RESEARCH ARTICLE

# The RTEL1 rs6010620 Polymorphism and Glioma Risk: a Meta-analysis Based on 12 Case-control Studies

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## Abstract

**Background: The association between the RTEL1 rs6010620 single nucleotide polymorphism (SNP) and glioma risk has been extensively studied. However, the results remain inconclusive. To further examine this association, we performed a meta-analysis. Materials and Methods: A computerized search of the PubMed and Embase databases for publications regarding the RTEL1 rs6010620 polymorphism and glioma cancer risk was performed. Genotype data were analyzed in a meta-analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated to assess the association. Sensitivity analyses, tests of heterogeneity, cumulative meta-analyses, and assessments of bias were performed in our meta-analysis. Results: Our meta-analysis confirmed that risk with allele A is lower than with allele G for glioma. The A allele of rs6010620 in RTEL1 decreased the risk of developing glioma in the 12 case-control studies for all genetic models: the allele model (OR=0.752, 95%CI: 0.715-0.792), the dominant model (OR=0.729, 95%CI: 0.685-0.776), the recessive model (OR=0.647, 95%CI: 0.569-0.734), the homozygote comparison (OR=0.528, 95%CI: 0.456-0.612), and the heterozygote comparison (OR=0.761, 95%CI: 0.713-0.812). Conclusions: In all genetic models, the association between the RTEL1 rs6010620 polymorphism and glioma risk was significant. This meta-analysis suggests that the RTEL1 rs6010620 polymorphism may be a risk factor for glioma. Further functional studies evaluating this polymorphism and glioma risk are warranted.**

**Keywords:** Meta-analysis - glioma - case-control studies - polymorphism - RTEL1 gene

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## Introduction

Gliomas are central nervous system neoplasms derived from glial cells that surround and support neurons (Liu et al., 2007). Gliomas account for approximately 80% of central nervous system malignant tumors and have a very poor prognosis (Schoemaker et al., 2010; Walsh et al., 2013b). Although the etiology of gliomas remains unclear, exposure to ionizing radiation has been identified as the only established risk factor (Little et al., 1998; Neglia et al., 2006). Glioma is associated with considerable morbidity and mortality, and occurs more often in males than in females (Chen et al., 2012).

In the past decade, many investigators have explored factors that contribute to inherited glioma susceptibility. Up to date previous published articles found that many gene variations may associate with glioma risk, such as XRCC1 mutations, XRCC3 mutations, IDH mutations etc. The gene polymorphisms increased or decreased glioma sensibility by regulating the proliferation and apoptosis of cells (Das et al., 2013; Liang et al., 2013). (Das et al., 2013; Li et al., 2013b) They revealed that gene mutations may contribute to the occurrence of glioma. Sequence variants in RTEL1 gene regions are associated with susceptibility to glioma (Shete et al., 2009; Wrensch et al., 2009; Jin et al., 2013; Li et al., 2013; Walcott et al., 2013; Walsh et al., 2013a; Walsh et al., 2013b). Several research groups have reported associations between the rs6010620 single nucleotide polymorphism (SNP) and glioma risk. However, the results are inconclusive. Consequently, we performed a meta-analysis to more precisely characterize this association.

## Materials and Methods

*Search strategy and selection criteria*

Relevant publications were identified by a comprehensive systematic literature search using PUBMED, EMBASE, Web of Knowledge, and Google Scholar databases for all studies published through September 2013. The following keywords were used: "glioma cancer" and "rs6010620". We also supplemented our database search by reviewing the reference lists from all retrieved publications.

For the meta-analysis, the following inclusion criteria were considered: *(i)* related case-control studies regarding the rs6010620 SNP and glioma; *(ii)* sufficient genotypic data were presented to calculate odds ratios (ORs); and

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*(iii)* cancer diagnoses and the sources of cases and controls were clearly described. Articles that were not about glioma research, contained duplicated or previous research, or did not include usable genotype data were excluded. Finally, we selected four reports, which included a total of 7,439 glioma cases and 12,815 healthy controls.

*Data extraction*

Two investigators independently extracted data and reached a consensus on all items. The following information was obtained from each report: the first author's name, year of publication, country of origin, ethnicity, source of controls (population- or hospital-based controls), number of cases and controls, and genotype frequencies for cases and controls.

