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ORIGINAL RESEARCH

Genetic variants and increased risk of meningioma: an updated meta-analysis

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Purpose: Various genetic variants have been reported to be linked to an increased risk of meningioma. However, no confirmed conclusion has been obtained. The purpose of the study was to investigate potential meningioma-associated gene polymorphisms, based on published evidence.

Materials and methods: An updated meta-analysis was performed in September 2016. After electronic database searching and study screening, we selected eligible case-control studies and extracted data for meta-analysis, using Mantel–Haenszel statistics. *P*-values, pooled odds ratios (ORs), and 95% confidence intervals were calculated.

Results: We finally selected eight genes with ten polymorphisms: *MLLT10* rs12770228, *CASP8* rs1045485, *XRCC1* rs1799782, rs25487, *MTHFR* rs1801133, rs1801131, *MTRR* rs1801394, *MTR* rs1805087, *GSTM*1 null/present, and *GSTT1* null/present. Results of meta-analyses showed that there was increased meningioma risk in case groups under all models of *MLLT10* rs12770228 (all OR >1, $P<0.001$), compared with control groups. Similar results were observed under the allele, homozygote, dominant, and recessive models of *MTRR* rs1801394 (all OR >1, $P<0.05$), and the heterozygote and dominant models of *MTHFR* rs1801131 in the Caucasian population (all OR >1, $P<0.05$). However, no significantly increased meningioma risks were observed for *CASP*8 rs1045485, *XRCC1* rs25487, rs1799782, *MTHFR* rs1801133, *MTR* rs1805087, or *GSTM1*/*GSTT1* null mutations.

Conclusion: Our updated meta-analysis provided statistical evidence for the role of *MLLT10* rs12770228, *MTRR* rs1801394, and *MTHFR* rs1801131 in increased susceptibility to meningioma.

Keywords: meningioma, meta-analysis, gene, SNP

Introduction

Meningiomata, common slow-growing intracranial tumors, originate from the derivatives between the meninges and meningeal gap of the central nervous system.[1,2] According to the World Health Organization (WHO) grading system, grade I meningioma lesions are usually benign, whereas grade II–III meningioma lesions are mostly atypical, anaplastic, or malignant.[3,4] Chromosomal abnormalities (chromosomes 22, 1p, 9p, 10p, 11, 14q, 15, 17, and 18q) and associated genetic variants have been reported to be associated with meningioma risk.[4–6] For example, mutation of the *NF2* gene is reportedly related to meningioma risk.[7] However, the role of various gene polymorphisms in susceptibility to meningioma remains unconfirmed.

In the present study, we aimed to analyze all the relevant publications and investigate potential functional gene polymorphisms associated with meningioma risk. Ten single-nucleotide polymorphisms (SNPs) of eight genes – *MLLT10* rs12770228, *CASP8* rs1045485, *XRCC1* rs1799782, *XRCC1* rs25487, *MTHFR* rs1801133, *MTHFR*

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rs1801131, *MTRR* rs1801394, *MTR* rs1805087, *GSTM1* null/present, and *GSTT1* null/present – were selected from 20 eligible articles to conduct our meta-analysis.

There were several previous meta-analyses for associations between meningioma risk and gene polymorphisms, including *MTHFR* rs1801133, *MTRR* rs1801394, *MTR* rs1805087, *GSTM1* null/present, and *GSTT1* null/present.[8–13] However, an updated meta-analysis was still required. Moreover, no previous meta-analyses have been conducted to evaluate the association between *MTHFR* rs1801131, *MLLT10* rs12770228, *CASP8* rs1045485, *XRCC1* rs1799782, rs25487 polymorphisms and meningioma risks. Our data highlighted the positive association between *MLLT10* rs12770228, *MTRR* rs1801394, *MTHFR* rs1801131, and increased meningioma risk.

Materials and methods

Information sources

We retrieved the available articles from the online databases PubMed, Embase, Central, Web of Science, and CNKI/Wanfang in September 2016. The following search terms were used: "polymorphism, genetic" or "polymorphisms, genetic" or "genetic polymorphism" or "polymorphism (genetics)" or "genetic polymorphisms" or "polymorphism" or "variant" or "variants" or "mutation" or "mutations" or "SNP" or "single nucleotide polymorphism"; "meningioma" or "meningiomas" or "angioblastic meningiomas" or "angiomatous meningiomas" or "clear cell meningiomas" or "fibrous meningiomas" or "hemangioblastic meningiomas" or "intracranial meningiomas" or "intraventricular meningiomas" or "malignant meningiomas" or "multiple meningiomas" or "meningiomatosis" or "microcystic meningioma" or "olfactory groove meningioma" or "papillary meningioma" or "posterior fossa meningioma" or "psammomatous meningiomas" or "secretory meningioma" or "sphenoid wing meningioma" or "spinal meningioma" or "transitional meningioma" or "xanthomatous meningioma" or "benign meningiomas" or "cerebral convexity meningioma".

Eligibility criteria and data extraction

We screened and collected eligible studies based on our exclusion/inclusion criteria. The selected case-control studies had to contain genotype distributions of the case-control group. Genotype distribution in the control group had to be in line with Hardy–Weinberg equilibrium (HWE). Exclusion criteria were comments, reviews, and letters; meeting abstracts; cases, trials, or not polymorphisms; not clinical data; other genes for which the number of case-control studies on specific variants was fewer than three; other diseases; meta-analyses; and lack of usable data. Then, four investigators independently performed methodological quality assessment using the Newcastle–Ottawa scale (NOS; http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), and extracted the specific data, mainly genes, SNP, first author, year of publication, country, ethnicity, genotype frequencies of case-control, source of control, disease group, *P*-values of HWE test, genotyping methods, number of studies, sample size, and NOS score. NOS scores ≥ 7 mean a high-quality study. Emails were sent for unavailable data, and a discussion was needed for discrepancies.

Data synthesis

Stata/SE 12.0 (StataCorp, College Station, TX, USA) was utilized. *P*-values of association, summary odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated via Mantel–Haenszel statistics, based on the allele, homozygote, heterozygote, dominant, and recessive models. Two-sided *P*-values less than 0.05 were interpreted as statistically different; χ^2 tests were used for HWE *P*-values.

Heterogeneity analysis and publication bias

Cochran's Q test and I^2 statistic were applied for assessment of potential between-study heterogeneity. *P*-values for Q tests >0.1 or I^2 index $<25\%$ indicate the existence of overall statistically significant heterogeneity and the utilization of a fixed-effect model. Otherwise, a random-effect model was used.[14,15] To analyze the main source of homogeneity, subgroup analysis by ethnicity and sensitivity analysis were conducted. In addition, Egger's test and Begg's test were carried out to evaluate potential publication bias.[16–18]

Results

Study selection and characteristics

To identify studies on the association between potential genetic variants and meningioma risk, five online databases (PubMed, Embase, Central, Web of Science, and CNKI/Wanfang) were searched in September 2016. A flow diagram of publication search and study screening for the meta-analysis is shown in Figure 1. The PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement was followed.[19] A total of 4,355 potentially relevant articles were retrieved initially from the databases. After the removal of duplicated articles, 2,268 articles were excluded by screening title and abstract, with reasons shown in Figure 1. A total of 35 full-text articles were assessed for

