

Association of the CCDC26 rs4295627 polymorphism with the risk of glioma: Evidence from 7,290 cases and 11,630 controls

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Abstract. Published data on the association between the coiled-coil domain-containing 26 (CCDC26) rs4295627 polymorphism and the risk of glioma have been inconclusive. To further investigate this association, a meta-analysis was performed. By a comprehensive literature search using PubMed and EMBASE databases, a total of 16 case-control studies were identified for inclusion in the meta-analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess this association. Our results confirmed that the risk with allele G was higher compared with that with allele T for glioma. The results indicated that the allele G of rs4295627 polymorphism in the CCDC26 gene was associated with increased risk of glioma in the homozygote model (GG vs. TT, OR=1.936, 95% CI: 1.500-2.658, P<0.001), the heterozygote model (GT vs. TT, OR=1.323, 95% CI: 1.241-1.412, P=0.206), the dominant model (GG+GT vs. TT, OR=1.375, 95% CI: 1.256-1.505, P=0.026), the recessive model (GG vs. GT+TT, OR=1.769, 95% CI: 1.302-2.403, P<0.001) and the allele model (G vs. T, OR=1.310, 95% CI: 1.185-1.448, P<0.001). Current evidence suggests that the rs4295627 polymorphism in the CCDC26 gene may contribute to glioma susceptibility. However, further case-control studies are required to confirm our results.

Introduction

Glioma is the most common type of central nervous system (CNS) tumor in adults, accounting for ~80% of CNS tumors, with a dismal prognosis (1). However, gliomagenesis is yet to be understood. Exposure to ionizing radiation is the only identified environmental risk factor for glioma supported

by strong evidence (2). However, not all individuals exposed to radiation ultimately develop glioma, suggesting that other causes, including host genetic factors, may play a critical role in the process of gliomagenesis.

In recent years, several genes have been identified as potential glioma susceptibility genes, including RAD51, TP53, telomerase reverse transcriptase and regulator of telomere elongation helicase 1 (3-8). Another important gene is coiled-coil domain-containing 26 (CCDC26), which increases the apoptosis of glioblastoma cells by modulating differentiation and apoptosis following induction by retinoic acid treatment (9). The CCDC26 gene is located on chromosome 8q24.21. The rs4295627 polymorphism is located in intron 3 of the CCDC26 gene. The G→A change in this single-nucleotide polymorphism (SNP) has been reported by several studies to affect CCDC26 expression and glioma risk (8,10-14). However, the results were inconclusive, partially due to the possible small effect of the polymorphism on glioma risk and the relatively small sample size in each of published studies. Therefore, a meta-analysis was performed to evaluate the association between the rs4295627 polymorphism and the risk of glioma.

Materials and methods

Publication search. A computerized literature search was conducted through PubMed and EMBASE databases to identify the relevant studies evaluating the association between the CCDC26 rs4295627 polymorphism and the risk of glioma, using the following search terms: 'CCDC26' or 'rs4295627', 'polymorphism' or 'variation' and 'glioma'. The search was limited to human studies. The last search was performed on March 28th, 2015. All selected studies were retrieved and their bibliographies were checked for other relevant publications. References from related articles were also reviewed for additional eligible studies. Only published studies with full-text articles were included.

Inclusion criteria. The inclusion criteria were as follows: i) Evaluation of the CCDC26 and glioma risk; ii) case-control studies; and iii) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI).

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Data extraction. Information was carefully extracted from all eligible publications by two authors independently, and any disagreements were resolved by discussion. Conflicting evaluations were resolved by discussion and by consulting a senior reviewer to reach a final decision. The following data were collected from each study: First author, publication year, country of origin, ethnicity, total number of cases and controls, and genotype frequency of cases and controls. We did not define any minimum number of patients for inclusion in our meta-analysis.

Statistical analysis. Crude ORs with 95% CIs were used to assess the strength of the association between the CCDC26 polymorphism and glioma risk. The pooled ORs were performed with the additive model (GT vs. TT; GG vs. TT), dominant model (GT+GG vs. TT), recessive model (GG vs. GT+TT) and allele model (G vs. T). Heterogeneity was assessed by the Chi-square-based Q test. If the P-value was >0.10, indicating a lack of heterogeneity among studies, the pooled OR estimate of the each study was calculated by the fixed-effects model. Otherwise, the random-effects model (DerSimonian-Laird method) was applied (15). A sensitivity analysis was performed to assess the stability of the results. A single study involved in the meta-analysis was deleted each time to reflect the effect of the individual data set on the pooled OR. Funnel plots, Begg's tests and Egger's tests were performed to diagnose potential publication bias (P<0.05 was considered representative of statistically significant publication bias) (16). All the statistical tests were performed with Stata software, version 11.0 (Stata Corporation, College Station, TX, USA).

