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ORIGINAL ARTICLE

Genetic Polymorphisms of CCDC26 rs891835, rs6470745, and rs55705857 in Glioma Risk: A Systematic Review and Meta-analysis

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Abstract

A genetic component is accepted in the etiology of the glioma. Evidence from candidate genes studies and GWAS reveal that CCDC26 gene could increase the risk of glioma. We performed a systematic review and up-to-date meta-analysis to explore if polymorphisms of CCDC26 gene (rs891835, rs6470745, and rs55705857) may be a susceptibility factor in developing glioma. An online search in PubMed, Web of Science, and SCOPUS up to September 2018 was performed. The pooled odds ratios were evaluated by fixed effects model and random effects model. Analyses of the overall sample and ethnic sub-groups were performed. In all the analyses, the allelic, additive, dominant, and recessive models were used. We found an association between all polymorphisms evaluated and an increased risk for glioma in the overall population in all the models studied. In sub-group analysis, we found that rs891835 and rs6470745 increased the risk of glioma in Europeans and Caucasians. On the other hand, the rs891835 polymorphism did not reveal any statistical association in Chinese population. Taken into consideration the limitations of this study, the present findings suggest a possible participation of rs891835, rs6470745, and rs55705857 as risk factors to develop glioma. Furthermore, it is possible that the involvement of CCDC26 variants depends on ethnicity. However, we recommend to perform further studies to have conclusive outcomes.

Keywords Meta-analysis · Glioma · CCDC26 · Biomarkers

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Introduction

Brain tumors are relatively rare; however, they represent a serious health problem due to the very poor prognosis, high morbidity, and mortality (Adel Fahmideh et al. 2015; Cui 2015; Vaubel et al. 2017; Walsh et al. 2013a). Furthermore, the brain tumors are a leading cause of pediatric death in children, while in adults, they are among the first causes of death (Di Stefano et al. 2013; Egan et al. 2011, 2012; Walsh et al. 2013b). Gliomas are the most common type of brain tumors, they are derived from glial cells that surround and support neurons; understanding their etiology is very important to identify strategies for prevention, surveillance, and potential targets for treatments (Enciso-Mora et al. 2013; Ghasimi et al. 2016; Jenkins et al. 2011).

Consequently, the genetic predisposition of glioma risk has been widely explored. In this sense, the chromosomal region 8q24.21 has been associated with the risk of several common cancer sites (Jenkins et al. 2012; Lachance et al. 2011; Lasho et al. 2012). Likewise, these loci contain the gene that codifies the coiled-coil domain-containing protein 26 (CCDC26) in which genome wide association studies support a linkage with tumor, including low-grade glioma (Li et al. 2012, 2013; Liu et al. 2010a). Evidence suggest that CCDC26 increases apoptosis induced by death stimuli in neuroblastoma cells and in glioblastoma cells with down-regulation of telomerase activity (Liu et al. 2010b, c; Lu et al. 2015).

Due to the importance of CCDC26, the association of this gene with glioma risk has been explored (Melin 2011; Oktay et al. 2016; Rajaraman et al. 2012), providing some candidate genetic variants of CCDC26. Some of the main ones are rs891835 (ancestral allele T>allele G), rs6470745 (ancestral allele A>allele G), and rs55705857 (ancestral allele A>G allele) (Egan et al. 2011; Enciso-Mora et al. 2013; Li et al. 2012; Oktay et al. 2016). The genetic variant rs55705857 has revealed an OR of approximately 6 to IDH-mutated tumor and the histopathological subtype oligodendroglioma (Enciso-Mora et al. 2013; Oktay et al. 2016). However, the etiology of glioma has not been very well understood for many years; probably because glioma is a rare cancer and in a considerable number of the studies there a serious limitations such as small sample sizes (a very low proportion have more than 500 cases or controls) also, the heterogeneity of gliomas could cause that the studies do not have the statistical power to establish precise interactions (Schoemaker et al. 2010; Shete et al. 2009; Simon et al. 2010). Therefore, in order to address the limitations of the single association studies, we considered it necessary to perform a systematic review and up-to-date meta-analysis. Our aim is to explore the role of the genetic variants of CCDC26 (rs891835, rs6470745 and rs55705857) as a probable markers of glioma risk in the pooled combination that offers the meta-analytic technique.

Methods

Data Sources and Search

The present systematic review and meta-analysis were performed based on the reported guidelines of the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA). Potentially related studies were searches in electronic databases of PubMed, Scopus, and Web of Sciences by two researchers (González-Castro and Tovilla-Zárate). Articles published before September 2018 were searched using the following keywords combination: "rs891835" AND "glioma" OR "glioblastoma" OR "brain tumor," "rs6470745" AND "glioma" OR "glioblastoma" OR "brain tumor," and "rs55705857" AND "glioma" OR "glioblastoma" OR "brain tumor." All eligible studies were retrieved and their reference lists also were reviewed to find other relevant studies.

Inclusion/Exclusion Criteria

The selected studies had to meet the following criteria: (1) studies that address the association between rs891835, rs6470745 or rs55705857, and glioma; (2) cases: patients diagnosed with glioma, controls: cancer-free individuals (Hospital-based or Health-based); (3) reporting numbers or frequencies of alleles or genotypes in both cases and controls; (4) provide adequate data to calculate odds ratios (ORs) with 95% confidence intervals (CIs); (5) case–control design. The exclusion criteria were family-based, case reports, case series, reviews, comments, letters, and conference presentations. No restriction on ethnicity, or geographic region was imposed.

Data Extraction

The following data were collected from the included studies: (i) name of the first author, (ii) publication year, (iii) country and ethnicity of individuals studied, (iv) diagnostic, (v) number of cases and controls, (vi) allelic or genotypic distribution, (vii) ORs or p values found, and (vii) methodological data of genotyping. The same two researchers extracted the information. When necessary, the reviewers wrote to the corresponding author for extra information.

Quality Assessment

The Newcastle–Ottawa scale (NOS) was used to measure the quality of the eligible studies included (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The NOS evaluated three aspects of the studies: (a) selection, (b) comparability, and (c) exposure between cases and controls. The NOS has score range of zero to nine stars, only studies with a score of 6 or more stars were included (Gonzalez-Castro et al. 2016; Hernandez-Diaz et al. 2016). Likewise the literature search and data

extraction, the researchers González-Castro and Tovilla-Zarate evaluated the quality of studies independently; when there was a disagreement, it was solved in a discussion with a third reviewer (Genis-Mendoza) until consensus was reached.

