



Familial glioblastoma: A case report of glioblastoma in two brothers and review of literature

Ifeoma Ugonabo, Nader Bassily,¹ Alexandra Beier,² Jacky T. Yeung,³ Lynette Hitchcock,⁴ Frances De Mattia,⁵ and Aftab Karim^{3*}

Department of Medicine, Oakwood Medical Center, Dearborn, MI, USA

¹Department of Pathology, McLaren Regional Medical Center, Flint, MI, USA

²Department of Neurosurgery, Providence Hospital, Southfield, MI, USA

³Department of Surgery, Michigan State University, East Lansing, MI, USA

⁴Department of Nursing, McClaren Regional Medical Center, Flint, MI, USA

⁵Department of Pathology, Providence Hospital, Southfield, MI, USA

Ifeoma Ugonabo: ify.okafor@gmail.com; Nader Bassily: bassilynader@hotmail.com; Alexandra Beier: alexandra.beier@gmail.com; Jacky T. Yeung: yeungtao@msu.edu; Lynette Hitchcock: lyhitchcock@charter.net; Frances De Mattia: fran.demattia@stjohn.org; Aftab Karim: aftabskarim@yahoo.com
*Corresponding author

Received July 7, 2011; Accepted September 22, 2011.

This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Background:

Gliomas that aggregate in families with history of malignancy may have an inheritable genetic basis. Gliomas can occur in several well known tumor syndromes. However, their occurrence in the absence of these syndromes is quite rare. High-grade gliomas, such as glioblastoma multiforme (GBM), are the most common and most lethal primary cancers of the central nervous system (CNS).

Case Description:

We present a case of two brothers both diagnosed with GBM. Both siblings underwent biopsy with debulking of the tumors by different surgeons. Only one sibling elected to undergo chemotherapy and radiation. Cytogenetic studies were possible only on one sibling and the tumor specimen revealed multiple chromosomal abnormalities, including triploidies 4, 8, 12, 22 and loss of heterozygosity of 1p, 9p, and 10. Histological samples for both tumors were similar, both revealing increased cellularity consisting of gemistocytic astrocytes, central necrosis, and microvascularization.

Conclusion:

We present two brothers who display a rare familial relationship in the development of their GBMs. Supplementary and improved genetic studies may allow for specific treatment modalities as certain genetic abnormalities have better response to tailored treatments and carry better prognoses.

Keywords: Familial glioma, genetic, loss of heterogeneity, glioblastoma

INTRODUCTION

Most cancers occur as a result of genetic mutations leading to either loss of function of tumor suppressor genes or activation of oncogenes.[2] Gliomas are known to occur in association with several well-defined hereditary tumor syndromes, such as neurofibromatosis type-1 and -2, tuberous sclerosis, Li-Fraumeni, and Turcot syndrome.[5,24] The familial occurrence of gliomas, specifically glioblastoma multiforme (GBM), in the absence of previously defined neurological tumor syndromes does occur. However, it is still a rare event.[1–3,6–8,11] GBM in two siblings is

described in this manuscript. Interestingly, virtually identical histopathology and anatomical localization were noted in these two clinical presentations.

CASE REPORT

Sibling 1 (Person F on pedigree diagram in [Figure 1](#)) was a 63-year-old Caucasian male who presented to his family physician with symptoms of dizziness, headache, and unstable gait. Along with these symptoms, the patient complained of immediate memory loss, impairment of immediate recall, as well as slurred speech for several days. He denied any symptoms of nausea, vomiting, or visual loss. The patient had only a medical history that included gastroesophageal reflux disease, diabetes mellitus, inflammatory bowel syndrome, and arthritis. Other than a slight slurring of his speech, his physical exam was without overt abnormalities. He subsequently received a magnetic resonance imaging (MRI) evaluation, which revealed a mass in the left temporal lobe approximately measuring $4.6 \times 3.6 \times 4.5$ cm. Another lesion was discovered in the left occipital lobe measuring $1.7 \times 1.5 \times 1.7$ cm [[Figure 2a](#) and [2b](#)]. Histological examination of fresh tissue revealed a malignant hypercellular astrocytoma with microvascularization, necrosis, abnormal mitoses, and bizarre nuclei [[Figure 2c](#) and [2d](#)].

Consequently, neurosurgery was consulted and two days after having presented initially with his symptoms, the patient underwent a left awake pterional craniotomy with left anterior temporal lobectomy and resection of the left mesotemporal lobe with stealth navigation as well as placement of eight gliadel wafers. He was discharged two days later with no focal deficits. A month later, the patient returned to his physician complaining of headaches, speech alteration, and right sided weakness. The night before the onset of these new symptoms, the patient again had episodes of severe headaches. MRI was performed and showed increase in size of the two previously noted lesions. The patient underwent a repeat pterional craniotomy with resection of the tumor. The patient was discharged a week later with a walker. The patient died four months later.

