# CCDC26, CDKN2BAS, RTEL1 and TERT Polymorphisms in pediatric brain tumor susceptibility

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Abstract: The role of genetic polymorphisms in pediatric brain tumor (PBT) etiology is poorly understood. We hypothesized that single nucleotide polymorphisms (SNPs) identified in genome-wide association studies (GWAS) on adult glioma would also be associated with PBT risk. The study is based on the Cefalo study, a population-based multicenter case-control study. Saliva DNA from 245 cases and 489 controls, aged 7-19 years at diagnosis/reference date, was extracted and genotyped for 29 SNPs reported by GWAS to be significantly associated with risk of adult glioma. Data were analyzed using unconditional logistic regression. Stratified analyses were performed for two histological subtypes: astrocytoma alone and the other tumor types combined. The results indicated that four SNPs, CDKN2BAS rs4977756 (p = 0.036), rs1412829 (p = 0.037), rs2157719 (p = 0.018) and rs1063192 (p = 0.021), were associated with an increased susceptibility to PBTs, whereas the TERT rs2736100 was associated with a decreased risk (p = 0.018). Moreover, the stratified analyses showed a decreased risk of astrocytoma associated with RTEL1 rs6089953, rs6010620 and rs2297440 (p trend = 0.022, p trend = 0.042, p trend = 0.029, respectively) as well as an increased risk of this subtype associated with RTEL1 rs4809324 (p trend = 0.033). In addition, SNPs rs10464870 and rs891835 in CCDC26 were associated with an increased risk of non-astrocytoma tumor subtypes (p trend = 0.009, p trend = 0.007, respectively). Our findings indicate that SNPs in CDKN2BAS, TERT, RTEL1 and CCDC26 may be associated with the risk of PBTs. Therefore, we suggest that pediatric and adult brain tumors might share common genetic risk factors and similar etiological pathways.

DOI: https://doi.org/10.1093/carcin/bgv074

# *CCDC26*, *CDKN2BAS*, *RTEL1*, and *TERT* Polymorphisms in Pediatric Brain Tumor Susceptibility

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Running title: Polymorphisms Associated with Pediatric Brain Tumor Susceptibility

**Abstract**

The role of genetic polymorphisms in pediatric brain tumor (PBT) etiology is poorly understood. We hypothesized that single nucleotide polymorphisms (SNPs) identified in genome-wide association studies (GWAS) on adult glioma would also be associated with PBT risk. The study is based on the Cefalo study, a population-based multicenter case-control study. Saliva DNA from 245 cases and 489 controls, aged 7-19 years at diagnosis/reference date, was extracted and genotyped for 29 SNPs reported by GWAS to be significantly associated with risk of adult glioma. Data were analyzed using unconditional logistic regression. Stratified analyses were performed for two histological subtypes: astrocytoma alone and the other tumor types combined. The results indicated thatfour SNPs, *CDKN2BAS* rs4977756 (p=0.036), rs1412829 (p=0.037), rs2157719 (p=0.018), and rs1063192 (p=0.021), were associated with an increased susceptibility to PBTs, whereas the *TERT* rs2736100 was associated with a decreased risk (p=0.018). Moreover, the stratified analyses showed a decreased risk of astrocytoma associated with *RTEL1* rs6089953, rs6010620, and rs2297440 ($p_{trend}$=0.022, $p_{trend}$=0.042, $p_{trend}$=0.029, respectively) as well as an increased risk of this subtype associated with *RTEL1* rs4809324 ($p_{trend}$=0.033). In addition, SNPs rs10464870 and rs891835 in *CCDC26* were associated with an increased risk of non-astrocytoma tumor subtypes ($p_{trend}$=0.009, $p_{trend}$=0.007, respectively). Our findings indicate that SNPs in *CDKN2BAS, TERT, RTEL1,* and *CCDC26* may be associated with the risk of PBTs. Therefore, we suggest that pediatric and adult brain tumors might share common genetic risk factors and similar etiological pathways.

**Summary**

The role of genetic polymorphisms in pediatric brain tumor (PBT) etiology is poorly understood. In this study, we tested the hypothesis that single nucleotide polymorphisms identified by genome-wide association studies on adult glioma are also associated with PBT risk.

## Introduction

Brain tumors are the second most common type of pediatric cancer and the leading cause of childhood cancer mortality. The etiology of pediatric brain tumors (PBTs) is poorly understood (1). As in adults (2), the only established risk factors for brain tumors in children are exposure to high doses of ionizing radiation and several inherited disorders, and these cause only a minority of cases. Therefore, it is likely that brain tumorigenesis results from complex interactions between genetic and epigenetic variations in concert with exposure to environmental factors (1).

Although large genetic studies on adult brain tumors have been conducted (3-7), very few and only small studies of brain tumors in children and adolescents have been reported (8-11). In the last few years, four genome-wide association studies (GWAS) on adult glioma identified seven susceptibility loci at 5p15.33 (*TERT*), 8q24.21 (*CCDC26*), 9p21.3 (*CDKN2A-CDKN2B*), 20q13.33(*RTEL1*), 11q23.3 (*PHLDB1*), and 7p11.2 (*EGFR*) (4-7). However, limited data are available on the role of genetic polymorphisms in the etiology of PBTs, probably because of difficulties in collecting a sufficient number of DNA samples. Considering this lack of knowledge about genetic risk factors for brain tumors in children, it is important to identify germ-line DNA polymorphisms that might influence the susceptibility to PBTs.

The aim of this study, based on the largest series of PBT cases to date, was to test the hypothesis that the single nucleotide polymorphisms (SNPs) identified by GWAS on adult glioma are also associated with the risk of brain tumors in children.

## Materials and methods

### Study population and procedures

This study is based on the Cefalo study, a large, international, population-based, case-control study of brain tumors in children and adolescents conducted in centers in Sweden, Denmark, Norway, and Switzerland. All centers followed a common protocol for data collection, as described in more detail elsewhere (12,13). Eligible cases were children aged 7-19 years during the period 1 April 2004 to 31 August 2008, diagnosed with a primary intracranial brain tumor defined according to the International Classification of Childhood Cancer, third edition (ICCC-3) (14), group III, restricted to ICD-O-3 location C71 and subclassified according to the fourth edition of the World Health Organization(WHO)classification of tumors of the central nervous system(15). Medulloblastoma cases will be the subject of a separate study, and therefore have been excluded from the present analysis. Two controls per case were randomly selected from the general population matched to the case by age, sex, and geographical region. Interviews were conducted with 352 (82%) cases and 646 (71%) controls. Participants with neurofibromatosis or tuberous sclerosis were excluded from the analyses. The study was approved by the national data protection boards and ethical committees in all participating countries, and written informed consent was obtained from all participants and/or their parents.

The Oragene self-collection kit (DNA Genotek, Ottawa, ON, Canada) was used for saliva collection and DNA extraction, following the manufacturer'srecommended protocol. DNA samples are stored at the KarolinskaInstitutetBiobank. The DNA yield was quantitated by

using PicoGreen (Invitrogen, Carlsbad, CA, USA). Overall, saliva DNA from 245 cases and 489 controls was included in this study.

**SNP selection and genotyping**

A total of 29 SNPs reported by GWAS to be significantly associated with risk of adult glioma were selected for genotyping (4-7). Genotyping was performed at the Mutation Analysis core Facility (MAF), Clinical Research Centre, Huddinge University Hospital, Stockholm, Sweden, with staff blinded to sample status, using the SequenomiPlex Gold platform with matrix-assisted laser desorption/ionization-time-of-flight (MALDI-TOF) mass spectrometry. The average success rate was 97% and the concordance rate for duplicate genotyping was 100%.

**Statistical analysis**

The consistency of allele frequencies with Hardy-Weinberg equilibrium (HWE) was assessed in the controls for all SNPs using the $\chi 2$ goodness-of-fit test, and $p<0.001$ was considered statistically significant. Analyses were performed based on the subset of Cefalo subjectswho provided saliva sample.Unconditional logistic regression was used to estimate the association between SNPs and PBT susceptibility based on the Cochran–Armitage trend test of additivity (trend) as well as dominant (DOM) and recessive (REC) models, with adjustment for the matching variables (age, sex, and country). The allelic frequencies of the genotyped SNPs were compared between cases and controls using the $\chi 2$ test. Analyses were also conducted stratified byastrocytoma alone and the combination of other tumor types, including ependymoma, intracranial embryonal tumors (except medulloblastoma), other gliomas, other specified intracranial neoplasms, and unspecified intracranial neoplasms. Country specific analyses were performed to assess consistency across countries.The Wald test was used to evaluate the significance of interactions between SNPs and demographic variablesand D′, a

measure of the linkage disequilibrium (LD) between the genotyped SNPs, was calculated.Haploblocks were defined based on the default LD block parameters in Haploview v4.2. Haplotype analyses were performed for the haplotype blocks harboring the SNPs that were found to be associated with PBTs. Haplotypes with a frequency of >1% were considered in the analyses. The effects of specific haplotypes were analyzed if the distribution of all the haplotypes was suggestively different between cases and controls ($p<0.05$ for all PBTs; $p<0.1$ for subgroup analyses). Selection of SNPs for the analyses was based on a priori knowledge from GWAS on adults, and therefore odds ratios (ORs) are presented with 95% confidence intervals (CIs). The possibility of false-positive findings was, however, considered by also providing the reference p value for an experiment-wide significance with Bonferroni correction. The analyses were performed using PLINK v1.07 (16) and SAS statistical software version 9.3 (SAS Institute, Inc., Cary, NC, USA).

