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RESEARCH ARTICLE

The Prognostic Value of Copy Number Variations and Gene Mutations in Glioblastoma: Insights from a Large-Scale Bioinformatic Study

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ABSTRACT: Glioblastoma is an aggressive and often fatal brain tumor characterized by poor prognosis and complex genetic underpinnings. Through extensive analysis of glioblastoma datasets on the cBioPortal, this study identifies critical gene mutations and copy number alterations (CNAs) that correlate strongly with patient survival rates. Key findings highlight significant CNAs in chromosomes 20, 19, 10, 1, and 7. Our deep dive into the genetic profiles of deceased patients revealed a notable enrichment of mutations in specific genes, including MUC19, which exhibits higher expression levels in the cerebral cortex—the brain region most frequently affected by glioblastoma. By mapping these genes on GeneMania, we uncovered their functions and potential implications in glioblastoma pathology, such as their involvement in mucus lining and epithelial barriers, focusing on MUC genes, which showed differential expression patterns correlating with patient outcomes. This bioinformatic exploration advances our understanding of glioblastoma's molecular landscape and sets the stage for targeted therapies that could improve prognosis and treatment strategies.

KEYWORDS: Biomedical and Health Sciences; Genetics and Molecular Biology of Disease; Glioblastoma; Patient survival; Copy number alterations.

Introduction

Glioblastomas are aggressive tumors arising from astrocytes, the star-shaped cells that comprise the brain's supportive tissue. They usually form in the cerebral cortex but can form in any location in the brain; Glioblastomas can also form in the spinal cord.[1] Glioblastoma usually appears in a mesh-like structure, making treatment challenging. Symptoms for Glioblastoma may vary. However, most commonly, there are headaches, nausea and vomiting, seizures, weakness or numbness on one side, memory loss or confusion, and personality changes.[2] What causes glioblastoma is unknown. However, some risk factors of glioblastoma are age, genetic mutation, radiation exposure, people who have received radiation treatment for other diseases have a higher risk of developing the tumor, and finally, family history. MRIs, CT scans, other imaging tests, and a biopsy can diagnose glioblastoma.[3] The treatment options for Glioblastoma mainly depend on the individual's health and how far the tumor has progressed. One option is surgery, which can help remove as much of the tumor as possible. Radiation therapy uses high-energy beams to target and kill cancer cells. Chemotherapy uses drugs to target and kill cancer cells throughout the body and, finally, treatment trials. The prognosis for Glioblastoma is poor since it is a rapidly growing cancer that can be difficult to treat.[4] However, the prognosis for Glioblastoma can depend on factors such as age, overall health, and response to treatment. The prevention of glioblastoma is unknown. However, maintaining a healthy lifestyle and avoiding any chemicals, such as smoking and drugs, can help increase the chances of a patient's survival. The average survival time of a patient with Glioblastoma can vary from 12-18 months. However, the incidence of Glioblastoma is relatively low, with it affecting 1/10,000 cases of cancer; however, Glioblastoma is responsible for around 45.2% of all cancerous primary brain tumors and CNS tumors.[5]

Previous research found many novel genetic alterations associated with glioblastoma cancer development.[6] However, the genetic alterations that are linked to glioblastoma cancer have not been thoroughly investigated. As a result of many different targeted gene therapies on GBM, research has concluded that these tumors evolve on a multitude of distinct pathways rather than a single one, and further analyses are needed to identify additional potentially useful genetic alterations for the classification and target therapy of GBMs, even though only a few specific genetic pathways are consistently highlighted, there are undoubtedly complex interactions among them as well as with additional yet unknown factors.

