

A Pigmented Intraventricular Tumor in a 10-Year-Old Girl: A Diagnostic Conundrum between Meningeal Melanocytoma and Melanotic Ependymoma with Integrated DNA Methylation and Next-Generation Sequencing Findings

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Case Report

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Abstract

A 10-year-old girl presented with two months of progressive headache and morning nausea. CT and MRI demonstrated a calcified, T1-hyperintense/T2-hypointense, hyperperfused, avidly and heterogeneously enhancing trigonal mass supplied by enlarged choroidal arteries; gross-total resection was achieved. Histopathology showed a densely pigmented neoplasm with perivascular pseudorosette-like arrangements, bland cytology and numerous melanophages. Two institutions reached divergent interpretations: the home report could not exclude melanotic ependymoma, whereas independent specialist review favored meningeal melanocytoma. GFAP was confined to marginal brain tissue, EMA was equivocally dot-like at both centers, SOX-10 and D2-40 were partially positive, HMB-45 was positive, S-100 and vimentin were negative, and the Ki-67 index was 5–8%. Genome-wide DNA methylation profiling yielded a non-diagnostic standalone signature (highest random-forest score 0.2822 for subependymal giant cell astrocytoma), and 460-gene next-generation sequencing found no melanocytic or ependymal driver alteration, a low tumor mutational burden (0.87/Mb) and balanced copy-number profiles on both platforms. Integrated findings favor a circumscribed meningeal melanocytoma (CNS WHO grade 1), with melanotic ependymoma retained only as a formal differential based on architecture. Only two intraventricular melanocytomas have previously been reported; gross-total resection with long-term surveillance is recommended.

Introduction

A pigmented mass within the cerebral ventricle of a child raises a narrow but difficult differential diagnosis. The principal candidates are melanotic (pigmented) ependymoma, a circumscribed meningeal melanocytic tumor such as meningeal melanocytoma, a pigmented choroid plexus papilloma or carcinoma, and—far more rarely—primary central nervous system (CNS) melanoma or a metastasis [1, 2]. These lesions share the paramagnetic imaging signature of melanin (intrinsic T1 hyperintensity and T2 hypointensity) but differ radically in grade and management, so histological and molecular precision is essential.

Under the fifth edition of the WHO Classification of Tumours of the CNS (WHO CNS5), primary meningeal melanocytic tumors span circumscribed meningeal melanocytoma (CNS WHO grade 1), intermediate-grade melanocytic tumor, primary CNS melanoma (grade 4) and diffuse meningeal melanocytosis [1, 3]. They are predominantly tumors of adults, most often spinal or posterior fossa, and circumscribed lesions frequently harbor activating GNAQ or GNA11 mutations and, less often, CYSLTR2, PLCB4, EIF1AX, SF3B1 or BAP1 variants [3–7]; a pediatric systematic review identified no intraventricular example [8]. Melanotic ependymoma is an exceedingly rare variant in which ependymal cells produce melanin; fewer than two dozen cases are reported, mostly fourth-ventricular tumors of middle-aged adults, with a glial immunophenotype (GFAP, dot-like EMA) and absent SOX-10 [9, 10]. DNA methylation profiling is now a powerful ancillary classifier of CNS tumors [11], including melanocytic neoplasms [12], although non-diagnostic results occur, particularly outside established reference classes.

We describe a 10-year-old girl with a pigmented trigonal tumor in whom two institutions reached divergent diagnoses—melanotic ependymoma versus meningeal melanocytoma—and methylation profiling was non-diagnostic, and we review the PubMed literature on intraventricular melanocytic tumors.

Clinical Summary

A 10-year-old girl presented with a two-month history of progressively worsening headache and intermittent morning nausea suggestive of raised intracranial pressure. Neurologic examination was unremarkable, with intact visual acuity and fields, normal cranial nerve, motor, cerebellar and gait testing, and no meningeal signs. There was no personal or family history suggestive of tuberous sclerosis complex or neurocutaneous melanosis, and no cutaneous or ocular pigmented lesion was identified.