Sibling 2 (Person D on pedigree diagram [Figure 1](#)) was an 81-year-old Caucasian male with a history significant for colorectal cancer, prostate cancer, and malignant melanoma. The patient presented to the emergency department after several days of headache, dizziness, nausea, vomiting, and dehydration. The initial computed tomography (CT) in the emergency room revealed a brain mass. Subsequent MRI studies showed a large peripherally enhanced lesion in the right temporal lobe extending from the dural to the ventricular surface [[Figure 3a](#) and [3b](#)]. Given his extensive history with different types of malignancies, there was initial concern of metastatic disease. A few days later, the patient underwent a right stealth guided craniotomy and microsurgical debulking with microscope and the Cavitron ultrasonic surgical aspirator. Frozen sections were sent for further analysis. The remainder of the tumor was then debulked superiorly, laterally, and inferiorly. Postoperatively, there were no complications and the patient was discharged four days later. Sibling 2 refused further radiation or chemotherapy. He died a few months after surgery. Histopathological evaluation and cytogenetic analysis on specimens were performed [[Table 1](#), [Figure 3c](#) and [3d](#)].

DISCUSSION

The familial cases of GBM presented here support a genetic basis for GBM. Given the rarity of GBM in the general population and the even rarer event that it occurs within the same family, a genetic basis needs to be further studied. It has been concluded that genetic factors are involved in the initiation and progression of gliomas. However, the earlier theory that a single major gene was the sole cause has been virtually dismissed.[4,19,20] There have been several characteristic genetic alterations documented in sporadic astrocytomas, especially glioblastoma.[4,19,31] On the basis of segregation analyses in families with multiple glioma patients, autosomal recessive and multifactorial Mendelian models have been suggested.[4,18]

Familial cases of GBM are rare occurrences.[1–3,6–8,11] [Table 2](#) provides a summary of various cases reported in literature. The rarity of familial GBM cases may be due to the fact that GBM is a relatively rare tumor so the incidence of two sporadic cases occurring in the same family may be low. GBM cases, absent of any apparent syndromes, especially those involving neurophakomatoses, such as neurofibromatosis, are hard to explain in familial cases, because this kind of tumor comprises numerous genetic aberrations. A study by Rao *et al.*, focusing on genomic amplifications and deletions in 456 GBM cases identified 41 possible sites of amplifications and 45 possible

sites of deletions.[25] Similarly, the fact that not every GBM case displays the same aberrations suggest that despite the histological similarities among GBM cases, each case may be of a different molecular entity. In reported cases of familial GBMs, although there appears to be a commonality in male disposition, there exist differences in age of diagnosis, locations of tumors, multicentricity of foci, and, in those with available molecular analysis, different genetic aberrations [Table 2]. Therefore, it is reasonable to argue that although familial cases of GBM may help elucidate important mechanisms for tumorigenesis and tumor survival, the results may only shed light on subsets of GBMs.

In recent years, research has revealed some genetic abnormalities relevant to GBM, such as high frequencies of allelic deletion on chromosome 9, 10 and 17, multiple tumor suppressor genes (TSGs) (e.g. *p53*, *p15*, *p16*, *RB*, *PTEN*, *DMBT1*) and oncogenes (e.g. *EGFR*, *MDM2*) that are important for the development and progression of GBM.[13,18,28,31] Figure 4 illustrates proposed combinations of mechanisms for the tumorigenesis of GBMs.[16,23] Among them, the loss of heterogeneity (LOH) on 10q is one of the most common aberrations in primary GBM, suggesting the presence of a gene critical for GBM formation on this chromosome.[17] Furthermore, according to Ueki *et al.*, when 1p or 19q LOH was accompanied by additional 10q LOH, such tumors were most likely (86%) GBMs on consensus diagnosis.[29] Sibling 2's cytogenetics seem to support these study findings. In familial cases, one may utilize gene expression studies in addition to cytogenetic analyses to provide more information regarding the subset of GBMs as the information may be well correlated with the histopathology of the tumor.[30]

Sibling 2's tumor had many of the typical chromosomal abnormalities expected in GBM, such as losses of chromosomes 1p, 9p, and 10.[18,27] However, previously reported abnormalities such as LOH in chromosome 19 and gain of chromosome 7 were absent.[10] Less common in GBMs is the combined loss of chromosomes 1p and 19q, a combination that is prognostically favorable as they are more chemosensitive.[12,27] This combination was not present in our patient. Also, there were additional abnormalities not typically seen in GBM that occurred with this patient, such as triploidies involving chromosomes 4, 8, 12, and 22. However, it should be noted that no abnormality aforementioned was found consistently in all atypical cells. In addition, the literature indicates that genetic aberrations may have predilection for specific histological variants of GBMs as summarized in Table 3. Unfortunately, there is a lack of available literature regarding genetic aberrations in gemistocytic GBMs, which may be the case in both of the present patients.

