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Unveiling Actionable Pathogenic Genes for Precision Oncology in Brain Cancers: Glioblastoma and Astrocytoma

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Abstract

Glioblastoma (GBM) and astrocytoma are aggressive primary brain tumors characterized by significant molecular heterogeneity, complicating effective treatment. This study employed targeted next-generation sequencing of 529 cancer-associated genes on matched tumor-normal pairs from GBM and astrocytoma patients. Somatic variants were identified using a rigorous bioinformatic pipeline adhering to GATK Best Practices, with variant allele frequencies (VAF) calculated to assess clonal dominance. Functional annotation and driver mutation classification were performed using Ensemble Variant Effect Predictor and Cancer Genome Interpreter. The clinical actionability of identified mutations was evaluated based on the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT). In the GBM sample, dominant near-clonal driver mutations were identified in EGFR (p.Asp256Ala; VAF = 0.976) and TP53 (p.Arg175His; VAF = 0.788), implicating proliferative signaling and tumor suppressor disruption. The astrocytoma sample exhibited hallmark driver mutations in IDH1 (p.Arg132His; VAF=0.601) and ATRX (frameshift deletion; VAF = 0.932), consistent with metabolic reprogramming and chromatin remodeling. Several additional high-confidence somatic drivers were detected, representing viable therapeutic targets. These findings align with ESCAT Tier 1/2 alterations, supporting their potential for molecularly matched therapies. The identification of distinct, actionable somatic drivers in GBM and astrocytoma underscores the critical importance of molecular stratification in neuro-oncology. This approach facilitates a shift from uniform treatment paradigms toward biomarker-driven precision medicine, promising improved patient stratification and targeted therapeutic interventions.

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INTRODUCTION

Glioblastoma and astrocytomas represent the most prevalent forms of primary malignant brain tumors [1–17]. Astrocytomas develop from astrocytes, which are star-shaped glial cells crucial for supporting central nervous system (CNS) functions such as maintaining the blood–brain barrier (BBB) and triggering immune responses. According to the World Health Organization (WHO) classification, glioblastoma is a rapidly growing, diffusely infiltrating, necrotic, and highly vascularized grade IV astrocytoma, making it a highly malignant condition with a poor clinical outlook [18]. Glioblastomas predominantly occur in adults, accounting for 60%, while astrocytomas are found in both adults

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and children [17, 19]. Among these, glioblastoma is the most aggressive and malignant form of astrocytoma, comprising about 65% of all astrocytomas and approximately 45–50% of all primary malignant brain tumors [17, 19]. The significant molecular diversity of gliomas, evident at genomic, epigenomic, and transcriptomic levels, poses a major challenge to effective treatment. Large-scale initiatives – like The Cancer Genome Atlas (TCGA) – have identified crucial molecular alterations, such as IDH1/2 mutations, EGFR amplification, and TP53 changes, which play a vital role in glioma development and progression (Cancer Genome Atlas Research Network, 2008). These discoveries have enhanced our understanding of glioma synthesis and underscored the importance of molecular profiling in clinical decision-making [20–22]. However, translating these insights into successful targeted therapies remains limited, primarily due to tumor heterogeneity, adaptability, and challenges associated with drug delivery across the blood–brain barrier [23].

Clinically, these tumors are marked by rapid progression and an almost universally fatal prognosis, with the survival rate for glioblastoma remaining around 15 months despite aggressive treatment [17, 24]. Despite advancements in surgery, radiotherapy, and chemotherapy, including the introduction of temozolomide-based treatments, the median survival for glioblastoma patients remains at 12–15 months, highlighting the need for improved therapeutic strategies [25–27]. A major challenge in treating these tumors is their diffuse and infiltrative nature, which makes complete surgical removal impossible, as infiltrating cells often extend beyond visible imaging margins, leading to inevitable recurrence [28]. Another significant obstacle is the blood–brain barrier (BBB), which prevents many pharmacological agents from reaching effective concentrations within the CNS, contributing to the failure of various targeted treatments and biological agents [29].

The limited success of uniform targeted treatments, such as anti-angiogenic trials with bevacizumab, underscores the inadequacy of a single “one-size-fits-all” targeted approach, emphasizing the need for genuinely personalized strategies that better reflect the biological complexity of each patient [30]. Precision oncology offers treatment based on a tumor’s specific genomic, genetic, and epigenetic vulnerabilities [31]. Precision oncology employs the Next Generation Sequencing approach to identify actionable genes, such as IDH, BRAF, and NTRK, which aid in determining suitable therapies that show better outcomes in large populations [32]. The current standard treatments for gliomas are not very effective, leading to poor patient outcomes, which is a significant concern. While next-generation sequencing (NGS) is increasingly employed to guide patient therapy, its routine clinical application is inconsistent. There is an urgent need to clearly identify “actionable” pathogenic genes genomic changes for which targeted therapies exist [33–35].

At present, only a small fraction of glioma patients possesses truly actionable alterations that can be treated with available drugs, necessitating systematic screening to move beyond generic treatments. Identifying these actionable genes could significantly enhance personalized treatment outcomes. Research utilizing the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) indicates that patients with Tier 1/2 alterations, such as IDH1/2 mutations, BRAF V600E, and NTRK1-3 fusions, experience notably longer progression-free survival (PFS) and higher objective response rates when receiving molecularly matched therapies [36]. By focusing on pathogenic genes with high therapeutic relevance, clinicians can better stratify patients for innovative clinical trials and improve overall survival rates [37]. Despite advancements in mapping the genes in these brain tumors, the exact drivers remain elusive. Unlike some other cancers, glioblastoma lacks a single “master” mutation that can be easily targeted. These tumors are a complex mix of different cell types, so a drug might be effective on one part but allow others to continue growing. Additionally, there is limited real-world evidence that targeting common genetic issues – like PTEN or PIK3CA – benefits patients. Even though these mutations frequently occur, finding treatments that can penetrate the brain’s natural defenses to reach them is challenging [38–45].

This research aims to employ advanced genetic testing (NGS) to identify specific mutations in brain cancer patients that can be treated with new, targeted drugs [46, 47]. Currently, the survival rate for

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glioblastoma is only 15 months, and standard treatments often fail because they do not consider the unique DNA of each tumor [17, 25]. The study is based on the hypothesis that glioblastoma and astrocytoma share both common and distinct sets of actionable pathogenic genes, which can be leveraged for targeted therapeutic interventions. It is also hypothesized that the integrative multi-omics analysis will uncover new therapeutic targets beyond the traditional driver mutations. Identifying and prioritizing such actionable genes is expected to enhance patient stratification and improve clinical outcomes within the precision oncology framework.

MATERIALS AND METHODS

1.Study Design and Data Source

The current investigation performed a systematic bioinformatic interrogation of targeted sequencing cohorts retrieved from the SRA database. By restricting the scope to glioblastoma and astrocytoma, the study sought to identify high-confidence somatic drivers. The methodology prioritized the use of matched tumor-normal pairs to provide a clear discriminatory boundary between de novo oncogenic mutations and inherent genetic variations or technical stochasticity. For the glioblastoma cohort, tumor sample SRR36669926 was analyzed against its matched normal sample SRR36669928, while for the astrocytoma cohort, tumor sample SRR36669910 was paired with its matched normal sample SRR36669918 [48].

