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Original Article

Association of *CCDC26* rs4295627 polymorphism with risk of glioma

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Abstract: Background: Glioma is one of the most deadly human tumours. Though the exact etiology of the disease remains unknown, hereditary factors have been implicated therein. A number of studies have pointed out that associations exist between coiled-coil domain containing protein 26 (*CCDC26*) rs4295627 polymorphism and the onset risk of glioma, but their results are not always consistent. Thus, we conducted this meta-analysis to systematically investigate this issue. Methods: A comprehensive literature search in PubMed, Wanfang, Embase and Chinese National Knowledge Infrastructure (CNKI) was performed to find relevant studies investigating associations between *CCDC26* rs4295627 polymorphism and glioma risk, and finally 6785 cases and 12375 controls were included. STATA software (V. 12.0) was used for all the statistical calculations and analyses. Crude odds ratios (ORs) and 95% confidence intervals were calculated for the association analysis of *CCDC26* rs4295627 polymorphism and the risk of glioma. Heterogeneity analysis and sensitivity analysis were also carried out. Results: The pooled results indicated that the *CCDC26* rs4295627 polymorphism contributed to the increased risk of glioma under GG vs. TT, GG+TG vs. TT, GG vs. TT+TG, allele G vs. allele T, and TG vs. TT genetic contrasts (OR=1.71, 95% CI=1.29-2.27; OR=1.23, 95% CI=1.16-1.30; OR=1.59, 95% CI=1.21-2.09; OR=1.25, 95% CI=1.15-1.36; OR=1.21, 95% CI=1.13-1.28). The stratified analysis based on source of control and ethnicity also revealed significantly increased glioma risk under all the five contrasts among both population-based and hospital-based populations as well as the Caucasian group. Conclusions: The *CCDC26* rs4295627 polymorphism may serve as an independent contributor to the risk of glioma, especially among Caucasians.

Keywords: *CCDC26*, glioma, polymorphism

Introduction

Glioma accounts for about 80% of all malignant brain tumors and 30% of all brain and central nervous system tumors [1]. There are approximately 21,000 annual cases of glioma in the United States, and 50% of the glioma patients can survive no longer than five years after being first diagnosed [2, 3]. Subtypes of the disease include astrocytoma, ependymoma, medulloblastoma, pinealoma, and glioblastoma (GBM). Exposure to ionizing radiation is the only conclusively identified environmental risk factor for glioma; and the importance of genetic factors in the pathology of the disease is indicated by family accumulation of glioma cases as well as studies investigating candidate genes [2, 4-7]. Well-established genetic syndromes correlated with the enhanced glioma risk include multiple enchondromatosis, neurofibromatosis type 1, and Turcot and Li-Fraumeni syndromes [8]. It has been suggested that the inherited disease risk is caused by the coinheritance of a number of low-risk mutations [9]. *IDH1* and *IDH2* polymorphisms act as molecular markers in diagnosis and prognosis of glioma assessment process [10].

To determine risk factors which can be modified to achieve the disease prevention purpose is the present epidemiology trend for glioma [11-13]. Fortunately, genome-wide association studies (GWA study) concerning single nucleotide polymorphisms (SNPs) associated with cancer have recently become possible due to advancements in commercial arrays which can capture most common genome mutations, and several hundred cancer-related common genetic mutations have been successfully identified [14]. Five SNPs significantly correlated with the

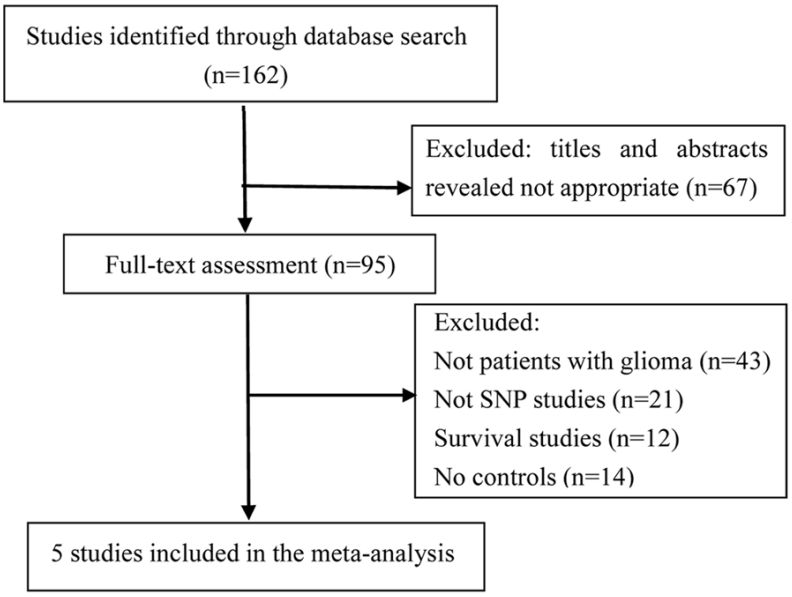

Figure 1. Flowchart showing the selection process of eligible studies.

