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Original Article

CCDC26 rs4295627 polymorphism and glioma risk: a meta-analysis

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Abstract: Several studies have examined the association of CCDC26 rs4295627 polymorphism and glioma risk. However, the results were conflicting. Thus, a meta-analysis was conducted. We searched for relevant studies up to Dec 2014 in both English and Chinese through the PubMed/MEDLINE, EMBASE, the China National Knowledge Infrastructure (CNKI) platforms, WanFang and VIP database. Overall, 14 studies with 17419 cases and 28465 controls were selected for final meta-analysis. CCDC26 rs4295627 polymorphism was significantly associated with an increased risk of glioma (OR = 1.25, 95% CI 1.15-1.36, $P < 0.00001$). Interestingly, CCDC26 rs4295627 polymorphism might decrease the risk of glioma in Asians (OR = 0.92, 95% CI 0.82-1.03, $P = 0.15$). However, Caucasians with CCDC26 rs4295627 polymorphism showed an increased risk of glioma (OR = 1.33, 95% CI 1.25-1.46, $P < 0.00001$). Subgroup analysis was performed by histology. Significant associations were observed among astrocytoma patients (OR = 1.31, 95% CI 1.17-1.47, $P < 0.00001$) and oligodendroglioma patients (OR = 1.79, 95% CI 1.47-2.17, $P < 0.00001$). No significant association was found between this polymorphism and glioblastoma risk (OR = 0.11, 95% CI 0.92-1.33, $P = 0.28$). This meta-analysis suggested that CCDC26 rs4295627 polymorphism was a risk factor for glioma.

Keywords: Glioma, CCDC26, meta-analysis, polymorphism

Introduction

Glioma is the most common and aggressive malignant primary brain tumor in humans, especially in adults, accounting for approximately 30% of all brain and central nervous system (CNS) tumors and 80% of all malignant brain tumors [1]. The therapy for glioma is a combined approach, using surgery, radiation therapy, and chemotherapy. However, the prognosis for glioma patients is still poor. The etiology and pathogenesis of glioma are still unclear. Some genome-wide association studies (GWAS) have reported that single nucleotide polymorphisms (SNPs) are associated with glioma susceptibility [2-5]. For example, some evidence suggests CCDC26 rs4295627 is significantly associated with glioma risk [6-19]. However, the results were conflicted and inconclusive. rs4295627 maps to intron 3 of CCDC26, encoding a retinoic acid modulator of differentiation and death [20]. As a single study may lack the power to provide reliable conclusion, we performed this meta-analysis.

Methods

Publication search

We searched for relevant studies up to Dec 2014 in both English and Chinese through the PubMed/MEDLINE, EMBASE, the China National Knowledge Infrastructure (CNKI) platforms, WanFang and VIP database with the following terms and their combinations: “CCDC26”, “rs4295627”, “glioma” and “polymorphism or variant”. We tried to identify potential relevant studies from the whole reference lists by orderly reviewing title, abstract and full text.

Inclusion criteria

Included studies were considered eligible if they met all of the following criteria: 1) studies with full text articles; 2) a case-control study evaluating CCDC26 rs4295627 polymorphism and glioma risk; 3) enough data to estimate an odds ratio (OR) with 95% confidence interval (CI); 4) no overlapping data. For the studies with