**Results**

We successfully genotyped 29 SNPs in 245 cases and 489 controls. The distributions of allele frequencies in the controls were in agreement with the Hardy-Weinberg equilibrium. Table 1 shows demographic characteristics of cases and controls, and the distributions of diagnostic subtypes. The age and sex distributions were similar in cases and controls. More than 50% of cases were diagnosed with astrocytoma. No significant interactions were detected between SNPs and confounders including age, sex and country (Table 2).

As shown in Table 2, *TERT* rs2736100 A allele was associated with a decreased risk of PBTs ($OR_{DOM}$ 0.66 [95% CI 0.46-0.93], p=0.018), whereas the SNPs rs4977756 G allele ($OR_{DOM}$ 1.45 [95% CI 1.03-2.06], p=0.036), rs1412829 G allele ($OR_{DOM}$ 1.45 [95% CI 1.02-2.05], p=0.037), rs2157719 C allele ($OR_{DOM}$ 1.53 [95% CI 1.08-2.19], p=0.018), and rs1063192 G

allele ($OR_{DOM}$ 1.53 [95% CI 1.07-2.19], p=0.021) in *CDKN2BAS* were associated with increased susceptibility to this tumors.

The stratified analyses of two histological subtypes indicated that the risk effects of *CDKN2BAS* rs1063192, rs2157719, rs1412829, and rs4977756 remained significant in patients with astrocytoma ($p_{trend}$=0.036, $p_{trend}$=0.034, $p_{trend}$=0.044, and $p_{trend}$=0.023, respectively), whereas the protective effect of *TERT* rs2736100 was more evident in patients with other brain tumor subtypes ($OR_{DOM}$ 0.53 [95% CI 0.34-0.85], p=0.007). Moreover, the stratified analyses showed a decreased risk of astrocytoma associated with the polymorphisms *RTEL1* rs6089953 A allele, rs6010620 A allele, and rs2297440 T allele ($p_{trend}$=0.022, $p_{trend}$=0.042, and $p_{trend}$=0.029, respectively), as well as an increased risk of this subtype associated with the C alleleof *RTEL1* rs4809324 ($p_{trend}$=0.033). In addition, an increased risk of non-astrocytoma tumor subtypes was associated with the SNPs rs10464870 C allele and rs891835 G allele in *CCDC26* ($p_{trend}$=0.009 and $p_{trend}$=0.007, respectively) (Table 3).

The non-significant findings, possibly resulting from the limited statistical power of the study, are shown in the online appendix Tables S1-S3 and the raw data showing the number of cases and controls for each genotype of significant SNPs are reported in Table S4.

Strong LD (D´≥0.95) was observed between three of the genotyped SNPs in *CDKN2BAS* (rs1412829, rs2157719, and rs1063192), and four SNPs in *RTEL1* (rs6089953, rs6010620, rs2297440, and rs4809324). For each of the two blocks, three haplotypes with frequency of >1% were found. The distribution of haplotypes was different for PBT patients compared to controls for the *CDKN2BAS* block ($\chi$2=7.0, df=2, p=0.030) and showed a tendency to be different for the *RTEL1* block ($\chi$2=5.9, df=2, p=0.053). The most common haplotype (ATA) of *CDKN2BAS* SNPs had a significant protective effect compared with the other haplotypes combined (OR 0.75 [95% CI 0.60-0.93], p=0.009) whereas the second most common

haplotype (GCG) had a significant risk effect (OR 1.32 [95% CI 1.06-1.64], p=0.012). The haplotype analyses suggested an increased risk of PBTs by increasing the numberof risk alleles in *CDKN2BAS* and*RTEL1*SNPs. In the astrocytoma subgroup, the same haploblocks and haplotypes with frequencies of >1% were detected. However, in this subgroup, the distribution of haplotypes in the *RTEL1* block was significantly different between patients and controls ($\chi 2$=9.0, df=2, p=0.011) while this difference was not statistically significant in the *CDKN2BAS* block ($\chi 2$=5.7, df=2, p=0.059). In the astrocytoma subgroup, a significant protective effect was observed for the most common haplotype (ATA) of *CDKN2BAS* SNPs compared with the other haplotypes combined (OR 0.73 [95% CI 0.56-0.95], p=0.021) whereas the second most common haplotype (GCG) showed a significant risk effect (OR 1.34 [95% CI 1.02-1.76], p=0.036). Moreover, in the *RTEL1* block, the second most common haplotype (AATT) had a significant protective effect compared with the other haplotypes combined (OR 0.67 [95% CI 0.47-0.95], p=0.023) whereas the third most common haplotype (GGCC) had a significant risk effect (OR 1.57 [95% CI 1.06-2.34], p=0.026) (Table 4).

Overall, we performed 116 testing procedures as described above. When the Bonferroni correction is applied, the reference p value is 0.0004 for an experiment-wide significance level of 0.05, and 0.0009 for a significance level of 0.10; none of the observed associations met these limits.The consistency of results across countries wasinvestigated and the results of stratified analyses are reported in the online appendix Tables S5-S8.No significant differences between countries were observed.**Discussion**

The results of this study indicate that several SNPs associated with adult glioma risk are also associated with the risk of PBTs. Our findings suggest that SNPs rs4977756 G allele, rs1412829 G allele, rs2157719 C allele, and rs1063192 G allele in *CDKN2BAS* may increase the risk of PBTs, whereas the A alleleof *TERT* rs2736100 polymorphism may confer protection against PBTs. In addition, polymorphisms rs6089953 A allele, rs6010620 A allele,

and rs2297440 T allele in *RTEL1* were associated with decreased susceptibility to astrocytoma, whereas the C allele of *RTEL1* rs4809324 was associated with an increased risk of this subtype. Furthermore, an increased risk of non-astrocytoma tumor subtypes associated with polymorphisms *CCDC26* rs10464870 C allele and rs891835 G allelewas detected. Our findings suggest that genetic risk profiles of PBTs differ by histology.

To our knowledge, this study represents the largest series of pediatric brain tumor cases assembled for genetic association testing to date. The association between the 29 SNPs investigated in this study and the risk of PBTs has not been examined in previous studies (8-11). The SNPs were selected a priori for analyses in this study based on findings in GWAS on adult glioma, and our significant findings of associations between SNPs in *CDKN2BAS*, *TERT*, *RTEL1*,and *CCDC26* and risk of PBTs were consistent with findings on adult brain tumors with respect to the direction of ORs for the minor alleles (4-7).

*CDKN2BAS* (*ANRIL*) encodes antisense non-coding RNA in the *INK4* locus which is a long non-coding RNA (ncRNA). The exact function of *CDKN2BAS* is unclear, but it is known to be involved in regulating the expression of *CDKN2A* and *CDKN2B* genes that encode cyclin-dependent kinase inhibitors and block cell cycle division during the G1/S phase. Therefore, *CDKN2BAS* has a regulatory role in the context of cellular proliferation, and its alterations result in abnormal self-renewing capabilities typical of cancer cells (17,18). Germ-line mutations in *CDKN2BAS* predispose to a wide variety of human cancers (19,20). _ENREF_17 _ENREF_4

Telomerase reverse transcriptase (TERT) is a catalytic subunit of telomerase that maintains telomere by adding telomeric repeat sequences onto chromosome ends. Telomerase expression can prevent telomere erosion in most eukaryotic cells, and cancer cells can prevent telomere loss through the abnormal upregulation of telomerase (21). _ENREF_18 The mutant

allele of *TERT* rs2736100, which is an intronic polymorphism, may downregulate telomerase expression and consequently decrease the risk of brain tumors.

*RTEL1* producesregulator of telomere elongation helicase 1 which is essential for telomere maintenance and genome stability by preventing homologous recombination (22). Polymorphisms in *RTEL1* are correlated withhigh grade glioma in adults (4,5,7,23). _ENREF_4In contrast, *CCDC26* variations are associated with low grade tumors (4,5,23). *CCDC26* encodes a retinoic acid–dependent regulator of cell differentiation and death. CCDC26increases apoptosis induced by death stimuli in neuroblastoma cells (24) and in glioblastoma cells with downregulation of telomerase activity (25).

The majority of genetic variations found in this study to be associated with the risk of PBTs are related to telomerase activity which has an important role in the initiation and progression of gliomas(26). Moreover, it has been shown that telomerase expression is related to high grade gliomas and poor survival (27,28). Thus, telomerase could be considered as a therapeutic target for brain tumors (29,30).

The aim of this study was to provide evidence of the associations between SNPs and PBT risk, and not to investigate the mechanisms behind such associations; nevertheless the fact that we did not consider the effect of environmental risk factors represents a limitation of this work. Therefore, additional studies are needed to examine potentially relevant gene-environment interactions and to explore the mechanisms through which these genetic polymorphisms influence cancer susceptibility.