An eighteen-year difference exists between the two brothers. Hypothetically, an interesting scenario would arise if the 81 year-old brother had died a few years earlier of another disease and examination of his brain is performed. As there is a lack of molecular information in the present cases, it is difficult to assess whether the tumors are primary or non-primary GBMs. Either case is possible, as there is no information on the tumorigenesis of the presented cases. The *TP53* and *EGFR* statuses would be useful as primary GBMs are often characterized by *EGFR* amplification and secondary GBMs by *TP53* amplifications within a certain degree of certainty.[23] If the tumors in the presented cases were secondary and evolved from lower grade gliomas, then theoretically, one should be able find pre-malignant changes in this hypothetical situation. The analysis of genes involved in angiogenesis, including *VEGF fms-related tyrosine kinase 1* and *IGFBP2*, may also help to differentiate whether the GBMs in these familial cases are *de novo*. [8] Histologically, the presence of gemistocytes in both brothers' samples warrant further molecular investigation as astrocytic tumors with greater than 5% gemistocytes have been reported to progress more rapidly to GBM and may harbor *TP53* mutations and cytogenetic abnormalities, such as chromosome 7p gains and 10q losses.[14,26,32]

Both siblings had almost identical histological findings and both tumor specimens had increased cellularity consisting of gemistocytic astrocytes, which are cells with abundant glassy deep pink cytoplasm and eccentrically placed nuclei.[15] Both had a high proliferation index of malignant cells and both patients' lesions showed areas of neovascularization, microhemorrhage, and central necrosis. It should be noted that the histological diagnosis of human gliomas is of great importance for estimating patient prognosis and guiding therapy. However, this method of diagnosis suffers from being subjective and does not distinguish the cases at the molecular level. Molecular genetic analysis could provide a more objective means to classify familial GBMs into certain subsets, reduce diagnostic variability, and provide more pertinent prognostic information for the patients.[25]

ACKNOWLEDGEMENT

We would like to thank Navnit Mitter, PhD, a geneticist from Dianon Systems, for his contribution to the analyses used in this paper. We would also like to thank the MRI Diagnostic Centers of Michigan for their help gathering the radiological information and images used in this report. Finally, we would like to thank the family members of the two cases discussed in this paper. They were not just subjects of a paper, but to their loved ones were beloved husbands, fathers, and friends.

Footnotes

Available FREE in open access from: <http://www.surgicalneurologyint.com/text.asp?2011/2/1/153/86833>

REFERENCES

1. Blumenthal DT, Cannon-Albright LA. Familiality in brain tumors. *Neurology*. 2008;71:1015–20. [PMCID: PMC2676956] [PubMed: 18809838]
2. Chemke J, Katznelson D, Zucker G. Familial glioblastoma multiforme without neurofibromatosis. *Am J Med Genet*. 1985;21:731–5. [PubMed: 2992272]
3. Daniels LB, Shaya M, Nordberg ML, Shorter CD, Fowler M, Nanda A. Glioblastoma multiforme in two non-nuclear family members. *J La State Med Soc*. 2007;159:215–22. [PubMed: 17987960]
4. De Andrade M, Barnholtz JS, Amos CI, Adatto P, Spencer C, Bondy ML. Segregation analysis of cancer in families of glioma patients. *Genet Epidemiol*. 2001;20:258–70. [PubMed: 11180451]
5. Dirven CM, Tuerlings J, Molenaar WM, Go KG, Louis DN. Glioblastoma multiforme in four siblings: A cytogenetic and molecular genetic study. *J Neurooncol*. 1995;24:251–8. [PubMed: 7595755]
6. Duhaime AC, Bunin G, Sutton L, Rorke LB, Packer RJ. Simultaneous presentation of glioblastoma in siblings two and five years old: Case report. *Neurosurgery*. 1989;24:434–9. [PubMed: 2538772]
7. Fountaine T, Lind CR, Law AJ. Primary glioblastomas and anaplastic astrocytoma in a glioma family. *J Clin Neurosci*. 2006;13:497–501. [PubMed: 16678736]
8. Godard S, Getz G, Delorenzi M, Farmer P, Kobayashi H, Desbaillets I, et al. Classification of human astrocytic gliomas on the basis of gene expression: A correlated group of genes with angiogenic activity emerges as a strong predictor of subtypes. *Cancer Res*. 2003;63:6613–25. [PubMed: 14583454]
9. Hardman PD, Bell J, Whittle IR, Gregor A. Familial glioma: A report of glioblastoma in identical twins and oligo-astrocytoma in siblings. *Br J Neurosurg*. 1989;3:709–15. [PubMed: 2697216]
10. Henn W, Blin N, Zang KD. Polysomy of chromosome 7 is correlated with overexpression of the erbB oncogene in human glioblastoma cell lines. *Hum Genet*. 1986;74:104–6. [PubMed: 3759084]
11. Heuch I, Blom GP. Glioblastoma multiforme in three family members, including a case of true multicentricity. *J Neurol*. 1986;233:142–4. [PubMed: 3014072]
12. Hill C, Hunter SB, Brat DJ. Genetic markers in glioblastoma: Prognostic significance and future therapeutic implications. *Adv Anat Pathol*. 2003;10:212–7. [PubMed: 12826827]
13. Kleihues P, Burger PC, Plate KH, Ohgaki H, Cavenee WK. Glioblastoma. In: Kleihues P, Cavenee WK, editors. *Pathology and genetics of tumors of the nervous system*. Lyon: IARC Press; 1997. pp. 16–24.
14. Kros JM, Waarsenburg N, Hayes DP, Hop WC, van Dekken H. Cytogenetic analysis of gemistocytic cells in gliomas. *J Neuropathol Exp Neurol*. 2000;59:679–86. [PubMed: 10952058]
15. Krouwer HG, Davis RL, Silver P, Prados M. Gemistocytic astrocytomas: A reappraisal. *J Neurosurg*. 1991;74:399–406. [PubMed: 1993905]
16. Lang FF, Miller DC, Koslow M, Newcomb EW. Pathways leading to glioblastoma multiforme: A molecular analysis of genetic alterations in 65 astrocytic tumors. *J Neurosurg*. 1994;81:427–36. [PubMed: 8057151]
17. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. World Health Organization classification of tumours of the central nervous system. In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, editors. Lyon: IARC Press; 2007. pp. 33–49.
18. Louis DN, Seizinger BR. Genetic basis of neurologic tumors. *Baillieres Clin Neurol*. 1994;3:335–52. [PubMed: 7952851]