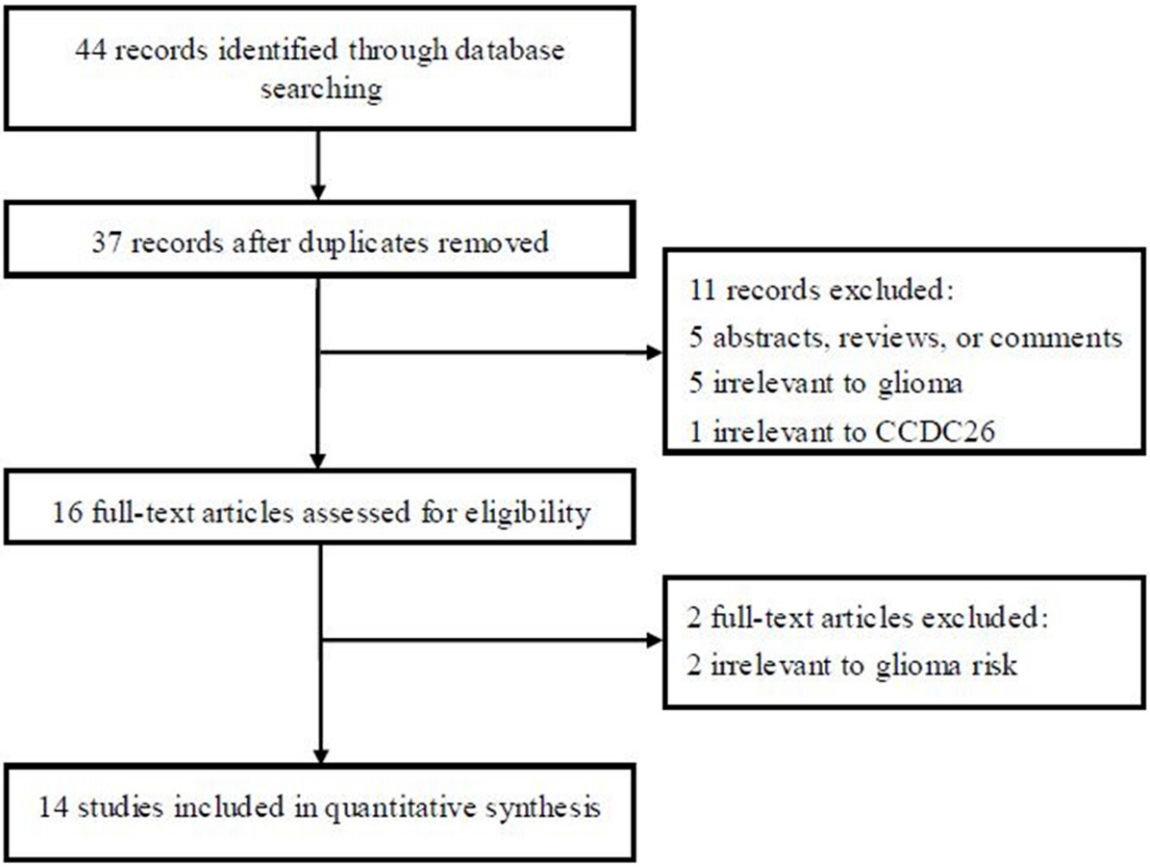

Figure 1. Flow of study identification, inclusion, and exclusion.

the same or overlapping data by the same authors, we selected the ones with the most subjects.

Data extraction

Data were extracted independently by two investigators. For conflicting evaluations, an agreement was reached following discussion. For each study, the following characteristics were collected: first author, publication year, country, ethnicity, histology, numbers of cases and controls, and the results of the Hardy-Weinberg equilibrium (HWE) test.

Statistical analysis

We assessed the deviation from HWE for the genotype distribution in controls using a chi-squared goodness-of-fit test ($P < 0.05$ was considered significant). ORs with the corresponding 95% CI were used as the common measures of assessing the strength of association between CCDC26 rs4295627 polymorphism and glioma risk for each study. The pooled ORs were calculated in an additive model. The significance of the pooled ORs was determined using a Z-test, and the level of statistical significance was established as $P < 0.05$. The heterogeneity among studies was checked by the Q test. The I^2 statistic, which is a quantitative measure of the proportion of the total variation across studies due to heterogeneity, was also calculated. The Mantel-Haenszel method-based fixed effects model was used to calculate the pooled OR. Sensitivity analysis was performed by omitting each study in turn to assess the stability of results, respectively. Potential publication bias was evaluated by visual inspection of the Begg funnel plots in which the standard error of log (OR) of each study was plotted against its log (OR). We also performed an Egger's linear regression test ($P < 0.05$ was considered a significant publication bias). All of the statistical analyses were performed using a software program, STATA version 11.0 (Stata, College Station, TX, USA).

