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Original Article

The functional TERT MNS16A polymorphic tandem repeat minisatellite contributes to gliomas development

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Abstract: Background: MNS16A, located on chromosome 5p15.33 downstream of the human telomerase reverse transcriptase (hTERT) gene, was demonstrated to have some promoter activity and involved in tumorigenesis. The association between MNS16A polymorphism and the susceptibility of cancers was inconsistent in previous studies. Methods: Pooled odds ratio (OR) and 95% confidence interval (95% CI) were calculated using fixed- or random-effect model. Results: We assessed published studies of the association between MNS16A polymorphism and cancer risk from 13 studies with 5920 cases and 8268 controls. In the overall analysis, no significant associations were found between MNS16a polymorphism and cancer risk. However, significant associations between MNS16a polymorphisms and glioma risk were observed in the comparison of homozygote (SS versus LL: OR = 1.51, 95% CI: 1.17-1.95; $P_{heterogeneity}$ = 0.248; I^2 = 25.2%), dominant model (OR = 1.24, 95% CI: 1.05-1.46; $P_{heterogeneity}$ = 0.412; I^2 = 0%), and recessive model (OR = 1.39, 95% CI: 1.09-1.77; $P_{heterogeneity}$ = 0.325; I^2 = 0%). Conclusion: Taken together, our results indicate that the MNS16A polymorphism is associated with gliomas susceptibility. Additional larger studies were warranted to validate our findings.

Keywords: Cancer, meta-analysis, polymorphism, MNS16A

Introduction

Telomeres, the physical ends of eukaryotic linear chromosomes composed of characteristic TTAGGG repeats, function to prevent chromosome from degradation and maintain genome stability [1, 2]. Telomerase is a cellular ribonucleoprotein with a rate-limiting determinant of the reverse transcriptase activity which maintenance of telomeric repeats at the end of chromosomes [3-5]. Human telomerase reverse transcriptase (hTERT) encodes the catalytic subunit of telomerase holoenzyme and protects chromosomes from degradation [6, 7]. It has been shown that telomere-driven genome instability is a widespread cause of genome instability in cancer. On the other hand, enhanced telomerase expression is intimately linked to the development of the malignancy [8, 9]. Recent discoveries have shown that telomerase is inactivated in primary normal tissues but present in > 90% of cancer cells underlining the importance of telomerase in cell immortalization and tumorigenesis [10-12]. TERT siRNA effectively suppressed the formation of dicentric chromosomes and susceptibility to oncogenic transformation. Together, these findings demonstrated that reactivated *TERT* contributes to cellular proliferation and abnormal telomere maintenance in cancer cells.

In light of the already abundant evidence linking telomerase activity to the development of many tumor types, many efforts have been made to test the hypothesis that TERT gene polymorphism might affect individual cancer predisposition. Recently, variable tandem repeat of MNS16A has been identified in the downstream region of the hTERT gene, which functions as the regulator of *hTERT* promoter activity with the ability to regulate the expression of this antisense RNA. The core sequence of MNS16A is a 23 bp or a 26 bp sequence with a CAT insertion. Moreover, it was demonstrated that the biological function of the 26 bp tandem repeat with a CAT trinucleotide is a binding site for the transcription factor GATA-1, which functions as a repressor for the promoter of antisense

TERT mRNA. Recently, the TERT MNS16A has been studied in several malignancies, but the results remain controversial [13-25]. Therefore, we conduct a meta-analysis to evaluate the association between the MNS16a polymorphisms and cancer susceptibility.

Materials and methods

Publication search

We conducted a comprehensive search through the PubMed, Embase databases and Chinese National Knowledge Infrastructure (CNKI) databases for relevant articles in English and Chinese before Jan 20, 2017. The following keywords were used in isolation and combination with one another: "MNS16A" and "polymorphism or variant or mutation" and "cancer or carcinoma". There was no sample size limitation. The search was limited to human populations and articles were written in English or Chinese. We also included additional studies by a hand search of references of original or review articles on this topic to find other potentially eligible publications not indexed in common databases. All studies matching the eligible criteria were included in our meta-analysis.

