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Known glioma risk loci are associated with glioma with a family history of brain tumours—A case–control gene association study

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Familial cancer can be used to leverage genetic association studies. Recent genome-wide association studies have reported independent associations between seven single nucleotide polymorphisms (SNPs) and risk of glioma. The aim of this study was to investigate whether glioma cases with a positive family history of brain tumours, defined as having at least one first- or second-degree relative with a history of brain tumour, are associated with known glioma risk loci. One thousand four hundred and thirty-one glioma cases and 2,868 cancer-free controls were identified from four case–control studies and two prospective cohorts from USA, Sweden and Denmark and genotyped for seven SNPs previously reported to be associated with glioma risk in case–control designed studies. Odds ratios were calculated by unconditional logistic regression. In analyses including glioma cases with a family history of brain tumours (n = 104) and control subjects free of glioma at baseline, three of seven SNPs were associated with glioma risk: rs2736100 (5p15.33, *TERT*), rs4977756 (9p21.3, *CDKN2A-CDKN2B*) and rs6010620 (20q13.33, *RTEL1*). After Bonferroni correction for multiple comparisons, only one marker was statistically

Key words: Glioma, brain tumours, genome-wide association study, single nucleotide polymorphism

Abbreviations: CI: confidence interval; FHBT-GBM: glioblastoma cases with a positive family history of brain tumours; FHBT-glioma: glioma cases with a positive family history of brain tumours; GWAS: genome-wide association study; MAF: minor allele frequency; NCI: National Cancer Institute; NIOSH: National Institute for Occupational Safety and Health; non-FHBT-glioma: glioma cases with no family history of brain tumours; NSHDS: Northern Sweden Health and Disease Study; OR: odds ratio; OR_{het}: odds ratio of heterozygote versus common homozygote genotype; OR_{hom}: odds ratio of rare homozygote versus common homozygote genotype; OR_{trend}: odds ratio per rare

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Short Report

significantly associated with glioma risk, rs6010620 (OR_{trend} for the minor (A) allele, 0.39; 95% CI: 0.25–0.61; Bonferroni adjusted p_{trend}, 1.7×10^{-4}). In conclusion, as previously shown for glioma regardless of family history of brain tumours, rs6010620 (*RTEL1*) was associated with an increased risk of glioma when restricting to cases with family history of brain tumours. These findings require confirmation in further studies with a larger number of glioma cases with a family history of brain tumours.

What's new?

Genomic research has recently identified seven single-nucleotide polymorphisms (SNPs) that are associated with an increased risk of glioma. In this study, the authors report that the association between one of these SNPs (rs6010620 in the *RTEL1* gene) and glioma is stronger in people with a family history of brain tumor compared to those without such a history. This correlation may help to define genetic factors that increase the risk of developing this form of cancer.

Glioma is the most common malignancy of the adult brain. Fifty-four percent of gliomas are glioblastomas, which have a very poor survival rate (5-year relative survival, <5%).[1] The aetiology of glioma is largely unknown. Exposure to ionising radiation is the only established environmental risk factor. In addition, asthma and allergies have consistently been inversely associated with risk for gliomas.[2] First-degree relatives of patients with brain tumour are at an increased risk of glioma, indicating that genetic factors are a possible contributing factor for the disease. However, only a minority of the cases can be explained by well-defined inherited syndromes known to predispose to glioma, such as the Li-Fraumeni syndrome, Turcot syndrome and neurofibromatosis Type 1 and 2.[3,4]

Genetic association studies, linkage studies and more recently genome-wide association studies (GWASs) have identified a number of genetic variants associated with an increased risk for glioma.[5] Replicated GWAS hits include loci at chromosomes 5p15.33 (rs2736100, *TERT*), 8q24.21 (rs4295627, *CCDC26*), 9p21.3 (rs4977756, *CDKN2A-CDKN2B*), 20q13.33 (rs6010620, *RTEL1*) and 11q23.3 (rs498872, *PHLDB1*), and two independent loci on 7p11.2 (rs11979158 and rs2252586, *EGFR*).[6–9] None of these initial GWASs reported results for familial glioma cases separately (i.e. considering family history of disease). In the present study, we investigate whether glioma cases with a positive family history of brain tumours (FHBT-glioma) are associated with known glioma risk loci as a family history could indicate a different genetic aetiology. In total, 1,431 glioma cases (including 104 FHBT-glioma cases) and 2,868 controls were identified from six different studies and included in this study.[3,10–14]