Data Synthesis and Statistical Analysis

The strength of the association between rs891835, rs6470745, rs55705857, and glioma risk was estimated by ORs and 95% CIs. Moreover, the significance of the pooled ORs was determined by the *Z* test, a *p* value less than 0.05 was considered as statistically significant. Furthermore, genetic models to evaluate for the pooled OR were used: allele contrast (m vs M), homozygote comparison (mm vs MM), heterozygote comparison (mM vs MM), dominant model (mm+mM vs MM), as well as recessive model (mm vs mM+MM). In addition, we examined the heterogeneity of the included studies assessed by χ^2-based Q statistical test and I^2 metric value. Heterogeneity presence based on I^2 was considered as 0–25% absent, 25–50% low, 50–75% moderate, and 75–100% high; p value of Q test < 0.10 was considered significant to heterogeneity. In addition, Galbraith plot was used to visualize the impact of individual studies on the overall heterogeneity, which spotted the outlier as the possible origin of heterogeneity. Subsequently, fixed effects model was used in the absence of heterogeneity; otherwise, random effects model was selected. Likewise, the Hardy–Weinberg equilibrium (HWE) was assessed in the control group in each article included, $p < 0.05$ was considered as a significant disequilibrium.

On the other hand, sensitivity analysis was performed by excluding a single article each time, to detect potential influence that could have each study in the pooled ORs. Publication bias was measured by Egger linear regression test and funnel plots. All the analyses were performed using the Comprehensive Meta-analysis (CMA Version 2.0, Biostat, Inc., USA) software. Finally, sub-group analyses were conducted: overall population (rs891835, rs6470745, rs55705857), Caucasian population (rs891835, rs6470745), European population (rs891835, rs6470745), USA (rs891835), and Chinese population (rs891835).

Results

Study Characteristics

The electronic database search generated 40 records from PubMed, 37 records from Scopus, and 38 records from Web of Science. After scanning titles and abstracts and discarding duplicates, 35 studies relevant to our aim were fully scrutinized. After full text evaluation of these 35 relevant studies, we excluded abstract and comments among others (6 studies), also if they did not accomplish our particular point of interest (7 studies), we also eliminated review articles or meta-analysis (9 studies). If the records did not detail data or those for which the authors could not be contacted were also eliminated (4 studies), Fig. 1. Finally, 10 studies met the inclusion criteria for this meta-analysis. The characteristics of the included studies are presented

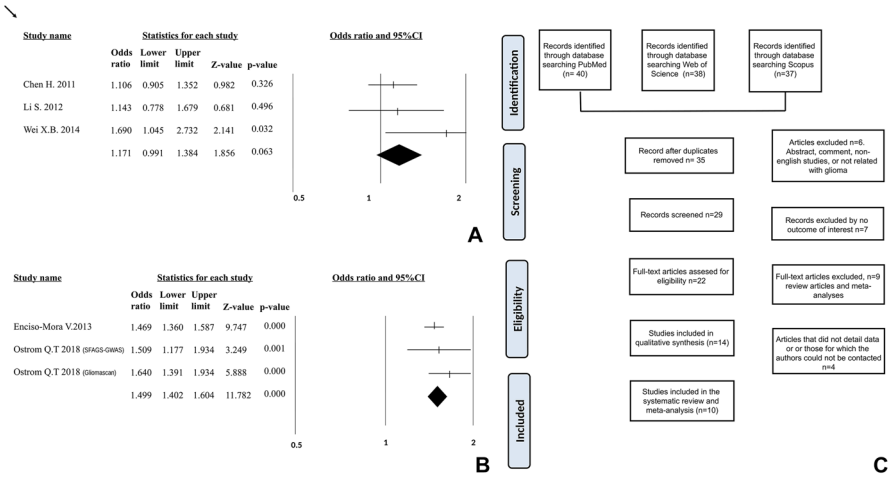

Fig. 1 Forest plot of **a** allelic model rs891835 in China sub-group, **b** dominant model rs55705857 in overall population, and **c** flow-chart of study selection

in Table 1. These studies were performed in 9 countries (France, Germany, Sweden, UK, USA, China, Norway, Denmark, and Switzerland) published from 2009 to 2018. The number of the cases sample sizes ranged from 72 to 2564; giving a total of 11,575 cases and 17,718 controls for rs891835; 9484 cases and 15,229 controls for rs6470745; and for rs55705857 10,543 cases and 19,331 controls. Some samples were stratified depending on the population origin or place of birth. For example, the group of Shete S. 2009 performed their analysis in individuals born in France, Germany, Sweden, UK, and USA. Another example is the group of Ostrom Q.T. 2018 that performed their investigations with individuals at the Glioma International Case–Control Study (GICC), San Francisco Adult Glioma study GWAS (SFAGS-GWAS), MD Anderson Glioma GWAS (MDA-GWAS); Gliomascan: National Cancer Institue's Gliomascan (Gliomascan). The articles by Shete S. and Ostrom Q.T. were consider for the stratified population (Ostrom et al. 2018).

Glioma Risk and CCDC26 Variants in Overall Population

Firstly, we explored the association of *rs8918358*, *rs6470745*, and *rs55705857* in the overall population. Initially, the analysis of *rs8918358* was statistically significant when the heterogeneity was excluded: allelic (OR 1.19, 95% CI 1.11–1.26, p value < 0.000), homozygous (OR 1.56 95% CI 1.33–1.84, p value < 0.001), heterozygous (OR 1.26, 95% CI 1.17–1.36, p value < 0.000), recessive (OR 1.46, 95% CI 1.24–1.71, p value < 0.001), and dominant (OR 1.32, 95% CI 1.23–1.42, p value < 0.001) models Fig. 2. Secondly, the analysis of *rs6470745* indicated an association in all the models evaluated, even in the existence of heterogeneity between the studies (allelic: OR 1.19 95% CI 1.11–1.26, p value < 0.000; homozygous OR 1.56 95% CI 1.33–1.84, p value < 0.001; heterozygous OR 1.26 95% CI 1.17–1.36, p value < 0.001; recessive OR 1.46 95% CI 1.24–1.71, p value < 0.000; and dominant