Sequencing and Library Preparation

To facilitate comprehensive genomic interrogation, Genomic DNA libraries were synthesized using a hybrid-capture enrichment strategy to provide robust and reproducible coverage of the target capture regions. Sequencing was performed using the Illumina NovaSeq 6000 platform in a paired-end format, ensuring high-fidelity data acquisition [49].

Bioinformatics Analysis – Tools and Pipelines

Bioinformatics analysis was performed in a Linux environment adhering to the GATK Best Practices for somatic short variant discovery in tumor-normal pairs. Initial quality control of raw FASTQ files was conducted using FastQC (v0.11.9), followed by adapter trimming and low-quality base filtering (Phred score < 20) via fastp (v0.23.2); post-trimming quality was verified to ensure data integrity. High-quality reads were aligned to the human reference genome (GRCh38/hg38) using BWA-MEM (v0.7.17), and the resulting alignments were converted to BAM format, sorted, and indexed using SAMtools (v1.16.1). To refine the alignments prior to variant calling, Picard was utilized to assign read group metadata and mark PCR duplicates, thereby mitigating potential amplification biases. Systematic technical errors in base quality scores were subsequently corrected using GATK Base Quality Score Recalibration (BQSR). Somatic variants were identified utilizing GATK Mutect2 (v4.3.0.0). To minimize false positives, read orientation artifacts were modeled, and cross-sample contamination was estimated using the dedicated GATK downstream tools, with only variants retaining a strict “PASS” filter status retained for downstream analysis [50].

Functional Annotation and Driver Analysis

Ensembl Variant Effect Predictor (VEP) was used to annotate the filtered variants, focusing specifically on those that alter proteins such as missense, frameshift, and splice-site mutations. To determine which of these mutations were likely” drivers” *of cancer* versus “passenger” events, they were submitted to the *Cancer Genome Interpreter (CGI)*. Finally, manual inspection of the high-priority variants using the *Integrative Genomics Viewer (IGV)* was done to ensure they were not the result of recurring sequencing artifacts.

Ethical Considerations

The authors declare that this retrospective study was conducted using publicly available, de-identified genomic data. As no primary patient samples were collected and no identifiable private information

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was accessed, the research met the criteria for IRB exemption in compliance with the Declaration of Helsinki and relevant institutional policies.

RESULTS

Somatic Variant Analysis in Brain Tumor Samples

To characterize the somatic mutational landscapes of two histologically distinct brain malignancies, targeted next-generation sequencing of 529 cancer-associated genes was performed on matched tumor–normal tissue pairs obtained from patients with glioblastoma (GBM) and astrocytoma, respectively. Somatic variants were identified through a rigorous analytical pipeline encompassing raw data quality control, reference genome alignment, variant calling with GATK Mutect2, systematic filtering for sequencing artifacts and sample contamination, and functional consequence annotation via Ensembl Variant Effect Predictor (VEP). Only protein-altering somatic variants satisfying all quality thresholds were retained for downstream characterization [51].

Glioblastoma

Somatic profiling of the glioblastoma sample (SRR36669926 tumor versus SRR36669928 normal) revealed seven protein-altering variants encompassing missense substitutions, a frameshift deletion, and additional functionally significant alterations, with variant allele frequencies (VAFs) spanning a broad range from 0.013 to 0.976 (Table 1). The breadth of this VAF distribution reflects both dominant clonal events and lower-frequency subclonal alterations within the tumor microenvironment. As given in Figure 1 below the mutational landscape of both the cancer types are significantly different.

Table 1. Bioinformatic tools and software versions utilized in the somatic variant analysis pipeline, including their specific roles in sequence processing, alignment, and functional annotation.

Tool	Version	Purpose
FastQC	v0.11.9	Raw and post-trimming read quality assessment.
fastp	v0.23.2	Adapter trimming and low-quality read filtering.
BWA-MEM	v0.7.17	Alignment to GRCh38 reference genome.
SAMtools	v1.16.1	SAM/BAM conversion, sorting, and indexing.
Picard	v2.27.5	Read group assignments and duplicate marking.
GATK	v4.3.0.0	Base quality recalibration and variant calling.
Ensembl VEP	Release 110	Functional annotation and consequence prediction.
CGI	Web-based	Driver vs. passenger mutation classification.
IGV	v2.16.2	Read-level visualization of somatic variants.

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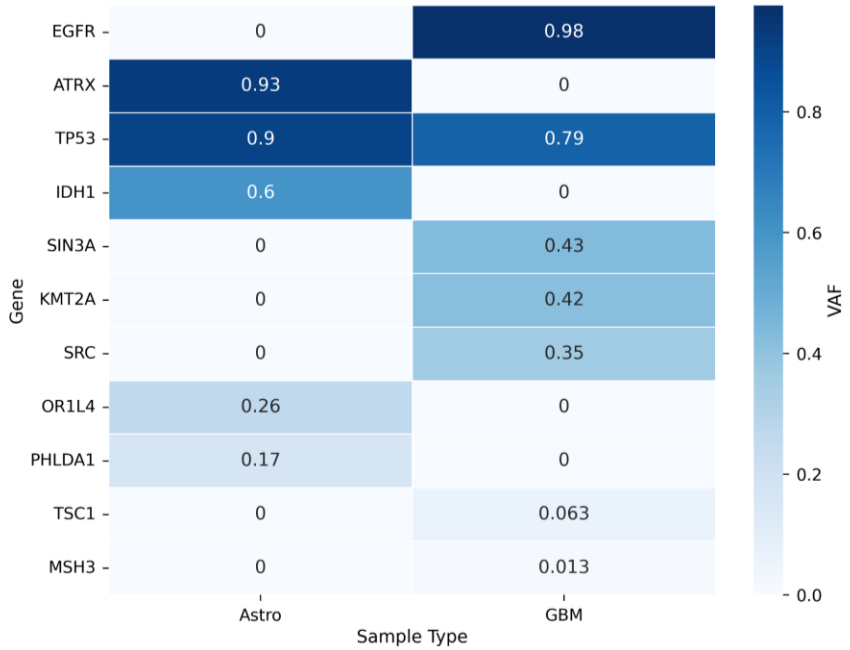

Figure 1. Heatmap depicts variant allele frequencies across key mutated genes in glioblastoma and astrocytoma, illustrating the distribution and relative clonal abundance of somatic mutations in each tumor type.

Among the identified variants, the *EGFR p.Asp256Ala* missense substitution (c.767A > C) exhibited the highest VAF at 0.976, at a sequencing depth of 4,713×, consistent with near-clonal fixation and indicative of a dominant early oncogenic event. This alteration affects the extracellular domain of the epidermal growth factor receptor and is recognized as a driver mutation conferring enhanced proliferative signaling in glioblastoma. Concurrently, the *TP53 p.Arg175His* mutation, a well-characterized hotspot that abrogates sequence-specific DNA binding, and thereby disrupts tumor suppressor function, was detected at a VAF of 0.788 against a sequencing depth of 258×, underscoring its prevalence across the tumor cell population. Secondary driver mutations were additionally identified in *KMT2A*, *SRC*, *MSH3*, and *TSC1*, collectively implicating dysregulation of epigenetic gene regulation, receptor tyrosine kinase signaling, DNA mismatch repair, and mTOR-mediated growth control, respectively. Refer to Figure 2 for somatic and driver mutations.

