Cancer Prone Disease Section

Review

Familial glioma

Riccardo Bazzoni, Angela Bentivegna

School of Medicine and Surgery, University of Milan-Bicocca, via Cadore, Monza, Italy (RB, AB); 2 NeuroMI, Milan center of Neuroscience, University of Milan-Bicocca, Dept. of Neurology and Neuroscience, San Gerardo Hospital, via Pergolesi, Monza, Italy (AB). r.bazzoni@campus.unimib.it; angela.bentivegna@unimib.it

Published in Atlas Database: September 2018

Online updated version: http://AtlasGeneticsOncology.org/Kprones/FamilialGliomaID10123.html

Printable original version: http://documents.revue.is/BitStream/Handle/2042/70461/09-2018-FamilialGliomaID10123.pdf

DOI: 10.4267/2042/70461

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.

© 2019 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Abstract

Glioma is the most common brain tumor, characterized by several histological and malignancy grade. The majority of gliomas are sporadic, but some familial cases have been reported (<5%). Despite hereditary predisposition to gliomas has been associated to rare inherited cancer syndromes, such as Li-Fraumeni and Turcot's syndromes, neurofibromatosis and tuberous sclerosis, not all familial gliomas can be explained by these syndromes. Most familial gliomas seem to be characterized by cluster of two cases, suggesting the involvement of low penetrance factor risks. Moreover, no sex-linked disorders or SNPs on the X chromosome have been associated with increased glioma risk, except for ATRX gene, whose loss-of-function has been observed in 20% of adult oligodendrogliomas and in 80% of grade 2 and 3 astrocytomas. Finally, the risk to inherit tumors such as glioma could also be related to combinations of multiple risk variants: besides GWAS analysis identified many SNPs involved in familial gliomas at 5p15.33 (TERT), 7p11.2 (EGFR), 8q24.21 (CCDC26), 9p21.3 (CDKN2A/CDKN2B), 11q23.3 (PHLDB1) and 20q13.33 (RTEL1), mutation could be associated with the risk of glioma ns in POT1 gene and rare variants in SPAG9 and RUNDC1 genes could be associated with the risk of glioma.

Keywords
Familial glioma, glioma

Identity

Note
Primary central nervous system (CNS) tumors can be divided into gliomas and non-gliomas. For the more recent classification of gliomas (2016 WHO classification), see Table 1.

Clinics

Note
Gliomas represent 30% of all brain and central nervous system (CNS) tumors and 80% of all malignant brain tumors. The most common and malignant glioma is glioblastoma multiforme (GBM) (Goodenberger and Jenkins, 2012). Although there are several histologic types of gliomas, the incidence rates for all sporadic gliomas range from 4.67 to 5.73 per 100,000 persons (Barbagallo et al., 2016). Gliomas are more common in men than in women and in white rather than in black population (Ostrom et al., 2013). Anyway, familial glioma cases are similar to sporadic ones in terms of gender distribution, age, morphology and grade as shown in Table 2 (results from Gliogene Consortium https://www.bcm.edu/centers/cancer-center/research/gliogene/) (Sadetzki et al., 2013).

Neoplastic risk

ENVIRONMENTAL: Some epidemiologic risk factors might lead to development of glioma such as therapeutic ionizing radiation, pesticides, smoking, petroleum refining or production work and employment in synthetic rubber manufacturing
Familial glioma

Bazzoni R., Bentivegna A

Atlas Genet Cytogenet Oncol Haematol. 2019; 23(6)

160

(Alifieris and Trafalis, 2015). An inverse association between glioma incidence and allergies, atopic diseases and systemic infections has been reported by multiple groups (Goodenberger and Jenkins, 2012).

FAMILIARITY: Excluding those gliomas known to be due to rare hereditary cancer syndromes such as Turcot’s and Li-Fraumeni syndromes as well as neurofibromatosis (NF1, NF2) or tuberous sclerosis (Melin et al., 2017), there is evidence that gliomas cluster in families. Most familial gliomas appear to comprise clusters of two cases, suggesting low penetrance and a low risk of developing additional gliomas (Sadetzki et al., 2013). It is currently thought that approximately 5-10% of patients have a family history of glioma (Lindor et al., 2008, Robertson et al., 2010). An increased risk of developing primary brain tumors among first-degree relatives of patients with gliomas has been shown (Robertson et al., 2010), and there is a greater risk for first-degree relatives of probands with a younger age of onset than for first-degree relatives of probands with later onset (Malmer et al., 2003, Blumenthal and Cannon-Albright, 2008), as shown in Table 3.