Results

Study characteristics. A total of 6 publications including 16 case-control studies met the inclusion criteria (8,10-14). The study selection process is outlined in Fig. 1. These studies were published between 2009 and 2015. Two studies were conducted in America, one in China, one in Sweden and two were multi-country studies. In total, 7,290 cases and 11,630 controls were used in the pooled analyses. In the 16 studies, the sample size ranged from 95 to 1,579 subjects. Of the 16 studies, 15 included a Caucasian population and 1 study included an Asian population. The main characteristics of the studies are summarized in Table I.

Meta-analysis results. The main results of the meta-analysis are listed in Table II. Our results confirmed that the risk for glioma with allele G was higher compared with that with allele T. The results indicated that the allele G of rs4295627 polymorphism in the CCDC26 gene was associated with increased risk of glioma in the homozygote model (GG vs. TT, OR=1.936, 95% CI: 1.500-2.658, P<0.001), the heterozygote model (GT vs. TT, OR=1.323, 95% CI: 1.241-1.412, P=0.206), the dominant model (GG+GT vs. TT, OR=1.375, 95% CI: 1.256-1.505, P=0.026), the recessive model (GG vs. GT+TT, OR=1.769, 95% CI: 1.302-2.403, P<0.001) and the allele model (G vs. T, OR=1.310, 95% CI: 1.185-1.448, P<0.001). Subgroup analyses by ethnicity and source of controls were not performed, as there was only one Asian case-control study with a small sample size and a small hospital-based

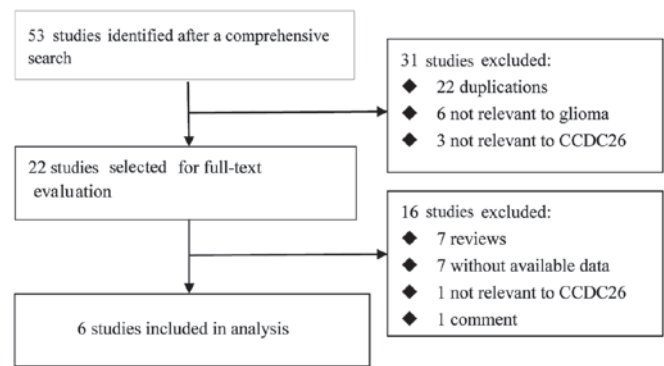


Figure 1. Flow diagram of the study selection process. CCDC26, coiled-coil domain-containing 26.

population. The forest plot for the CCDC26 rs4295627 polymorphism in the homozygote model is presented in Fig. 2.

Sensitivity analysis. A sensitivity analysis was performed to evaluate the stability of the overall results by sequential omission of individual studies. The results of sensitivity analysis demonstrated that any single study did not affect the overall results qualitatively, indicating robustness and reliability of our results (data not shown).

Publication bias. The shape of the funnel plot did not reveal any obvious asymmetry (Fig. 3). In addition, the results of Egger's test did not suggest any evidence of publication bias (P=0.667 for GG vs. TT; P=0.578 for GT vs. TT; P=0.669 for GG+GT vs. TT; P=0.605 for GG vs. GT+TT; and P=0.670 for G vs. T).

Discussion

Although glioma is a rare type of cancer, it accounts for ~80% of malignant brain tumors in adults (17). However, the risk factors for glioma remain largely unknown. Gene susceptibility for glioma has been suggested in numerous case-control studies (18). The majority of studies conducted to date have evaluated a number of polymorphisms in a certain pathway, such as those affecting methylation, carcinogen metabolism, DNA repair, cell cycle, or inflammation. Polymorphisms may affect protein function, promoter activity, messenger RNA stability and splice variants and, therefore, may result in a change in the cellular ability to cope with DNA damage, which contributes to altered disease susceptibility (19).

Recently, the association between CCDC26 rs4295627 polymorphism and risk of glioma has been reported in a number of studies, and CCDC26 has been identified as a potential cancer susceptibility gene. The CCDC26 gene is located on chromosome 8q24.21. The rs4295627 polymorphism is located in intron 3 of the CCDC26 gene and encodes a retinoic acid modulator of differentiation and apoptosis (20). Retinoic acid induces caspase-8 transcription through phosphorylation of cyclic adenosine monophosphate response element binding, and increases apoptosis in glioblastoma cells via downregulation of telomerase activity (9). Variations of the 8q24.21 have been implicated in the risk of a number

Table I. Characteristics of studies included in the present meta-analysis.

