Int J Clin Exp Med 2018;11(3):1525-1533
www.ijcem.com /ISSN:1940-5901/IJCEM0065784

Review Article

Association of miR-502-binding site single nucleotide polymorphism in the 3'-untranslated region of SET8 with cancer risk: a meta-analysis based on 4905 subjects

Si Huang[1*], Anbang He[2*], Depeng Xu[1], Qiwen Chen[1], Suwen Qi[1]

[1]Department of Biomedical Engineering, School of Medicine, Shenzhen University, Shenzhen, China; [2]Department of Urology, Peking University The First Hospital, The Institute of Urology, Peking University, National Urological Cancer Centre, Beijing, China. [*]Equal contributors.

Received September 17, 2017; Accepted January 9, 2018; Epub March 15, 2018; Published March 30, 2018

Abstract: Accumulating evidence demonstrates that the miR-502-binding site in the 3'-UTR of SET8 (rs16917496 C/T) may contribute to the development of several cancers, including epithelial ovarian cancer and cervical cancer. However, the results are inconsistent and inconclusive. Therefore, this meta-analysis was conducted to derive a more reliable conclusion of the association between rs16917496 polymorphism in SET8 and cancer risk. Ten eligible case control studies were included in the present meta-analysis by using electronic databases PubMed, Cochrane Library and Web of Science. The odds ratio with 95% confidence interval was calculated to evaluate the association between the rs16917496 polymorphism and cancer susceptibility. Our study revealed that no significant association was observed between the rs16917496 polymorphism in SET8 and overall cancer risk in all genetic models. However, as for the subgroups sorted by ethnicities, it suggested a decreased susceptibility to Iranian only in dominant model (TT+TC *vs.* CC: OR=0.496, 95% CI=0.266-0.925). In conclusion, our meta-analysis indicated that the SET8 dominant genotype (TT+TC) acts as a protective factor for Iranian only in dominant model.

Keywords: SET8, SETD8, polymorphisms, cancer, susceptibility

Introduction

Cancers are becoming a major public health problem worldwide because of the increasing incidence and mortality in recent years [1]. A mass of previous research has commenced to systematically explore single nucleotide polymorphisms (SNPs) in crucial genes to illustrate specific genotypes that contribute to an increased risk for cancer development and progression [2, 3]. Rs16917496, one of SET8 gene polymorphisms, is located in the miR-502-binding site in the 3'-untranslated region of SET8 gene [4-6]. SET8 could be regulated by miRNA-502 via binding to the 3'UTR of the SET8 mRNA. Set domain-containing protein 8 (SET8, also known as SETD8 or KMT5A or PR-SET7), located on chromosome 12q24.31, encodes a histone H4 lysine 20 monomethyltransferase that is essential for several biological processes, including cell-cycle-dependent transcriptional silencing [2, 7, 8]. Accumulating evidence demonstrates that the miR-502-binding site in the 3'-UTR of the SET8 (rs16917496 C/T) may contribute to the development of several cancers, including epithelial ovarian cancer [9], cervical cancer [10] and so forth. However, the results are inconsistent and inconclusive. Therefore, we conducted this meta-analysis to derive a more reliable conclusion of the association between rs16917496 polymorphism in SET8 and cancer risk.

Materials and methods

Search strategy

Electronic databases PubMed, Cochrane Library, Web of Science, Wanfang databases and CNKI (China National Knowledge Infrastruc-

Table 1. Characteristics of studies included in the meta-analysis

Reference	Year	Ethnicity	Genotyping method	Source of control	Cancer type	Sample size (case/control)	Case			Control			HWE	Y/N
							TT	TC	CC	TT	TC	CC		
Song	2009	China	RFLP-PCR	HB	BRC	11100/1097	504	491	115	518	475	104	0.7449	Y
Yang	2013	China	RFLP-PCR	HB	NSCLC	164/199	95	57	12	102	69	28	0.0059	N
Wang	2012	China	LDR	PB	EOC	342/344	160	155	27	167	132	45	0.0235	N
Xu	2016	China	PCR	PB	CCRCC	140/130	79	47	14	68	32	30	1E-07	N
Zhao	2013	China	PCR	PB	EC	65/60	32	25	8	29	25	6	0.8579	Y
Narouie	2017	Iranian	RFLP-PCR	HB	PC	169/182	29	94	46	65	83	34	0.4132	Y
Hashemi	2014	Iranian	RFLP-PCR	HB	ALL	75/115	3	59	13	0	108	7	2E-21	N
Guo	2011	China	PCR	HB	HCC	143/142	72	50	11	73	55	14	0.4477	Y
Ding	2012	China	LDR	PB	SCLC	44/44	22	12	8	24	12	6	0.0519	Y
Yang	2014	China	RFLP-PCR	HB	CC	144/200	44	42	28	111	63	26	0.0011	N

BRC, breast cancer; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; EOC, epithelial ovarian cancer; PC, prostate cancer; HCC, hepatocellular carcinoma; CCRCC, clear cell renal cell carcinoma; EC, esophageal carcinoma; CC, cervical cancer; ALL, acute lymphoblastic leukemia; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction restriction fragment length polymorphism; LDR, ligation detection reaction, PB population-based; HB, hospital-based; HWE, Hardy-Weinberg equilibrium of controls. Y: P (HWE) > 0.05; N: P (HWE) ≤ 0.05.

ture) were searched by using (Set domain-containing protein 8 OR SET8 OR SETD8 OR KMT5A OR Lysine Methyltransferase 5A OR PR-SET7) and (polymorphism OR variant OR SNP) and (tumor OR carcinoma OR cancer) as the keyword, in order to identify potentially relevant studies. The data retrieval was performed without any language restriction. The last update of time of search was July 19, 2017.