*Statistical analyses*

The strength of RTEL1 rs6010620 polymorphisms and glioma risk was assessed by odds ratios (ORs), with the corresponding 95% confidence interval (CI) for each study. Based on the individual ORs, the pooled OR was estimated. Different ORs were calculated using the following models: the allele model (A *vs* a), the additive genetic model (AA *vs* aa), the dominant genetic mode (AA+Aa *vs* aa), and the recessive genetic model (AA *vs* Aa+aa). Heterogeneity assumption was evaluated using chi-square-based Q-tests. If the *p* value was greater than 0.100 of the Q-test, indicating a lack of heterogeneity among the studies, the summary OR estimate of each study was calculated using a fixed effects model (Mantel-Haenszel method) (DerSimonian and Laird, 1986). Otherwise, the random-effects model (DerSimonian-Laird method) was performed (Mantel and Haenszel, 1959). Heterogeneity was also assessed using the $I^2$ statistic, which takes values between 0% and 100% and higher values denote a greater degree of heterogeneity ($I^2$=0-25%: no heterogeneity; $I^2$=25-50%: moderate heterogeneity; $I^2$=50-75%: large heterogeneity; $I^2$=75-100%: extreme heterogeneity) (Higgins and Thompson, 2002; Higgins et al., 2003). The significance of the pooled OR was determined using the Z test.

To explore the reasons for heterogeneity, subgroup analyses were performed by grouping studies that showed similar characteristics, such as ethnicity and control source. For sensitivity analyses, each study was removed in turn from the total, and the remaining studies were reanalyzed to assess the stability of the results. Funnel plots, Begg's tests, and Egger's tests were used to diagnose potential publication bias. All statistical analyses were performed using Stata software (version 11.0; StataCorp LP, College Station, TX), with two-sided *p* values. $p<0.05$ was considered statistically significant in all analyses, except the heterogeneity test (Egger et al., 1997).

## Results

*Eligible studies*

In total, four articles written in English, including 12 case-control studies with 7,439 cases and 12,815 controls, were included in this meta-analysis. The characteristics of the studies are listed in Table 1. The 12 studies examined in this meta-analysis included 11 studies of Caucasians and one study of Asians. RTEL1 rs6010620 genotype distributions in the controls from all studies conformed to Hardy-Weinberg equilibrium. Figure 1 shows the study selection procedure.

*Meta-analysis databases*

The association between the RTEL1 rs6010620 gene polymorphism and glioma risk, as well as heterogeneity tests, are shown in Table 2. The combined results showed that the variant genotypes were not associated with decreased glioma risk in different genetic models (OR=0.528, 95%CI =0.456-0.612 for the homozygote comparison model AA *vs* GG; OR=0.761, 95%CI=0.713-0.812 for the heterozygote comparison model AG *vs* GG;