Table 1. Characteristics of the case-control studies included in meta-analysis

First author	Year	Country	Ethnicity	Histology	Case number	Control number	HWE
Shete	2009	USA/UK	Caucasian	NA	1878	3670	Yes
Schoemaker	2010	Europe	Caucasian	NA	1029	1668	Yes
Chen	2011	China	Asian	NA	976	1057	Yes
Egan	2011	USA	Caucasian	Mixed	639	649	Yes
Jenkins	2011	USA	Caucasian	Mixed	1446	1134	Yes
Lachance	2011	USA	Caucasian	NA	855	1160	Yes
Wang	2011	USA	Caucasian	NA	357	822	Yes
Li	2012	China	Asian	NA	226	254	Yes
Rajaraman	2012	Europe	Caucasian	Mixed	1856	4955	Yes
Enciso-Mora	2013	Europe	Caucasian	Mixed	4147	7435	Yes
Melin	2013	Sweden	Caucasian	NA	1431	2868	Yes
Stefano	2013	France	Caucasian	NA	845	1190	Yes
Walsh	2013	USA	Caucasian	NA	1662	1301	Yes
Wei	2014	China	Asian	NA	72	302	Yes

NA, not available; HWE, Hardy-Weinberg equilibrium.

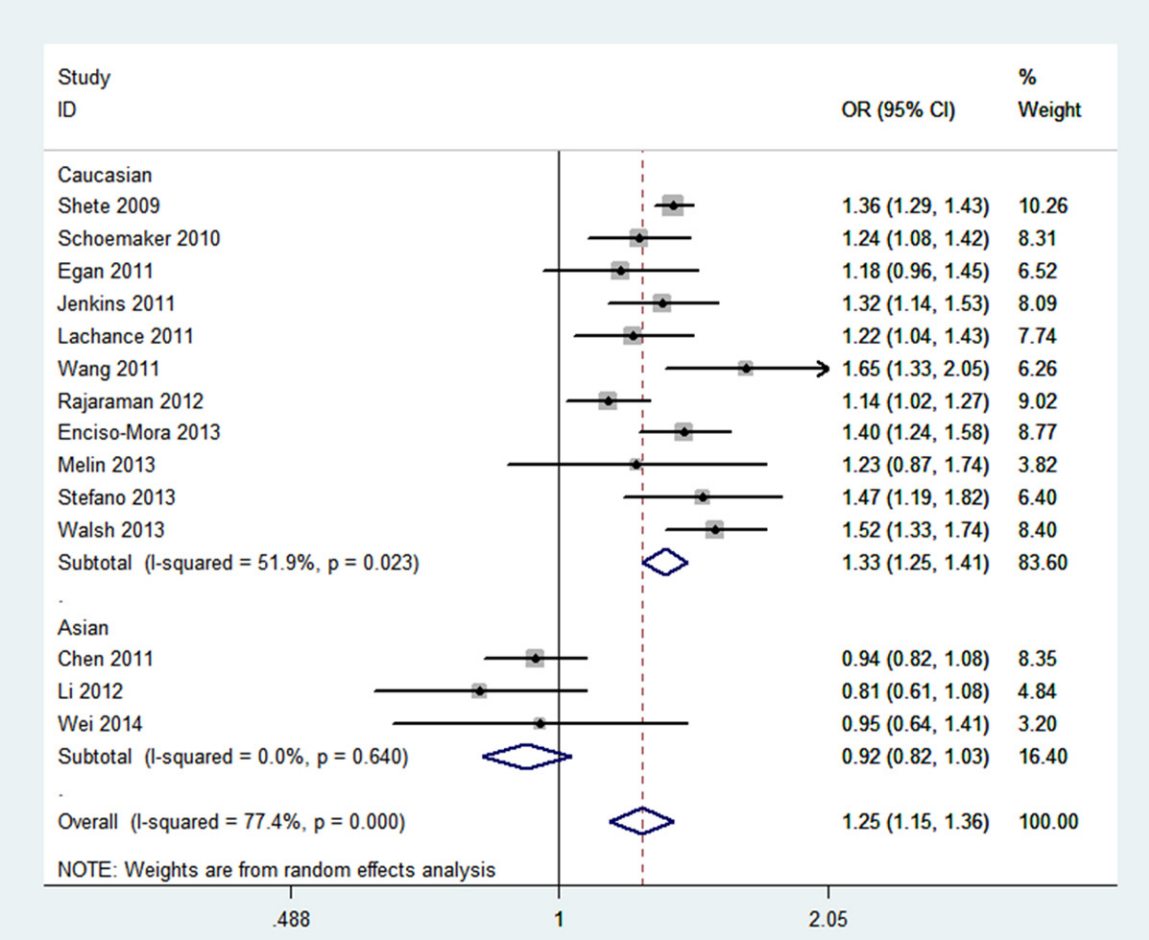

Figure 2. Meta-analysis of the association between CCDC26 rs4295627 polymorphism and glioma risk.

