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Molecular Biology of Astroblastoma-An Essential Review

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Abstract

Astroblastoma is a rare, well-circumscribed neuroepithelial central nervous system tumor that predominantly affects children, young adults, and females, accounting for 0.45% to 2.8% of all primary brain gliomas. At the molecular level, its defining pathognomonic hallmark is the rearrangement of the MN1 (Meningioma 1) gene located on chromosome 22q12.1. This genetic alteration typically results in oncogenic fusions with various partner genes, most frequently BEND2 or CXXC5, which serve as crucial diagnostic bio-markers readily detectable *via* Fluorescence *In Situ* Hybridization (FISH) analysis. Advanced molecular profiling further categorizes these neoplasms into a specific, distinct "astroblastoma, MN1-altered" DNA methylation class. This unique epigenetic signature is essential for separating true astroblastomas from morphological mimics, such as ependymomas or glioblastomas, which can occasionally exhibit focal astroblastic patterns. Beyond MN1 rearrangements, Comparative Genomic Hybridization (CGH) has identified other recurrent large-scale chromosomal copy number variations, most notably copy number gains on chromosome arm 20q and chromosome 19, which frequently co-occur across both well-differentiated and malignant variants. Histopathologically, the tumor is characterized by classic astroblastic perivascular pseudorosettes formed by tumor cells with broad, tapering cytoplasmic processes radiating toward vessels, accompanied by prominent stromal and perivascular hyalinization and a pushing, non-infiltrative border. Immunohistochemically, astroblastomas demonstrate consistent and distinct positivity for Epithelial Membrane Antigen (EMA) and Glial Fibrillary Acidic Protein (GFAP), along with variable immunoreactivity for S-100 protein, vimentin, OLIG2, and D2-40, supporting a transitional histogenesis between astrocytic and ependymal lineages. Clinical management and prognosis are heavily driven by histopathological grading. While low-grade variants carry a favorable prognosis, high-grade or malignant variants exhibit prominent anaplasia. These malignant phenotypes are characterized molecularly and cellularly by hypercellularity, brisk mitotic activity (>5 mitoses per 10 high-power fields), pseudopalisading necrosis, microvascular proliferation, and nuclear pleomorphism. Integrating these precise molecular signatures with established immunophenotypic profiles is now mandatory to secure an accurate diagnosis, differentiate them from tanycytic ependymomas, and guide therapeutic strategies including complete surgical resection and targeted adjuvant radiotherapy.

Keywords: Astroblastoma; Brain Neoplasms; Gliomas; Molecular Characterization; Gene Fusion

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Introduction

Astroblastoma is an uncommon and highly controversial primary neuroepithelial tumor of the Central Nervous System (CNS) characterized by an uncertain histogenesis [1, 2]. This rare neoplasm is estimated to account for only 0.45% to 2.8% of all primary cerebral neuroglial tumors and approximately 0.92% of all pediatric brain tumors [1-4].

Historically, the tumor was first described by Bailey and Cushing in 1924 and 1926 [5] and was further characterized by Bailey and Bucy in 1930 [6]. Despite its long-standing recognition, significant confusion and debate have persisted for decades regarding its precise cellular origin and validity as a distinct pathological entity [3]. Various historical hypotheses have categorized astroblastoma as a specific stage in the process of glioma dedifferentiation [7], as an astrocytoma composed of large fiber-producing cells [8], or as a rare tumor originating from tanycytes or ependymal astrocytes [9].

Demographically, astroblastomas predominantly affect children, teenagers, and young adults, showing a well-documented female predominance [1, 2-4, 10]. However, cases involving older adult patients have also been reported in the literature. Clinically, these tumors are typically located supratentorially within the cerebral hemispheres, with a strong predilection for the frontoparietal lobes. Less frequent anatomical sites include the cerebellum, brainstem, intraventricular space, and the hypothalamus. Because astroblastomas often manifest as large, well-circumscribed, and lobulated peripheral brain masses on standard Magnetic Resonance Imaging (MRI) evaluation [10], patients commonly present with symptoms dictated by mass effect and increased intracranial pressure. These clinical findings typically include headaches, nausea, vomiting, epileptic seizures, and a progressive decay in consciousness levels.

Securing a precise diagnosis of astroblastoma remains exceptionally challenging in routine clinical practice because its radiological and histopathological features frequently overlap with more common glial neoplasms. In particular, ependymoma represents a critical differential diagnosis due to shared histopathologic features, including a prominent perivascular orientation, pseudorosette formation, and overlapping immunohistochemical positivity for Glial Fibrillary Acidic Protein (GFAP) and Epithelial Membrane Antigen (EMA) [2]. Morphologically, true astroblastomas are defined by characteristic astroblastic perivascular pseudorosettes formed by tumor cells with short, thick, and broad cytoplasmic processes with blunt-ended foot plates radiating toward the central vessels, accompanied by extensive perivascular and stromal hyalinization [11].

Historically, astroblastomas were broadly separated into low-grade (well-differentiated) variants associated with a favorable prognosis after gross total resection, and high-grade (anaplastic/malignant) variants whose features merge with those of Glioblastoma (GBM) [1, 10-13]. While this histopathologic subtyping was widely applied by neuropathologists it was not initially integrated into older classification systems, and the tumor was provisionally listed under "other neuroepithelial tumors" due to a lack of sufficient clinicopathological data [3, 14, 15]. Interestingly, the clinical evolution of some malignant variants has occasionally contradicted their aggressive histopathological appearance, yielding an unexpectedly favorable prognosis [13]. Due to its extreme scarcity, the existing literature on astroblastoma is largely restricted to case reports-with a search of the title yielding approximately 101 results-which has historically prevented large-scale clinical trials.

Driven by recent scientific advances, contemporary studies have definitively demonstrated that astroblastoma represents a distinct histological and genetic entity [3, 16]. Reflecting these advancements, the most recent World Health Organization (WHO) classification update has reclassified astroblastoma as a high-grade (Grade 4) neuroepithelial tumor. This modern classification is heavily supported by the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) update 6, which formalizes the identification of *MN1* gene alterations as the defining molecular hallmark of this disease [17].