Inclusion criteria

Eligible studies included in the current meta-analysis had to meet all the following criteria: (1) articles that evaluated the association between the MNS16A and cancer risk; (2) designed in case-control study; (3) providing sufficient information to calculate odds ratios (ORs) with their 95% confidence interval (CI).

Data extraction and quality assessment

Relevant data were independently extracted according to the inclusion criteria listed above by two reviewers and disagreement was resolved by discussion. From each of the eligible studies the following information was extracted: the name of first author, year of publication, ethnicity (Caucasian or Asian), cancer type, published language, genotyping methods, source of controls (population- or hospital-based controls), total number of cases and controls and numbers of cases and controls with MNS16A polymorphism genotypes, respectively.

The quality of the included studies was evaluated through a checklist originated from Strengthening the Reporting of Genetic Association (STREGA) recommendations for reports on genetic association studies [26].

Statistical methods

All statistical analyses were performed with the software Stata (version 11; Stata Corporation, College Station, Texas), and all tests were two sided. We classified the allele 213 bp, 240 bp, 243 bp, 271 bp, 272 bp, 274 bp as the S-allele, and 299 bp, 302 bp, 331 bp, 333 bp, 364 bp as the L-allele on the basis of their functional relevance. HWE among controls for each study was examined by goodness-of-fit chi-square test [27]. The crude odds ratios (ORs) and 95% confidence intervals (95% CIs) for genotypes were employed to assess the strength of the risk of cancer associated with the MNS16A polymorphism. The statistical significance of the summary OR was determined by *Z* test ($P < 0.05$ was considered statistically significant). The pooled ORs were calculated for a homozygote comparison model (SS versus LL), a heterozygote comparison model (SL versus LL), a dominant model (SS+SL versus LL), a recessive model (SS versus SL+LL), respectively. We performed stratification analyses on ethnicity, source of control and cancer types (if one cancer type contained less than two individual studies, they were combined into the 'other' group). Between-study heterogeneity was estimated using the chi-square-based Q-test [28]. If obvious heterogeneity existed among those included studies ($P < 0.05$), the pooled ORs were analyzed using the random effects model. Otherwise, If the Q-test revealed a *P* value of more than 0.05, the fixed-effects model was selected [29]. We also quantified the effect of heterogeneity by I^2 test to quantify the proportion of the total variation due to heterogeneity ($I^2 = 100\% \times (Q\text{-}df)/Q$), with $I^2 < 25\%$, 25-75% and > 75% to represent low, moderate and high degrees of inconsistency, respectively [30]. To assess the effects of individual studies on the overall risk of cancer, sensitivity analyses were performed by omitting each study. Finally, publication bias of literatures was estimated using the Begg's funnel plot and the degree of asymmetry was tested by Egger's test ($P < 0.05$ was considered a significant publication bias) [31, 32].