The study aims to find a novel genetic alteration that affects Glioblastoma patients' survival rates and to find a novel linkage between genetic alterations and their functions on brain cancer progression.[7] This study further investigates the association between specific copy number alterations (CNAs) and gene mutations with patient survival in glioblastoma, focusing on identifying novel genetic alterations that could serve as potential therapeutic targets. The importance of finding a novel genetic alteration that affects Glioblastoma patient's survival rates is crucial to finding a novel treatment and accurate diagnosis for the aggressive tumor. Finding these novel mutations will help oncologists detect these cancers early on, which will

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help extend treatment plans. Finding novel genetic alterations will also help develop targeted and patient-specific therapies. These treatment plans can be designed for the specific genetic changes of a particular patient. Gene therapy can also have a helpful impact on finding a novel genetic alteration. Gene therapy is a process used to repair or replace damaged genes.[8] This can also make treatments such as immune cell therapy, gene manipulation, Oncolytic virotherapy, and Prodrug activating suicide gene therapy possible.

Methods

cBioPortal brain cancer patients' survival analysis:

The cBioportal was the main database used to help collect the data.[9] We organized 16 studies, selected the clinical tab on the cBioportal, and selected the graph that displayed the survival of the patients with the best and most accurate p-value, with around 2444 patients in the living group and around 3226 patients in the deceased group.

Analysis of patient's clinical attributes regarding chromosome copy number alteration and mutation:

In the cBioportal, we accessed the clinical attributes containing copy number alterations and mutations. We examined the chromosomes containing the most significant p-values. We conducted many different analyses, plotting them on the Gene network using GeneMania and selecting specific genes with a p-value under 0.05.

Gene network analysis using GeneMania:

In the Genemania website, we selected the Homo sapiens tab. We selected 10 genes from chromosomes 7, 10, 19, 20, and 1, with the p-value of most significant, and plotted them on the website. The website displayed different gene networks that explain the relationship between the genes.

Statistical test:

The Logrank Test was used to calculate the p-value for the patient's survival. For the clinical attributes, a student t-test was used to calculate the p-value. GeneMANIA evaluates the statistical significance of the predicted genes by using permutation tests or other resampling-based methods.

Result and Discussion

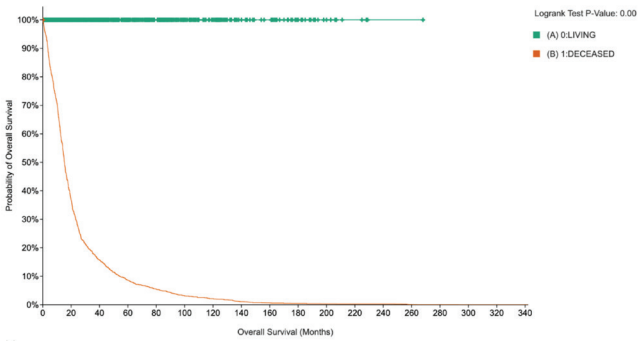

Figure 1: The comparison of the overall survival rate of glioblastoma patients divided into two groups: living (n=2444) and deceased (n=3226), using 16 studies provided in the cBioPortal database. This result indicates that the two groups were successfully isolated depending on their survival status.

We aim to find novel genetic alterations associated with the glioblastoma patient's survival. Therefore, we divided the patients into two groups, living and deceased, to find the enriched genetic alterations in both groups. To analyze the overall survival rate of glioblastoma patients, we selected 16 studies regarding glioblastoma and organized the data. After that, we plotted the graph by selecting the x-axis as the overall survival in months and making the y-axis the overall survival probability. After we analyzed the data, we found the median to be 15.22 for the survival time of deceased patients. There was no median survival time for the living group because they were not deceased at the time of the collection of the data. This data accurately represents and isolates the patients, which is shown by the living group having a 100% survival rate throughout data collection, which was about 340 months. With the information presented regarding overall survival, we can conclude that the median is 15.22 months for the survival time of deceased patients. In comparison, the living groups had a 100% survival rate throughout the data collection, which was 340 months.