The present study was conducted based on a specific hypothesis that may lead to detection of clinically meaningful risk and protective factors. Moreover, the selection of SNPs for analysis was based on a priori knowledge from GWAS on adults, and therefore Bonferroni correction may be overly conservative and may make researchers miss important findings (31). To be

able to evaluate potential false-positive findings, reference p values with Bonferroni corrections have been presented and the consistency of results across four countries has beenreported. No significant differences between countries were observed.Replication studies are necessary to confirm these results in larger sample sizes.

In conclusion, the present findings indicate that SNPs in *CDKN2BAS* are associated withincreased susceptibility to PBTs, whereas *TERT* polymorphisms may decrease the risk of these tumors. Moreover, polymorphisms in *RTEL1* and *CCDC26* genes are associated with the risk of astrocytoma and non-astrocytoma subtypes, respectively. Thus, we suggest that pediatric and adult brain tumors might share common genetic risk factors and similar etiological pathways.

**Supplementary material**

Supplementary Tables S1-S3 can be found at http://carcin.oxfordjournals.org/.

**Funding**

The Swedish part of the CEFALO study was supported by grants from the Swedish Council for Working Life and Social Research [grant numbers 2004-0504 and 2007-0224]; the Swedish Research Council [grant number K2008-70X-15366-04-3]; the Swedish Cancer Society [grant number 09 0666]; the Swedish Childhood Cancer Society [grant numbers PROJ06/050 and PROJ09/086]; and the Swedish Radiation Protection Authority [grant number SSI P 1572]. The Danish CEFALO study was supported by the Danish Strategic Research Council [grant numbers 2103-05-0006 and 2064-04-0010]. The Swiss part of the CEFALO study was supported by the Swiss Federal Office of Public Health [grant number 05.001626]; the Swiss Research Foundation on Mobile Communication [grant number A2006.18]; and the Swiss National Science Foundation [grant number PDFMP3_122873].

The Norwegian CEFALO study was supported by the Research Council of Norway [grant number 175163/V40].

## Acknowledgments

We gratefully acknowledge collaboration with and support from clinicians and other hospital staff in all countries, as well as assistance from national and local cancer registers with identification of patients. We also acknowledge the skillful work of the research nurses, interviewers, and research assistants in all countries. Finally, we acknowledge all those with whom we have collaborated previously within the CEFALO study. Please see Aydin et al. for an exhaustive list(12).

## Conflict of Interest Statement

None declared.

## URLs

PLINK: http://pngu.mgh.harvard.edu/~purcell/plink/

SAS: http://www.sas.com/

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**Table 1. Characteristics of cases and controls**

| Characteristics | Cases | Controls |
|---|---|---|
| **No. of participants** | 245 | 489 |

| | | |
|---|---|---|
| **Sex** | | |
| Males | 136 (56%) | 261 (53%) |
| Females | 109 (44%) | 228 (47%) |
| **Age-group (at reference date)** | | |
| 7-9 years old | 48 (20%) | 112 (23%) |
| 10-14 years old | 108 (44%) | 219 (45%) |
| 15-19 years old | 89 (36%) | 158 (32%) |
| **Country** | | |
| Sweden | 106 (43%) | 174 (36%) |
| Norway | 24 (10%) | 62 (13%) |
| Denmark | 62 (25%) | 134 (27%) |
| Switzerland | 53 (22%) | 119(24%) |
| **Type of tumor (ICCC-3 group III)[a]** | | |
| Astrocytoma (IIIb) | 134 (55%) | |
| Pilocyticastrocytoma | 93 | |
| Supependymalgiant cell astrocytoma | 5 | |
| Pleomorphicxanthoastrocytoma | 4 | |
| Diffuse astrocytoma | 13 | |
| Anaplastic astrocytoma | 11 | |
| Fibrillaryastrocytoma | 2 | |
| Glioblastoma | 5 | |
| Giant cell glioblastoma | 1 | |
| Other gliomas (IIId) | 20 (8%) | |
| Malignantglioma | 11 | |
| Oligoastrocytoma | 2 | |
| Oligodendroglioma | 6 | |
| Anaplastic oligodendroglioma | 1 | |
| Ependymoma (IIIa) | 19 (8%) | |
| Subependymoma | 2 | |
| Choroidplexuspapilloma | 4 | |
| Choroidplexuscaricinoma | 1 | |
| Ependymoma | 7 | |
| Papillaryependymoma | 1 | |
| Anaplastic ependymoma | 4 | |
| Intracranial embryonal tumors (IIIc) | 7 (3%) | |
| CNS primitive neuroectodermaltumor | 6 | |
| Neuroepithelioma | 1 | |
| Other specified intracranial neoplasms (IIIe) | 49 (20%) | |

| | |
|---|---|
| Germinoma | 7 |
| Yolksactumor | 1 |
| Teratoma, mature | 1 |
| Haemangioblastoma | 1 |
| Desmoplastic infantile ganglioglioma | 2 |
| Dysembryoplastic neuroepithelialtumor | 6 |
| Ganglioglioma | 26 |
| Anaplasticganglioglioma | 1 |
| Centrolneurocytoma | 3 |
| Neurilemoma | 1 |
| Unspecified intracranial neoplasm (IIIf) | 16 (6%) |

**a**: Restricted to ICD-O-3 location C71, subclassified according to WHO histological subclassification, 2007; patients with neurofibromatosis and tuberous sclerosis were excluded.

**Table 2. Summary results for SNPs associated with pediatric brain tumors**

| SNP | Chr. | Gene | Location (bp) | Minor allele | MAF[a] in cases | MAF[a] in controls | Model | OR[b] | 95% CI | P | CHISQ | Pinteraction[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs2736100 | 5 | *TERT* | 1286516 | A | 0.47 | 0.50 | Dominant | 0.66 | 0.46-0.93 | 0.018 | | 0.702 |
| | | | | | | | Recessive | 1.19 | 0.82-1.71 | 0.359 | | |
| | | | | | | | Additive | 0.89 | 0.72-1.12 | 0.351 | | |
| | | | | | | | Allelic | | | 0.333 | 0.94 | |
| rs1063192 | 9 | *CDKN2BAS* *CDKN2B* | 22003367 | G | 0.52 | 0.45 | Dominant | 1.53 | 1.07-2.19 | 0.021 | | 0.889 |
| | | | | | | | Recessive | 1.36 | 0.95-1.95 | 0.095 | | |
| | | | | | | | Additive | 1.31 | 1.05-1.63 | 0.015 | | |
| | | | | | | | Allelic | | | 0.009 | 6.64 | |
| rs2157719 | 9 | *CDKN2BAS* | 22033366 | C | 0.51 | 0.44 | Dominant | 1.53 | 1.08-2.19 | 0.018 | | 0.825 |
| | | | | | | | Recessive | 1.36 | 0.94-1.97 | 0.099 | | |
| | | | | | | | Additive | 1.32 | 1.06-1.64 | 0.014 | | |
| | | | | | | | Allelic | | | 0.009 | 6.67 | |
| rs1412829 | 9 | *CDKN2BAS* | 22043926 | G | 0.50 | 0.43 | Dominant | 1.45 | 1.02-2.05 | 0.037 | | 0.734 |
| | | | | | | | Recessive | 1.38 | 0.95-1.99 | 0.089 | | |
| | | | | | | | Additive | 1.29 | 1.04-1.61 | 0.021 | | |
| | | | | | | | Allelic | | | 0.014 | 6.04 | |
| rs4977756 | 9 | *CDKN2BAS* | 22068652 | G | 0.49 | 0.42 | Dominant | 1.45 | 1.03-2.06 | 0.036 | | 0.954 |
| | | | | | | | Recessive | 1.30 | 0.89-1.91 | 0.176 | | |
| | | | | | | | Additive | 1.27 | 1.02-1.59 | 0.032 | | |
| | | | | | | | Allelic | | | 0.024 | 5.09 | |

**a**: MAF=Minor Allele Frequency **b:** ORadjusted for age, sex, and country**c:** P value for interactions between SNPs and demographic variables including age, sex and country