Table 1. Main characteristics of all studies included in the meta-analysis

First author	Year	Ethnicity	Cancer type	HWE	Genotyping methods	Source of controls	Cases	Controls	Case			Control		
									LL	LS	SS	LL	LS	SS
Wang	2003	Caucasians	Lung cancer	0.38	PCR	HB	53	72	30	17	6	33	29	10
Carpentier	2007	Caucasian	Glioma	0.21	PCR	PB	352	305	126	174	52	133	144	28
Wang	2008	Asian	Breast cancer	0.55	PCR	PB	1006	1095	860	141	5	984	107	4
Andersson	2009	Caucasian	Glioma	0.09	PCR	PB	648	1359	282	277	89	650	560	149
Jin	2011	Asian	Lung cancer	0.57	PCR	PB	937	943	820	110	7	840	101	2
Hofer	2011	Caucasian	Colorectal cancer	0.50	PCR	PB	88	1712	36	44	8	770	747	195
Zhang	2011	Asian	Nasopharyngeal carcinoma	0.20	PCR	PB	798	1019	725	71	2	891	121	7
Chang	2011	Asian	Lung cancer	0.59	PCR	PB	205	219	181	24	0	197	21	1
Zagouri	2012	Caucasian	Breast cancer	0.00	PCR	HB	113	124	50	36	27	63	29	32
Hofer	2013	Caucasian	Prostate cancer	0.81	PCR	HB	1137	650	501	499	137	308	277	65
Hashemi	2014	Asian	Breast cancer	0.00	PCR	PB	266	224	115	136	15	66	153	5
Wysoczanska	2015	Caucasian	Lymphoma	0.40	PCR	PB	75	126	28	37	10	53	54	19
Martino	2015	Caucasian	Renal cell cancer	0.84	PCR	PB	242	420	116	106	20	148	201	71

PB, Population Based; HB, Hospital Based.

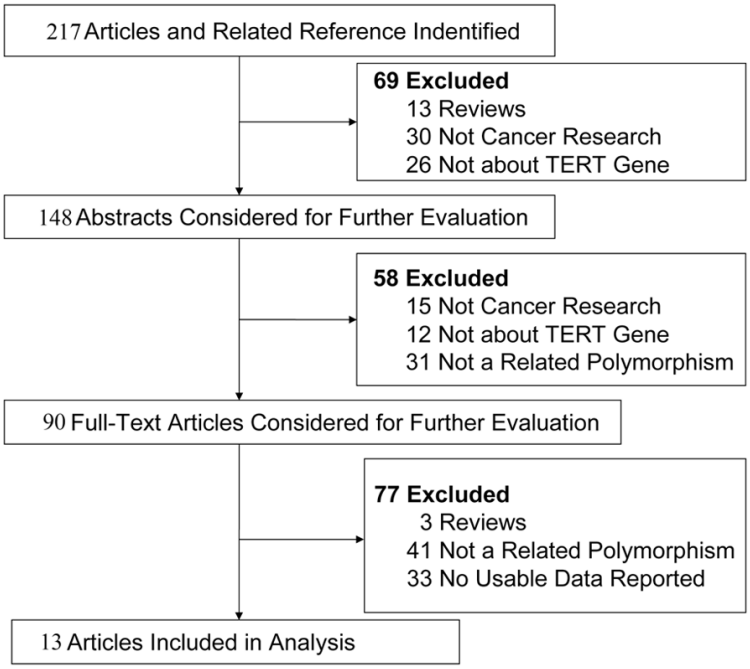

Figure 1. Flow chart showing study selection procedure.

Results

Literature search and study selection

Table 1 listed the main characteristics of eligible studies included in this meta-analysis. We identified a total of 13 relevant publications after initial screening (shown in **Figure 1**). Our final data consisted of 13 case-control studies [13-25], including 5920 cases and 8268 controls met the selection criteria. Among the 13 studies, 8 studies are of Caucasians and 5 studies are of Asians. There are 3 studies of hospital-based controls and the rest are population-based controls. Four cancer types were addressed: 2 studies on glioma, 3 studies on breast cancer, 3 studies on lung cancer and 5 on other cancers. The quality assessment of these included studies was provided in **Table 2**.

Quantitative synthesis

The results of meta-analysis based on 13 independent population samples with 5920 cases and 8268 controls for the MNS16A polymorphism and cancer risk are shown in **Table 3**. In the overall analysis, no significant associations were found between MNS16a polymorphism and cancer risk (SS versus LL: OR = 1.07, 95% CI: 0.78-1.47; $P_{heterogeneity}$ = 0.003; SL versus LL: OR = 1.03, 95% CI: 0.86-1.23; $P_{heterogeneity}$ = 0.000; dominant model: OR = 1.02, 95% CI: 0.85-1.22; $P_{heterogeneity}$ = 0.000; recessive model: OR = 1.06, 95% CI: 0.80-1.40; $P_{heterogeneity}$ = 0.011) (**Figure 2**).

