Neuropathology and Applied Neurobiology

WILEY

Neuropathology and Applied Neurobiology
JOURNAL OF THE BRITISH NEUROPATHOLOGICAL SOCIETY

ORIGINAL ARTICLE OPEN ACCESS

Glioneuronal Tumour With Neurocytic Differentiation (GNTN): a Molecularly Defined Tumour Type Formerly Referred to as Extraventricular Neurocytoma

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Received: 20 April 2026 | **Revised:** 27 April 2026 | **Accepted:** 30 April 2026

Keywords: DNA methylation | extraventricular neurocytoma | *FGFR1::TACC1* | glioneuronal tumour with neurocytic differentiation (GNTN) | *NTRK* fusions | supratentorial tumours

ABSTRACT

Tumours historically classified as extraventricular neurocytoma (EVN), initially in comparison with central neurocytoma, are defined by location and morphology; however, emerging molecular data demonstrate that this term is outdated. We report 14 previously unpublished tumours with a robust EVN DNA methylation profile, independent of original histopathologic diagnosis or anatomic location. Integrated molecular analyses identified *FGFR1* alterations, particularly *FGFR1::TACC1* fusions, as the predominant molecular driver of this tumour class. A smaller number of tumours harboured *FGFR1* hotspot mutations (p.N546K and p.K656E). Among these, two cases additionally showed *NF1* variants, and one tumour carried a *PIK3CA* mutation (p.H1047L). In addition, a single case exhibited an *NTRK2* fusion. Histologically, tumours exhibited neurocytic differentiation with neuropil islands and a minor glial component, while immunohistochemistry showed frequent OLIG2 expression, contrasting with the typical immunophenotype of central neurocytoma. Notably, tumours with an EVN DNA methylation profile were identified in both extraventricular and intraventricular locations, demonstrating that anatomy-based definitions are inadequate for this tumour type. Clinical follow-up (median 33.2 months) showed predominantly lower grade behaviour, with occasional recurrence. Collectively, these findings support the view that tumours previously labelled as EVN do not represent a direct counterpart of central neurocytoma but instead constitute a molecularly and epigenetically distinct glioneuronal tumour type.

Pascale Varlet and Philipp Sievers are co-senior authors.

We propose the designation glioneuronal tumour with neurocytic differentiation (GNTN) to reflect its biological identity and to align the terminology with contemporary molecular neuropathology, and recommend DNA methylation profiling as an essential diagnostic criterion.

1 | Introduction

Extraventricular neurocytoma (EVN) is a rare neuroepithelial tumour that historically has been defined histologically by its resemblance to central neurocytoma while arising outside the ventricular system. In the pre-molecular era, this anatomical distinction, together with shared morphologic features such as uniform round cells, a neuropil-like background, and synaptophysin expression, formed the basis of its classification. However, reliance on histology alone has proven insufficient, as a substantial proportion of tumours diagnosed as EVN based on morphology show significant overlap with other glioneuronal and low-grade neuroepithelial neoplasms [1]. This lack of clear histological boundaries has been paralleled by marked diagnostic heterogeneity and limited reproducibility in reported clinical presentations and radiological features, further complicating consistent tumour classification.

The introduction of genome-wide DNA methylation profiling has fundamentally altered the understanding of EVN. In a landmark study, methylation analysis demonstrated that only a subset of tumours previously classified as EVN forms a distinct epigenetic cluster that is clearly separable from central neurocytoma and from a broad range of histological mimics, establishing EVN as a molecularly defined tumour type [1, 2]. Importantly, this molecular class is characterised by recurrent oncogenic kinase fusions, most notably *FGFR1::TACC1*, providing a robust biological rationale for its separation [1, 3].

Subsequent studies have confirmed and refined these findings, showing that tumours clustering within the EVN methylation class may arise not only in extraventricular locations but also in rare instances within the ventricular system itself, challenging the traditional anatomy-based definition of the tumour type [4]. Collectively, these findings indicate that EVN cannot be reliably defined by anatomical location and histology alone but is more accurately delineated by its molecular and epigenetic features.

More recently, the molecular spectrum of EVN has expanded beyond *FGFR1::TACC1* fusions, with the identification of alternative oncogenic drivers, including rare *NTRK* fusions, in tumours sharing the same methylation profile [4]. These findings further underscore the biological coherence of this tumour class while highlighting previously unrecognised genetic heterogeneity within it. Together, these data argue for a refined, molecularly grounded definition of EVN and provide the framework for reassessing its nomenclature, diagnostic criteria, and clinical correlates.