| Glioma entity | WHO Grade |
|---------------|-----------|
| Diffuse astrocytoma, IDH-mutant | II |
| Gemistocytic astrocytoma, IDH-mutant | II |
| Diffuse astrocytoma, IDH-wildtype | II |
| Diffuse astrocytoma, NOS | II |
| Anaplastic astrocytoma, IDH-mutant | III |
| Anaplastic astrocytoma, IDH-wildtype | III |
| Anaplastic astrocytoma, NOS | III |
| Glioblastoma, IDH-wildtype | IV |
| Giant cell glioblastoma | IV |
| Gliosarcoma | IV |
| - Epithelioid glioblastoma | IV |
| Glioblastoma, IDH-mutant | IV |
| Glioblastoma, NOS | IV |
| Diffuse midline glioma, H3K27M-mutant | IV |
| Oligodendroglioma, IDH-mutant and 1p/19q-codeleted | II |
| Oligodendroglioma, NOS | II |
| Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted | III |
| Anaplastic oligodendroglioma, NOS | III |
| Oligoastrocytoma, NOS | II |
| Anaplastic oligoastrocytoma, NOS | III |
| Pilocytic astrocytoma | I |
| Pilomyxoid astrocytoma | II |
| Subependymal giant cell astrocytoma | I |
| Pleomorphic xanthoastrocytoma | II |
| Anaplastic pleomorphic xanthoastrocytoma | III |
| Subependymoma | I |
| Myxopapillary ependymoma | I |
| Ependymoma | II |
| - Papillary ependymoma | II |
| - Clear cell ependymoma | II |
| - Tanyctic ependymoma | II |
| Ependymoma, RELA fusion-positive | II or III |
| Anaplastic ependymoma | III |
| Angiocentric glioma | I |
| Chordoid glioma of third ventricle | II |
| Astroblastoma | Low/high grade |

Table 1.
Familial glioma

Bazzoni R., Bentivegna A

Atlas Genet Cytogenet Oncol Haematol. 2019; 23(6)

Table 2

Distribution of glioma cases by date of diagnosis* and selected demographic and clinical characteristics.

*When the glioma in the proband was diagnosed from 2007 all gliomas in the family were included in the incident cases column; when the glioma in the proband was diagnosed before 2007 all gliomas in the family were included in the prevalent cases column; **Excluding three cases with unknown age at diagnosis; comparison between mean age at diagnosis of incident and prevalent p = 0.003; ***p-value = 0.00009 (total incidents versus prevalent); ****For 92 cases of the 831 verified tumours, tumour histological behavior was unknown, and for 58 cases of the 481 verified tumours from the total incident cases, tumour histological behavior was unknown; *****For grades I-II p-value = 0.3 (total incident versus total prevalent). [Modified from Sadetzki et al., 2013]

Clinics

Gliomas represent 30% of all brain and central nervous system (CNS) tumors and 80% of all malignant brain tumors. The most common and malignant glioma is glioblastoma multiforme (GBM) (Goodenberger and Jenkins, 2012). Although there are several histologic types of gliomas, the incidence rates for all sporadic gliomas range from 4.67 to 5.73 per 100,000 persons (Barbagallo et al., 2016). Gliomas are more common in men than in women and in white rather than in black population (Ostrom et al., 2013). Anyway, familial glioma cases are similar to sporadic ones in terms of gender distribution, age, morphology and grade as shown in Table 2 (results from Gliogene Consortium https://www.bcm.edu/centers/cancer-center/research/gliogene/) (Sadetzki et al., 2013).

Neoplastic risk

ENVIRONMENTAL: Some epidemiologic risk factors might lead to development of glioma such as therapeutic ionizing radiation, pesticides, smoking, petroleum refining or production work and employment in synthetic rubber manufacturing (Alifieris and Trafalis, 2015). An inverse association between glioma incidence and allergies, atopic diseases and systemic infections has been reported by multiple groups (Goodenberger and Jenkins, 2012).

FAMILIARITY: Excluding those gliomas known to be due to rare hereditary cancer syndromes such as Turcot’s and Li-Fraumeni syndromes as well as neurofibromatosis (NF1, NF2) or tuberous sclerosis (Melin et al., 2017), there is evidence that gliomas cluster in families. Most familial gliomas appear to
comprise clusters of two cases, suggesting low penetrance and a low risk of developing additional gliomas (Sadetzki et al., 2013). It is currently thought that approximately 5-10% of patients have a family history of glioma (Lindor et al., 2008, Robertson et al., 2010). An increased risk of developing primary brain tumors among first-degree relatives of patients with gliomas has been shown (Robertson et al., 2010), and there is a greater risk for first-degree relatives of probands with a younger age of onset than for first-degree relatives of probands with later onset (Malmer et al., 2003, Blumenthal and Cannon-Albright, 2008), as shown in Table 3.

