Regional Differences in Brain Tumors: Genetic Drivers and Spatial Molecular Ecology

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Abstract

The human brain exhibits pronounced regional specialization in cellular composition, gene expression, and tissue organization. Increasing evidence indicates that these spatial differences influence where brain tumors arise and how they evolve. Across tumor entities such as gliomas, meningiomas, and brain metastases, specific molecular subtypes frequently display characteristic anatomical distributions, suggesting a functional coupling between tumor genetics and regional brain microenvironments.

In this mini review, we summarize recent advances in understanding how regional brain biology shapes the molecular and ecological landscapes of brain tumors. We discuss evidence linking anatomical location with tumor genotype, cellular states, and microenvironmental interactions. We further highlight the emerging concept of "region-aware oncology," in which tumor behavior is interpreted within the anatomical and molecular context of the surrounding brain tissue.

A deeper understanding of this spatial coupling may improve tumor classification and support the development of region-informed diagnostic and therapeutic strategies.

Keywords

regional heterogeneity; glioma; brain metastasis; meningiomas; tumor microenvironment

Introduction

The human brain is an extraordinarily heterogeneous organ, composed of numerous anatomically and functionally distinct regions that differ in developmental origin, cellular composition, and regulatory landscape. Such regional heterogeneity forms the molecular and cellular foundation of diverse neural functions. Recent advances in multi-

omics and spatial transcriptomic technologies have begun to unravel the region-specific molecular architecture of the normal brain, revealing that each area possesses unique gene-expression profiles, co-expression networks, and signaling environments [1-3].

Mounting evidence suggests that this intrinsic regional diversity may profoundly influence the initiation, evolution, and therapeutic response of brain tumors. Gliomas, meningiomas, and brain metastases all exhibit clear spatial preferences: specific mutations and transcriptional programs are enriched in defined anatomical locations. For example, *IDH*-mutant gliomas frequently occur in the frontal and temporal lobes [4], whereas *H3K27M*-mutant diffuse midline gliomas arise in the thalamus and brainstem [5]. Similarly, *NF2*-driven meningiomas predominate on the convexity, while *TRAF7–KLF4–AKT1–SMO* variants localize mainly to the skull base [6-8].

These spatial-genetic patterns indicate that tumor genotypes and anatomical environments may be functionally coupled, reflecting co-evolution between cancer genetics and regional brain ecology [9,10].

However, despite increasing recognition of these relationships, a systematic understanding of region-specific tumor biology remains limited. Most studies have focused on individual tumor types or isolated brain regions, and integrative analyses combining developmental lineage, epigenetic regulation, and microenvironmental context are still scarce. Understanding how the regional molecular baseline of the human brain constrains or enables specific oncogenic pathways could provide new insights into tumor heterogeneity, regional vulnerability, and therapeutic targeting.

In this review, we summarize current progress on regional molecular heterogeneity in the normal brain and discuss how these intrinsic differences might shape the genetic, transcriptomic, and ecological landscapes of gliomas, meningiomas, and brain metastases. We further propose a “region-aware” framework for oncology, which we define as the integration of genetic, spatial, and anatomical information to sharpen our understanding of tumor biology and to inform more precise therapeutic strategies. Together, these observations support the concept that brain tumors arise within regionally defined molecular ecosystems, where anatomical context and oncogenic mutations interact to shape tumor behavior.

Literature Search Strategy

Relevant studies were identified through searches of PubMed and Web of Science for articles published in English. Keywords included “brain tumor”, “glioma”, “meningioma”, “brain metastasis”, “spatial heterogeneity”, and “brain

region". Priority was given to recent studies investigating regional molecular features and tumor microenvironment interactions in brain tumors.