Noncontrast head computed tomography (CT) demonstrated a well-circumscribed hyperdense mass with focal calcification in the trigone of the left lateral ventricle (Fig. 1a). Brain magnetic resonance imaging (MRI) showed a heterogeneous intraventricular lesion growing along the ventricular wall, with intrinsic T1 hyperintensity and T2 hypointensity, mixed FLAIR and susceptibility-weighted signal, and no restricted diffusion on diffusion-weighted imaging/ADC (Fig. 1b–g). Arterial spin-labeling perfusion imaging demonstrated elevated regional cerebral blood volume. Post-contrast images revealed marked heterogeneous enhancement, peritumoral cystic fluid, and enlarged anterior and posterior choroidal feeding arteries (Fig. 1h–l).

The patient underwent microsurgical gross-total resection via a left parieto-occipital transcortical transventricular approach. Intraoperatively, the darkly pigmented, soft and friable tumor occupied the trigone, with its base broadly attached to the choroid plexus and a robust blood supply from branches of the anterior and posterior choroidal arteries; the tumor–ventricular wall interface was well demarcated, permitting en bloc resection with preservation of adjacent ependyma and periventricular brain. The postoperative course was uneventful.

Given the diagnostic uncertainty, the patient's age and the low-grade cytological features reported by both institutions, no adjuvant radiotherapy or chemotherapy was administered, and close clinical and imaging surveillance was planned. Six months after surgery, examination and serial neuroimaging showed no evidence of recurrence, leptomeningeal dissemination or new neurologic deficit.

This study was approved by the Institutional Review Board of West China Second University Hospital, Sichuan University, and conducted in accordance with the Declaration of Helsinki. Written informed consent for publication of clinical details and accompanying images was obtained from the patient's legal guardian.

Pathological Findings

Histopathology at the home institution demonstrated a densely pigmented neoplasm containing perivascular pseudorosette-like arrangements of cells with abundant intracytoplasmic dark pigment granules (Fig. 2a–d). The formal report concluded that this was a pigment-rich tumor in which melanotic ependymoma could not be excluded on morphology and immunohistochemistry, and explicitly recommended next-generation sequencing or methylation profiling to establish the final diagnosis.

Immunohistochemistry on two tissue blocks showed GFAP reactivity confined to marginal, entrapped brain tissue on block 1 and absent GFAP on block 14; equivocal focal dot-like EMA on both blocks; negative OLIG-2, S-100, SOX-10, vimentin, SSTR2, TTF-1, pan-cytokeratin, CD10 and α -inhibin; negative chromogranin A, synaptophysin and NeuN; HMB-45 positivity with partial melan-A and progesterone receptor positivity; CD34 and SMA confined to vessels with desmin negativity; and a Ki-67 index of 8% (Fig. 2e–h; Online Resource 1, Table S1).

Because of the unusual pigmented morphology, unstained sections underwent independent specialist review. The consultants described numerous histiocytoid, round-to-oval cells with abundant pigment, numerous melanophages, hemorrhage and calcification, inconspicuous atypia, and no definite mitotic figures or necrosis. Tumor cells were GFAP-negative and partially positive for SOX-10 and D2-40, with equivocal EMA, negative S-100, HMB-45 positivity and partial melan-A; they were negative for pan-cytokeratin, CD1a, langerin, ALK and BRAF V600E, CD68 and CD163 highlighted the histiocytic population, p53 labeled about 5% of nuclei, and the Ki-67 index was approximately 5%. The consultant diagnosis was a circumscribed pigment-rich meningeal melanocytic tumor, favoring meningeal melanocytoma (Online Resource 1, Table S1).

Genome-wide DNA methylation profiling was performed on FFPE tissue using the Infinium MethylationEPIC v2.0 array (approximately 935,000 CpG sites) with the random-forest classifier of Capper et al. (reference library of 90 CNS tumor

and eight control-tissue classes, including dedicated melanocytoma and malignant melanoma classes). The tumor received no definitive entity assignment and was reported as a standalone cluster; the highest random-forest score was 0.2822 for subependymal giant cell astrocytoma (SEGA), far below the 0.4 low-confidence threshold. On t-distributed stochastic neighbor embedding (t-SNE), the sample lay at the interface between the SEGA, TSC1/TSC2-altered reference cluster and the control-tissue/reactive tumor-microenvironment cluster, rather than within any ependymoma or melanocytic class (Fig. 3a). Array-based copy-number analysis detected no significant chromosomal alteration; all interrogated loci, including BCOR (mean log2 copy-ratio 0.318), were called normal.