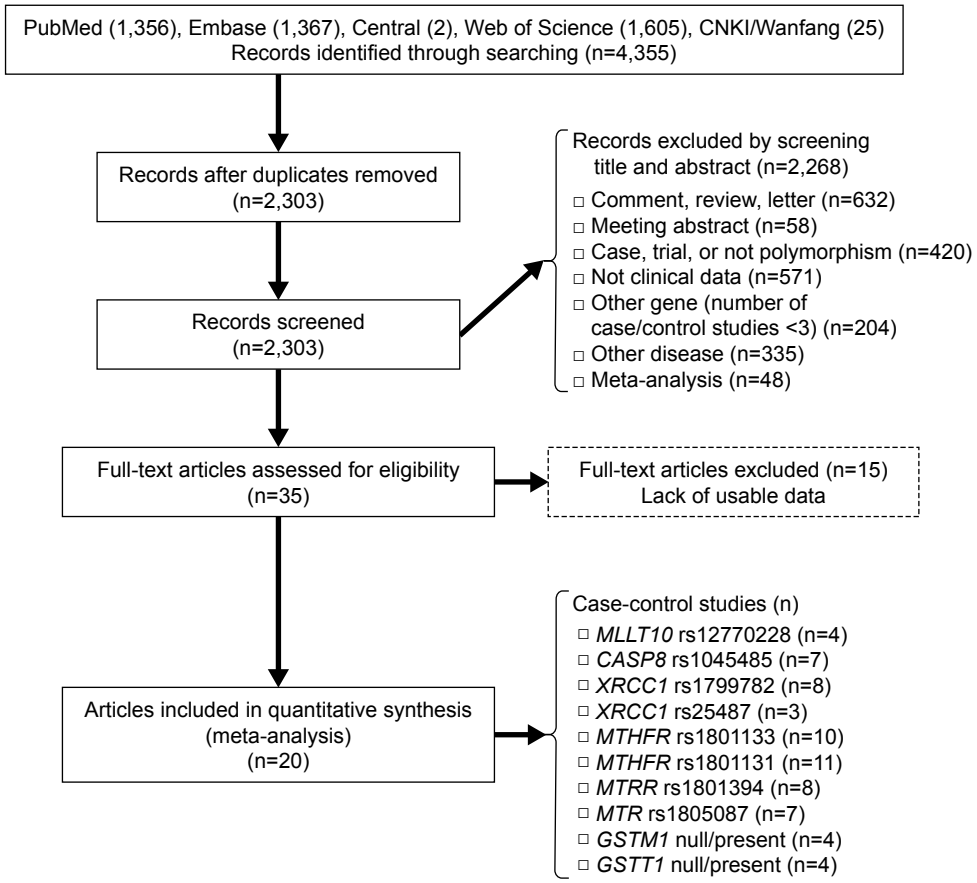

Figure 1 Flow diagram of publication search and study screening for the meta-analysis.

eligibility, and 15 were excluded for lack of usable data. As a result, 20 articles with ten polymorphisms of eight genes met our eligibility criteria and were selected for the meta-analysis.[20–39] Table 1 summarizes the characteristics of the articles included. NOS scores of all the studies were larger than or equal to 7, which indicated high quality. No significant deviation from HWE was found for any of the studies. The SNPs *MLLT10* rs12770228, *CASP8* rs1045485, *XRCC1* rs1799782, *XRCC1* rs25487, *MTHFR* rs1801133, *MTHFR* rs1801131, *MTRR* rs1801394, *MTR* rs1805087, *GSTM1* null/present, and *GSTT1* null/present were analyzed (Table 2).

MLLT10 rs12770228

We first evaluated the association between rs12770228 of *MLLT10* and meningioma risk. As shown in Figure 2A and Table 3, a fixed-effect model was used under the allele (A vs G), homozygote (AA vs GG) and recessive (AA vs GG+GA) models, due to low degree or no heterogeneity (heterogeneity, all $P>0.1$, $I^2<25\%$), whereas a random-effect model was applied for others. Pooled analysis data suggested that increased meningioma risk was detected under all genetic models (Table 3, test of association, all ORs >1, $P<0.001$). In addition, the existence of publication bias was excluded (Figure 2B and C, Table 4, Begg's test, Egger's test, all $P>0.05$). We also performed a sensitivity meta-analysis and found that the corresponding pooled OR value did not differ significantly from that of the overall meta-analysis (Figure 2D for allele model; data not shown for other models). These results suggested that the *MLLT10* rs12770228 A/G polymorphism may be associated with increased meningioma risk.

CASP8 rs1045485

The association between *CASP8* rs1045485 and susceptibility to meningioma was then analyzed. As shown in Table 3, a fixed-effect model was utilized for the allele, homozygote, dominant, and recessive models (heterogeneity, all $P>0.1$, $I^2<25\%$), but not the heterozygote model (Table 3, $I^2=26.4\%$). The genetic association between the rs1045485 G/C allele frequency of *CASP8* and increased meningioma risk was obtained under the C vs G model (OR 1.14, 95% CI 0.94–1.4; $P=0.181$). In addition, we did not observe significantly increased

Table 1 Characteristics of studies included in the meta-analysis

Study	Year	Country/region	Ethnicity	Gene	SNP	Case	Disease group	Control	Source of controls	HWE, *P*-value	Genotyping methods	NOS score
						MM/Mm/mm		MM/Mm/mm				
Ahn et al[39]	2002	South Korea	Asian	*MTHFR*	rs1801133	16/13/3	Meningioma	91/129/34	PB	0.27	PCR-RFLP	7
Bethke et al[38]	2009	Finland	Caucasian	*CASP8*	rs1045485	60/16/0	Meningioma	65/7/0	PB	0.66	Illumina customized GoldenGate array	7
		Denmark	Caucasian	*CASP8*	rs1045485	81/20/0		84/23/1	PB	0.67		
		UK – South	Caucasian	*CASP8*	rs1045485	92/21/6		93/24/1	PB	0.68		
		UK – North	Caucasian	*CASP8*	rs1045485	128/37/2		133/29/4	PB	0.13		
		Sweden	Caucasian	*CASP8*	rs1045485	115/27/2		115/27/1	PB	0.67		
Bethke et al[37]	2008	UK – North	Caucasian	*MTHFR*	rs1801131	80/73/20	Meningioma	94/64/17	PB	0.22	Illumina GoldenGate array	7
		UK – North	Caucasian	*MTHFR*	rs1801133	57/98/19		73/78/24	PB	0.66		
		UK – North	Caucasian	*MTRR*	rs1801394	54/83/37		74/78/23	PB	0.73		
		UK – North	Caucasian	*MTR*	rs1805087	113/54/7		106/60/8	PB	0.89		
		UK – Southeast	Caucasian	*MTHFR*	rs1801131	54/59/8		62/48/13	PB	0.42		
		UK – Southeast	Caucasian	*MTHFR*	rs1801133	50/57/14		48/60/15	PB	0.57		
		UK – Southeast	Caucasian	*MTRR*	rs1801394	41/57/23		39/59/25	PB	0.76		
		UK – Southeast	Caucasian	*MTR*	rs1805087	77/39/5		75/42/6	PB	0.97		
		Sweden	Caucasian	*MTHFR*	rs1801131	61/77/11		64/66/19	PB	0.76		
		Sweden	Caucasian	*MTHFR*	rs1801133	64/68/17		82/57/10	PB	0.98		
		Sweden	Caucasian	*MTRR*	rs1801394	39/84/26		53/74/22	PB	0.64		
		Sweden	Caucasian	*MTR*	rs1805087	98/45/6		94/51/4	PB	0.34		
		Denmark	Caucasian	*MTHFR*	rs1801131	44/57/9		53/43/17	PB	0.1		
		Denmark	Caucasian	*MTHFR*	rs1801133	45/55/10		56/45/12	PB	0.52		
		Denmark	Caucasian	*MTRR*	rs1801394	41/47/22		40/55/18	PB	0.90		
		Denmark	Caucasian	*MTR*	rs1805087	73/33/4		70/40/3	PB	0.33		
		Finland	Caucasian	*MTHFR*	rs1801131	38/31/8		37/32/8	PB	0.78		
		Finland	Caucasian	*MTHFR*	rs1801133	46/26/5		47/25/5	PB	0.51		
		Finland	Caucasian	*MTRR*	rs1801394	26/37/14		30/33/14	PB	0.36		
		Finland	Caucasian	*MTR*	rs1805087	50/24/3		56/17/4	PB	0.1		
Cacina et al[36]	2015	Turkey	Caucasian	*CASP8*	rs1045485	28/8/3	Meningioma	66/42/6	PB	0.84	PCR-RFLP	7
Cengiz et al[35]	2008	Turkey	Caucasian	*XRCC1*	rs25487	25/41/5	Meningioma	43/41/3	PB	0.07	PCR-RFLP	8
De Roos et al[34]	2003	US	Caucasian	*GSTM1*	Present/null	85[b]/84[c]	Meningioma	254[b]/321[c]	HB	–	PCR	7
				GSTT1	Present/null	121[b]/38[c]		445[b]/100[c]	HB	–		
Dobbins et al[33]	2011	Germany	Caucasian	*MLLT10*	rs12770228	309/426/123	Meningioma	328/302/74	PB	0.72	[a]	7
		UK	Caucasian	*MLLT10*	rs12770228	144/187/73		361/321/76	PB	0.71		
		Scandinavia	Caucasian	*MLLT10*	rs12770228	145/158/47		463/424/91	PB	0.67		
Egan et al[32]	2015	US	Caucasian	*MLLT10*	rs12770228	111/111/46	Meningioma	287/267/74	PB	0.33	TaqMan assays	7
Elexpuru-Camiruaga et al[31]	1995	UK	Caucasian	*GSTM1*	Present/null	22[b]/27[c]	Meningioma	262[b]/315[c]	HB	–	PCR	7
		UK	Caucasian	*GSTT1*	Present/null	26[b]/21[c]		403[b]/91[c]	HB	–		
Huang et al[30]	2012	China	Asian	*XRCC1*	rs1799782	100/80/25	Meningioma	95/102/21	PB	0.39	Snapshot multiplex	8
		China	Asian	*XRCC1*	rs1799782	53/24/11	<50 years old	41/51/12	PB	0.52		
		China	Asian	*XRCC1*	rs1799782	47/56/14	≥50 years old	54/51/9	PB	0.52		