risk of glioma have been recently discovered, including *CDKN2A-CDKN1B* rs4977756 at 9p21.3, *RTTEL1* rs6010620 at 20q13.33, *PHLDB1* rs498872 at 11q23.3, *TERT* rs27-36100 at 5p15.33, and *CCDC26* rs4295627 at 8q24.21 [11, 12].

The *CCDC26* gene is involved in the modulation of cell differentiation and death, and association between the rs4295627 polymorphism in the gene and the glioma susceptibility has been discussed by many researches though the results are inconclusive. In this study, we decided to summarize a total of 6785 cases and 12375 controls so as to shed some more light on the susceptibility to glioma linked to *CCDC26* rs4295627 polymorphism.

Materials and methods

Study identification

A comprehensive literature search in electronic databases such as PubMed, Embase, and Wanfang was carried out for identification of eligible studies. Terms and keywords used in the searching process included: "glioma", "*CCDC26*", "risk" or "susceptibility", "association" or "relationship", "polymorphism" or "variation" or "mutation". We also manually screened the reference lists of relevant reviews and articles to avoid missing any additional studies.

Inclusion and exclusion criteria

We utilized the following criteria to identify eligible studies: a case-control study containing sufficient information about genotype frequencies for the calculation of odds ratios (ORs) and 95% confidence intervals (95% CIs); having information on the estimation of *CCDC26* rs4295627 polymorphism and glioma risk; and when more than one article contained the same study population, the most informative one was included in our meta-analysis. The exclusion criteria we used included: not concerning *CCDC26* rs4295627 polymorphism or the risk of glioma; having no usable data; and duplicates of other articles.

Data extraction

Two researchers carefully completed the extraction of information from all the eligible articles according to a standard data extraction form. Conflicting opinions were resolved through discussion. The information extracted from each eligible study included: first author's name, publication year, country, ethnicity, control source, genotyping method, sample size, genotype and allele frequency, and *P* value for HWE.

Statistical methods

We evaluated the risk of glioma associated with *CCDC26* rs4295627 polymorphism under genetic contrasts of GG vs. TT, GG+TG vs. TT, GG vs. TT+TG, allele G vs. allele T, and TG vs. TT by calculating summary ORs with their corresponding 95% CIs. We also carried out subgroup analyses according to ethnicity and source of control. The STATA software (V. 12.0) was used to perform the statistical analysis. The Chi-square-based Q-statistic test was employed for the testing of heterogeneity across the selected studies. When a *P* value >0.05 for the Q-test indicated no significant

Table 1. Major characteristics of eligible studies accepted into the present meta-analysis

First author		Shete (France)	Shete (German)	Shete (Sweden)	Shete (England)	Shete (America)	Schoemaker (Denmark)	Schoemaker (Finland)	Schoemaker (Sweden)	Schoemaker (UK-North)	Schoemaker (UK-South)	Wang	Li	Safaeian (NCI)	Safaeian (NIOSH)	Safaeian (AHS)	Safaeian (ATBC)	Safaeian (PLCO)
Year		2009	2009	2009	2009	2009	2010	2010	2010	2010	2010	2011	2012	2013	2013	2013	2013	2013
Country		America	America	America	America	America	England	England	England	England	England	America	China	America	America	America	Finland	America
Ethnicity		Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Asian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
Control source		PB	PB	PB	PB	HB	PB	PB	PB	PB	PB	Mixed	PB	PB	PB	PB	PB	PB
Genotyping method		PCR/MALDI-TOF MS	PCR/MALDI-TOF MS	PCR/MALDI-TOF MS	PCR/MALDI-TOF MS	PCR/MALDI-TOF MS	PCR	PCR	PCR	PCR	PCR	HumanHap	MassARRAY	HumanHap	HumanHap	HumanHap	HumanHap	HumanHap
Sample size	Case	1374	498	643	631	1246	123	97	199	375	232	332	225	322	300	18	37	133
	Control	1579	571	775	1434	2235	147	95	372	617	396	817	254	385	538	23	1270	855
TT	Case	885	283	393	386	735	76	47	130	237	137	187	121	182	179	17	22	83
	Control	1133	414	492	976	1496	98	58	241	434	266	556	127	267	357	12	794	584
TG	Case	418	185	223	216	451	40	34	63	122	83	121	92	123	107	1	13	40
	Control	421	144	247	410	667	46	31	117	156	119	242	102	107	158	0	410	248
GG	Case	71	30	27	29	60	7	16	6	16	12	24	12	17	14	0	2	10
	Control	25	13	36	48	72	3	6	14	27	11	19	25	11	23	0	66	23
T	Case	2188	751	1009	988	1921	192	128	323	596	357	495	334	487	465	35	57	206
	Control	2687	972	1231	2362	3659	242	147	599	1024	651	1354	356	641	872	58	1998	1416
G	Case	560	245	277	274	571	54	66	75	154	107	169	116	157	135	1	17	60
	Control	471	170	319	506	811	52	43	145	210	141	280	152	129	204	12	542	294
HWE		0.04	0.91	0.49	0.54	0.75	0.37	0.51	0.97	0.01	0.59	0.22	0.50	0.94	0.30	0.22	0.17	0.58