**Table 3. Summary results for SNPs associated with pediatric brain tumors stratified by histological subtypes**

| SNP | Chr. | Gene | Location (bp) | Minor allele | MAF[a] in cases | MAF[a] in controls | Model | OR[b] | 95% CI | P | CHISQ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Astrocytoma** | | | | | | | | | | | |
| rs1063192 | 9 | *CDKN2BAS* | 22003367 | G | 0.52 | 0.45 | Dominant | 1.84 | 1.15-2.94 | 0.011 | |
| | | *CDKN2B* | | | | | Recessive | 1.21 | 0.76-1.91 | 0.419 | |
| | | | | | | | Additive | 1.34 | 1.02-1.76 | 0.036 | |
| | | | | | | | Allelic | | | 0.038 | 4.29 |
| rs2157719 | 9 | *CDKN2BAS* | 22033366 | C | 0.51 | 0.44 | Dominant | 1.75 | 1.11-2.77 | 0.016 | |
| | | | | | | | Recessive | 1.26 | 0.79-1.99 | 0.329 | |
| | | | | | | | Additive | 1.34 | 1.02-1.76 | 0.034 | |
| | | | | | | | Allelic | | | 0.035 | 4.43 |
| rs1412829 | 9 | *CDKN2BAS* | 22043926 | G | 0.50 | 0.43 | Dominant | 1.64 | 1.05-2.57 | 0.029 | |
| | | | | | | | Recessive | 1.28 | 0.81-2.03 | 0.294 | |
| | | | | | | | Additive | 1.32 | 1.01-1.74 | 0.044 | |
| | | | | | | | Allelic | | | 0.043 | 4.09 |
| rs4977756 | 9 | *CDKN2BAS* | 22068652 | G | 0.5 | 0.42 | Dominant | 1.85 | 1.17-2.91 | 0.008 | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Recessive | 1.25 | 0.78-2.01 | 0.358 | |
| | | | | | | | Additive | 1.38 | 1.05-1.82 | 0.023 | |
| | | | | | | | Allelic | | | 0.025 | 5.02 |
| rs6089953 | 20 | *RTEL1* | 62291008 | A | 0.18 | 0.25 | Dominant | 0.64 | 0.43-0.96 | 0.032 | |
| | | | | | | | Recessive | 0.49 | 0.19-1.31 | 0.157 | |
| | | | | | | | Additive | 0.67 | 0.48-0.95 | 0.022 | |
| | | | | | | | Allelic | | | 0.019 | 5.46 |
| rs6010620 | 20 | *RTEL1* | 62309839 | A | 0.19 | 0.25 | Dominant | 0.66 | 0.44-0.99 | 0.048 | |
| | | | | | | | Recessive | 0.59 | 0.24-1.45 | 0.254 | |
| | | | | | | | Additive | 0.71 | 0.50-0.99 | 0.042 | |
| | | | | | | | Allelic | | | 0.039 | 4.27 |
| rs2297440 | 20 | *RTEL1* | 62312299 | T | 0.17 | 0.24 | Dominant | 0.64 | 0.41-0.98 | 0.038 | |
| | | | | | | | Recessive | 0.52 | 0.19-1.37 | 0.187 | |
| | | | | | | | Additive | 0.68 | 0.47-0.96 | 0.029 | |
| | | | | | | | Allelic | | | 0.023 | 5.18 |
| rs4809324 | 20 | *RTEL1* | 62318220 | C | 0.15 | 0.10 | Dominant | 1.54 | 0.98-2.39 | 0.060 | |
| | | | | | | | Recessive | 2.94 | 0.78-11.14 | 0.112 | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Additive | 1.54 | 1.04-2.28 | 0.033 | |
| | | | | | | | Allelic | | | 0.029 | 4.74 |
| **Other** | | | | | | | | | | | |
| rs2736100 | 5 | *TERT* | 1286516 | A | 0.44 | 0.50 | Dominant | 0.54 | 0.34-0.85 | 0.007 | |
| | | | | | | | Recessive | 1.07 | 0.64-1.77 | 0.802 | |
| | | | | | | | Additive | 0.78 | 0.57-1.07 | 0.122 | |
| | | | | | | | Allelic | | | 0.139 | 2.19 |
| rs10464870 | 8 | *CCDC26* | 130477823 | C | 0.32 | 0.23 | Dominant | 1.70 | 1.11-2.60 | 0.014 | |
| | | | | | | | Recessive | 1.78 | 0.87-3.66 | 0.115 | |
| | | | | | | | Additive | 1.53 | 1.11-2.11 | 0.009 | |
| | | | | | | | Allelic | | | 0.004 | 8.11 |
| rs891835 | 8 | *CCDC26* | 130491752 | G | 0.34 | 0.24 | Dominant | 1.59 | 1.04-2.44 | 0.032 | |
| | | | | | | | Recessive | 2.32 | 1.18-4.57 | 0.015 | |
| | | | | | | | Additive | 1.55 | 1.13-2.14 | 0.007 | |
| | | | | | | | Allelic | | | 0.003 | 8.65 |

**a**: MAF=Minor Allele Frequency **b:** ORadjusted for age, sex, and country

**Table 4. Haplotype analysis of SNPs in *CDKN2BAS* and *RTEL1***

| SNPs | Haplotype | Frequency | OR[a] | 95% CI | P |
|---|---|---|---|---|---|
| *CDKN2BAS*: rs1412829, rs2157719, rs1063192 | ATA | 0.52 | 0.75 | 0.60-0.93 | 0.009 |
| | GCG | 0.45 | 1.32 | 1.06-1.64 | 0.012 |
| | ATG | 0.02 | 0.89 | 0.56-1.43 | 0.814 |
| *RTEL1*: rs6089953, rs6010620, rs2297440, rs4809324 | GGCT | 0.65 | 1.03 | 0.81-1.32 | 0.787 |
| | AATT | 0.23 | 0.79 | 0.61-1.02 | 0.074 |
| | GGCC | 0.11 | 1.39 | 0.99-1.95 | 0.055 |
| **Astrocytoma** | | | | | |
| *CDKN2BAS*: rs1412829, rs2157719, rs1063192 | ATA | 0.53 | 0.73 | 0.56-0.95 | 0.021 |
| | GCG | 0.44 | 1.34 | 1.02-1.76 | 0.036 |
| | ATG | 0.02 | 0.79 | 0.21-2.94 | 0.725 |
| *RTEL1*: rs6089953, rs6010620, rs2297440, rs4809324 | GGCT | 0.65 | 1.06 | 0.81-1.39 | 0.676 |
| | AATT | 0.23 | 0.67 | 0.47-0.95 | 0.023 |
| | GGCC | 0.11 | 1.57 | 1.06-2.34 | 0.026 |

