



# Butterfly Glioblastoma: Genetic alterations and outcomes

Christian Amezcua-Contreras <sup>a,1</sup>, Antonio Dono <sup>a,1</sup>, Angel Bueno <sup>a</sup>,  
Jowah Gorbachev <sup>a</sup>, Kristina Ramirez Garcia <sup>a</sup>, Aria Sabbagh <sup>a</sup>,  
Sigmund Hsu <sup>a,b</sup>, Mark Amsbaugh <sup>a,b</sup>, Jay-Jiguang Zhu <sup>a,b</sup>,  
Leomar Y. Ballester <sup>c,d</sup>, Nitin Tandon <sup>a,b</sup>,  
Yoshua Esquenazi <sup>a,b,e</sup>

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<https://doi.org/10.1016/j.jocn.2026.112007>

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## Abstract

### Purpose

Butterfly glioblastoma (bGBM) is an aggressive variant of glioblastoma (GBM) characterized by invasion of both hemispheres through the corpus callosum. The cause of its poor prognosis remains unclear, whether due to complex anatomy or intrinsic molecular traits. In this cohort, we aim to identify the genetic features of bGBM and factors associated with its prognosis.

### Methods

We retrospectively identified GBM patients from our institutional database and grouped them into non-butterfly glioblastoma (non-bGBM) and bGBM. Clinical features, genomic profiles, and survival outcomes were compared using statistical analysis.

### Results

We analyzed 324 GBM patients, including 36 with bGBM. Confusion was a common presenting symptom in bGBM ( $p=0.005$ ), and these tumors rarely invaded the temporal lobes ( $p=0.0004$ ). bGBM was associated with higher mutation rates in CDK6 (13.64% vs. 3.11%,  $p=0.04$ ), PIK3R1 (22.73% vs. 7.64%,  $p=0.03$ ), and TSC2 (9.09% vs. 0.69%,  $p=0.02$ ); however, these results were not significant after adjustment for multiple comparisons. Median overall survival was significantly shorter in bGBM patients (9 months) compared to non-bGBM (18 months,  $p=0.001$ ).

### Conclusions

This study provides novel insights into the genetic blueprint of bGBM. Further research with larger cohorts is needed to validate these findings and better understand the molecular features of bGBM.

## Introduction

Glioblastoma (GBM) is a highly malignant brain tumor and the most prevalent primary nervous system malignant neoplasm [1]. It typically arises in the cerebral hemispheres' white matter. The largest white matter component of the brain, the corpus callosum (CC), is a brain structure that connects the cerebral hemispheres. GBM is one of the few pathologies that can arise from the CC and expand into both hemispheres, a phenotype known as butterfly glioblastomas (bGBM). This phenotype has historically been associated with aggressive behavior and a dire prognosis [2], [3], [4], [5], [6], [7], [8]. Although the incidence of bGBM is low (2.2% – 14.3%) [9], [10], its prognosis compared to the overall GBM population is dismal, with a median overall survival (OS) of 6 months [11]. Despite this previously reported poor prognosis for bGBM patients, it is unclear what is the reasoning behind such a poor prognosis. The hypothesis for this includes different tumor molecular characteristics as identified in other aggressive gliomas with particular phenotypes such as diffuse midline glioma H3 K27M [12], diffuse nature of the disease and consequently lower resection rates due to the anatomic complexity of the tumor's location [12]. Even though there have been a lot of advancements in the field of genetics and neuro-oncology, there is limited data on the genetics of bGBM and its relationship with prognosis [13]. This study aims to investigate genetic alterations in relation to phenotypic bGBM, as well as evaluate survival differences of bGBM compared to non-bGBM in a molecularly defined GBM cohort according to the most recent WHO classification [14].

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### Study population

We included patients from our prospectively maintained institutional database that fulfilled the following criteria: diagnosis of GBM according to the 2021 World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS) [14], available pre-operative and post-operative magnetic resonance imaging (MRI), and available clinical information. bGBM was defined as a contrast-enhancing tumor in the corpus callosum and extending bilaterally into the hemispheres [9], [10], [11] ...

### Non-butterfly glioblastoma cohort characteristics

A total of 324 patients with GBM were included in this study. The non-bGBM group, comprising 288 cases, had a median age of 60 years (range 13–87) and included 181 (62.84%) males and 107 (37.15%) females. Two-hundred and four (70.83%) patients were White, 41 (14.24%) were Hispanic, 24 (8.33%) were Black, 17 (5.90%) were Asians, and 2 (0.69%) had other ethnicities. The most predominant symptoms were headaches in 115 (39.93%), language deficits in 99 (34.38%), and confusion in 97 (33.68%). The ...

### Discussion

In this retrospective cohort study, we identified significant clinical and genetic differences between bGBM and non-bGBM. Patients with bGBM were more likely to present with confusion and less likely to exhibit temporal lobe involvement, suggesting distinct clinical manifestations. Although not statistically significant after multiple comparison adjustments, bGBM potentially has a higher incidence of CDK6, PIK3R1, and TSC2 compared to their non-bGBM counterparts. Additionally, our results did ...

### Limitations

Limitations of this cohort include the small number of bGBM cases and the retrospective nature of the study. There is also a selection bias, as not all bGBM cases underwent NGS. The lack of MGMT methylation status for most cases and the use of different targeted NGS panels also represent limitations. Additionally, we did not implement the current Response Assessment in Neuro-Oncology (RANO) volumetric classification for tumor resection, and proper neurocognitive testing was not performed due to ...

### Conclusion

This study provides novel insights into the genetic blueprint of bGBM. Alterations in CDK6, PIK3R1, and TSC2 might be associated with bGBM. In our population, harboring a butterfly phenotype was associated with worsened survival after adjustment for multiple variables; Nevertheless, the EOR did not show a correlation with survival. Future multi-institutional collaborations are needed to further clarify the genomic landscape of bGBM, and its prognosis. ...

### CRediT authorship contribution statement

**Christian Amezcua-Contreras:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Antonio Dono:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization. **Angel Bueno:** Writing – review & editing, Conceptualization. **Jowah Gorbachev:** Writing – review & editing, Data curation. **Kristina ...**

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. ...

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<sup>1</sup> These authors contributed equally as co-first authors.

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