1 The Molecular Landscape of Normal Brain Regions

1.1 Regional Cellular Composition and Molecular Heterogeneity in the Normal Brain

Understanding the intrinsic molecular organization of the normal brain is essential for interpreting regional differences observed in brain tumors. The adult human brain is highly regionally specialized at the molecular and cellular levels. This diversity is evident not only in the types and proportions of cells present, but also in region-specific gene expression patterns, co-expression modules, and regulatory programs. In a landmark study, Siletti et al. generated a single-nucleus atlas of roughly three million cells sampled from about 100 anatomically defined locations across the forebrain, midbrain, and hindbrain, uncovering systematic variation in both neuronal and glial populations. The cerebral cortex shows a characteristic laminar architecture, with upper- and deep-layer excitatory neurons—including intratelencephalic, near-projecting, and corticothalamic subtypes—alongside inhibitory neurons derived from distinct developmental lineages. By contrast, the midbrain, brainstem, and hypothalamus contain highly heterogeneous neuronal assemblies that frequently co-express multiple neurotransmitters and neuropeptides, pointing to potentially more complex, multimodal functional organizations outside the cortex. Regional specialization is equally evident among glial cells: astrocytes and oligodendrocyte progenitor cells (OPCs) in telencephalic areas differ substantially from their counterparts in non-telencephalic regions in both molecular signatures and relative abundance, suggesting that even shared lineages can follow distinct differentiation paths and assume different roles depending on their anatomical milieu [1].

1.2 Cross-Regional Single-Cell Atlases Reveal Region-Specific Cellular Ecosystems

Extending these efforts, Chen et al. assembled 70 single-cell and single-nucleus transcriptomic datasets, comprising approximately 11.3 million cells, to generate a Brain Cell Atlas spanning 14 major brain regions and 30 subregions. This integrative analysis defined region-specific cellular landscapes and associated gene regulatory circuits. In this atlas, the cerebral cortex is dominated by upper- and deep-layer intratelencephalic neurons, whereas the hippocampus contains neuronal populations specific to CA1–CA4 fields and the dentate gyrus. By contrast, the thalamus and amygdala are distinguished by excitatory nuclear neurons together with specialized regulatory glial subsets. Regional specialization is also apparent at the levels of cell–cell communication and transcriptional control, not just in

which cell types are present. Microglia, for example, display distinct transcriptional states and ligand–receptor interaction patterns in the prefrontal cortex versus the hippocampus, consistent with region-specific modes of immune surveillance and metabolic support. Together, these integrative atlases indicate that brain-region specialization is shaped not only by the distribution of developmental lineages, but also by ongoing functional adaptation driven by local microenvironmental signals [2].

1.3 Gene Co-Expression Networks and Functional Modularization Across Brain Regions

From a systems-level perspective, analysis of GTEx RNA-seq data across 13 normal brain regions enabled the construction of a genome-wide gene co-expression network (GCN), uncovering distinct co-expression modules and functional enrichments. Characteristic genes of the cerebral cortex are primarily enriched in synaptic transmission and neuronal signaling pathways; those of the basal ganglia relate to motor control and neurotransmitter metabolism; cerebellar modules are involved in ion homeostasis and neurodevelopment; and the spinal cord exhibits a highly unique co-expression pattern that forms a separate cluster in dimensional reduction analyses. The number of eQTLs and the degree of gene connectivity differ substantially among regions, implying a hierarchical variation in the complexity and robustness of regional gene-regulatory networks. These differences align closely with functional compartmentalization: the prefrontal and parietal cortices, which mediate cognition and perception, are enriched for signaling and synaptic plasticity genes, whereas the basal ganglia, hypothalamus, and brainstem, associated with motor and autonomic regulation, predominantly express genes linked to energy metabolism and neurotransmitter pathways [3].

Taken together, molecular distinctions among brain regions appear to be deeply shaped by developmental origins and organizational hierarchies. According to Siletti et al., telencephalon-derived structures such as the cortex, hippocampus, and striatum possess lineage-specific excitatory neuron repertoires, while the midbrain and hindbrain retain a higher proportion of mixed-neurotransmitter cell types, which could underlie the exceptional heterogeneity of non-cortical regions [1]. Meanwhile, Chen et al. highlighted locally driven variations in cell–cell communication—such as divergent microglial signaling networks in the hippocampus versus prefrontal cortex [2]. Moreover, key genes within region-specific co-expression modules tend to exhibit higher mutation frequencies in various neurological disorders and brain tumors, suggesting that these baseline regional molecular differences might represent a foundational layer predisposing certain areas to disease vulnerability [3]. Taken together, these studies demonstrate that the human brain

is organized into region-specific molecular ecosystems defined by distinct cellular compositions, regulatory networks, and intercellular signaling patterns. These intrinsic differences may create regionally permissive environments for specific tumor types.

