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A Study of Platelet-Derived Growth Factor A and Its Ligand among Patients with Glioblastoma and Astrocytoma in Imam Khomeini Hospital Complex, Tehran

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ABSTRACT

Background&Objective: The platelet-derived growth factor receptor (PDGFR) signaling pathway has a vital function as a regulator of glioma development. PDGFRA alterations have been observed in a variety of cancers and have been important clinical targets for tyrosine kinase inhibitors like Imatinib. The aim of this study was to evaluate the role of PDGFRA and PDGFA in the pathogenesis of GBM and to determine whether the constitutive activation of PDGFRA is driven by gene mutations or protein expression.

Materials&Methods: PDGFRA-activating gene mutations (exons 12, 18) were assessed in a subset of 75 samples, of which 65 were GBM and 10 were pilocytic astrocytoma, using PCR followed by direct sequencing. PDGFA expression was evaluated by immunohistochemistry in a series of 20 cases including 15 cases of glioblastoma multiforme and 5 cases of pilocytic astrocytoma.

Results: No PDGFRA-activating mutations were found by Sanger sequencing. In addition, this study found polymorphism in PDGFRA exon 12, c.1701A> G, which was a silent mutation. Immunohistochemical analysis showed elevated PDGFA expression in 25% (5 out of 20) of glioma cases. PDGFA expression was not detected in any pilocytic astrocytoma; however, 33.33% (5 out of 15) of GBM samples showed increased PDGFA expression.

Conclusion: Consistent with previous studies, the findings of the present study underline the importance of PDGFA and PDGFRA alterations as a possible potential predictive biomarker and a therapeutic target in GBM. Further research is needed to better understand the underlying genetic mechanisms driving abnormal PDGFRA activity in gliomas.

Keywords: Glioblastoma, Imatinib, Mutations, PDGFRA, PDGFA, Receptor Tyrosine Kinase

Introduction

The most common glial tumors are astrocytic tumors with an incidence of 3–4 per 100,000 population (1). As stated by the World Health Organization (WHO),astrocytic tumors are divided into grades I to IV. Grade I or pilocyticastrocytoma is a benign tumor; however, grade II–IV are malignant, can spread to adjacent brain tissues, and progress into glioblastoma (2). GBM is the most frequent and fatal astrocytic tumor (3). About 90% of GBM are considered ‘‘primary’’ and arise de novo whereas 5%–10% are ‘‘secondary’’ and originate from lower grade gliomas in younger patients (4). The incidence of GBM is higher among men than women with a ratio of 1.6:1 (5). Age is another risk factor in GBM patients; the risk of developing GBM increases with age with a median diagnosis at 64 years old and a peak incidence between 55 and 84 years old (6, 7). GBM has apoorprognosis and the mortality rate is high with a median survival of 12 to 15 months despite intensive treatments (8).

Numerous studies have been performed to determine the underlying cause of these tumors; however, the cause

of GBM is not well established, which has limited the development of effective treatment strategies **(9, 10)**. Studies indicate that several oncogenes like epidermal growth factor receptor, platelet-derived growth factor(PDGF) and its receptor(PDGFR), and tumor suppressor genes (p16INK4a, p14ARF, PTEN, RB1, and TP53) are involved in the development of glioblastomas **(11, 12)**.

PDGFRA is a trans membrane protein that belongs to the class III tyrosine kinase receptor family with five immunoglobulin-like repeats in the extracellular domain and a split intracellular tyrosine kinase domain **(13)**.The PDGF signaling pathway serves crucial roles in proliferation, differentiation, invasion, and survival. MAP kinase, PI3-kinase/AKT and JAK/STAT signal transduction pathways are triggered by PDGF/PDGFR signaling **(14)**. Protein overexpression, autocrine and paracrine ligand stimulation, and mutations of the PDGF/PDGFR signal-transduction pathway are some of the major genetic alterations found in GBM**(15, 16)**.One study showed an association between PDGFRA mutation and older age in pediatric high-grade glioma**(17)**.

However, the molecular and genetic alterations of the PDGFR pathway in gliomas remain poorly understood. The aim of this study was to evaluate the role of PDGFR-*α*/A in the pathogenesis of GBM, to define the frequency of PDGFRA mutations in grade IV astrocytoma compared to grade I, and to determine whether the constitutive activation of PDGFRA is driven by gene mutations or protein expression.