		China	Asian	*XRCC1*	rs1799782	27/20/7	Male	29/36/9	PB	0.67		
		China	Asian	*XRCC1*	rs1799782	73/60/18	Female	66/66/12	PB	0.42		
Huang et al[29]	2015	China	Asian	*XRCC1*	rs1799782	63/41/20	Skull-base meningioma	95/102/21	PB	0.39	Snapshot multiplex	8
Kafadar et al[28]	2006	Turkey	Caucasian	*MTHFR*	rs1801133	20/12/3	Meningioma	53/38/7	PB	0.96	PCR-RFLP	9
Kiuru et al[27]	2008	Mixed	Caucasian	*XRCC1*	rs1799782	469/50/2	Meningioma	1,377/177/2	PB	0.13	PCR-RFLP	9
		Mixed	Caucasian	*XRCC1*	rs25487	212/233/74		645/728/176	PB	0.17		
Li et al[26]	2013	China	Asian	*MTHFR*	rs1801133	101/147/69	Meningioma	159/129/32	PB	0.44	PCR-RFLP	9
		China	Asian	*MTHFR*	rs1801131	205/96/16		201/98/21	PB	0.06		
Pinarbasi et al[25]	2005	Turkey	Caucasian	*GSTM1*	Present/null	12[b]/11[c]	Meningioma	116[b]/37[c]	HB	–	PCR	7
		Turkey	Caucasian	*GSTT1*	Present/null	17[b]/6[c]		122[b]/31[c]	HB	–		
Rajaraman et al[24]	2010	US	Caucasian	*XRCC1*	rs1799782	104/18/0	Meningioma	394/73/1	HB	0.21	TaqMan assay	7
		US	Caucasian	*XRCC1*	rs25487	56/62/14		205/201/72	HB	0.05		
Rajaraman et al[23]	2007	US	Caucasian	*CASP8*	rs1045485	117/38/5	Meningioma	426/118/6	HB	0.87	Medium-throughput TaqMan assay	7
Schwartzbaum et al[22]	2007	Mixed	Caucasian	*GSTM1*	Present/null	68[b]/108[c]	Meningioma	193[b]/237[c]	PB	–	PCR	8
		Mixed	Caucasian	*GSTT1*	Present/null	149[b]/27[c]		362[b]/68[c]	PB	–		
Semmler et al[21]	2008	Germany	Caucasian	*MTHFR*	rs1801133	131/133/26	Meningioma	132/135/20	PB	0.06	PCR-RFLP	8
		Germany	Caucasian	*MTHFR*	rs1801131	116/142/32	Meningioma	132/123/32	PB	0.68		
		Germany	Caucasian	*MTR*	rs1805087	197/81/12	Meningioma	184/92/11	PB	0.91		
		Germany	Caucasian	*MTHFR*	rs1801133	10/7/1	WHO grade III	132/135/20	PB	0.91		
		Germany	Caucasian	*MTHFR*	rs1801131	7/10/1	WHO grade III	132/123/32	PB	0.91		
		Germany	Caucasian	*MTR*	rs1805087	18/0/0	WHO grade III	184/92/11	PB	0.91		
Zhang et al[20]	2013	China	Asian	*MTHFR*	rs1801131	184/157/50	WHO grade I	289/245/66	PB	0.2	PCR-RFLP	8
		China	Asian	*MTRR*	rs1801394	135/176/80	WHO grade I	225/282/93	PB	0.77		
		China	Asian	*MTHFR*	rs1801131	79/67/21	WHO grade II	289/245/66	PB	0.2		
		China	Asian	*MTRR*	rs1801394	59/74/34	WHO grade II	225/282/93	PB	0.77		
		China	Asian	*MTHFR*	rs1801131	20/17/5	WHO grade III	289/245/66	PB	0.2		
		China	Asian	*MTRR*	rs1801394	15/19/8	WHO grade III	225/282/93	PB	0.77		

Notes: M, major allele; m, minor allele. [a]Illumina Infinium HD human 662 quad or OmniExpress BeadChip, competitive allele-specific KASP chemistry; [b]number of samples with *GSTM1* or *GSTT1* null genotype; [c]number of samples with *GSTM1* or *GSTT1* null/present genotype. '–' indicates not available.

Abbreviations: SNP, single-nucleotide polymorphism; HWE, Hardy–Weinberg Equilibrium; NOS, Newcastle–Ottawa Scale; PB, population-based; PCR-RFLP, polymerase chain reaction–restriction fragment-length polymorphism; HB, hospital-based; WHO, World Health Organization.