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

First author	Country/ population	*N*	Age reported	Gender reported M/F		Clinical features cases	Type method	*p* value[f]	Homozygote GG	HWE	NOS
		Case/control	Case/control	Cases	Control				Case/control	Case/control	
rs891835											
Shete S. $2009_{(a)}$ (Shete et al. 2009)	France	1362/1452	NA/36–60	NA	NA	WHO classification AI, AII, AIII, OII, OIII, OAII, OAIII, GBM-IV	Illumina	2.93×10^{-3}	85/55	0.05/0.66	7
Shete S. $2009_{(b)}$(Shete et al. 2009)	Germany	501/568	NA/31	NA	288/288[g]	NA	Illumina	3.07×10^{-6}	52/19	0.06/0.24	7
Shete S. $2009_{(c)}$ (Shete et al. 2009)	Sweden	640/758	Matched	Matched	Matched	NA	Illumina	0.7822	42/42	0.33/0.49	7
Shete S. $2009_{(d)}$ (Shete et al. 2009)	UK	631/1409	46/NA	401/235[g]	NA	ICD-O codes 9380-9384, 9390-9411, 9420-9451 and 9505; ICD10 code C71	Illumina	0.0436	41/77	0.83/0.76	7
Shete S. $2009_{(e)}$ (Shete et al. 2009)	USA	1247/2232	47/NA	768/479[g]	NA	ICD10 code C71; ICD-O codes 9380-9384, 9390-9411, 9420-9451, and 9505	Illumina	2.16×10^{-6}	88/115	0.71/0.76	7
Egan K.M. 2011 (Egan et al. 2011)	USA	639/649	55/58	396/243	370/279	Glioblastoma (ICD-O code 9440/3); lower grade pure astrocytic tumors (ICD-O 9401/3) astrocytomas (ICD-O 9384/1, 9421/1, 9400/3, 9424/3); mixed oligodendroglial and astrocytic tumors (ICD-O 9382/3) or pure oligodendrogliomas (ICD-O 9450/3, 9451/3)	Illumina	0.826	21/11	0.89/0.99	8

Table 1 (continued)

First author	Country/population	*N*	Age reported	Gender reported M/F		Clinical features cases	Type method	*p* value[f]	Homozygote GG	HWE	NOS
		Case/control	Case/control	Cases	Control				Case/control	Case/control	
Chen H. 2011 (Chen et al. 2011)	China	946/1057	42.3/42.1	581/377[g]	633/419[g]	Astrocytic glioma ($n=360$); Glioblastoma ($n=312$); Other glioma ($n=296$); Missing data ($n=8$)	MassARRAY	0.37	16/15	0.94/0.88	7
Jenkins R.B. 2011 (Jenkins et al. 2011)	USA	1056/1134	49.45/52.8	878/568[g]	626/508	Grade 2 Astrocytoma, Grade 3 Anaplastic Astrocytoma, Grade 4 Glioblastoma Multiform, Grades 2 and 3 Oligodendroglioma, Grades 2 and 3 Oligoastrocytoma	Illumina	1.55×10^{-4}	563/690	0.98/0.98	7
Li S. 2012 (Li et al. 2012)	China	225/251	41/55	118/107	132/122[g]	Astrocytoma ($n=126$), Glioblastoma ($n=26$), Oligodendroglioma ($n=38$), Medulloblastoma ($n=5$), Others ($n=30$)	MassARRAY	0.24	10/5	0.87/0.95	8

Table 1 (continued)

First author	Country/ population	*N*	Age reported	Gender reported M/F		Clinical features cases	Type method	*p* value[f]	Homozygote GG	HWE	NOS
		Case/control	Case/control	Cases	Control				Case/control	Case/control	
Enciso-Mora V. 2013 (Enciso-Mora et al. 2013)	Europe	4147/7435	46/> 35	NA	NA	Grade II: Low-grade astrocytoma, Oligoastrocytoma, Oligodendroglioma; Grade III: Anaplastic astrocytoma, Anaplastic oligoastrocytoma, Anaplastic oligodendroglioma, Grade IV: Glioblastoma	Illumina/ TaqMan	1.543×10^{-12}		0.71/0.94	6
Wei X.B. 2014 (Wei et al. 2014)	China	72/299	41.18/55.12	34/38	150/152[g]	Glioblastoma	MassARRAY	0.009	2/6	0.21/0.96	7
Adel Fahmideh M. 2015 (Adel Fahmideh et al. 2015)	Sweden, Norway, Denmark, Switzerland	109/474	7-19/7-19	61/48	251/223	ICCC-3, group III, restricted to ICD-O-3 location C71 and subclassified according to WHO classification	MassARRAY	0.2989	15/29	0.28/0.61	7
rs6470745											
Shete S. $2009_{(a)}$ (Shete et al. 2009)	France	1380/1586	NA/36-60	NA	NA	WHO classification AI, AII, AIII, OII, OIII, OAII, OAIII, GBM-IV	Illumina	1.84×10^{-6}	86/41	0.02/0.16	7
Shete S. $2009_{(b)}$ (Shete et al. 2009)	Germany	502/568	NA/31	NA	288/288[g]	NA	Illumina	4.33×10^{-7}	33/17	0.90/0.88	7
Shete S. $2009_{(c)}$ (Shete et al. 2009)	Sweden	641/767	Matched	Matched	Matched	NA	Illumina	0.9271	31/41	0.90/0.46	7
Shete S. $2009_{(d)}$ (Shete et al. 2009)	UK	631/1433	46/NA	401/235[g]	NA	ICD-O codes 9380-9384, 9390-9411, 9420-9451 and 9505; ICD10 code C71	Illumina	0.0037	37/64	0.97/0.31	7

Table 1 (continued)

First author	Country/ population	*N*	Age reported	Gender reported M/F		Clinical features cases	Type method	*p* value[f]	Homozygote GG	HWE	NOS
		Case/control	Case/control	Cases	Control				Case/control	Case/control	
Shete S. 2009[(e)] (Shete et al. 2009)	USA	1247/2235	47/NA	768/479[g]	NA	ICD10 code C71; ICD-O codes 9380-9384, 9390-9411, 9420-9451, and 9505	Illumina	4.20×10^{-6}	79/90	0.97/0.79	7
Egan K.M. 2011 (Egan et al. 2011)	USA	639/649	55/58	396/243	370/279	Glioblastoma (ICD-O code 9440/3); lower grade pure astrocytic tumors (ICD-O 9401/3) astrocytomas (ICD-O 9384/1, 9421/1, 9400/3, 9424/3); mixed oligodendroglial and astrocytic tumors (ICD-O 9382/3) or pure oligodendrogliomas (ICD-O 9450/3, 9451/3)	Illumina	0.232	23/21	0.97/0.98	8
Li S. 2012 (Li et al. 2012)	China	225/254	41/55	118/107	132/122	Astrocytoma ($n=126$), Glioblastoma ($n=26$), Oligodendroglioma ($n=38$), Medulloblastoma ($n=5$), Others ($n=30$)	MassARRAY	0.07	16/35	0.26/0.33	8