19. Malmer B, Iselius L, Holmberg E, Collins A, Henriksson R, Grönberg H. Genetic epidemiology of glioma. *Br J Cancer*. 2001;84:429–34. [PMCID: PMC2363745] [PubMed: 11161412]
20. Martinez R, Esteller M. The DNA methylome of Glioblastoma multiforme. *Neurobiol Dis*. 2010;39:40–6. [PubMed: 20064612]
21. Meyer-Puttlitz B, Hayashi Y, Waha A, Rollbrocker B, Boström J, Wiestler OD, et al. Molecular genetic analysis of giant cell glioblastomas. *Am J Pathol*. 1997;151:853–7. [PMCID: PMC1857850] [PubMed: 9284834]
22. Miller CR, Duhnam CP, Scheithauer BW, Perry A. Significance of necrosis in grading of oligodendroglial neoplasms: A clinicopathologic and genetic study of newly diagnosed high-grade gliomas. *J Clin Oncol*. 2006;24:5419–26. [PubMed: 17135643]
23. Ohgaki H, Dessen P, Jourde B, Horstmann S, Nishikawa T, Di Patre PL, et al. Genetic pathways to glioblastoma: A population-based study. *Cancer Res*. 2004;64:6892–9. [PubMed: 15466178]
24. Patel A, van Meyel DJ, Mohapatra G, Bollen A, Wrensch M, Cairncross JG, et al. Gliomas in families: Chromosomal analysis by comparative genomic hybridization. *Cancer Genet Cytogenet*. 1998;100:77–83. [PubMed: 9406586]
25. Rao SK, Edwards J, Joshi AD, Siu IM, Riggins GJ. A survey of glioblastoma genomic amplifications and deletions. *J Neurooncol*. 2010;96:169–79. [PubMed: 19609742]
26. Reis RM, Hara A, Kleihues P, Ohgaki H. Genetic evidence of the neoplastic nature of gemistocytes in astrocytomas. *Acta Neuropathol*. 2001;102:422–5. [PubMed: 11699553]
27. Reis RM, Konu-Leblebicioglu D, Lopes JM, Kleihues P, Ohgaki H. Genetic profile of gliosarcomas. *Am J Pathol*. 2000;156:425–32. [PMCID: PMC1850048] [PubMed: 10666371]
28. Salvati M, Formichella AI, D'Elia A, Brogna C, Frati A, Giangaspero F, et al. Cerebral glioblastoma with oligodendroglial component: Analysis of 36 cases. *J Neurooncol*. 2009;94:129–34. [PubMed: 19343483]
29. Shete S, Hosking FJ, Robertson LB, Dobbins SE, Sanson M, Malmer B, et al. Genome-wide association study identifies five susceptibility loci for glioma. *Nat Genet*. 2009;41:899–904. [PubMed: 19578367]
30. Ueki K, Nishikawa R, Nakazato Y, Hirose T, Hirato J, Funada N, et al. Correlation of histology and molecular genetic analysis of 1p, 19q, 10q, TP53, EGFR, CDK4, and CDKN2A in 91 astrocytic and oligodendroglial tumors. *Clin Cancer Res*. 2002;8:196–201. [PubMed: 11801559]
31. Vital AL, Taberner MD, Castrillo A, Rebelo O, Tao H, Gomes F, et al. Gene expression profiles of human glioblastomas are associated with both tumor cytogenetics and histopathology. *Neuro Oncol*. 2010;12:991–1003. [PMCID: PMC2940695] [PubMed: 20484145]
32. Watanabe K, Tachibana O, Yonekawa Y, Kleihues P, Ohgaki H. Role of gemistocytes in astrocytoma progression. *Lab Invest*. 1997;76:277–84. [PubMed: 9042164]