The present research presents a comprehensive review of current knowledge regarding the molecular features of tumorigenesis from the molecular biology perspective, focused on the principal intracellular signaling pathways involved in the pathogenesis, and the genomic and epigenetic relevant characteristics of a very rare primary brain tumor, astroblastoma.

Molecular Biology of Astroblastoma

Molecular pathogenesis and oncogenic fusions

The primary molecular signature of an astroblastoma involves rearrangements of the *MN1 (Meningioma 1)* gene, a transcriptional co-regulator located on chromosome *22q12.1* [18].

In the recent fifth edition of the World Health Organization (WHO) classification of Central Nervous System (CNS) tumors, "Astroblastoma, MN1-altered" was formally designated as a distinct clinicopathological entity that predominantly manifests in pediatric and young adult populations [19]. Owing to its extreme rarity and recent nosological characterization, the comprehensive clinical behavior and molecular architecture of this neoplasm remain incomplete. To address this knowledge gap, were aggregated tissue specimens alongside clinical and molecular datasets from a cohort of 176 patients with MN1-altered astroblastomas, all verified via genome-wide DNA methylation profiling [20, 21]. Unsupervised DNA methylation-based t-SNE clustering analysis demonstrated that these tumors divide into two distinct epigenetic subpopulations [18, 21]. The vast majority of cases (n=158) clustered into a primary cohort driven by pathognomonic *MN1::BEND2* fusions, distributed with isolated incidents harboring *EWSR1::BEND2* re-arrangements [18, 22]. Conversely, a smaller, adjacent but molecularly segregated cluster (n=18) was identified, which was predominantly defined by *MN1::CXXC5* fusions. Although both fusion partner-specific subgroups exhibited an identical median age at diagnosis of 12 years, they displayed divergent secondary chromosomal Copy-Number Aberrations (CNAs) [18]. Specifically, a somatic gain of chromosome 5 was identified in approximately one-third of the *CXXC5*-fused subgroup, whereas a recurrent structural loss of chromosome 16q was documented in one-third of the *BEND2*-fused cohort [18].

Despite the fact literature highlights a pronounced female predominance in MN1-altered tumors, recent data indicated that this skew is highly subgroup-dependent [18, 23]. It has been confirmed a striking female predominance within the *BEND2*-fused cohort (85%). In complete contrast, the *CXXC5*-fused subgroup demonstrated a distinct male preference, with male patients accounting for 75% of the cohort [18]. Furthermore, an interesting clinicoradiological association was observed among the few male patients within the *BEND2*-fused group (n=10), where 90% (9/10) of the tumors appeared infratentorially or within the spinal cord [18]. Conversely, the overwhelming majority of female *BEND2*-fused cases presented with supratentorial hemispheric masses (85/87) [18, 23].

In the same report by Schmitt-Hoffner *et al.,* [18], from a histopathological perspective, the original diagnoses varied considerably between the two molecular groups. While 39% of the *BEND2*-fused tumors were initially classified as conventional astroblastomas, the *CXXC5*-fused variants were frequently misclassified, with 31% originally designated as CNS Primitive Neuroectodermal Tumors (CNS-PNETs) and an only 8% recognized as astroblastomas.

Preliminary survival analyses revealed distinct clinical courses between the subgroups [18]. The *BEND2*-fused cohort demonstrated a highly favorable prognosis, with 5-year and 10-year Overall Survival (OS) rates of 97% and 89%, respectively. However, this subgroup exhibited a high propensity for disease recurrence, with less favorable 5-year and 10-year Progression-Free Survival (PFS) rates of 48% and

35%, mirroring findings from historical series [18, 23]. In comparison, patients harboring *CXXC5*-fused neoplasms (n=8 available for survival analysis) demonstrated 5-year and 10-year OS and PFS rates of 83% and 83%, and 60% and 60%, respectively. Expanded longitudinal survival analyses and deep molecular sequencing are currently underway to further refine the prognostic stratification of these *MN1*-altered astroblastoma subgroups [18].

Histopathological profile and diagnostic criteria

Astroblastoma exhibits a wide morphological spectrum, with histological findings ranging from papillary to solid architectures. The defining characteristics of this entity include the presence of perivascular pseudorosettes, vascular hyalinization, and a notable lack of a fibrillary background [24]. Its neuroepithelial and glial lineage is supported by immunoreactivity for GFAP and OLIG2, while common positivity for EMA frequently suggests a transitional glial-ependymal differentiation pattern. High-grade features, including cellular pleomorphism, microvascular proliferation, necrosis, and an elevated proliferation rate, can be present and are associated with a worse prognosis [25].

Currently, aside from achieving gross total surgical resection, no additional clinical prognostic factors have been definitively identified [26]. Owing to this highly variable biological behavior [24-27], the 2021 WHO classification for CNS tumors deferred assigning a formal, definitive numerical grade to this entity [28]. Because these overlapping histological features are frequently shared by other neuroepithelial tumors with completely different molecular alterations and clinical outcomes, the specific detection of the *MN1* gene rearrangement at chromosome *22q12.1* represents an indispensable prerequisite for a definitive diagnosis [21].

The microRNA expression profile and prognostic value

Given that genome-wide investigations have demonstrated a close relationship between microRNA (miRNA) dysregulation and human oncogenesis [29], these non-coding RNAs serve as robust signatures associated with tumor type, tumor grade, and clinical outcomes. In an institutional cohort of eight cases-optimally classified *via* DNA methylation profiling within the class "CNS high grade neuroepithelial tumor with *MN1* alteration"-we characterized the comprehensive miRNA expression landscape against two non-neoplastic brain tissue controls. The analysis identified 39 significantly deregulated miRNAs relative to normal brain tissues, comprising 22 overexpressed and 17 downregulated transcripts [30]. Correlative analyses between these deregulated microRNAs and clinicopathological features revealed an interesting, asymmetrical pattern. While upregulated miRNAs showed no significant association with histological grade or recurrence risk, downregulated mi-RNAs demonstrated a powerful, statistically significant association with an increased risk of disease recurrence.