Table 1 (continued)

First author	Country/ population	*N*	Age reported	Gender reported M/F		Clinical features cases	Type method	*p* value[f]	Homozygote GG	HWE	NOS
		Case/control	Case/control	Cases	Control				Case/control	Case/control	
Enciso-Mora V. 2013 (Enciso-Mora et al. 2013)	Europe	4147/7435	46/> 35	NA	NA	Grade II: Low-grade astrocytoma, Oligoastrocytoma, Oligodendroglioma; Grade III: Anaplastic astrocytoma, Anaplastic oligoastrocytoma, Anaplastic oligodendroglioma, Grade IV: Glioblastoma	Illumina/ TaqMan	4.02×10^{-17}		0.85/0.65	6
Wei X.B. 2014 (Wei et al. 2014)	China	72/302	41.18/55.12	34/38	150/152	Glioblastoma	MassARRAY	0.396	4/39	0.17/0.37	7
rs55705857											
Enciso-Mora V. 2013 (Enciso-Mora et al. 2013)	Europe	4147/7435	46/> 35			Grade II: Low-grade astrocytoma, Oligoastrocytoma, Oligodendroglioma; Grade III: Anaplastic astrocytoma, Anaplastic oligoastrocytoma, Anaplastic oligodendroglioma, Grade IV: Gliobastoma	Illumina/ TaqMan	2.31×10^{-94}		0.69/0.78	6
Rice T. 2013	USA	359/1300	> 18/> 18	223/136[g]	NA	ICD-O codes 9380– 9481	Illumina	6.8×10^{-29}	236/1173	0.96/0.88	8

Table 1 (continued)

First author	Country/ population	*N*	Age reported	Gender reported M/F		Clinical features cases	Type method	*p* value[f]	Homozygote GG	HWE	NOS
		Case/control	Case/control	Cases	Control				Case/control	Case/control	
Ostrom Q.T. $2018_{(GICC)}$ (Ostrom et al. 2018)	Mixed	2564/3265	51.9/54.75	2733/1831[g]	1868/1397	Gliobastoma, Astrocytoma (WHO grade IIII), Oligodendroglioma (WHO grade II-III)	Illumina	$< 1.0 \times 10^{-12}$	49/11	0.01/0.66	6
Ostrom Q.T. $2018_{(SFAGS\text{-}GWAS)}$ (Ostrom et al. 2018)	Mixed	677/2367	53.65/49.95	440/237	749/1618	Gliobastoma, Astrocytoma (WHO grade IIII), Oligodendroglioma (WHO grade II-III)	Illumina	$< 1.0 \times 10^{-12}$	4/7	0.93/0.97	6
Ostrom Q.T. $2018_{(MDA\text{-}GWAS)}$ (Ostrom et al. 2018)	Mixed	1143/2239	47.4/60-69	714/429	1097/1142	Gliobastoma, Astrocytoma (WHO grade IIII), Oligodendroglioma (WHO grade II-III)	Illumina	$< 1.0 \times 10^{-12}$	14/9	0.97/0.92	6
Ostrom Q.T. $2018_{(Gliomascan)}$ (Ostrom et al. 2018)	Mixed	1653/2725	55.55/66.65	944/709	1465/1260	Gliobastoma, Astrocytoma (WHO grade IIII), Oligodendroglioma (WHO grade II-III)	Illumina	$< 1.0 \times 10^{-12}$	18/13	0.02/0.78	6

ICD-O International Classification of Diseases for Oncology, *ICCC-3* International Classification of Childhood Cancer third edition, *MDACC* M.D. Anderson Cancer Center, *UCSF* University of California San Francisco, *GICC* Glioma International Case–Control Study, *SFAGS-GWAS* San Francisco Adult Glioma study GWAS, *MDA-GWAS* MD Anderson Glioma GWAS, *Gliomascan* National Cancer Institue's Gliomascan

[(a)]Population of France

[(b)]Population of Germany

[(c)]Population of Sweden

[(d)]Popuation of UK

[(e)]Population of USA

[f]*p* value reported in the original article

[g]Not matched with the total number, *NA* not available data

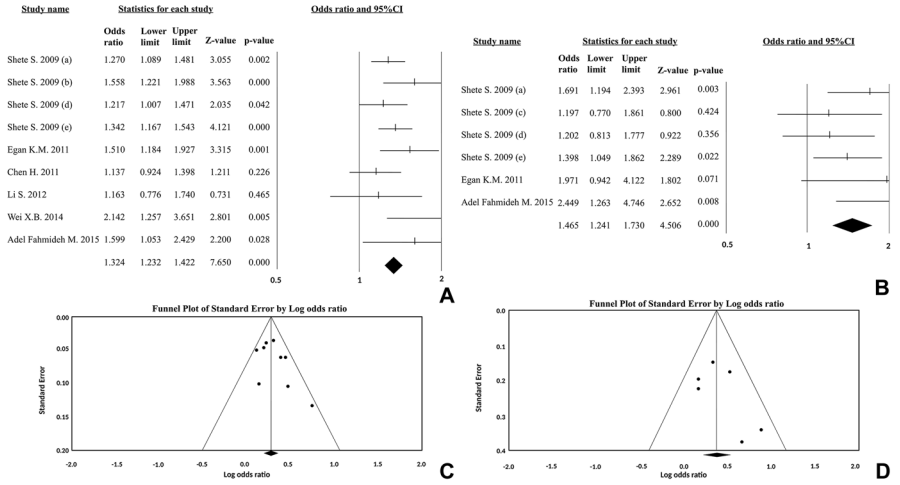

Fig. 2 Forest plot of rs891835 in **a** dominant model in overall population, **b** recessive model in Europeans sub-group, and Funnel plot of rs891836 in **c** dominant model in overall population, **d** recessive model in Europeans sub-group