First Author	Year	Country	Ethnicity	Simple size		Case genotype				Control genotype				Source of controls	Genotyping method	(Refs.)
				Cases	Controls	GG	GT	TT	GG	GT	TT	GG	GT			
Shete (France)	2009	USA	Caucasian	1,374	1,579	0	418	885	25	421	1,133	PB	Illumina	(14)		
Shete (German)	2009	USA	Caucasian	498	571	30	185	283	13	144	414	PB	Illumina	(14)		
Shete (Sweden)	2009	USA	Caucasian	643	775	27	223	393	36	247	492	PB	Illumina	(14)		
Shete (UK)	2009	USA	Caucasian	631	1,434	29	216	386	48	410	976	PB	Illumina	(14)		
Shete (US)	2009	USA	Caucasian	1,246	2,235	60	451	735	72	667	1,496	PB	Illumina	(14)		
Schoemaker (Denmark)	2010	UK	Caucasian	123	147	7	40	76	3	46	98	PB	PCR	(13)		
Schoemaker (Finland)	2010	UK	Caucasian	97	95	16	34	47	6	31	58	PB	PCR	(13)		
Schoemaker (Sweden)	2010	UK	Caucasian	199	372	6	63	130	14	117	241	PB	PCR	(13)		
Schoemaker (UK-North)	2010	UK	Caucasian	375	617	16	122	237	27	156	434	PB	Illumina, PCR	(13)		
Schoemaker (UK-South)	2010	UK	Caucasian	232	396	12	83	137	11	119	266	PB	Illumina, PCR	(13)		
Wang	2011	USA	Caucasian	332	817	24	121	187	19	242	556	HB	Illumina	(12)		
Li	2012	China	Asian	225	254	12	92	121	25	102	127	HB	MassArray	(11)		
Safaian (NCI)	2013	USA	Caucasian	322	385	17	123	182	11	107	267	HB	Illumina	(10)		
Safaian (NIOSH)	2013	USA	Caucasian	300	538	14	107	179	23	158	357	PB	Illumina	(10)		
Safaian (PLCO)	2013	USA	Caucasian	133	855	10	40	83	23	248	584	PB	Illumina	(10)		
Wibom	2015	Sweden	Caucasian	560	560	36	174	350	6	163	391	HB	PCR	(8)		

PB, population-based; HB, hospital-based; PCR, polymerase chain reaction; NCI, National Cancer Institute; NIOSH, National Institute for Occupational Safety and Health; PLCO, prostate, lung, colorectal and ovarian cancer screening trial.

Table II. Summary of total pooled results in different comparative genetic models.

Genetic models	OR (95% CI)	Z	P-value	I ² (%)	Effects model
GG vs. TT	1.936 (1.500-2.658)	4.08	<0.001	72.60	Random
GT vs. TT	1.323 (1.241-1.412)	8.49	0.206	21.80	Fixed
GG+GT vs. TT	1.375 (1.256-1.505)	6.91	0.026	45.10	Random
GG vs. GT+TT	1.769 (1.302-2.403)	3.64	<0.001	71.30	Random
G vs. T	1.310 (1.185-1.448)	5.27	<0.001	68.20	Random

OR, odds ratio; CI, confidence interval.