HB: hospital-based; PB: population-based; PCR: polymerase chain reaction; MALDI-TOF: matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; TaqMan: TaqManSNP; NCI: the National Cancer Institute; NIOSH: the National Institute for Occupational Safety and Health; PLCO: the Prostate, Lung, Colorectal and Ovarian; ATBC: the Alpha-Tocopherol, Beta-Carotene; AHS: the Agricultural Health Study; HWE: Hardy-Weinberg equilibrium.

Table 2. *CCDC26* rs4295627 polymorphism and glioma risk

		Ethnicity		Source of control			Total
		Caucasian	Asian	Population	Hospital	Mixed	
GG versus TT	OR (95% CI)	1.85 (1.43, 2.39)	0.55 (0.27, 1.13)	1.62 (1.17, 2.24)	1.64 (1.15, 2.34)	3.44 (1.85, 6.41)	1.71 (1.29, 2.27)
	Ph	0.006	0.000	0.001	0.000	0.000	0.000
GG+TG versus TT	OR (95% CI)	1.24 (1.17, 1.32)	0.92 (0.67, 1.27)	1.21 (1.13, 1.30)	1.24 (1.09, 1.42)	1.37 (1.08, 1.74)	1.23 (1.16, 1.30)
	Ph	0.571	0.000	0.331	0.000	0.000	0.410
GG versus TT+TG	OR (95% CI)	1.71 (1.32, 2.20)	0.54 (0.27, 1.10)	1.51 (1.10, 2.07)	1.49 (1.05, 2.12)	3.11 (1.68, 5.75)	1.59 (1.21, 2.09)
	Ph	0.006	0.000	0.001	0.000	0.000	0.000
G versus T	OR (95% CI)	1.28 (1.19, 1.38)	0.86 (0.66, 1.13)	1.23 (1.12, 1.35)	1.26 (1.12, 1.42)	1.49 (1.20, 1.83)	1.25 (1.15, 1.36)
	Ph	0.079	0.000	0.012	0.000	0.000	0.013
TG versus TT	OR (95% CI)	1.22 (1.14, 1.30)	0.97 (0.69, 1.36)	1.19 (1.11, 1.28)	1.23 (1.07, 1.42)	1.30 (1.00, 1.67)	1.21 (1.13, 1.28)
	Ph	0.735	0.000	0.568	0.000	0.000	0.678

Ph: *P*-value of heterogeneity test.

