present meta-analysis of 6 case-control studies evaluated the association between ZBTB20 rs9841504 polymorphism and gastric cancer risk. 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-

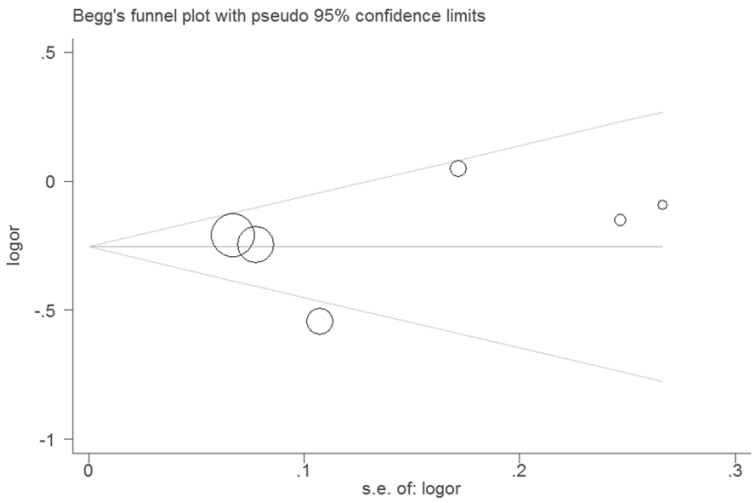

Figure 4. Funnel plot of the association between ZBTB20 rs9841504 polymorphism gastric cancer risk.

lating TRP channels expression in nociceptors [12]. Cordeddu and coworkers found that a genetic link between these disorders and delineates the impact of ZBTB20 dysregulation on development, growth and metabolism [13].

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

[1] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9-29.

[2] Coburn N, Seevaratnam R, Paszat L, Helyer L, Law C, Swallow C, Cardosa R, Mahar A, Lourenco LG, Dixon M, Bekaii-Saab T, Chau I, Church N, Coit D, Crane CH, Earle C, Mansfield P, Marcon N, Miner T, Noh SH, Porter G, Posner MC, Prachand V, Sano T, van de Velde C, Wong S, McLeod R. Optimal management of gastric cancer: results from an international RAND/UCLA expert panel. Ann Surg 2014; 259: 102-8.

[3] Xie Z, Zhang H, Tsai W, Zhang Y, Du Y, Zhong J, Szpirer C, Zhu M, Cao X, Barton MC, Grusby MJ, Zhang WJ. Zinc finger protein ZBTB20 is a key repressor of alpha-fetoprotein gene transcription in liver. Proc Natl Acad Sci U S A. 2008; 105: 10859-64.

[4] Kojima K, Takata A, Vadnais C, Otsuka M, Yoshikawa T, Akanuma M, Kondo Y, Kang YJ, Kishikawa T, Kato N, Xie Z, Zhang WJ, Yoshida H, Omata M, Nepveu A, Koike K. MicroRNA122 is a key regulator of α-fetoprotein expression and influences the aggressiveness of hepatocellular carcinoma. Nat Commun 2011; 2: 338.

[5] Shi Y, Hu Z, Wu C, Dai J, Li H, Dong J, Wang M, Miao X, Zhou Y, Lu F, Zhang H, Hu L, Jiang Y, Li Z, Chu M, Ma H, Chen J, Jin G, Tan W, Wu T, Zhang Z, Lin D, Shen H. A genome-wide association study identifies new susceptibility loci for non-cardia gastric cancer at 3q13.31 and 5p13.1. Nat Genet 2011; 43: 1215-1218.

[6] Song HR, Kim HN, Kweon SS, Choi JS, Shim HJ, Cho SH, Chung IJ, Park YK, Kim SH, Choi YD, Joo KW, Shin MH. Genetic variations in the PRKAA1 and ZBTB20 genes and gastric cancer susceptibility in a Korean population. Mol Carcinog 2013; 52 Suppl 1: E155-160.

[7] Sun Y, Gu J, Ajani JA, Chang DW, Wu X, Stroehlein JR. Genetic and intermediate phenotypic susceptibility markers of gastric cancer in Hispanic Americans: a case-control study. Cancer 2014; 120: 3040-3048.

[8] Dong Y, Chen J, Chen Z, Tian C, Lu H, Ruan J, Yang W. Evaluating the Association of Eight Polymorphisms with Cancer Susceptibility in a Han Chinese Population. PLoS One 2015; 10: e0132797.

[9] Zhang H, Cao D, Zhou L, Zhang Y, Guo X, Li H, Chen Y, Spear BT, Wu JW, Xie Z, Zhang WJ. ZBTB20 is a sequence-specific transcriptional repressor of alpha-fetoprotein gene. Sci Rep 2015; 5: 11979.

[10] Zhou G, Jiang X, Zhang H, Lu Y, Liu A, Ma X, Yang G, Yang R, Shen H, Zheng J, Hu Y, Yang X, Zhang WJ, Xie Z. Zbtb20 regulates the terminal differentiation of hypertrophic chondrocytes via repression of Sox9. Development 2015; 142: 385-93.

[11] Jiang X, Zhang H, Yin S, Zhang Y, Yang W, Zheng W, Wang L, Wang Z, Bukhari I, Cooke HJ, Iqbal F, Shi Q. Specific deficiency of Plzf paralog, Zbtb20, in Sertoli cells does not affect spermatogenesis and fertility in mice. Sci Rep 2014; 4: 7062.

[12] Ren AJ, Wang K, Zhang H, Liu A, Ma X, Liang Q, Cao D, Wood JN, He DZ, Ding YQ, Yuan WJ, Xie Z, Zhang WJ. ZBTB20 regulates nociception and pain sensation by modulating TRP channel expression in nociceptive sensory neurons. Nat Commun 2014; 5: 4984.
[13] Cordeddu V, Redeker B, Stellacci E, Jongejan A, Fragale A, Bradley TE, Anselmi M, Ciolfi A, Cecchetti S, Muto V, Bernardini L, Azage M, Carvalho DR, Espay AJ, Male A, Molin AM, Posmyk R, Battisti C, Casertano A, Melis D, van Kampen A, Baas F, Mannens MM, Bocchinfuso G, Stella L, Tartaglia M, Hennekam RC. Mutations in ZBTB20 cause Primrose syndrome. Nat Genet 2014; 46: 815-7.