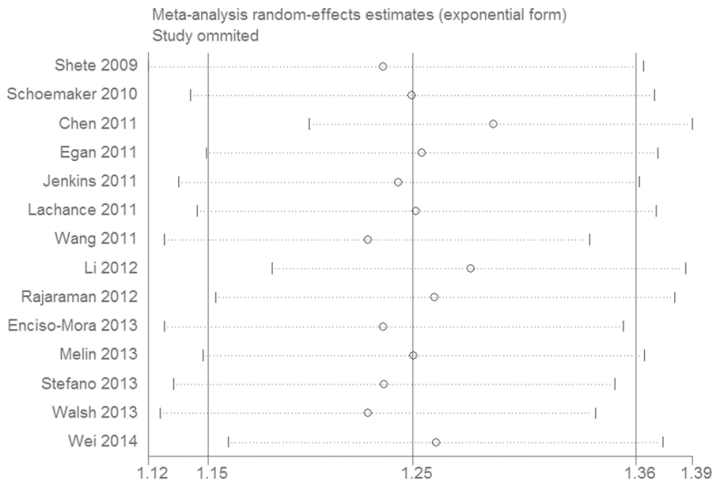

Figure 3. Sensitivity analysis for the CCDC26 rs4295627 polymorphism and glioma risk.

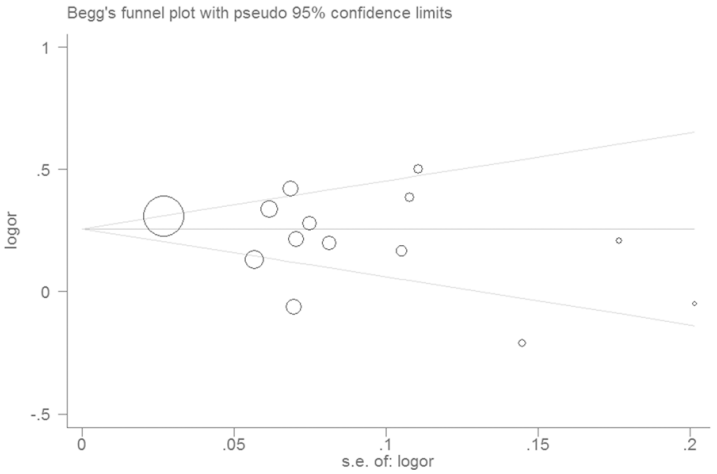

Figure 4. Funnel plot for the CCDC26 rs4295627 polymorphism and glioma risk.

Results

Study characteristics

The result of study selection process was shown in **Figure 1**. The initial search produced 44 studies from PubMed/MEDLINE, EMBASE, CNKI, WanFang and VIP database. After exclusion of duplicates, 37 potentially eligible studies were selected. After detailed evaluations, 14 studies with 17419 cases and 28465 controls were selected for final meta-analysis. There were 3 studies on Asians and 11 studies on Caucasians. Four studies provided the information of histology, while other studies did not report detailed information. The characteristics of each study included in this meta-analysis are shown in **Table 1**.