Subgroup analyses

In addition, a subgroup analysis stratified by study characteristics was performed for a better understanding of the relationship between the MNS16A polymorphism and cancer risk.

In Caucasian and Asian population, MNS16a polymorphism was not associated with an increased risk in all genetic models.

As for cancer type, significant associations between MNS16a polymorphisms and gliomas risk were observed in the comparison of homozygote (SS versus LL: OR = 1.51, 95% CI: 1.17-1.95; $P_{heterogeneity}$ = 0.248; I^2 = 25.2%), dominant model (OR = 1.24, 95% CI: 1.05-1.46; $P_{heterogeneity}$ = 0.412; I^2 = 0%), and recessive model (OR = 1.39, 95% CI: 1.09-1.77; $P_{heterogeneity}$ = 0.325; I^2 = 0%). No significant associations were found for the other cancers.

Stratification based on the source of controls showed no significant associations between the polymorphism and risk of cancer in the population-based subgroup and hospital-based subgroup.

Test of heterogeneity

In this meta-analysis, substantial heterogeneities were observed in overall comparison in all genetic models (SS versus LL: $P_{heterogeneity}$ = 0.003, SL versus LL: $P_{heterogeneity}$ = 0.000; dominant model: $P_{heterogeneity}$ = 0.000; recessive model: $P_{heterogeneity}$ = 0.011). When stratified by ethnicity, cancer type and source of control, the heterogeneity was partly decreased in Caucasians (SL versus LL: $P_{heterogeneity}$ = 0.080), Asians (SS versus LL: $P_{heterogeneity}$ = 0.272; recessive model: $P_{heterogeneity}$ = 0.187), gliomas (SS versus LL: $P_{heterogeneity}$ = 0.248; SL versus LL:

Table 2. Table Quality assessment of included studies

Last name of first author	Year	Clear description of background, objectives and study design	Clear eligibility criteria	Clear Definition of variables	Credible genotyping methods	Hardy-Weinberg equilibrium assessment	Clear Description of statistical methods	Summary of characteristics of participants	Publicly available genotype data	Comprehensive discussion
Wang	2003	+	+	+	+	+	+	+	+	+
Carpentier	2007	+	+	+	+	+	+	+	+	+
Wang	2008	+	+	+	+	-	+	+	+	+
Andersson	2009	+	+	+	+	-	+	+	+	+
Jin	2011	+	+	+	+	-	+	+	+	+
Hofer	2011	+	+	+	+	+	+	+	+	+
Zhang	2011	+	+	+	+	+	+	+	+	+
Chang	2011	+	+	+	+	-	+	+	+	+
Zagouri	2012	+	+	+	+	+	+	+	+	+
Hofer	2013	+	+	+	+	+	+	+	+	+
Hashemi	2014	+	+	+	+	+	+	+	+	+
Wysoczanska	2015	+	+	+	+	-	+	+	+	+
Martino	2015	+	+	+	+	-	+	+	+	+

"+": detailed description; "±": incomplete description; "-": no description.