Here, we describe a series of 14 previously unpublished EVNs confirmed by DNA methylation-based classification and analysed using dimensionality-reduction approaches (t-SNE/UMAP). We characterise these tumours comprehensively with respect to their clinicopathological, histological, molecular, and radiological features to further refine the integrated diagnostic spectrum of EVN.

2 | Materials and Methods

2.1 | Patient Samples

We retrospectively collected clinical data and archived formalin-fixed, paraffin-embedded (FFPE) tumour samples ($n = 14$) from multiple collaborating centres that were not part of previously published EVN DNA methylation cohorts. Centralised molecular analyses were performed at the Department of Neuropathology, Sainte-Anne Hospital (GHU Psychiatrie et Neurosciences, Paris, France) and the Department of Neuropathology, University Hospital Heidelberg (Germany). Case inclusion was strictly based on assignment to the EVN DNA methylation class, as previously defined [1, 2]. Histological diagnosis and tumour location were not used as primary selection criteria.

2.2 | Nucleic Acid Extraction

Genomic DNA and total RNA were extracted from FFPE tissue sections enriched for tumour cell content. DNA extraction was performed using automated Maxwell RSC instruments (Promega) with the Maxwell RSC FFPE Plus DNA Kit according to the manufacturer's instructions. DNA concentration was quantified using the Qubit dsDNA BR Assay Kit (Thermo Fisher Scientific). RNA was extracted using the Maxwell RSC RNA FFPE Kit (Promega), and RNA quality was assessed using the DV200 metric on an Agilent 4150 TapeStation system, with samples exceeding a DV200 threshold of 200 bp considered suitable for downstream analysis.

2.3 | DNA Methylation Profiling and Copy Number Analysis

Genome-wide DNA methylation profiling was performed using Illumina Infinium HumanMethylation450 or MethylationEPIC BeadChip arrays, following standard protocols as previously described [5]. Raw IDAT files were processed using established pipelines implemented in R. Briefly, background correction, dye-bias correction, and normalisation were applied, and EPIC and 450k datasets were merged using the intersection of shared probes. Batch effects related to the array type were corrected using linear modelling approaches. Unsupervised dimensionality reduction was performed using *t*-distributed stochastic neighbour embedding (t-SNE) and Uniform Manifold Approximation and Projection (UMAP), incorporating reference datasets of established CNS

Summary

- A glioneuronal tumour type with neurocytic differentiation, formerly referred to as extraventricular neurocytoma, is reclassified based on a characteristic DNA methylation signature.
- Tumours occur in both intraventricular and extraventricular locations, indicating that anatomical site is not a defining feature.
- The tumour type is characterised by predominant *FGFR1* alterations with additional MAPK pathway changes.

tumour methylation classes for comparative classification. Copy number variation profiles were derived from methylation array data using the conumee package, and focal alterations were assessed by manual review of log2 ratio plots. Only cases showing a confident assignment to the EVN DNA methylation class (calibrated score ≥ 0.9) were included in the final cohort.

2.4 | Targeted DNA Sequencing

Targeted next-generation DNA sequencing was performed using a custom-designed enrichment-based panel covering coding exons and selected intronic regions of 220 CNS tumour-associated genes [6]. Libraries were sequenced on Illumina NovaSeq 6000 platforms. Sequence reads were aligned to the GRCh38 (hg38) reference genome using BWA, and variant calling focused on single-nucleotide variants, small insertions/deletions, and structural alterations, including gene fusions. Variants with an allele frequency below 5% were excluded. Pathogenicity was assessed according to ACMG guidelines.

2.5 | RNA Sequencing and Fusion Detection

RNA sequencing was performed to identify oncogenic gene fusions. Library preparation was conducted using the Agilent SureSelect XT HS2 RNA workflow with subsequent enrichment using SureSelect Human All Exon V8 probes. Paired-end sequencing (2×100 bp) was carried out on an Illumina NovaSeq 6000 platform. Fusion detection was performed using the Arriba algorithm on RNA-Seq data aligned with STAR (two-pass mode), and only high-confidence fusion events were considered for analysis.