Anyway, the third-degree relative risks were not significantly elevated for astrocytoma, GBM or for the two types combined (Blumenthal and Cannon-Albright, 2008). However, familial aggregation of cancer can indicate a genetic etiology but may also indicate shared familial environmental exposures. Unfortunately, a multifactorial inheritance model could not be clearly rejected (Table 4) (de Andrade et al., 2001, Malmer et al., 2001, Shete et al., 2011). The variation in inherited risk of glioma could be related to combinations of multiple risk variants. Here, we reported the most significant variants (SNPs) figured out from GWASs (Table 5 and 6).

### Table 3 - Relative risks (RR) for brain tumor among: first-degree relatives of patients (A), second-degree relatives of patients (B), first-degree relatives of patients with early onset brain tumor (C). [Modified from Blumenthal and Cannon-Albright, 2008].

| Cancer in proband | Cancer in relative | No. relatives | Observed | Expected | RR | p Value |
|-------------------|--------------------|---------------|----------|----------|----|---------|
| **A**
| Astrocytoma/GBM   | Astrocytoma/GBM   | 11,498       | 38       | 11.6     | 3.29 | <0.00001 |
| Astrocytoma       | Astrocytoma       | 5,637        | 10       | 2.5      | 3.82 | 0.0004   |
| GBM               | GBM               | 5,939        | 8        | 3.5      | 2.29 | 0.026    |
| **B**
| Astrocytoma/GBM   | Astrocytoma/GBM   | 36,650       | 31       | 25.3     | 1.22 | 0.15     |
| Astrocytoma       | Astrocytoma       | 17,163       | 12       | 6.3      | 1.91 | 0.03     |
| GBM               | GBM               | 19,940       | 8        | 6.3      | 1.32 | 0.30     |
| **C**
| Astrocytoma/GBM <20y (n=214) | Astrocytoma/GBM | 1,059 | 4 | 0.6 | 6.44 | 0.004 |
| Astrocytoma <15y (n=161) | Astrocytoma | 801 | 3 | 0.3 | 9.65 | 0.004 |
| GBM <55y (n=187) | GBM               | 1,470        | 0        | 0.7      | -    | -        |

### Table 4 - Epidemiologic studies in families with gliomas and other tumors. *Utah Population Data Base; RR=risk relative; CI=confidential interval; SIR=standardized incidence ratio; FDR=first-relative degree [Modified from Kyritsis et al., 2010].

| Observed Cancers | Patients Numbers | Relatives Numbers | Etiology of Familial Cancers | Studies |
|------------------|------------------|-------------------|-----------------------------|---------|
| Clustering of multiple cancers in relatives of glioma patients. | 639 (under age 65 years) | 508 first degree 3810 second degree 1278 | Multigenic action (unknown environmental exposure) | de Andrade et al. (2001) |
| SIR 5.08 (FDRs, 45 years) melanoma, brain tumors, sarcoma; SIR 0.95 (FDRs, 45 years). | 1476 (under age 75 years) | 6746 (all first degree) | Unknown similar genetic contribution | Scheerer et al. (2007) |
| SIR 1.1, 95% CI 0.8-1.4 for all cancers (melanoma SIR 4.0, 95% CI 1.5-8.8; meningioma: SIR 5.5, 95% CI 1.1-16) | Multiple adult glioma patients in 17 Finnish families | | Unknown cancer susceptibility trait | Pisano et al. (2002) |
| RR 3.29, 95% CI 2.33-4.51; P 0.00001 | UPDM* in 1:40 primary brain tumor cases with at least 3 generations of germline data | First degree: 11 406 Second degree: 36620 | Heritable glioma risk and shared environment | Blumenthal and Cannon-Albright (2008) |

---

*Table 3 - Relative risks (RR) for brain tumor among: first-degree relatives of patients (A), second-degree relatives of patients (B), first-degree relatives of patients with early onset brain tumor (C). [Modified from Blumenthal and Cannon-Albright, 2008].