Materials and Methods

Tissue samples

In the present study, the following inclusion criteria were applied: a histologic diagnosis of glioma, age ≥18 years at pathologic diagnosis, detailed clinical information at diagnosis and during follow-up, and availability of pathology slides and tumor samples. Formalin-fixed paraffin-embedded tumor tissue blocksof145glioma patients who underwent craniotomy for a brain tumor over the past 10 years were retrieved from the archive of the Department of Pathology, Imam Khomeini Hospital, Tehran, Iran. Ethical approval was obtained from the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.REC.1394.2026).The cases were classified according to the WHO criteria **(2)**.

DNA extraction

Two 10-µm thick formalin-fixed paraffin-embedded sections were cut using a microtome and stored in autoclaved plastic microtubes (1.5 mL). DNA isolation was performed using Norgen's FFPE DNA Purification Product # 47400 (Norgen Bioteck Corporation, Canada).Instead of using xylene to deparaffinize FFPE tissues and to eliminate formalin from the tissues as much as possible, the tissues were incubated in PBS and tween 20at 50°Cfor 30minutes in a digital thermomixer (Eppendorf, Hamburg, Germany) and were then centrifuged at 4ºC (RT) at 12000rpm for 10 min. Paraffin accumulated around the meniscus in the supernatant was carefully removed using a pipette tip. This step was repeated until all the tissues were finely ground. The rest of the steps were performed according to the manufacturer's protocol. The quality and concentration of DNA were determined by spectrophotometry (Nano Drop, United States) and gel electrophoresis.

Polymerase Chain Reaction

PDGFR-α (exons 12 and 18) mutations were discovered by PCR followed by direct DNA sequencing. The forward and reverse oligonucleotide primers used to amplify PDGFRA exons 12 and 18 were designed using the Primer 3 and provided by Metabion Company (Germany). PDGFRA exons were numbered according to the human genome project available athttp://www.ensembl.org; exons 12 and 18 of Gen Bank accession no. D50013 (http://www.ncbi.nlm.nih.gov:80/entrez/).

	Forward primer	Reverse primer
Exons 12	TGTCCAGTCACTGTGCTGCT	TCTCTATTCTGCCAAGGCCTATAA
Exon 18	ACAGATGGCTTGATCCTGAGT	GGCACCGAATCTCTAGAAGC

PCR was performed in a total volume of 25 ml, including 3.5 ml of DNA solution,2.5 mM of both sense and anti-sense primers, and10 ml Taq DNA Polymerase 2x Master Mix RED(Ampliqon, Denmark).

The PCR steps included an initial denaturation step at 95°C for 5 min followed by 32 cycles at 95°C for 45 s, annealing at 55°C for 45 s and extension for 50 s at 72°C, and final extension at 72°C for 5 min in a thermo cycler (peqSTAR, Peqlab, Wilmington, DE, United States).

DNA Sequencing

The quality of the PCR products was determined by gel electrophoresis on a 1.5% agarose gel. The amplified fragments of the PCR product (20 *µ*l) were stored in autoclaved plastic microtubes (0.5 mL) with 5*µ*l of both primers and then sent to Codon Genetic Group Co (Tehran, Iran) for sequencing. The Sanger technique was used to sequence all samples using the ABI 3500 Genetic Analyzer (Applied Biosystems, United States) with POP-7 polymer and a 50-cm array.

The DNA sequences generated by the Codon Genetic Group Co were analyzed using a sequencing analysis software 1.4.0 (Finch TV) and then aligned using the Basic Local Alignment Search Tool (BLAST) (http://blast.ncbi.nlm.nih.gov/Blast.cgi). The SNP

numbering was referenced from http://www.ensembl.org as of September 2019.