Recent oncological studies support these findings. For instance, the tumor-suppressive *let-7* family of miRNAs is systematically downregulated in recurrent gliomas regardless of the initial WHO tumor grade, directly contributing to enhanced cell proliferation and resistance to apoptosis [31]. Mechanistically, this decreased expression might impair core tumor-suppressive pathways regulating cell cycle control, apoptosis, or immune response. Specific miRNAs, such as *miR-30* and *let-7*, highlight identical roles in other malignancies, underscoring their broader biological relevance. Clinically, these results show the way for miRNA-based assays to optimize the risk-stratification of high-risk patients and enable personalized treatment strategies. Integrating miRNA profiling into standard histopathological evaluation could significantly improve predictions of recurrence risk, while therapeutic strategies aimed at restoring the function of these downregulated miRNAs offer a promising future direction. Furthermore, because the WHO classification increasingly integrates molecular alterations alongside histopathological criteria, these unique miRNA signatures could serve as additional molecular markers to complement existing diagnostic platforms, aiding in distinguishing *MN1*-altered astroblastoma from morphologically similar entities.

Mechanisms of aberrant miRNA regulation: Epigenetic and genomic drivers

The aberrant expression of miRNAs in cancer can occur *via* various mechanisms [32], which include epigenetic modifications [33], genomic abnormalities [34, 35], transcriptional deregulation [36], and altered miRNA processing machinery [37].

To investigate the role of epigenetic silencing Gianno *et al.,* [30], analyzed the DNA methylation status of CpG islands on miRNA promoters at the core level and at different distances relative to the Transcription Start Site (TSS). Evaluation of the known promoter regions of 32 deregulated miRNAs (15 upregulated and 17 downregulated) revealed that 14 are epigenetically modulated by their promoter. Specifically, 7 miRNAs were overexpressed while their promoters were hypomethylated, and 7 miRNAs were downregulated by their hypermethylated promoters. The expression of the remaining 18 miRNAs appeared independent of promoter methylation status. While a uniform methylation trend was maintained between tumor samples and normal brain tissue for 29 out of the 32 miRNAs, three specific downregulated transcripts-*miR-146B, miR-330*, and *miR-7-2*-demonstrated an opposite hypermethylation profile in astroblastoma tissues compared to normal brain controls. Subsequent Copy-Number Variation (CNV) analysis of the chromosomal regions harboring the 18 non-epigenetically regulated miRNAs highlighted no significant deletions or gains, suggesting alternative transcriptional or processing defects drive their aberrant expression.

Target gene deregulation and oncogenic pathways

It is well known that miRNA alterations routinely lead to target gene deregulation and the overthrow of critical signaling pathways [38].

Interrogating these pathways provides deep insight into tumor biology and potential therapeutic vulnerabilities, particularly regarding networks regulating cell proliferation, apoptosis, and cellular differentiation. Importantly, Kyoto Encycloprdia of Genes and Genomes (KEGG) pathway enrichment analysis of the deregulated miRNAs revealed a highly specific association with the TGF-beta signaling cascade, glycosaminoglycan biosynthesis, and ECM-receptor interaction pathways. This molecular signature is associated with the defining histological phenotype of stromal sclerosis and perivascular hyalinosis, a mechanistic link well-documented for the *miR-30* family, where targeted dysregulation modulates liver fibrosis via the direct regulation of TGF-beta signaling [39, 40].

Another highly conclusive cascade is the estrogen and steroid synthesis signaling pathway [41], which is highly relevant given the pronounced female prevalence of these tumors, reflecting the known association of specific miRNA profiles with ER-positive and ER-negative breast cancer subtypes [42]. Additionally, the involvement

of the MAPK signaling pathway represents a critical finding for potential target therapies. Supporting this therapeutic hypothesis, functional data has demonstrated that the overexpression of *miR-30E* powerfully inhibits adhesion, migration, and cell cycle progression in neoplastic cells via the direct suppression and inactivation of the MAPK signaling cascade [43].

In conclusion, *MN1*-altered astroblastomas harbor a highly specialized miRNA expression signature that dictates prognostic associations, coordinates specific biological processes, and modulates core molecular pathways across multiple regulatory levels. Nonetheless, the results presented in such studies must be interpreted with appropriate caution due to limited sample sizes. Such restricted cohorts represent an inherent, unavoidable limitation in the study of ultra-rare malignancies like astroblastoma, naturally restricting overall statistical power and universal generalizability.

Epigenetic Profiling (DNA Methylation)

Epigenetic profiling and global non-coding RNA regulation

CNS astroblastomas are most robustly characterized by their genome-wide DNA methylation profiles, which molecularly segregate this entity from histologically overlapping neuroepithelial tumors, such as ependymomas and pilocytic astrocytomas [44]. Importanly, more than 70% of true astroblastomas cluster into a highly uniform and distinct epigenetic group. In broad genomic profiling investigations targeting Primitive Neuro-Ectodermal Tumors (PNETs), this specific signature is systematically designated as the CNS-HGNET-MN1 (Central Nervous System High-Grade Neuroepithelial Tumor with MN1 alteration) methylation class [45].

High-throughput transcriptomic and epigenetic technologies provide indispensable tools for mapping the global microRNA (miRNA) landscape, enabling the precise identification of cellular lineage and predicting long-term clinical outcomes [34, 46].

Within this integrated regulatory framework, the aberrant expression of miRNAs in human cancers can be driven by several distinct mechanisms [32]. These predominantly encompass structural genomic abnormalities-such as focal deletions, locus amplifications, or chromosomal translocations of specific miRNA loci [35, 47] - alongside epigenetic modifications, particularly the aberrant DNA methylation of regulatory promoter CpG islands [48-50]. Additionally, this non-coding landscape is heavily modulated by transcription factor-mediated transcriptional regulation [36, 51, 52] and defects or mutations in downstream miRNA processing machinery, including the *DICER* and *DROSHA* complexes [53].