*Table 4 - Epidemiologic studies in families with gliomas and other tumors. *Utah Population Data Base; RR=risk relative; CI=confidential interval; SIR=standardized incidence ratio; FDR=first-relative degree [Modified from Kyritsis et al., 2010].
Table 5 - Heritable variants associated with glioma risk from GWASs. Data from Kinnersley et al., 2015, Kinnersley et al., 2017, Melin et al., 2017, Ostrom et al., 2014.

| Gene and/or chromosome location | SNP               | Odds Ratio | Risk Allele Frequency (controls) | Associated Glioma Subtypes | Other Association                                                                 |
|--------------------------------|-------------------|------------|----------------------------------|---------------------------|-------------------------------------------------------------------------------------|
| TERT (5p13.33)                 | rs7254100         | 1.35       | 0.34                             | All glioma subtypes        | Increases risk of cancer at other sites, including lung, testis, pancreas and colon |
| EGFR (7p11.2)                  | rs2252586, rs1979158 | 1.20       | 0.28                             | All glioma subtypes        |                                                                                     |
| CCDC26 (8q24.21)               | rs5705857         | 5.00       | 0.03                             | Oligodendroglial tumors, Ewing's tumor, astrocytic tumors                     |                                                                                     |
| CDKN2B (9p21.3)                | rs4121829, rs977756 | 1.13       | 0.41                             | Astrocytic tumors, WHO grade II-IV Glioma                                    |                                                                                     |
| PHLD1 (11q23.5)                | rs998782          | 1.50       | 0.32                             | IDH-resistant gliomas        |                                                                                     |
| TP53 (17p13.1)                 | rs8378222         | 2.70       | 0.01                             | All glioma subtypes          | Increases risk of several Li-Fraumeni tumors, including basal cell carcinoma, prostate cancer, GBM and colorectal adenoma |
| RET1 (20q13.33)                | rs6016620         | 1.40       | 0.75                             | All glioma subtypes          |                                                                                     |
| ZFEB1 (11q24.2)                | rs180091         | 1.20       | 0.22                             | All glioma subtypes          |                                                                                     |
| LPL1.3                          | rs72552552        | 1.18       | 0.87                             | All glioma subtypes          |                                                                                     |
| LPL2.1                          | rs2452707         | 1.12       | 0.22                             | All glioma subtypes          |                                                                                     |
| LPL4                            | rs1206373         | 1.09       | 0.54                             | All glioma subtypes          |                                                                                     |
| LPL3                            | rs7572265         | 1.11       | 0.76                             | All glioma subtypes          |                                                                                     |
| LPL4.1                          | rs1706832         | 1.08       | 0.86                             | All glioma subtypes          |                                                                                     |
| 10q24.3                         | rs1598018         | 1.10       | 0.36                             | All glioma subtypes          |                                                                                     |
| 11q24.1                         | rs12233250         | 1.14       | 0.77                             | All glioma subtypes          |                                                                                     |
| 11q21                           | rs1307785         | 1.03       | 0.48                             | All glioma subtypes          |                                                                                     |
| 14q12                           | rs3121052         | 1.17       | 0.72                             | All glioma subtypes          |                                                                                     |
| 14p13.3                         | rs502152, rs7316667 | 1.09       | 0.85                             | All glioma subtypes          |                                                                                     |
| 16q2.1                          | rs15982606        | 1.14       | 0.71                             | All glioma subtypes          |                                                                                     |
| 2q13.1                          | rs2235573         | 1.09       | 0.51                             | All glioma subtypes          |                                                                                     |
| VIIA1 (10q25.2)                | rs11169667        | 0.89       | 0.92                             | All glioma subtypes          |                                                                                     |
| ZBTB46 (11q23.5)                | rs640044          | 1.10       | 0.51                             | All glioma subtypes          |                                                                                     |
| Intersect (12q21.2)             | rs112240122        | 0.88       | 0.97                             | All glioma subtypes          |                                                                                     |
| POLD1 (12q23.3)                | rs1035634         | 0.87       | 0.87                             | All glioma subtypes          |                                                                                     |

Table 6 - Representative recent studies describing genetic polymorphism linked to glioma risk. OD= odd ratio [Modified from Kyritsis et al., 2010]