**a:** Odds ratio for haplotype compared with all other haplotypes adjusted for age, sex, and country

**Table S1. Summary results for SNPs unassociated with pediatric brain tumors**

| SNP | Chr. | Location (bp) | Minor allele | MAF[Ψ] in cases | MAF[Ψ] in controls | Model | OR[£] | 95% CI | P | CHISQ |
|---|---|---|---|---|---|---|---|---|---|---|
| rs7530361 | 1 | 100462860 | C | 0.144 | 0.1656 | Dominant | 0.7977 | 0.5631-1.13 | 0.2032 | |
| | | | | | | Recessive | 0.9425 | 0.347-2.56 | 0.9075 | |
| | | | | | | Additive | 0.8339 | 0.6127-1.135 | 0.2479 | |
| | | | | | | Allelic | | | 0.2881 | 1.129 |
| rs501700 | 1 | 100520311 | A | 0.148 | 0.1607 | Dominant | 0.861 | 0.5991-1.238 | 0.4188 | |
| | | | | | | Recessive | 0.9696 | 0.3565-2.637 | 0.9518 | |
| | | | | | | Additive | 0.8895 | 0.6477-1.222 | 0.4693 | |
| | | | | | | Allelic | | | 0.5454 | 0.3657 |
| rs2072532 | 2 | 40366301 | G | 0.4604 | 0.4317 | Dominant | 1.395 | 0.99-1.967 | 0.05706 | |
| | | | | | | Recessive | 1.008 | 0.6833-1.487 | 0.9679 | |
| | | | | | | Additive | 1.152 | 0.9256-1.434 | 0.2048 | |
| | | | | | | Allelic | | | 0.3019 | 1.066 |
| rs2853676 | 5 | 1288547 | T | 0.2845 | 0.2763 | Dominant | 0.9819 | 0.7169-1.345 | 0.9092 | |
| | | | | | | Recessive | 1.292 | 0.7517-2.222 | 0.3535 | |
| | | | | | | Additive | 1.04 | 0.8165-1.324 | 0.7516 | |
| | | | | | | Allelic | | | 0.7426 | 0.1079 |
| rs6869535 | 5 | 40597618 | A | 0.1667 | 0.1632 | Dominant | 0.9696 | 0.6894-1.364 | 0.8591 | |
| | | | | | | Recessive | 1.495 | 0.5472-4.086 | 0.4328 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Additive | 1.011 | 0.7462-1.37 | 0.9438 | |
| | | | | | | Allelic | | | 0.8664 | 0.02829 |
| rs10079250 | 5 | 149450132 | C | 0.06042 | 0.06394 | Dominant | 0.9751 | 0.6051-1.571 | 0.9175 | |
| | | | | | | Recessive | 1.061e-009 | 0-inf | 0.9993 | |
| | | | | | | Additive | 0.9558 | 0.5977-1.529 | 0.8503 | |
| | | | | | | Allelic | | | 0.7951 | 0.06744 |
| rs2252586 | 7 | 54978924 | T | 0.2562 | 0.2901 | Dominant | 0.7588 | 0.5537-1.04 | 0.08594 | |
| | | | | | | Recessive | 1.106 | 0.6142-1.991 | 0.7375 | |
| | | | | | | Additive | 0.8544 | 0.6639-1.1 | 0.2214 | |
| | | | | | | Allelic | | | 0.178 | 1.815 |
| rs6969537 | 7 | 55082418 | A | 0.1402 | 0.1224 | Dominant | 1.239 | 0.863-1.778 | 0.2457 | |
| | | | | | | Recessive | 0.6967 | 0.1371-3.541 | 0.6631 | |
| | | | | | | Additive | 1.184 | 0.8456-1.657 | 0.3259 | |
| | | | | | | Allelic | | | 0.3426 | 0.9005 |
| rs11979158 | 7 | 55159349 | G | 0.1757 | 0.1576 | Dominant | 1.16 | 0.8276-1.626 | 0.3889 | |
| | | | | | | Recessive | 1.291 | 0.4567-3.648 | 0.6303 | |
| | | | | | | Additive | 1.151 | 0.8507-1.556 | 0.3625 | |
| | | | | | | Allelic | | | 0.381 | 0.7676 |
| rs10488631 | 7 | 128594183 | C | 0.1125 | 0.1174 | Dominant | 0.9275 | 0.6301-1.365 | 0.7028 | |
| | | | | | | Recessive | 0.7406 | 0.2226-2.464 | 0.6245 | |
| | | | | | | Additive | 0.9194 | 0.6529-1.295 | 0.6305 | |
| | | | | | | Allelic | | | 0.7843 | 0.07492 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| rs12531711 | 7 | 128617466 | G | 0.1176 | 0.117 | Dominant | 0.9908 | 0.6659-1.474 | 0.9636 | |
| | | | | | | Recessive | 0.7565 | 0.2272-2.518 | 0.6492 | |
| | | | | | | Additive | 0.9689 | 0.6834-1.374 | 0.8591 | |
| | | | | | | Allelic | | | 0.9722 | 0.00121 |
| rs10464870 | 8 | 130477823 | C | 0.2531 | 0.2284 | Dominant | 1.163 | 0.8463-1.598 | 0.3522 | |
| | | | | | | Recessive | 1.153 | 0.6177-2.154 | 0.6541 | |
| | | | | | | Additive | 1.126 | 0.875-1.449 | 0.3563 | |
| | | | | | | Allelic | | | 0.2989 | 1.079 |
| rs891835 | 8 | 130491752 | G | 0.2668 | 0.2384 | Dominant | 1.124 | 0.8186-1.543 | 0.4704 | |
| | | | | | | Recessive | 1.428 | 0.7914-2.577 | 0.2368 | |
| | | | | | | Additive | 1.143 | 0.8918-1.466 | 0.2907 | |
| | | | | | | Allelic | | | 0.2415 | 1.372 |
| rs6470745 | 8 | 130641921 | G | 0.2045 | 0.2019 | Dominant | 1.131 | 0.8196-1.561 | 0.4537 | |
| | | | | | | Recessive | 0.5598 | 0.2359-1.329 | 0.1883 | |
| | | | | | | Additive | 1.022 | 0.7792-1.342 | 0.8726 | |
| | | | | | | Allelic | | | 0.9055 | 0.01409 |
| rs9656979 | 8 | 130664407 | C | 0.4463 | 0.429 | Dominant | 0.9949 | 0.7121-1.39 | 0.9761 | |
| | | | | | | Recessive | 1.253 | 0.8483-1.851 | 0.2572 | |
| | | | | | | Additive | 1.072 | 0.8587-1.338 | 0.5395 | |
| | | | | | | Allelic | | | 0.5324 | 0.3899 |
| rs16904140 | 8 | 130665643 | A | 0.2234 | 0.2204 | Dominant | 1.07 | 0.7799-1.469 | 0.6734 | |
| | | | | | | Recessive | 0.8109 | 0.3921-1.677 | 0.5716 | |
| | | | | | | Additive | 1.018 | 0.7841-1.323 | 0.8914 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Allelic | | | 0.897 | 0.01675 |
| rs4295627 | 8 | 130685457 | G | 0.175 | 0.1867 | Dominant | 1.007 | 0.7228-1.404 | 0.9661 | |
| | | | | | | Recessive | 0.3676 | 0.1239-1.091 | 0.07126 | |
| | | | | | | Additive | 0.9176 | 0.6882-1.223 | 0.5577 | |
| | | | | | | Allelic | | | 0.5886 | 0.2925 |
| rs11823971 | 11 | 72388561 | A | 0.09426 | 0.09129 | Dominant | 1.085 | 0.7221-1.629 | 0.6952 | |
| | | | | | | Recessive | 0.6434 | 0.1306-3.17 | 0.5878 | |
| | | | | | | Additive | 1.041 | 0.7195-1.507 | 0.8299 | |
| | | | | | | Allelic | | | 0.8532 | 0.03425 |
| rs498872 | 11 | 118477367 | A | 0.2875 | 0.3126 | Dominant | 0.8322 | 0.6085-1.138 | 0.25 | |
| | | | | | | Recessive | 0.9407 | 0.5489-1.612 | 0.824 | |
| | | | | | | Additive | 0.8866 | 0.6965-1.128 | 0.328 | |
| | | | | | | Allelic | | | 0.3293 | 0.9515 |
| rs17748 | 11 | 118528424 | T | 0.2045 | 0.2322 | Dominant | 0.8394 | 0.6089-1.157 | 0.2852 | |
| | | | | | | Recessive | 0.6521 | 0.2997-1.419 | 0.281 | |
| | | | | | | Additive | 0.8374 | 0.6391-1.097 | 0.1979 | |
| | | | | | | Allelic | | | 0.2333 | 1.42 |
| rs6089953 | 20 | 62291008 | A | 0.2049 | 0.249 | Dominant | 0.7755 | 0.5631-1.068 | 0.1195 | |
| | | | | | | Recessive | 0.6218 | 0.3087-1.252 | 0.1835 | |
| | | | | | | Additive | 0.7885 | 0.6069-1.024 | 0.07524 | |
| | | | | | | Allelic | | | 0.06119 | 3.505 |
| rs6010620 | 20 | 62309839 | A | 0.2104 | 0.2505 | Dominant | 0.7913 | 0.5734-1.092 | 0.1546 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Recessive | 0.6774 | 0.3429-1.338 | 0.2622 | |
| | | | | | | Additive | 0.8092 | 0.623-1.051 | 0.1125 | |
| | | | | | | Allelic | | | 0.09215 | 2.836 |
| rs2297440 | 20 | 62312299 | T | 0.1903 | 0.242 | Dominant | 0.7335 | 0.5225-1.03 | 0.07344 | |
| | | | | | | Recessive | 0.589 | 0.2828-1.227 | 0.1573 | |
| | | | | | | Additive | 0.7555 | 0.5733-0.9957 | 0.04654 | |
| | | | | | | Allelic | | | 0.03246 | 4.574 |
| rs4809324 | 20 | 62318220 | C | 0.1379 | 0.1034 | Dominant | 1.401 | 0.9676-2.029 | 0.07416 | |
| | | | | | | Recessive | 2.021 | 0.5735-7.121 | 0.2737 | |
| | | | | | | Additive | 1.386 | 0.991-1.937 | 0.05651 | |
| | | | | | | Allelic | | | 0.05273 | 3.752 |