Inclusion and exclusion criteria

Potentially eligible studies were selected according to the following criteria: 1) Evaluation of a link between SET8 (including SETD8 or KMT5A or PR-SET7) polymorphisms and cancer or tumor susceptibility; 2) Only case control studies ; and 3) Studies that included available data (allele and genotype frequencies) to calculate the crude ORs at 95% CIs. We excluded studies when they were 1) Case only studies, reviews, case reports, meta-analysis, and comments; 2) Duplicate publications; and 3) Studies without available data of SET8 (including SETD8 or KMT5A or PR-SET7) genotype.

Quality assessment

The quality of all eligible studies was evaluated independently by Si Huang and Anbang He on the basis of the Newcastle-Ottawa scale. Disagreements were resolved with all investigators in conference (**Table 4**).

Data extraction

Data extraction from each article was executed independently by two investigators (Si Huang, Anbang He). The following data were extracted: the name of the first author, year of publication, ethnicity of each population, control source, genotyping method, total number of cases and controls, and *P*-value of HWE (Hardy-Weinberg equilibrium). Any disagreements were discussed with all investigators in conference until a consensus was reached.

Statistical analysis

All statistical analyses were performed by STATA 12.0 software version (STATA Corp, College Station, TX, USA). $P < 0.05$ was considered as statistically significant. The significance of the pooled ORs was evaluated by a Z-test. We used the Chi-square test to assess HWE among controls. Publication bias was tested by Egger's test and Begg's funnel plot test. Between-study heterogeneity was evaluated by using Chi-square based Q-test and I^2 statistics [11, 12]. No significant heterogeneity was observed when $I^2 < 50\%$ and $P > 0.10$, and ORs were pooled by a fixed-effects model. Otherwise, the random-effects model was utilized. Sensitivity analyses were performed by deletion of each single study in the meta-analysis to evaluate the stability of the results.

Result

Characteristics of eligible studies

As presented in the flow diagram (**Figure 1**), a total of 70 published articles were discovered in our initial search by using the keywords. After checking titles and abstracts, 18 duplicated studies and 32 irrelevant studies were exclud-

Table 2. Methodological quality of the included studies according to the Newcastle-Ottawa Scale

Reference	Year	Ethnicity	Adequacy of Case Definition	Representativeness of the Cases	Selection of Controls	Definition of Controls	Comparability Cases/Controls	Ascertainment of Exposure	Same Method of Ascertainment	Non-response rate
Song	2009	China	*	*	NA	*	**	*	*	*
Yang	2013	China	*	*	NA	*	**	*	*	*
Wang	2012	China	*	*	*	*	**	*	*	*
Xu	2016	China	*	*	*	*	**	*	*	*
Zhao	2013	China	*	*	NA	*	**	*	*	*
Narouie	2017	Iranian	*	*	*	NA	**	*	*	*
Hashemi	2014	Iranian	*	*	*	NA	**	*	*	*
Guo	2011	China	*	*	NA	*	**	*	*	*
Ding	2012	China	*	*	*	*	**	*	*	*
Yang	2014	China	*	*	*	*	**	*	*	*

This table identifies 'high' quality choices with a 'star'. A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability. *, Yes; NA, not applicable. (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm).

Table 3. Results of meta-analysis for rs16917496 polymorphism in SET8 and cancer susceptibility

Variables (rs16917496)	Case/Control	T vs. C				TT vs. CC				TC vs. CC			
		OR (95% CI)	P	*P*-value[a]	I^2 (%)	OR (95% CI)	P	*P*-value[a]	I^2 (%)	OR (95% CI)	P	*P*-value[a]	I^2 (%)
Total	2394/2511	0.935 (0.769, 1.137)	0.502	0	74.3	0.985 (0.624, 1.553)	0.947	0	75.7	1.062 (0.733, 1.538)	0.751	0.002	65.8
Ethnicity													
China	2150/2214	1.009 (0.824, 1.236)	0.928	0.001	70.4	1.113 (0.717, 1.728)	0.634	0.001	71.4	1.253 (0.843, 1.862)	0.264	0.011	61.6
Iranian	244/297	0.689 (0.467, 1.015)	0.06	0.125	57.5	0.702 (0.074, 6.639)	0.758	0.123	58	0.539 (0.196, 1.482)	0.231	0.064	70.8
Genotyping method													
RFLP-PCR	1662/1793	0.815 (0.599, 1.107)	0.19	0	83.6	0.743 (0.370, 1.492)	0.403	0	81.7	0.825 (0.542, 1.255)	0.368	0.037	60.9
LDR	384/386	1.048 (0.845, 1.300)	0.67	0.393	0	1.257 (0.597, 2.647)	0.547	0.209	36.6	1.481 (0.631, 3.477)	0.367	0.188	42.2
PCR	348/332	1.220 (0.956, 1.558)	0.11	0.342	6.9	1.539 (0.824, 2.876)	0.176	0.223	33.4	1.512 (0.647, 3.531)	0.34	0.084	59.6
Source of control													
HB	1805/1935	0.855 (0.655, 1.116)	0.25	0	80.7	0.805 (0.441, 1.468)	0.479	0	78.3	0.862 (0.597, 1.246)	0.43	0.06	52.8
PB	589/576	1.127 (0.908, 1.397)	0.278	0.286	20.6	1.467 (0.884, 2.434)	0.138	0.207	34.2	1.636 (0.885, 3.023)	0.116	0.121	48.3
Cancer type													
OT	1185/1212	0.933 (0.827, 1.053)	0.262	0.703	0	0.892 (0.667, 1.193)	0.439	0.348	0	0.578 (0.189, 1.765)	0.336	0.026	79.9
LC	206/241	1.140 (0.674, 1.927)	0.626	0.137	54.9	1.356 (0.447, 4.113)	0.59	0.11	60.9	1.415 (0.594, 3.372)	0.433	0.227	31.6
FGSN	486/544	0.770 (0.386, 1.536)	0.458	0.001	91.2	0.776 (0.184, 3.268)	0.729	0	91.8	1.120 (0.363, 3.459)	0.844	0.008	85.9
UN	309/312	0.925 (0.365, 2.346)	0.87	0	93.5	0.899 (0.124, 6.524)	0.916	0	94.3	1.573 (0.430, 5.752)	0.494	0.006	86.8
DSN	208/202	1.063 (0.783, 1.443)	0.694	0.675	0	1.086 (0.545, 2.166)	0.814	0.573	0	0.994 (0.490, 2.016)	0.987	0.567	0
Y/N													
Y	1529/1523	0.856 (0.672, 1.090)	0.208	0.037	60.8	0.715 (0.437, 1.168)	0.18	0.056	56.6	0.914 (0.721, 1.160)	0.46	0.964	0