| Type of polymorphism | Genetic Locus | Glioma risk | Studies |
|----------------------|---------------|-------------|---------|
| 2013 glioma cases, 316 controls, 1127 SNPs, and 280 protective functional SNPs on 186 DNA repair genes | rs243356 (鲟鱼 3 CHAF1A gene) | OR: 1.32 | Barlocco et al. (2008) |
| 237 cases, 371 controls IL-6, IL-13, CyclinD/gene-2 | rs1003015, rs612735 (T-G, IL-6 Rha haplotype) | OR: 2.16 | Schmiech et al. (2007) |
| 466 cases and 541 controls IL-4 and IL-13 polymorphisms | A IL-4 haplotype, borderline increased risk A non IL-4 haplotype, decreased risk A carriage IL-13 haplotype, decreased risk OR: 1.5 | Wang et al. (2006) |
| 2014 glioma cases, 3131 controls, MTHFR C677T, and A1298C, MTRR A4900, and MTR A2756 polymorphisms | MTHFR C677T, A1298C, diplotypes | OR: 1.78 | Wang et al. (2006) |
| 771 glioma patients, 752 controls, 894 and XCHCC4 SNPs | Single locus: variant LIG4 SNP rs1887397 T>C, increased risk LIG4 SNP on XCHCC4 G>T, TTRX4 SNP2 rs143361104 C>G, T, CO25 A1506 T34 G>C, T versus than additive associated risk OR: 2.16 | Wang et al. (2006) |
| 773 Caucasians glioma patients, 335 Caucasians controls, XCHCC4, XCHCC1, APEX1, PARP1, MMET, LIG1, 8 SNPs, | MTHFR C1754T, XCHCC4 rs195962, APEX1 rs714037, PARP1 A674T, MMET rs44, and LIG1 rs3446120, increased glioma risk; MMET F4L, main risk factor. MMET F4L, plus PARP1 A674V, dramatic increased glioma risk OR: 1.33 | Li et al. (2009) |
| 771 glioma cases, 1560 controls, XCHCC1 and XCHCC3 SNPs, | Single SNP, increased risk, SNP combinations, homozygous genotypes, XCHCC1 G19906A and XCHCC3 5631H515, 3-4 fold glioma risk OR: 1.18 | Li et al. (2009) |
| 2001 cases, 1011 controls, CASP3 D202H polymorphism, | CASP3, A202H increased risk OR: 1.37 | Barlocco et al. (2008) |
| 2001 cases, 1011 controls, CASP3 D202H polymorphism | CASP3, A202H increased risk OR: 1.37 | Barlocco et al. (2008) |
| 2001 cases, 1011 controls, CASP3 D202H polymorphism | CASP3, A202H increased risk OR: 1.37 | Barlocco et al. (2008) |
| 2001 cases, 1011 controls, CASP3 D202H polymorphism | CASP3, A202H increased risk OR: 1.37 | Barlocco et al. (2008) |
| 2001 cases, 1011 controls, CASP3 D202H polymorphism | CASP3, A202H increased risk OR: 1.37 | Barlocco et al. (2008) |
| 2001 cases, 1011 controls, CASP3 D202H polymorphism | CASP3, A202H increased risk OR: 1.37 | Barlocco et al. (2008) |
A particular attention goes to POT1 gene, which belongs to the telomere-shelterin complex. Indeed, Bainbridge et al. found two different mutations in POT1 in two families (A and B) (Bainbridge et al., 2015). In family A, six individuals had POT1 mutation (NM_015450:p.G95C, HG19:chr7:g.124503667C>A), of whom three developed glioma. In family B, also six individuals had POT1 mutation (NM_015450:p.E450X, HG19:chr7:g.124481048C>A) and two developed glioma. Moreover, they identified, in a third family (C), a third protein-changing mutation (NM_015450:p.D617Efs*8, HG19:chr7:g.12446068TTA>T). In families with POT1 mutations, they reported that the affected members suffered from oligodendroglioma, which is substantially sensitive to irradiation. Anyway, the association between familial glioma and POT1 mutations still needs to be validated.

Jalali et al. figured out that MYO19 and KIF18B genes and rare variants in SPAG9 and RUNDC1 are potentially involved in familial gliomas (Jalali et al., 2015).

**MENDELIAN CANCER SYNDROMES:** A heritable genetic contribution to gliomagenesis was initially suggested by the increased incidence of these tumors in families with Mendelian cancer syndromes (Table 7). Although numerous familial cancer syndromes are associated with increased glioma risk, monogenic Mendelian disorders account for only a small proportion of adult glioma incidence at the population level (Ostrom et al., 2014). However, germline mutations of PTEN, TP53, CDKN2A, p16(INK4A)/p14(ARF), and CDK4 are not common events in familial glioma, but occasionally they may account for a subset of familial glioma cases (Tachibana et al., 2000). Several syndromes are associated to pediatric gliomas. To date, no sex-linked disorders have been associated with increased glioma risk, nor has any SNP on the X chromosome been identified as a glioma risk factor in previous genome-wide association studies. However, somatic loss-of-function mutations in the X chromosome gene Alpha thalassemia/mental retardation syndrome X-linked (ATRX) have been observed in 20% of adult oligodendroglioma tumors and in 80% of grade 2 and 3 astrocytomas (Osorio et al., 2015).

**Treatment**
Multimodal therapies including surgical resection, radio- and chemotherapy (Bush et al., 2017).

**Evolution**
The lower-grade gliomas can evolve towards higher-grade ones.

**Prognosis**
Except for pilocytic astrocytomas ID: 5773, the median survival of glioma patients is still poor (12-14 months). The 5-years survival of GBM patients is <10%, with a final mortality rate of close to 100% (Roy et al., 2015).