Quantitative data synthesis

The association between CCDC26 rs4295627 polymorphism and glioma risk was investigated in 14 case-control studies. As shown in **Figure 2**, the CCDC26 rs4295627 polymorphism was significantly associated with an increased risk of glioma (OR = 1.25, 95% CI 1.15-1.36, $P < 0.00001$). Interestingly, CCDC26 rs4295627 polymorphism might decrease the risk of glioma in Asians (OR = 0.92, 95% CI 0.82-1.03, $P = 0.15$). However, Caucasians with CCDC26 rs4295627 polymorphism showed an increased risk of glioma (OR = 1.33, 95% CI 1.25-1.46, $P < 0.00001$). Subgroup analysis was performed by histology. Significant associations were observed among astrocytoma patients (OR = 1.31, 95% CI 1.17-1.47, $P < 0.00001$) and oligodendroglioma patients (OR = 1.79, 95% CI 1.47-2.17, $P < 0.00001$). No significant association was found between this polymorphism and glioblastoma risk (OR = 0.11, 95% CI 0.92-1.33, $P = 0.28$). In order to assess the stability of the results of the meta-analysis, we performed a sensitivity analysis through sequentially excluded individual studies. Statistically similar results were obtained after sequentially excluding each study (**Figure 3**). Publication bias was assessed by funnel plot. The shape of the funnel plot showed symmetric (**Figure 4**). Furthermore, no significant publication bias was detected by Egger's test ($P = 0.265$). Summary results of comparisons are listed in **Table 2**.

Discussion

This meta-analysis of 14 case-control studies systematically evaluated the associations between CCDC26 rs4295627 polymorphism and glioma risk. We found that CCDC26 rs4295627 polymorphism was significantly associated with glioma risk. This result suggested that individuals with CCDC26 rs4295627 polymorphism had increased glioma risk. In the subgroup analysis, we found

Table 2. Main results of the meta-analysis

	Test of association		Heterogeneity	
	OR (95% CI)	*P* Value	χ^2	I^2 (%)
Overall	1.25 (1.15-1.36)	< 0.00001	57.41	77
Asian	0.92 (0.82-1.03)	0.15	0.89	0
Caucasian	1.33 (1.25-1.41)	< 0.00001	20.80	52
GBM	1.11 (0.92-1.33)	0.28	6.51	69
Astrocytoma	1.31 (1.17-1.47)	< 0.00001	1.41	0
Oligodendroglioma	1.79 (1.47-2.17)	< 0.00001	3.36	40

GBM, glioblastoma.

that CCDC26 rs4295627 polymorphism carriers had increased glioma risk in Caucasians. No significant association was found in Asians. In the subgroup analyses by histology, we observed that there were significant associations between CCDC26 rs4295627 polymorphism and astrocytoma, and oligodendroglioma risk.

CCDC26 is a retinoic acid modulator of cell differentiation and death. Retinoic acid induces caspase-8 transcription through phosphorylation of cAMP response element-binding protein, and it increases apoptosis following death stimuli in neuroblastoma and glioblastoma cells, accompanied by downregulation of telomerase activity [21]. Genetic variants of CCDC26 are associated with a number of common tumors, such as colorectal, breast, bladder, and prostate cancers [22-24].

Sensitivity analysis was performed by omitting one study each time to observe the change of effects. No significant change was observed. We then looked for publication bias using Egger's test and funnel plot. No significant publication bias existed in this meta-analysis. This indicated that the results in this meta-analysis were generally reliable.

When interpreting the results of the current study, some limitations should be addressed. First, lacking the original data for the included studies limited our further evaluation of the association between glioma risk and other risk factors, such as age, gender, smoking status, alcohol consumption and other variables, which might have caused a serious confounding bias. Second, we did not estimate the potential interactions among gene–gene, gene–environment, or even between various polymorphic loci of the same gene, which may alter the risk of glioma. Third, selection bias should be considered which may not be very representative of the general population. Finally, some inevitable publication bias might exist in the results because only published studies were retrieved although the funnel plot and Egger's test indicated no remarkable publication bias.

This meta-analysis found that CCDC26 rs4295627 polymorphism was significantly associated with an increased risk of glioma.

Disclosure of conflict of interest

None.