The functional relevance of these non-coding signatures is well-established in wider neuro-oncology. Previous studies characterizing miRNA expression profiles in diffuse gliomas have demonstrated that deregulated miRNAs can function as strong oncogenes, particularly in glioblastomas, where they block the expression of key apoptosis-enabling genes [54]. Beyond driving oncogenesis, specific miRNA signatures play a pivotal role in tumor biology by distinguishing distinct glioma subtypes and serving as robust prognostic biomarkers for the risk of disease progression. For instance, in Diffuse Intrinsic Pontine Glioma (DIPG), a specific miRNA signature effectively identifies patient subgroups predisposed to a poor response to radiotherapy. In clinical practice, this molecular stratification enables clinicians to avoid unnecessary adjuvant courses or re-irradiation at relapse, which has otherwise become a common management paradigm for recurrent DIPG [55]. Similarly, investigations in adult low-grade gliomas have demonstrated the direct involvement of miRNAs in pathogenesis, identifying key non-coding transcripts strictly associated with accelerated tumor progresssion and shortened patient survival [56]. Generally, these findings underscore the complicated interplay between miRNA dysregulation and broader epigenetic alterations in neuro-oncology, highlighting their fundamental contribution to the molecular heterogeneity of CNS neoplasms [57].

Copy Number Variations (CNVs)

Copy Number Variations (CNVs) and structural chromosomal aberrations

Genomic landscape investigations utilizing array Comparative Genomic Hybridization (aCGH) have revealed highly recurrent chromosomal Copy Number Alterations (CNAs) that characterize true astroblastomas. These predominantly encompass the monosomy of chromosome 16 (or isolated 16q structural loss), alongside partial chromosomal losses localized on arm 22q (the locus of the *MN1* gene) and chromosome X [24, 58]. Importantly, high-risk molecular subgroups frequently display a synchronized combined loss of 14q and 16q, which serves as an independent, predictive genomic biomarker for early tumor recurrence and aggressive clinical behavior [6, 24, 58]. The conventional cytogenetic and Comparative Genomic Hybridization (CGH) studies provided the initial insights into these alterations, though with lower sensitivity and specificity. In a study of 20 cases, Brat *et al.,* [16] identified recurrent chromosomal changes, including genomic gains of 20q (4 of 7 tumors) and chromosome 19, alongside structural losses affecting 9q, 10, 21, 22, and chromosome X. This historical data, however, demonstrated some discrepancy with modern high-resolution arrays, which is fundamentally attributed to the technical limitations of conventional cytogenetics versus contemporary aCGH platforms [16, 59].

A highly interesting finding from modern molecular analyses is the identification of numerous heterozygous deletions distributed across almost the entirety of the X chromosome, a pattern that strongly suggests the involvement of localized chromothripsis in the pathogenesis of these structural aberrations [16, 60]. Furthermore, multiple deletions or focal copy-number gains are frequently documented adjacent to the *MN1* locus on chromosome 22q12.1. This specific pattern of focal copy-number alterations is highly reminiscent of site-specific, localized chromothripsis, which potentially drives the mechanical formation of the pathognomonic *MN1::BEND2* fusion gene, given that the *BEND2* partner is localized on the Xp22.13 locus [21, 60].

According to a recent study by Federico *et al.,* [61], and based on DNA methylation analyses three groups of Astroblastomas were identified. Table 1 represents the biological hallmarks, transcriptome condition, Copy Number Aberrations, and Oncogenic pathways.

Integrated molecular and immunohistochemical differentiation

To ensure diagnostic precision, these structural genomic copy-number changes must be contextualized within the tumor's immunohistochemical profile, which corresponds to that of a neuroepithelial glial neoplasm. True astroblastomas demonstrate robust immunoreactivity for Glial Fibrillary Acidic Protein (GFAP), S-100 protein,and Olig2 [24, 62, 63]. While GFAP expression can vary greatly in intensity between individual specimens, S-100 protein immunostaining routinely highlights a larger proportion of positive

Table 1: Molecular Biology of Astroblastomas according to DNA methylation analyses (Modified by Federico A, Schmitt-Hoffner F, Fonseca A, Geisemeyer N, Bruckner K, Mauermann M, et al. Molecular and clinical stratification of astroblastomas: Three distinct fusion-defined groups informing risk-adapted treatment strategies. Neuro Oncol. 2026; 28(4): 1005-1019. [61]).

Astroblastoma Group	Biological hallmark	Transcriptome	Copy Number Alterations (CNA)	Oncogenic pathways
Group A	*MN1::BEND2*	*ABCC1, DLX5, KITLG, COL4A1/2, FZD2*	14q$^-$, 16q$^-$, Xp$^-$, Xq, X chromothripsis	NOTCH, PDGFRA
Group B	*EWSR1::BEND2 other rare XX::BEND2 fusions (XX=MAMLD1, FUS, TCF3)*	*MUC1, KCNMB4, HOXB2/3/4*	10p$^-$, 10q$^-$, X chromothripsis	PDGFRA
Group C	*MN1::CXXC5*	*PAX5, SHC3, DCX, EFNA5, CNTN1*	11p$^-$	KRAS, FGFR

neoplastic cells [62,63]. Crucially, true astroblastomas consistently lack immunoreactivity for L1 CAM, providing a vital diagnostic axis to differentiate this entity from supratentorial ependymomas harboring *ZFTA/C11orf95::RELA* fusions, which are characteristically L1 CAM-positive [64].

Furthermore, modern classification frameworks have successfully distinguished true *MN1*-altered astroblastomas from morphological mimics through integrated testing [21, 65]. For instance, while Lehman *et al.,* documented the presence of the oncogenic *BRAF V600E* mutation in 38% (8 of 21) of cases diagnosed strictly on morphology, subsequent molecular series investigating verified *MN1* rearrangements have systematically failed to identify this mutation. This discrepancy is explained by the fact that astroblastic perivascular pseudorosettes are relatively non-specific morphological structures. They can occasionally be observed in other high-grade diffuse gliomas, including epithelioid glioblastoma, which frequently harbors the *BRAF V600E* alteration [24].

Consequently, the mandatory integration of aCGH for copy-number analysis, linked with the exclusion of canonical glioma mutations, is vital to prevent the misclassification of these rare neuro-oncological entities [21, 24].

Structural biology of pathognomonic fusion partners

The *MN1* gene, localized on chromosome 22q12.1, encodes a large transcriptional regulatory cofactor exceeding 1,300 amino acids. Structurally, the vast majority of the *MN1* protein comprises an Intrinsically Disordered Region (IDR) and lacks definitive secondary structures or canonical functional domains. Consequently, *MN1* operates strictly as a transcriptional co-regulator, modulating downstream gene expression by scaffolding with distinct transcription factors. True astroblastomas are universally characterized by *MN1* alterations, most frequently involving in-frame fusions with *BEND2* or *CXXC5* [23, 66].