In contrast, the *SIN3A frameshift mutation* (p.Val362LeufsTer28; c.1084del; VAF 0.431; depth 842×) was classified as a passenger variant, lacking evidence of positive selection based on Cancer Genome Interpreter analysis.

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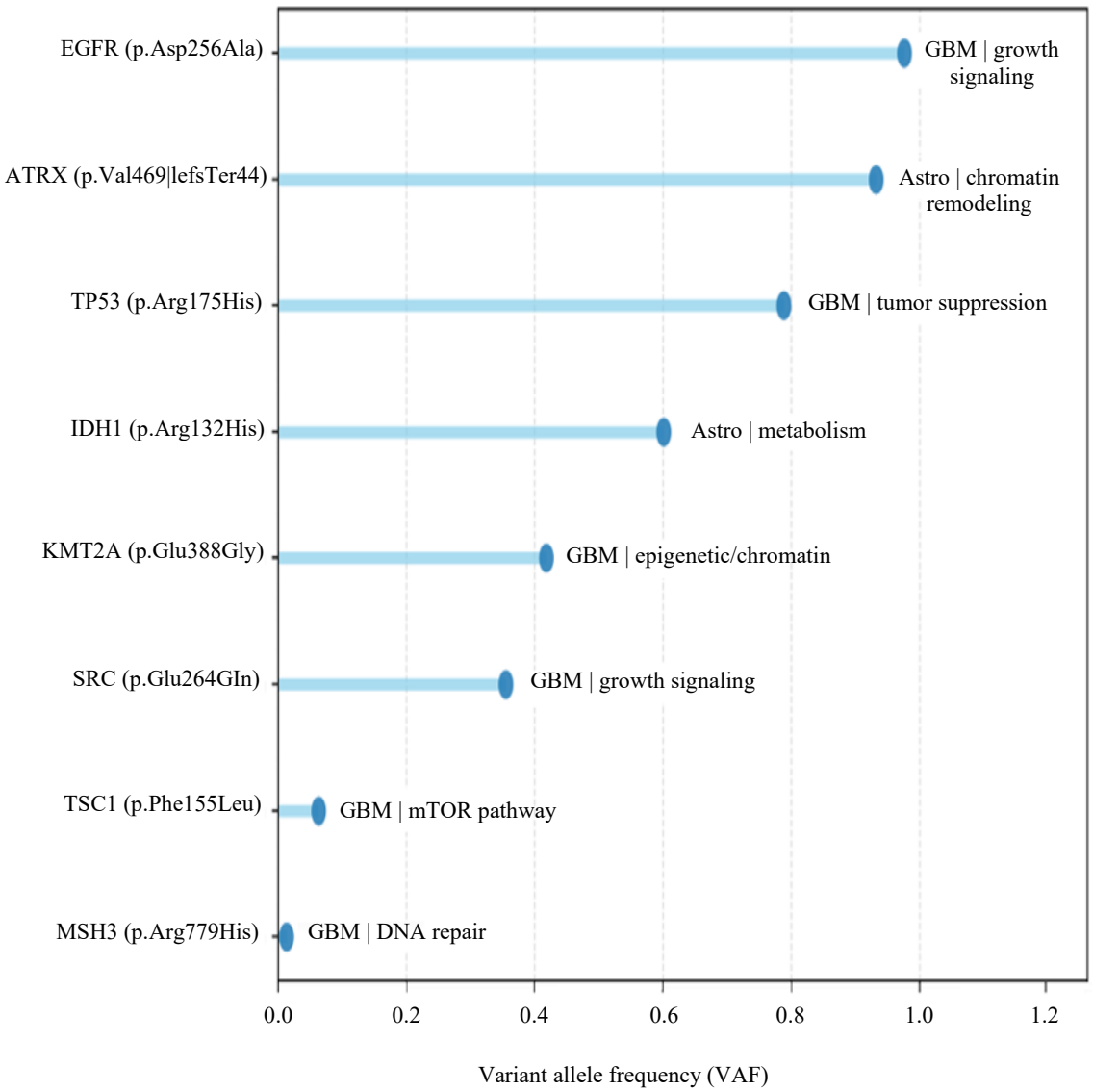

Figure 2. Summary of key somatic driver mutations identified in the glioblastoma sample, depicting variant allele frequencies alongside the corresponding functional consequences and implicated oncogenic pathways.

Astrocytoma

Parallel analysis of the astrocytoma sample (SRR36669910 tumor versus SRR36669918 normal) identified five protein-altering somatic variants, with VAFs ranging from 0.167 to 0.932 (Table 2). Notably, the overall variant burden was lower relative to the glioblastoma case; however, the identified alterations converged on molecularly defined pathways that are characteristic of this glioma subtype (Table 3).

Table 2. Protein-altering somatic variants identified in the glioblastoma tumor sample, detailing specific genetic alterations, variant types, variant allele frequencies (VAF), and sequencing depths.

Gene	Protein change	cDNA change	Variant type	VAF	Depth
KMT2A	p.Glu388Gly	c.1163A > G	Missense	0.418	803
SIN3A	p.Val362LeufsTer28	c.1084del	Frameshift	0.431	842
TP53	p.Arg175His	c.524G > A	Missense	0.788	258
SRC	p.Glu264Gln	c.790G > C	Missense	0.355	61
MSH3	p.Arg779His	c.2336G > A	Missense	0.013	554
EGFR	p.Asp256Ala	c.767A > C	Missense	0.976	4713

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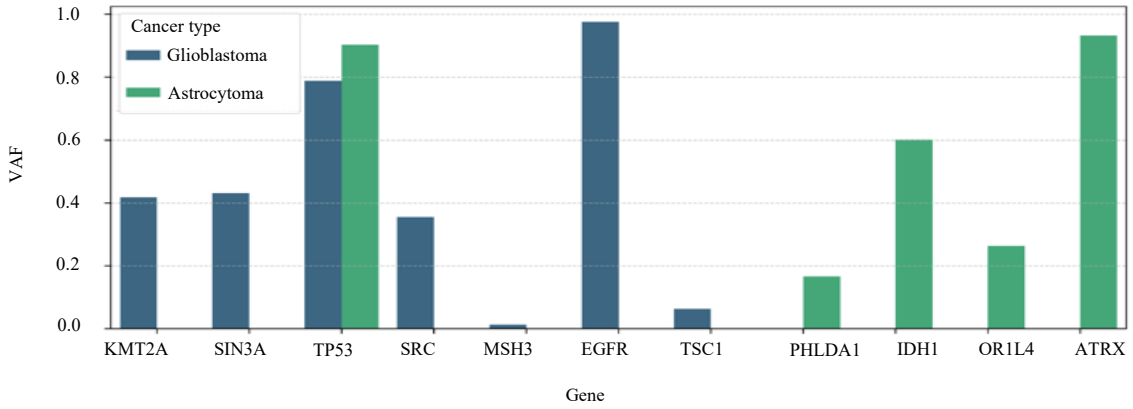
TSC1	p.Phe155Leu	c.463T > C	Missense	0.063	599

Table 3. Summary of somatic genomic alterations detected in the astrocytoma case, detailing protein and cDNA level changes alongside the clonal distribution (VAF) for each variant.