Figures and Tables

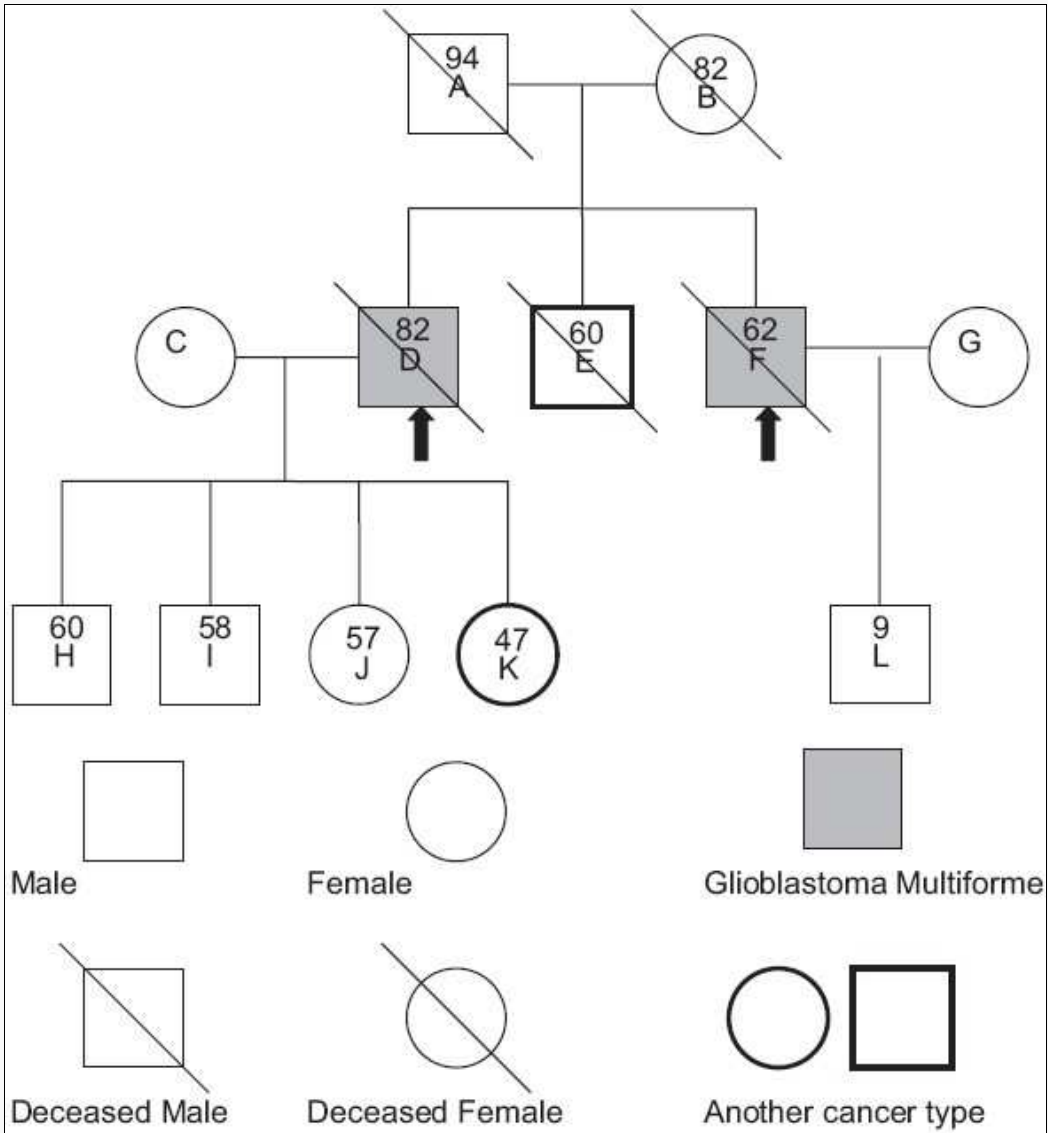


Figure 1
 Family Pedigree. Arrows refer to index patients. Causes of death for A and B—natural causes. B had been diagnosed with a benign pituitary tumor. Cause of death for D and F (Sibling 2 and 1 respectively) - Glioblastoma Multiforme. Cause of death for E - Acute Myeloid Leukemia at the age of 60. Family member K was diagnosed with colorectal cancer in 2008 at the age of 45. All other members of family in pedigree are alive and healthy