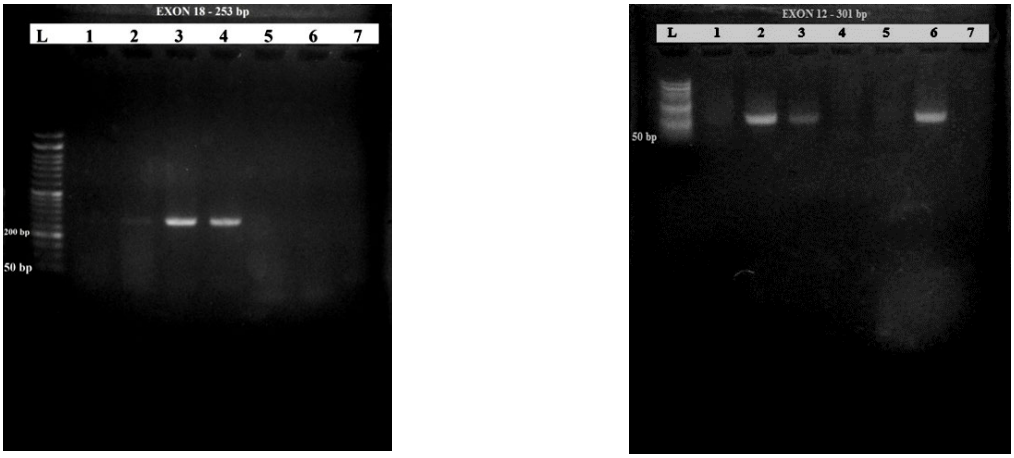

Figure 1.PCR product electrophoresis of exon 18, (253 bp) of PDGFRA, TK2 domain .L= 50 bp ladder, 3 and 4 = cases amplified by PCR, the rest of the samples were not amplified. PCR product electrophoresis of exon 12, (301 bp) of PDGFRA, TK2 domain .L= 50 bp ladder, 2,3 and 6 = cases amplified by PCR, the rest of the samples were not amplified

PDGFA Immunohistochemistry

Three-millimeter thick sections were cut from formalin-fixed, paraffin-embedded tissue blocks and subjected to immunohistochemical analysis. Heat-induced antigen retrieval was performed on deparaffinized and rehydrated sections by microwaving in 10mM citrate buffer (pH 6.0) for 10 min at 90-100°C. In order to exhaust endogenous peroxidase activity, all sections were treated with H2O2. After incubating with PDGFA rabbit polyclonal antibody (PA5-11722, Thermo Fisher, United States) at room temperature for 60 min, the remaining steps were performed according to the HRP Detection IHC Kit manufacturer's protocol.

The proportion score was based on the percentage of cells that became immune reactive. The second parameter was the intensity score, which was calculated according to the intensity of immune reactivity. For the interpretation of proportion and intensity scores, the evaluation and results were shown as negative, weak, moderate or strong.

Results

Patient and tumor characteristics

Tumor tissues from 86 of the 145 patients who had glioma were retrieved for this study. Of145gliomapatients, 75 had a final diagnosis of glioblastoma and 11 had a diagnosis of pilocyticastrocytoma. Among glioblastoma cases, 55 were primary and usually presented with a few days to a few weeks' history and 20were secondary glioblastomas arising from low-grade astrocytoma. Eleven cases had recurrent glioblastoma. The median age of the patients at diagnosis was 49 years and the female/male ratio was1:1.5.

Table 1. Patients and tumors characteristics

Tumor WHO grade	Grade I (11Patients)	Grade IV (75 Patients)
Tumor phenotype	Classic GBMs (74 Patients)	GBM with oligodendroglioma component (1 Patients)
GBM(Gender)	Female (30 Patients)	Male (45 Patients)
Age	29-71	
Median age(years)	49	
Primary glioblastoma	55	
Secondary glioblastoma	20	

PDGFRA gene mutations

The Sanger sequencing analysis of PDGFRA gene mutations in exons 12 and 18 produced results in 75 samples, of which65 were GBM and 10 were pilocytic astrocytoma. No activating mutations were found. The results showed a silent mutation in 100% of GBM and pilocytic astrocytoma patients. This homozygous

polymorphism was in PDGFRA exon 12 and included a substitution of G with A at position 1701(P567P).