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References

[1] Ricard D, Idbaih A, Ducray F, Lahutte M, Hoang-Xuan K, Delattre JY. Primary brain tumours in adults. Lancet 2012; 379: 1984-96.

[2] Wrensch M, Jenkins RB, Chang JS, Yeh RF, Xiao Y, Decker PA, Ballman KV, Berger M, Buckner JC, Chang S, Giannini C, Halder C, Kollmeyer TM, Kosel ML, LaChance DH, McCoy L, O'Neill BP, Patoka J, Pico AR, Prados M, Quesenberry C, Rice T, Rynearson AL, Smirnov I, Tihan T, Wiemels J, Yang P, Wiencke JK. Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility. Nat Genet 2009; 41: 905-8.

[3] Zhao B, Ye J, Li B, Ma Q, Su G, Han R. DNA repair gene XRCC3 Thr241Met polymorphism and glioma risk: a meta-analysis. Int J Clin Exp Med 2013; 6: 438-43.

[4] Chen M, Liu Z, Deng Y, Chen X, Zhang J. Methylation status of promoter 1 region of GDNF gene in human glioma cells. Int J Clin Exp Med 2014; 7: 1735-40.

[5] Niu H, Wang K, Wang Y. Polymeric immunoglobulin receptor expression is predictive of poor prognosis in glioma patients. Int J Clin Exp Med 2014; 7: 2185-90.

[6] Shete S, Hosking FJ, Robertson LB, Dobbins SE, Sanson M, Malmer B, Simon M, Marie Y, Boisselier B, Delattre JY, Hoang-Xuan K, El Hallani S, Idbaih A, Zelenika D, Andersson U, Henriksson R, Bergenheim AT, Feychting M, Lönn S, Ahlbom A, Schramm J, Linnebank M, Hemminki K, Kumar R, Hepworth SJ, Price A, Armstrong G, Liu Y, Gu X, Yu R, Lau C, Schoemaker M, Muir K, Swerdlow A, Lathrop M, Bondy M, Houlston RS. Genome-wide asso-