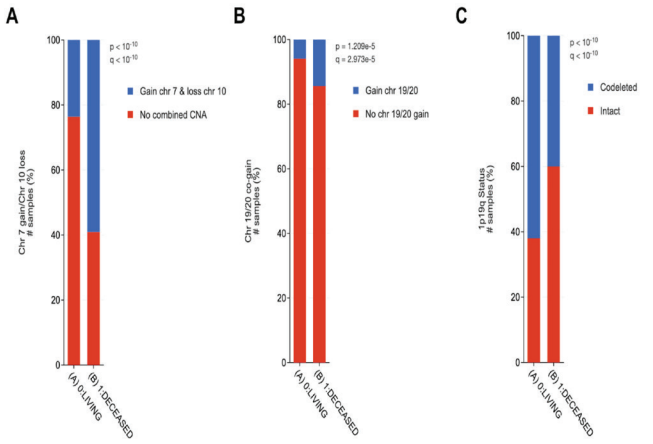

Figure 2: Many alterations in living and deceased patients were obtained using 16 studies in the cBioPortal database. (A) The comparison between living and deceased groups regarding the gaining of chromosome 7 and the loss of chromosome 10, with no copy number alterations. (B) The comparison between living and deceased groups regarding the gain of chromosomes 19/20 and no chromosome 19/20 gains. (C) Comparison between living and deceased groups regarding the co-deletion of 1p and 19q and whether it is intact. This result successfully measures the rates at which various copy number alterations occur in deceased and living groups.

Our objective is to identify new genetic changes that may be associated with the survival of glioblastoma patients. To achieve this, we analyzed the clinical attributes and DNA copy number changes in patients in each group. We used the cBioportal database to analyze 16 selected studies and calculate the p-values and q-values using the chi-squared test. The analysis of chromosome 7 gain and chromosome 10 loss showed that survival patients had more samples with no combined changes, while deceased patients had higher samples of the alteration. Similarly, for the chromosome 19/20 co-gain alteration, living patients had more samples of the unchanged alteration, while deceased patients had higher samples. Lastly, in the analysis of 1p19q samples, living patients had higher amounts of deleted samples, while deceased patients had higher samples of

intact. Based on this information, we concluded that deceased patients had more samples with the copy number alteration "chromosome 7 gain/chromosome 10 loss" than living patients.

On the other hand, living patients had more samples with no change. Additionally, the deceased group had more chromosome 19/20 co-gain alteration samples than the living group. The living group had more samples with the codeleted change in the 1p19q study than the deceased group.

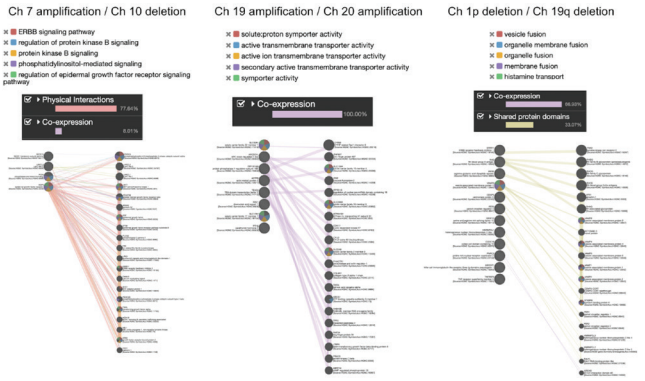

Figure 3: The result of GeneMania gene network analysis predicts the function of the gene sets from Ch 7 amplification and Ch 10 deletion, Ch 19 amplification, and Ch 20 amplification, as well as Ch 1p deletion and Ch 19q deletion. This result displays the different functions of various gene sets involved in different copy number alterations and successfully shows their interactions.