Table 3. Stratified analyses of the *MNS16A* polymorphism on cancer risk

Variables	n	Cases/controls	SS versus LL		LS versus LL		Dominant model		Recessive model	
			OR (95% CI)	P^a	OR (95% CI)	P^a	OR (95% CI)	P^a	OR (95% CI)	P^a
Total	13	5920/8268	1.07 (0.78-1.47)	0.003	1.03 (0.86-1.23)	0.000	1.02 (0.85-1.22)	0.000	1.06 (0.80-1.40)	0.011
Source of control										
Hospital based	3	1303/846	1.19 (0.90-1.58)	0.488	1.11 (0.92-1.34)	0.215	1.12 (0.94-1.34)	0.270	1.13 (0.86-1.47)	0.529
Population based	10	4617/7422	1.06 (0.67-1.69)	0.001	1.01 (0.81-1.26)	0.000	1.01 (0.80-1.27)	0.000	1.07 (0.71-1.61)	0.004
Ethnicity										
Caucasian	8	2708/4768	1.02 (0.71-1.47)	0.001	1.09 (0.97-1.22)	0.080	1.06 (0.87-1.30)	0.006	0.99 (0.74-1.34)	0.010
Asian	5	3212/3500	1.31 (0.72-2.37)	0.272	0.95 (0.64-1.40)	0.000	0.95 (0.65-1.40)	0.000	1.53 (0.85-2.75)	0.187
Cancer type										
Glioma	2	1000/1664	1.51 (1.17-1.95)	0.248	1.18 (0.99-1.39)	0.568	1.24 (1.05-1.46)	0.412	1.39 (1.09-1.77)	0.325
Breast cancer	3	1385/1443	1.25 (0.76-2.05)	0.725	1.05 (0.49-2.26)	0.000	1.02 (0.53-1.99)	0.000	1.23 (0.77-1.96)	0.207
Lung cancer	3	1195/1234	1.14 (0.51-2.57)	0.180	1.07 (0.84-1.37)	0.379	1.09 (0.86-1.39)	0.315	1.23 (0.56-2.73)	0.229
Other cancer	5	2340/3927	0.73 (0.39-1.38)	0.002	0.94 (0.72-1.23)	0.020	0.91 (0.66-1.24)	0.002	0.74 (0.44-1.24)	0.015

[a]*P* value of Q-test for heterogeneity test.