2.6 | Histopathological and Immunohistochemical Analysis

A retrospective histopathological review was conducted by experienced neuropathologists (AM, PV, PS) to assess tumour morphology and immunohistochemical features. Samples were stained with haematoxylin-phloxine-saffron (HPS) or haematoxylin and eosin (H&E) according to standard protocols. Immunohistochemistry was performed when the following immunostainings were not available from the originating centre: OLIG2 (Sigma Polyclonal or Dako 6F2), CD34 (QBEnd10, Dako), GFAP (6F2, Dako), neurofilament (2F11, Dako or 2F11, Menarini), synaptophysin (DAK-SYNAP, Dako), Chromogranin A (LK2 H10, Diagnostic Biosystem), and Ki67 (MIB1, Dako). For each case, the following pathological features were scored as present or absent: calcification, presence of a specific glioneuronal element, eosinophilic granular bodies, perivascular lymphocytic infiltrates, glial component subtype (oligodendroglioma-like, astrocytic, piloid), Rosenthal fibres, microvascular proliferation, hyalinised vessels, and tumour necrosis. Mitotic activity was expressed as mitoses per mm^2. The growth pattern was assessed as diffuse (at least regionally) or circumscribed on anti-neurofilament immunostaining. The occurrence of a neuronal component (ganglionic or neurocytic)

TABLE 1 | Main clinical and molecular features of the cohort.

Sex	
Male	$N = 9$ (64%)
Female	$N = 5$ (36%)
Sex-ratio M/F	1.8
Clinical presentation	
Seizures	$N = 2$
Incidental finding	$N = 2$
Not available	$N = 10$
Age at surgery	
Mean	39 years (range 12–77)
Median	36 years [IQR 26–58]
Tumour location	
Frontal	$N = 4$
Temporal	$N = 2$
Occipital	$N = 2$
Fronto-parietal	$N = 1$
Parieto-occipital	$N = 1$
Supratentorial	$N = 2$
Lateral ventricle	$N = 2$
Extent of resection	
GTR	$N = 5$
Unknown	$N = 9$
Median follow-up	33.2 months (range 2.3–121.2)
Lost to follow-up	$N = 6$
Progression	$N = 3$
Median time between first surgery and progression	60 months (7–67)
Molecular features	
FGFR1::TACC1	$N = 9$
FGFR1 hotspot variant	$N = 4$
With additional *NF1* variant	$N = 2$
With additional *PIK3CA* variant	$N = 1$
NTRK2 fusion	N = 1

and of neuropil islands was also analysed. CD34 expression was considered positive if extravascular.

2.7 | Central Radiological Review

A review of the available MRIs was conducted by expert neuroradiologists (MEG) specialising in neuro-oncology. The following features were assessed: tumour location (lobe, deep location near the ventricles, or peripheral location close to or involving the cortex) and primary morphological characteristics, including well-circumscribed nodular versus infiltrative appearance, presence of a cystic component, and signal characteristics on T1- and T2-weighted images relative to normal-appearing cortex. Additional analyses included susceptibility-weighted imaging (SWI) and post-gadolinium T1-weighted sequences, assessing the presence and homogeneity of enhancement, the occurrence of contrast-enhancing microcysts, high-signal FLAIR areas, and perilesional oedema. When available, calcification was evaluated on CT scans. Preoperative imaging follow-up, when available, allowed assessment of lesion progression between diagnosis and surgery, while postoperative imaging follow-up was collected to evaluate the completeness of surgical resection and subsequent tumour evolution.

3 | Results

3.1 | Clinical Presentation and Course Reflect Adult-Type Supratentorial Tumours With Predominantly Lower Grade Behaviour

Fourteen tumours met the inclusion criteria. The cohort included nine males and five females (M:F ratio 1.8:1), with a mean age of 39 years (median 36 years; range 12–77). All tumours were supratentorial. Twelve cases (86%) were extraventricular, predominantly involving the frontal and occipital lobes, whereas two tumours (14%) arose intraventricularly within the lateral ventricle. Twelve tumours were evaluated at initial presentation, while two cases represented recurrent disease at the time of surgical resection. A summary of the demographic, clinical, and molecular features is provided in Table 1.

Clinical follow-up data were available for 8 of 14 patients (57%). The mean follow-up duration was 41.0 months, with a median of 33.2 months (range 2.3–121.2). Progression status was available for seven patients; tumour progression occurred in three cases (43%) at 7, 60 and 67 months after surgery.