Material and Methods

Study subjects

Glioma cases (ICDO-3 9380–9480 or equivalent) and controls were identified from six different studies (Table 1 and Supporting Information Table 1). All studies except Gliogene Sweden have previously been described in detail.[10–14] In Sweden, in conjunction with the Gliogene family study,[3] blood samples were collected from incident glioma cases participating in the initial screen for family history (2007–2010). Age- and sex-matched controls for cases within Gliogene Sweden were provided by the prospective Northern Sweden Health and Disease Study (NSHDS), which draws from a highly comparable study population.[12] Family history of brain tumours was assessed in all studies by the study questionnaire, except in the NSHDS control population, in which family history of brain tumours was not assessed. Family history of brain tumour was defined as at least one first- or second-degree relative with a history of primary brain tumours. This definition comprises brain tumours without further specification, hence including glioma as well as meningioma and other types. In the Swedish Gliogene cases, the report of family history was validated by review of the relatives' medical records and pathology reports. Glioma cases and control subjects in the present study have previously been included in a recent GWAS in which cases from 18 different studies were included regardless of family history of brain tumours.[9] Genotype information for specific single nucleotide polymorphisms (SNPs) was derived from a genome-wide association scan performed on Human660W-Quad BeadChips (Illumina).[9] Cases and controls with genotypes that failed the following per sample quality control measures were excluded from the study: samples with low completion rates (<95%), unexpectedly low/high heterozygozity (<22% or >35%), unexpected duplicates and individuals detected to have less than 80% European ancestry. Additionally, subjects who were less than 18 years of age were excluded from further analysis (Supporting Information Figure 1).

Statistical analysis

For the seven SNPs previously associated with glioma risk,[6–9] odds ratios (ORs) and 95% confidence intervals (CIs) for glioma risk were calculated using unconditional logistic regression models adjusted for age, sex and study. The rare allele for each SNP was defined based on allele frequencies among controls. ORs comparing heterozygote and homozygote rare genotypes *vs.* homozygote wild-type genotypes, as well as per allele ORs, were calculated for FHBT-glioma cases *vs.* control subjects (Tables 2 and 3). Case-case analyses were conducted by comparison of cases with *vs.* cases without a family history of brain tumours. *p* Values for statistical significance were based on the Wald test. Multiple testing was adjusted for using Bonferroni correction, assuming one independent test for each

Short Report

Table 1. Distribution of cases and controls in the six studies

		Controls			Cases		
		Total[1], *n*	Without family history[2], *n* (%)	With family history[2], *n* (%)	Total[1], *n*	Without family history[2], *n* (%)	With family history[2], *n* (%)
Gliogene (Ref. 3)	Case–control, Sweden	0	0	0	400	332 (83.8)	64 (16.2)
NSDHS (Ref. 12)	Cohort, Sweden	707	0 (0)	0 (0)	0	0 (0)	0 (0)
Interphone (Ref. 14)	Case–control, Sweden, Denmark	381	373 (98.4)	6 (1.6)	277	265 (96.4)	10 (3.6)
NCI Brain Tumor Study (Ref. 10)	Case–control, USA (AZ, MA, PA)	385	377 (99.2)	3 (0.8)	322	305 (96.8)	10 (3.2)
NIOSH Upper Midwest Health Study (Ref. 13)	Case–control, USA (IA, MI, MN, WI)	540	521 (96.5)	19 (3.5)	300	285 (95.0)	15 (5.0)
PLCO (Ref. 11)	Cohort, USA (10 states[3])	855	819 (96.5)	30 (3.5)	132	127 (96.2)	5 (3.8)
Total		2,868	2,090	58	1,431	1,314	104
Age at diagnosis, mean (range)					53 (18–89)	53 (18–89)	54 (26–81)
Sex (%)							
Males, *n*		1,596 (55.6)	1,141 (54.6)	31 (53.4)	828 (57.9)	758 (57.7)	59 (56.7)
Females, *n*		1,272 (44.4)	949 (45.4)	27 (46.6)	603 (42.1)	556 (42.3)	45 (43.3)