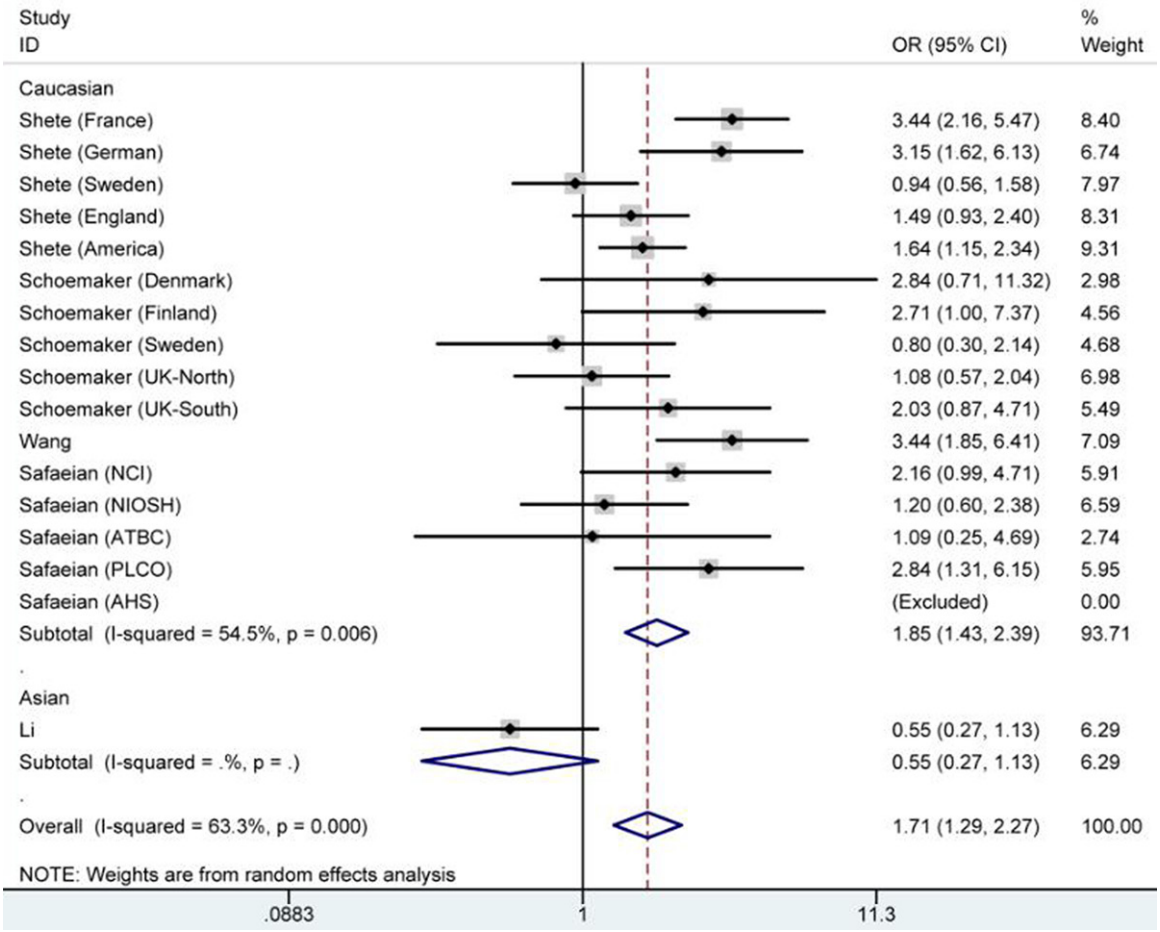

Figure 2. *CCDC26* rs4295627 polymorphism and glioma risk under GG vs. TT model.

heterogeneity, we applied the Mantel-Haenszel method (the fixed-effects model) to calculate the pooled ORs; and the Dersimonian and Laird method (the random-effects model) was adopted in the opposite case. Z-test was used to illustrate the significance of the overall ORs. The Chi-square test was utilized to detect deviations from Hardy-weinberg Equilibrium (HWE) of genotypic and allelic distributions of the control group. The stability of the results was examined through sensitivity test in which each individual study was excluded one by one. The potential

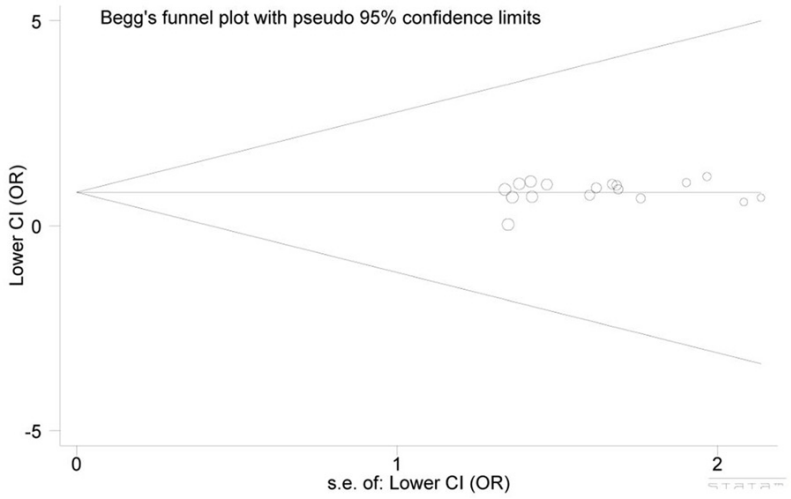

Figure 3. Begg's funnel plot indicating publication bias.

publication bias was assessed with Begg's and Egger's tests.

