

SCIENTIFIC CORRESPONDENCE

A rare case of paediatric astroblastoma with concomitant *MN1-GTSE1* and *EWSR1-PATZ1* gene fusions altering management

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Brain tumours are the commonest childhood neoplasm, with a worldwide incidence of 29.9–47.1/million [1]. Childhood brain tumours carry substantial morbidity/mortality and are the largest cause of paediatric cancer deaths [2]. Historically, classification was largely based on histological features. In recent years, the expansion of high-resolution genomic, epigenetic and transcriptomic profiling has led to improved molecular understanding and categorisation, as well as targeted therapies [3]. Consequently, the 2016 WHO classification incorporated molecular features in some brain tumour entities [4]. According to this classification, astroblastomas are extremely rare, not formally graded, and listed under 'other gliomas'. Astroblastomas are generally treated by surgery alone but can display intermediate behaviour with high recurrence rates and unpredictable behaviour [5,6]. Controversy exists as to whether astroblastomas are a truly distinct entity as they have histological features in common with both astrocytomas and ependymomas [7–9]. Diagnosing astroblastomas is therefore challenging and misclassification can alter subsequent

management [8]. The present case demonstrates how recent molecular advances identified two gene fusions for this patient, confirmed a more precise tumour diagnosis and guided subsequent management decisions. The findings here have general importance to other rare paediatric brain tumour entities.

A 13-year-old girl presented with a 2-week history of morning headaches, vomiting and visual loss. There was no prior history of note. On examination, bilateral papilloedema and central visual field loss were confirmed. MRI head showed a 6.0 × 5.5 × 4.2 cm mixed solid-cystic lesion centred in the right cingulate gyrus/corpus callosum (Figure 1A–C) with associated hydrocephalus, treated with intravenous dexamethasone. No other lesions were identified, and spinal MRI was clear. Serum AFP/HCG tumour markers were negative. The patient underwent a stealth-guided craniotomy with complete macroscopic resection of the frontal tumour. The patient recovered well postoperatively with no complications. Postoperative MRI head scan with contrast showed no residual tumour (Figure 1D).

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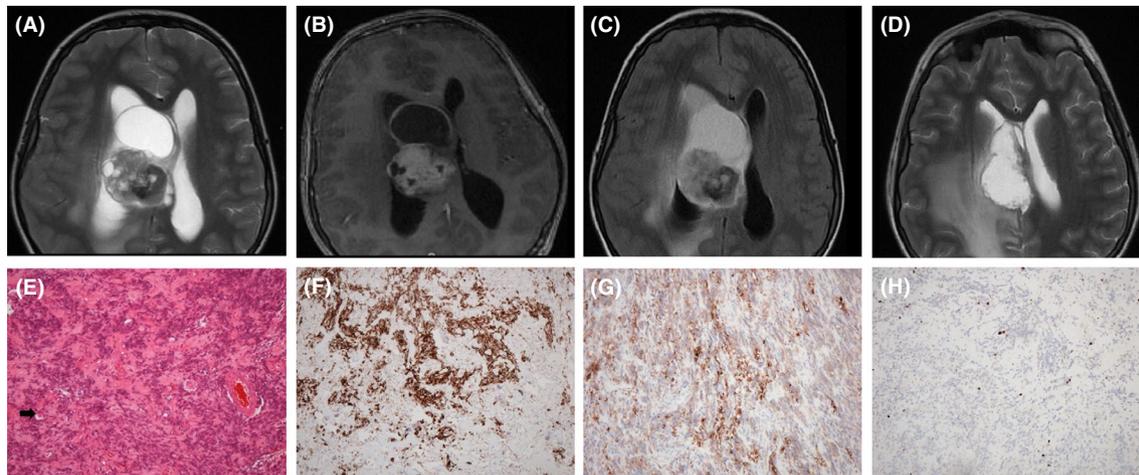


