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Review

Familial glioma

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Abstract

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 involvment 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), mutatio 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

(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 astrocytic and oligodendroglial tumors	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
Other (astrocytic) gliomas	Pilocytic astrocytoma	I
	- Pilomyxoid astrocytoma	II
	Subependymal giant cell astrocytoma	I
	Pleomorphic xanthoastrocytoma	II
	Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumors	Subependymoma	I
	Myxopapillary ependymoma	I
	Ependymoma	II
	- Papillary ependymoma	II
	- Clear cell ependymoma	II
	- Tanycytic ependymoma	II
	Ependymoma, RELA fusion-positive	II or III
	Anaplastic ependymoma	III
Other gliomas	Angiocentric glioma	I
	Chordoid glioma of third ventricle	II
	Astroblastoma	Low/high grade

Table 1.

	Total		Incident* (diagnosed from 2007)						Prevalent* (diagnosed before 2007)	
			Total		Europe & Israel		US		Total	
	n=376 families		n=219 families		n=73 families		n=146 families		n=157 families	
	n=841 gliomas		n=481 gliomas		n=159 gliomas		n=322 gliomas		n=360 gliomas	
	n	%	n	%	n	%	n	%	n	%
Gender										
Males	450	53.5	267	55.5	93	58.5	174	54	183	50.8
Females	391	46.5	214	44.5	66	14.5	148	46	177	49.2
M/F ratio (all)	1.15		1.25		1.14		1.18		1.10	
Age at diagnosis ** (n=831)										
Mean SD	49.4 18.7		51.0 19.0		51.1 16.4		50.9 20.1		47.2 18.1	
Range	1-92		1-92		4-82		1-92		1-91	
<20	59	7.0	34	7.1	4	2.5	30	9.4	25	6.9
20-39	186	22.2	96	20.1	34	21.4	62	19.4	90	25.1
40-59	316	37.7	162	33.8	62	39.0	100	31.3	154	42.9
60-69	169	20.2	116	24.2	40	25.2	76	2.8	5	14.8
70+	108	12.9	71	14.8	19	11.9	52	16.3	37	10.3
Tumor grade *** (n=739)										
I	35	4.7	20	4.7	6	4	14	5.1	15	4.7
II	165	22.5	77	18.2	36	24	41	15.0	88	27.8
III	126	17.0	70	16.5	30	20	40	14.7	56	17.7
IV	413	55.9	256	60.5	78	52	178	65.2	157	49.7
Age at diagnosis by grade *****										
Grades I-II	37.2 16.1		38.5 17.4		42.7 16.2		35.3 17.8		35.9 14.8	
Grades III-IV	54.8 16.4		55.8 16.4		55.1 14.8		56.1 17.2		53.4 16.3	
Tumor grade by gender (n=739) ****										
Grades I-II total	200	100	97	100	42	100	55	100	103	100
Males	99	49.5	44	450.4	21	50	23	41.8	55	5.4
Females	101	50.5	53	54.6	21	50	32	58.2	48	46.6
Grades III-IV total	539	100	326	100	108	100	21	100	213	100
Males	300	55.7	191	58.6	68	63	123	56.4	109	51.2
Females	239	44.3	135	41.4	40	37	95	43.6	104	48.8

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

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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)

	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	1.26	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 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].

Observed Cancers	Patients Numbers	Relatives Numbers	Etiology of Familial Cancers	Studiess
Clustering of multiple cancers in relatives of glioma patients.	639 (under age 65 years)	5088 (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)	8746 (all first degree)	Unknown similar genetic contribution	Scheurer 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	Paunu et al. (2002)
RR 3.29, 95% CI: 2.33-4.51, P 0.00001 RR 1.22, 95% CI: 0.83-1.74, P 0.15.	UPDB* in 1401 primary brain tumor cases with at least 3 generations of genealogy data	First degree: 11 498 Second degree: 36 650	Heritable glioma risk and shared environment	Blumenthal and Cannon-Albright (2008)

Table 4 - Epidemologic 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]