The *CXXC5* (CXXC Finger Protein 5) partner gene encodes a member of the CXXC protein family that specifically recognizes and binds to unmethylated CpG islands within genomic DNA. Functionally, *CXXC5* acts as a strong negative regulator of the canonical Wnt/β-catenin signaling pathway by directly binding to β-catenin, thereby suppressing its transcriptional activity and downstream cell proliferation, differentiation, and migration. Recent multi-omic characterizations have expanded this oncogenic spectrum, identifying a rare subset of astroblastomas harboring alternative *EWSR1::BEND2* fusions [6]. The *EWSR1* locus, situated on chromosome 22q12, belongs to the TET family and encodes a 656-amino-acid RNA-binding nuclear protein spanning 17 exons, which is heavily implicated in mesenchymal and neuroepithelial oncogenesis [67-69]. Mechanistically, the N-terminal transactivation domain of EWSR1 undergoes recurrent fusions with the DNA-binding domains of various transcription factors, generating highly potent,chimeric oncogenic transcription factors [70].

The common fusion partner *BEND2*, localized on chromosome Xp22.13, encodes one of nine human proteins characterized by BEN domains, featuring two tandem BEN domains at its C-terminus [71]. These highly conserved domains facilitate sequence-specific DNA-protein interactions and coordinate chromatin remodeling, playing a critical role in tumorigenesis and developmental arrest [72, 73]. Generally, integrating the structural biology of these partner genes into molecular stratification platforms is crucial to optimize diagnostic accuracy and differentiate true astroblastomas from morphological mimics.

Exon junction architecture and cross-entity pleiotropy

At the transcriptional level, the MN1 locus spans approximately 53 Kb and consists of two exons. Exon 1 encodes the vast majority of the protein product (1,260 amino acids), while exon 2 encodes the terminal 60 amino acids. Genomic mapping has identified a critical co-regulatory gene adjacent to *MN1* on chromosome 22, which is recurrently implicated in oncogenic mutations associated with broader human brain tumors [74].

Functional transcriptomic disruptions of this locus are primary drivers in pathogenesis. Specifically, Burford *et al.,* [75] reported a highly illustrative recurrent case of an *MN1::BEND2* rearrangement, strongly supporting the hypothesis that structural *MN1* disruption plays a direct, causative role in neoplastic transformation. Characterizing this specific junction break-point, this cohort identified a pathognomonic recurrent *MN1* (exon 1)::*BEND2* (exon 2) fusion transcript [75]. Fundamentally, downstream transcriptomic landscapes differ significantly based on the specific chimeric construct. For instance, robust *BEND2* overexpression is exclusively restricted to *MN1::BEND2*-fused tumors and is characteristically absent in *MN1::CXXC5* neoplasms [21]. This transcriptional divergence underscores the distinct biological phenotypes and clinical courses dictated by different fusion partners. Furthermore, the oncogenic potential of this chimeric transcript extends beyond neuro-oncology, as the *MN1::BEND2* fusion gene has been recurrently identified in soft tissue sarcomas, demonstrating its role as a pleiotropic oncogenic driver across highly varying histogenetic tumor lineages [66].

Molecular Mimics and Exclusions

Molecular mimics and exclusionary criteria

From a diagnostic perspective, securing a definitive diagnosis of true astroblastoma necessitates not only the identification of pathognomonic MN1 alterations but also the strict exclusion of canonical molecular profiles characteristic of other glial lineages.

Many neuro-oncological entities act as molecular mimics, presenting with histopathologigical features that are virtually indistinguishable from astroblastomas under standard light microscopy. To address this diagnostic challenge, true *MN1*-altered

astroblastomas are molecularly defined by a specific profile of exclusions and wildtype states [22, 66, 75], and concern: - the IDH1/IDH2 Status: True *MN1*-altered astroblastomas are universally IDH-wildtype, the absolute absence of somatic mutations in the *IDH1* (typically at codon R132) and *IDH2* (typically at codon R172) genes is a mandatory exclusionary criterion, effectively separating astroblastomas from diffuse astrocytomas and oligodendrogliomas [22, 66], -ATRX Expression: Nuclear expression of the Alpha-Thalassemia/Mental Retardation Syndrome X-linked (*ATRX*) protein is characteristically retained in this entity. True astroblastomas lack the mutational inactivation or structural loss of *ATRX* that characteristically defines molecularly high-grade astrocytic gliomas [2], -BRAF V600E Mutation: The oncogenic *BRAF V600E* missense mutation is absent in molecularly verified *MN1*-altered cases. While previous cohorts diagnosed purely on morphology reported high rates of *BRAF* mutations, subsequent genomic sequencing has demonstrated that true astroblastomas are wildtype for *BRAF*, helping differentiate them from Pleomorphic Xanthoastrocytomas (PXA) and gangliogliomas [22, 66, 75].

By implementing this board of molecular exclusions alongside high-throughput profiling, clinicians and neuropathologists can robustly distinguish true *MN1*-altered astroblastomas from morphological mimics, thereby ensuring precise tumor categorization and optimizing patient management [22, 66, 75].

Molecular Characterization of CNS Astroblastomas

Integrative taxonomy, cellular lineage, and evolutionary trajectories

Recent high-throughput genomic and epigenetic profiling has confirmed that neoplasms exhibiting an astroblastoma-like morphology under light microscopy are molecularly heterogeneous. These lesions encompass distinct diagnostic entities defined by divergent DNA methylation classes, pathognomonic gene fusions, and unique mutational landscapes. Beyond standard diagnostics, integrative analyses linking genome-wide methylation patterns, transcriptomic signatures, and fusion detection have traced the cellular origins of true *MN1*-rearranged tumors back to developmental stem cell lineages of radial glia [45].