Gene	Protein change	cDNA change	Variant type	VAF	Depth
PHLDA1	p.Gln305His	c.915G > C	Missense	0.167	11
TP53	p.Asp281His	c.841G > C	Missense	0.904	628
IDH1	p.Arg132His	c.395G > A	Missense	0.601	627
OR1L4	p.Leu48Pro	c.143T > C	Missense	0.263	19
ATRX	p.Val469IlefsTer44	c.1405_1408del	Frameshift	0.932	347

The hallmark *IDH1 p.Arg132His* missense mutation (c.395G>A) was identified with a VAF of 0.601 at a sequencing depth of 627×, consistent with its well-established role as an initiating metabolic driver that promotes oncometabolite accumulation and epigenome-wide hypermethylation in lower-grade gliomas. A high-VAF frameshift deletion in *ATRX* (p.Val469IlefsTer44; c.1405_1408del; VAF 0.932; depth 347×) is consistent with complete loss of function, impairing chromatin remodeling and telomere maintenance through the ALT (alternative lengthening of telomeres) pathway. The *TP53 p.Asp281His* mutation was detected at an elevated frequency (VAF 0.904; depth 628×), reflecting widespread disruption of p53-mediated tumor suppressor signaling across the tumor cell population. The remaining variants, affecting *PHLDA1* and *OR1L4*, were detected at lower allelic frequencies (VAFs of 0.167 and 0.263, respectively) and classified as likely passenger mutations, pending functional validation. Refer Figure 3 for more details [52].



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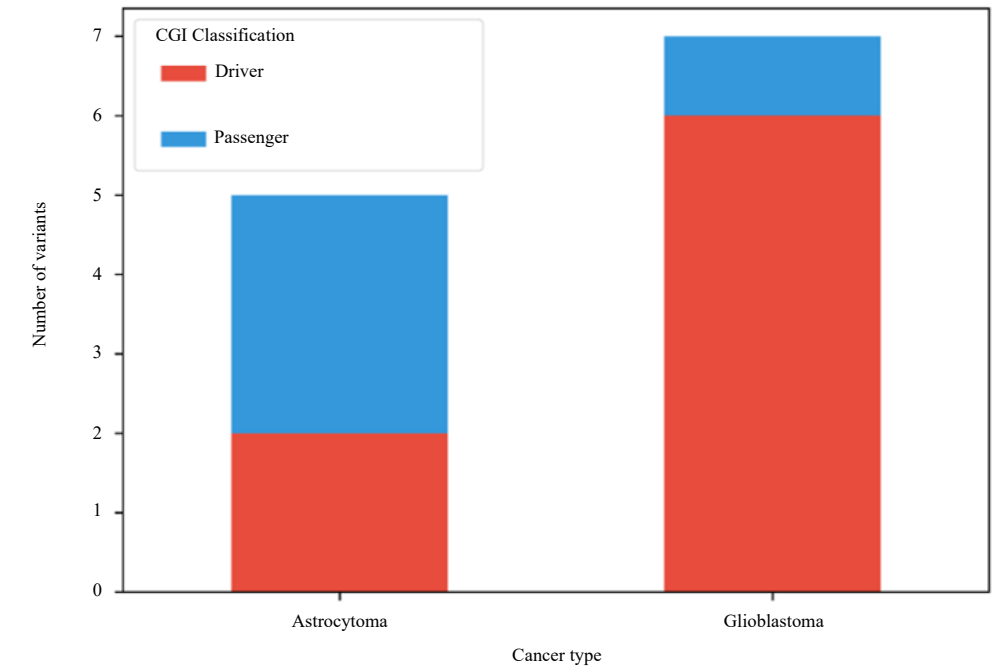

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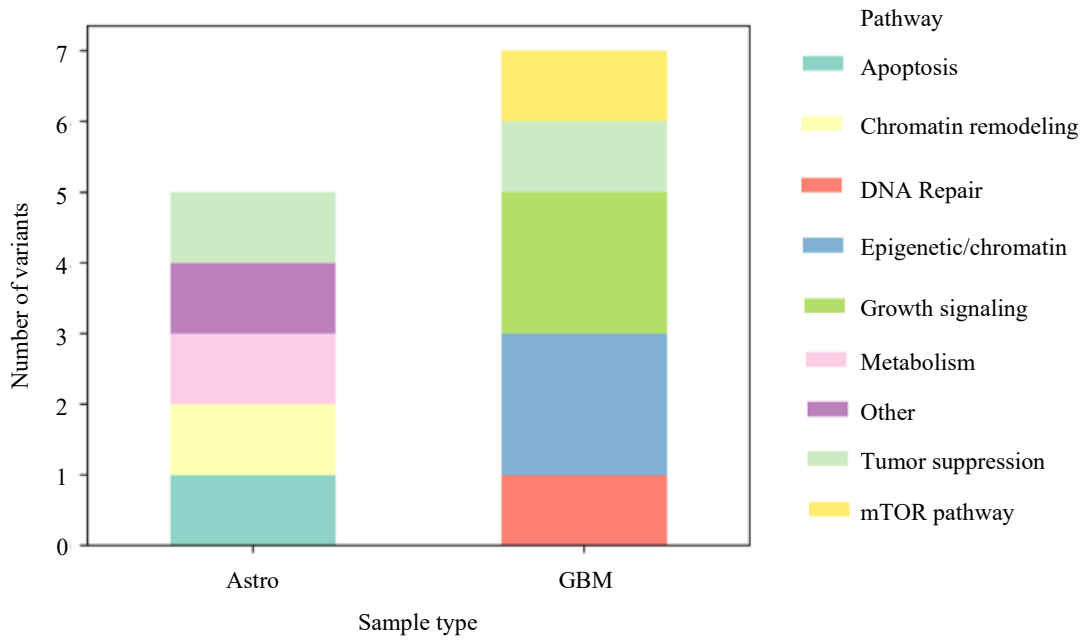

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Figure 3. A. Bar chart comparing variant allele frequencies across mutated genes in glioblastoma and astrocytoma, highlighting inter-tumor differences in mutational prevalence and clonal composition. B. Stacked bar chart depicting the proportional distribution of driver and passenger mutations identified in glioblastoma and astrocytoma samples, as classified by Cancer Genome Interpreter. C. This figure presents a stacked bar chart comparing the number of protein-altering somatic variants across key biological pathways in glioblastoma (GBM) and astrocytoma (Astro) samples. Glioblastoma shows a higher frequency of mutations in epigenetic/chromatin regulation, growth signaling, tumor suppression, and the mTOR pathway. In contrast, astrocytoma variants predominantly affect apoptosis, chromatin remodeling, metabolism, tumor suppression, and other pathways. Each color denotes a specific pathway, providing a clear comparison of the functional mutation profiles between the two tumor types.