After we plotted 10 genes that were enriched for deceased groups with the most significant p-values for the copy number alterations chromosome 7 deletion and chromosome 10 gain, co-gain of chromosome 19 and 20, and the codeletion of chromosomes 1 and 19, we found respective of their order that there was a physical interaction rate of 77.64% and a co-expression percentage of 8.01 were the genes had to do mainly with the regulation of protein kinase B signaling and the ERBB signaling pathway, a 100% co-expression rate, with the main functions being in the soluble protein symporter, transmembrane, and the ion transmembrane, and finally a 69.3% coexpression rate, and 33.07% of shared protein domains and had played a role in the fusion of vesicles, organelle membrane fusion, and organelle fusion.

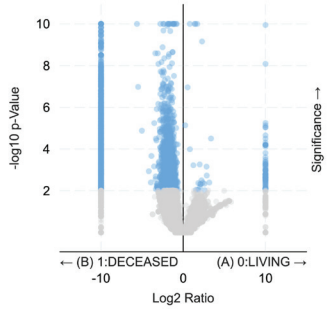

Figure 4: Volcano plot illustrating the distribution of mutated genes in deceased and living groups. The y-axis displays the -log10 p-value, indicating increasing significance upwards, and the x-axis represents the Log2 ratio of mutated genes between the two groups. Each dot represents a mutated gene; blue dots indicate genes with p-values less than 0.05 and an absolute Log2 fold change greater than 1. This result shows that the mutated genes were much more significant in the deceased group than in the living group.

As we aimed to identify the number of mutations in the deceased and the living groups, we made a graph, with the y-axis being -log 10 p-value and the significance increasing directly with the y-axis. The x-axis represents the Log2 ratio for the deceased and the living groups. For this Log2 ratio plot, each dot, regardless of color, represented a mutated gene. As for the blue dots specifically, they indicate a value that is less than 0.05 and have an absolute Log2 Fold change greater than 1. As for the number of mutated genes enriched in the deceased group, it is 3509, while for the living group, it is 182, which allows us to conclude that there were more mutated genes enriched in deceased groups.

Table 1: Top ten mutated genes enriched in the deceased group. This table successfully identifies ten of the most significant genes enriched in the deceased groups. The table also displays the gene's cytobands, their rates in both deceased and living groups, their log2 ratio, their p-value (identifying their significance level), and finally, their q-value.

Gene	Cytoband	LIVING	DECEASED	Log2 Ratio	p-Value	q-Value	Enriched in
PTEN	10q23.31	274 (12.16%)	674 (26.37%)	-1.12	4.84E-36	3.11E-32	DECEASED
AQP7P1	9q13	0 (0.00%)	22 (23.16%)	<-10	1.26E-32	6.09E-29	DECEASED
EGFR	7p11.2	198 (8.75%)	513 (20.41%)	-1.22	1.63E-30	6.27E-27	DECEASED
MUC19	12q12	0 (0.00%)	39 (4.55%)	<-10	5.06E-23	1.39E-19	DECEASED
FRG2B	10q26.3	3 (0.62%)	29 (30.53%)	-5.63	9.61E-22	2.32E-18	DECEASED
MUC17	7q22.1	42 (2.68%)	205 (9.93%)	-1.89	2.34E-19	5.02E-16	DECEASED
TMEM191A	22q11.21	0 (0.00%)	11 (11.58%)	<-10	2.25E-16	3.77E-13	DECEASED
MUC16	19p13.2	132 (8.14%)	355 (17.19%)	-1.08	2.35E-16	3.77E-13	DECEASED
ARHGEF33	2p22.1	0 (0.00%)	28 (3.15%)	<-10	2.35E-16	3.77E-13	DECEASED
NWD2	4p14	0 (0.00%)	27 (3.04%)	<-10	8.58E-16	1.27E-12	DECEASED