2 Regional Differences and Molecular Mechanisms in Brain Tumors

2.1 Regional Features of Gliomas

Among primary brain tumors, gliomas provide one of the clearest examples of spatially structured molecular heterogeneity. Extensive evidence indicates that the anatomical location of gliomas is tightly associated with their molecular profiles, cellular states, and clinical outcomes. Distinct neurodevelopmental backgrounds, lineage compositions, and epigenetic landscapes across brain regions shape tumor mutational spectra and biological behaviors. From the frontal and temporal lobes to the thalamus, brainstem, spinal cord, and cerebellum, clear spatial preferences have been observed.

For instance, Qi et al. reported that *IDH-mutant* gliomas predominantly occur in the frontal or temporal lobes [4], while Vuong et al. demonstrated that *H3 K27M-mutant diffuse midline gliomas (DMG)* are concentrated in the brainstem, thalamus, and spinal cord [5]. In contrast, Dandapatha et al. found that *low-grade BRAF-fusion* tumors are mainly located in the cerebellum and posterior fossa. Collectively, these findings support the paradigm that "location determines biology"—a central principle underlying the spatial heterogeneity of gliomas [9] (Table 1).

2.1.1 Supratentorial Regions: Molecular Distribution Across Frontal, Temporal, Parietal, and Occipital Lobes

Within the supratentorial compartment, gliomas arising in different cortical lobes exhibit distinct molecular characteristics and clinical behaviors.

Frontal lobe: The frontal lobe represents the most frequent site of adult gliomas. According to Qi et al., *IDH1/2-mutant* tumors are significantly enriched in this region, showing well-demarcated margins, homogeneous MRI signals, and weak enhancement, features suggestive of low invasiveness and favorable prognosis [4]. Integrated radiomic analyses further indicate that frontal tumors often display *MGMT* promoter methylation and *1p/19q* codeletion, predicting better chemotherapy response [11]. Functionally, Qi et al. reported that left-frontal *IDH-mutant* patients exhibit enhanced contralesional frontoparietal network activity, implying an interaction between molecular subtype and neural plasticity [12].

Temporal lobe: Temporal gliomas frequently show *EGFR* amplification and enrichment of RTK II subtypes, which are associated with higher invasiveness and angiogenic activity [13]. Spatial transcriptomics has revealed that in temporal-lobe GBM, perivascular and neuron-interaction layers are especially prominent, suggesting that the local microenvironment might play a key role in shaping tumor multilayered architecture [14].

Parietal lobe: Glioblastomas in the parietal region tend to have the poorest survival. Multimodal analyses indicate enrichment of *PTEN* mutations and *FGFR3-TACC3* fusions, along with high-texture heterogeneity and aggressive radiographic features, reflecting stronger spatial heterogeneity and unfavorable biological behavior [11].

Occipital lobe: Occipital gliomas are relatively rare. Cini et al. noted that their mutational spectra are not distinctive and that many lesions likely represent secondary infiltration or dissemination from parietal or temporal tumors, implying a lower intrinsic tendency for primary tumorigenesis in this area [15].

2.1.2 Insular and Lateralization Effects: Structural Connectivity and Hemispheric Differences

Yang et al. demonstrated pronounced hemispheric asymmetry in insular gliomas [16]. In the left hemisphere, *MGMT* methylation levels positively correlated with damage to the IFOF tract, whereas the opposite pattern was observed on the right. This finding suggests that gliomas may remodel white-matter connectivity in a hemisphere-specific manner. Systematic reviews further noted higher frequencies of *TP53* mutations and *MGMT* methylation in left-sided gliomas, often associated with poorer prognosis, implying that molecular features could be intricately linked to functional hemispheric lateralization [15].

2.1.3 Midline Regions: Spatial Stratification of the Thalamus, Brainstem, and Spinal Cord

Thalamus and Pulvinar subregion: Pediatric thalamic gliomas account for about 5 % of CNS tumors. Chiba et al. found that lesions in the Pulvinar (posterior thalamic nucleus) display higher malignancy, enrichment of *H3 K27M* mutations, and early ventricular dissemination [17]. The aggressiveness of Pulvinar tumors suggests that biological stratification might exist even within thalamic subregions.