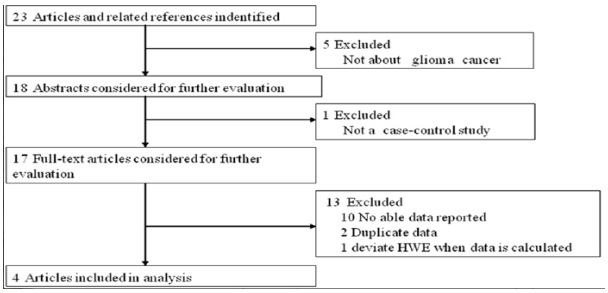


**Figure 1. Flow Chart Showing Study Selection Procedure**

**Table 1. Study Characteristics Regarding the Relationship between the RTEL1 rs6010620 Polymorphism and Glioma Risk**

| No. | Study | Year | Population | Source of Controls | Sample Size (case/control) | Case GG | Case GA | Case AA | Control GG | Control GA | Control AA | HWE *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Li et al. | 2013 | Asian | HB | 629/644 | 75 | 261 | 293 | 40 | 267 | 337 | 0.18 |
| 2 | Schoemaker et al. | 2010 | Caucasian | PB | 122/147 | 83 | 38 | 1 | 83 | 56 | 8 | 0.72 |
| 3 | Schoemaker et al. | 2010 | Caucasian | PB | 95/96 | 69 | 22 | 4 | 63 | 30 | 3 | 0.8 |
| 4 | Schoemaker et al. | 2010 | Caucasian | PB | 200/371 | 144 | 52 | 4 | 230 | 116 | 25 | 0.05 |
| 5 | Schoemaker et al. | 2010 | Caucasian | PB | 376/632 | 252 | 106 | 18 | 376 | 212 | 44 | 0.06 |
| 6 | Schoemaker et al. | 2010 | Caucasian | PB | 232/390 | 159 | 65 | 8 | 233 | 129 | 28 | 0.09 |
| 7 | Shete et al. | 2009 | Caucasian | PB | 1247/2235 | 796 | 405 | 46 | 1327 | 785 | 123 | 0.62 |
| 8 | Shete et al. | 2009 | Caucasian | PB | 631/1433 | 426 | 179 | 26 | 818 | 533 | 82 | 0.69 |
| 9 | Shete et al. | 2009 | Caucasian | PB | 1332/1545 | 912 | 386 | 34 | 978 | 508 | 59 | 0.49 |
| 10 | Shete et al. | 2009 | Caucasian | PB | 645/774 | 430 | 195 | 20 | 456 | 264 | 54 | 0.07 |
| 11 | Shete et al. | 2009 | Caucasian | PB | 499/557 | 336 | 147 | 16 | 352 | 177 | 28 | 0.35 |
| 12 | Wrensch et al. | 2009 | Caucasian | PB | 1431/3991 | 978 | 409 | 44 | 2395 | 1383 | 213 | 0.47 |

*PB: population-based; HB: hospital-based

**Table 2. Stratified Analyses of the Association between RTEL1 rs6010620 Polymorphisms and Glioma Risk**

| Variables | Homozygote (AA *vs* GG) | | Heterogeneity (AG *vs* GG) | | Allele Model | | Dominant Model | | Recessive Model | |
|---|---|---|---|---|---|---|---|---|---|---|
| | OR (95%CI) | $p^a$ | OR (95%CI) | $p^a$ | OR (95%CI) | $p^a$ | OR (95%CI) | $p^a$ | OR (95%CI) | $p^a$ |
| Total | 0.53 (0.46-0.61) | 0.64 | 0.76 (0.71-0.81) | 0.45 | 0.75 (0.72-0.79)[b] | 0.57 | 0.73 (0.69-0.78)[b] | 0.33 | 0.65 (0.57-0.73)[b] | 0.33 |
| Ethnicity | | | | | | | | | | |
| Asian | 0.46 (0.31-0.70) | - | 0.52 (0.34-0.79) | - | 0.76 (0.64-0.90)[b] | - | 0.49 (0.33-- 0.73)[b] | - | 0.79 (0.64-0.99)[b] | - |
| Caucasian | 0.54 (0.46-0.63) | 0.6 | 0.77 (0.72-0.82) | 0.65 | 0.75 (0.71-0.79)[b] | 0.483 | 0.74 (0.69-0.79)[b] | 0.573 | 0.59 (0.50-0.69)[b] | 0.61 |

*$p^a$ values obtained from chi-square tests for heterogeneity; [b]A fix-effects model was used when the $p$ value from the heterogeneity test was < 0.05; otherwise, [a]random-effects model was used

**Table 3. The Degree of Heterogeneity in Meta-Analyses of RTEL1 rs6010620 Polymorphisms and Glioma Risk**

| Genetic Model | | Heterogeneity Statistic | | | *p* | | | I- squared (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Asian | Caucasian | Overall | Asian | Caucasian | Overall | Asian | Caucasian | Overall |
| Allele model | A *vs* G | 0 | 9.52 | 9.54 | - | 0.48 | 0.57 | - | 0.00% | 0.00% |
| Dominant model | AA/AG *vs* GG | 0 | 8.57 | 12.5 | - | 0.57 | 0.33 | - | 0.00% | 12.00% |
| Recessive model | AA *vs* AG/ GG | 0 | 8.15 | 12.54 | - | 0.61 | 0.33 | - | 0.00% | 12.30% |
| Homozygote comparison | AA *vs* GG | 0 | 8.29 | 8.79 | - | 0.6 | 0.64 | - | 0.00% | 0.00% |
| Heterogeneity comparison | AG *vs* GG | 0 | 7.76 | 10.97 | - | 0.65 | 0.45 | - | 0.00% | 0.00% |