Hybrid-capture next-generation sequencing of a 460-gene brain-tumor panel was performed with a matched peripheral-blood control (tumor cellularity 90%; mean depth 7,891×). A single variant was reported: MDM4 c.59C > T (p.Ser20Phe), a class-III variant of uncertain significance at a variant allele fraction of 2.84%, interpreted as non-driver. GNAQ, GNA11, CYSLTR2, PLCB4, EIF1AX, SF3B1, BAP1 and PRKAR1A were wild type, as were BRAF, NRAS, KRAS, HRAS and TSC1/TSC2; ZFTA (C11orf95) and YAP1 fusions, MYCN amplification, NF2 alteration, CDKN2A/B deletion, TERT promoter mutation and 1q gain, 6q loss and 13q loss were absent, and no pathogenic germline variant was detected. Tumor mutational burden was 0.87 mutations/Mb with microsatellite stability. Panel copy-number analysis showed a balanced autosomal genome without high-level amplification or homozygous deletion (Fig. 3b); a whole-chromosome X signal (with chromosome Y loss, as expected for a female sample) was not reproduced by the EPIC array and was interpreted as a sex-chromosome normalization/constitutional signal, with no focal BCOR rearrangement.

Discussion

This case illustrates how closely a circumscribed meningeal melanocytic tumor can mimic a pigmented ependymoma when it arises within a ventricle. Importantly, neither pathology service committed to ependymoma: the home report described pseudorosette-like architecture but confined GFAP to marginal brain, found EMA only equivocally positive and itself requested molecular studies, whereas the specialist reviewers found bland melanocytic cells with melanophages, partial SOX-10 and D2-40 expression and a Ki-67 index of about 5%, favoring meningeal melanocytoma.

A PubMed search through September 2026 (terms “melanocytoma”, “melanotic”, “pigmented”, “intraventricular”, “ventricle”; reference lists hand-searched) identified only two pathologically confirmed primary intraventricular meningeal melanocytomas (Table 1): a black vascular cystic temporal-horn tumor in a young woman supplied by the anterior choroidal artery [13], and an eighth-decade case defined by CYSLTR2 and EIF1AX mutations [14]; a malignant pineal melanocytic tumor invading the third-ventricular wall is also listed for comparison [15]. A spinal melanocytoma with secondary fourth-ventricular seeding is not a primary ventricular lesion [16], and a recent systematic review of 19 pediatric CNS meningeal melanocytomas included no intraventricular tumor [8]. The present case would, to our knowledge, be the first documented pediatric intraventricular example.

Table 1
Reported primary circumscribed melanocytic neoplasms arising within or immediately adjacent to the cerebral ventricles (PubMed-based review).

Reference	Age/sex	Ventricular site	Diagnosis and evidence	Molecular findings	Treatment	Outcome
Suzuki, 2001 [15]	50 F	Pineal region, invading the third-ventricular wall; hippocampal dissemination	Malignant melanocytic tumor with well-differentiated melanocytoma-like areas; mature melanosomes on electron microscopy	Not reported	STR + whole-brain irradiation	Died 11 months postoperatively
Tandon, 2008 [13]	Young adult F	Temporal horn, left lateral ventricle	Melanocytoma; immunohistochemistry and electron microscopy (melanosomes); black vascular cystic mass supplied by the anterior choroidal artery	Not reported	GTR	No recurrence on follow-up; first reported intraventricular case
Knappe, 2018 [14]	Aged (80s) M	Intraventricular (site not specified)	Melanocytoma; metastatic melanoma excluded	CYSLTR2 L129Q and EIF1AX G9R mutations; BRAF/NRAS wild type	Resection	Not reported; second reported intraventricular case
Present case	10 F	Trigone, left lateral ventricle	Disputed: meningeal melanocytoma favored on specialist review; melanotic ependymoma not excluded at home institution; methylation standalone (top score SEGA 0.2822)	GNAQ, GNA11, CYSLTR2, PLCB4, EIF1AX, SF3B1, BAP1, PRKAR1A, BRAF, NRAS wild type; no ZFTA/YAP1 fusion or MYCN amplification; MDM4 S20F VUS (VAF 2.84%); TMB 0.87/Mb; balanced copy-number profile	GTR; no adjuvant therapy	No recurrence at 6 months; first pediatric intraventricular example
<i>F, female; M, male; GTR, gross-total resection; STR, subtotal resection; VAF, variant allele fraction; TMB, tumor mutational burden; VUS, variant of uncertain significance; SEGA, subependymal giant cell astrocytoma. A spinal melanocytoma with secondary leptomeningeal spread to the fourth ventricle [16] is not a primary ventricular tumor and is excluded.</i>						