N	865/988	1.012 (0.716, 1.429)	0.947	0	82.1	1.404 (0.626, 3.147)	0.41	0	81.1	1.208 (0.568, 2.568)	0.624	0	81.9

Variables (rs16917496)	Case/Control	TT+TC vs. CC				TT vs. TC+CC			
		OR (95% CI)	P	*P*-value	I^2 (%)	OR (95% CI)	P	*P*-value	I^2 (%)
Total	2394/2511	0.972 (0.658, 1.435)	0.886	0	73.4	0.878 (0.688, 1.120)	0.294	0.002	65.4
Ethnicity									
China	2150/2214	1.166 (0.767, 1.770)	0.472	0.001	70.9	0.951 (0.797, 1.135)	0.58	0.149	35
Iranian	244/297	0.496 (0.266, 0.925)	0.027	0.218	34	1.480 (0.054, 40.878)	0.817	0.025	80
Genotyping method									
RFLP-PCR	1662/1793	0.727 (0.445, 1.187)	0.202	0.003	74.7	0.761 (0.466, 1.242)	0.274	0	82.8
LDR	384/386	1.303 (0.565, 3.006)	0.534	0.159	49.7	0.920 (0.693, 1.220)	0.561	0.793	0
PCR	348/332	1.508 (0.737, 3.082)	0.261	0.125	51.9	1.126 (0.831, 1.526)	0.445	0.955	0
Source of control									
HB	1805/1935	0.780 (0.505, 1.206)	0.264	0.005	70.1	0.813 (0.543, 1.216)	0.314	0	79.5
PB	589/576	1.507 (0.866, 2.623)	0.147	0.126	47.6	0.987 (0.784, 1.242)	0.91	0.834	0
Cancer type									
OT	1185/1212	0.588 (0.209, 1.652)	0.313	0.037	77.1	2.029 (0.211, 19.494)	0.54	0.102	62.6
LC	206/241	1.341 (0.477, 3.772)	0.578	0.121	58.4	1.199 (0.825, 1.745)	0.342	0.344	0
FGSN	486/544	0.906 (0.243, 3.376)	0.883	0.001	91.3	0.704 (0.387, 1.283)	0.252	0.03	78.6
UN	309/312	1.263 (0.296, 5.392)	0.752	0.001	91.4	0.665 (0.215, 2.059)	0.479	0.001	90.6
DSN	208/202	1.044 (0.536, 2.032)	0.9	0.549	0	1.090 (0.736, 1.615)	0.666	0.865	0
Y/N									
Y	1529/1523	0.844 (0.674, 1.057)	0.14	0.624	0	0.802 (0.549, 1.173)	0.256	0.012	68.9
N	865/988	1.105 (0.507, 2.409)	0.803	0	85.4	0.969 (0.649, 1.445)	0.875	0.013	68.6

Lung cancer LC: NSCLC+SCLC, Urologic neoplasms UN: CCRCC+PC, Female genital system neoplasms FGSN: EOC+CC, Digestive system neoplasm DSN: HCC+EC, Other tumor OT: BRC+ALL BRC breast cancer, NSCLC non-small cell lung cancer, SCLC small cell lung cancer, EOC epithelial ovarian cancer, PC prostate cancer, HCC hepatocellular carcinoma, CCRCC clear cell renal cell carcinoma, EC esophageal carcinoma, CC cervical cancer, ALL acute lymphoblastic leukemia, PCR: polymerase chain reaction, PCR-RFLP polymerase chain reaction restriction fragment length polymorphism, LDR ligation detection reaction, PB population-based, HB hospital-based, Y: P (HWE) > 0.05; N: P (HWE) ≤ 0.05.