**Cytogenetics**

Note
Here, we reported the most karyotype abnormalities associated with familial gliomas found in literature (Table 8).

**Genes involved and proteins**

Note
Many SNPs could be associated with the risk of glioma at 5p15.33 ( TERT), 7p11.2 ( EGFR), 8q24.21 ( CCDC26), 9p21.3 (CDKN2A/CDKN2B), 11q23.3 (PHLDB1) and 20q13.33 (RTEL1), mutations in POT1 gene, MYO19 and KIF18B genes and rare variants in SPAG9 and RUNDC1 genes could be associated with the risk of glioma. PTEN, TP53, CDKN2A, and CDK4 are not common events in familial glioma.

Table 7 - Known germline gene mutations associated with increased risk of glioma. Data from Ostrom et al., 2014, Kyritsis et al., 2010.
Table 8 - Summary of karyotype abnormalities associated with familial gliomas found in literature.

| Patient | Relationship | Karyotype abnormalities | Note |
|---------|--------------|-------------------------|------|
| Patient 1 | Fourth proband of family | Tumor karyotype: 46, XX, +46, XX, -4, +p15/del(16), X chromosome from peripheral blood lymphocytes was normal, 46, XX | Both patients presented GBM. Familial history showed no genetic syndromes or cancers. Authors suggested some possible agents in environment to which the siblings were exposed, causing the formation of their tumors. |
| Patient 2 | Siblings | Involvement of the CTS8 gene, its expression, and methylation changes. | Familial glioma cases with CTS8 gene expression changes have been reported. |

References

Alifieris C, Trafalis DT. Glioblastoma multiforme: Pathogenesis and treatment. Pharmacol Ther. 2015 Aug;152:63-82.

Arruda WO, Clemente RS, Ramina R, Pedrozo AA, Pilotto RF, Pinto Júnior W, Bleggi-Lopes LF, Familial glioblastoma. Arq Neuropsiquiatr. 1995 Jun;53(2):312-7.

Bainbridge MN, Armstrong GN, Gramatges MM, Bertuch AA, Jhangiani SN, Doddapaneni H, Lewis L, Tombrello J, Tsavachidis S, Liu Y, Jalali A, Plon SE, Lau CC, Parsons DW, Claus EB, Barnholtz-Sloan J, Ilyasova D, Schildkraut J, Ali-Osman F, Sadetzki S, Johansen C, Houlston RS, Jenkins RB, Lachance D, Olson SH, Bernstein JL, Merrell RT, Wrensch MR, Walsh KM, Davis FG, Lai R, Shete S, Aldape K, Amos CI, Thompson PA, Muzny DM, Gibbs RA, Melin BS, Bondy ML. Germline mutations in shelterin complex genes are associated with familial glioma. J Natl Cancer Inst. 2015 Jan;107(1):384.

Bethke L, Sullivant K, Webb E, Murray A, Schoemaker M, Auvine A, Kriu A, Salminen T, Johansen C, Christensen HC, Muir K, McKinney P, Heworth S, Dimitropoulos P, Lophatananon A, Feychting M, Lönns A, Ahlborn A, Halonen R, Henriksson R, Shete S, Aldape K, Amos CI, Thompson PA, Muzny DM, Gibbs RA, Melin BS, Bondy ML. Germline mutations in shelterin complex genes are associated with familial glioma. Cancer Epidemiol Biomarkers Prev. 2008 Apr;17(4):967-9.

Bethke L, Webb E, Murray A, Schoemaker M, Feychting M, Lönns A, Ahlborn A, Halonen R, Henriksson R, Shete S, Aldape K, Amos CI, Thompson PA, Muzny DM, Gibbs RA, Melin BS, Bondy ML. Functional Polymorphisms in Folate Metabolism Genes Influence the Risk of Meningioma and Glioma. Cancer Epidemiology Biomarkers & Prevention 2008; 17:1195-1202.

Blumenthal DT, Cannon-Albright LA. Familiarity in brain tumors. Neurology 2008; 71:1015-1020.

Bush NA, Chang SM, Berger MS.. Current and future strategies for treatment of glioma. Neurosurgical review 2017; 40:1-14.

Dirven CM, Tuerlings J, Molenaar WM, Go KG, Louis DN.. Glioblastoma multiforme in four siblings: a cytogenetic and molecular genetic study. Journal of neuro-oncology 1995; 24:251-258.

Duhaime AC, Bunin G, Sutton L, Rorke LB, Packer RJ.. Simultaneous presentation of glioblastoma multiforme in siblings two and five years old: case report. Neurosurgery 1989; 24:434-439.