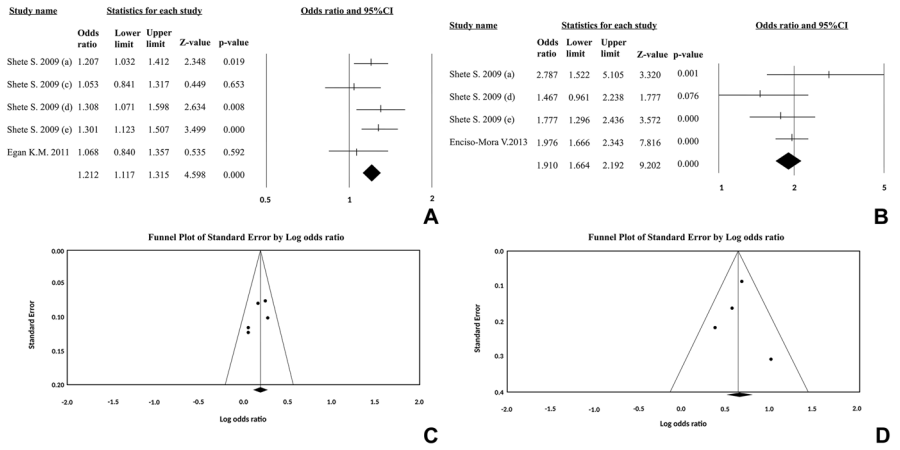

Fig. 3 Forest plot of rs6470745 in **a** heterozygous model in Caucasians sub-group, **b** homozygous model in overall population, and Funnel plot of rs6470745 in the models: **c** Heterozygous model in Caucasians sub-group, **d** homozygous model in overall population

OR 1.32, 95% CI 1.23–1.42, p value < 0.000 models); Fig. 3. Thirdly, when evaluating the *rs55705857*, we observed an association after discarding the heterogeneity in the studies: allelic (OR 1.43, 95% CI 1.35–1.52, p value < 0.000), homozygous (OR 2.04 95% CI 1.73–2.39, p value < 0.000), heterozygous (OR 1.64, 95% CI 1.46–1.84, p value < 0.001), recessive (OR 1.80, 95% CI 1.53–2.11, p value < 0.001), and dominant (OR 1.49, 95% CI 1.40–1.60, p value < 0.001) models. No publication bias was observed, Table 2.

Table 2 Meta-analysis of the associations of CCDC26 variants and glioma risk

Allele				Homozygous				Heterozygous				Recessive				Dominant			
OR (95% CI)	*Z*	I^2	*E*	OR (95% CI)	*Z*	I^2	*E*	OR (95% CI)	*Z*	I^2	*E*	OR (95% CI)	*Z*	I^2	*E*	OR (95% CI)	*Z*	I^2	*E*
Overall																			
rs891835																			
1.1 (0.9–1.3)	0.17	91.0	0.00	1.4 (0.8–2.3)	0.16	94.5	0.00	1.1 (0.9–1.4)	0.25	92.8	0.01	1.3 (0.9–1.9)	0.09	91.9	0.00	1.1 (0.8–1.5)	0.24	95.4	0.01
1.1 (1.1–1.2)	0.00*	20.0	0.27	1.5 (1.3–1.8)	0.00*	0.00	0.40	1.2 (1.1–1.3)	0.00*	0.00	0.28	1.4 (1.2–1.7)	0.00*	0.00	0.36	1.3 (1.2–1.4)	0.00*	0.00	0.18
rs6470745																			
1.2 (1.0–1.3)	0.00*	81.4	0.05	1.4 (1.0–1.9)	0.03*	80.1	0.08	1.2 (1.1–1.3)	0.00*	56.3	0.17	1.3 (0.9–1.7)	0.08	77.9	0.09	1.2 (1.1–1.4)	0.00*	72.1	0.08
1.3 (1.3–1.4)	0.00*	0.00	0.09	1.9 (1.6–2.1)	0.00*	10.4	0.96	1.1 (1.1–1.2)	0.00*	0.00	0.15	1.6 (1.4–1.8)	0.00*	3.85	0.50	1.2 (1.1–1.4)	0.00*	0.00	0.11
rs55705857																			
1.3 (0.7–2.2)	0.29	98.8	0.77	1.7 (0.7–4.0)	0.22	90.4	0.88	1.6 (1.0–2.5)	0.03*	97.5	0.96	1.7 (0.5–5.1)	0.33	97.4	0.80	1.5 (0.9–2.3)	0.08	97.7	0.90
1.4 (1.3–1.5)	0.00*	20.0	0.43	2.0 (1.7–2.3)	0.00*	0.00	0.22	1.6 (1.4–1.8)	0.00*	0.00	0.73	1.8 (1.5–2.1)	0.00*	0.00	0.16	1.4 (1.4–1.6)	0.00*	0.00	0.54
Sub-group: Caucasians																			
rs891835																			
1.0 (0.9–1.3)	0.36	92.9	0.00	1.3 (0.7–2.4)	0.27	95.8	0.00	1.0 (0.8–1.4)	0.51	94.3	0.05	1.3 (0.8–1.9)	0.15	93.9	0.00	1.1 (0.8–1.5)	0.49	96.4	0.04

Table 2 (continued)