Gene and/or chromosome location	SNP	Odds Ratio	Risk Allele Frequency (controls)	Associated Glioma Subtype	Other Association
TERT (5p15.33)	rs2736100	1.35	0.50	All glioma subtypes	Increases risk of cancer at other sites, including lung, testis, pancreas and colon
EGFR (7p11.2)	rs2252586 rs11979158	1.20 1.25	0.28 0.83	All glioma subtypes	
CCDC26 (8q24.21)	rs55705857	5.00	0.05	Oligodendroglial tumors/IDH-mutant astrocytic tumors	
CDKN2B (9p21.3)	rs1412829 rs4977756	1.3	0.41	Astrocytic tumors, WHO grades II-IV Glioma	
PHLDB1 (11q23.3)	rs498872	1.50	0.32	IDH-mutant gliomas	
TP53 (17p13.1)	rs78378222	2.70	0.01	All glioma subtypes	Increases risk of several Li-Fraumeni tumors, including basal cell carcinoma, prostate cancer, GBM and colorectal Adenoma
RTEL1 (20q13.33)	rs6010620	1.40	0.75	All glioma subtypes	
ETFA (15q24.2)	rs180591	1.20		All glioma subtypes	
1p31.3	rs127552552	1.18	0.87	All glioma subtypes	
1q32.1	rs4252707	1.12	0.22	All glioma subtypes	
1q44	rs12076373	1.09	0.84	All glioma subtypes	
2q33.3	rs7572263	1.11	0.76	All glioma subtypes	
3p14.1	rs11706832	1.08	0.46	All glioma subtypes	
10q24.33	rs11598018	1.10	0.46	All glioma subtypes	
11q14.1	rs11233250	1.14	0.87	All glioma subtypes	
11q21	rs7107785	1.07	0.48	All glioma subtypes	
14q12	rs10131032	1.17	0.92	All glioma subtypes	
16p13.3	rs2562152 rs3751667	1.09 1.14	0.85 0.21	All glioma subtypes	
16q.12.1	rs10852606	1.14	0.71	All glioma subtypes	
22q13.1	rs2235573	1.09	0.51	All glioma subtypes	
VTI1A (10q25.2)	rs111696067	0.89		All glioma subtypes	
ZBTB16 (11q23.2)	rs648044	1.10		All glioma subtypes	
Intergenic (12q21.2)	rs12230172	0.88		All glioma subtypes	
POLR3B (12q23.3)	rs3851634	0.87		All glioma subtypes	

Table 5 - Heritable variants associated with glioma risk from GWASs. Data from Kinnersley et al., 2015, Kinnersley et al., 2015, Melin et al., 2017, Ostrom et al., 2014.