3.2 | DNA Methylation and Oncogenic Alterations Confirm a Distinct Molecular Tumour Type

All tumours included in this study were selected based on a robust match to the EVN DNA methylation class by genome-wide profiling. Unsupervised dimensionality reduction analyses, including t-SNE and UMAP, demonstrated tight clustering of the study cases with reference EVN samples and clear separation from central neurocytoma and other glioneuronal tumour types (Figure 1). Copy number profiles derived from DNA methylation array data did not reveal recurrent chromosomal alterations.

Targeted DNA and RNA sequencing further characterised the molecular landscape of these methylation-classified tumours, identifying recurrent oncogenic signalling pathway alterations. *FGFR1::TACC1* fusions were detected in the majority of tumours (9/14; 64%), confirming this alteration as the predominant molecular driver. Lower frequency *FGFR1* hotspot mutations were observed (p.N546K, p.K656E. p.N546D). Additional pathway-associated alterations included *NF1* variants in two tumours, a single *PIK3CA* mutation (p.H1047L), and one tumour harbouring an *NAV1::NTRK2* fusion, with breakpoints at chr1:201,755,705 (*NAV1*) and chr9:87,356,807 (*NTRK2*). The predicted fusion preserves the tyrosine kinase domain of *NTRK2*, suggesting potential oncogenic activity. A summary of molecular alterations is provided in Table 1.

3.3 | Morphologic and Immunophenotypic Features Show Glioneuronal Tumours With Neurocytic Differentiation

Histological examination revealed predominantly well-circumscribed tumours with a nodular architecture, which were often calcified. Neurocytic differentiation was consistently present, as shown by the almost constant presence of neurocytes and neuropil islands. There was no cytological atypia. Abundant vascularisation was observed, consisting of hyalinised vessels, sometimes calcified and frequently associated with haemorrhagic changes accompanied by siderophages (50%). In haemorrhagic tumours, papillary or pseudopapillary features reminiscent of papillary glioneuronal tumour (PGNT) could be observed. Furthermore, a minor glial component was associated with oligodendroglia-like and/or astrocytic or pilocytic features, as well as a ganglioid or glioneuronal element showing somewhat more pleomorphic aspects. Rosenthal fibres and perivascular lymphocytes were absent.

Immunohistochemistry demonstrated diffuse, strong and nearly omnipresent synaptophysin expression, often associated with neuropil islands, together with chromogranin expression in ganglioid component when present and focal positivity for neurofilament protein (NFP) staining. OLIG2 was consistently positive or at least focally expressed, while GFAP was either negative or limited to focal interstitial positivity, confirming the predominance of a neuronal component with a secondary glial element. There was no CD34 extravascular expression. There were no signs of aggressiveness, no microvascular proliferation, and no necrosis. Mitotic activity and the Ki-67 proliferation index remained low. Histological and immunophenotypic features are summarised in Figures 2 and S1.

3.4 | Radiological Features Demonstrate Well-Circumscribed Lesions With a Characteristic Imaging Pattern

Preoperative magnetic resonance imaging (MRI) was available for five cases. Tumours were located in both extraventricular and intraventricular compartments. Imaging revealed well-circumscribed lesions associated with solid enhancing nodules. All cases had a solid component isointense or slightly hypointense on T1-weighted images and hyperintense on