Allele				Homozygous				Heterozygous				Recessive				Dominant			
OR (95% CI)	*Z*	I^2	*E*	OR (95% CI)	*Z*	I^2	*E*	OR (95% CI)	*Z*	I^2	*E*	OR (95% CI)	*Z*	I^2	*E*	OR (95% CI)	*Z*	I^2	*E*
1.2 (1.1–1.3)	0.00*	0.00	0.09	1.5 (1.3–1.8)	0.00*	24.9	0.37	1.2 (1.1–1.3)	0.00*	0.00	0.32	1.4 (1.2–1.7)	0.00*	8.69	0.28	1.3 (1.2–1.4)	0.00*	0.00	0.13
rs6470745																			
1.2 (1.1–1.4)	0.00*	74.1	0.32	1.7 (1.3–2.2)	0.00*	65.7	0.44	1.2 (1.1–1.4)	0.00*	61.1	0.36	1.5 (1.2–1.9)	0.00*	59.8	0.51	1.3 (1.1–1.4)	0.00*	70.1	0.32
1.3 (1.3–1.4)	0.00*	0.00	0.09	1.8 (1.6–2.1)	0.00*	0.00	0.15	1.2 (1.1–1.3)	0.00*	1.00	0.15	1.6 (1.4–1.8)	0.00*	3.85	0.50	1.2 (1.1–1.4)	0.00*	0.00	0.15
Sub-group: Europeans																			
rs891835																			
1.0 (0.8–1.4)	0.48	93.5	0.01	1.4 (0.6–3.2)	0.34	96.7	0.00	1.0 (0.7–1.4)	0.72	94.5	0.03	1.3 (0.8–1.9)	0.15	93.9	0.00	1.1 (0.7–1.6)	0.58	96.8	0.02
1.2 (1.1–1.3)	0.00*	0.00	0.26	1.5 (1.2–1.9)	0.00*	24.9	0.58	1.2 (1.1–1.3)	0.00*	0.00	0.14	1.4 (1.2–1.7)	0.00*	8.69	0.28	1.3 (1.1–1.4)	0.00*	14.9	0.23
rs6470745																			
1.3 (1.1–1.5)	0.00*	72.2	0.64	1.8 (1.3–2.5)	0.00*	73.0	0.74	1.3 (1.1–1.5)	0.00*	66.4	0.68	1.1 (1.2–2.2)	0.00*	69.4	0.79	1.3 (1.1–1.5)	0.00*	73.4	0.64
1.3 (1.3–1.4)	0.00*	0.00	0.27	2.2 (1.7–2.3)	0.00*	24.4	0.71	1.3 (1.2–1.4)	0.00*	23.4	0.40	1.7 (1.4–1.9)	0.00*	13.5	0.98	1.4 (1.3–1.5)	0.00*	3.52	0.18

Table 2 (continued)

Allele				Homozygous				Heterozygous				Recessive				Dominant			
OR (95% CI)	*Z*	I^2	*E*	OR (95% CI)	*Z*	I^2	*E*	OR (95% CI)	*Z*	I^2	*E*	OR (95% CI)	*Z*	I^2	*E*	OR (95% CI)	*Z*	I^2	*E*
Sub-group: USA																			
rs891835																			
1.0 (0.8–1.4)	0.54	89.5	0.90	1.2 (0.5–2.6)	0.62	90.1	0.90	1.1 (0.8–1.5)	0.26	74.4	0.55	1.1 (0.6–2.0)	0.56	89.3	0.38	1.1 (0.7–1.6)	0.54	87.6	0.53
1.2 (1.1–1.3)	0.00*	0.00		1.6 (1.2–2.1)	0.00*	0.00		1.3 (1.1–1.5)	0.00*	0.00		1.4 (1.1–1.9)	0.00*	0.00		1.3 (1.2–1.5)	0.00*	0.00	
Sub-group: China																			
rs891835																			
								1.2 (0.9–1.8)	0.14	61.2						1.3 (0.9–1.8)	0.09	58.2	0.42
1.1 (0.9–1.3)	0.06	22.0	0.40	1.5 (0.8–2.6)	0.14	0.00	0.50	1.1 (0.9–1.3)	0.25	0.00	0.52	1.4 (0.8–2.5)	0.19	0.00	0.67	1.1 (0.9–1.3)	0.158	0.00	

*Statistical significance

Meta-regression Analysis

Lastly, in order to explore the source of the heterogeneity, we performed a meta-regression based on the age of the population in the three polymorphism: first the polymorphism *rs8918358* (Slope: OR 0.009, 95% CI − 0.01 to 0.02, *p* value 0.34; intercept -0.51), then the variant *rs6470745* (Slope: OR 0.0006, 95% CI − 0.01 to 0.02, *p* value 0.94; intercept 0.24), and finally *rs55705857* (Slope: OR -0.019, 95% CI − 0.04 to 0.008, *p* value 0.177; intercept 0.49); Fig. 4.