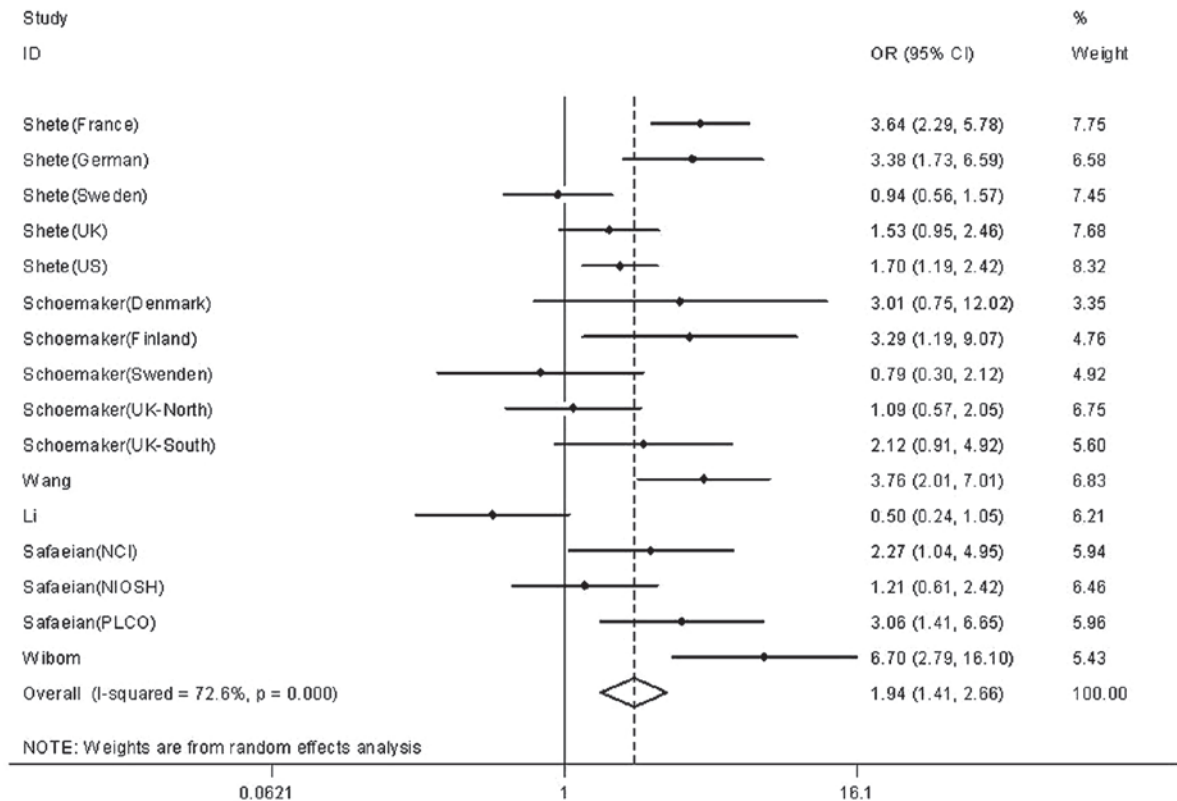


Figure 2. Forest plot for the coiled-coil domain-containing 26 rs4295627 polymorphism (homozygote model). OR, odds ratio; CI, confidence interval.

of common tumors, including colorectal, breast, bladder and prostate cancer (21-23).

To the best of our knowledge, this is the first comprehensive meta-analysis investigating the association between the CCDC26 rs4295627 polymorphism and risk of glioma. The present meta-analysis, including 7,290 cases and 11,630 controls, investigated the association between the CCDC26 rs4295627 polymorphism and risk of glioma and the results indicated that the CCDC26 rs4295627 polymorphism is associated with increased risk of glioma (GG vs. TT, OR=1.936, 95% CI: 1.500-2.658, $P<0.001$; GT vs. TT, OR=1.323, 95% CI: 1.241-1.412, $P=0.206$; GG+GT vs. TT, OR=1.375, 95% CI: 1.256-1.505, $P=0.026$; GG vs. GT+TT, OR=1.769, 95% CI: 1.302-2.403, $P<0.001$; and G vs. T, OR=1.310, 95% CI: 1.185-1.448, $P<0.001$). These findings may be biologically plausible. A subgroup analysis by ethnicity was not performed, as only one Asian case-control study with a

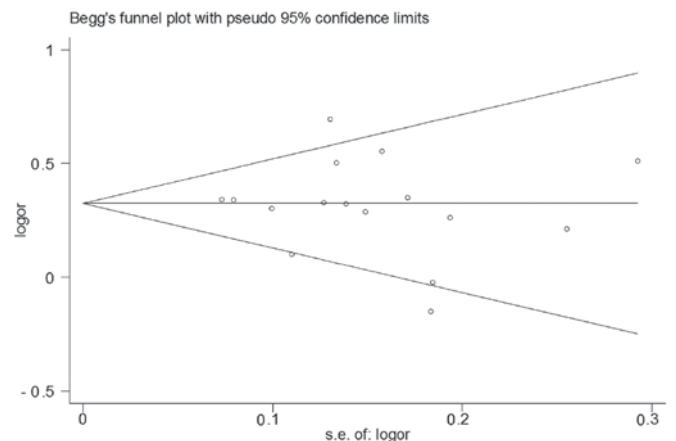


Figure 3. Begg's funnel plot with pseudo 95% confidence limits for publication bias among selected studies on the coiled-coil domain-containing 26 rs4295627 polymorphism (dominant model). s.e., standard error; or, odds ratio.

small sample size was included. In previous studies, different results in the CCDC26 gene have been found in different populations (French results: OR=1.36; German results: OR=1.73; UK results: OR=1.26; and Asian results: OR=1.32) (4,14). However, the ethnic specificity of this SNP requires further investigation and analysis.

Several limitations in this meta-analysis should be mentioned. First, only published studies in the selected databases were included in the meta-analysis, whereas some relevant published studies or unpublished studies with null results were not identified, which may bias our results. Second, heterogeneity is a potential problem in all meta-analyses. In the present meta-analysis, we found moderate to large heterogeneity in most genetic models, indicating that caution should be taken when interpreting our results. Third, more accurate ORs should be adjusted for age, gender, smoking, alcohol consumption and other factors associated with cancer risk (24). In addition, the small sample size (<100 cases and controls) may overestimate the true association, due to deficiencies in statistical power.

In conclusion, the currently available evidence suggests that the rs4295627 polymorphism in the CCDC26 gene may contribute to glioma susceptibility; however, further case-control studies are required to confirm our results.

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