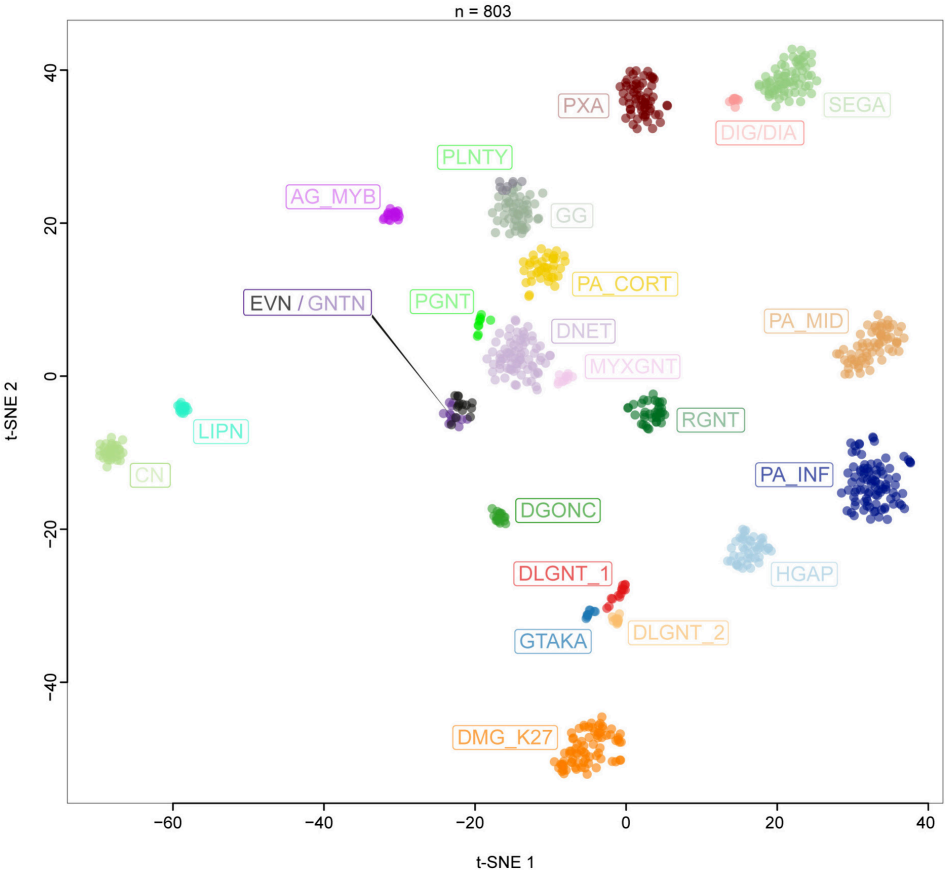

FIGURE 1 | Unsupervised nonlinear t-distributed stochastic neighbour embedding (t-SNE) projection of genome-wide DNA methylation profiles from 803 CNS tumours. The study cases cluster tightly with reference samples of the DNA methylation class extraventricular neurocytoma (EVN) and segregate clearly from other tumour types.

T2-weighted and FLAIR images. Cystic components were observed in four cases, showing T1 hypointensity and T2 hyperintensity. Well-demarcated margins were observed in all cases, distinguishing EVN from infiltrative gliomas. Perilesional oedema was present in one case. The T2* and SWI sequences of two patients were consistent with haemorrhagic remodelling, which was confirmed histologically. Microcalcification was observed on the CT scan for one case. No aggressive imaging features (larger volume, cross-lobe growth, lobulated appearance with unclear boundaries, flow voids from abnormal vessels, necrosis, and haemorrhage) were observed. Representative radiological features are shown in Figure 3.

4 | Discussion

In this study, we present 14 previously unpublished tumours classified within the EVN DNA methylation class based on stringent classifier scores and concordant clustering with reference samples. The majority of tumours harboured *FGFR1::TACC1* fusions, whereas a minority carried alternative oncogenic alterations, including *FGFR1* hotspot mutations, *NF1* variants, a single *PIK3CA* mutation and one tumour with an *NTRK2* fusion. By applying strict molecular inclusion criteria, independent of anatomical location or morphological interpretation, this cohort enables comprehensive clinical, radiological and histopathological characterisation of EVN and extends previous DNA methylation-based reports supporting it as a distinct epigenetic tumour type [1, 3, 4, 7, 8].

The predominance of *FGFR1::TACC1* fusions in our cohort is consistent with previous descriptions of the EVN DNA methylation class, in which *FGFR1* rearrangements represent recurrent characteristic molecular events [1]. The presence of additional kinase pathway alterations, including *NTRK* fusion and rare signalling variants, supports the concept that MAP kinase pathway dysregulation constitutes a central biological theme rather than a single pathognomonic driver in glioneuronal tumours [4, 9–11]. Together, these findings reinforce DNA methylation profiling as the most robust diagnostic framework for EVN, particularly in cases with ambiguous histology or atypical location.