**Ψ**: MAF=Minor Allele Frequency **£:** OR adjusted for age, sex, and country

**Table S2. Summary results for SNPs unassociated with astrocytoma subtype**

| SNP | Chr. | Location (bp) | Minor allele | MAF[Ψ] in cases | MAF[Ψ] in controls | Model | OR[£] | 95% CI | P | CHISQ |
|---|---|---|---|---|---|---|---|---|---|---|
| rs7530361 | 1 | 100462860 | C | 0.1477 | 0.1656 | Dominant | 0.8099 | 0.5246-1.25 | 0.3413 | |
| | | | | | | Recessive | 1.196 | 0.3775-3.788 | 0.7612 | |
| | | | | | | Additive | 0.8653 | 0.5905-1.268 | 0.4582 | |
| | | | | | | Allelic | | | 0.4843 | 0.4891 |
| rs501700 | 1 | 100520311 | A | 0.1513 | 0.1607 | Dominant | 0.8714 | 0.5523-1.375 | 0.5542 | |
| | | | | | | Recessive | 1.26 | 0.3966-4.001 | 0.6953 | |
| | | | | | | Additive | 0.9245 | 0.6225-1.373 | 0.6973 | |
| | | | | | | Allelic | | | 0.7228 | 0.1259 |
| rs2072532 | 2 | 40366301 | G | 0.4773 | 0.4317 | Dominant | 1.316 | 0.8606-2.013 | 0.205 | |
| | | | | | | Recessive | 1.214 | 0.7672-1.919 | 0.4082 | |
| | | | | | | Additive | 1.19 | 0.9125-1.551 | 0.1993 | |
| | | | | | | Allelic | | | 0.1873 | 1.739 |
| rs2736100 | 5 | 1286516 | A | 0.4924 | 0.4958 | Dominant | 0.7539 | 0.4876-1.165 | 0.2037 | |
| | | | | | | Recessive | 1.298 | 0.8349-2.019 | 0.2466 | |
| | | | | | | Additive | 0.9888 | 0.7476-1.308 | 0.9369 | |
| | | | | | | Allelic | | | 0.9212 | 0.009789 |
| rs2853676 | 5 | 1288547 | T | 0.303 | 0.2763 | Dominant | 1.047 | 0.7102-1.544 | 0.8161 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Recessive | 1.588 | 0.8522-2.959 | 0.1453 | |
| | | | | | | Additive | 1.131 | 0.843-1.518 | 0.4115 | |
| | | | | | | Allelic | | | 0.3924 | 0.7314 |
| rs6869535 | 5 | 40597618 | A | 0.1641 | 0.1632 | Dominant | 0.9237 | 0.6021-1.417 | 0.7161 | |
| | | | | | | Recessive | 2.072 | 0.6797-6.317 | 0.2002 | |
| | | | | | | Additive | 1.011 | 0.6934-1.475 | 0.9536 | |
| | | | | | | Allelic | | | 0.9708 | 0.001336 |
| rs10079250 | 5 | 149450132 | C | 0.04924 | 0.06394 | Dominant | 0.7689 | 0.407-1.453 | 0.4182 | |
| | | | | | | Recessive | 2.186e-009 | 0-inf | 0.9993 | |
| | | | | | | Additive | 0.7602 | 0.406-1.423 | 0.3916 | |
| | | | | | | Allelic | | | 0.3763 | 0.7829 |
| rs2252586 | 7 | 54978924 | T | 0.2652 | 0.2901 | Dominant | 0.7586 | 0.5136-1.12 | 0.1649 | |
| | | | | | | Recessive | 1.277 | 0.6409-2.546 | 0.4866 | |
| | | | | | | Additive | 0.8796 | 0.6438-1.202 | 0.4202 | |
| | | | | | | Allelic | | | 0.4272 | 0.6304 |
| rs6969537 | 7 | 55082418 | A | 0.1346 | 0.1224 | Dominant | 1.129 | 0.7183-1.773 | 0.5996 | |
| | | | | | | Recessive | 1.205 | 0.2371-6.125 | 0.8221 | |
| | | | | | | Additive | 1.12 | 0.7413-1.691 | 0.5913 | |
| | | | | | | Allelic | | | 0.5967 | 0.2801 |
| rs11979158 | 7 | 55159349 | G | 0.2061 | 0.1576 | Dominant | 1.49 | 0.9933-2.235 | 0.05391 | |
| | | | | | | Recessive | 1.541 | 0.4693-5.061 | 0.4759 | |
| | | | | | | Additive | 1.424 | 0.9948-2.038 | 0.05341 | |
| | | | | | | Allelic | | | 0.06275 | 3.463 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| rs10488631 | 7 | 128594183 | C | 0.1174 | 0.1174 | Dominant | 1.027 | 0.6402-1.648 | 0.912 | |
| | | | | | | Recessive | 0.7715 | 0.1624-3.664 | 0.7441 | |
| | | | | | | Additive | 1.001 | 0.6571-1.524 | 0.9976 | |
| | | | | | | Allelic | | | 0.9992 | 1.133e-006 |
| rs12531711 | 7 | 128617466 | G | 0.1293 | 0.117 | Dominant | 1.171 | 0.7184-1.908 | 0.527 | |
| | | | | | | Recessive | 0.8077 | 0.1698-3.843 | 0.7884 | |
| | | | | | | Additive | 1.11 | 0.7224-1.705 | 0.6342 | |
| | | | | | | Allelic | | | 0.606 | 0.2661 |
| rs10464870 | 8 | 130477823 | C | 0.1962 | 0.2284 | Dominant | 0.8254 | 0.5495-1.24 | 0.3552 | |
| | | | | | | Recessive | 0.6168 | 0.2334-1.63 | 0.3299 | |
| | | | | | | Additive | 0.8234 | 0.5873-1.154 | 0.2597 | |
| | | | | | | Allelic | | | 0.2669 | 1.233 |
| rs891835 | 8 | 130491752 | G | 0.2093 | 0.2384 | Dominant | 0.8313 | 0.5557-1.244 | 0.3685 | |
| | | | | | | Recessive | 0.7296 | 0.2952-1.803 | 0.4946 | |
| | | | | | | Additive | 0.8448 | 0.6059-1.178 | 0.3201 | |
| | | | | | | Allelic | | | 0.3264 | 0.963 |
| rs6470745 | 8 | 130641921 | G | 0.1641 | 0.2019 | Dominant | 0.8657 | 0.5726-1.309 | 0.4941 | |
| | | | | | | Recessive | 0.1466 | 0.0196-1.097 | 0.06147 | |
| | | | | | | Additive | 0.7826 | 0.5451-1.123 | 0.1839 | |
| | | | | | | Allelic | | | 0.1707 | 1.877 |
| rs9656979 | 8 | 130664407 | C | 0.416 | 0.429 | Dominant | 0.9272 | 0.6145-1.399 | 0.7186 | |
| | | | | | | Recessive | 0.9248 | 0.5521-1.549 | 0.7663 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Additive | 0.9433 | 0.7124-1.249 | 0.6839 | |
| | | | | | | Allelic | | | 0.7064 | 0.1419 |
| rs16904140 | 8 | 130665643 | A | 0.1917 | 0.2204 | Dominant | 0.8733 | 0.5848-1.304 | 0.5081 | |
| | | | | | | Recessive | 0.5263 | 0.1801-1.538 | 0.2407 | |
| | | | | | | Additive | 0.843 | 0.6008-1.183 | 0.3231 | |
| | | | | | | Allelic | | | 0.3135 | 1.016 |
| rs4295627 | 8 | 130685457 | G | 0.1477 | 0.1867 | Dominant | 0.8255 | 0.5404-1.261 | 0.3751 | |
| | | | | | | Recessive | 0.1668 | 0.02217-1.255 | 0.08194 | |
| | | | | | | Additive | 0.7625 | 0.5244-1.109 | 0.1558 | |
| | | | | | | Allelic | | | 0.1433 | 2.143 |
| rs11823971 | 11 | 72388561 | A | 0.08271 | 0.09129 | Dominant | 0.879 | 0.5153-1.499 | 0.6358 | |
| | | | | | | Recessive | 1.112 | 0.2245-5.512 | 0.8962 | |
| | | | | | | Additive | 0.9115 | 0.5677-1.464 | 0.7014 | |
| | | | | | | Allelic | | | 0.6642 | 0.1884 |
| rs498872 | 11 | 118477367 | A | 0.2885 | 0.3126 | Dominant | 0.8131 | 0.5509-1.2 | 0.2975 | |
| | | | | | | Recessive | 1.021 | 0.5314-1.96 | 0.9513 | |
| | | | | | | Additive | 0.8895 | 0.659-1.201 | 0.4444 | |
| | | | | | | Allelic | | | 0.4542 | 0.5601 |
| rs17748 | 11 | 118528424 | T | 0.2099 | 0.2322 | Dominant | 0.916 | 0.6152-1.364 | 0.6655 | |
| | | | | | | Recessive | 0.5087 | 0.1739-1.489 | 0.2173 | |
| | | | | | | Additive | 0.8681 | 0.6205-1.214 | 0.4089 | |
| | | | | | | Allelic | | | 0.4456 | 0.5817 |