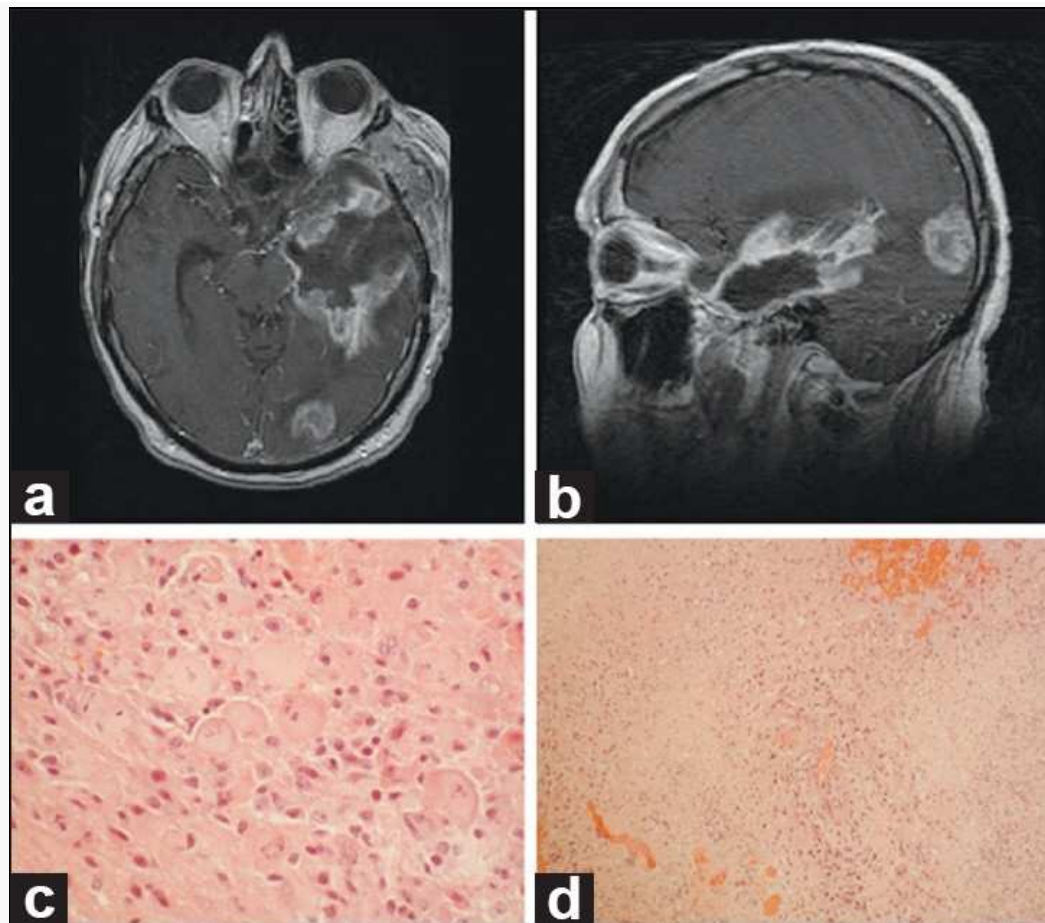


Figure 2

Sibling 1. (a) MRI Brain Axial view T1 with contrast. Large mass located in left temporal lobe region as well as second mass in left occipital region. (b) MRI Brain sagittal T1 with contrast - note the ring enhancement of both lesions. (c) Areas of mitotic activity in tumor cells with increased cellularity consisting of gemistocytic astrocytes (H and E, ×100). (d) Areas of tumor, tumor necrosis and endothelial/vascular proliferation; all necessary to make a diagnosis of glioblastoma (H and E, ×10)

Table 1

Cytogenetics of tumor specimen (Sibling 2)

KARYOTYPE

67-81, XXY, +Y[6], del(1)(p13)[2], del(1)(p34)[6], -2[3], +4[5], -5[7], -7[3], del(7)(q22)[2], +8[5], add(9)(p24)[5], del(9)(p22)[8], -10[6], del(11)(q13q23)[8], +12[8], del(12)(p13)[8], -13[7], -14[8], -15[6], -16[6], +19[6], +19[3], +21[2], +22[8], +22[7], 45X, -Y[8].

Number of cells examined: 20

Cells analyzed: 5

Cells karyotyped: 5

Caption: del (1)(p13)[2] deletion of the short arm of chromosome 1 as seen in cell #2. (five cells were analyzed) Note that loss of Y chromosome in cell #8 is usually a normal phenomenon associated with increasing age. There were frequent copy number aberrations on many chromosomes, including sex chromosomes.