Diffuse midline glioma (DMG): An integrated analysis of 804 cases revealed region-specific distinctions: *brainstem DMGs* occur at younger ages, show the highest Ki-67 index, and have the poorest prognosis; *thalamic DMGs* fare somewhat better; *spinal DMGs* occur mainly in adults and often harbor *TERT-promoter* mutations; whereas *brainstem DMGs* are enriched for *HIST1H3B/C* and *ACVR1* mutations. Thus, even under a shared *H3 K27M* background, the anatomical location and accompanying mutational landscape may determine tumor evolution and survival outcomes [5]. These findings suggest that even within the midline compartment, anatomical subregions correspond to

biologically distinct tumor states.

Single-cell multi-omics analyses further revealed that *H3 K27M DMGs* share an OPC-like stem-cell state, but differentiation trajectories and immune microenvironments vary by site: *pontine* lesions contain more hypoxic, stem-like populations; *thalamic* lesions exhibit more mature glial lineages; and *adult-type DMGs* show enrichment of MES-like states, suggesting that location, age, and immune milieu jointly shape the tumor's spatial and cellular architecture [18].

2.1.4 Infratentorial Regions: Distinct Subtype Signatures of the Cerebellum and Posterior Fossa

Dandapatha et al. reported that 91 % of pilocytic astrocytomas (PAs) carry *BRAF* fusions and almost all are located in the cerebellum or posterior fossa. These pediatric, developmentally driven tumors have excellent prognosis and represent a MAPK-activated benign lineage [9].

In contrast, Oki et al. described that cerebellar GBMs, though rare, constitute a biologically distinct subgroup—lacking *IDH*, *H3F3A*, and *TERT* mutations but showing a strong tendency for distant dissemination and ventricular invasion. This suggests that the infratentorial region might constitute an independent tumor ecosystem [19].

Overall, these findings indicate that glioma molecular subtypes are not randomly distributed across the brain but instead show clear anatomical predilections. Recognizing these spatial patterns may help refine diagnostic stratification and guide region-adapted therapeutic strategies.

2.2 Coupling Between Anatomical Location and Molecular Subtypes in Meningiomas

Meningiomas provide another clear example in which tumor genotype and anatomical location are tightly coupled. Meningiomas, the most common primary intracranial tumors in adults, exhibit clear location-specific molecular and clinical differences. Their biological behaviors correlate closely with anatomical origin. Tumors driven by *NF2* mutations and *22q* loss predominantly arise on the cerebral convexity or supratentorial compartments and tend to recur more frequently, whereas non-NF2 variants (including *TRAF7, KLF4, AKT1, SMO, POLR2A*) are enriched at the skull base and posterior fossa, typically presenting as benign, stable WHO grade I tumors [6]. This position-genotype coupling suggests that cell of origin, developmental lineage, and local microenvironment collectively shape meningioma biology (Table 2).

2.2.1 Supratentorial Meningiomas: NF2-Driven, Convexity-Dominant, and Aggressive

Whole-exome sequencing of 300 cases revealed *NF2* mutations in about 36 % of patients, primarily located on the cerebral convexity and supratentorial tentorium. These tumors frequently exhibit *22q* deletion, genomic instability,

and higher histologic grades, indicative of stronger invasiveness and recurrence potential. In contrast, *TRAF7/KLF4/AKT1/SMO* mutations are largely restricted to skull-base tumors, showing mutual exclusivity with NF2-driven lesions [7]. The biology of supratentorial meningiomas thus appears to depend on the NF2–YAP signaling axis, which could represent a key driver pathway for high-risk subtypes [6].

2.2.2 Skull-Base Meningiomas: The TRAF7–KLF4–AKT1–SMO Benign Lineage

Arising from the sphenoid ridge, olfactory groove, petrous apex, and sellar region, skull-base meningiomas represent approximately one-quarter of all cases. These "non-NF2" tumors are typically driven by *TRAF7* mutations (24 %), often co-occurring with *KLF4 K409Q* or *AKT1 E17K* alterations. Nearly all are located in the medial skull base or sphenoid region, characterized by chromosomal stability and benign histology. *SMO-mutant* meningiomas cluster in the olfactory groove and anterior cranial fossa, suggesting activation of the Hedgehog pathway [6]. Collectively, this group may form a developmentally stable, low-invasive, and anatomically confined lineage, primarily driven by PI3K–AKT–mTOR, rather than NF2–YAP signaling [8].