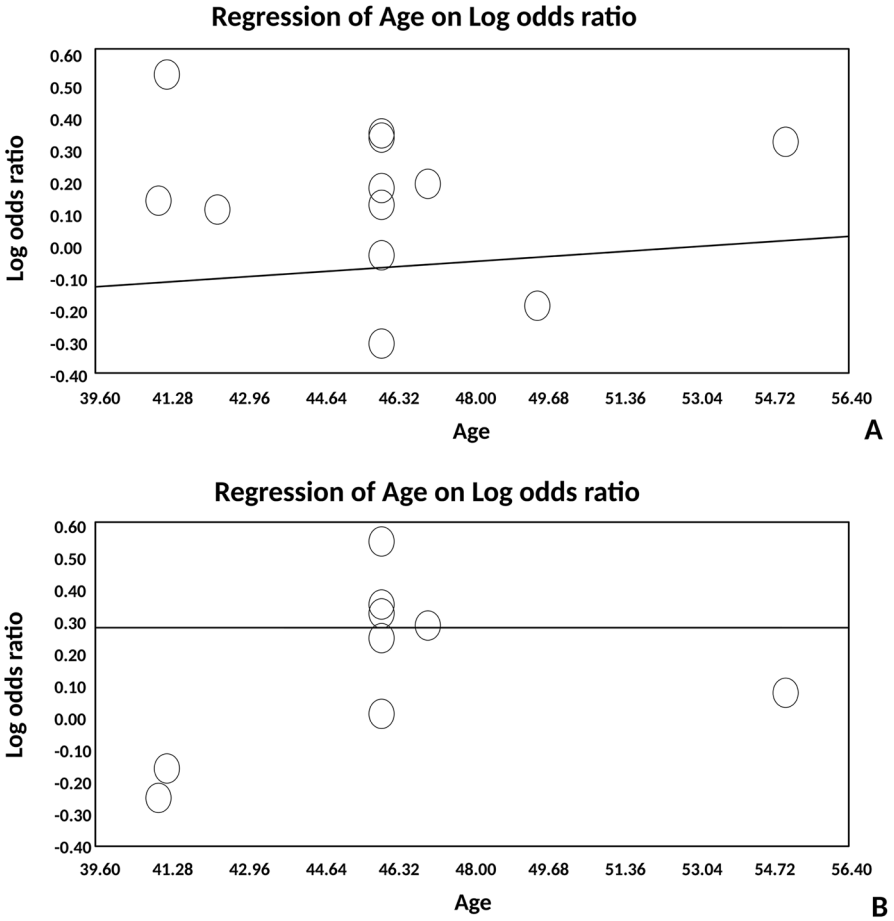

Fig. 4 Meta-regression based on ages: **a** rs891835 and **b** rs6470745

Sub-group Analysis

Glioma Risk and CCDC26 Variants in Caucasian Individuals

Due to previous results, we explored the role that *rs8918358* and *rs6470745* could have as markers of glioma risk in Caucasian populations. In a first step, we analyzed the participation of *rs891835* by the genetic models assigned; only when studies that favored heterogeneity were excluded, we obtained statistical significance (allelic: OR 1.22 95% CI 1.14–1.32, p value < 0.001; homozygous OR 1.57 95% CI 1.32–1.86, p value < 0.001; heterozygous OR 1.28 95% CI 1.18–1.39, p value < 0.001; recessive OR 1.46 95% CI 1.24–1.73, p value < 0.001; and dominant OR 1.34, 95% CI 1.24–1.45, p value < 0.001 models). We followed the same procedure to explore the role of *rs6470745* in Caucasian populations and even when there were studies that favored heterogeneity in the analysis, we observed statistical significance (allelic: OR 1.37 95% CI 1.30–1.43, p value < 0.001; homozygous OR 1.87 95% CI 1.62–2.15, p value < 0.000; heterozygous OR 1.21 95% CI 1.11–1.31, p value < 0.001; recessive OR 1.65 95% CI 1.45–1.89, p value < 0.001; and dominant OR 1.29, 95% CI 1.19–1.41, p value < 0.000 models); Fig. 3. We did not observe any publication bias, Table 2.

Glioma Risk and CCDC26 Variants in European Individuals

Due to the fact that genetic influence differs among ethnicities, we explored the participation of CCDC26 variants in European populations. Subsequently, the analysis of *rs891835* polymorphism revealed a significance p value in all the models when heterogeneity was discarded: allelic (OR 1.22, 95% CI 1.11–1.34, p value < 0.000), homozygous (OR 1.53 95% CI 1.23–1.90, p value < 0.000), heterozygous (OR 1.23, 95% CI 0.11–1.38, p value < 0.000), recessive (OR 1.46, 95% CI 1.24–1.73, p value < 0.000), and dominant (OR 1.32, 95% CI 1.19–1.46, p value < 0.000) models. Likewise, the variant rs6470745 was evaluated and in the presence and absence of heterogeneity, we found an association with glioma risk (allelic: OR 1.38 95% CI 1.31–1.45, p value < 0.000; homozygous OR 2.02 95% CI 1.76–2.33, p value < 0.000; heterozygous OR 1.35 95% CI 1.26–1.45, p value < 0.000; recessive OR 1.70 95% CI 1.47–1.98, p value < 0.000; and dominant OR 1.42, 95% CI 1.33–1.51, p value < 0.000 models); Fig. 2. Any publication bias were observed in the analysis, Table 2.

Glioma Risk and CCDC26 Variants in Individuals Born in USA

In order to better understand the association of *rs891835* and glioma, we performed another sub-group analysis exploring the role of this polymorphism with glioma risk in individuals born in the USA. The analysis revealed no association with glioma risk in the presence of heterogeneity (allelic: OR 1.09 95% CI 0.81–1.47, p value 0.54; homozygous OR 1.21 95% CI 0.55–2.62, p value 0.62; heterozygous OR 1.18 95% CI 0.88–1.58, p value 0.26; recessive OR 1.18 95% CI 0.66–2.09, p value 0.56; and dominant OR 1.12, 95% CI 0.76–1.66, p value 0.54 models). However, when

we excluded the study that favored heterogeneity, we observed a significant association: allelic (OR 1.23, 95% CI 1.10–1.38, p value < 0.000), homozygous (OR 1.62 95% CI 1.24–2.13 p value < 0.000), heterozygous (OR 1.34, 95% CI 1.18–1.52, p value < 0.000), recessive (OR 1.46, 95% CI 1.11–1.91, p value < 0.000), and dominant (OR 1.38, 95% CI 1.22–1.56, p value < 0.000) models. Concerning publication bias, no significant p value was observed, Table 2.

Glioma Risk and CCDC26 Variants in Subjects Born in China

Similarly, we evaluated the involvement of *rs891835* as a glioma risk in individuals born in China. In this case, the models that presented heterogeneity were the heterozygous (OR 1.29, 95% CI 0.91–1.84, p value 0.14) and dominant (OR 1.32, 95% CI 0.95–1.83, p value 0.09). However, even we discarded the study that favored the presence of heterogeneity (Wei et al. 2014), no association was observed: allelic (OR 1.17, 95% CI 0.99–1.38, p value 0.06), homozygous (OR 1.51 95% CI 0.86 -2.65 p value 0.14), heterozygous (OR 1.11, 95% CI 0.92–1.35, p value 0.25), recessive (OR 1.44, 95% CI 0.82–2.52, p value 0.19), and dominant (OR 1.14, 95% CI 0.95–1.37, p value 0.15) models, Fig. 1. There was no publication bias in the analyses, Table 2.

Meta-regression Based on Ages

Lastly, in order to explore the source of the heterogeneity, we performed meta-regression based on age of the populations. Firstly, the polymorphism *rs8918358* (Slope: OR 0.009, 95% CI − 0.01 to 0.02, p value 0.34; intercept -0.51), then the variant *rs6470745* (Slope: OR 0.0006, 95% CI − 0.01 to 0.02, p value 0.94; intercept 0.24), and finally *rs55705857* (Slope: OR -0.019, 95% CI − 0.04 to 0.008, p value 0.177; intercept 0.49); Fig. 4.

Discussion

Glioma is one of the least understood and most aggressive tumors affecting humans (Wang et al. 2011, 2018). The risk factors are largely unknown but some studies have suggested a heredity factor that increases the risk of developing theses tumors (Wang et al. 2016; Wei et al. 2014). In this sense, some investigations have focused on the role of genetic polymorphisms in glioma risk; however, it remains unclear (Wibom et al. 2015; Wu et al. 2016). Therefore, our aim was to perform a systematic review and meta-analysis in order to address the possible involvement between CCDC26 variants (rs891835, rs6470745, and rs55705857) and the predisposition to glioma.