Historically, the term ‘extraventricular neurocytoma’ has been applied to tumours exhibiting neurocytoma-like morphology, characterised by monotonous round nuclei within a neuropil-rich matrix that arise outside the ventricular system. However, accumulating evidence indicates that this morphology-driven designation does not adequately reflect the immunophenotypic, molecular or epigenetic features of these tumours. In our cohort, all tumours demonstrated strong and diffuse synaptophysin expression, confirming neurocytic differentiation, in conjunction with nuclear OLIG2 positivity and variable GFAP expression, a pattern that is more consistent with a glioneuronal lineage

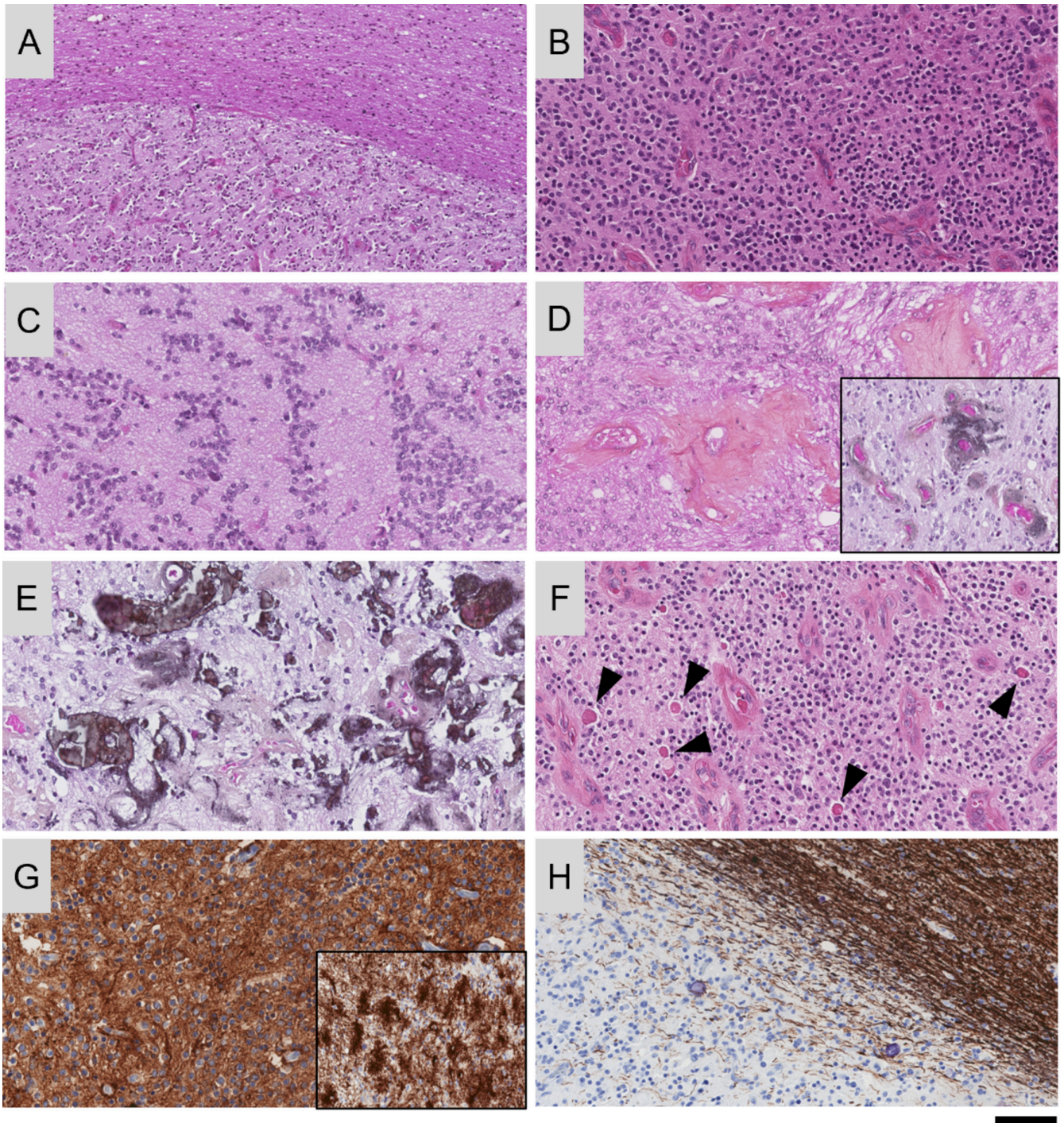

FIGURE 2 | Histopathological features of glioneuronal tumour with neurocytic differentiation: (A) circumscribed tumour; (B) neurocytic component; (C) neuropil islands; (D) hyalinised vessels, occasionally calcified (inset); (E) calcifications; (F) eosinophilic granular bodies (black arrowheads); (G) diffuse synaptophysin expression with neuropil islands (inset); (H) circumscribed tumour highlighted by anti-neurofilament immunostaining of the surrounding CNS parenchyma. Scale bar corresponds to 50 μm in Panel A and 100 μm in Panels B, C, D, E, F, G, and H.