Table 2 Genes and SNPs included in the meta-analysis

Gene	Chromosome	SNP	Sequence	Global MAF	Variants	Description
MLLT10	10:21494705	rs12770228	CTTTCGCTTGCGGTTTGCAACCCCT [A/G]GGGTGGGTCTGACCCCGCGCGGCAC	A =0.156/781	C895T	Transcription factor and partner gene involved in several chromosomal rearrangements
CASP8	2:201284866	rs1045485	GCTTCATTTTGAGATCAAGCCCCAC [C/G]ATGACTGCACAGTAGAGCAAATCTA	C =0.0527/264	D302H	Apoptosis-related cysteine peptidase
XRCC1	19:43553422	rs1799782	GAGGCCGGGGGCTCTCTTCTTCAGC [C/T]GGATCAACAAGACATCCCCAGGTGA	A =0.1238/620	R194W	DNA repair of single-strand breaks and base excision
	19:43551574	rs25487	CGCATGCGTCGGCGGCTGCCCTCCC [A/G]GAGGTAAGGCCTCACACGCCAACCC	T =0.2604/1,304	Q399R	
MTHFR	1:11796321	rs1801133	TTGAAGGAGAAGGTGTCTGCGGGAG [C/T]CGATTTCATCATCACGCAGCTTTTC	A =0.2454/1,229	C677T	Catalyzes the conversion of 5,10-methylenetetrahydrofolate to
	1:11794419	rs1801131	TGGGGGGAGGAGCTGACCAGTGAAG [A/C]AAGTGTCTTTGAAGTCTTCGTTCTT	G =0.2494/1,249	A1298C	5-methyltetrahydrofolate, and a cosubstrate for homocysteine remethylation to methionine
MTRR	5:7870860	rs1801394	AGGCAAAGGCCATCGCAGAAGAAAT [A/G]TGTGAGCAAGCTGTGGTACATGGAT	G =0.3642/1,824	A66G	Involved in the reductive regeneration of cobalamin cofactor required for the maintenance of methionine synthase in a functional state
MTR	1:236885200	rs1805087	GAAGAATATGAAGATATTAGACAGG [A/G]CCATTATGAGTCTCTCAAGGTAAGT	G =0.2183/1,093	A2756G	Cobalamin-dependent methionine synthase, catalyzes the final step in methionine biosynthesis
GSTM1	–	–	–	–	Null/present	Member of GST family that conjugates with glutathione and functions in the detoxification of carcinogens, environmental toxins and products of oxidative stress
GSTT1	–	–	–	–	Null/present	Member of GST family that catalyzes the conjugation of reduced glutathione to a variety of electrophilic and hydrophobic compounds

Note: '–' indicates not available.

Abbreviations: SNPs, single-nucleotide polymorphisms; MAF, minor allele frequency; GST, glutathione S-transferase; A, adenine; G, guanine; C, cytosine; T, thymine.

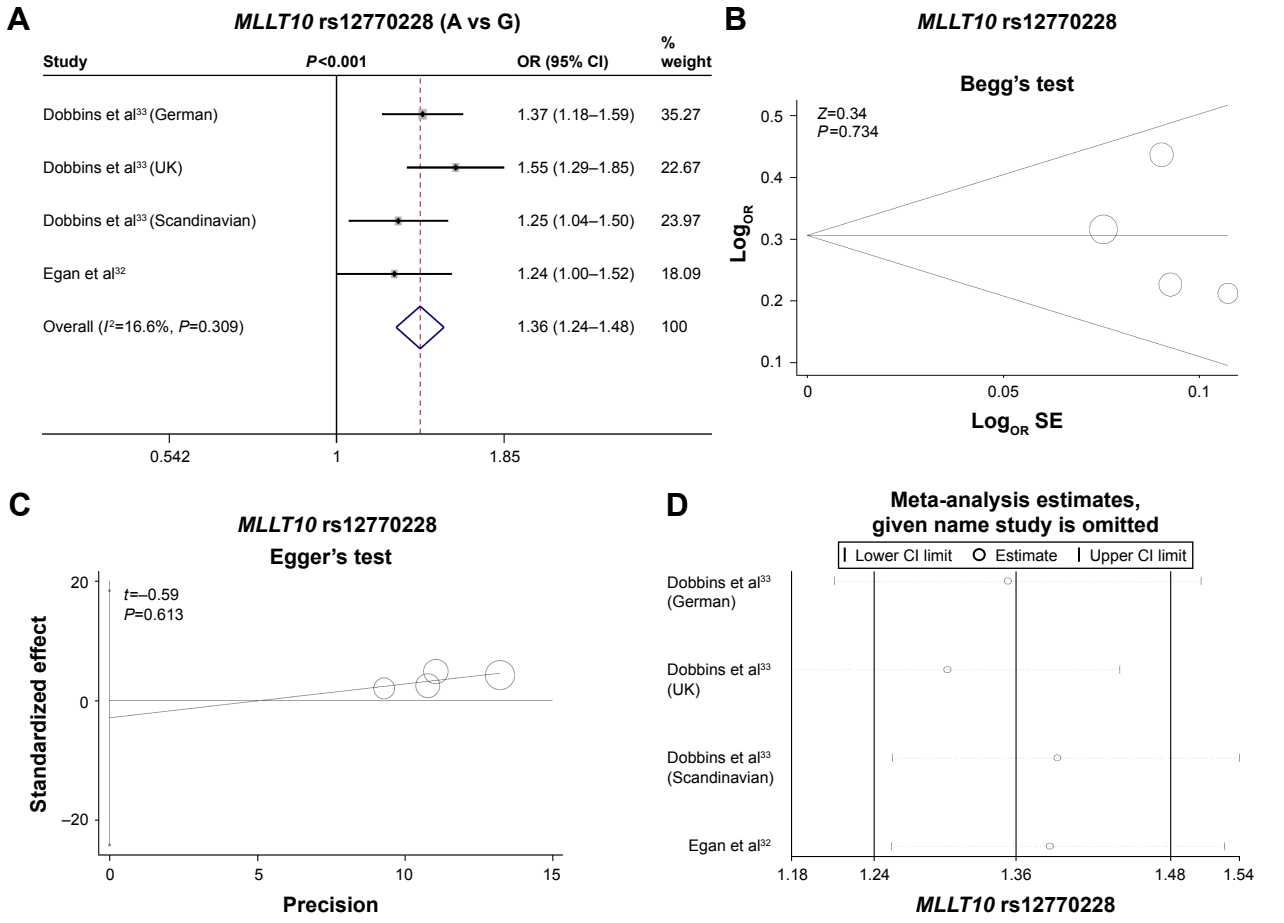

Figure 2 Meta-analysis of the association between the *MLLT10* polymorphism and meningioma risk under the allele model.
Notes: (**A**) Forest plot analysis; (**B**) Begg's test with size graph symbol by weights; (**C**) Egger's test with size graph symbol by weights; and (**D**) sensitivity meta-analysis. Weights are from fixed-effect analysis. The "given name study is omitted" was produced by the STAT12.0 software. It means the given name studies were omitted, and the meta-analysis data by other studies were showed.
Abbreviations: A, adenine; G, guanine; OR, odds ratio; CI, confidence interval; SE, standard error.

meningioma risk in any genetic model (Table 3, test of association, all $P>0.05$). No publication bias was observed under any model either (Table 4, Begg's test, Egger's test, all $P>0.05$). Sensitivity meta-analyses further confirmed the results (data not shown). Therefore, the *CASP8* rs1045485 polymorphism seems not to be associated with meningioma risk.

XRCC1 rs1799782 and rs25487

Next, we conducted meta-analyses of the associations between *XRCC1* rs1799782 and rs25487 polymorphisms and meningioma risk. For *XRCC1* rs1799782, no or low heterogeneity was observed, and a fixed-effect model was thus used for all genetic models (Table 3, heterogeneity, all $P>0.1$, $I^2<25\%$), apart from the heterozygote model ($I^2=34.2\%$). The results of Table 3 show that significant differences were observed under the heterozygote (OR 0.75, 95% CI 0.61–0.94; $P=0.01$), dominant (OR 0.82, 95% CI 0.7–0.97; $P=0.018$), and recessive models (OR 1.43, 95% CI 1.05–1.95; $P=0.022$), but not other models. Furthermore, subgroup analyses based on ethnicity were performed under all models. A similar change for increased meningioma risk was observed in the Asian population under the heterozygote, dominant, and recessive models (Table 5). Begg's test and Egger's test data excluded the presence of large publication bias (Table 4, Begg's test and Egger's test, all $P>0.05$).