Table 4. Results for rs16917496 polymorphism in SET8 and each cancer susceptibility

Reference	Year	Cancer type	T vs. C		TT vs. CC		TC vs. CC	
			OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Song	2009	BRC	0.940 (0.828, 1.067)	0.337	0.880 (0.657, 1.179)	0.391	0.935 (0.697, 1.254)	0.653
Yang	2013	NSCLC	1.396 (1.005, 1.939)	0.046	2.173 (1.045, 4.517)	0.038	1.928 (0.900, 4.129)	0.091
Wang	2012	EOC	1.083 (0.862, 1.360)	0.495	1.597 (0.945, 2.697)	0.08	1.957 (1.151, 3.327)	0.013
Xu	2016	CCRCC	1.497 (1.037, 2.160)	0.031	2.489 (1.221, 5.076)	0.012	3.147 (1.447, 6.847)	0.004
Zhao	2013	EC	0.968 (0.566, 1.653)	0.904	0.828 (0.256, 2.671)	0.752	0.750 (0.227, 2.477)	0.637
Narouie	2017	PC	0.579 (0.430, 0.781)	0	0.330 (0.177, 0.615)	0	0.837 (0.491, 1.426)	0.513
Hashemi	2014	ALL	0.864 (0.571, 1.307)	0.488	3.889 (0.176, 85.870)	0.39	0.294 (0.111, 0.778)	0.014
Guo	2011	HCC	1.113 (0.767, 1.614)	0.574	1.255 (0.534, 2.949)	0.602	1.157 (0.481, 2.783)	0.745
Ding	2012	SCLC	0.800 (0.415, 1.541)	0.505	0.688 (0.206, 2.297)	0.543	0.750 (0.199, 2.827)	0.671
Yang	2014	CC	0.535 (0.381, 0.752)	0	0.368 (0.195, 0.697)	0.002	0.619 (0.320, 1.199)	0.155
Reference	Year	Cancer type	TT+TC vs. CC		TT vs. TC+CC			
			OR (95% CI)	P	OR (95% CI)	P		
Song	2009	BRC	0.880 (0.657, 1.179)	0.489	0.930 (0.786, 1.099)	0.393		
Yang	2013	NSCLC	2.173 (1.045, 4.517)	0.044	1.309 (0.863, 1.986)	0.205		
Wang	2012	EOC	1.597 (0.945, 2.697)	0.028	0.932 (0.690, 1.257)	0.644		
Xu	2016	CCRCC	2.489 (1.221, 5.076)	0.005	1.181 (0.731, 1.908)	0.497		
Zhao	2013	EC	0.828 (0.256, 2.671)	0.683	1.037 (0.514, 2.092)	0.92		
Narouie	2017	PC	0.614 (0.371, 1.016)	0.058	0.373 (0.226, 0.616)	0		
Hashemi	2014	ALL	0.309 (0.117, 0.816)	0.018	11.152 (0.568, 219.050)	0.112		
Guo	2011	HCC	1.213 (0.530, 2.776)	0.647	1.116 (0.695, 1.792)	0.651		
Ding	2012	SCLC	0.708 (0.223, 2.254)	0.559	0.825 (0.349, 1.950)	0.661		
Yang	2014	CC	0.459 (0.254, 0.830)	0.01	0.504 (0.315, 0.806)	0.004		

BRC, breast cancer; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; EOC, epithelial ovarian cancer; PC, prostate cancer; HCC, hepatocellular carcinoma; CCRCC, clear cell renal cell carcinoma; EC, esophageal carcinoma; CC, cervical cancer; ALL, acute lymphoblastic leukemia.

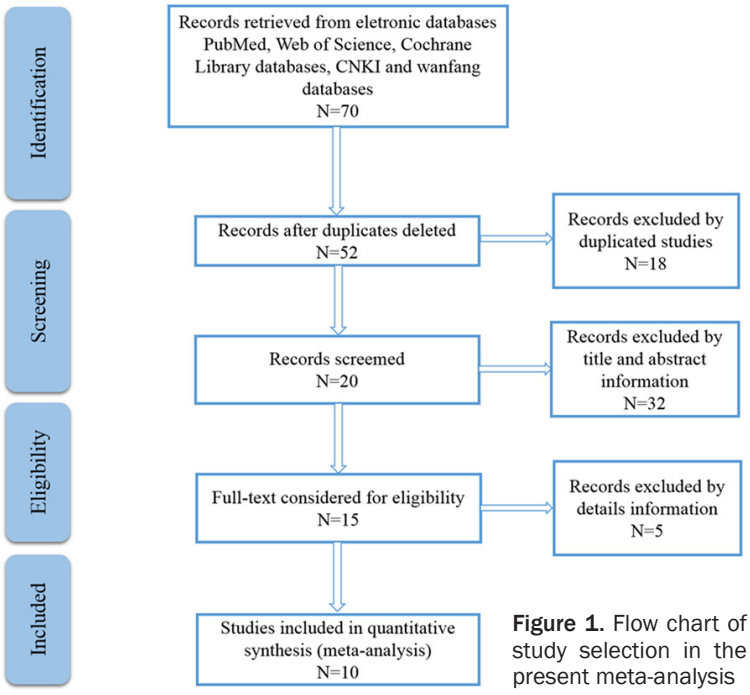

Figure 1. Flow chart of study selection in the present meta-analysis

ed. After further inspection of the full studies, there were 5 studies to be excluded due to the reason that they lacked data for SET8 polymorphism or control groups or they were about survival and treatment. Finally, a total of 10 studies were included in this meta-analysis.