Goodenberger ML, Jenkins RB.. Genetics of adult glioma. Cancer genetics 2012; 205:613-621.

Jalali A, Amirian ES, Bainbridge MN, Armstrong GN, Liu Y, Tsavachidis S, Jhangiani SN, Plon SE, Lau CC, Claus EB, Barnholtz-Sloan JS, Ilyasova D, Schildkraut J, Ali-Osman F, Sadetzki S, Johansen C, Houlston RS, Jenkins RB, Lachance D, Olson SH, Bernstein JL, Merrell RT, Wrensch MR, Walsh KM, Davis FG, Lai R, Shete S, Aldape K, Amos CI, Thompson PA, Muzny DM, Gibbs RA, Melin BS, Bondy ML. Targeted sequencing in chromosome 17q linkage region identifies familial glioma candidates in the Gliogene Consortium. Scientific reports 2015; 5:8278.

Kinnears B, Mitchell JS, Gousias K, Schramm J, Idbaih A, Labussière M, Marie Y, Rahimian A, Wichmann HE,
Schreiber S, Hoang-Xuan K, Delattre J-Y, Nöthen MM, Mokhtari K, Lathrop M, Bondy M, Simon M, Sanson M, Houlston RS. Quantifying the heritability of glioma using genome-wide complex trait analysis. Scientific reports 2015; 5:17267.

Kiuru A, Lindholm C, Heinavara S, Ilus T, Jokinen P, Haapasalo H, Salminen T, Christensen HC, Feychtling M, Johansen C, Lonn S, Malmer B, Schoemaker MJ, Swedlow AJ, Auvinen A.. XRCC1 and XRCC3 variants and risk of glioma and meningioma. Journal of neuro- oncology 2008; 88:135-142.

Kyritsis AP, Bondy ML, Rao JS, Sioka C. Inherited predisposition to glioma. Neuro- oncology 2010; 12:104-113.

Lindor NM, McMaster ML, Lindor CJ, Greene MH, National Cancer Institute DoPCPO, Prevention Trials Research G.. Concise handbook of familial cancer susceptibility syndromes - second edition. Journal of the National Cancer Institute Monographs 2008; 1-93.

Liu Y, Scheurer ME, El-Zein R, Cao Y, Do K-A, Gilbert M, Aldape KD, Wei W, Etzel C, Bondy ML.. Association and Interactions between DNA Repair Gene Polymorphisms and Adult Glioma. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2009; 18:204-214.

Liu Y, Zhang H, Zhou K, Chen L, Xu Z, Zhong Y, Liu H, Li R, Shugart YY, Wei Q, Jin L, Huang F, Lu D, Zhou L.. Tagging SNPs in non-homologous end-joining pathway genes and risk of glioma. Carcinogenesis 2007; 28:1906-1913.

Liu Y, Zhou K, Zhang H, Shugart YY, Chen L, Xu Z, Zhong Y, Liu H, Jin L, Wei Q, Huang F, Lu D, Zhou L.. Polymorphisms in LIG4 and XRCC4 involved in the NHEJ pathway interact to modify risk of glioma. Human Mutation 2008; 29:381-389.

Lu Z, Cao Y, Wang Y, Zhang Q, Zhang X, Wang S, Li Y, Xie H, Jiao B, Zhang J.. Polymorphisms in the matrix metalloproteinase 9 (MMP-9), TIMP-1, and MMP-14 genes and susceptibility to adult astrocytoma in northern China. Journal of neuro- oncology 2007; 85:65-73.

Malmer B, Henriksson R, Grönb erg H.. Familial brain tumours: genotypes or environment? A nationwide cohort study of cancer risk in spouses and first-degree relatives of brain tumour patients. International Journal of Cancer 2003; 106:260-263.

Malmer B, Iselius L, Holmberg E, Collins A, Henriksson R, Gronberg H.. Genetic epidemiology of glioma. British journal of cancer 2001; 84:429-434.

Melin BS, Barnholtz-Sloan JS, Wrensch MR, Johansen C, Ilyasova D, Kinnung L, Ostrom QT, Lobroche K, Chen Y, Armstrong G, Liu Y, Eckel-Passow JE, Decker PA, Labussiere M, Idbaih A, Hoang-Xuan K, Di Stefano AL, Mokhtari K, Delattre JY, Broderick P, Galan P, Gousias K, Schramm J, Schoemaker MJ, Fleming SJ, Herms S, Heilmann S, Nöthen MM, Wichmann HE, Scheurer S, Swedlow A, Lathrop M, Simon M, Sanson M, Andersson U, Rajaraman P, Wang SS, Rothman N, Brown MM, Fine HA, Loeffler JS, Kharipova SH, Shete S, Linet M, Wang Z, Yeager M, Fine HA, Loeffler JS, Selker RG, Shapiro WR, Chanock SJ, Inskip PD.. Polymorphisms in Apoptosis and Cell Cycle Control Genes and Risk of Brain Tumors in Adults. Cancer Epidemiology Biomarkers & Prevention 2007; 16:1655-1661.