As we aimed to identify the most significant and most occurring genes in the deceased groups, we selected 10 mutated genes that were enriched in the deceased group. These genes were sorted from the lowest q value to the highest q value and the lowest p value to the greatest value. The gene's locations varied, found on chromosomes 10, 9, 12, 7, 22, 2, 19, and 4. These genes were also highly present in the deceased rather than the living group. Interestingly, three mucin (MUC) genes were found in the top 10 most significant genes enriched in the deceased group. The functions of these three genes, which were MUC19, MUC17, and MUC16, varied. MUC19 is a mucin gene that plays a role in forming protective mucous barriers in the body.[10] MUC16 plays a role in forming a protective barrier on the ocular surface and other epithelial surfaces and its important roles in cellular adhesion and immune response.[11] MUC17 was found to play a role in creating a mucous barrier that protects the lining of the digestive system.[12]

The analysis pinpointed ten key mutated genes notably enriched in deceased patients, highlighting their potential link to disease severity and mortality. These genes, including three mucin genes (MUC19, MUC17, and MUC16), crucial for forming protective mucous barriers in various bodily systems, were selected based on their low q-values and p-values, indicating strong statistical significance. Compared to the living group, their diverse chromosomal locations and high presence in deceased individuals emphasize their possible roles in critical biological processes impacting patient outcomes.

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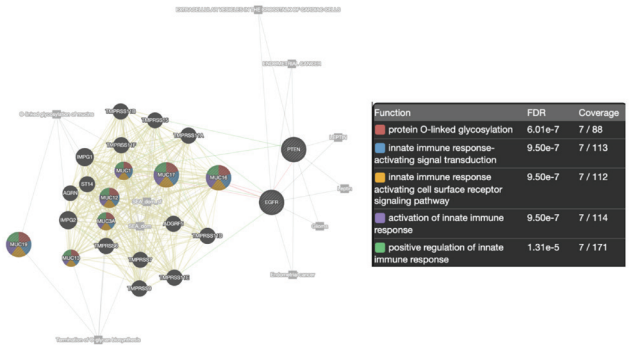

Figure 5: GeneMania analysis of the top ten mutated genes enriched in the deceased groups. This result shows the potential roles of multiple MUC genes in biological processes among deceased brain cancer patients.

Next, we analyzed the gene network of the top ten genes enriched in the deceased group. Interestingly, we found that the main functions of the MUC gene were ranked top-line in terms of their FDR significance. We highlighted the functions associated with the MUC genes: MUC19, MUC13, MUC17, MUC1, MUC16, MUC12, and MUC3A. These functions, concerning their order, were protein O-linked glycosylation, innate immune response-activating signal transduction, and cell surface receptor signaling pathway, as well as the activation of inane immune response and positive regulation of the innate immune response. These findings highlight the potential roles of MUC genes in critical biological processes among deceased brain cancer patients.

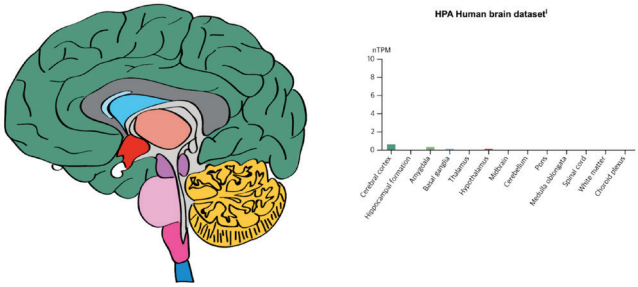

Figure 6: Expression levels of MUC19 in different regions of the human brain. This shows the normalized Transcripts Per Million (nTPM) for MUC19 across various brain regions, illustrating its highest expression in the cerebral cortex (0.6 nTPM), followed by the amygdala (0.3 nTPM), and lower expression in the basal ganglia and hypothalamus (0.1 nTPM each). This result indicates that MUC19 may play a crucial function in the cerebral cortex.

The analysis highlighted MUC19 as the most significantly mutated gene enriched in the deceased group, prompting a focused investigation of its expression levels in the human brain. We found that MUC19 is primarily expressed in the cerebral cortex, with a normalized Transcripts Per Million (nTPM) of 0.6, followed by the amygdala at 0.3 nTPM, and both the basal ganglia and hypothalamus at 0.1 nTPM. This distribution is particularly relevant to understanding glioblastoma multiforme, a brain tumor predominantly found in the cerebral cortex, suggesting a potential role for MUC19 in the pathology of this aggressive cancer.