The main characteristics of the enrolled studies are shown in **Table 1**. These studies included a total of 10 studies with 2394 cases and 2511 controls. Eight studies were from Chinese and 2 studies were from Iranian. Ten different types of cancer were included, with 1 breast cancer (BRC) [13], 1 non-small cell lung cancer (NSCLC) [14], 1 small cell lung cancer (SCLC) [15], 1 epithelial ovarian cancer (EOC) [9], 1 prostate cancer (PC) [16], 1 hepatocellular carcinoma (HCC) [17], 1 clear cell renal cell carcinoma (CCRCC) [18], 1 esophageal carcinoma (EC) [19], 1 cervical cancer (CC) [10]

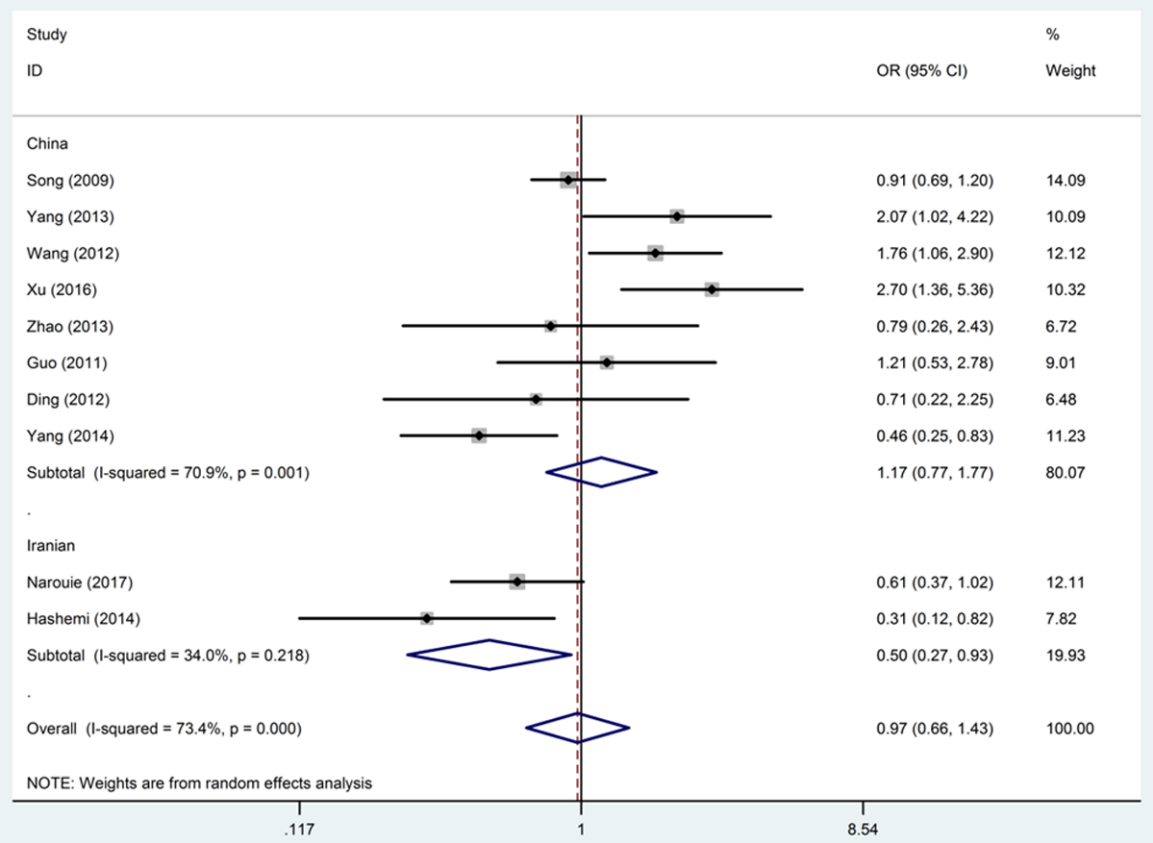

Figure 2. Forest plots of the relationship between rs16917496 polymorphism in SET8 and cancer risk in the dominant model (TT+TC *vs.* CC).

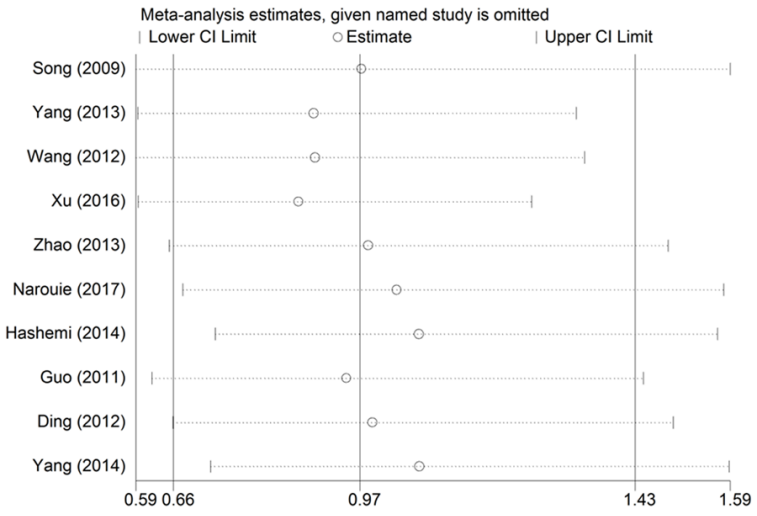

Figure 3. Sensitivity analysis of SET8 rs16917496 polymorphism and cancer risk in the dominant model (TT+TC *vs.* CC).

and 1 acute lymphoblastic leukemia (ALL) [20]. The Newcastle-Ottawa Scale (NOS) is summarized in **Table 2**.