This molecular taxonomy is critical for clinical prognostication and treatment stratification, as true *MN1*-altered tumors routinely demonstrate a significantly more favorable clinical course compared to their *BRAF V600E*-driven or other high-grade neuro-oncological counterparts. Multi-institutional cohort studies utilizing methylation arrays and copy-number analysis have confirmed that histologically defined astroblastomas comprise multiple overlapping molecular classes-including *MN1*-altered, *BRAF V600E*-mutant, and *ZFTA::RELA*-fusion groups-each correlating with highly divergent survival outcomes [45]. For instance, recent pediatric series have described early ependymal-like neuroepithelial tumors harboring the *MN1::BEND2* fusion as a molecularly segregated subgroup associated with an excellent prognosis under surgical resection alone [76].

Generally, substantial clinical heterogeneity persists among adult variants, which frequently harbor alternative alterations in the MAPK pathway, or rare chimeric fusions such as *EWSR1::PATZ1* and *MN1::GTSE1*. To map these complex evolutionary courses, phylogenetic reconstruction of longitudinal, decade-long recurrent cases harboring the *MN1::BEND2* fusion has elucidated patterns of tumor dissemination and convergent evolution. These temporal genomic models have identified key secondary alterations, particularly the subversion of the NF-κB signaling cascade, as acquired molecular vulnerabilities. Collectively, these comprehensive multi-omic insights establish a robust framework for merging classical histopathology with molecular taxonomy, emphasizing that the underlying epigenetic context dictates tumor behavior, therapeutic resistance, and response to targeted personalized therapy [71].

Conclusions

Astroblastoma represents an exceedingly rare primary CNS malignancy that presents significant diagnostic and therapeutic challenges. Due to its low incidence, elucidating the tumor's precise pathophysiological characteristics and establishing standardized, effective treatment algorithms remains highly problematic. Clinically, astroblastomas exhibit an unpredictable biological behavior, characterized by an elevated propensity for recurrence and rapid disease progression. Diagnostic ambiguity frequently arises due to overlapping astroblastic features observed in other neuroglial and non-neuroepithelial neoplasms, such as astrocytic tumors and ependymomas, which led to considerable debate regarding its histogenesis and classification. Histopathologically, these tumor are distinctly characterized by the presence of perivascular astroblastic pseudorosettes and prominent vascular hyalinization. Immunohistochemical profiling typically reveals immunoreactivity for GFAP, EMA, pancytokeratin, Olig2, vimentin, podoplanin, and S100, concurrently with the absence of IDH1/2 and TP53 mutations. Furthermore, recent molecular characterization has identified *MN1* alterations as a diagnostic hallmark deeply implicated in the pathogenesis of this distinct tumor entity.

References

1. Agarwal V, Mally R, Palande DA, Velho V. Cerebral astroblastoma: A case report and review of literature. Asian J Neurosurg. 2012;7: 98-100.
2. Shen F, Chen LC, Yu Y, Zhou LF. Astroblastoma: Rare Incidence and Challenges in the Pattern of Care. World Neurosurg. 2014; 82: e125-e127.
3. Port JD, Brat DJ, Burger PC, Pomper MG. Astroblastoma: Radiologic-Pathologic Correlation and Distinction from Ependymoma. Am J Neuroradiol. 2002; 23:243-247.
4. de la Garma VH, Arcipreste AA, Vázquez FP, Aguilar RR, Castruita UO, Guerra RM. High-grade astroblastoma in a child: Report of one case and review of literature. Surg Neurol Int. 2014; 5: 111.
5. Bailey P, Cushing H. Classification of the Tumors of the Glioma Group on a Histogenic Basis with a Correlation Study of Prognosis. Lippincott. 1926.
6. Bailey P, Bucy PC. Astroblastoma of the brain 1. Acta Psychiatr Neurol. 1930; 5: 439-461.
7. Kernohan JW, Mabon RF, Svien HJ. A simplified classification of the gliomas. Proc Staff Meet Mayo Clin. 1949; 24(3): 71-75.
8. Zülch KJ. Biology and pathology of brain tumors. Springer; 1956.
9. Kubota T, Hirano A, Sato K, Yamamoto S. The fine structure of astroblastoma. Cancer. 1985; 55(4):745-750.
10. Brem H, Chiocca EA, Sawaya R. Brain tumours. Youmans neurological surgery. 6th edition. Elsevier. 2011.
11. Barakat MI, Ammar MG, Salama HM, Abuhashem S. Astroblastoma: Case Report and Review of Literature. Turk Neurosurg. 2016; 26(5): 790-794.
12. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016;

131(6): 803-820.

13. Miranda P, Lobato RD, Cabello A, Gómez PA, de Aragón AM. Complete surgical resection of high-grade astroblastoma with long time survival: case report and review of the literature. Neurocirugia. 2006; 17(1): 60-63.

14. Aldape KD, Rosenblum MK. Astroblastoma. 2007.

15. Janz C, Buhl R. Astroblastoma: Report of two cases with unexpected clinical behavior and review of the literature. Clin Neurol Neurosurg. 2014; 125:114-124.

16. Brat D, Hirose Y, Cohen K, Feuerstein BG, Burger PC. Astroblastoma: Clinicopathologic features and chromosomal abnormalities defined by comparative genomic hybridization. Brain Pathol. 2000; 10: 342-352.

17. Louis DN, Wesseling P, Aldape K, Brat DJ, Capper D, Cree IA, et al. cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. Brain Pathol. 2020; 30: 844-856.

18. Schmitt-Hoffner F, Gojo J, Mauermann M, von Hoff K, Sill M, Stichel D, et al. RARE-15. Astroblastoma, MN1 altered comprises two molecularly and clinically distinct subgroups defined by the fusion partners BEND2 and CXXC5. Neuro Oncol. 2022; 24: i12-i13.

19. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro-Oncology. 2021; 23(8): 1231-1251.

20. Capper D, Jones DTW, Sill M, Hovestadt V, Schrimpf D, Sturm D, et al. DNA methylation-based classification of central nervous system tumours. Nature. 2018; 555(7697): 469-474.

21. Sturm D, Orr BA, Toprak UH, Hovestadt V, Jones DTW, Capper D, et al. New Brain Tumor Entities Emerge from Molecular Classification of CNS-PNETs. Cell. 2016; 164(5): 1060-1072.