ciation study identifies five susceptibility loci for glioma. Nat Genet 2009; 41: 899-904.
[7] Schoemaker MJ, Robertson L, Wigertz A, Jones ME, Hosking FJ, Feychting M, Lönn S, McKinney PA, Hepworth SJ, Muir KR, Auvinen A, Salminen T, Kiuru A, Johansen C, Houlston RS, Swerdlow AJ. Interaction between 5 genetic variants and allergy in glioma risk. Am J Epidemiol 2010; 171: 1165-73.
[8] Chen H, Chen Y, Zhao Y, Fan W, Zhou K, Liu Y, Zhou L, Mao Y, Wei Q, Xu J, Lu D. Association of sequence variants on chromosomes 20, 11, and 5 (20q13.33, 11q23.3, and 5p15.33) with glioma susceptibility in a Chinese population. Am J Epidemiol 2011; 173: 915-22.
[9] Egan KM, Thompson RC, Nabors LB, Olson JJ, Brat DJ, Larocca RV, Brem S, Moots PL, Madden MH, Browning JE, Ann Chen Y. Cancer susceptibility variants and the risk of adult glioma in a US case-control study. J Neurooncol 2011; 104: 535-42.
[10] Jenkins RB, Wrensch MR, Johnson D, Fridley BL, Decker PA, Xiao Y, Kollmeyer TM, Rynearson AL, Fink S, Rice T, McCoy LS, Halder C, Kosel ML, Giannini C, Tihan T, O'Neill BP, Lachance DH, Yang P, Wiemels J, Wiencke JK. Distinct germ line polymorphisms underlie glioma morphologic heterogeneity. Cancer Genet 2011; 204: 13-8.
[11] Lachance DH, Yang P, Johnson DR, Decker PA, Kollmeyer TM, McCoy LS, Rice T, Xiao Y, Ali-Osman F, Wang F, Stoddard SM, Sprau DJ, Kosel ML, Wiencke JK, Wiemels JL, Patoka JS, Davis F, McCarthy B, Rynearson AL, Worra JB, Fridley BL, O'Neill BP, Buckner JC, Il'yasova D, Jenkins RB, Wrensch MR. Associations of high-grade glioma with glioma risk alleles and histories of allergy and smoking. Am J Epidemiol 2011; 174: 574-81.
[12] Wang SS, Hartge P, Yeager M, Carreón T, Ruder AM, Linet M, Inskip PD, Black A, Hsing AW, Alavanja M, Beane-Freeman L, Safaiean M, Chanock SJ, Rajaraman P. Joint associations between genetic variants and reproductive factors in glioma risk among women. Am J Epidemiol 2011; 174: 901-8.
[13] Li S, Jin T, Zhang J, Lou H, Yang B, Li Y, Chen C, Zhang Y. Polymorphisms of TREH, IL4R and CCDC26 genes associated with risk of glioma. Cancer Epidemiol 2012; 36: 283-7.
[14] Rajaraman P, Melin BS, Wang Z, McKean-Cowdin R, Michaud DS, Wang SS, Bondy M, Houlston R, Jenkins RB, Wrensch M, Yeager M, Ahlbom A, Albanes D, Andersson U, Freeman LE, Buring JE, Butler MA, Braganza M, Carreon T, Feychting M, Fleming SJ, Gapstur SM, Gaziano JM, Giles GG, Hallmans G, Henriksson R, Hoffman-Bolton J, Inskip PD, Johansen C, Kitahara CM, Lathrop M, Liu C, Le Marchand L, Linet MS, Lonn S, Peters U, Purdue MP, Rothman N, Ruder AM, Sanson M, Sesso HD, Severi G, Shu XO, Simon M, Stampfer M, Stevens VL, Visvanathan K, White E, Wolk A, Zeleniuch-Jacquotte A, Zheng W, Decker P, Enciso-Mora V, Fridley B, Gao YT, Kosel M, Lachance DH, Lau C, Rice T, Swerdlow A, Wiemels JL, Wiencke JK, Shete S, Xiang YB, Xiao Y, Hoover RN, Fraumeni JF Jr, Chatterjee N, Hartge P, Chanock SJ. Genome-wide association study of glioma and meta-analysis. Hum Genet 2012; 131: 1877-88.
[15] Enciso-Mora V, Hosking FJ, Kinnersley B, Wang Y, Shete S, Zelenika D, Broderick P, Idbaih A, Delattre JY, Hoang-Xuan K, Marie Y, Di Stefano AL, Labussière M, Dobbins S, Boisselier B, Ciccarino P, Rossetto M, Armstrong G, Liu Y, Gousias K, Schramm J, Lau C, Hepworth SJ, Strauch K, Müller-Nurasyid M, Schreiber S, Franke A, Moebus S, Eisele L, Forsti A, Hemminki K, Tomlinson IP, Swerdlow A, Lathrop M, Simon M, Bondy M, Sanson M, Houlston RS. Deciphering the 8q24.21 association for glioma. Hum Mol Genet 2013; 22: 2293-302.
[16] Melin B, Dahlin AM, Andersson U, Wang Z, Henriksson R, Hallmans G, Bondy ML, Johansen C, Feychting M, Ahlbom A, Kitahara CM, Wang SS, Ruder AM, Carreón T, Butler MA, Inskip PD, Purdue M, Hsing AW, Mechanic L, Gillanders E, Yeager M, Linet M, Chanock SJ, Hartge P, Rajaraman P. Known glioma risk loci are associated with glioma with a family history of brain tumours -- a case-control gene association study. Int J Cancer 2013; 132: 2464-8.
[17] Di Stefano AL, Enciso-Mora V, Marie Y, Desestret V, Labussière M, Boisselier B, Mokhtari K, Idbaih A, Hoang-Xuan K, Delattre JY, Houlston RS, Sanson M. Association between glioma susceptibility loci and tumour pathology defines specific molecular etiologies. Neuro Oncol 2013; 15: 542-7.
[18] Walsh KM, Anderson E, Hansen HM, Decker PA, Kosel ML, Kollmeyer T, Rice T, Zheng S, Xiao Y, Chang JS, McCoy LS, Bracci PM, Wiemels JL, Pico AR, Smirnov I, Lachance DH, Sicotte H, Eckel-Passow JE, Wiencke JK, Jenkins RB, Wrensch MR. Analysis of 60 reported glioma risk SNPs replicates published GWAS findings but fails to replicate associations from published candidate-gene studies. Genet Epidemiol 2013; 37: 222-8.
[19] Wei XB, Jin TB, Li G, Geng TT, Zhang JY, Chen CP, Gao GD, Chen C, Gong YK. CCDC26 gene polymorphism and glioblastoma risk in the Han Chinese population. Asian Pac J Cancer Prev 2014; 15: 3629-33.
[20] Yin W, Rossin A, Clifford JL, Gronemeyer H. Co-resistance to retinoic acid and TRAIL by inser-