[1]Information on family history was missing for 13 cases and 720 controls. [2]Family history was defined as having at least one first- or second-degree relative with a history of primary brain tumours. [3]AL, AZ, DC, HI, MI, MN, MO, PA, UT, WI.
Abbreviations: NCI: National Cancer Institute; NIOSH: National Institute for Occupational Safety and Health; NSHDS: Northern Sweden Health and Disease Study; PLCO: Prostate, Lung, Colorectal and Ovarian Screening Trial.

SNP, hence $p < 7.14 \times 10^{-3}$ (unadjusted) was considered statistically significant. Statistical analyses and data management were performed using the software SAS.

Ethics

Study protocols of the cohorts and case–control studies included in the present study have been approved by ethics committees local to the respective study centres.

Results

Study subjects

One thousand four hundred and thirty-one glioma cases and 2,868 control subjects were successfully genotyped (Table 1 and Supporting Information Figure 1). One hundred and four glioma cases and 58 controls reported having a first- or second-degree relative with a history of brain tumour, whereas 1,314 cases (non-FHBT-glioma) and 2,090 controls did not. For 13 cases and 720 controls family history of brain tumour was unknown. Cases were aged 18–89 years (mean age 53 years). The numbers of men/women were 828/603 (57.9/42.1%) in cases and 1,596/1,272 (55.6/44.4%) in controls, respectively (Table 1).

Genetic variation related to glioma risk

When comparing genotypes in FHBT-glioma to all controls, three SNPs were associated with risk for glioma; rs2736100 (*TERT*; OR_{trend}: 1.41; 95% CI: 1.05–1.89), rs4977756 (*CDKN2A-CDKN2B*; OR_{trend}: 1.40; 95% CI: 1.04–1.88) and rs6010620 (*RTEL1*; OR_{trend}: 0.39; 95% CI: 0.25–0.61; Table 2). After Bonferroni correction for multiple comparisons, rs6010620 (*RTEL1*) was the only marker significantly associated with risk for glioma (Bonferroni corrected p_{trend}: 1.7×10^{-4}). The risk-reducing effect of rs6010620 (*RTEL1*) was larger for FHBT-glioma than in analyses restricted to non-FHBT-glioma (OR_{trend}: 0.68; 95% CI: 0.60–0.78). In case–case comparisons, the minor (A) allele was also inversely associated with a family history of brain tumours (OR_{trend}: 0.61; 95% CI: 0.38–0.97).

Genetic variation related to glioblastoma risk

A glioblastoma diagnosis was confirmed in 57 (55%) FHBT-glioma cases (FHBT-GBM) and 689 (52%) non-FHBT-glioma cases. In analyses including FHBT-GBM and controls, OR_{trend} for rs6010620 was 0.51 (95% CI: 0.30–0.87; p_{trend}: 0.012; Table 3). None of the seven risk loci was associated with glioblastoma risk after correcting for multiple comparisons.

Discussion

In four recent genome-wide association studies, seven independent SNP markers in six genomic loci have been associated with the risk for glioma.[6–9] The present study focused on glioma cases having at least one first- or second-degree relative with a history of a brain tumour diagnosis. In analyses including FHBT-glioma cases, we found an association between three of the seven markers and risk for the disease (rs2736100 (*TERT*), rs4977756, (*CDKN2A-CDKN2B*) and rs6010620 (*RTEL1*)).