2.2.3 Posterior-Fossa Meningiomas: Anatomical Sub-Regions and Chromosomal Instability

Comprehensive genomic profiling of 132 posterior-fossa meningiomas identified three molecular subtypes: Group A: NF2-intact tumors without Merlin-pathway abnormalities, typically located in lateral infratentorial or petrous areas.Group B: NF2-mutant or *22q-deleted* tumors without high-risk CNAs, showing broad distribution. Group C: Genomically unstable tumors with multiple high-risk CNAs (*1p/14q* co-deletion, *9p* loss, *TERT/CDKN2A* mutations), 81 % of which occur in midline structures (tentorial notch, clivus, foramen magnum). Group C meningiomas have the worst prognosis, with significantly shorter progression-free survival even after gross-total resection [10]. These results suggest that proximity to midline structures might correlate with greater genomic instability and malignant potential, reflecting a developmental lineage-linked risk gradient.

2.2.4 Cerebellopontine-Angle (CPA) Meningiomas: Prognostic Implications of POLR2A Mutation

In a cohort of 70 WHO grade I CPA meningiomas, *POLR2A* mutations were found in 17 % of cases—all in women and predominantly of the meningothelial subtype. The mutation significantly increased recurrence risk, particularly among subtotal-resection patients. These tumors were most frequently located in the petroclival junction and posterior petrous ridge [20]. Thus, *POLR2A* might serve as a skull-base–specific molecular biomarker, potentially influencing transcriptional regulation and cellular differentiation in region-defined contexts.

Collectively, these studies highlight a strong position–genotype coupling in meningiomas, suggesting that developmental lineage and local microenvironment jointly shape tumor biology.

2.3 Regional Adaptation of Brain Metastases

Brain metastasis (BrM) represents the most common intracranial malignancy in adults and displays a cortical predilection, frequently involving the frontal, parietal, and cerebellar hemispheres, while deep structures such as the thalamus, basal ganglia, and brainstem are less often affected. At the systems level, BrM formation is not merely determined by vascular perfusion patterns but may reflect a coevolution between metastatic cells and regional brain microenvironments. Differences in vascular architecture, glial composition, and immune–stromal context across brain regions likely influence metastatic susceptibility.

In the study by Gonzalez et al., 15 parenchymal brain metastases from diverse primaries (breast, lung, melanoma, ovarian, colorectal, renal, etc.) were analyzed, and nearly all were located in the cerebral cortex, indicating a preference for vascular-rich cortical territories [21]. Single-cell transcriptomics and mass cytometry revealed that cortical metastases are characterized by complex vascular networks enriched for arterio-venous-transition endothelial clusters (*APLNR*$^{+}$*, EFNB2*$^{+}$*, NR2F2*$^{+}$), abundant pericytes and MSC-like cells expressing ECM-remodeling genes (*COL1A1, TINAGL1, TGFB3*), and scarcity of astrocytes, implying local breakdown of the glial barrier during cortical invasion.

Cross-tissue transcriptome-wide association analysis (TWAS) further identified CASP8 as a key driver gene of breast-cancer brain metastasis, showing specific overexpression in the cerebellar hemispheres and frontal cortex [22]. This finding suggests that breast-cancer cells might preferentially colonize the cerebellar–frontal axis, where distinctive metabolic and immune properties, combined with vascular permeability and glial-fiber density, could provide a favorable niche for metastatic establishment.

Together, these observations indicate that metastatic tumor cells adapt to region-specific vascular and glial niches, supporting the idea that the brain microenvironment plays a decisive role in shaping metastatic colonization patterns.