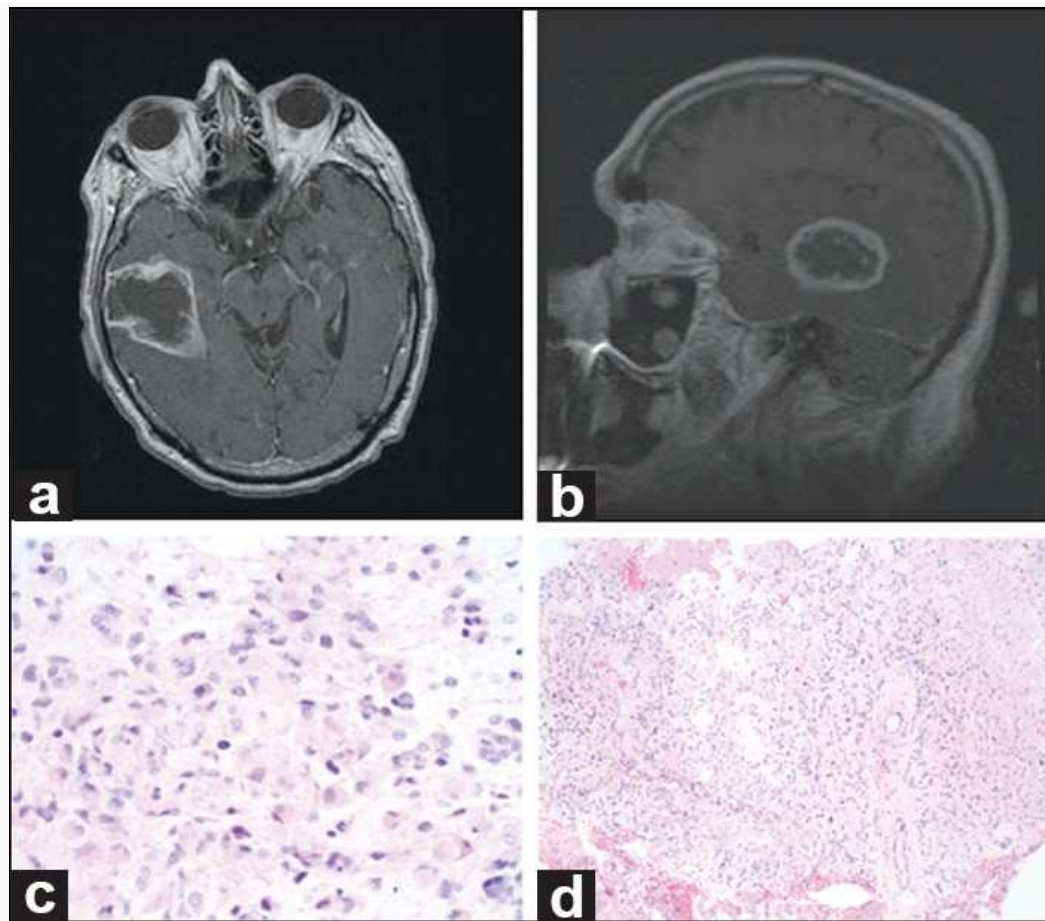


Figure 3

Sibling 2. (a) MRI Brain with contrast enhanced T1 axial peripherally enhanced lesion in right temporal lobe region extending to the dural surface. (b) MRI Brain T1 sagittal view of same lesion. (c) Cellular glial neoplasm with gemistocytic astrocytes (H and E, $\times 100$) (d) Cellular glial neoplasm with vascular proliferation and focal necrosis (H and E, $\times 10$)

Table 2

Summary of selected familial cases of glioblastoma multiforme in literature

	Sex (age at diagnosis)	Relationships	Location(s) of tumors (patient #)	Molecular findings	Note
Chemke <i>et al.</i> (1985) ^[2]	1) Male (11) 2) Male (6) 3) Male (7) 4) Male (5) 5) Male (4)	Brothers (1,2,3,4) First cousin with others (5)	Right frontotemporal (1,2,3) Right temporoparietal (4,5)	N/A	High degree of consanguinity Parents of patients are first cousins Presence of cystic fibrosis in family
Heuch <i>et al.</i> (1986) ^[10]	1) Male (65) 2) Male (68) 3) Female (81)	Patient 3 is the paternal aunt of brothers' patients 1 and 2.	Left temporal lobe, corpus callosum to the right of midline, and left parietal region (1) Left temporoparietal (2) Right temporal (3)	N/A	Multicentric tumor sites in patient 1
Duhaime <i>et al.</i> (1989) ^[6]	1) Girl (2.5) 2) Male (5)	Siblings	Right cerebellar hemisphere (1) Right frontal (2)	Patient 1: Translocation between 11 and 14 (48,XX,-14,+der(11)t(11;14)(p11.2-3;q11),+marker,+marker) Patient 2: Normal chromosomal study	No genetic syndromes or cancer history in family
Hardman <i>et al.</i> (1989) ^[5]	1) Male (61) 2) Male (63)	Identical twins	Right frontal lobe (1) Left occipital lobe (2)	Normal karyotype (2)	Similar life histories GBM (2) Anaplastic Astrocytoma (3) Rapidly fatal brain lesion(4)
Fontaine <i>et al.</i> (2006) ^[7]	1) Male (72) 2) Male (20s) 3) Male (20s) 4) Female (30s)	Patient 1 is the father of the other cases	Right fronto-parietal (1) Not reported (2,3,4)	N/A	Heterogeneous abnormalities exist between two cases
Daniels <i>et al.</i> (2007) ^[3]	1) Male (54) ^A 2) Female (71)	First cousins	Left occipital (1) Right corpus callosum, right frontal lobe, right frontal gyrus, right basal ganglia (2)	Ki67 expression was positive in 28% (patient 1) and 21% of nuclei (patient 2) LOH in 1 9 q 1 3, 1 p 3 6, 1 0q2 3/ phosphate and tensin homolog (PTEN), chromosome 3, and chromosome 17 (multiple loci)	Significantly increased risks to first-degree relatives ($P = 0.026$)
Blumenthal <i>et al.</i> (2008) ^[11]	N = 658 ^B	N/A ^B	N/A	N/A	Chromosomal abnormalities not found in all tumor cells
Present cases	1) Male (63) 2) Male (81)	Brothers	Left temporal and occipital (1) Right temporal (2)	Triploidies 4, 8, 12, 22 and LOH of 1p, 9p, and 10 (2)	