Ripperger T. et al.. Childhood cancer predisposition syndromes-A concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. Am J Med Genet A.; 2017; 173:1017-1037.

Robertson LB, Armstrong GN, Olver BD, Lloyd AL, Shete S, Lau C, Claus EB, Barnholtz-Sloan J, Lai R, Ilyasova D, Schildkraut J, Bernstein JL, Olson SH, Jenkins RB, Yang P, Rynnerson AL, Wrensch M, McCoy L, Wernicke JK, McCarthy B, Davis F, Vick NA, Johansen C, Boddicker H, Sadetzki S, Bruchim RB, Yechzekel GH, Andersson U, Melin BS, Bondy ML, Houlston RS.. Survey of familial glioma and role of germline p16INK4A/p14ARF and p53 mutations. Familial cancer 2010; 9:413-421.

Roy S, Lahiri D, Maji T, Biswa J.. Recurrent Glioblastoma: Where we stand. South Asian Journal of Cancer 2015; 4:163-173.

Sadetzki S, Bruchim R, Oberman B, Armstrong GN, Lau CC, Claus EB, Barnholtz-Sloan JS, Ilyasova D, Schildkraut J, Johansen C, Houlston RS, Shete S, Amos CI, Bernstein JL, Olson SH, Jenkins RB, Lachance D, Vick NA, Merrell R, Wrensch M, Davis FG, McCarthy BJ, Lai R, Melin BS, Bondy ML, Gliogene C.. Description of selected characteristics of familial glioma patients - results from the Gliogene Consortium. European journal of cancer 2013; 49:1335-1345.

Scheurer ME, Etzel CJ, Liu M, El-Zein R, Aireweare GE, Malmer B, Aldape KD, Weinberg JS, Yang WK, Bondy ML.. Aggregation of cancer in first-degree relatives of patients with glioma. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2007; 16:2491-2495.

Schwarzbaum JA, Aihbom A, Lonn S, Malmer B, Wigertz A, Auvinen A, Brookes AJ, Collatz Christensen H, Henriksson R, Johansen C, Salminen T, Schoemaker MJ, Swedlow AJ, Debinski W, Foychting M.. An international
case-control study of interleukin-4Ralpha, interleukin-13, and cyclooxygenase-2 polymorphisms and glioblastoma risk. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2007; 16:2448-2454.

Shete S, Lau CC, Houlston RS, Claus EB, Barnholtz-Sloan J, Lai R, Il'yasova D, Schildkraut J, Sadetzki S, Johansen C, Bernstein JI, Olson SH, Jenkins RB, Yang P, Vick NA, Wrensch M, Davis FG, McCarthy BJ, Leung EH-c, Davis C, Cheng R, Hosking FJ, Armstrong GN, Liu Y, Yu PK, Henriksson R, Consortium TG, Melin BS, Bondy ML.. Genome-wide high-density SNP linkage search for glioma susceptibility loci: results from the Gliogene Consortium. Cancer research 2011; 71:7568-7575.

Tachibana I, Smith JS, Sato K, Hosek SM, Kimmel DW, Jenkins RB.. Investigation of germline PTEN, p53, p16INK4A/p14ARF, and CDK4 alterations in familial glioma. American journal of medical genetics 2000; 92:136-141.

Ugonabo I, Bassily N, Beier A, Yeung JT, Hitchcock L, De Mattia F, Karim A.. Familial glioblastoma: A case report of glioblastoma in two brothers and review of literature. Surgical neurology international 2011; 2:153.

Wang LE, Bondy ML, Shen H, El-Zein R, Aldape K, Cao Y, Pudavall V, Levin VA, Yung WK, Wei Q.. Polymorphisms of DNA repair genes and risk of glioma. Cancer research 2004; 64:5560-5563.

Wiemels JL, Wiencke JK, Kelsey KT, Moghadassi M, Rice T, Urayama KY, Mike R, Wrensch M.. Allergy-related polymorphisms influence glioma status and serum IgE levels. Allergy-related polymorphisms influence glioma status and serum IgE levels. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2007; 16:1229-1235.

de Andrade M, Barnholtz JS, Amos CI, Adatto P, Spencer C, Bondy ML.. Segregation analysis of cancer in families of glioma patients. Genetic epidemiology 2001; 20:258-270.