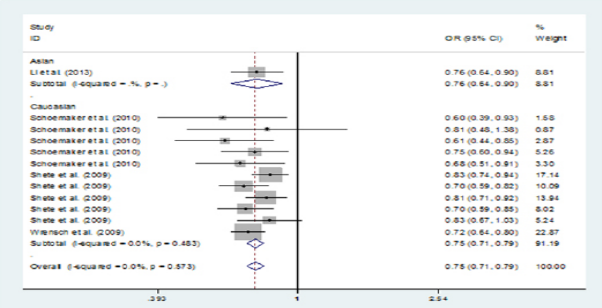

**Figure 2. Forest Plots for the rs6010620 Polymorphism and Glioma Risk in the Allele Model**

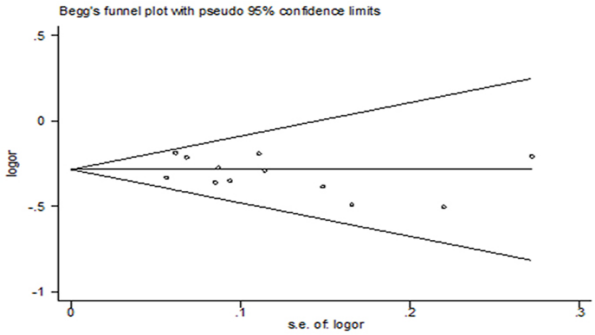


**Figure 3. Begg's Funnel Plot from the Meta-Analysis of Glioma Risk and the rs6010620 Polymorphism in the Allele Model**

OR=0.752, 95%CI: 0.715-0.792 for A *vs* G; OR=0.729, 95%CI: 0.685-0.776 for the dominant model GA + AA *vs* GG; and OR=0.647, 95%CI: 0.569-0.734 for the recessive model AA *vs* AG+GG) (Table 2). In subgroup analyses by ethnicity, the results were similar in the Caucasian population. The forest plots for rs6010620 in the allele model are shown in Figure 2.

*Test of heterogeneity*

Statistically significant heterogeneity was observed in trials using the following analyses with Q statistic tests

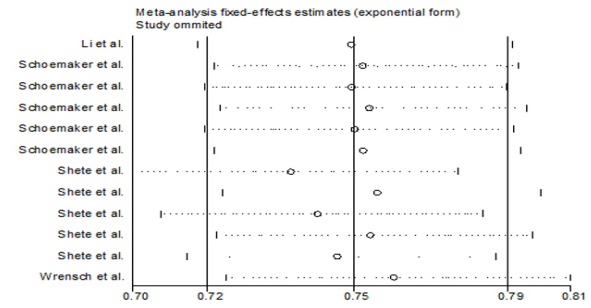


**Figure 4. Sensitivity Analysis of the Summary Odds Ratio Coefficients for the Allele Model in the Overall Meta-Analysis**

and employing the fixed effects model (Allele model A *vs* G: $p$=0.573, $I^2$=0.0%; dominant model GA+AA *vs* GG: $p$=0.327, $I^2$=12.0%; recessive model AA *vs* AG/ GG: $p$=0.325, $I^2$=12.3%; homozygote comparison model AA *vs* GG: $p$=0.641, $I^2$=0.0%; heterozygote comparison model GA *vs* GG: $p$=0.446, $I^2$=0.0%) (Table 3).

*Bias diagnostics*

Begg's funnel plots and Egger's tests were performed to assess the publication bias of the studies examined in this meta-analysis. The Funnel plot shapes did not reveal obvious evidence of asymmetry. Additionally, all $p$ values from Egger's tests were greater than 0.05, providing statistical evidence of the funnel plots' symmetry (Figure 3). Thus, these results suggest that publication bias did not occur in this meta-analysis.

*Sensitivity analyses*

Sensitivity analyses were performed to assess the influence of each individual study on the pooled OR by sequential removal of individual studies. The results suggest that no individual study significantly affected the pooled ORs (Figure 4).

## Discussion

Previous studies investigating the association between the RTEL1 SNP6010620 polymorphism with glioma risk have provided unclear results. In addition, most studies involved only a few hundred glioma cases, which is too few to reliably assess genetic effects. Meta-analysis has been recognized as an important tool to precisely define the effect of selected genetic polymorphisms on disease risk and to identify potentially important sources of between-study heterogeneity (Qin et al., 2013).