Table 2.Sanger sequencing analysis of PDGFRA gene mutations in exons 12 and 18

Exon	GBM Patients	Pilocytic astrocytoma Patients	Condition
18	65	10	No activating mutations
12	65	10	c.1701A>G cDNA.2032A>G g.45792A>G POL
18	65	10	No activating mutations

Table 3.Sequence variants of PDGFRA gene in glioma patients

Exon	Nucleotide change	Amino-acid codon	No of cases	dbSNP
12	c.1701A>G	P [CCA] > P [CCG]	75	rs1873778

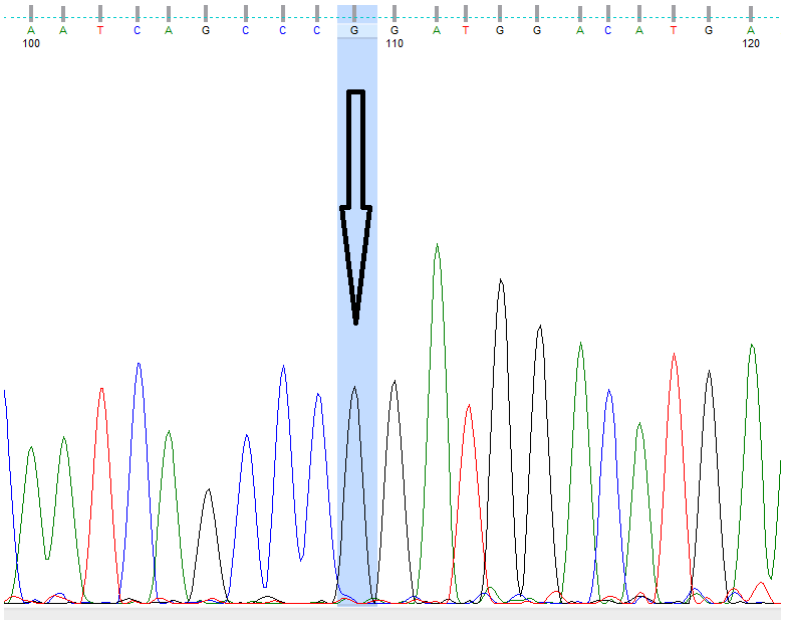

Figure 2.Sequencing analysis of PDGFR-A, SNPrs1873778, arrow indicates G to A substitution at position 1701

Table 4.Frequency of rs1873778SNPin different populations

Study	Population	Group	Sample Size	Ref Allele	Alt Allele
gnom AD-Exomes	Global	Study-wide	245926	A=0.00972	G=0.99028
gnom AD-Exomes	European	Sub	133712	A=0.00153	G=0.99847
gnom AD-Exomes	Asian	Sub	48022	A=0.0002	G=0.9998
gnom AD-Exomes	American	Sub	33578	A=0.0088	G=0.9912
gnom AD-Exomes	African	Sub	15302	A=0.1151	G=0.8849

Our results, in agreement with the distribution reported in (https://www.ncbi.nlm.nih.gov/snp/rs1873778#frequency_tab),showed that the G allele was the most frequent allele in 75 Iranian patients.

PDGFA expression

Immunohistochemical analysis was conducted on 20 glioma cases. The study included 15 cases of

glioblastoma multiforme and 5 cases of pilocytic astrocytoma.

Immunohistochemical analysis showed PDGFA overexpression in 25% (5 out of 20) of glioma cases. PDGFA was expressed in the cytoplasm of tumor cells (Figure 3d), and PDGFA-negative staining was observed in both GBM and pilocytic astrocytoma (Figure 3a, b, c). Gain of PDGFA overexpression was observed in 40% (2 out of 5) of recurrent GBM tumors. Moreover, 20% (1 out of 5) of secondary glioblastomas had amplified PDGFA as compared with 40% (4 out of 10) of primary glioblastomas. PDGFA expression analysis was also performed in 4 cases of recurrent primary tumors and overexpression was observed in 2 of them. There was also a significant correlation between PDGFA expression and WHO histological grade as increased PDGFA expression was not detected in any pilocytic astrocytoma tumor samples, while its expression was significantly increased in 33.33% of GBM samples. The highest PDGFA expression was observed in case number 16, a 34-year-old man with GBM with oligodendroglioma component (GBMO). Patients with PDGFA-expressed tumors were older (48.4 years vs 40 years). No significant correlation was found between PDGFRA expression and gender.

There was also no correlation between PDGFA expression and PDGFRA mutation. Furthe more, no mutations were found in PDGFRA in the GBMO case.