Short Report

Table 2. Risk of glioma with a family history of brain tumours (FHBT-glioma)

SNP, alleles (major/minor)	Controls/cases, *n*	MAF controls	MAF cases	OR_{het} (95% CI)[1], p[2]	OR_{hom} (95% CI)[1], p[2]	OR_{trend} (95% CI)[1], p[2]	Loci, gene
rs11979158, A/G	2,866/104	0.18	0.16	0.67 (0.41–1.09) 0.11	0.91 (0.34–2.39) 0.85	0.78 (0.53–1.15) 0.21	7p11.2, *EGFR*
rs2252586, G/A	2,868/104	0.28	0.30	1.68 (1.10–2.54) 0.01	0.74 (0.25–2.13) 0.58	1.23 (0.89–1.70) 0.20	7p11.2, *EGFR*
rs2736100, T/G	2,865/104	0.50	0.57	1.10 (0.64–1.88) 0.73	1.87 (1.06–3.30) 0.03	1.41 (1.05–1.89) 0.02	5p15.33, *TERT*
rs4295627, T/G	2,866/104	0.19	0.26	1.20 (0.78–1.85) 0.39	1.58 (0.67–3.71) 0.30	1.23 (0.87–1.72) 0.23	8q24.21, *CCDC26*
rs4977756, A/G	2,865/103	0.43	0.55	2.01 (1.15–3.52) 0.01	2.10 (1.11–3.95) 0.02	1.40 (1.04–1.88) 0.02	9p21.3, *CDKN2A-CDKN2B*
rs498872, C/T	2,866/104	0.31	0.33	0.93 (0.60–1.44) 0.74	1.31 (0.68–2.51) 0.41	1.07 (0.78–1.46) 0.66	11q23.3, *PHLDB1*
rs6010620, G/A	2,868/104	0.24	0.12	0.43 (0.26–0.70) 6.5×10^{-4}	0.09 (0.01–0.66) 0.02	0.39 (0.25–0.61) 2.4×10^{-5}	20q13.33, *RTEL1*

Odds ratios for heterozygote and homozygote rare genotypes *vs.* the homozygote common allele.
[1]Unconditional logistic regression model adjusted for age (<45 years; 45–64 years; >65 years), sex and study (Gliogene/NSHDS; Interphone; NCI Brain tumor study; NIOSH Upper Midwest Health Study; PLCO). [2]Wald test.
Abbreviations: MAF: minor allele frequency; OR_{het}: odds ratio of heterozygote *vs.* common homozygote genotype; OR_{hom}: odds ratio of rare homozygote *vs.* common homozygote genotype; OR_{trend}: odds ratio per rare allele; SNP: single nucleotide polymorphism.

Table 3. Risk of glioblastoma with a family history of brain tumours (FHBT-GBM)

SNP, alleles (major/minor)	Controls/cases, *n*	MAF controls	MAF cases	OR_{het} (95% CI)[1], p[2]	OR_{hom} (95% CI)[1], p[2]	OR_{trend} (95% CI)[1], p[2]	Loci, gene
rs11979158, A/G	2,866/57	0.18	0.14	0.50 (0.24–1.01) 0.05	0.91 (0.26–3.09) 0.88	0.67 (0.39–1.15) 0.14	7p11.2, *EGFR*
rs2252586, G/A	2,868/57	0.28	0.29	1.41 (0.81–2.46) 0.22	0.99 (0.29–3.36) 0.98	1.19 (0.77–1.82) 0.43	7p11.2, *EGFR*
rs2736100, T/G	2,865/57	0.50	0.56	0.89 (0.44–1.79) 0.75	1.67 (0.81–3.43) 0.16	1.34 (0.91–1.98) 0.14	5p15.33, *TERT*
rs4295627, T/G	2,866/57	0.19	0.22	1.20 (0.69–2.09) 0.52	0.43 (0.05–3.22) 0.41	1.00 (0.62–1.61) 0.99	8q24.21, *CCDC26*
rs4977756, A/G	2,865/56	0.43	0.53	2.21 (1.04–4.67) 0.04	1.75 (0.71–4.24) 0.22	1.28 (0.86–1.89) 0.21	9p21.3, *CDKN2A-CDKN2B*
rs498872, C/T	2,866/57	0.31	0.28	0.78 (0.44–1.38) 0.39	0.81 (0.30–2.14) 0.67	0.85 (0.55–1.30) 0.44	11q23.3, *PHLDB1*
rs6010620, G/A	2,868/57	0.24	0.15	0.56 (0.30–1.04) 0.06	0.17 (0.02–1.29) 0.09	0.51 (0.30–0.87) 0.01	20q13.33, *RTEL1*