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Driver and Passenger Mutation Classification

Systematic variant classification using Cancer Genome Interpreter established that glioblastoma mutations in *TP53, EGFR, KMT2A, SRC, MSH3*, and *TSC1* were each classified as driver mutations based on established oncogenic activity, whereas the *SIN3A* mutation was designated a passenger variant. In the astrocytoma sample, mutations in *IDH1* and *ATRX* were designated as bona fide oncogenic drivers, while *TP53*, *PHLDA1*, and *OR1L4* were each categorized as passenger mutations. The complete classification profile, inclusive of protein changes, cDNA alterations, and functional annotations for all variants, is presented in the table below (Table 4).

Table 4. Functional classification of somatic variants in glioblastoma and astrocytoma, identifying driver and passenger mutations and their respective roles in oncogenic signaling and cellular regulation.

Cancer type	Gene	Protein change	cDNA change	Classification	Functional role
Glioblastoma	TP53	p.Arg175His	c.524G > A	Driver	Tumor suppressor, DNA-binding disruption.
Glioblastoma	EGFR	p.Asp256Ala	c.767A > C	Driver	Growth factor receptor, proliferative signaling.
Glioblastoma	KMT2A	p.Glu388Gly	c.1163A > G	Driver	Epigenetic regulation.
Glioblastoma	SRC	p.Glu264Gln	c.790G > C	Driver	Signaling kinase.
Glioblastoma	MSH3	p.Arg779His	c.2336G > A	Driver	DNA mismatch repair.
Glioblastoma	TSC1	p.Phe155Leu	c.463T > C	Driver	mTOR pathway regulation.
Glioblastoma	SIN3A	p.Val362LeufsTer28	c.1084del	Passenger	Transcriptional repression.
Astrocytoma	IDH1	p.Arg132His	c.395G > A	Driver	Metabolic reprogramming.
Astrocytoma	ATRX	p.Val469IlefsTer44	c.1405_1408del	Driver	Chromatin remodeling, telomere maintenance.
Astrocytoma	TP53	p.Asp281His	c.841G > C	Passenger	Tumor suppressor.
Astrocytoma	PHLDA1	p.Gln305His	c.915G > C	Passenger	Apoptosis regulation.
Astrocytoma	OR1L4	p.Leu48Pro	c.143T > C	Passenger	Unknown/uncertain role.

Potential Novel Variants and Pathways

Beyond the established driver mutations, several somatic variants detected in this study represent potential novel alterations that are not currently catalogued as oncogenic drivers and may warrant independent functional investigation. Below listed are the top 25 pathway enrichment genes from both the cancer types, please refer to Figure 4. In the glioblastoma sample, candidate novel variants were identified as missense and frameshift mutations in KMT2A, SIN3A, SRC, MSH3, and TSC1 genes that are functionally implicated in epigenetic gene regulation, transcriptional repression, receptor tyrosine kinase signaling, DNA mismatch repair, and mTOR pathway control, respectively. The detection of several of these variants at moderate to high VAFs raises the possibility that they may exert functional contributions to tumor biology that extend beyond their current passenger classification, potentially modulating the penetrance or aggressiveness of co-occurring driver events.

In the astrocytoma sample, missense mutations in PHLDA1 (p.Gln305His; VAF 0.167) and OR1L4 (p.Leu48Pro; VAF 0.263) were identified as novel candidates. Although both are provisionally classified as passenger mutations, definitive exclusion of biological relevance requires dedicated functional experimentation. PHLDA1 participates in the regulation of apoptotic signaling, and gain- or loss-of-function perturbations at this locus could conceivably modulate tumor cell survival thresholds. The oncological role of OR1L4 in brain tumors remains poorly characterized, representing a potential avenue for future mechanistic inquiry.

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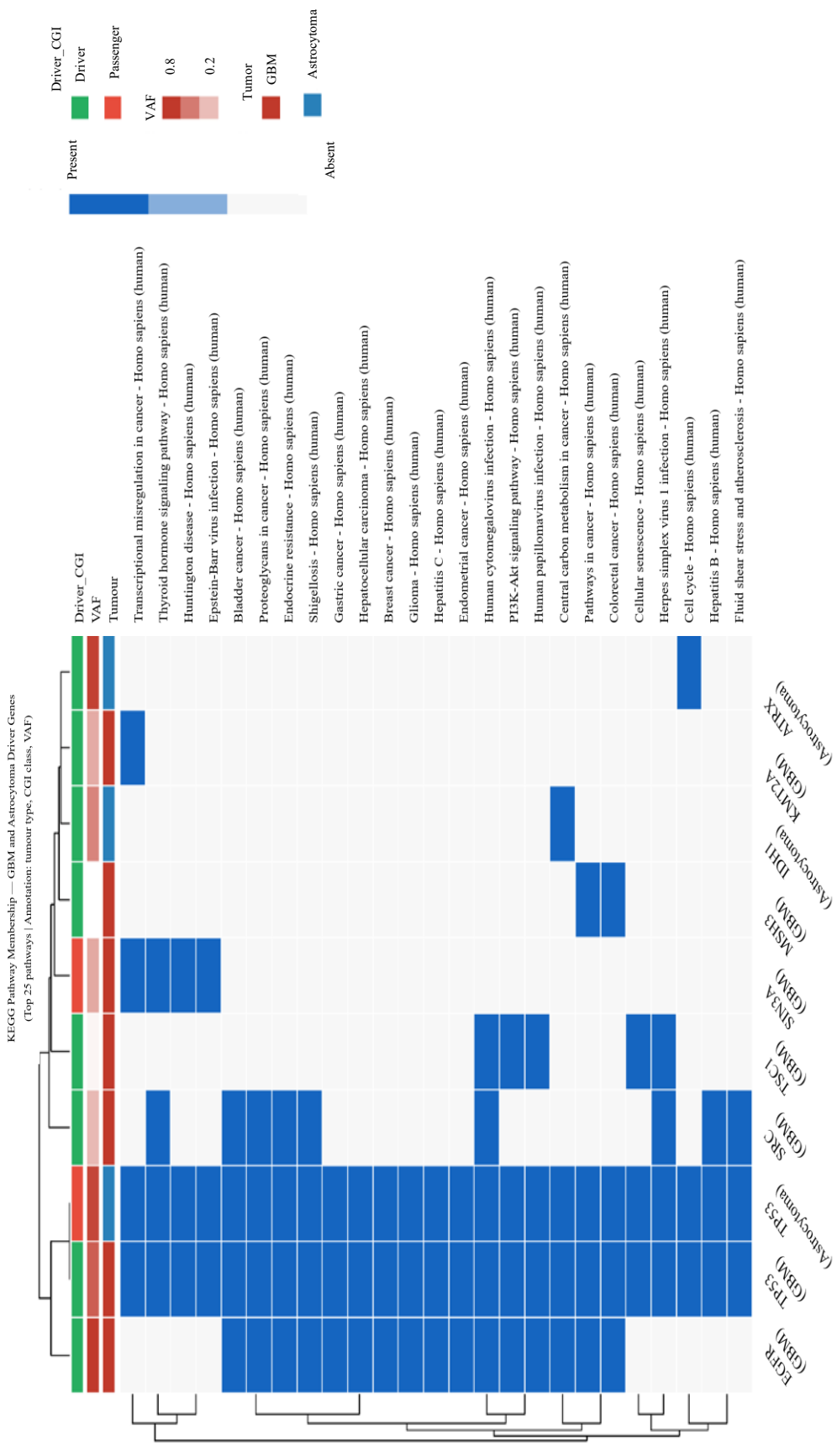

Figure 4. Heatmap of KEGG pathway membership for GBM and astrocytoma driver genes. Hierarchical clustering of the top 25 enriched KEGG pathways associated with driver mutations in glioblastoma (GBM) and astrocytoma. Columns represent individual genes (e.g., EGFR, TP53, IDH1) and are annotated by tumor type (GBM vs. Astrocytoma), variant allele frequency (VAF), and Cancer Genome Interpreter (CGI) classification (Driver vs. Passenger). Rows indicate presence (blue) or absence (light grey) of the gene within the specified KEGG pathway.