Type of polymorphism	Genetic Locus	Glioma risk	Studies
1013 glioma cases, 1016 controls, 1127 SNPs, and 388 putative functional SNPs in 136 DNA repair genes.	rs243356 (intron 3 CHAF1A gene).	OR 1.32	Bethke et al. (2008)
217 cases, 1171 controls IL-4Rα, IL-13, Cyclooxygenase-2.	rs1805015, rs1801275 (T-G IL-4Rα haplotype).	OR 2.26	Schwartzbaum et al. (2007)
456 cases and 541 controls IL-4 and IL-13 pathways.	A IL-4 haplotype, borderline increased risk A rare IL-4 haplotype, decreased risk A common IL-13 haplotype, decreased risk.	OR 1.5 OR 0.23 OR 0.73	Wiemels et al. (2007)
309 patients with newly diagnosed glioma; 342 control subjects; XRCC1, XRCC3, RAD51, XRCC7, p53.	XRCC7 G6721T (GT heterozygotes) TT genotype increased in cases.	OR 1.78 OR 1.86	Wang et al. (2004)
1005 glioma cases; 1101 controls; MTHFR C677A and A1298C, MTRR A66G, and MTR A2756G variants.	MTHFR C677T A1298C diplotypes, increased risk.	OR 1.23	Bethke et al. (2009)
771 glioma patients; 752 controls; LIG4 and XRCC4 SNPs.	Single locus: variant LIG4 SNP2 rs3093739:T > C, increased risk; 3 locus: LIG4 SNP4 rs1805388:C > T, XRCC4 SNP12 rs7734849:A > T, SNP15 rs1056503:G > T; more than additive increased risk P = .001		Liu et al. (2008)
373 Caucasian glioma patients; 365 Caucasian controls; ERCC1, XRCC1, APEX1, PARP1, MGMT, LIG1, SNPs.	6 SNPs (ERCC1 3'UTR, XRCC1 R399Q, APEX1 E148D, PARP1 A762V, MGMT F84L, and LIG1 5'UTR) increased glioma risk; MGMT F84L, main risk factor; MGMT F84L plus PARP1 A762V, dramatic increase glioma risk.	OR 5.95	Liu et al. (2009)
701 glioma cases; 1560 controls; XRCC1 and XRCC3 SNPs.	Studied SNPs, not increased risk; SNP combinations: homozygous genotypes, XRCC1 Gln399Gln and XRCC3 Met241Met, 3-fold glioma risk.	OR 3.18	Kiuru et al. (2008)
1005 cases; 1011 controls; CASP8 D302H polymorphism.	Carriers, 1.37 increased risk.	OR 1.37	Bethke et al. (2008)
CASP8, CCND1, CCNH, CDKN1A, CDKN2A, CHEK1, CHEK2, MDM2, PTEN, TP53 polymorphisms.	CCND1 Ex4-1G > A and CCNH Ex8 + 49T > C variants, increased glioma risk; MDM2 Ex12 + 162A > G, reduced glioma risk.		Rajaraman et al. (2007)
236 glioma patients; 366 controls; MMP-1, MMP-3, MMP-9 polymorphisms.	MMP-1 -1607 1G/1G genotype and MMP-1 1G-MMP-3 6A haplotype may play protective role in the development of adult astrocytoma.	OR 0.45	Lu et al. (2007)
771 glioma patients; 752 healthy controls XRCC5, XRCC6, XRCC7 polymorphisms.	XRCC5 haplotype 'CAGTT,' 40% reduction in glioma risk.	OR 0.60	Liu et al. (2007)

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

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.124464068TTA>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
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.

Disorder/Syndrome (OMIM code)	Gene name (chromosome location)	Mode of inheritance	Associated gliomas
Neurofibromatosis 1 (#162200)	NF1 (17q11.2)	Dominant	Astrocytoma
Neurofibromatosis 2 (#607379)	NF2 (22q12.2)	Dominant	Ependymoma
Tuberous sclerosis(#191100; #613254)	TSC1 (9q34.14) TSC2 (16p13.3)	Dominant	Giant cell astrocytoma
Lynch syndrome/Turcot's syndrome (type 1)(#120435; #276300) constitutional mismatch repair deficiency syndrome(CMMRDS#276300)	MSH2 (2p21) MLH1 (3p22.2) MSH6 (2p16.3) PMS2 (7p22.1)	Dominant and recessive	Glioblastoma, other gliomas , childhood cancer for recessive form
Turcot's syndrome (type 2)(#175100)	APC (5q22.2)	Probably recessive	Primary brain tumor
Li-Fraumeni syndrome/Families with patients with multifocal glioma, glioma + second cancer (#137800)	TP53 (17p13.1)	Dominant	Glioblastoma, other gliomas
Melanoma-neural system tumor syndrome (#155755)	p16/CDKN2A (9p21.3)	Dominant	Glioma
Ollier disease/Maffucci syndrome (#166000;#614569)	IDH1 (2q33.3) IDH2 (15q26.1)	Acquired postzygotic mosaicism; dominant with reducedpenetrance	Glioma
Retinoblastoma (#180200)	RB1 (13q14.2)	Dominant	Glioblastoma, other gliomas
FANCD1(# 605724), GLM3(#613029)	BRCA2 (13q13.1)	Recessive	Glioma, multicentric GBM

Table 7 -| Known germline gene mutations associated with increased risk of glioma. Data from Ostrom et al., 2014, Kyritsis et al., 2010.