Odds ratios for heterozygote and homozygote rare genotypes *vs.* the homozygote common allele.
[1]Unconditional logistic regression model adjusted for age (<45 years; 45–64 years; >65 years), sex and study (Gliogene/NSHDS; Interphone; NCI Brain tumor study; NIOSH Upper Midwest Health Study; PLCO). [2]Wald test.
Abbreviations: MAF: minor allele frequency; OR_{het}: odds ratio of heterozygote *vs.* common homozygote genotype; OR_{hom}: odds ratio of rare homozygote *vs.* common homozygote genotype; OR_{trend}: odds ratio per rare allele; SNP: single nucleotide polymorphism.

Short Report

The evidence for an association between genetic variation and heritable disease was strongest for SNP rs6010620, located on chromosome 20q13.33 within the region of the *RTEL1* gene. An association between this SNP and risk of glioma regardless of family history has been previously shown.[6–9,15] Hence, we propose that the chromosomal area harbouring *RTEL1*, a gene essential for telomere maintenance and the regulation of homologous recombination[16] is involved in glioma aetiology in the familial as well as sporadic setting. There was some indication that, in analyses of FHBT-glioma cases, the risk reducing effect of rs6010620 (*RTEL1*) was larger than in analyses restricted to non-FHBT-glioma, and in previous studies of glioma regardless of family history of brain tumours.[6–9] However, we cannot rule out that this variation could be due to chance given the low statistical power in the analyses restricted to FHBT-glioma cases.

In several large GWASs, rs2736100 (*TERT*) and rs4977756 (*CDKN2A-CDKN2B*) have been conclusively associated with glioma risk.[6–9] An association between these SNPs and glioma risk was also found in the present study focusing on FHBT-glioma cases, which was however not statistically significant after adjusting for multiple comparisons. Previous studies investigating familial glioma have found linkage at chromosomes 17q12-21.32 and 15q23-26.3 but not for the chromosomal regions identified by GWASs.[17–19]

Previous studies have indicated that some risk loci are associated with risk of higher rather than lower grade disease.[15,20,21] In the present study, none of the seven risk loci were statistically significantly associated with FHBT-GBM after Bonferroni correction for multiple comparisons. However, our analysis was based on only 57 FHBT-GBM cases.

Despite our access to a large number of glioma samples in five different studies, the number of FHBT-glioma cases was limited, thereby reducing the power of the present study. Only one loci, rs6010620 (*RTEL1*) remained associated with FHBT-glioma after adjustment for multiple comparisons. The lack of significant findings in the other SNPs, may be due to the low power of this study, and analysis of independent datasets is necessary to confirm our findings. Notably, the functional importance of *RTEL1* and *TERT* (both being telomere-associated genes) and *CDKN2A-CDKN2B* (encoding the tumour suppressors p16 and p14) increases the likelihood of a true association.

Our study is limited by the fact that family history of brain tumours was largely self-reported, and was validated only in a subset of cases. It is thus possible that some of the reported family history may actually be secondary, rather than primary, brain tumours, or other conditions not originally intended by the study design. Additionally, there is a possibility of recall bias in the case–control studies. Despite these limitations, this is the first large study to our knowledge to examine the established glioma risk loci in individuals with a family history of brain tumours. Our findings that the magnitude of odds ratio for rs6010620 (*RTEL1*) was more pronounced in FHBT-glioma cases compared to non-FHBT glioma cases need confirmation in larger studies with information on family history of brain tumours.

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Short Report