**Ψ**: MAF=Minor Allele Frequency **£:** OR adjusted for age, sex, and country

**Table S3. Summary results for SNPs unassociated with non-astrocytoma subtypes**

| SNP | Chr. | Location (bp) | Minor allele | MAF[ψ] in cases | MAF[ψ] in controls | Model | OR[£] | 95% CI | P | CHISQ |
|---|---|---|---|---|---|---|---|---|---|---|
| rs7530361 | 1 | 100462860 | C | 0.1396 | 0.1656 | Dominant | 0.8026 | 0.5004-1.287 | 0.3617 | |
| | | | | | | Recessive | 0.7271 | 0.1586-3.333 | 0.6816 | |
| | | | | | | Additive | 0.817 | 0.5339-1.25 | 0.3517 | |
| | | | | | | Allelic | | | 0.3421 | 0.9025 |
| rs501700 | 1 | 100520311 | A | 0.1442 | 0.1607 | Dominant | 0.866 | 0.5328-1.408 | 0.5617 | |
| | | | | | | Recessive | 0.7255 | 0.1583-3.326 | 0.6796 | |
| | | | | | | Additive | 0.869 | 0.5639-1.339 | 0.5243 | |
| | | | | | | Allelic | | | 0.5567 | 0.3455 |
| rs2072532 | 2 | 40366301 | G | 0.4398 | 0.4317 | Dominant | 1.508 | 0.941-2.416 | 0.08778 | |
| | | | | | | Recessive | 0.7903 | 0.4447-1.405 | 0.4225 | |
| | | | | | | Additive | 1.115 | 0.8256-1.505 | 0.4783 | |
| | | | | | | Allelic | | | 0.8285 | 0.04695 |
| rs2853676 | 5 | 1288547 | T | 0.2617 | 0.2763 | Dominant | 0.9002 | 0.5865-1.382 | 0.6307 | |
| | | | | | | Recessive | 0.9824 | 0.4376-2.206 | 0.9657 | |
| | | | | | | Additive | 0.9332 | 0.6636-1.312 | 0.6908 | |
| | | | | | | Allelic | | | 0.6656 | 0.1868 |
| rs6869535 | 5 | 40597618 | A | 0.1697 | 0.1632 | Dominant | 1.012 | 0.6412-1.598 | 0.9584 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Recessive | 0.8717 | 0.1822-4.17 | 0.8635 | |
| | | | | | | Additive | 1 | 0.6607-1.514 | 0.9999 | |
| | | | | | | Allelic | | | 0.814 | 0.05535 |
| rs10079250 | 5 | 149450132 | C | 0.07407 | 0.06394 | Dominant | 1.257 | 0.6855-2.303 | 0.4602 | |
| | | | | | | Recessive | 2.145e-009 | 0-inf | 0.9993 | |
| | | | | | | Additive | 1.218 | 0.6728-2.204 | 0.5152 | |
| | | | | | | Allelic | | | 0.5876 | 0.2941 |
| rs2252586 | 7 | 54978924 | T | 0.2454 | 0.2901 | Dominant | 0.77 | 0.5012-1.183 | 0.233 | |
| | | | | | | Recessive | 0.8852 | 0.3769-2.079 | 0.7795 | |
| | | | | | | Additive | 0.8259 | 0.5816-1.173 | 0.2849 | |
| | | | | | | Allelic | | | 0.1874 | 1.738 |
| rs6969537 | 7 | 55082418 | A | 0.1468 | 0.1224 | Dominant | 1.389 | 0.8617-2.24 | 0.1774 | |
| | | | | | | Recessive | 2.685e-009 | 0-inf | 0.9984 | |
| | | | | | | Additive | 1.257 | 0.8045-1.965 | 0.3149 | |
| | | | | | | Allelic | | | 0.3286 | 0.9543 |
| rs11979158 | 7 | 55159349 | G | 0.1389 | 0.1576 | Dominant | 0.8264 | 0.5105-1.338 | 0.438 | |
| | | | | | | Recessive | 0.8848 | 0.1845-4.242 | 0.8784 | |
| | | | | | | Additive | 0.8477 | 0.5475-1.312 | 0.4586 | |
| | | | | | | Allelic | | | 0.4925 | 0.471 |
| rs10488631 | 7 | 128594183 | C | 0.1065 | 0.1174 | Dominant | 0.8154 | 0.4766-1.395 | 0.4564 | |
| | | | | | | Recessive | 0.6751 | 0.1403-3.248 | 0.624 | |
| | | | | | | Additive | 0.8262 | 0.5169-1.321 | 0.4251 | |
| | | | | | | Allelic | | | 0.6501 | 0.2057 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| rs12531711 | 7 | 128617466 | G | 0.1048 | 0.117 | Dominant | 0.8133 | 0.4701-1.407 | 0.4601 | |
| | | | | | | Recessive | 0.6777 | 0.141-3.257 | 0.6271 | |
| | | | | | | Additive | 0.8255 | 0.5128-1.329 | 0.4299 | |
| | | | | | | Allelic | | | 0.6161 | 0.2514 |
| rs6470745 | 8 | 130641921 | G | 0.2523 | 0.2019 | Dominant | 1.543 | 1.009-2.36 | 0.04533 | |
| | | | | | | Recessive | 1.061 | 0.4152-2.709 | 0.9022 | |
| | | | | | | Additive | 1.341 | 0.9536-1.886 | 0.09157 | |
| | | | | | | Allelic | | | 0.09774 | 2.742 |
| rs9656979 | 8 | 130664407 | C | 0.482 | 0.429 | Dominant | 1.101 | 0.6968-1.741 | 0.6794 | |
| | | | | | | Recessive | 1.755 | 1.071-2.877 | 0.02563 | |
| | | | | | | Additive | 1.264 | 0.9367-1.705 | 0.1255 | |
| | | | | | | Allelic | | | 0.1519 | 2.053 |
| rs16904140 | 8 | 130665643 | A | 0.2613 | 0.2204 | Dominant | 1.365 | 0.8956-2.081 | 0.1477 | |
| | | | | | | Recessive | 1.182 | 0.4929-2.836 | 0.7075 | |
| | | | | | | Additive | 1.256 | 0.8964-1.759 | 0.1856 | |
| | | | | | | Allelic | | | 0.1906 | 1.713 |
| rs4295627 | 8 | 130685457 | G | 0.2083 | 0.1867 | Dominant | 1.288 | 0.8312-1.996 | 0.2574 | |
| | | | | | | Recessive | 0.6115 | 0.1763-2.121 | 0.4383 | |
| | | | | | | Additive | 1.136 | 0.7867-1.639 | 0.4974 | |
| | | | | | | Allelic | | | 0.4654 | 0.533 |
| rs1063192 | 9 | 22003367 | G | 0.5229 | 0.4506 | Dominant | 1.253 | 0.7802-2.012 | 0.3508 | |
| | | | | | | Recessive | 1.594 | 0.9966-2.55 | 0.05169 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Additive | 1.288 | 0.9646-1.72 | 0.08627 | |
| | | | | | | Allelic | | | 0.05402 | 3.712 |
| rs2157719 | 9 | 22033366 | C | 0.5093 | 0.4383 | Dominant | 1.324 | 0.8259-2.122 | 0.2438 | |
| | | | | | | Recessive | 1.527 | 0.9445-2.468 | 0.0842 | |
| | | | | | | Additive | 1.292 | 0.9665-1.728 | 0.08364 | |
| | | | | | | Allelic | | | 0.05833 | 3.584 |
| rs1412829 | 9 | 22043926 | G | 0.5 | 0.4338 | Dominant | 1.253 | 0.7896-1.989 | 0.3382 | |
| | | | | | | Recessive | 1.532 | 0.9485-2.474 | 0.08117 | |
| | | | | | | Additive | 1.267 | 0.9494-1.691 | 0.108 | |
| | | | | | | Allelic | | | 0.07408 | 3.19 |
| rs4977756 | 9 | 22068652 | G | 0.4673 | 0.4224 | Dominant | 1.11 | 0.7018-1.756 | 0.6556 | |
| | | | | | | Recessive | 1.4 | 0.844-2.324 | 0.1924 | |
| | | | | | | Additive | 1.167 | 0.8676-1.571 | 0.3069 | |
| | | | | | | Allelic | | | 0.231 | 1.434 |
| rs11823971 | 11 | 72388561 | A | 0.1081 | 0.09129 | Dominant | 1.419 | 0.8441-2.385 | 0.1867 | |
| | | | | | | Recessive | 3.647e-009 | 0-inf | 0.9983 | |
| | | | | | | Additive | 1.269 | 0.7834-2.054 | 0.3334 | |
| | | | | | | Allelic | | | 0.4397 | 0.5971 |
| rs498872 | 11 | 118477367 | A | 0.2864 | 0.3126 | Dominant | 0.8545 | 0.5609-1.302 | 0.4641 | |
| | | | | | | Recessive | 0.8299 | 0.3899-1.766 | 0.6285 | |
| | | | | | | Additive | 0.8778 | 0.6322-1.219 | 0.4365 | |
| | | | | | | Allelic | | | 0.4469 | 0.5786 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| rs17748 | 11 | 118528424 | T | 0.1982 | 0.2322 | Dominant | 0.767 | 0.4953-1.188 | 0.2344 | |
| | | | | | | Recessive | 0.8286 | 0.3069-2.237 | 0.7105 | |
| | | | | | | Additive | 0.8104 | 0.561-1.171 | 0.2625 | |
| | | | | | | Allelic | | | 0.2748 | 1.193 |
| rs6089953 | 20 | 62291008 | A | 0.2342 | 0.249 | Dominant | 0.9747 | 0.6365-1.493 | 0.906 | |
| | | | | | | Recessive | 0.7992 | 0.3233-1.976 | 0.6275 | |
| | | | | | | Additive | 0.9504 | 0.6737-1.341 | 0.7721 | |
| | | | | | | Allelic | | | 0.6461 | 0.2109 |
| rs6010620 | 20 | 62309839 | A | 0.2361 | 0.2505 | Dominant | 0.9816 | 0.6375-1.511 | 0.9329 | |
| | | | | | | Recessive | 0.8028 | 0.3236-1.992 | 0.6356 | |
| | | | | | | Additive | 0.9552 | 0.6749-1.352 | 0.796 | |
| | | | | | | Allelic | | | 0.6578 | 0.1962 |
| rs2297440 | 20 | 62312299 | T | 0.2108 | 0.242 | Dominant | 0.8803 | 0.56-1.384 | 0.5805 | |
| | | | | | | Recessive | 0.6877 | 0.258-1.833 | 0.454 | |
| | | | | | | Additive | 0.8708 | 0.6042-1.255 | 0.458 | |
| | | | | | | Allelic | | | 0.345 | 0.8917 |
| rs4809324 | 20 | 62318220 | C | 0.1216 | 0.1034 | Dominant | 1.203 | 0.726-1.994 | 0.4729 | |
| | | | | | | Recessive | 0.7842 | 0.08663-7.099 | 0.8288 | |
| | | | | | | Additive | 1.158 | 0.7253-1.849 | 0.539 | |
| | | | | | | Allelic | | | 0.4282 | 0.6276 |