As a first step, we conducted an analysis in the overall population following the genetics models allelic, homozygous, heterozygous, recessive, and dominant. After discarding the studies that favoring the heterogeneity, we found a statistical significance in the analysis of rs891835 and rs55705857; only the rs6470745 showed a

significant *p* value in the presence and absence of heterogeneity. Our results suggest that genetic variants of CCDC26 gene increase the risk for glioma. One explanation could be that CCDC26 has a direct or indirect participation in controlling cellular checkpoints of DNA damage recovering that may be interfering in the prompting cell cycle or maintenance of genomic stability; hence, we recommend to perform a systematic scrutiny of CCDC26 gene mutations or rearrangements in primary tumors (Liu et al. 2010b; Schoemaker et al. 2010; Simon et al. 2010; Zeng et al. 2017).

To date, GWAS research on the susceptibility of glioma has been performed (Melin et al. 2017; Richardson et al. 2017). After the identification through fine-mapping, rs55705857 represents the likely causal variant at the 8q24.21 glioma risk locus; this association was confined to IDH-mutated gliomas, in particular those with 1p/19q codeletion (Enciso-Mora et al. 2013; Jenkins et al. 2012) This positive evidence and the results of our meta-analysis suggest that CCDC26 polymorphisms may represent a predictive biomarkers for glioma. Derived from these, it could be suggested that CCDC26 variant could be a retinoic acid-dependent modulator of myeloid cell differentiation and death (Kinnersley et al. 2018). Future studies with large sample size that confirm this outcome are necessary; the detection of CCDC26 variants as biomarkers in patients with primary tumors may help to select, in future clinical trials, those patients who could benefit of target therapies, although these polymorphisms (rs891835, rs55705857, rs6470745) did not have significant eQTLs in tissues.

On the other hand, we understand that the genetic background of patients could have a considerable contribution in the genotype frequency distribution. For example, data of HapMap-CEU in a European population revealed a frequency of 0.761 for AA, 0.212 for AG, and 0.027 for GG, while data from HapMap-CHD in Asian population revealed that the frequencies go to 0.365, 0.488, and 0.147 for AA, AG, and GG, respectively; Table 3 for checking minor allele frequency. Subsequently, we consider important address the association of rs891835, rs6470745, and rs55705857 variants as glioma risk factors depend of origin of the patients. The available data allowed us to perform the following sub-group analyses: Caucasian populations, individuals born in Europe, individuals born in USA, and finally, individuals born in China. The sub-group analysis in Caucasians and Europeans revealed that rs89183 and rs64707455 showed a statistical significance for glioma risk; in the case of

Table 3 Minor allele frequencies of the CCDC26 variants included in the meta-analysis by 1000 Genomes panel reference, phase 3

SNP	CEU	MXL	YRI	CHS
rs891835	T = 0.8030 G = 0.1970	T = 0.7969 G = 0.2031	T = 0.9907 G = 0.0093	T = 0.8810 G = 0.1190
rs6470745	A = 0.8485 G = 0.1515	A = 0.7734 G = 0.2266	A = 0.9352 G = 0.0648	A = 0.6667 G = 0.3333
rs55705857	A = 0.9596 G = 0.0404	A = 0.9992 G = 0.0078	A = 1.0000 G = 0.0000	A = 1.0000 G = 0.0000

CEU Utah Resident with, *MXL* Mexican Ancestry in Los Angeles, *YRI* Yoruba in Ibadan, *CHS* Southern Han Chinese

rs64707455, the association remained regardless of the presence of the heterogeneity. In the case of USA individuals, we only conducted an evaluation of the rs89183 variant, we excluded heterogeneity and found that the polymorphism may play a role as risk factor, but we need to take into consideration that this sub-group included a small number of studies; hence, we could not evaluate publication bias and for these reasons, we need to interpret the findings with caution.

Finally, we conducted an analysis in Chinese individuals and could not observe any relation with glioma. A possible explanation of the differences observed between Caucasians, Asians, or USA sub-groups and what we observed in Chinese people, could be the strong involvement of genetic background specific of ethnics. For example, it has been reported that incidence and survival rates of gliomas vary between different ethnicities (Barnholtz-Sloan et al. 2007; Shabihkhani et al. 2017; Wei et al. 2014). This variation has been investigated with emphasis on White and Black populations. Some studies have shown that glioma rates are highest in non-Latino Whites followed by Hispanics/Latinos and Blacks; while Asian/Pacific Islanders tend to have the lowest incidence (Barnholtz-Sloan et al. 2007; Shabihkhani et al. 2017). Derived from this, we could assume that there is a different participation of CCDC26 variants in Chinese individuals and due to their particular genetic background, the polymorphism did not have a participation in glioma development. We have to consider that may be other factors in Chinese individuals such as epigenetic regulation or cell metabolism could play irreplaceable roles in tumorigenesis (Pop et al. 2018).

Our analysis presents a statistical association of CCDC26 variants in the majority of the sub-groups; nevertheless, it essential to take into consideration some limitations. Firstly, the sample size, although the pathogenesis of glioma is poorly understood, the number of studies that have evaluated the association between glioma with CCDC26 is limited; hence, it is possible that in some sub-analysis, the power of the sample might not be enough to detect small effect of these genetic variants. Nevertheless, to our knowledge, this is the first meta-analysis that englobes three variants of CCDC26 and their role in glioma risk. Furthermore, we performed several evaluations of CCDC26 variants using several models; due to lack of data, we did not evaluate the role of these polymorphisms on different types of glioma, age, or gender among others factors that could participate in the manifestation of glioma (Simon et al. 2010; Wang et al. 2011). Therefore, we recommend that in future studies, outcomes are adjusted by the raw OR for age, gender, smoking, radiation exposure among other factors associated with tumors. There was no detailed information about gene–gene or gene–environment interactions and we were unable to perform more precise analysis. We also tried to address the problems that could cause heterogeneity between studies, but it was not completed, which may reduce the quality of the analysis.

In conclusion, based on the outcomes obtained in the present analysis, we could assume that rs891835, rs6470745, or rs55705857 variants of CCDC26 gene are possible risk biomarkers to glioma. However, we consider that rs891835 polymorphism may not participate in the pathogenesis of glioma in Chinese individuals. Nevertheless, we need to take into consideration the limitations of this study to make definite

conclusions. Further studies with larger samples and different populations are necessary to fully understand the development of glioma.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

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