Several lines of evidence converge on melanocytoma. Both services described bland histiocytoid cells without definite mitoses or necrosis, numerous melanophages, hemorrhage and calcification, and a Ki-67 index of 5–8%—a constellation typical of melanocytoma [3, 7]. Partial SOX-10 expression is strong evidence of melanocytic lineage: none of 44 ependymomas in a systematic immunohistochemical study expressed SOX-10 [17]. GFAP-negative tumor parenchyma (with positivity only in entrapped marginal brain), equivocal EMA at both centers, and negative S-100, vimentin and SSTR2 leave no convincing ependymal phenotype, while partial D2-40 supports meningeal differentiation; weak or absent S-100 with strong HMB-45 and melan-A is typical of meningeal melanocytomas [3]. The imaging pattern—an

intensely enhancing, partly cystic, T1-hyperintense/T2-hypointense vascular mass fed by an enlarged anterior choroidal artery—closely mirrors the first reported lateral-ventricular melanocytoma [13]. Finally, the flat copy-number landscape and very low mutational burden are consistent with a benign circumscribed lesion, and methylation matched no ependymoma class.

The case for melanotic ependymoma rests almost entirely on the pseudorosette-like architecture, which melanocytic cells arranged around vessels with stromal fibrosis can mimic in a pigmented, histiocyte-rich lesion. The two molecularly characterized pigmented ependymomas in the literature both matched defined ependymoma methylation classes (posterior fossa group B and supratentorial YAP1 fusion-positive) [9, 18], whereas this tumor matched neither and lacked ZFTA/YAP1 fusions, MYCN amplification and the 1q/6q/13q copy-number patterns of established ependymoma classes [19]. Melanotic ependymoma therefore remains a formal differential on morphological grounds alone.

Primary CNS melanoma is disfavored by the bland cytology, absent mitoses and necrosis, Ki-67 around 5%, absence of a cutaneous, mucosal or uveal primary, wild-type BRAF/NRAS, low mutational burden and quiet copy-number profile [3, 6, 7]. A pigmented choroid plexus neoplasm would show frond-like papillary architecture with epithelial marker expression, neither of which was present (pan-cytokeratin negative) [2, 20]. SEGA, suggested by the t-SNE proximity, arises at the foramen of Monro in the tuberous sclerosis setting, shows large ganglioid cells with dual glial/neuronal markers, is HMB-45-negative and harbors TSC1/TSC2 alterations—all absent here [21]. CD68/CD163-positive, CD1a/langerin- and ALK-negative histiocytes represent reactive melanophages (Online Resource 1, Table S2).

A non-diagnostic methylation result must not be read as evidence for either diagnosis. The SEGA score (0.2822) fell far below threshold and the lesion lacks SEGA morphology, site, tuberous sclerosis context and dual glioneuronal phenotype; its position beside the reactive-microenvironment cluster plausibly reflects the conspicuous melanophage infiltrate, which may inflate the tumor-purity estimates on which classifiers depend [11]. The library contains dedicated melanocytoma and melanoma classes, yet the sample matched neither; reference melanocytomas are overwhelmingly adult dural or spinal tumors and include no pediatric intraventricular exemplar, so genuinely unusual tumors may form standalone clusters [11, 12]. Driver-wild-type melanocytomas constitute a recognized minority: GNAQ/GNA11 mutations were present in 21 of 24 sequenced cases in a recent series [7], and integrated genomic studies document heterogeneous, partly wild-type profiles [6, 12, 22], while the only molecularly characterized intraventricular melanocytoma carried CYSLTR2 and EIF1AX mutations [14]. The low-frequency MDM4 variant is below clonal representation and cannot be considered a driver; the unconfirmed chromosome X signal encompasses BCOR at Xp11.4 but shows no BCOR rearrangement.