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Collectively, the shared tumor specific pathways are significant, these observations underscore the need for comprehensive functional assays and replication in larger, well-annotated cohorts to elucidate the oncogenic potential of these candidate variants and to evaluate their utility as novel biomarkers or actionable therapeutic targets in glioblastoma and astrocytoma. Please refer to Figure 5 below.

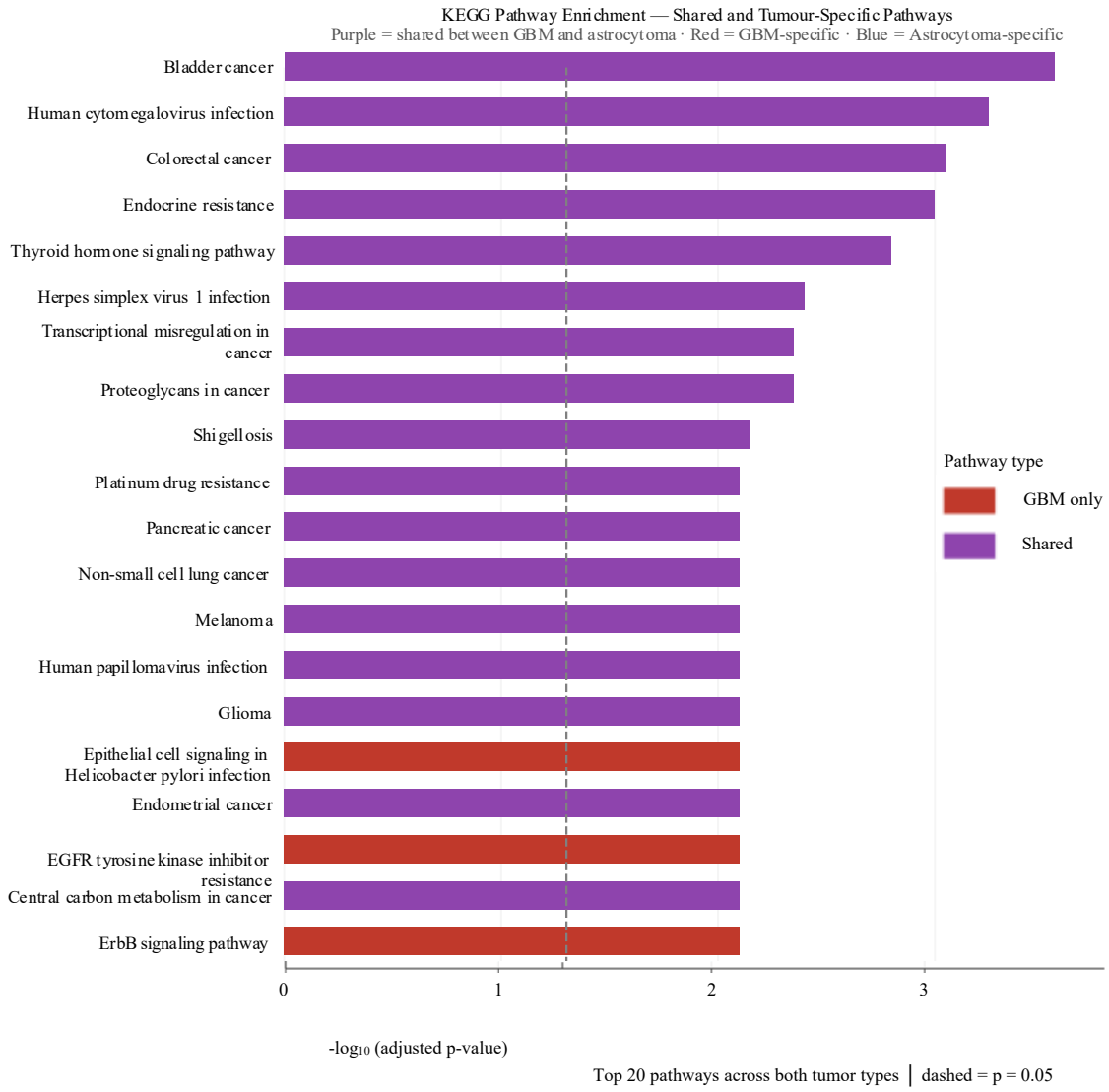

Figure 5. Shared and Tumor-Specific KEGG Pathway Enrichment. Pathways are color-coded to distinguish those shared between GBM and astrocytoma (purple) from those uniquely enriched in GBM (red) such as the ErbB signaling pathway and EGFR tyrosine kinase inhibitor resistance. The vertical dashed line denotes the statistical significance threshold of 0.5.

These somatic variant profiling delineated divergent and histotype-specific mutational landscapes in glioblastoma and astrocytoma. The glioblastoma sample was characterized by a mutational spectrum dominated by high-frequency alterations in growth factor receptor and tumor suppressor pathways, most prominently exemplified by near-clonal mutations in *EGFR* and *TP53*. Please refer to Figure 6 for comparative pathway analysis of Glioblastoma and astrocytoma. By contrast, the astrocytoma sample recapitulated the classical WHO-defined molecular signature of lower-grade glioma, with co-occurring pathogenic alterations in *IDH1*, *ATRX*, and *TP53*, collectively reflecting metabolic reprogramming, alternative telomere maintenance, and loss of tumor suppressor integrity. Across both tumors, variants exhibiting elevated VAFs are interpreted as early clonal events that confer selective growth advantage, whereas those with lower VAFs likely represent subclonal heterogeneity arising during tumor evolution.