tion mutagenesis into RAM. Oncogene 2006; 25: 3735-44.
[21] Jiang M, Zhu K, Grenet J, Lahti JM. Retinoic acid induces caspase-8 transcription via phospho-CREB and increases apoptotic responses to death stimuli in neuroblastoma cells. Biochim Biophys Acta 2008; 1783: 1055-67.
[22] Easton DF, Pooley KA, Dunning AM, Pharoah PD, Thompson D, Ballinger DG, Struewing JP, Morrison J, Field H, Luben R, Wareham N, Ahmed S, Healey CS, Bowman R; SEARCH collaborators, Meyer KB, Haiman CA, Kolonel LK, Henderson BE, Le Marchand L, Brennan P, Sangrajrang S, Gaborieau V, Odefrey F, Shen CY, Wu PE, Wang HC, Eccles D, Evans DG, Peto J, Fletcher O, Johnson N, Seal S, Stratton MR, Rahman N, Chenevix-Trench G, Bojesen SE, Nordestgaard BG, Axelsson CK, Garcia-Closas M, Brinton L, Chanock S, Lissowska J, Peplonska B, Nevanlinna H, Fagerholm R, Eerola H, Kang D, Yoo KY, Noh DY, Ahn SH, Hunter DJ, Hankinson SE, Cox DG, Hall P, Wedren S, Liu J, Low YL, Bogdanova N, Schürmann P, Dörk T, Tollenaar RA, Jacobi CE, Devilee P, Klijn JG, Sigurdson AJ, Doody MM, Alexander BH, Zhang J, Cox A, Brock IW, MacPherson G, Reed MW, Couch FJ, Goode EL, Olson JE, Meijers-Heijboer H, van den Ouweland A, Uitterlinden A, Rivadeneira F, Milne RL, Ribas G, Gonzalez-Neira A, Benitez J, Hopper JL, McCredie M, Southey M, Giles GG, Schroen C, Justenhoven C, Brauch H, Hamann U, Ko YD, Spurdle AB, Beesley J, Chen X; kConFab; AOCS Management Group, Mannermaa A, Kosma VM, Kataja V, Hartikainen J, Day NE, Cox DR, Ponder BA. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007; 447: 1087-93.
[23] Tomlinson I, Webb E, Carvajal-Carmona L, Broderick P, Kemp Z, Spain S, Penegar S, Chandler I, Gorman M, Wood W, Barclay E, Lubbe S, Martin L, Sellick G, Jaeger E, Hubner R, Wild R, Rowan A, Fielding S, Howarth K; CORGI Consortium, Silver A, Atkin W, Muir K, Logan R, Kerr D, Johnstone E, Sieber O, Gray R, Thomas H, Peto J, Cazier JB, Houlston R. A genome-wide association scan of tag SNPs identifies a susceptibility variant for colorectal cancer at 8q24.21. Nat Genet 2007; 39: 984-8.
[24] Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P, Wacholder S, Minichiello MJ, Fearnhead P, Yu K, Chatterjee N, Wang Z, Welch R, Staats BJ, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E, Willett WC, Cancel-Tassin G, Cussenot O, Valeri A, Andriole GL, Gelmann EP, Tucker M, Gerhard DS, Fraumeni JF Jr, Hoover R, Hunter DJ, Chanock SJ, Thomas G. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet 2007; 39: 645-9.