Figures, tables and schemes

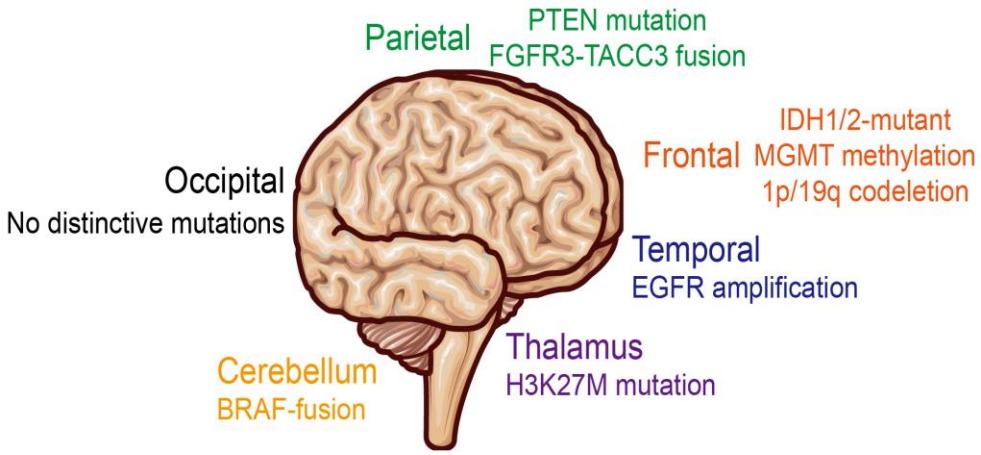

Figure 1: Molecular landscape of gliomas across main brain regions.

Table 1: Molecular landscape of gliomas across main brain regions.

Brain Region	**Representative Subtype / Mutation**	**Molecular / Genetic Features**	**Microenvironmental & Functional Traits**	**Clinical / Prognostic Implications**
Frontal lobe	IDH1/2-mutant glioma	MGMT methylation, 1p/19q codeletion	Low invasiveness, weak enhancement, preserved network plasticity	Favorable prognosis, good chemo-response
Temporal lobe	RTK II subtype GBM	EGFR amplification	Perivascular & neuron-interaction layers enriched	Highly invasive, angiogenic
Parietal lobe	GBM with PTEN mutation, FGFR3-	High texture heterogeneity	Aggressive phenotype	Poorest survival

	TACC3 fusion			
Occipital lobe	Secondary infiltration from parietal/temporal	No distinctive mutations	Low intrinsic tumorigenesis	Rare primary lesions
Insula / Left vs Right Hemisphere	IDH-mutant glioma (lateralized)	Left: ↑TP53 mutation, ↑MGMT methylation	White-matter remodeling (IFOF asymmetry)	Left-sided → poorer outcome
Thalamus / Pulvinar	Pediatric H3K27M-mutant glioma	H3 K27M mutation, ventricular spread	High malignancy in Pulvinar subregion	Poor prognosis
Brainstem (DMG)	H3 K27M-mutant DMG	HIST1H3B/C, ACVR1	Hypoxic, OPC-like stem states	Worst prognosis
Spinal cord (DMG)	Adult DMG	TERT-promoter mutation	MES-like enrichment	Intermediate prognosis
Cerebellum / Posterior fossa	BRAF-fusion PA; rare cerebellar GBM	BRAF fusion (MAPK activation); IDH/H3F3A-negative GBM	Developmental benign lineage (PA); invasive GBM niche	PA: excellent prognosis; cerebellar GBM: high dissemination

Table 2: Regional–Molecular Coupling in Meningiomas.

Anatomical Region	Dominant Molecular Subtype(s)	Key Genetic Alterations	Biological / Pathway Features	Clinical / Prognostic Traits
Cerebral Convexity / Supratentorial	NF2-driven meningioma	NF2 mutation, 22q loss	NF2–YAP signaling activation; genomic instability	High-grade (II–III), aggressive, recurrent
Skull Base (Sphenoid ridge, Olfactory groove, Sellar region)	Non-NF2 lineage: TRAF7, KLF4, AKT1, SMO	TRAF7 ± KLF4 (K409Q), AKT1 (E17K), SMO mutation	PI3K–AKT–mTOR and Hedgehog pathway activation	WHO grade I, benign, chromosomally stable, low recurrence
Posterior Fossa (Tentorial notch, Clivus, Foramen magnum)	Group A–C stratification	NF2-intact (A), NF2/22q loss (B), 1p/14q loss, 9p loss, TERT/CDKN2A (C)	Gradual increase in genomic instability from lateral → midline	Group C (midline): worst prognosis, rapid recurrence

Cerebellopontine Angle (CPA)	POLR2A-mutant subtype	POLR2A mutation (female-predominant)	Altered transcriptional regulation, meningothelial histology	Grade I but higher recurrence risk
Posterior Skull Base (Petrous apex, Petroclival junction)	TRAF7–KLF4–AKT1 lineage overlap	TRAF7, AKT1 E17K	PI3K–AKT signaling	Benign, stable
Overall Pattern	NF2 vs non-NF2 dichotomy	NF2–YAP vs PI3K–AKT–mTOR pathways	Location-dependent developmental lineage	"Position–Genotype Coupling" defines biology