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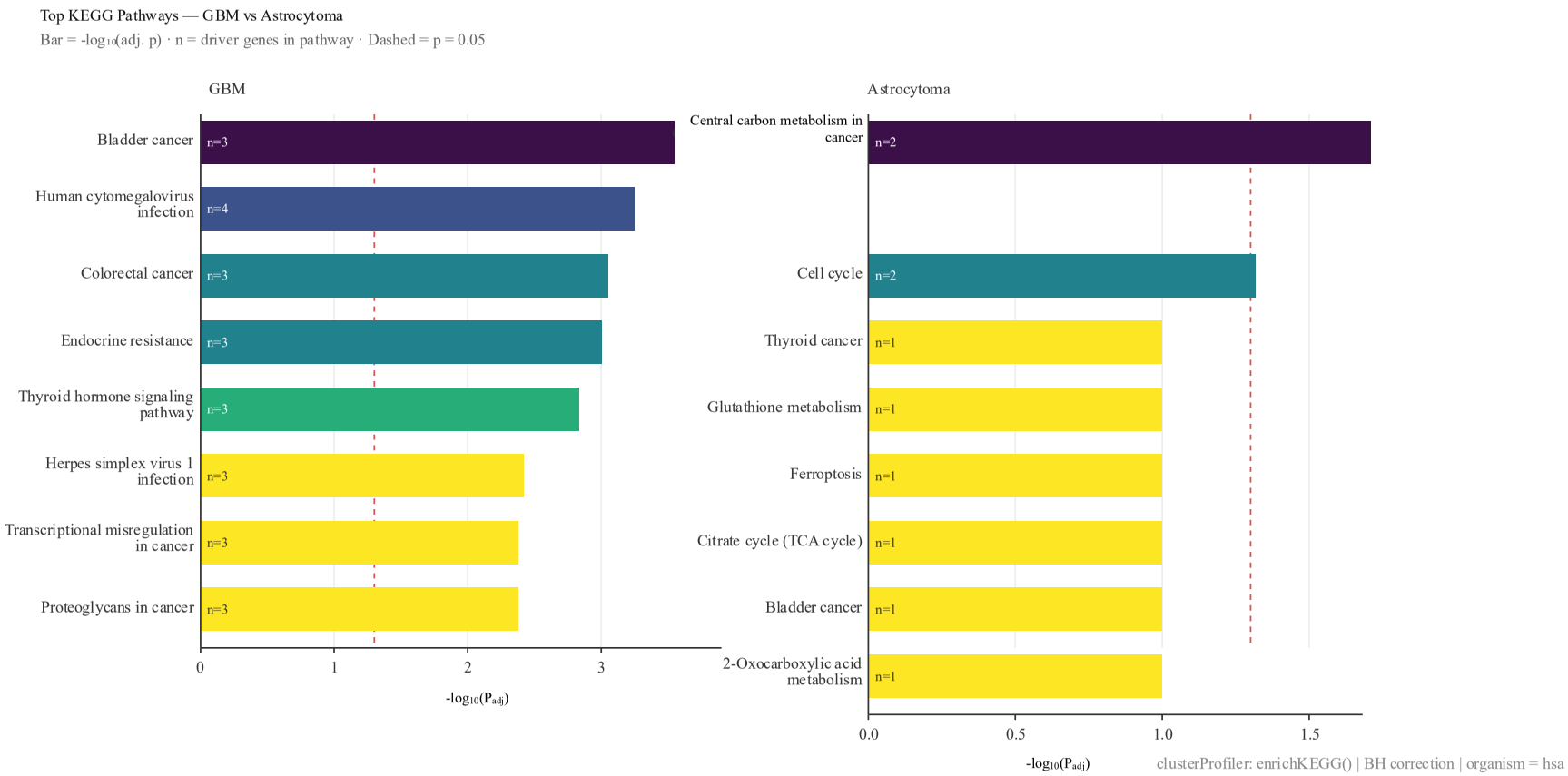

Figure 6. Comparative analysis of Top enriched KEGG pathways in GBM vs. astrocytoma. Side-by-side comparison of pathway enrichment profiles for GBM (left) and astrocytoma (right). The x-axis represents the significance of enrichment. The number of identified driver genes mapped to each respective pathway is annotated within the bars. The vertical red dashed line indicates the significance threshold of adjusted p = 0.05. Notably, astrocytoma is distinctly driven by disruptions in central carbon metabolism and the cell cycle, while GBM shows highly significant enrichment in a broader array of pathways.

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DISCUSSION

The somatic mutational landscapes observed in this study demonstrate histotype-specific patterns of dysregulation of oncogenic pathways in glioblastoma (GBM) and astrocytoma and also identify shared vulnerabilities that could be targeted in a precision therapeutic approach for the two tumor subtypes.

The near-clonal fixation of EGFR p.Asp256Ala (VAF = 0.976) in GBM suggests it represents a dominant onset event, consistent with the critical role of EGFR amplification and mutation in aberrant proliferative signaling in glioblastoma (Cancer Genome Atlas Research Network, 2008). The mechanistic interpretation is also supported by the KEGG enrichment analysis, as genes associated with the bladder cancer, endocrine resistance, colorectal cancer, and human cytomegalovirus infection pathways are enriched among the GBM driver genes, and are mapped to the same genes ratio and overlap, as shown in the pathway maps overlain with the VAF in the pathway viewer, on the two key pathways, EGFR-initiated RAS–RAF–MEK–ERK (MAPK) and PI3K–AKT–mTOR. The VAF overlay on the endocrine resistance pathway (hsa01522) is instructive, as EGFR seems to be the upstream regulator of both the MAPK and PI3K–AKT cascades at once, and the propagation of the pathway to mTOR and cell cycle regulatory nodes suggests that the EGFR p.Asp256Ala substitution is a systemic amplifier of proliferative and survival signals through multiple effector arms. At the same time, the TP53 p.Arg175His mutation (VAF = 0.788), a well characterized hotspot that inactivates sequence specific DNA binding and, therefore, tumor suppressor signaling, is highlighted in all cell cycle, bladder cancer and colorectal cancer KEGG overlays, indicating an overall disruption of p53-mediated tumor suppressor signaling among the tumor cell population (Cancer Genome Atlas Research Network, 2008). EGFR mutation is nearly always accompanied by near-clonal EGFR mutation, creating a dual-hit oncogenic architecture in GBM, which has been linked to the aggressive clinical phenotype that is typical for GBM [45].

In addition to this basic oncogenic dyad, the GBM driver gene complement identifies other, mechanistically different gene regulatory layers. A missense alteration that is predicted to disrupt transcriptional control programs is present in KMT2A (VAF = 0.418) which is involved in epigenetic gene regulation (Table 4). SRC (VAF = 0.355), another signaling kinase driver (Table 4), is shown as an activated downstream node in the bladder cancer pathway overlay (hsa05219), alongside with EGFR, as part of the receptor-proximal signal transduction. MSH3 (VAF = 0.013), considered a driver affecting DNA mismatch repair (Table 4), is highlighted in the microsatellite instability module of the colorectal cancer pathway overlay (hsa05210) as a DNA repair gene, and its mutation is at sub clonal frequency, suggesting that there may be a more pronounced attrition of mismatch repair genes in some regions that could accelerate intratumorally mutational diversification. The human cytomegalovirus infection pathway overlay (hsa05163) contained a pathway-level feed-forward amplification of anabolic growth signaling as shown by the appearance of TSC1 (VAF = 0.063), a regulator of the mTOR pathway (Table 4), as an active node in this pathway, further reinforcing mTOR hyperactivation when initiated upstream by EGFR and AKT. Together the GBM mutation profile represents a network level deregulatory process, involving growth factor receptor signaling, epigenetic regulation, loss of tumor suppressors, DNA mismatch repair, and growth control mediated by the mTOR pathway.