^APresented with recurrent GBM, ^BUtah population data base

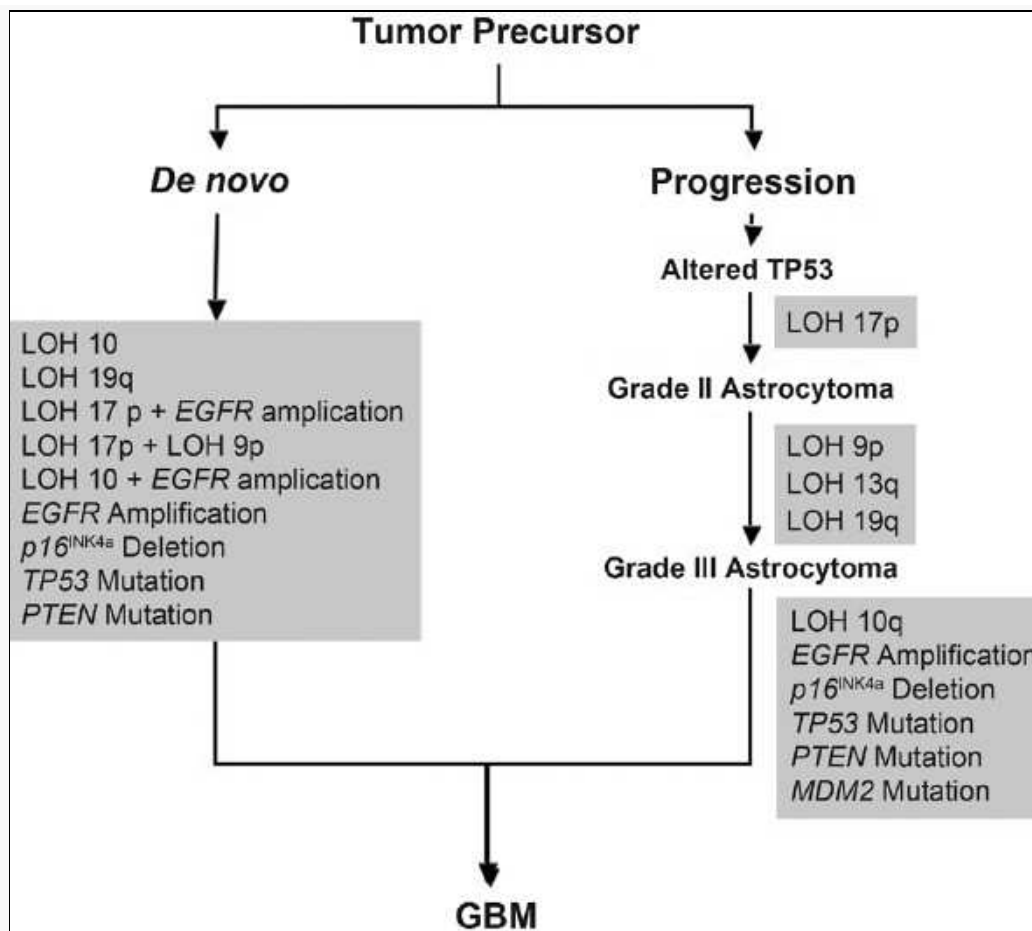


Figure 4

Genetic aberrations for the tumorigenesis of GBM. The genetic mechanisms for the different pathways of GBM development was initially proposed by Lang *et al.* 1994.[16] Additional aberrations were added to the original proposed mechanisms.[23] loss of heterogeneity represents a significant mechanism for glioblastoma multiforme tumorigenesis in both the de novo and progressive pathways

Table 3

Cytogenetic aberrations of glioblastoma multiforme variants

Genetic aberration (% cases)	GBM Variants					
	Primary ^[23]	Secondary ^[23]	Giant cell ^[21]	Gliosarcoma ^[26]	Small cell astrocytoma ^[22]	GBM with oligodendrial features ^[22]
1p deletion					3	24
19q deletion					6	43
1p/19q codeletions					0	22
EGFR amplification	36	8	5	4	63	7
9p (CDKN2A) deleton	31	19	0	37	89	
10q (PTEN) deletion	70	4	5		56	27
EGFR amplification/10q deletion						4
TP53 mutations	28	65	89	23		
PTEN mutations ^[26]	32	4	27	38		

Certain cytogenetic aberrations are found more commonly in some GBM variants. The diagnosis of a specific GBM variant is based on histopathological findings. Only variants with cytogenetic aberrations available in the literature are reported in this table. Sources of aberration frequencies are referenced in superscript. Shaded areas indicate aberration frequencies as unavailable. GBM: Glioblastoma multiforme