**Ψ**: MAF=Minor Allele Frequency **£:** OR adjusted for age, sex, and country

**Table S4. Number of subjects for each genotype of SNPs associated with pediatric brain tumors**

| SNP | Gene | Genotype | Cases | Controls |
|---|---|---|---|---|
| **All brain tumors** | | | | |
| rs2736100 | *TERT* | CC | 76 | 113 |
| | | CA | 103 | 256 |
| | | AA | 61 | 109 |
| rs1063192 | *CDKN2BAS* | AA | 56 | 150 |
| | *CDKN2B* | AG | 116 | 212 |
| | | GG | 67 | 104 |
| rs2157719 | *CDKN2BAS* | TT | 58 | 159 |
| | | TC | 117 | 219 |
| | | CC | 63 | 100 |
| rs1412829 | *CDKN2BAS* | AA | 62 | 159 |
| | | AG | 118 | 221 |
| | | GG | 63 | 96 |
| rs4977756 | *CDKN2BAS* | AA | 62 | 164 |
| | | AG | 121 | 223 |
| | | GG | 55 | 90 |
| **Astrocytoma** | | | | |
| rs1063192 | *CDKN2BAS* | AA | 27 | 150 |
| | *CDKN2B* | AG | 70 | 212 |
| | | GG | 33 | 104 |
| rs2157719 | *CDKN2BAS* | TT | 29 | 159 |
| | | TC | 69 | 219 |
| | | CC | 32 | 100 |
| rs1412829 | *CDKN2BAS* | AA | 31 | 159 |
| | | AG | 69 | 221 |
| | | GG | 32 | 69 |
| rs4977756 | *CDKN2BAS* | AA | 29 | 164 |
| | | AG | 73 | 223 |
| | | GG | 29 | 90 |
| rs6089953 | *RTEL1* | GG | 90 | 277 |
| | | GA | 38 | 170 |
| | | AA | 5 | 35 |
| rs6010620 | *RTEL1* | GG | 88 | 272 |
| | | GA | 38 | 168 |
| | | AA | 6 | 35 |
| rs2297440 | *RTEL1* | CC | 86 | 258 |
| | | CT | 33 | 145 |

| | | | | |
|---|---|---|---|---|
| | | TT | 5 | 33 |
| rs4809324 | *RTEL1* | TT | 96 | 381 |
| | | TC | 32 | 88 |
| | | CC | 4 | 5 |
| **Other** | | | | |
| rs2736100 | *TERT* | CC | 38 | 113 |
| | | CA | 46 | 256 |
| | | AA | 25 | 109 |
| rs10464870 | *CCDC26* | TT | 52 | 287 |
| | | TC | 47 | 159 |
| | | CC | 12 | 29 |
| rs891835 | *CCDC26* | TT | 51 | 277 |
| | | TG | 43 | 168 |
| | | GG | 15 | 29 |

**Table S5. Summary results for SNPs associated with pediatric brain tumors in Denmark**

| SNP | Chr. | Gene | Location (bp) | Minor allele | MAF[a] in cases | MAF[a] in controls | Model | OR[b] | 95% CI | P | CHISQ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs2736100 | 5 | *TERT* | 1286516 | A | 0.47 | 0.48 | Dominant | 0.76 | 0.38-1.50 | 0.427 | |
| | | | | | | | Recessive | 1.18 | 0.58-2.41 | 0.647 | |
| | | | | | | | Additive | 0.95 | 0.62-1.47 | 0.826 | |
| | | | | | | | Allelic | | | 0.864 | 0.03 |
| rs1063192 | 9 | *CDKN2BAS* *CDKN2B* | 22003367 | G | 0.54 | 0.49 | Dominant | 1.12 | 0.56-2.26 | 0.751 | |
| | | | | | | | Recessive | 1.56 | 0.76-3.21 | 0.227 | |
| | | | | | | | Additive | 1.21 | 0.80-1.82 | 0.362 | |
| | | | | | | | Allelic | | | 0.33 | 0.95 |
| rs2157719 | 9 | *CDKN2BAS* | 22033366 | C | 0.54 | 0.46 | Dominant | 1.78 | 0.85-3.73 | 0.125 | |
| | | | | | | | Recessive | 1.27 | 0.63-2.56 | 0.496 | |
| | | | | | | | Additive | 1.34 | 0.87-2.05 | 0.179 | |
| | | | | | | | Allelic | | | 0.159 | 1.96 |
| rs1412829 | 9 | *CDKN2BAS* | 22043926 | G | 0.52 | 0.46 | Dominant | 1.45 | 0.73-2.91 | 0.283 | |
| | | | | | | | Recessive | 1.19 | 0.60-2.38 | 0.611 | |
| | | | | | | | Additive | 1.23 | 0.81-1.85 | 0.336 | |
| | | | | | | | Allelic | | | 0.315 | 1.01 |
| rs4977756 | 9 | *CDKN2BAS* | 22068652 | G | 0.48 | 0.43 | Dominant | 1.61 | 0.81-3.19 | 0.174 | |
| | | | | | | | Recessive | 1.04 | 0.49-2.20 | 0.909 | |
| | | | | | | | Additive | 1.23 | 0.80-1.88 | 0.343 | |
| | | | | | | | Allelic | | | 0.337 | 0.92 |

**a**: MAF=Minor Allele Frequency **b:** OR adjusted for age, and sex

**Table S6. Summary results for SNPs associated with pediatric brain tumors in Norway**

| SNP | Chr. | Gene | Location (bp) | Minor allele | MAF[a] in cases | MAF[a] in controls | Model | OR[b] | 95% CI | P | CHISQ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs2736100 | 5 | *TERT* | 1286516 | A | 0.42 | 0.58 | Dominant | 0.42 | 0.12-1.41 | 0.161 | |
| | | | | | | | Recessive | 0.39 | 0.13-1.17 | 0.093 | |
| | | | | | | | Additive | 0.50 | 0.24-1.03 | 0.059 | |
| | | | | | | | Allelic | | | 0.052 | 3.78 |
| rs1063192 | 9 | *CDKN2BAS* *CDKN2B* | 22003367 | G | 0.48 | 0.43 | Dominant | 2.06 | 0.67-6.34 | 0.206 | |
| | | | | | | | Recessive | 1.02 | 0.31-3.31 | 0.979 | |
| | | | | | | | Additive | 1.33 | 0.68-2.61 | 0.407 | |
| | | | | | | | Allelic | | | 0.545 | 0.37 |
| rs2157719 | 9 | *CDKN2BAS* | 22033366 | C | 0.50 | 0.40 | Dominant | 2.19 | 0.73-6.56 | 0.161 | |
| | | | | | | | Recessive | 1.49 | 0.47-4.73 | 0.493 | |
| | | | | | | | Additive | 1.57 | 0.79-3.08 | 0.193 | |
| | | | | | | | Allelic | | | 0.244 | 1.36 |
| rs1412829 | 9 | *CDKN2BAS* | 22043926 | G | 0.48 | 0.39 | Dominant | 2.29 | 0.77-6.83 | 0.138 | |
| | | | | | | | Recessive | 1.19 | 0.36-3.97 | 0.774 | |
| | | | | | | | Additive | 1.49 | 0.76-2.94 | 0.248 | |
| | | | | | | | Allelic | | | 0.317 | 1.00 |
| rs4977756 | 9 | *CDKN2BAS* | 22068652 | G | 0.44 | 0.40 | Dominant | 1.70 | 0.59-4.91 | 0.326 | |
| | | | | | | | Recessive | 0.83 | 0.24-2.93 | 0.774 | |
| | | | | | | | Additive | 1.18 | 0.61-2.31 | 0.620 | |
| | | | | | | | Allelic | | | 0.710 | 0.14 |

**a**: MAF=Minor Allele Frequency **b:** OR adjusted for age, and sex

**Table S7. Summary results for SNPs associated with pediatric brain tumors in Sweden**

| SNP | Chr. | Gene | Location (bp) | Minor allele | MAF[a] in cases | MAF[a] in controls | Model | OR[b] | 95% CI | P | CHISQ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| rs2736100 | 5 | *TERT* | 1286516 | A | 0.48 | 0.50 | Dominant | 0.58 | 0.33-1.01 | 0.055 | |
| | | | | | | | Recessive | 1.44 | 0.81-2.55 | 0.216 | |
| | | | | | | | Additive | 0.92 | 0.65-1.31 | 0.651 | |
| | | | | | | | Allelic | | | 0.587 | 0.29 |
| rs1063192 | 9 | *CDKN2BAS* *CDKN2B* | 22003367 | G | 0.57 | 0.46 | Dominant | 1.77 | 1.02-3.09 | 0.044 | |
| | | | | | | | Recessive | 1.76 | 0.97-3.18 | 0.061 | |
| | | | | | | | Additive | 1.53 | 1.08-2.18 | 0.018 | |
| | | | | | | | Allelic | | | 0.016 | 5.75 |
| rs2157719 | 9 | *CDKN2BAS* | 22033366 | C | 0.54 | 0.45 | Dominant | 1.64 | 0.93-2.88 | 0.089 | |
| | | | | | | | Recessive | 1.68 | 0.96-2.94 | 0.068 | |
| | | | | | | | Additive | 1.45 | 1.03-2.05 | 0.032 | |
| | | | | | | | Allelic | | | 0.029 | 4.73 |
| rs1412829 | 9 | *CDKN2BAS* | 22043926 | G | 0.54 | 0.44 | Dominant | 1.57 | 0.89-2.75 | 0.113 | |
| | | | | | | | Recessive | 1.85 | 1.06-3.25 | 0.031 | |
| | | | | | | | Additive | 1.49 | 1.05-2.09 | 0.024 | |
| | | | | | | | Allelic | | | 0.021 | 5.34 |
| rs4977756 | 9 | *CDKN2BAS* | 22068652 | G | 0.53 | 0.44 | Dominant | 1.57 | 0.89-2.77 | 0.122 | |
| | | | | | | | Recessive | 1.72 | 0.96-3.08 | 0.067 | |
| | | | | | | | Additive | 1.45 | 1.02-2.07 | 0.039 | |
| | | | | | | | Allelic | | | 0.039 | 4.28 |

**a:** MAF=Minor Allele Frequency **b:** OR adjusted for age, and sex