Therefore, to provide the most comprehensive assessment of the association between the RTEL1 SNP6010620 polymorphism and glioma risk, we performed a meta-analysis of all available studies. The meta-analysis was performed by critically reviewing 12 individual case-control studies regarding the RTEL1 SNP6010620 polymorphism and glioma risk. Subgroup analyses were predominantly conducted by ethnicity. Heterogeneity analyses and sensitivity analyses were also performed to ensure the epidemiological credibility of this meta-analysis. We found that the G allele of RTEL1 was associated with an increased glioma risk among Asians and Caucasians.

DNA helicase regulator of telomere length 1 (RTEL1) is an anti-recombinase that dismantles D-loop recombination intermediates to counter toxic DNA repair. The RTEL1 gene is located on chromosome 20q13.3. It is 40.889 kb, and includes 40 exons. RTEL1 functions include nucleic acid binding, ATP-dependent DNA helicase activity, DNA repair, apoptosis, and cell survival. Previous studies proposed that RTEL1 maintains genomic stability by suppressing homologous recombination(Barber et al., 2008; Uringa et al., 2012) and implements a second level of meiotic crossover control by promoting non-crossovers (Mirabello et al., 2010; Youds et al., 2010). A recent review indicated that RTEL1 is an essential helicase for telomere maintenance and regulation of homologous recombination (Adelman and Boulton, 2010; Uringa et al., 2011). RTEL1 is overexpressed in human gastrointestinal tract tumors (Bai et al., 2000), and RTEL1 gene polymorphisms are associated with glioblastoma survival (Liu et al., 2010).

Shete et al. (Shete et al., 2009) conducted a meta-analysis of two genome-wide association studies by genotyping tagging SNPs including a total of 1878 cases and 3670 controls, with validation in three additional independent series totaling 2545 cases and 2953 controls. These authors identified the G allele of RTEL1 appeared to be a risk factor for glioma in Caucasian populations. Li et al. (Li et al., 2013) reported the RTEL1 gene was associated with glioma risk in a Han Chinese population based on 629 glioma patients and 645 controls. Therefore, a meta-analysis was necessary to evaluate the relationship between the RTEL1 gene and glioma. The current meta-analysis summarized the results from 12 case-control studies and found that RTEL1 was associated with glioma risk. Our meta-analysis data confirms that the glioma risk of allele A is lower than allele G of the RTEL1 gene.

Our meta-analysis has some limitations. First, the lack of detailed information, including the age and sex of patients, in some studies limited further stratification. A more accurate OR would be corrected for age, sex, and other factors that are associated with cancer risk. Second, in our meta-analysis, the origins of heterogeneity may include many factors, including differences in control characteristics and diverse genotyping methods. In addition, the small sample size (<100 cases and controls) may overestimate the true association due to deficiencies in statistical power.

Based on these limitations, detailed studies are warranted to confirm our findings. Nevertheless, our meta-analysis has some advantages. First, the well-designed search and selection method significantly increased the statistical power of this meta-analysis. Second, in all studies analyzed, genotype distribution in the controls was consistent with Hardy-Weinberg equilibrium ($p>0.01$). Finally, the results did not show any evidence of publication bias.

In conclusion, the overall results from this meta-analysis indicate that the RTEL1 rs6010620 polymorphism is associated with glioma risk. Further functional studies between this polymorphism and cancer risk are warranted.

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## References

Adelman CA, Boulton SJ (2010). Metabolism of postsynaptic recombination intermediates. *FEBS Lett*, **584**, 3709-16.

Bai C, Connolly B, Metzker ML, et al (2000). Overexpression of M68/DcR3 in human gastrointestinal tract tumors independent of gene amplification and its location in a four-gene cluster. *Proc Natl Acad Sci USA*, **97**, 1230-5.

Barber LJ, Youds JL, Ward JD, et al (2008). RTEL1 maintains genomic stability by suppressing homologous recombination. *Cell*, **135**, 261-71.

Chen H, Sun B, Zhao Y, et al (2012). Fine mapping of a region of chromosome 11q23.3 reveals independent locus associated with risk of glioma. *PLoS One*, **7**, 52864.