Despite a lower burden of mutations, the astrocytoma molecular landscape is also molecularly precise in its representation of the one defined by the WHO classification of astrocytoma [22]. IDH1 p.Arg132His (VAF = 0.601) is the driver initiating event, that is associated with accumulation of oncometabolites, leading to epigenome-wide hypermethylation reminiscent of its known metabolic reprogramming activity in lower-grade gliomas [22]. This metabolic aspect was further highlighted by the results of the KEGG enrichment analysis, which resulted in the highest signal for enrichment in the central carbon metabolism in cancer pathway (hsa05230) with IDH1 specifically being shown in the isocitrate-to-2-oxoglutarate conversion step in the citrate cycle module of the malignant cell panel. The TCA cycle pathway overlay (hsa00020) further confirmed IDH1's impact on central oxidative metabolism, with the enzyme nodes highlighted in the pathway directly corresponding to the metabolic diversion caused by this new IDH1 substitution. The concomitant ATRX frameshift deletion (VAF = 0.932)

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appears to be an "extremely serious deletion" and affects the ATM function in two pathways: chromatin remodeling, which was highlighted as a node in the cell cycle pathway overlay (hsa04110), and telomere maintenance (ALT), consistent with its functional link with DNA damage surveillance machinery. Even though the TP53 p.Asp281His alteration was assigned as a passenger alteration by Cancer Genome Interpreter, it was found at almost the same frequency in the tumor cell population, indicating that the TP53 alteration in the tumor suppressor pathway is widely distributed (Table 3), suggesting that the p.Asp281His alteration has a biological role to understand in relation to co-occurring IDH1 and ATRX driver alterations.

The genes in the shared pathway analysis were enriched in both tumor types, including pathways that involve genes shared by the two, such as bladder cancer, human cytomegalovirus infection, colorectal cancer, endocrine resistance, glioma, and the PI3K–AKT, MAPK, and ErbB signaling pathways, all of which include constituents from both types of tumor, including TP53 and EGFR genes. GBM-specific enrichment was limited to the pathways that were highly EGFR–ErbB–SRC network connected, such as ErbB signaling, EGFR tyrosine kinase inhibitor resistance, and epithelial cell signaling in Helicobacter pylori infection, which indicates that EGFR has a disproportionate signaling role in the oncogenic architecture of GBM. In contrast, the enrichment of the citrate cycle and central carbon metabolism in cancer pathways in astrocytoma, but not in the GBM driver gene set, highlights the metabolic reprogramming that occurs as an astrocytoma-defining oncogenic mechanism missing in GBM. The unified pathway heatmap confirmed the functional neurogliomas. In GBM, the combination of EGFR, SRC and TSC1 mutations around the PI3K–AKT–mTOR axis suggests that targeting two or three of them simultaneously could be more effective at inhibiting adaptive signaling bypass than targeting them individually, a principle that is consistent with broader observations that targeting has been unsuccessful in the absence of more thorough molecular stratification in GBM [45]. The sub clonal MSH3 alteration further raises the question of whether there is a subset of cells which may have a different mutation load or response to immunotherapy due to focal mismatch repair deficiency. equation of driver genes within these pathway spaces shared and specific to GBM, highlighting that GBM and astrocytoma use similar signaling infrastructure at the network level, but use different molecular lesions to reach the same pathway space, using receptor tyrosine kinase signaling in GBM, and epigenetic signaling/structural remodeling of chromatin in astrocytoma.

The results have implications straight away for precision oncology strategy in the case of diffuse IDH1 p.Arg132His is a directly druggable target within a new class of IDH-mutant gliomas therapies: patients with tier 1/2 alterations, including IDH1/2 mutations, have a significantly longer progression-free survival with molecularly matched therapy [25]. The use of the single tumor–normal pair design and inclusion of only somatic SNVs and small indels in the present study necessarily limits generalizability, and larger, well-annotated cohorts with genomic sequencing of the entire genome and matched epigenomic profiling will be needed to further validate these pathway-level observations and to translate these into clinically implementable, biomarker-stratified treatment algorithms within the framework of precision oncology in the case of diffuse gliomas [45, 25].

Limitations

The present study was restricted to high-confidence somatic single nucleotide variants (SNVs) and small insertion-deletion variants (indels) identified through targeted panel sequencing. Copy number variation (CNV) analysis was not undertaken owing to technical constraints inherent to panel-based library design and uneven coverage across the targeted region. Future studies employing whole-genome or whole-exome sequencing platforms with matched normal controls would substantially augment these findings by enabling comprehensive and unbiased CNV profiling, structural variant detection, and assessment of non-coding regulatory alterations.

FUTURE DIRECTIONS

Future research should focus on expanding cohort sizes to include diverse, multi-omic datasets integrating genomic, epigenomic, and transcriptomic profiles to validate and refine pathway-level insights.

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Comprehensive whole-genome sequencing and structural variant analyses are essential to capture the full spectrum of actionable alterations beyond single nucleotide variants. Functional characterization of novel candidate mutations will clarify their oncogenic potential and therapeutic relevance. Ultimately, these efforts will facilitate the development and clinical implementation of robust, biomarker-driven precision oncology algorithms tailored to glioblastoma and astrocytoma subtypes.

CONCLUSION

This study successfully identified high-confidence somatic driver mutations in glioblastoma and astrocytoma, with the glioblastoma sample characterized by dominant near-clonal alterations in EGFR (p.Asp256Ala) and TP53 (p.Arg175His), underscoring their central role in proliferative signaling and tumor suppression disruption. In contrast, the astrocytoma sample exhibited hallmark driver mutations in IDH1 (p.Arg132His) and ATRX (frameshift deletion), reflecting metabolic reprogramming and chromatin remodeling consistent with lower-grade glioma biology. These findings reinforce the imperative to move beyond uniform treatment paradigms toward precision oncology approaches that leverage tumor-specific genomic vulnerabilities. Notably, the identification of actionable mutations, such as IDH1 supports the clinical utility of molecularly matched therapies, which have demonstrated improved progression-free survival in patients harboring tier 1/2 alterations. Looking forward, expanding this work through larger, multi-omic cohorts integrating genomic, epigenomic, and transcriptomic data will be critical to validate these pathway-level insights and to develop robust, biomarker-driven treatment algorithms that can be effectively implemented in clinical practice for personalized management of diffuse gliomas.

Author Contributions

Conceptualization: ARK, DP; Data Curation & Bioinformatics Analysis: ARK, SS, DP, TS; Methodology & Pipeline Development: ARK, SS, DP; Formal Analysis & Interpretation: ARK, SS, SPH, DP, TS, AST; Writing – Original Draft: ARK, DP, TS, PV, SD; Writing – Review & Editing: ARK, DP, TS; Supervision & Project Administration: ARK, SPH, DP; Final Approval: All authors.

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Conflict of Interest

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

Ethics Approval

Not applicable. This manuscript is a comprehensive scientific article and does not involve primary data collection. All data used in this study are publicly available from the NCBI Sequence Read Archive (SRA) and were analyzed using freely available bioinformatics tools. All cited genetic and clinical data were derived from previously published, peer-reviewed studies.

Consent for Publication

Not applicable. The manuscript does not contain any individual person’s data in any form (including individual details, images, or videos).

Competing Interests

The authors declare that they have no competing interests.

Data Availability

All data synthesized in this article are available within the manuscript and its supplementary materials.

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