Results of pooled meta-analysis

The results of rs16917496 polymorphism and cancer susceptibility are presented in **Table 3**. No significant association was observed between rs16917496 polymorphism in SET8 and overall cancer risk in all genetic models. **Table 3** also demonstrates the results of subgroup analysis, the data revealed that rs16917496 polymorphism in SET8 has no significant association with cancer susceptibility in the subgroups categorized by either genotyping methods or source of control or cancer type or HWE. However, as for the subgroup of sorted by ethnicities, it suggests a decreased susceptibility to Iranian only in dominant model (TT+TC vs. CC: OR=0.496,

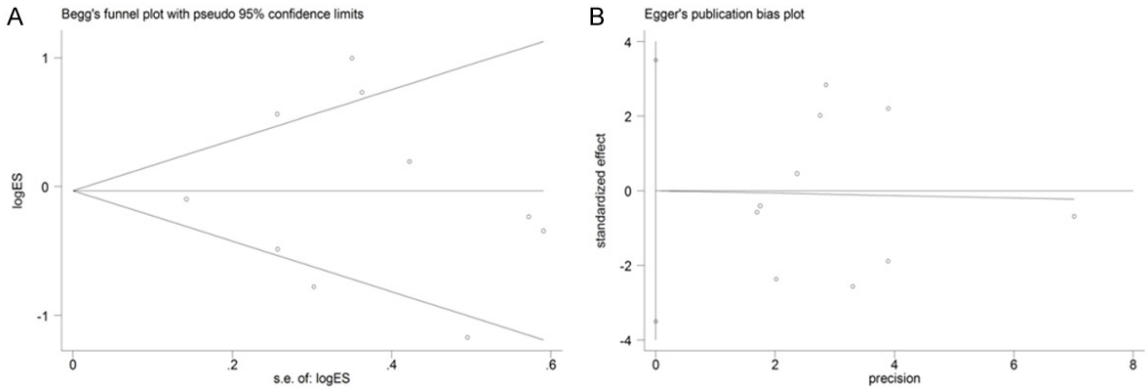

Figure 4. Begg's and Egger's test funnel plot for publication bias test under SET8 rs16917496 polymorphism in the dominant model (TT+TC *vs.* CC).

95% CI=0.266-0.925, **Figure 2**), which appeared to play a protective role in the process.

Sensitivity analysis and publications bias

Sensitivity analysis was used to evaluate the influence of individual case control study on the pooled ORs by deleting one study at a time and no significant influence on the pooled ORs was observed (Supplementary Table 1). Sensitivity analysis of the rs16917496 polymorphism in the dominant model is shown in **Figure 3** (Supplementary Table 1). Besides, both Begg's test and Egger's test were used to detect potential publication bias. The funnel plot of rs16917496 polymorphism is shown in **Figure 4** (TT+TC *vs.* CC: Begg's test, P > |z|=0.721, Egger's test, P > |t|=0.999). According to Supplementary Table 2, no significant publication bias was identified.

Discussion

Single nucleotide polymorphisms (SNPs), which are located in microRNA-binding sites, regulate expression of target genes [2, 3]. SET8 is regulated by miRNA-502 through binding to the 3'UTR of the SET8 mRNA, due to the fact that rs16917496 is located in the miR-502-binding site in the 3'-untranslated region of SET8 gene. Lys-382, encoded by TP53, could be methylated by the histone methyltransferase SET8, which plays vital roles in p53 function and the following genome stability [21]. Mutation in SET8 may contribute to loss of homeostatic control during human tumorigenesis and tumor progression. Growing evidence has revealed that rs16917496 polymorphism in SET8 gene contributes to the development and progression of various cancers, including epithelial ovarian cancer, cervical cancer and so forth. Previous studies demonstrated that the SET8 CC genotype is associated with a decreased risk of patients with epithelial ovarian cancers [9] and prostate cancers (**Table 4**). On the contrary, some research revealed that the SET8 CC genotype is related to an increased susceptibility to non-small cell lung cancer and clear cell renal cell carcinoma [16]. Moreover, meta-analysis has been regarded as a critical method to assess the influence of genetic polymorphisms on cancer risk. Therefore, this meta-analysis was conducted to clarify the influence of rs16917496 polymorphism of SET8 gene in cancer risk.

To the best of our knowledge, this is the first comprehensive meta-analysis of genetics studies on the relationship between rs16917496 polymorphism in SET8 and cancer susceptibility. No significant association was observed between rs16917496 polymorphism in SET8 and overall cancer risk in all genetic models. As for the results of subgroup analysis categorized by either genotyping methods or source of control or cancer type or HWE, rs16917496 polymorphism in SET8 had no significant association with cancer susceptibility. Only in the subgroup sorted by ethnicities, was rs16917496 polymorphism in SET8 related to a decreased susceptibility to Iranian only in dominant model.

Although an extensive retrieve of data was conducted, several drawbacks should still be mentioned. First, the meta-analysis results

may lack statistical power because of the limited number of eligible studies enrolled. Second, all eligible studies were conducted only in the Chinese and Iranian populations. So, the results may merely be suitable for these two populations. Third, only publications included in PubMed, Web of Science, and CNKI were retrieved while some eligible studies may have been neglected in other databases, which may lead to discrepant results. Fourth, because of the lack of original data, an assessment of gene-gene and gene-environment effects could not be conducted in the present meta-analysis.

In conclusion, our meta-analysis revealed that no significant association was identified between rs16917496 polymorphism in SET8 and overall cancer risk in all genetic models. Only in the subgroup sorted by ethnicities, was rs16917496 polymorphism in SET8 related to a decreased susceptibility to Iranian only in dominant model, which suggests that the SET8 dominant genotype (TT+TC) acts as a protective factor for Iranian only in dominant model. However, larger sized and well-designed studies should be conducted to explore the association between rs16917496 polymorphism in SET8 and cancer risk.