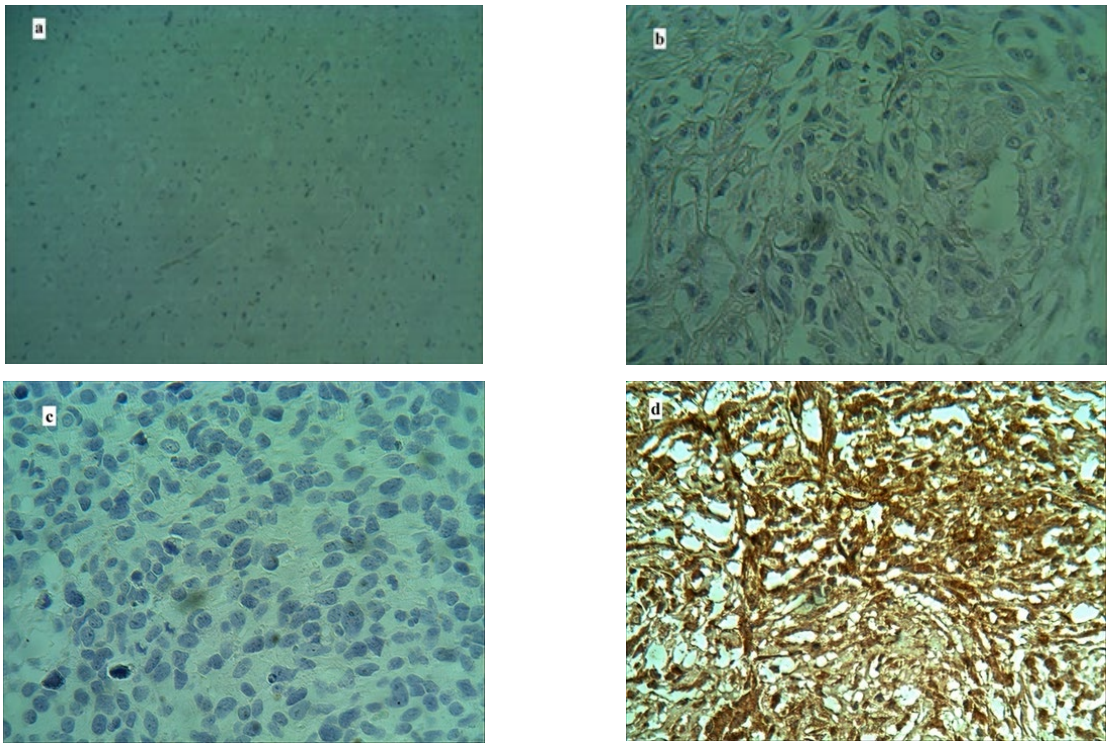

Figure 3.Immunohistochemistry analysis of PDGFA in gliomas; (a)Pilocytic astrocytoma with (negative) score for PDGFA expression in tumor cells (×100) ; (b-c) Glioblastoma with (negative) score for PDGFA expression (×100) ; (d) Glioblastoma with (strong) score for PDGFA expression (×100)

Discussion

One of the most frequently altered cellular signaling systems in glial tumorigenesis is the PDGF pathway(18, 19). PDGFRA and PDGFA overexpression have been reported in tumor cells while PDGFB and its receptor have been shown in glioma associated endothelial cells(20).The role of PDGF signaling in gliomagenesis has been elucidated by its potential role in the cancer stem cell hypothesis of gliomagenesis. Previous studies suggest that the transformation of neural stem progenitor cells into glioma tumors can be a result of the activation of PDGFRA signaling, which creates a favorable microenvironment niche(19, 21).About6-9% of all PDGFRA mutations reported in Gastrointestinal Stromal Tumors (GISTs) are in PDGFRA-JM domain and exon 12, while the most common PDGFRA mutational “hot spot” in GISTs is in exon 18 encoding part of TK2 domain(22).

There has therefore been a growing interest in PDGFR as a cancer drug target with the availability of clinically useful small-molecule inhibitors, such as Imatinib mesylate (Glivec) and Sunitinib (Sutent) (23). Imatinibis an orally available drug that directly inhibits the constitutive tyrosine kinase activity of PDGFRs, KIT, c-Abl, Bcr–Abl, and Arg (24).Imatinib prevents phosphorylation required for signal transduction, which is essential for cell proliferation and apoptosis

inhibition in chronic myelogenous leukemia and GIST cells by inhibiting the kinase-catalyzed transfer of phosphate from ATP to substrate proteins (25).There are ongoing clinical trials on recurrent GBM patients treated with Imatinib(26, 27).