Results

Study characteristics

The study selection process is outlined in **Figure 1**. A total of 162 articles were initially identified through the search in electronic databases. First, we excluded 67 studies for their inappropriate titles and abstracts. After reviewing the remained 95 articles, we excluded 43 with no glioma patients, 21 not about *CCDC26* rs4295627 polymorphism, 12 survival studies, and 14 with no controls. Consequently, we included altogether 6785 cases and 12375 controls into our meta-analysis [3, 12, 15-17]. All characteristics of each study accepted into the present meta-analysis are described in **Table 1**.

Quantitative data synthesis

As shown in **Table 2**, the overall ORs and 95% CIs reflected that the *CCDC26* rs4295627 polymorphism increased the risk of glioma under all the five genetic models of GG vs. TT, GG+TG vs. TT, GG vs. TT+TG, allele G vs. allele T, and TG vs. TT (OR=1.71, 95% CI=1.29-2.27; OR=1.23, 95% CI=1.16-1.30; OR=1.59, 95% CI=1.21-2.09; OR=1.25, 95% CI=1.15-1.36; OR=1.21, 95% CI=1.13-1.28) (**Figure 2**). Furthermore, we found apparently increased susceptibility to glioma under all genetic comparisons in both the population- and hospital-based groups as well as the Caucasian group in the stratification analyses on the basis of source of control and ethnicity.

Sensitivity analysis

We examined the influence of each included study on the summary results by repeatedly performing the meta-analysis process after excluding the eligible studies one at a time. Since the pooled ORs had no excessive change, our results proved to be robust and reliable.

Publication bias

Begg's funnel plot and Egger's linear regression test were respectively employed to qualitatively and quantitatively assess the existence of any possible publication bias. The funnel plots under all genetic models had obviously symmetrical shapes (**Figure 3**), and *P* values greater than 0.05 in Egger's test also showed no great publication bias (*P*=0.272).

Discussion

Glioma is the most common brain tumor in both adults and pediatric individuals [18, 19]. The disease has the characteristics of no definite boundary with normal brain tissues, low response rate to surgery and infiltrative growth, so the prognosis thereof is very poor [20]. In spite of great advances in people's understanding of the etiology of glioma due to more and more relevant researches, the public health is still subjected to great damages caused by the disease [18, 19, 21]. Therefore, it is of great significance to figure out the pathogenesis of glioma. Except exogenous factors, genetic factors have been indicated by increasing evidence to play essential roles in the susceptibility of the host to glioma [22-24]. The *CCDC26* rs4295627 polymorphism has been reported to be a susceptible locus for glioma, but the conclusions are controversial.

After a summarized analysis of 17 groups of data contained in five studies, we obtained an

overall conclusion that the *CCDC26* rs4295627 polymorphism might confer an increased risk of glioma under all comparisons of GG vs. TT, GG+TG vs. TT, GG vs. TT+TG, allele G vs. allele T, and TG vs. TT. Population- and hospital-based populations as well as the Caucasian group also showed an obviously enhanced glioma risk under the above genetic models in ethnicity- and control source-specific analyses. Nevertheless, mixed opinions are held by different studies.

Shete et al. have performed a meta-analysis of two GWA studies conducted in UK and US respectively by genotyping 550,000 tagging DNAs to find out risk loci for glioma, and have discovered *CCDC26* rs4295627 polymorphism as a susceptible locus for glioma [12]. Another study performed by Wang et al. has also found that the *CCDC26* rs4295627 polymorphism is statistically correlated with the risk of glioma in women [15]. Furthermore, Safaeian et al. have drawn the same conclusion with the above two studies [16]. However, there are also different results. Based on the fact that five SNPs have been identified by two GWAS, Robert et al. have explored whether the five SNPs are associated with the risk of glioma in general or with that of specific glioma subtypes, and their conclusion is that polymorphisms in the region 8q24 of *CCDC26* where rs4295627 is located are linked to the risk of oligodendroglial tumor, but not the risk of GBM [25]. The controversies described above about the association between *CCDC26* rs4295627 and glioma risk are possibly due to several aspects such as restricted sample sizes, case subjects selected not according to the same selection and exclusion criteria, and different genotyping methods.

Since the statistical evidence of our meta-analysis is powerful and subgroup analyses based on ethnicity and control source were also conducted, our conclusions are relatively convincing. Nevertheless, some limitations need to be acknowledged. First of all, the connection between *CCDC26* rs4295627 polymorphism and various subtypes of glioma was not discussed owing to insufficient data. Second, effects of gene-environment and gene-gene interactions on the risk of glioma were not researched. Third, no adjustment of exogenous factors may lead to biased results. In conclusion, the *CCDC26* rs4295627 polymorphism may be independently correlated with glioma risk. Considering the above shortcomings of our study, further studies are required to ascertain our results.

Disclosure of conflict of interest

None.

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