than with a purely neuronal neoplasm. Notably, strong OLIG2 expression contrasts with the typical immunophenotype of central neurocytoma, which is generally OLIG2-negative, challenging the concept of EVN as a simple anatomical variant of the same tumour type. At the molecular level, EVN is characterised by *FGFR1* or, less commonly, *NTRK* alterations, whereas central neurocytoma lacks these drivers and instead demonstrates distinct epigenetic features, including *FGFR3* hypomethylation [1, 7, 12, 13].

Furthermore, the designation 'extraventricular' is increasingly difficult to reconcile with molecular data. Tumours with unequivocal EVN DNA methylation profiles, including two cases in our series, have arisen within the ventricular system, demonstrating that anatomical location does not reliably correspond to underlying biology [4]. In this context, maintaining a nomenclature that implies strict extraventricular localisation may be misleading and risks obscuring the biological unity of this tumour type.

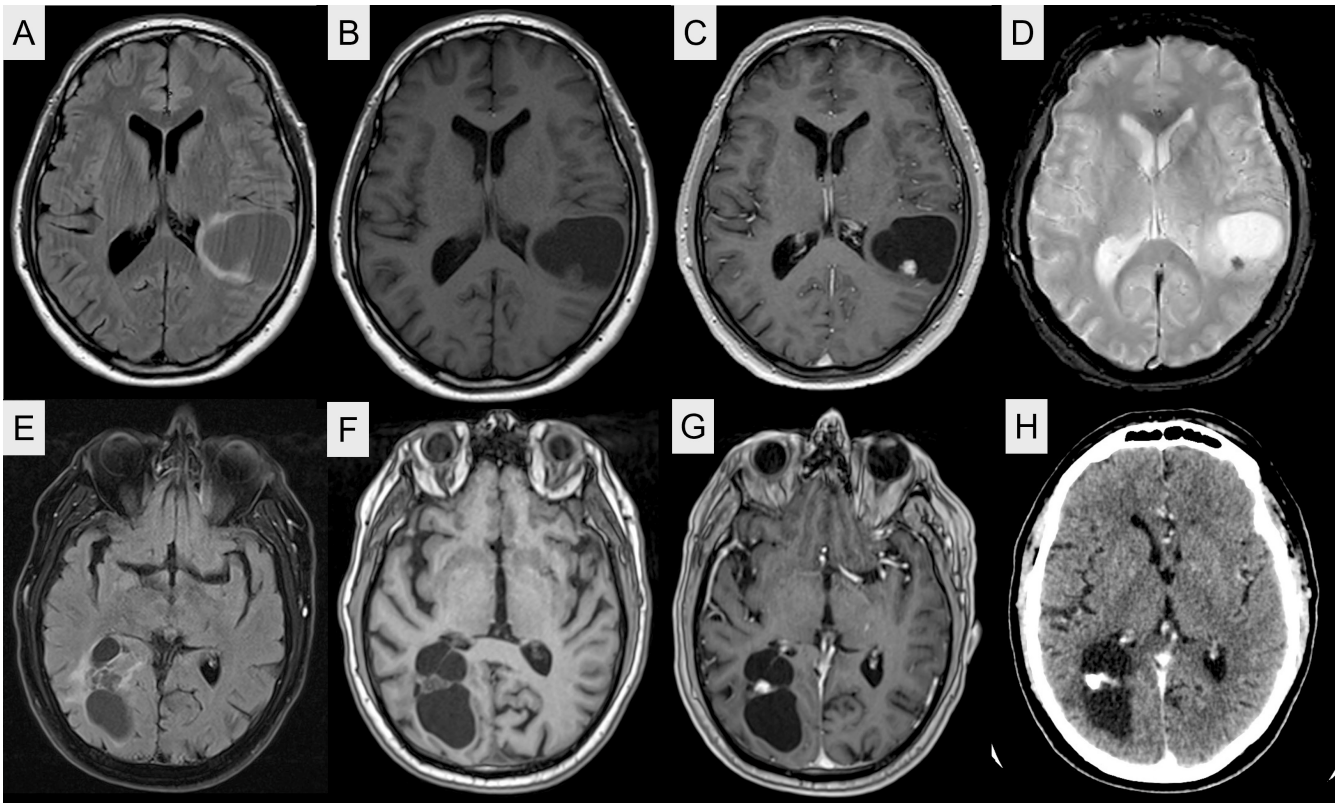

FIGURE 3 | Axial brain MRI and CT images of two representative cases. (A–D) Right fronto-parietal lesion showing a large cystic component with a mural nodule on FLAIR (A) and T1-weighted (B) images, thin peripheral and nodular enhancement after gadolinium administration on post-contrast T1-weighted imaging (C), and a marked susceptibility effect from haemorrhagic foci on susceptibility-weighted imaging (D). (E–H) Right occipital lesion with a similar cystic cavity and an eccentric mural nodule on FLAIR and T1-weighted images (E, F), demonstrating nodular enhancement on post-contrast T1-weighted imaging (G); CT scan (H) showing hyperdensities associated with microcalcification.

Taken together, these observations argue strongly against retaining 'EVN' as a primary diagnostic label. While the presence of neurocytic differentiation remains a consistent and meaningful feature, the current terminology does not adequately reflect the shared epigenetic identity and glioneuronal immunophenotype of these tumours. We therefore propose that this tumour type be redefined in a biologically neutral and conceptually more appropriate manner as a glioneuronal tumour with neurocytic differentiation (GNTN). Such a designation preserves the descriptive histological component while avoiding unsupported assumptions regarding tumour location or lineage and aligns classification with contemporary molecular neuropathology. We note that DNA methylation-based classification, while highly informative, is evolving. This group may be further refined as additional tumours are characterised, particularly given heterogeneity in drivers and clinical behaviour.