The efficacy of anti-PDGFRA drugs in patients with glioblastomas is measured by clinical trials. Recent studies evaluated anti-PDGFRA drugs in combination with chemotherapy agents (26). However, the genetic alterations underlying the observed response of glioma patients to PDGFRA antagonists are unknown. Two studies evaluated the prevalence of PDGFRA mutations in recurrent glioblastoma patients enrolled in phase I/II study of Imatinib mesylate(27, 28).Patient selection for Imatinib mesylate therapy is important due to potential side effects and high costs of therapy; moreover ,a small group of patients may benefit from this therapy.

In this study, we investigated the prevalence of PDGFRA-activating mutations and PDGFA protein expression in grade IV versus grade I astrocytoma in order to evaluate the role of PDGFRA in the pathogenesis of GBM and suggest a possible treatment for Iranian patients. Previous studies demonstrated that PDGFRA mutations in GBM of adults ranged from 0 to 5.2% (29-31). In accordance with previous studies (27, 28), no PDGFRA-activating mutations were found. However, one silent mutation was identified. This mutation was previously described as a genetic polymorphism (20, 32). PDGFRA exon 12 SNP (rs1873778) was homozygous in 100% of analyzed tumor samples.

The SNP A12has also been described in a smaller percentage of patients suffering from other neoplasms including14% of 35 patients with acute myeloid leukemia(33),30% of 30 patients with cervical adeno squamous carcinoma(34), and 7% of 86 patients with glioma (20).However, there is no relationship between PDGFA expression and this SNP. According to the results of this study, mutations in PDGFRA gene exons 12 and 18 were not common in Imam Khomeini Hospital patients over the past 10 years.

PDGFA and PDGFRA protein expression levels in gliomas were previously studied. One study found that 81.2% of gliomas overexpress PDGFA (20). Another study found that 100% of gliosarcomas express PDGFA (35). It should be noted, however, that there is a lack of data on the prevalence of PDGFA protein expression in glioma specimens. In the present study, PDGFA overexpression was detected in 25% of all gliomas, and it was only found in GBM samples. The previous study observed PDGFA overexpression in low-grade gliomas, including pilocytic astrocytoma(20).In the present study, none of 5 WHO grade I astrocytomas displayed overexpression of PDGFA. Further investigation is required to specify the frequency of PDGFA expression in pilocytic astrocytoma.

In a report of 36 patients, PDGFA overexpression was detected in 63.9% of GBM samples (20). Our results showed PDGFA overexpression in 33.33% of GBM samples. Given the wide range of PDGFA expression level in GBM samples reported by other groups and in the present study, further research is needed in this regard.

We found possible associations between PDGFA expression and age as patients with PDGFA-overexpressed tumors were significantly older (48.4 years vs. 40 years). Additionally, an association can be suggested between the absence of PDGF expression and poor prognosis and younger age. However, further studies with larger sample size are required.

The highest level of PDGFA expression was observed in a GBMO sample. GBMOs account for 4% to 27% of all GBMs. These tumors feature both astrocytic and oligodendroglial differentiation. In a previous study, the expression levels of EGFR, PTEN, p53 and IDH1 were investigated in GBMO (36). In this study, we evaluated PDGFA expression level and found that the GBMO sample had the highest level of PDGFA expression.

Although there was only one sample, our findings suggest that GBMO is associated with higher PDGFA protein levels. However, further studies are warranted to specify the exact prevalence of this abnormality in GBM, GBMO, and pilocytic astrocytoma.

Conclusion

In conclusion, PDGFA is an important gene in GBM that was overexpressed in 33.33% of GBM samples in the present study. Additionally, we observed an absence of its expression in patients with a poor prognosis. Our data also suggests that PDGFA overexpression might be a negative prognostic indicator in pilocytic astrocytoma. These findings, in combination with previous studies, highlight the importance of PDGFA and PDGFRA alterations as a possible potential predictive biomarker and a therapeutic target in GBM. Additional studies with larger sample sizes that further characterize the PDGFA and PDGFRA gene amplification in GBM are needed to better understand the underlying genetic mechanisms driving abnormal PDGFRA activity in gliomas.

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Conflict of Interest

Not applicable.

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