For *XRCC1* rs25487, a random-effect model was used under all genetic models (Table 3, heterogeneity, all $I^2>25\%$). No significant difference and no publication bias were observed under any genetic models (Table 3, test of association, all $P>0.05$; Table 4, Begg's test and Egger's test, all $P>0.05$). Sensitivity meta-analyses further confirmed these results (data not shown). The data failed to provide strong evidence for an association between *XRCC1* rs1799782 or rs25487 polymorphisms and increased meningioma risk.

MTHFR rs1801133 and rs1801131

As shown in Table 3, a random-effect model was used for *MTHFR* rs1801133 (heterogeneity, all $I^2>25\%$), while a fixed-effect model was used for *MTHFR* rs1801131 (heterogeneity, all $P>0.1$, $I^2=0\%$). No significant difference

Table 3 Pooled analysis of the associations between *MLLT10*, *CASP8*, *XRCC1*, *MTHFR*, *MTRR*, and *MTR* polymorphisms and meningioma risk

Gene	SNP	Comparison	Number of studies	Sample size		Test of association		Heterogeneity		Model
				Case	Control	OR (95% CI)	*P*-value	I^2	*P*-value	
MLLT10	rs12770228	A vs G	4	1,880	3,068	1.36 (1.24–1.48)	<0.001	16.6	0.309	F
		AA vs GG	4	1,880	3,068	1.84 (1.53–2.23)	<0.001	0	0.438	F
		GA vs GG	4	1,880	3,068	1.32 (1.13–1.54)	<0.001	27.7	0.246	R
		GA+AA vs GG	4	1,880	3,068	1.42 (1.23–1.64)	<0.001	28.7	0.24	R
		AA vs GG+GA	4	1,880	3,068	1.36 (1.24–1.48)	<0.001	0	0.552	F
CASP8	rs1045485	C vs G	7	806	1,271	1.14 (0.94–1.4)	0.181	2.6	0.406	F
		CC vs GG	6	730	1,199	1.67 (0.86–3.26)	0.129	5.5	0.382	F
		GC vs GG	7	806	1,271	1.06 (0.8–1.4)	0.687	26.4	0.227	R
		GC+CC vs GG	7	806	1,271	1.11 (0.89–1.39)	0.181	14.7	0.318	F
		CC vs GG+GC	6	730	1,199	1.14 (0.94–1.4)	0.102	3.6	0.393	F
XRCC1	rs1799782	T vs C	8	1,382	2,896	0.94 (0.82–1.07)	0.327	0	0.469	F
		TT vs CC	8	1,382	2,896	1.22 (0.89–1.69)	0.219	0	0.83	F
		CT vs CC	8	1,382	2,896	0.75 (0.61–0.94)	0.010	34.2	0.155	R
		CT+TT vs CC	8	1,382	2,896	0.82 (0.7–0.97)	0.018	23.8	0.24	F
		TT vs CC+CT	8	1,382	2,896	1.43 (1.05–1.95)	0.022	0	0.969	F
XRCC1	rs25487	A vs G	3	722	2,114	1.08 (0.89–1.31)	0.440	37	0.205	R
		AA vs GG	3	722	2,114	1.14 (0.67–1.95)	0.632	49.3	0.139	R
		GA vs GG	3	722	2,114	1.09 (0.85–1.4)	0.495	27.8	0.25	R
		GA+AA vs GG	3	722	2,114	1.1 (0.87–1.39)	0.429	25.3	0.262	R
		AA vs GG+GA	3	722	2,114	1.09 (0.63–1.86)	0.766	54.2	0.112	R
MTHFR	rs1801133	T vs C	10	1,323	1,883	1.14 (0.93–1.39)	0.222	64.2	0.003	R
		TT vs CC	10	1,323	1,883	1.31 (0.87–1.98)	0.201	52	0.027	R
		CT vs CC	10	1,323	1,883	1.19 (0.95–1.49)	0.132	43.8	0.066	R
		CT+TT vs CC	10	1,323	1,883	1.19 (0.92–1.53)	0.180	58.9	0.009	R
		TT vs CC+CT	10	1,323	1,883	1.22 (0.87–1.71)	0.239	36.6	0.115	R
MTHFR	rs1801131	C vs A	11	1,855	3,331	1.05 (0.95–1.15)	0.335	0	0.97	F
		CC vs AA	11	1,855	3,331	1.01 (0.82–1.24)	0.597	0	0.829	F
		AC vs AA	11	1,855	3,331	1.13 (0.99–1.29)	0.060	0	0.793	F
		AC+CC vs AA	11	1,855	3,331	1.11 (0.98–1.25)	0.108	0	0.935	F
		CC vs AA+AC	11	1,855	3,331	0.94 (0.77–1.15)	0.574	0	0.594	F
MTRR	rs1801394	G vs A	8	1,231	2,437	1.18 (1.06–1.31)	0.002	0	0.682	F
		GG vs AA	8	1,231	2,437	1.4 (1.14–1.73)	0.002	0	0.756	F
		AG vs AA	8	1,231	2,437	1.1 (0.93–1.3)	0.250	0	0.67	F
		AG+GG vs AA	8	1,231	2,437	1.18 (1.01–1.37)	0.036	0	0.622	F
		GG vs AA+AG	8	1,231	2,437	1.33 (1.1–1.61)	0.003	0	0.883	F
MTR	rs1805087	G vs A	7	939	1,210	0.89 (0.75–1.04)	0.140	0	0.51	F
		GG vs AA	7	939	1,210	0.96 (0.6–1.53)	0.867	0	0.985	F
		AG vs AA	7	939	1,210	0.84 (0.69–1.02)	0.074	10.4	0.35	F
		AG+GG vs AA	7	939	1,210	0.85 (0.7–1.02)	0.084	5.7	0.384	F
		GG vs AA+AG	7	939	1,210	1.02 (0.64–1.61)	0.946	0	0.986	F

Abbreviations: SNP, single-nucleotide polymorphism; OR, odds ratio; CI, confidence interval; F, fixed; R, random; A, adenine; G, guanine; C, cytosine; T, thymine.

was observed for rs1801133 or rs1801131 under any genetic model (Table 3, test of association, all $P>0.05$). No publication bias was observed under any models (Table 4, Begg's test and Egger's test, all $P>0.05$), apart from the allele and homozygote models of rs1801133 (Table 4, Egger's test, $P<0.05$). Subgroup analyses of ethnicity further showed a significant difference only for rs1801131 under the heterozygote (AC vs AA, OR 1.32, 95% CI 1.09–1.59; $P=0.004$) and dominant (AC+CC vs AA, OR 1.23, 95% CI 1.03–1.48; $P=0.023$) models of rs1801131 in the Caucasian population (Table 5), suggesting that the AC genotype of *MTHFR* rs1801131 might be associated with increased meningioma risk in the Caucasian population. Sensitivity meta-analyses further confirmed these results (data not shown).