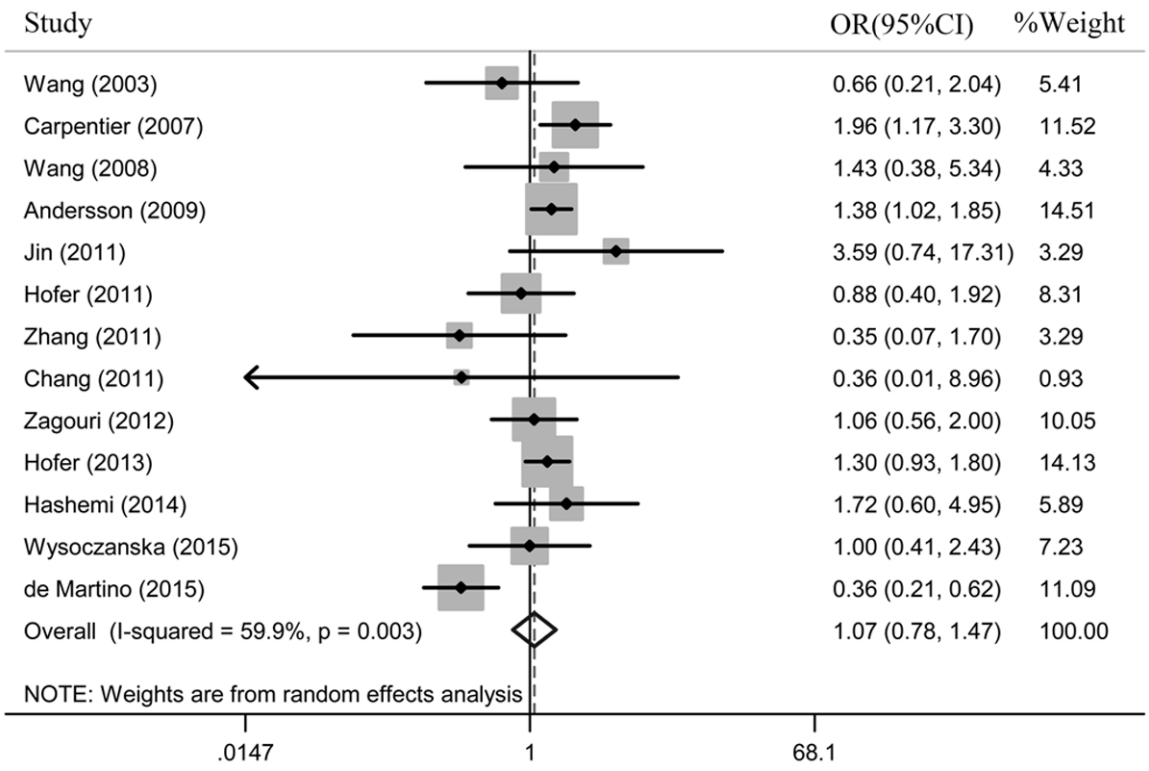

Figure 2. Meta-analysis of the association between MNS16A polymorphism and susceptibility to cancer (SS versus LL).

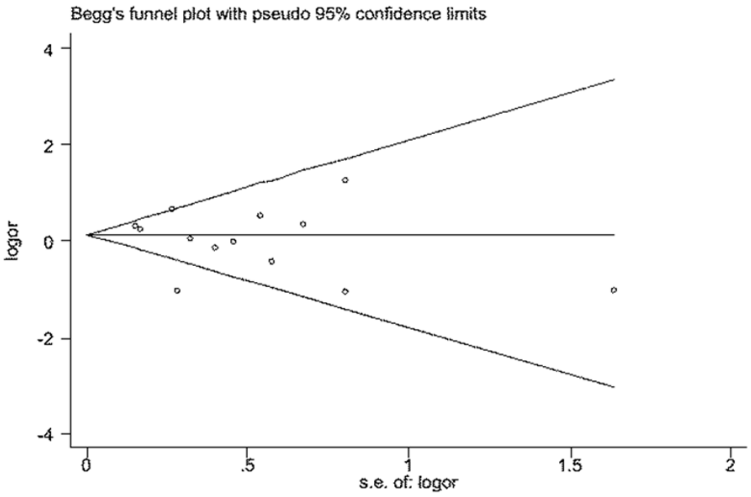

Figure 3. Begg's funnel plot for publication bias test (SS versus LL).

$P_{heterogeneity}$ = 0.568; dominant model: $P_{heterogeneity}$ = 0.412; recessive model: $P_{heterogeneity}$ = 0.325), lung cancers (SS versus LL: $P_{heterogeneity}$ = 0.180; SL versus LL: $P_{heterogeneity}$ = 0.379; dominant model: $P_{heterogeneity}$ = 0.315; recessive model: $P_{heterogeneity}$ = 0.229), breast cancers (SS versus LL: $P_{heterogeneity}$ = 0.725; recessive model: $P_{heterogeneity}$ = 0.207) and hospital-based populations (SL versus LL: $P_{heterogeneity}$ = 0.215; dominant model: $P_{heterogeneity}$ = 0.270).

Although there 2 studies [20, 22] that deviated from HWE for the MNS16a polymorphism, respectively, the corresponding pooled ORs were not materially altered by not including these studies (SS versus LL: OR = 1.03, 95% CI: 0.71-1.49; $P_{heterogeneity}$ = 0.001; I^2 = 65.9%).

Sensitivity analysis

Then the leave-one-out sensitivity analysis was performed by excluding each study individually to evaluate the influence of the individual data set to pooled ORs. The statistical significance of the results was not impacted by single study, confirming the stability of the results.

Assessment of bias

Begg's funnel plot and Egger's test were performed to assess the publication bias. The shape of the funnel plot did not reveal any evidence of obvious asymmetry (**Figure 3**). The results did not suggest any evidence of publication bias (P = 0.433 for SS versus LL), and the 95% confidence interval (95% CI: -2.49, 1.14) included zero, indicating no publication bias.