22. Lehman NL, Usubalieva A, Lin T, Allen SJ, Tran QT, Mobley BC, et al. Genomic analysis demonstrates that histologically-defined astroblastomas are molecularly heterogeneous and that tumors with MN1 rearrangement exhibit the most favorable prognosis. Acta Neuropathol Commun. 2019; 7(1): 42.

23. Hirose T, Nobusawa S, Sugiyama K, Amatya VJ, Fujimoto N, Sasaki A, et al. Astroblastoma: a distinct tumor entity characterized by alterations of the X chromosome and MN1 rearrangement. Brain Pathol. 2018; 28(5): 684-694.

24. Lehman NL, Hattab EM, Mobley BC, Usubalieva A, Schniederjan MJ, McLendon RE, et al. Morphological and molecular features of astroblastoma, including BRAFV600E mutations, suggest an ontological relationship to other cortical-based gliomas of children and young adults. Neuro Oncol. 2017; 19: 31-42.

25. Thiessen B, Finlay J, Kulkarni R, Rosenblum MK. Astroblastoma: Does histology predict biologic behavior? J Neurooncol. 1998; 40: 59-65.

26. Tauziède-Espariat A, Pagès M, Roux A, Siegfried A, Uro-Coste E, Nicaise Y, et al. Pediatric methylation class HGNETMN1: Unresolved issues with terminology and grading. Acta Neuropathol Commun. 2019; 7: 176.

27. Lau PP, Thomas TM, Lui PC. 'Low-grade' astroblastoma with rapid recurrence: A case report. Pathology. 2006; 38: 78-80.

28. WHO Classification of Tumours Editorial Board. Central nervous system tumours. Lyon. 2021.

29. Bartel DP. MicroRNAs: Genomics, biogenesis, mechanism, and function. Cell. 2004; 116: 281-297.

30. Gianno F, Miele E, Sabato C, Ferretti E, Minasi S, Buttarelli FR, et al. MicroRNAs Expression Profile in MN1-Altered Astroblastoma. Biomedicines. 2025; 13(1):112.

31. Lee ST, Chu K, Oh HJ, Im WS, Lim JY, Kim SK, et al. Let-7 microRNA inhibits the proliferation of human glioblastoma cells. J Neurooncol. 2011; 102: 19-24.

32. Lee YS, Dutta A. MicroRNAs in cancer. Annu Rev Pathol. 2009; 4: 199-227.

33. Hua X, Chen L, Wang J, Li J, Wingender E. Identifying cell-specific microRNA transcriptional start sites. Bioinformatics. 2016; 32: 2403-2410.

34. Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, et al. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci USA. 2006; 103: 2257-2261.

35. Wu M, Jolicoeur N, Li Z, Zhang L, Fortin Y, L'Abbe D, et al. Genetic variations of microRNAs in human cancer and their effects on the expression of miRNAs. Carcinogenesis. 2008; 29: 1710-1716.

36. Deng S, Calin GA, Croce CM, Coukos G, Zhang L. Mechanisms of microRNA deregulation in human cancer. Cell Cycle. 2008; 7: 2643-2646.

37. Kumar MS, Lu J, Mercer KL, Golub TR, Jacks T. Impaired microRNA processing enhances cellular transformation and tumorigenesis. Nat. Genet. 2007; 39: 673-677.

38. Macfarlane LA, Murphy PR. MicroRNA: Biogenesis, Function and Role in Cancer. Curr Genom. 2010; 11: 537-561.

39. Tu X, Zheng X, Li H, Cao Z, Chang H, Luan S, et al. MicroRNA-30 Protects Against Carbon Tetrachloride-induced Liver Fibrosis by Attenuating Transforming Growth Factor Beta Signaling in Hepatic Stellate Cells. Toxicol Sci. 2015; 146: 157-169.

40. Vettori S, Gay S, Distler O. Role of MicroRNAs in Fibrosis. Open Rheumatol J. 2012; 6: 130-139.

41. Pérez-Cremades D, Mompeón A, Vidal-Gómez X, Hermenegildo C, Novella S. miRNA as a New Regulatory Mechanism of Estrogen Vascular Action. Int J Mol Sci. 2018; 19: 473.

42. Howard EW, Yang X. microRNA Regulation in Estrogen Receptor-Positive Breast Cancer and Endocrine Therapy. Biol Proced Online. 2018; 20: 17.

43. Xu G, Cai J, Wang L, Jiang L, Huang J, Hu R, et al. MicroRNA-30e-5p suppresses non-small cell lung cancer tumorigenesis by regulating USP22-mediated Sirt1/JAK/STAT3 signaling. Exp Cell Res. 2018; 362: 268-278.

44. Boisseau W, Euskirchen P, Mokhtari K, Dehais C, Touat M, Hoang-Xuan K, et al. Molecular Profiling Reclassifies Adult Astroblastoma into Known and Clinically Distinct Tumor Entities with Frequent Mitogen-Activated Protein Kinase Pathway Alterations. Oncologist. 2019; 24(12): 1584-1592.

45. Frederico SC, Vera E, Abdullaev Z, Acquaye A, Aldape K, Boris L, et al. Heterogeneous clinicopathological findings and patient-reported outcomes in adults with MN1-altered CNS tumors: A case report and systematic literature review. Front Oncol. 2023; 13:1099618.

46. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, et al. MicroRNA expression profiles classify human cancers. Nature. 2005; 435: 834-838.

47. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, et al. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Natl Acad Sci. USA. 2004; 101: 2999-3004.

48. Kim DH, Saetrom P, Snøve O, Rossi JJ. MicroRNA-directed transcriptional gene silencing in mammalian cells. Proc Natl Acad Sci USA. 2008;105: 16230-16235.

49. Tuna M, Machado AS, Calin GA. Genetic and epigenetic alterations of microRNAs and implications for human cancers and other diseases. Genes Chromosomes Cancer. 2016; 55(3): 193-214.

50. Wang S, Wu W, Claret FX. Mutual regulation of microRNAs and DNA methylation in human cancers. Epigenetics. 2017; 12(3): 187-197.

51. Chang TC, Yu D, Lee YS, Wentzel EA, Arking DE, West KM, et al.

Widespread microRNA repression by Myc contributes to tumorigenesis. Nat Genet. 2008; 40(1): 43-50.