Taken together, the morphological, immunohistochemical, imaging and molecular evidence favors a circumscribed meningeal melanocytic neoplasm, most consistent with meningeal melanocytoma (CNS WHO grade 1), driver-wild-type and methylation-unclassified; only focal pseudorosette-like architecture keeps melanotic ependymoma in the formal differential. Gross-total resection is the treatment of choice and was achieved here, but progression is documented even after apparently complete resection—including five of six melanocytomas in a recent series and recurrence in 15% of pediatric cases—so long-term craniospinal MRI surveillance is warranted, whereas radiotherapy should be reserved for confirmed anaplasia, progression or unresectable recurrence [3, 7, 8, 16]. Limitations of this report include the unresolved inter-institutional discrepancy in SOX-10 and only six months of follow-up. This case demonstrates that a pigmented intraventricular mass in a child is not necessarily an ependymoma, and that integrated imaging, immunohistochemical and molecular assessment is required before a diagnosis with treatment consequences is finalized.

Declarations

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Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions: Conceptualization, C.W., Y.C. and Y.S.; investigation and data curation, C.W. and Y.C.; writing—original draft preparation, C.W. and Y.C.; writing—review and editing, Y.S.; supervision, Y.S. All authors have read and approved the final manuscript.

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Figures

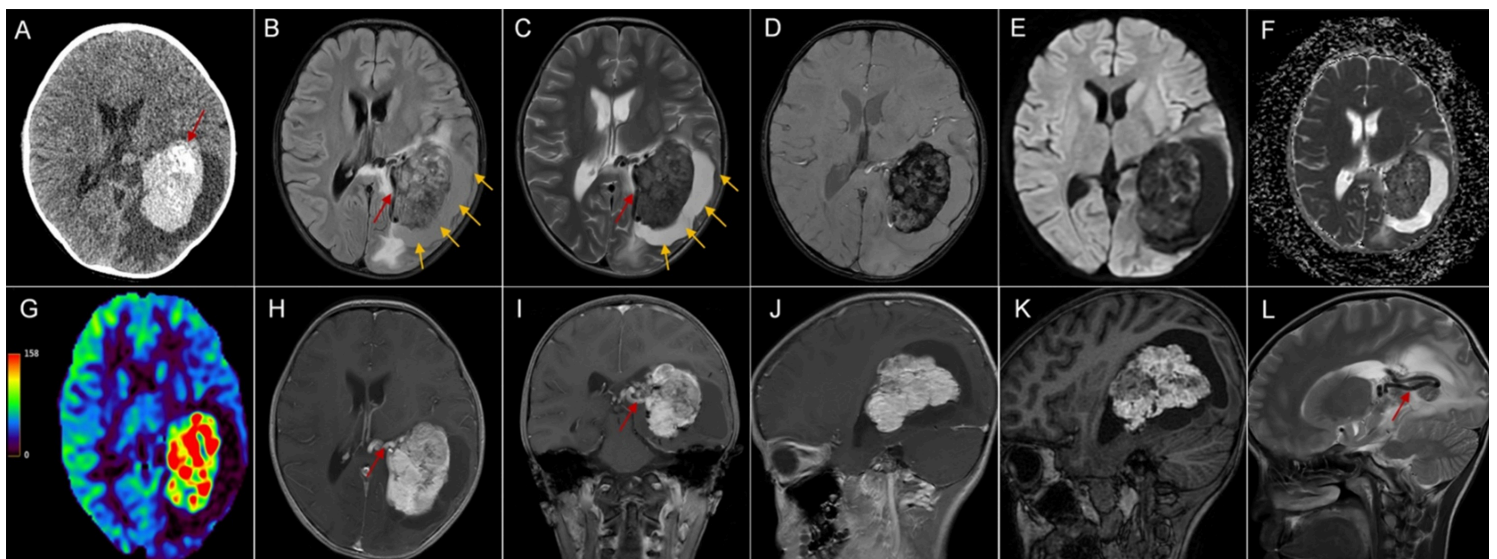


Figure 1

Preoperative neuroimaging. (a) CT demonstrates intratumoral calcification (red arrow). (b–g, k, l) MRI shows a mass growing along the lateral ventricular wall, with T1 hyperintensity, T2 hypointensity, mixed signal on FLAIR and SWI, no restricted diffusion on DWI/ADC, and hyperperfusion on ASL; enlarged anterior and posterior choroidal feeding arteries

(red arrows) and peritumoral cystic fluid (yellow arrows) are visible. (h–j) The tumor exhibits marked heterogeneous contrast enhancement.