Adopting a revised nomenclature grounded in DNA methylation profiling and recurrent, but non-defining, oncogenic drivers may facilitate more accurate diagnosis, improve comparability across studies and provide a clearer framework for future investigations. A confirmed GNTN DNA methylation profile should be considered an essential criterion for the classification of these tumours. Although comprehensive molecular and clinical data are limited and a formal WHO grade cannot yet be assigned, available evidence suggests low-grade behaviour. Moving forward, this framework will not only support robust tumour classification and prognostication but also inform the potential application of targeted therapies, including *FGFR1* and *NTRK* inhibitors, in appropriate cases. Overall, these findings provide a coherent molecular and biological framework supporting the recognition of GNTN as a distinct tumour type within the spectrum of low-grade glioneuronal tumours.

Author Contributions

Conception and design: A.M., P.V., P.S. Methodology: A.M., P.V., P.S. Resources: A.M., M.E.G., F.Sas., G.C., E.U-C., B.L., R.A., C.T., L.B., M.R., S.M.K., A.V.D., F.Sah., P.V., P.S. Investigation: A.M., F.Sas., G.P., P.V., P.S. Analysis: A.M., F.Sas., G.P., P.V., P.S. Writing: A.M., P.V., P.S., with assistance from all authors. Funding acquisition: P.S. Supervision: P.V., P.S.

Acknowledgements

The authors gratefully acknowledge the technical teams of the neuropathology laboratories at GHU Paris—Psychiatry and Neurosciences and the University Hospital Heidelberg for their expert technical support. Open Access funding enabled and organized by Projekt DEAL.

Funding

This study was supported by the Else Kröner-Fresenius-Stiftung (P.S.; 2024_EKES.12) and Dr. Rolf M. Schwiete Stiftung (P.S.).

Ethics Statement

The study was approved by the Ethics Committee of the University of Heidelberg (S-318/2022). Owing to the retrospective nature of the study,

informed consent was waived, and all data were pseudonymised prior to analysis.

Consent

The authors have nothing to report.

Conflicts of Interest

A.V.D. and F.Sah. are co-founders and shareholders of Heidelberg Epignostix GmbH, a company that develops and commercialises DNA methylation-based classifiers for CNS and other tumours.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

For transparency, the peer review documents associated with this article are available at https://doi.org/10.1111/nan.70080.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **FIGURE S1:** Histopathological and immunohistochemical features. Representative sections show haematoxylin-phloxine-saffron staining (HPS; A, E, I, M, Q), synaptophysin expression (B, F, J, N, R), GFAP expression (C, G, K, O, S) and OLIG2 expression (D, H, L, P, T) of Cases 10–14.