52. He L, He X, Lowe SW, Hannon GJ. microRNAs join the p53 network--another piece in the tumour-suppression puzzle. Nat Rev Cancer. 2007; 7(11): 819-822.

53. Adams BD, Kasinski AL, Slack FJ. Aberrant regulation and function of microRNAs in cancer. Curr Biol. 2014; 24(16): R762-76.

54. Chan JA, Krichevsky AM, Kosik KS. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. Cancer Res. 2005; 65(14): 6029-6033.

55. Iannó MF, Biassoni V, Schiavello E, Carenzo A, Boschetti L, Gandola L, et al. A microRNA Prognostic Signature in Patients with Diffuse Intrinsic Pontine Gliomas through Non-Invasive Liquid Biopsy. Cancers. 2022; 14(17): 4307.

56. Catanzaro G, Besharat ZM, Miele E, Chiacchiarini M, Po A, Carai A, et al. The miR-139-5p regulates proliferation of supratentorial paediatric low-grade gliomas by targeting the PI3K/AKT/mTORC1 signalling. Neuropathol Appl Neurobiol. 2018; 44(7): 687-706.

57. Catanzaro G, Besharat ZM, Carai A, Jäger N, Splendiani E, Colin C, et al. MiR-1248: a new prognostic biomarkerable to identify supratentorial hemispheric pediatric low-grade gliomas patients associated with progression. Biomark Res. 2022; 10(1): 44.

58. Asha U, Mahadevan A, Sathiyabama D, Ravindra T, Sagar BKC, Bhat DI, et al. Lack of IDH1 mutation in astroblastomas suggests putative origin from ependymoglial cells? Neuropathology. 2015; 35(4):303-311.

59. Jay V, Edwards V, Squire J, Rutka J. Astroblastoma: report of a case with ultrastructural, cell kinetic, and cytogenetic analysis. Pediatr Pathol. 1993; 13(3): 323-332.

60. Stephens PJ, Greenman CD, Fu B, Yang F, Bignell GR, Mudie LJ, et al. Massive genomic rearrangement acquired in a single catastrophic event during cancer development. Cell. 2011; 144(1): 27-40.

61. Federico A, Schmitt-Hoffner F, Fonseca A, Geisemeyer N, Bruckner K, Mauermann M, et al. Molecular and clinical stratification of astroblastomas: Three distinct fusion-defined groups informing risk-adapted treatment strategies. Neuro Oncol. 2026; 28(4): 1005-1019.

62. Bonnin JM, Rubinstein LJ. Astroblastomas: a pathological study of 23 tumors, with a postoperative follow-up in 13 patients. Neurosurgery. 1989; 25(1): 6-13.

63. Rosenblum MK. Astroblastoma. Hodder Arnold. 2006.

64. Parker M, Mohankumar KM, Punchihewa C, Weinlich R, Dalton JD, Li Y, et al. C11orf95-RELA fusions drive oncogenic NF-κB signalling in ependymoma. Nature. 2014; 506(7489): 451-455.

65. Wood MD, Tihan T, Perry A, Chacko G, Turner C, Pu C, et al. Multimodal molecular analysis of astroblastoma enables reclassification of most cases into more specific molecular entities. Brain Pathol. 2018; 28(2): 192-202.

66. Lehman NL, Spassky N, Sak M, et al. Astroblastomas exhibit radial glia stem cell lineages and differential expression of imprinted and X-inactivation escape genes. Nat Commun. 2022; 13(1): 2083.

67. Alhalabi KT, Stichel D, Sievers P, Peterziel H, Sommerkamp AC, Sturm D, et al. PATZ1 fusions define a novel molecularly distinct neuroepithelial tumor entity with a broad histological spectrum. Acta Neuropathol. 2021; 142(5): 841-857.

68. Jo VY. EWSR1 fusions: Ewing sarcoma and beyond. Cancer Cytopathol. 2020; 128(4): 229-231.

69. Agaimy A, Kasajima A, Stoehr R, Haller F, Schubart C, Tögel L, et al. Gene fusions are frequent in ACTH-secreting neuroendocrine neoplasms of the pancreas, but not in their non-pancreatic counterparts. Virchows Arch. 2023; 482(3): 507-516.

70. Arroteia IF, Licci M, Hench J, Bartoli A, Ansari M, Plavsky P, et al. Long-Term Follow-Up of a Child with EWSR1-BEND2 Fused Spinal Astroblastoma. Pediatr Neurosurg. 2024; 59: 202-209.

71. Lehman NL. Early ependymal tumor with MN1-BEND2 fusion: a mostly cerebral tumor of female children with a good prognosis that is distinct from classical astroblastoma. J Neurooncol. 2023; 161(3): 425-439.

72. Dai Q, Ren A, Westholm JO, Serganov AA, Patel DJ, Lai EC. The BEN domain is a novel sequence-specific DNA-binding domain conserved in neural transcriptional repressors. Genes Dev. 2013; 27(6): 602-14.

73. Nakayama N, Sakashita G, Nagata T, Kobayashi N, Yoshida H, Park SY, et al. Nucleus Accumbens-Associated Protein 1 Binds DNA Directly through the BEN Domain in a Sequence-Specific Manner. Bio-medicines. 2020; 8(12): 608.

74. Miyake N, Takahashi H, Nakamura K, Isidor B, Hiraki Y, Koshimizu E, et al. Gain-of-Function MN1 Truncation Variants Cause a Recognizable Syndrome with Craniofacial and Brain Abnormalities. Am J Hum Genet. 2020; 106(1): 13-25.

75. Burford A, Mackay A, Popov S, Vinci M, Carvalho D, Clarke M, et al. The ten-year evolutionary trajectory of a highly recurrent paediatric high grade neuroepithelial tumour with MN1: BEND2 fusion. Sci Rep. 2018; 8(1): 1032.

76. Chadda KR, Holland K, Scoffings D, Dean A, Pickles JC, Behjati S, et al. Genomics England Research Consortium. A rare case of paediatric astroblastoma with concomitant MN1-GTSE1 and EWSR1-PATZ1 gene fusions altering management. Neuropathol Appl Neurobiol. 2021 ;47(6): 882-888.