MTRR rs1801394 and MTR rs1805087

Fixed-effect models were used for *MTRR* rs1801394 and *MTR* rs1805087 (Table 3, heterogeneity, all $P>0.1$, $I^2<25\%$). Sig-

Table 4 Begg's test and Egger's test data

Gene	SNP	Comparison	Begg's test		Egger's test	
			z	*P*-value	t	*P*-value
MLLT10	rs12770228	A vs G	0.34	0.734	−0.59	0.613
		AA vs GG	1.02	0.308	−0.32	0.778
		GA vs GG	1.02	0.308	−2.02	0.18
		GA+AA vs GG	0.34	0.734	−1.24	0.341
		AA vs GG+GA	0.34	0.734	0.27	0.814
CASP8	rs1045485	C vs G	0.6	0.548	−0.17	0.87
		CC vs GG	0.38	0.707	−0.61	0.572
		GC vs GG	0.6	0.548	−0.4	0.708
		GC+CC vs GG	0.90	0.368	−0.31	0.77
		CC vs GG+GC	0.38	0.707	−0.64	0.56
XRCC1	rs1799782	T vs C	0.12	0.902	−0.71	0.506
		TT vs CC	0.37	0.711	0.36	0.731
		CT vs CC	0.37	0.711	−0.79	0.46
		CT+TT vs CC	0.62	0.536	−0.6	0.569
		TT vs CC+CT	−0.12	1	0.28	0.792
XRCC1	rs25487	A vs G	0	1	0.35	0.784
		AA vs GG	0	1	0.07	0.955
		GA vs GG	1.04	0.296	4.08	0.153
		GA+AA vs GG	1.04	0.296	1.3	0.418
		AA vs GG+GA	0	1	−0.16	0.897
MTHFR	rs1801133	T vs C	1.43	0.152	−2.33	0.048
		TT vs CC	0.54	0.592	−2.51	0.036
		CT vs CC	1.61	0.107	−1.88	0.097
		CT+TT vs CC	1.43	0.152	−2.23	0.056
		TT vs CC+CT	0.54	0.592	−1.96	0.086
MTHFR	rs1801131	C vs A	1.09	0.276	−0.59	0.571
		CC vs AA	1.09	0.276	−2.14	0.061
		AC vs AA	0.93	0.35	1.45	0.181
		AC+CC vs AA	0.47	0.64	0.92	0.38
		CC vs AA+AC	1.4	0.161	−2.37	0.042
MTRR	rs1801394	G vs A	1.11	0.266	−0.55	0.605
		GG vs AA	1.11	0.266	−0.64	0.544
		AG vs AA	−0.12	1	0.33	0.753
		AG+GG vs AA	−0.12	1	0.01	0.99
		GG vs AA+AG	1.61	0.108	−1.21	0.272
MTR	rs1805087	G vs A	0	1	−1.55	0.183
		GG vs AA	0.3	0.764	−0.73	0.497
		AG vs AA	0.3	0.764	−0.95	0.385
		AG+GG vs AA	0.3	0.764	−1.21	0.28
		GG vs AA+AG	0.3	0.764	−0.46	0.662

Abbreviations: SNP, single-nucleotide polymorphism; A, adenine; G, guanine; C, cytosine; T, thymine.

nificantly increased meningioma risk was observed for *MTRR* rs1801394 under the allele (G vs A), homozygote (GG vs AA), dominant (AG+GG vs AA), and recessive (GG vs AA+AG) models (Table 3, test of association, all OR>1, $P<0.05$). Nevertheless, no increased meningioma risk was observed for *MTR* rs1805087 under any model (Table 3, test of association, all $P>0.05$). Subgroup analyses further indicated that there was increased meningioma risk for *MTRR* rs1801394 under the allele, homozygote, and recessive models in the Asian population and the allele and homozygote models in the Caucasian population (Table 5, test of association, all $P<0.05$). No publication bias was detected for *MTRR* rs1801394 or *MTR* rs1805087 under any model (Table 4, Begg's test and Egger's test, all $P>0.1$). The results were further confirmed by sensitivity meta-analyses (data not shown). These data demonstrated that *MTRR* rs1801394, but not *MTR* rs1805087, is more likely to be linked to increased meningioma risk.

GSTM1 and *GSTT1* null/present

Finally, we investigated the genetic relationship between the null/present genotype of *GSTM1* and *GSTT1* and meningioma risk. A fixed model was used for *GSTM1* (Figure 3A, heterogeneity, $P=0.289$, $I^2=20.1\%$), whereas a random model was used for *GSTT1* (Figure 4A, heterogeneity, $P=0.108$, $I^2=50.6\%$). No increased or decreased meningioma risk was observed for the null genotype of *GSTM1* (Figure 3A, test of association, $P=0.73$) or *GSTT1* (Figure 4A, test of association, $P=0.099$). No publication bias was detected (Figure 3B and C, Figure 4B and C, Begg's test and Egger's test, all $P>0.05$). Sensitivity meta-analyses (Figures 3D and 4D) further confirmed the results. These results demonstrated that the polymorphisms of *GSTM1* and *GSTT1* may not be associated with meningioma risk.

Discussion

In the present study, we performed an updated meta-analysis to investigate potential genetic variants associated with meningioma risk. Ten genetic variants of eight genes were targeted. These genes can be classified into five categories: 1) chromosomal rearrangement-associated gene, *MLLT10*; 2) apoptosis-associated gene, *CASP8*; 3) DNA repair-associated gene, *XRCC1*; 4) folate-metabolism genes, *MTHFR*, *MTRR*, and *MTR*; 5) and drug metabolism-related genes, *GSTM1* and *GSTT1*.

Folate metabolism-associated gene mutations have been reported to be associated with several diseases.[12,40] The MTHFR protein, a kind of folate-metabolizing enzyme, is required for the methylation of homocysteine to methionine.[41–44] Both the *MTRR* and *MTR* genes are also indispensable for the folate metabolic pathway.[40] Polymorphisms of *MTHFR*, *MTRR*, and *MTR* have been reported to be linked to susceptibility to meningioma in certain populations. For example, *MTHFR* rs1801133 or MTRR rs1801394 was found to be associated with meningioma risk in the Chinese population.[20,26] However, the role of *MTHFR* polymorphisms in the presence of meningioma is still conflicting. For instance, there was no significant genetic association between *MTHFR* rs1801133

Table 5 Subgroup analysis of the association between *XRCC1*, *MTHFR*, and *MTRR* polymorphisms and meningioma risk

Comparison	*XRCC1* rs1799782		*MTHFR* rs1801133		*MTHFR* rs1801131		*MTRR* rs1801394	
	Asian	Caucasian	Asian	Caucasian	Asian	Caucasian	Asian	Caucasian
m vs M								
Studies, n	6	2	2	8	4	7	3	5
Case-control	739/872	643/2,024	349/574	974/1,309	917/2,120	938/1,211	600/1,800	631/637
OR	0.95	0.89	1.19	1.11	1.02	1.07	1.17	1.19
95% CI	0.82–1.1	0.68–1.17	0.42–3.22	0.97–1.27	0.9–1.16	0.94–1.23	1.01–1.34	1.02–1.4
P-value	0.511	0.408	0.775	0.129	0.73	0.301	0.032	0.03
mm vs MM								
Studies, n	6	2	2	8	4	7	3	5
Case-control	739/872	643/2,024	349/574	974/1,309	917/2,120	938/1,211	600/1,800	631/637
OR	1.2	2.3	1.44	1.18	1.08	0.92	1.41	1.4
95% CI	0.86–1.66	0.45–11.8	0.22–9.34	0.86–1.62	0.81–1.44	0.68–1.26	1.06–1.86	1.01–1.94
P-value	0.283	0.32	0.703	0.302	0.592	0.618	0.016	0.04
Mm vs MM								
Studies, n	6	2	2	8	4	7	3	5
Case-control	739/872	643/2,024	349/574	974/1,309	917/2,120	938/1,211	600/1,800	631/637
OR	0.7	0.86	1.07	1.17	0.99	1.32	1.02	1.21
95% CI	0.52–0.95	0.64–1.14	0.35–3.26	0.97–1.42	0.83–1.19	1.09–1.59	0.82–1.27	0.94–1.54
P-value	0.022	0.282	0.902	0.11	0.931	0.004	0.827	0.136
Mm+mm vs MM								
Studies, n	6	2	2	8	4	7	3	5
Case-control	739/872	643/2,024	349/574	974/1,309	917/2,120	938/1,211	600/1,800	631/637
OR	0.8	0.87	1.13	1.17	1.01	1.23	1.12	1.26
95% CI	0.66–0.97	0.66–1.15	0.31–4.17	0.98–1.4	0.85–1.19	1.03–1.48	0.91–1.37	1–1.59
P-value	0.026	0.331	0.85	0.08	0.932	0.023	0.277	0.052
mm vs MM+Mm								
Studies, n	6	2	2	8	4	7	3	5
Case-control	739/872	643/2,024	349/574	974/1,309	917/2,120	938/1,211	600/1,800	631/637
OR	1.41	2.33	1.48	1.07	1.09	0.8	1.39	1.26
95% CI	1.03–1.93	0.45–11.99	0.42–5.25	0.79–1.44	0.83–1.43	0.6–1.08	1.08–1.78	0.94–1.68
P-value	0.031	0.31	0.547	0.674	0.552	0.146	0.01	0.121