Acknowledgements

This work was supported by the Project of the National Science Foundation of China (Grant No. 81401750), Guangdong Science Plan (No.2014A020212038), and Shenzhen Science Plan (Nos. JCYJ20140418182819179, JCYJ20150330102720122, JCYJ2014041509305-2190, and cxzz201418182638764) and PhD Start-up Fund of Shenzhen University (No. 80100036104).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Suwen Qi, Department of Biomedical Engineering, School of Medicine, Shenzhen University, 3688 Nanhai Blvd, Nanshan District, Shenzhen 518060, China. Tel: +86 755 86671929; Fax: +86 755 86671929; E-mail: qisuwen@szu.edu.cn

References

[1] Siegel RL, Miller KD and Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017; 67: 7-30.

[2] Chen K, Song F, Calin GA, Wei Q, Hao X and Zhang W. Polymorphisms in microRNA targets: a gold mine for molecular epidemiology. Carcinogenesis 2008; 29: 1306-1311.

[3] Nicoloso MS, Sun H, Spizzo R, Kim H, Wickramasinghe P, Shimizu M, Wojcik SE, Ferdin J, Kunej T, Xiao L, Manoukian S, Secreto G, Ravagnani F, Wang X, Radice P, Croce CM, Davuluri RV and Calin GA. Single-nucleotide polymorphisms inside microRNA target sites influence tumor susceptibility. Cancer Res 2010; 70: 2789-2798.

[4] Fang J, Feng Q, Ketel CS, Wang H, Cao R, Xia L, Erdjument-Bromage H, Tempst P, Simon JA and Zhang Y. Purification and functional characterization of SET8, a nucleosomal histone H4-lysine 20-specific methyltransferase. Curr Biol 2002; 12: 1086-1099.

[5] Nishioka K, Rice JC, Sarma K, Erdjument-Bromage H, Werner J, Wang Y, Chuikov S, Valenzuela P, Tempst P, Steward R, Lis JT, Allis CD and Reinberg D. PR-Set7 is a nucleosome-specific methyltransferase that modifies lysine 20 of histone H4 and is associated with silent chromatin. Mol Cell 2002; 9: 1201-1213.

[6] Beck DB, Oda H, Shen SS and Reinberg D. PR-Set7 and H4K20me1: at the crossroads of genome integrity, cell cycle, chromosome condensation, and transcription. Genes Dev 2012; 26: 325-337.

[7] Wu S, Wang W, Kong X, Congdon LM, Yokomori K, Kirschner MW and Rice JC. Dynamic regulation of the PR-Set7 histone methyltransferase is required for normal cell cycle progression. Genes Dev 2010; 24: 2531-2542.

[8] Jorgensen S, Eskildsen M, Fugger K, Hansen L, Larsen MS, Kousholt AN, Syljuasen RG, Trelle MB, Jensen ON, Helin K and Sorensen CS. SET8 is degraded via PCNA-coupled CRL4 (CDT2) ubiquitylation in S phase and after UV irradiation. J Cell Biol 2011; 192: 43-54.

[9] Wang C, Guo Z, Wu C, Li Y and Kang S. A polymorphism at the miR-502 binding site in the 3' untranslated region of the SET8 gene is associated with the risk of epithelial ovarian cancer. Cancer Genet 2012; 205: 373-376.

[10] Yang SD, Cai YL, Jiang P, Li W and Tang JX. Association of a miR-502-binding site single nucleotide polymorphism in the 3'-untranslated region of SET8 and the TP53 codon 72 polymorphism with cervical cancer in the Chinese population. Asian Pac J Cancer Prev 2014; 15: 6505-6510.

[11] Lau J, Ioannidis JP and Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997; 127: 820-826.

[12] Higgins JP, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.

[13] Song F, Zheng H, Liu B, Wei S, Dai H, Zhang L, Calin GA, Hao X, Wei Q, Zhang W and Chen K. An miR-502-binding site single-nucleotide polymorphism in the 3'-untranslated region of the SET8 gene is associated with early age of breast cancer onset. Clin Cancer Res 2009; 15: 6292-6300.

[14] Yang S, Guo H, Wei B, Zhu S, Cai Y, Jiang P and Tang J. Association of miR-502-binding site single nucleotide polymorphism in the 3'-untranslated region of SET8 and TP53 codon 72 polymorphism with non-small cell lung cancer in Chinese population. Acta Biochim Biophys Sin (Shanghai) 2014; 46: 149-154.

[15] Ding C, Li R, Peng J, Li S and Guo Z. A polymorphism at the miR-502 binding site in the 3' untranslated region of the SET8 gene is associated with the outcome of small-cell lung cancer. Exp Ther Med 2012; 3: 689-692.

[16] Narouie B, Ziaee SAM, Basiri A and Hashemi M. Functional polymorphism at the miR-502-binding site in the 3' untranslated region of the SETD8 gene increased the risk of prostate cancer in a sample of Iranian population. Gene 2017; 626: 354-357.

[17] Guo Z, Wu C, Wang X, Wang C, Zhang R and Shan B. A polymorphism at the miR-502 binding site in the 3'-untranslated region of the histone methyltransferase SET8 is associated with hepatocellular carcinoma outcome. Int J Cancer 2012; 131: 1318-1322.