	Sex (age at diagnosis)	Relationship	Karyotype abnormalities	Note
Duhaime et al. (1989)	1) Female (2,5) 2) Male (5)	Siblings.	Patient 1: The stem line karyotype of the tumor showed translocation t(11;14) and was often seen in a tetraploid version of the basic karyotype (48, XX, -14, +der(11)t(11;14) (p11.2-3;q11), +marker, +marker). Chromosomes from peripheral blood lymphocytes were normal Patient 2: tumor contained normal 46, XY cell as well as cells with both numerical and structural abnormalities, even if a consistent stem line could not be discerned.	Both patients presented GBM. Family 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.
Arruda et al. (1995)	1) Female (7)	Fourth proband generation. Sister of two brothers. One of these two brothers died by brain tumor.	Tumor karyotype: 46, XX, 7q-/ 46 ,XX ,-2 ,4p- ,7p- ,+15 / 46, XX Peripheral blood lymphocytes were normal: 46, XX.	Patient presented GBM. Patient was in a family with several members having GBM or other malignant tumors in other areas (breast, larynx and colon).
Dirven et al. (1995)	1) Male (22) 2) Female (29) 3) Female (33) 4) Female (41)	Siblings.	Kayotypes from peripheral blood lymphocytes for all patients were normal. Patient 4 showed mutations in codon 220 (T-->G; exon 6) and in codon 273 (C-->T; exon 8) of TP53 in tumor cells.	Patients 1 and 2 presented glioma. Patients 3 and 4 presented GBM. No other family members in three generations were affected by malignant brain tumors.
Patel et al. (1998)	1) Male (6) 2) Male (13) 3) Male (73)	Patient 3 is the granduncle of patient 1. Patient 3 is the grandfather of patient 2	CNAs from tumor specimens: Patient 1: No detectable abnormality. Patient 2: -Y. Patient 3: +7q, -10, -13q(21-->33), -21.	Patient 1 presented an anaplastic astrocytoma. Patient 2 presented an astrocytoma. Patient 3 presented GBM. In the family, there were other three cases of GBM and of other brain tumors.
	4) Female (25) 5) Male (52)	Patient 5 is the paternal uncle of patient 4.	CNAs from tumor specimens: Patient 4: -1p, +3q(13.3-->9), -4q, +12, -15, -19q, -X Patient 5: ++7p(11.1-->12), +19.	Patient 4 presented anaplastic oligodendroglioma. Patient 5 presented GBM.
	6) Male (44) 7) Male (77)	Patient 7 is the paternal uncle of patient 6.	CNAs from tumor specimens: Patient 6: +7, -10, +12p, ++12p(11-->12), ++12q(13.2-->14), -13q(21-->33). Patient 7: ++7p(11.21), ++7p(11.1-->12), ++(21.233), -9q34, -10, -16p, -19, -22.	Both patients presented GBM.
	8) Male (68)	Patient has one first cousin with GBM and one with an astrocytoma.	CNAs from tumor specimen: Patient 8: +7, -10, 18.	Patient presented GBM.
Ugonabo et al. (2011)	1) Male (63) 2) Male (81)	Brothers.	Tumor karyotype of patient 2 revealed trisomies of 4, 8, 12, 22 and LOH of 1p, 9p, and 10.	Both patients presented GBM. Chromosomal abnormalities not found in all tumor cells.
Osorio et al. (2014)	1) Male (17) 2) Male (21)	Brothers.	Tumor karyotype: Both patients had 1p and 19q deleted.	Both patients presented oligodendroglioma.
	3) Male (55) 4) Male (59)	Brothers.	Tumor karyotype of patient 3 showed 1p and 19q deleted. Tumor karyotype of patient 4 showed 1p/19q intact.	Patient 3 presented anaplastic oligodendroglioma Patient 4 presented GBM w/oligo features.

Table 8 -| Summary of karyotype abnormalities associated with familial gliomas found in literature. = copy number alterations

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-Torres 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, Il'yasova 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, Sullivan K, Webb E, Murray A, Schoemaker M, Auvinen A, Kiuru A, Salminen T, Johansen C, Christensen HC, Muir K, McKinney P, Hepworth S, Dimitropoulou P, Lophatananon A, Feychting M, Lönn S, Ahlbom A, Malmer B, Henriksson R, Swerdlow A, Houlston R. The common D302H variant of CASP8 is associated with risk of glioma. Cancer Epidemiol Biomarkers Prev. 2008 Apr;17(4):987-9

Bethke L, Webb E, Murray A, Schoemaker M, Feychting M, Lönn S, Ahlbom A, Malmer B, Henriksson R, Auvinen A, Kiuru A, Salminen T, Johansen C, Christensen HC, Muir K, McKinney P, Hepworth S, Dimitropoulou P, Lophatananon A, Swerdlow A, Houlston R.. 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, Il'yasova D, Schildkraut J, Ali-Osman F, Sadetzki S, Johansen C, Houlston RS, Jenkins RB, Lachance D, Olson SH, Bernstein JL, Merrell RT, Wrensch MR, Davis FG, Lai R, Shete S, Aldape K, Amos CI, 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.