Notes: M, major allele; m, minor allele.
Abbreviations: OR, odds ratio; CI, confidence interval.

and meningioma risk in the Turkish population.[28] The TT genotype of *MTHFR* rs1801133 may be related to the lower risk of meningioma in the Korean population.[39]

Ding et al conducted a meta-analysis of nine case-control studies, and found that the CT genotype of *MTHFR* rs1801133 might be linked to high meningioma risk in Caucasians.[13] Xu et al found that significantly increased meningioma risk was only observed under the TC vs CC model in a meta-analysis of four studies.[9] A meta-analysis by Zeng et al showed that the *MTRR* rs1801394 polymorphism (seven case-control studies), but not *MTR* rs1805087 (seven case-control studies), may be associated with meningioma risk in adults.[8] We removed data that did not meet the HWE, such as the rs1805087 data of Zhang et al,[20] and added data from case-control studies, such as the WHO grade III meningioma group.[21] As such, *MTHFR* rs1801133 (eleven case-control studies), *MTRR* rs1801394 (eight case-control studies) and *MTR* rs1805087 (seven case-control studies, all in the Caucasian population) were enrolled in the present updated meta-analysis. Our results indicated that *MTRR* rs1801394, but not *MTHFR* rs1801133 or *MTR* rs1805087, is likely to be associated with meningioma risk, and the AC genotype of *MTHFR* rs1801131 may confer high susceptibility to meningioma in the Caucasian population. The precise molecular mechanisms of *MTHFR* and *MTR* mutations in the incidence of meningioma remain unclear. Due to its close relationship with the synthesis, methylation, and repair of DNA, folate is essential for the production or maintenance of normal cells and the inhibition of tumor cells.[45–47] It is possible that the harmful mutation of *MTHFR* rs1801131 or *MTRR* rs1801394 confers susceptibility to meningioma via abnormal of enzyme activity and folate-involved DNA metabolism. More experiments are needed.

In addition to folate-metabolism genes, susceptibility loci of drug metabolism-related genes *GSTM1* and *GSTT1*, apoptosis-associated gene *CASP8*, DNA repair-associated

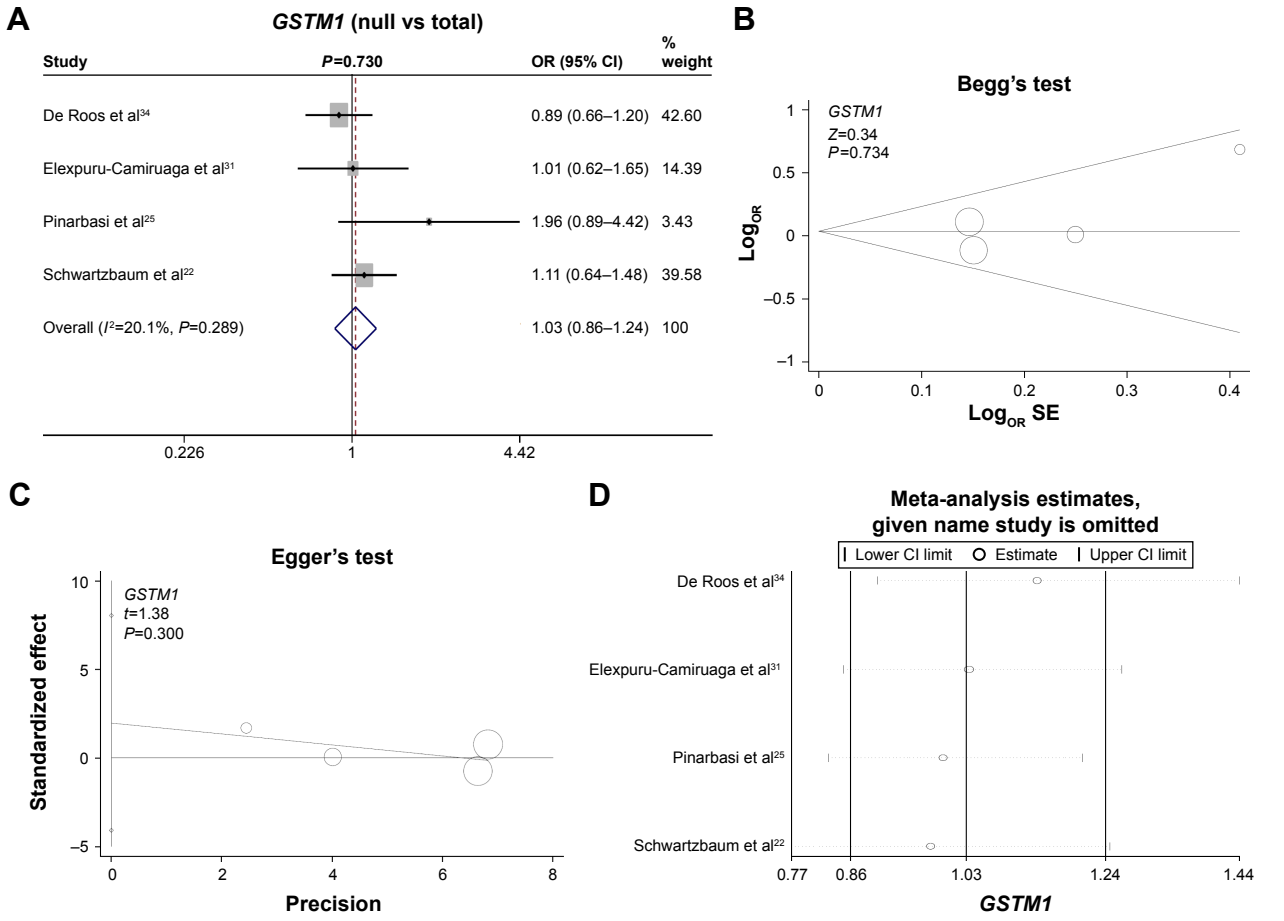

Figure 3 Meta-analysis of the association between the *GSTM1* polymorphism and meningioma risk.
Notes: (**A**) Forest plot analysis; (**B**) Begg's test with size graph symbol by weights; (**C**) Egger's test with size graph symbol by weights; and (**D**) sensitivity meta-analysis. Weights are from fixed-effect analysis. The "given name study is omitted" was produced by the STAT12.0 software. It means the given name studies were omitted, and the meta-analysis data by other studies were showed.
Abbreviations: OR, odds ratio; CI, confidence interval; SE, standard error.

gene *XRCC1*, and chromosomal rearrangement-associated gene *MLLT10* have also been reported in various clinical diseases.[48–52] For instance, *GSTM1* and *GSTT1* polymorphisms might be associated with renal cell carcinoma risk or treatment outcomes of breast cancer.[48,49] *XRCC1* polymorphisms are likely linked to the risk of lung cancer in Caucasian population.[51] Cryptic *XPO1–MLLT10* translocation was related to homeobox A-locus deregulation in T-cell acute lymphoblastic leukemia.[52] Here, the results of our meta-analysis under all genetic models showed that the rs12770228 polymorphism of *MLLT10* was significantly associated with increased meningioma risk. However, no strong association between *GSTM1*, *GSTT1*, *CASP8*, *XRCC1* and meningioma susceptibility was obtained. The negative associations between *GSTM1* and *GSTT1* null/present and meningioma risk were partly in line with previous results on the role of *GSTM1* and *GSTT1* polymorphisms in brain-tumor risk.[10,11] In spite of this, the possibility of potential roles of these polymorphisms in inherited meningioma risk still cannot be ruled out.