[18] Xu JS, Bai YL, Zhang JX, Cui LW, Zhang HR and Zhang SL. Polymorphism at the miR-502 binding site in the 3' untranslated region of SET8 gene is associated with the risk of clear cell renal cell carcinoma. Zhonghua Zhong Liu Za Zhi 2016; 38: 476-480.

[19] Wang C, Guo Z, Wu C, Li Y, Kang S. A polymorphism at the miR-502 binding site in the 3'-untranslated region of the SET8 gene is associated with clinical characteristics and the prognosis of esophageal cancer. Cancer Genet 2012; 373-6.

[20] Hashemi M, Sheybani-Nasab M, Naderi M, Roodbari F and Taheri M. Association of functional polymorphism at the miR-502-binding site in the 3' untranslated region of the SETD8 gene with risk of childhood acute lymphoblastic leukemia, a preliminary report. Tumour Biol 2014; 35: 10375-10379.

[21] Tardat M, Murr R, Herceg Z, Sardet C and Julien E. PR-Set7-dependent lysine methylation ensures genome replication and stability through S phase. J Cell Biol 2007; 179: 1413-1426.

Supplementary Table 1. Details of the sensitivity analyses of the association between rs16917496polymorphism and cancer risk

Comparison	Study omitted	Estimate	Lower CI	Upper CI	Effect Model
T vs. C	Song (2009)	0.9338345	0.7249795	1.2028572	Random
	Yang (2013)	0.8920857	0.7305038	1.0894082	
	Wang (2012)	0.9161704	0.7316713	1.1471929	
	Xu (2016)	0.8889888	0.731027	1.0810833	
	Zhao (2013)	0.9326813	0.7569617	1.149192	
	Narouie (2017)	0.9944007	0.8265139	1.1963896	
	Hashemi (2014)	0.9425711	0.7619994	1.1659331	
	Guo (2011)	0.9176617	0.7416962	1.1353745	
	Ding (2012)	0.9440494	0.7687409	1.1593362	
	Yang (2014)	0.9973612	0.832228	1.1952607	
	Combined	0.9352541	0.7691781	1.1371882	
TT vs. CC	Song (2009)	1.0122812	0.5618224	1.8239096	Random
	Yang (2013)	0.8918439	0.5558963	1.4308164	
	Wang (2012)	0.9195159	0.5563051	1.5198664	
	Xu (2016)	0.8736534	0.5532239	1.3796772	
	Zhao (2013)	1.0005877	0.6140037	1.6305696	
	Narouie (2017)	1.1376862	0.7382992	1.7531238	
	Hashemi (2014)	0.9587656	0.60374	1.5225619	
	Guo (2011)	0.9601704	0.5830304	1.5812676	
	Ding (2012)	1.0151067	0.6244079	1.6502699	
	Yang (2014)	1.1203983	0.7115149	1.7642529	
	Combined	0.9846242	0.6240913	1.5534344	
TC vs. CC	Song (2009)	1.0733203	0.6758051	1.7046578	Random
	Yang (2013)	0.9939165	0.672514	1.468921	
	Wang (2012)	0.9723813	0.6649934	1.4218568	
	Xu (2016)	0.9547507	0.6780625	1.3443434	
	Zhao (2013)	1.0852402	0.7330195	1.6067053	
	Narouie (2017)	1.0933292	0.7157036	1.6702008	
	Hashemi (2014)	1.1831013	0.8369752	1.6723659	
	Guo (2011)	1.0502313	0.7009816	1.5734877	
	Ding (2012)	1.0819071	0.732374	1.5982585	
	Yang (2014)	1.1352502	0.7638752	1.6871773	
	Combined	1.0617567	0.733061	1.5378355	
TT+TC vs. CC	Song (2009)	0.9740056	0.594881	1.5947508	Random
	Yang (2013)	0.893796	0.5982791	1.3352818	
	Wang (2012)	0.8960053	0.5947917	1.3497592	
	Xu (2016)	0.8688652	0.5989154	1.26049	
	Zhao (2013)	0.985509	0.6515081	1.4907381	
	Narouie (2017)	1.0333093	0.6740712	1.5839992	
	Hashemi (2014)	1.0704316	0.7283189	1.5732446	
	Guo (2011)	0.9490401	0.6217878	1.4485281	
	Ding (2012)	0.9928483	0.6575411	1.4991424	
	Yang (2014)	1.071435	0.7207018	1.5928544	
	Combined	0.971915	0.6584963	1.434509	
TT vs. TC+CC	Song (2009)	0.8718028	0.6325784	1.2014957	Random
	Yang (2013)	0.8310675	0.6411284	1.0772775	

Wang (2012)	0.8703581	0.6489091	1.1673795
Xu (2016)	0.846744	0.6490481	1.1046568
Zhao (2013)	0.8660991	0.6666593	1.1252039
Narouie (2017)	0.9615302	0.7941751	1.1641517
Hashemi (2014)	0.8641741	0.6821531	1.0947644
Guo (2011)	0.8523606	0.6515032	1.1151419
Ding (2012)	0.8811335	0.6804513	1.141002
Yang (2014)	0.9389866	0.7401436	1.1912497
Combined	0.8776976	0.68779	1.1200411

Supplementary Table 2. *P*-values of the Begg's test and Egger's test for rs16917496 polymorphism in all model

Polymorphism	Comparison	Subgroup	Begg'test (p > z)	Egger'test (p > t)
rs16917496	T vs. C	Overall	0.721	0.938
	TT vs. CC	Overall	0.721	0.707
	TC vs. CC	Overall	1	0.994
	TT+TC vs. CC	Overall	0.721	0.999
	TT vs. TC+CC	Overall	1	0.934