Discussion

Growing evidence from these studies indicates that these region-specific molecular baselines exert a profound influence on brain tumor biology. Across gliomas (Fig. 1), meningiomas, and brain metastases, each tumor type shows characteristic anatomical predilections and molecular features that track with its site of origin, underscoring the importance of the local host microenvironment in tumor initiation and subsequent evolution. From a translational standpoint, the spatial molecular ecology of brain tumors is likely to be a major determinant of clinical course and treatment sensitivity. Bringing together information on anatomical localization with single-cell, spatial transcriptomic, and imaging-based omic data could enable a more nuanced, region-oriented classification framework that better supports precision neurosurgery and region-adapted adjuvant therapies. Looking ahead, it will be im-

portant to dissect how developmental patterning cues, intercellular signaling circuits, and metabolic microenvironments jointly confer regional vulnerability or resistance to oncogenesis, thereby clarifying the intrinsic links between brain regionality and tumor behavior.

Despite these advances, our understanding of region-specific mechanisms in brain tumors remains limited. Although the regional molecular features of gliomas have been partially delineated, integrative studies combining developmental lineage, epigenetic regulation, and microenvironmental signaling are still insufficient. In meningiomas, the coupling between location and genotype has been well established, yet the developmental and biomechanical underpinnings of this relationship remain poorly characterized. By contrast, research on regional heterogeneity in brain metastases remains the least developed.

Future studies should focus on integrating spatial omics with neuroimaging and radiomic analyses to better characterize region-specific tumor ecosystems. In addition, combining anatomical location with molecular features may help develop region-informed risk stratification models, while clinical studies stratified by both tumor genotype and anatomical site could further clarify therapeutic responses across distinct brain regions. Such efforts may advance the emerging concept of "region-aware oncology" and support more precise diagnosis and treatment strategies for brain tumors.

Conclusion

In summary, growing evidence indicates that brain tumors are shaped not only by intrinsic genetic alterations but also by the region-specific molecular and cellular context of the host brain. Across gliomas, meningiomas, and brain metastases, distinct anatomical locations are associated with characteristic molecular features, tumor behaviors, and microenvironmental interactions, supporting the concept of region-aware oncology. A better understanding of this spatial coupling may improve brain tumor classification and provide a foundation for more precise diagnostic and therapeutic strategies.

Abbreviations

APLNR, Apelin receptor; AKT1, AKT serine/threonine kinase 1; BrM, brain metastasis; CNS, central nervous system; CPA, cerebellopontine angle; COL1A1, collagen type I alpha 1 chain; DMG, diffuse midline glioma; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; eQTL, expression quantitative trait locus; FGFR3–

TACC3, fibroblast growth factor receptor 3–transforming acidic coiled-coil containing protein 3 fusion; GBM, glioblastoma; GCN, gene co-expression network; GTEx, Genotype-Tissue Expression Project; H3 K27M, lysine-to-methionine substitution at position 27 of histone H3; H3F3A, H3 histone family member 3A; IDH, isocitrate dehydrogenase; IFOF, inferior fronto-occipital fasciculus; KLF4, Krüppel-like factor 4; MGMT, O6-methylguanine-DNA methyltransferase; NF2, neurofibromin 2 (Merlin); OPC, oligodendrocyte progenitor cell; PA, pilocytic astrocytoma; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; POLR2A, RNA polymerase II subunit A; RTK, receptor tyrosine kinase; SMO, Smoothened frizzled class receptor; TERT, telomerase reverse transcriptase; TWAS, transcriptome-wide association study; YAP, Yes-associated protein.

Author Contributions

Yunzhi Zou: Conceptualization, Literature review, Data curation, Writing – original draft preparation. Rong Xiang: Supervision, Conceptualization, Writing – review & editing. Jixiang Zhao: Methodology, Visualization, Validation, Writing – review & editing. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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AI-declaration

During manuscript preparation, the authors used ChatGPT only for language polishing and improving readability. All scientific content, interpretation of the literature, and final conclusions were reviewed and approved by the authors.

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