Kinnersley 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, Heinavaara S, Ilus T, Jokinen P, Haapasalo H, Salminen T, Christensen HC, Feychting M, Johansen C, Lonn S, Malmer B, Schoemaker MJ, Swerdlow 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 DoCPCO, 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 Q, 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 of 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-1, 3, and 9 promoters and susceptibility to adult astrocytoma in northern China. Journal of neuro-oncology 2007; 85:65-73.

Malmer B, Henriksson R, Grönberg H.. Familial brain tumoursgenetics 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, Il'yasova D, Kinnersley B, Ostrom QT, Labreche 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, Nothen MM, Wichmann HE, Schreiber S, Swerdlow A, Lathrop M, Simon M, Sanson M, Andersson U, Rajaraman P, Chanock S, Linet M, Wang Z, Yeager M, GliomaScan C, Wiencke JK, Hansen H, McCoy L, Rice T, Kosel ML, Sicotte H, Amos CI, Bernstein JL, Davis F, Lachance D, Lau C, Merrell RT, Shildkraut J, Ali-Osman F, Sadetzki S, Scheurer M, Shete S, Lai RK, Claus EB, Olson SH, Jenkins RB, Houlston RS, Bondy ML.. Genome-wide association study of glioma subtypes identifies specific differences in genetic susceptibility to glioblastoma and non-glioblastoma tumors. Nature genetics 2017.

Osorio JA, Hervey-Jumper SL, Walsh KM, Clarke JL, Butowski NA, Prados MD, Berger MS.. Familial gliomas: cases in two pairs of brothers. Journal of neuro-oncology 2015; 121:135-140.

Ostrom QT, Bauchet L, Davis FG, Deltour I, Fisher JL, Langer CE, Pekmezci M, Schwartzbaum JA, Turner MC, Walsh KM, Wrensch MR, Barnholtz-Sloan JS. The epidemiology of glioma in adults: a 'state of the science' review. Neuro-oncology 2014; 16:896-913.

Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, Stroup NE, Kruchko C, Barnholtz-Sloan JS.. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. Neuro-oncology 2013; 15 Suppl 2:ii1-56.

Patel A, van Meyel DJ, Mohapatra G, Bollen A, Wrensch M, Cairncross JG, Feuerstein BG.. Gliomas in families: chromosomal analysis by comparative genomic hybridization. Cancer genetics and cytogenetics 1998; 100:77-83.

Paunu N, Lahermo P, Onkamo P, Ollikainen V, Rantala I, Helén P, Simola KOJ, Kere J, Haapasalo H.. A Novel Low-Penetrance Locus for Familial Glioma at 15q23-q26.3. Cancer research 2002; 62:3798-3802.

Rajaraman P, Wang SS, Rothman N, Brown MM, Black PM, 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, Il'yasova D, Schildkraut J, Bernstein JL, Olson SH, Jenkins RB, Yang P, Rynearson AL, Wrensch M, McCoy L, Wienkce JK, McCarthy B, Davis F, Vick NA, Johansen C, Bodtcher H, Sadetzki S, Bruchim RB, Yechezkel GH, Andersson U, Melin BS, Bondy ML, Houlston RS.. Survey of familial glioma and role of germline p16INK4A/p14ARF and p53 mutation. Familial cancer 2010; 9:413-421

Roy S, Lahiri D, Maji T, Biswas 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, Il'yasova 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, Airewele GE, Malmer B, Aldape KD, Weinberg JS, Yung 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.

Schwartzbaum JA, Ahlbom A, Lonn S, Malmer B, Wigertz A, Auvinen A, Brookes AJ, Collatz Christensen H, Henriksson R, Johansen C, Salminen T, Schoemaker MJ, Swerdlow AJ, Debinski W, Feychting 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 JL, 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 RK, 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, Pudavalli 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, Miike 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.

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