Limitations

Although the strict exclusion and inclusion criteria were utilized to select eligible studies, several limitations in our meta-analysis must be acknowledged. We tried our best to search the electronic databases for relevant articles, and analyzed the potential meningioma-associated genetic variants via meta-analysis. Multiple genes, such as *CDKN2* and *PON1*, were initially retrieved.[23,53] However, genes for which the number of case-control studies on specific variants was fewer than three were removed. As such, only eight genes were collected. We admit that there was a very limited number of included studies and very small sample size in case-control studies for our meta-analysis. Considering the limitation of small study numbers on the evaluation efficiency of publication bias via Begg's test,[16] there is still the potential of publication bias, which may have affected our conclusions.

Even though the Mantel–Haenszel statistics under the random-effect model and sensitivity analyses were used for between-study heterogeneity, there were small sample sizes,

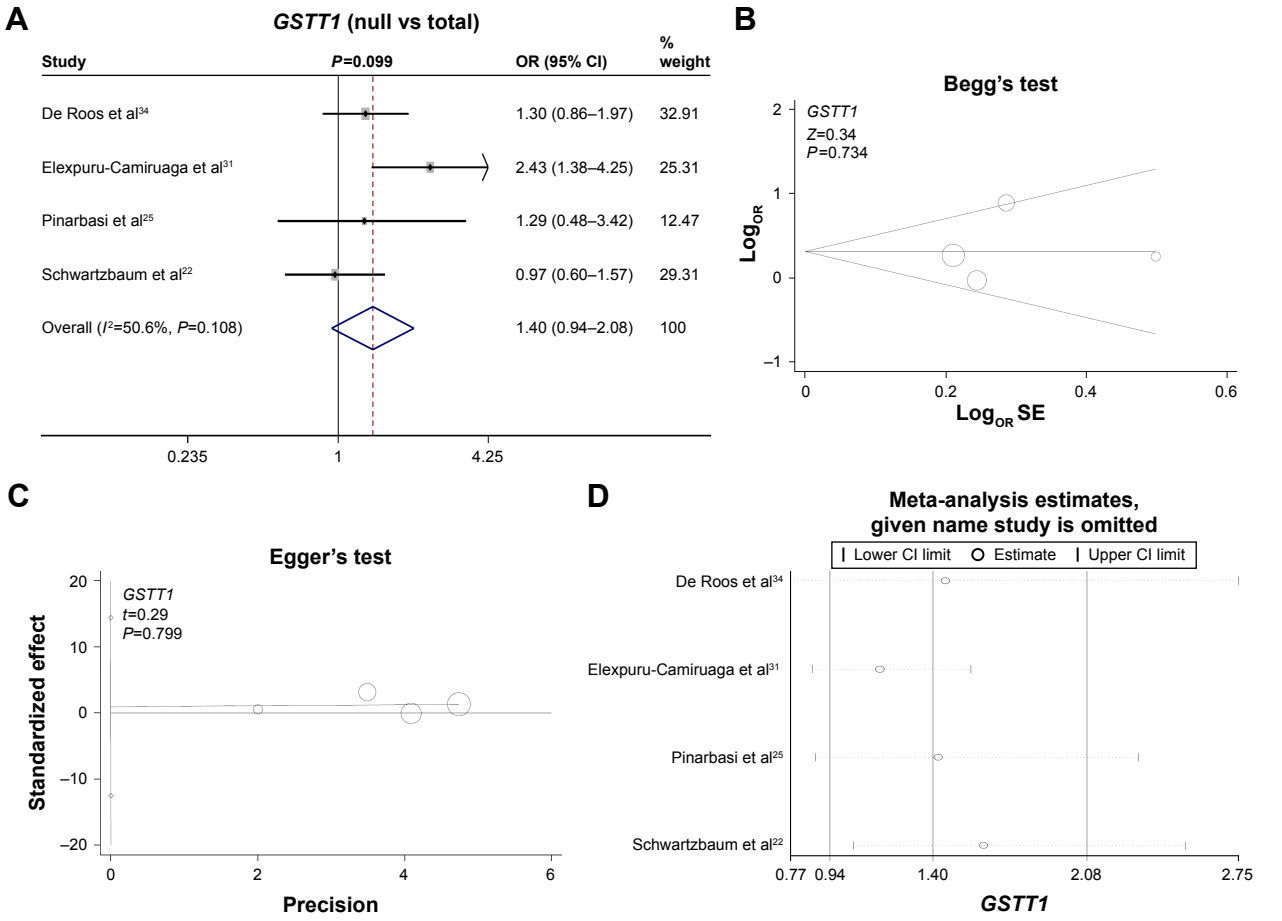

Figure 4 Meta-analysis of the association between the *GSTT1* polymorphism and meningioma risk.
Notes: (**A**) Forest plot analysis; (**B**) Begg's test with size graph symbol by weights; (**C**) Egger's test with size graph symbol by weights; and (**D**) sensitivity meta-analysis. Weights are from random-effect analysis. The "given name study is omitted" was produced by the STAT12.0 software. It means the given name studies were omitted, and the meta-analysis data by other studies were showed.
Abbreviations: OR, odds ratio; CI, confidence interval; SE, standard error.

and other unpublished or unavailable data are still needed. SNPs, disease characteristics, and other environmental effect modifiers contribute to meningioma risk. Several factors, such as ionizing radiation, estrogen level, and traumatic brain injury, might be involved in the complicated etiology or pathology of meningiomas.[54–56] Unfortunately, only stratified analysis according to ethnic background was performed for *XRCC1* rs1799782, *MTHFR* rs1801133, rs1801131, and *MTRR* rs1801394. More subgroup analysis based on more factors (eg, sex, disease type, or other clinical characteristics) were needed for a proper judgment of the genetic association between the measured variants and meningioma risk.

Very limited genome-wide association study (GWAS) data, genome-wide SNP linkage-disequilibrium mapping, or exome sequencing was obtained.[33,57,58] We found that the *MLLT10* gene was identified from the GWAS data on meningioma risk.[32,33] However, the positive association of *MTRR* rs1801394 and *MTHFR* rs1801131 failed to obtain the support of GWAS data. Further investigations with more subjects are warranted to confirm the role of *CASP8*, *XRCC1*, *MTHFR*, *MTRR*, *MTR*, *GSTM1*, *GSTT1*, and other genes identified from high-throughput analysis, such as *PIAS2* and *KATNAL2*.

Conclusion

Our updated meta-analysis concluded that *MLLT10* rs12770228 and *MTRR* rs1801394 polymorphisms may be meningioma risk factors. Also, the AC genotype of *MTHFR* rs1801131 appears to be associated with increased susceptibility to meningioma in the Caucasian population.

Disclosure

The authors report no conflicts of interest in this work.

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