Das BR, Tangri R, Ahmad F, et al (2013). Molecular investigation of isocitrate dehydrogenase gene (IDH) mutations in gliomas: first report of IDH2 mutations in Indian patients. *Asian Pac J Cancer Prev*, **14**, 7261-4.

DerSimonian R, Laird N (1986). Meta-analysis in clinical trials. *Control Clin Trials*, **7**, 177-88.

Egger M, Davey Smith G, Schneider M, et al (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, **315**, 629-34.

Higgins JP, Thompson SG (2002). Quantifying heterogeneity in a meta-analysis. *Stat Med*, **21**, 1539-58.

Higgins JP, Thompson SG, Deeks JJ, et al (2003). Measuring inconsistency in meta-analyses. *BMJ*, **327**, 557-60.

Jin TB, Zhang JY, Li G, et al (2013). RTEL1 and TERT polymorphisms are associated with astrocytoma risk in the Chinese Han population. *Tumour Biol*, **34**, 3659-66.

Li G, Jin TB, Liang HJ, et al (2013). RTEL1 tagging SNPs and haplotypes were associated with glioma development. *Diagnostic Pathology*, **8**, 83.

Liang HJ, Yan YL, Liu ZM, et al (2013). Association of XRCC3 Thr241Met polymorphisms and glioma risk: evidence from a meta-analysis. *Asian Pac J Cancer Prev*, **14**, 4243-7.

Little MP, de Vathaire F, Shamsaldin A, et al (1998). Risks of brain tumour following treatment for cancer in childhood: modification by genetic factors, radiotherapy and chemotherapy. *Int J Cancer*, **78**, 269-75.

Liu Y, Shete S, Etzel CJ, et al (2010). Polymorphisms of LIG4, BTBD2, HMGA2, and RTEL1 genes involved in the double-strand break repair pathway predict glioblastoma survival. *J Clin Oncol*, **28**, 2467-74.

Liu Y, Zhang H, Zhou K, et al (2007). Tagging SNPs in non-homologous end-joining pathway genes and risk of glioma. *Carcinogenesis*, **28**, 1906-13.

Mantel N, Haenszel W (1959). Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*, **22**, 719-48.

Mirabello L, Yu K, Kraft P, et al (2010). The association of telomere length and genetic variation in telomere biology genes. *Hum Mutat*, **31**, 1050-8.

Neglia JP, Robison LL, Stovall M, et al (2006). New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst*, **98**, 1528-37.

Qin X, Peng Q, Tang W, et al (2013). An updated meta-analysis on the association of MDM2 SNP309 polymorphism with colorectal cancer risk. *PLoS One*, **8**, 76031.

Schoemaker MJ, Robertson L, Wigertz A, et al (2010). Interaction between 5 genetic variants and allergy in glioma risk. *Am J Epidemiol*, **171**, 1165-73.

Shete S, Hosking FJ, Robertson LB, et al (2009). Genome-wide association study identifies five susceptibility loci for glioma. *Nat Genet*, **41**, 899-904.

Uringa EJ, Lisaingo K, Pickett HA, et al (2012). RTEL1 contributes to DNA replication and repair and telomere maintenance. *Mol Biol Cell*, **23**, 2782-92.

Uringa EJ, Youds JL, Lisaingo K, et al (2011). RTEL1: an essential helicase for telomere maintenance and the regulation of homologous recombination. *Nucleic Acids Res*, **39**, 1647-55.

Walcott F, Rajaraman P, Gadalla SM, et al (2013). Telomere length and risk of glioma. *Cancer Epidemiol*, **37**, 935-8.

Walsh KM, Anderson E, Hansen HM, et al (2013a). Analysis of 60 reported glioma risk SNPs replicates published GWAS findings but fails to replicate associations from published candidate-gene studies. *Genet Epidemiol*, **37**, 222-8.

Walsh KM, Rice T, Decker PA, et al (2013b). Genetic variants in telomerase-related genes are associated with an older age at diagnosis in glioma patients: evidence for distinct pathways of gliomagenesis. *Neuro-Oncology*, **15**, 1041-7.

Wrensch M, Jenkins RB, Chang JS, et al (2009). Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility. *Nat Genet*, **41**, 905-8.

Youds JL, Mets DG, McIlwraith MJ, et al (2010). RTEL-1 enforces meiotic crossover interference and homeostasis. *Science*, **327**, 1254-8.