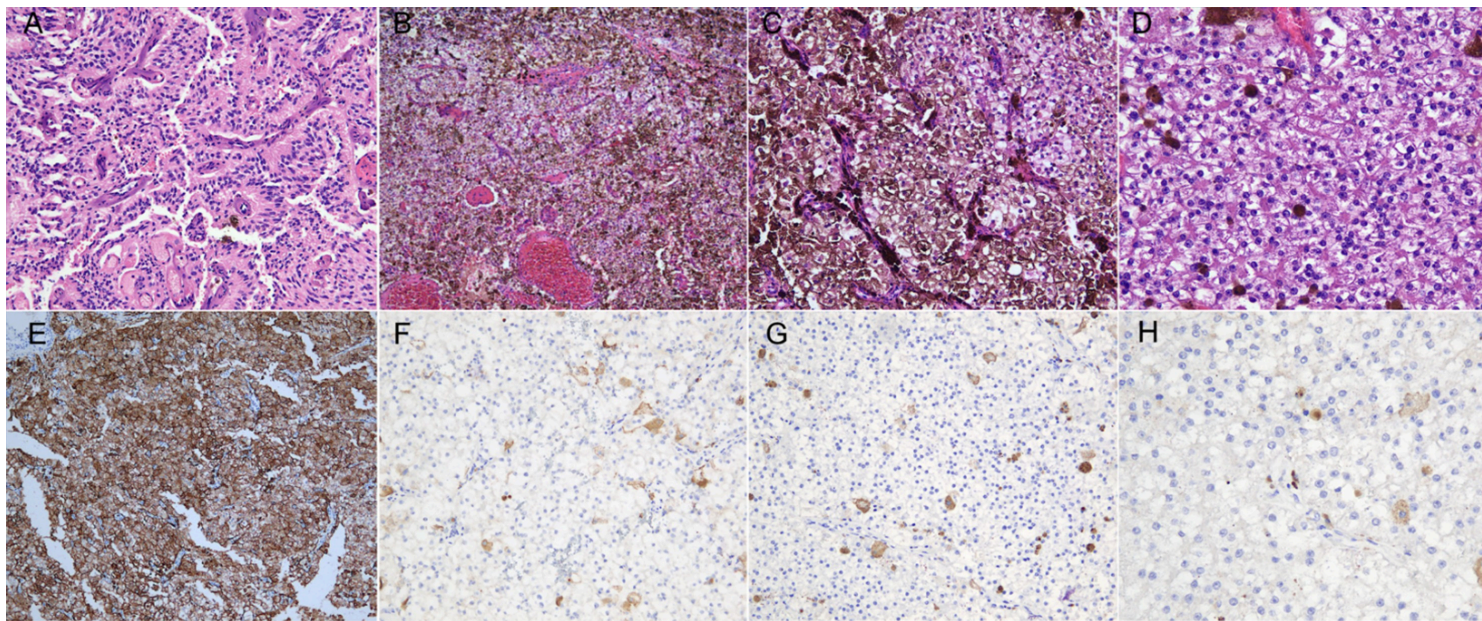


Figure 2

Histopathology at the home institution. (a–d) Hematoxylin and eosin staining demonstrates perivascular pseudorosette-like arrangements with abundant intracytoplasmic dark pigment granules ($\times 40$, $\times 100$ and $\times 200$). (e–h) Immunohistochemistry reveals diffuse HMB-45 positivity (e), focal melan-A expression (f), absent S-100 staining (g), and equivocal dot-like EMA reactivity (h).