Discussion

Telomerase regulation and telomere maintenance have been the subject of intense research focus in the past decade. In this study, we conducted a comprehensive literature search in different databases and assessed the associations of the functional TERT gene MNS16A polymorphism with the risk of cancer. Compared with the previous study, our meta-analysis included 3 additional studies on the polymorphism [22-24]. Therefore, this update meta-analysis has more statistical power than the 2 previous studies [33, 34]. Overall, we observed positive association between the MNS16A polymorphism and the glioma risk in the homozygote comparison model, dominant model and the recessive model.

The TERT gene encodes the catalytic subunit of telomerase complex and plays a critical role in protecting the ends of the chromosome which are truncated during cell division [35]. The cancer-specific expression of TERT contributes to malignant transformation and progression [36]. Recent findings indicate that 90% of human tumors possess telomerase activity, irrespective of tumor type [37-39]. Telomerase activation in most cancer cells suggests that enhanced telomerase expression is critical for cellular immortality and carcinogenesis. The role of telomerase activation has been identified for human carcinogenesis, but the activation mechanism remains unclear. Recent discoveries have suggested that the modification of *TERT* and alternate *TERT* mRNA splicing play a critical role in the regulation of telomerase activity [40]. Wang et al. suggested a novel *TERT* gene regulating mechanism based on the finding of a variable tandem repeat polymorphism MNS16A by in situ hybridization. MNS16A, located in the downstream region of the TERT gene locus, is identified in the putative promoter region of this antisense RNA transcript with the ability to regulate the expression of antisense hTERT messenger RNA level as well as telomerase activity. The VNTR-302 allele, which contains two 23 bp repeats and three 26 bp repeats, has a significantly lower promoter activity and antisense *TERT* mRNA expression when compared with the VNTR-243 allele, which contains one 23 bp repeat and two 26 bp repeats. Luciferase reporter assay have shown that shorter VNTRs had higher promoter activity in cell lines of colorectal, lung and prostate cancer. These findings support the role of *TERT* MNS16A polymorphism in malignant progression.

In present work, we observed that the MNS16A polymorphism might modulate the gliomas risk. One possible reason is that cancer of different sites has variant tumor microenvironment that regulates or influences the gene expression profiles. The same polymorphism may exert different effects in variant cancers.

Heterogeneity is a potential problem when interpreting the results of all meta-analysis. In this meta-analysis, heterogeneity was found in all genetic models. When stratified by ethnicity, cancer type and source of control, heterogeneity was partly decreased in Caucasians, Asians, gliomas, lung cancers, breast cancers and hospital-based populations. Then sensitivity analyses were conducted by successively excluding one study. The estimated pooled odd ratio changed quite little, strengthening the results from this meta-analysis. No publication bias was shown suggesting this possible true result.

Although meta-analysis is robust, there are several limitations in the current study need to be addressed in interpreting the results. First, original data shortage limited our further evaluation of potential gene-environment interactions. Second, lacking sufficient eligible studies limited our further stratified analysis, particularly for subgroup analysis by cancer type. Third, this meta-analysis was based on unadjusted ORs, while a more precise estimation should take into account the effect of multiple confounders such as smoking and drinking status. Fourth, most studies in the meta-analysis were retrospective design which could suffer more risk of bias owing to the methodological deficiency of retrospective studies. Despite those limitations above, our meta-analysis also

has some advantages. First, it contains the latest data about association between MNS16A polymorphism and cancer risk. Second, we conducted four types of genotype analysis and subgroup analysis by cancer site, ethnicity and source of controls. Third, publication bias was not found in our meta-analysis.

In conclusion, this comprehensive meta-analysis of high-quality studies provides substantial evidence that the MNS16A polymorphism is associated with gliomas susceptibility. Our findings need to be validated by further functional studies as well as well-designed larger studies.

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Disclosure of conflict of interest

None.

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