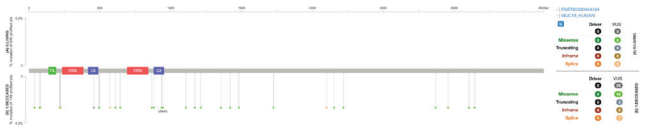

Figure 7: Distribution of mutations in protein domains among deceased group patients in MUC19 gene. This illustrates the frequency and types of mutations identified in the deceased group. The mutations are categorized into three types: missense, truncating, and splice mutations, with a focus on their localization in specific protein domains. This data shows a genetic alteration between living and deceased brain cancer patients in the MUC19 gene.

In our research, we successfully collected and analyzed mutation data from the cBioPortal, focusing on the differences in amino acid sequences between living and deceased groups. Remarkably, our findings showed no mutations were observed in the living group, whereas 104 distinct mutations were identified in the deceased group. The types of mutations varied, with 42 being missense mutations, 3 truncating mutations, and 7 splice mutations. Notably, a significant proportion of these mutations were missense and truncating types.

Most of these mutations were localized in the C8 and VWD protein domains. The C8 domain is often involved in membrane attack complex formation, playing a crucial role in immune defense mechanisms by mediating cell lysis. The VWD domain, found in von Willebrand factor and other blood coagulation proteins, is essential for proper blood clotting and cellular adhesion processes.[13] The frequent occurrence of mutations in these domains suggests they may be critical sites for molecular disruptions linked to the conditions observed in the deceased group, potentially influencing disease outcomes through impacts on immune response and hemostasis. This data provides a clearer picture of the genetic alterations influencing disease severity and patient mortality.

Previous studies indicated that elevated MUC19 levels are associated with increased glycolysis, cell viability, migration, and invasion of breast cancer cells, contributing to tumor growth and aggressiveness.[14] Also, another study showed that the upregulation of MUC19, driven by the LOC102724163/miR-508-5p axis, enhances breast cancer cell proliferation, migration, and invasion. This suggests that LOC102724163 plays a carcinogenic role in breast cancer.[15] These studies indicate that MUC19 may play a crucial function in cancer progression.

■ Conclusion

Our research focused on the critical impact of copy number alterations (CNAs) across various chromosomes—particularly chromosomes 19, 20, 7, 9, and 1—on the prognosis of glioblastoma patients. These alterations significantly influence patient outcomes by affecting gene expression and tumor behavior. Additionally, our findings highlight the importance of specific mutations that profoundly affect prognosis. Notably, our analysis through the GeneMania platform revealed interconnected functions among genes, especially those coding for mucins like MUC19, which are essential in synthesizing mucus for epithelial cell barriers. MUC19, in particular, demonstrated elevated expression levels in the cerebral cortex (0.6 nTPM), amygdala (0.3 nTPM), basal ganglia, and hypothalamus (0.1 nTPM

each). This is significant, considering the cerebral cortex is the most common site for glioblastoma occurrence. The correlation between MUC19 expression in the cerebral cortex and the high incidence of glioblastoma in this region may offer insights into the pathogenesis of the disease and potential therapeutic targets. These findings pave the way for further research into the genetic drivers of glioblastoma and underscore the potential of targeted therapies that address these specific genetic alterations.

The limitation of this study is that only glioblastoma patients' genomic information was analyzed. Therefore, additional wet lab experiments must be performed in the future. Another limitation would be that gene network analysis was performed only using the GeneMANIA database. The gene network analysis has to be performed again with a different database to validate our results. Finally, we do not investigate the molecular mechanism of how alterations in MUCIN genes affect patient survival. Therefore, further experiments should be performed to analyze the function of MUCIN genes on glioblastoma development.

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