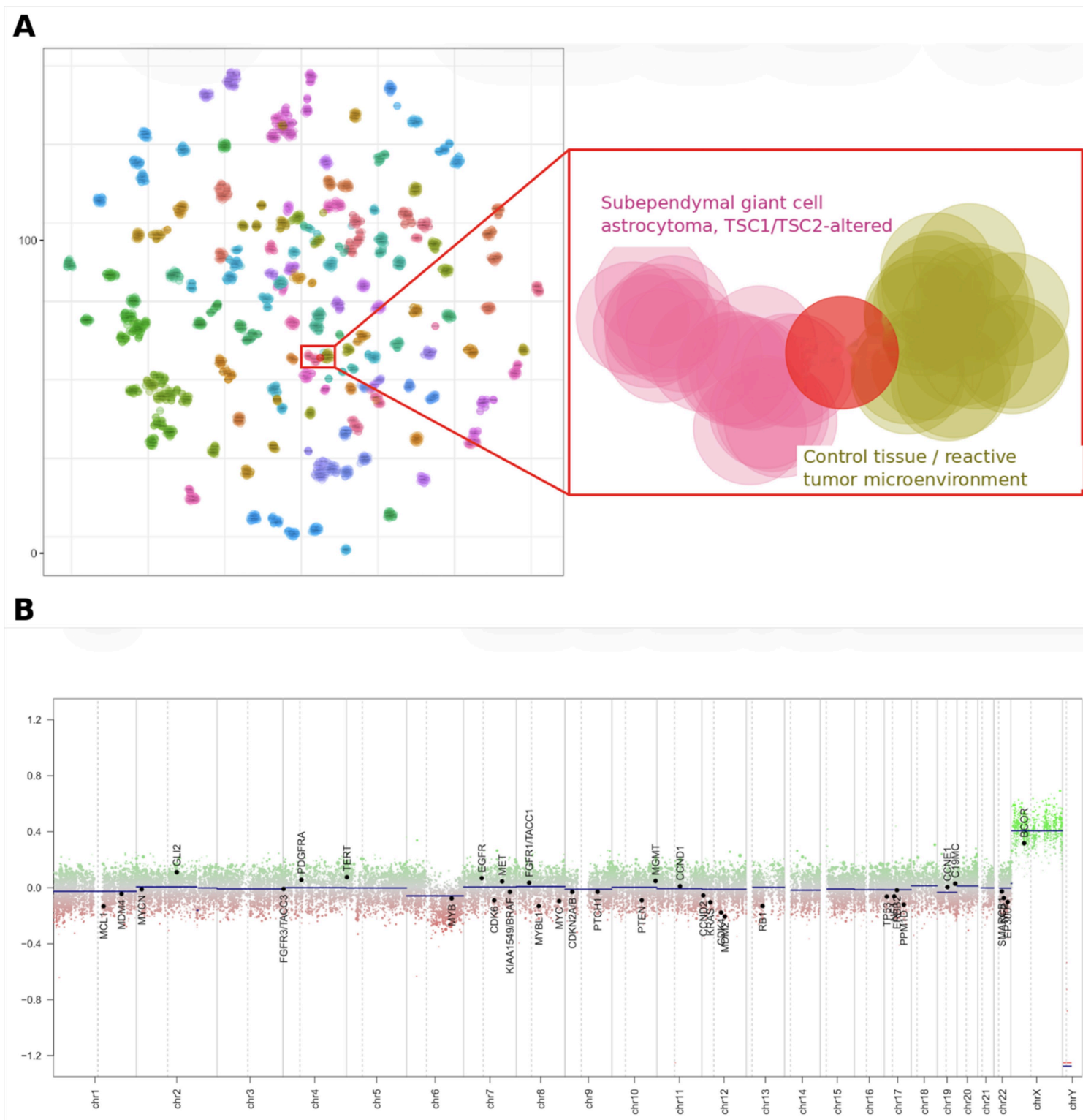


Figure 3

Integrated molecular profiling. (a) DNA methylation t-SNE projection: the patient sample (red circle) does not co-localize with any established CNS tumor class; its highest random-forest score was 0.2822 for subependymal giant cell astrocytoma, TSC1/TSC2-altered (pink), below the 0.4 low-confidence threshold, and it sits at the interface between that cluster and the control-tissue/reactive tumor-microenvironment cluster (olive); the dedicated melanocytoma and malignant melanoma classes were not matched. (b) Panel-based genome-wide copy-number profile: the autosomal genome is balanced, without high-level amplification or homozygous deletion of canonical CNS tumor drivers; a whole-chromosome X signal (with chromosome Y loss, expected in a female sample) was not reproduced by the EPIC

methylation array and is regarded as a normalization/constitutional signal; no focal BCOR rearrangement is demonstrated.

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