FIGURE 1 Representative neuroradiological imaging (A–D) and neuropathology (E–H) of the tumour. *Neuroradiology* (A–D): (A) Axial T2W; (B) Axial postgadolinium 3D T1; and (C) Axial FLAIR sequences showed a well-circumscribed solid-cystic tumour in the right cingulate gyrus and corpus callosum, which crossed the midline and extended into the right lateral ventricle. The lesion had a local mass effect causing a large area of surrounding vasogenic oedema and secondary hydrocephalus. The solid components enhanced and contain some areas of low T2W signal intensity from calcification. The large anterior tumoural cyst was of high signal on FLAIR because of proteinaceous content. To assess the vascularity of the tumour preoperatively, digital subtraction angiography was also performed which demonstrated displacement of the anterior cerebral arteries to the left side, consistent with mass effect secondary to tumour, but minimal tumour 'blush' following contrast phasing through the brain centrally. Consequently, no embolisation was performed. (D) Early postoperative axial T2W showing complete resection of the tumour. *Neuropathology* (E–H): all images taken at 10× magnification. (E) Representative haematoxylin and eosin (H&E) staining of the tumour, showing perivascular pseudo-rosette formation (black arrow) and stromal collagenisation; (F) GFAP staining showing strong and diffuse staining in glial cells surrounding blood vessels. Cells with neurocytic differentiation are negative; (G) Synaptophysin staining revealing positivity in cells with neurocytic or neuronal differentiation; (H) Sparse MIB1 staining, confirming a low Ki67 proliferation index (2.5%)

Histological examination demonstrated a cellular neuroepithelial tumour with a perivascular growth pattern forming vague pseudo-rosettes (Figure 1E). In some areas, there was marked stromal and vascular collagenisation. There was no mitotic activity and no microvascular proliferation. The tumour had a generally noninfiltrative border with surrounding brain tissue. There were occasional eosinophilic granular bodies and no Rosenthal fibres or ganglion cell components. The tumour had focal strong staining for GFAP and only weak staining for synaptophysin (Figure 1F/G). There was only very sparse mitotic activity and a low Ki67 proliferation index (2.5%), as evidenced by MIB1 staining (Figure 1H). The histological and immunohistochemical features were most consistent with a diagnosis of astroblastoma.

Methylation profiling of the tumour [10] using the Illumina EPIC array platform and analysed using the DKFZ Heidelberg classifier, gave a very low calibration score of <0.9 (specifically 0.0475 at the time of reporting using classifier version MNPv11b4, and 0.0764 with the most recent version MNPv11b6). These scores were too low for reliable classification despite excellent probe hybridisation (only 0.09% of probes failed), suggesting that the tumour was unclassifiable compared with currently recognised tumour entities. This was confirmed by comparing the tumour's methylation profile with other CNS tumour entities (Figure 2A). Regarding genomic alterations, inter-chromosomal gene fusions involving the *MN1* gene (*MN1-BEND2* and *MN1-CXXC5*) have previously been reported in CNS high-grade neuroepithelial tumours (HGNETs) [11], and recently it has been reported that a proportion of these

CNS-HGNET-*MN1* tumours exhibited histological features compatible with astroblastomas [12]. Following informed consent, whole-genome sequencing (WGS) was performed under the 100,000 Genomes Project [13] and under appropriate ethical approvals. WGS deployed Version 1.8 of the analysis pipeline developed by Genomics England (Supplementary Results). This analysis revealed a quiescent genome harbouring 6,218 substitutions and 1,214 small insertions/deletions. Of these, just 28 genic nonsynonymous variants were identified, all likely benign passengers. In addition, 721 structural variants were reported, almost exclusively concentrated via complex intra- and inter-chromosomal rearrangements between chromosomes 17, 19 and 22. Loss of chromosome 9 was the only additional chromosomal imbalance. Of note, the X chromosome remained intact in this patient, which is often disrupted in CNS-HGNET-*MN1* tumours (Supplementary Results, Figure S1). The structural variant data included a somatically acquired paracentric inversion on the chromosome 22 long arm. The intragenic breakpoints were located in intron 1 of the *MN1* gene and intron 2 of the *GTSE1* gene (Figure 2B). Fluorescent sequencing analysis confirmed the presence of the novel *MN1-GTSE1* gene fusion. The predicted chimeric protein retained the uninterrupted coding sequence of *MN1* exon 1, apposed in frame, with exons 3–12 of *GTSE1*. This pattern of rearrangement closely resembled the genomic features of the previously reported *MN1* gene fusions involving *BEND2* and *CXXC5*. Similar disruptive *MN1* variants were absent from 1,903 other 100,000 Genomes Project cancer cases, mainly derived from breast, ovary, endometrium, colon and

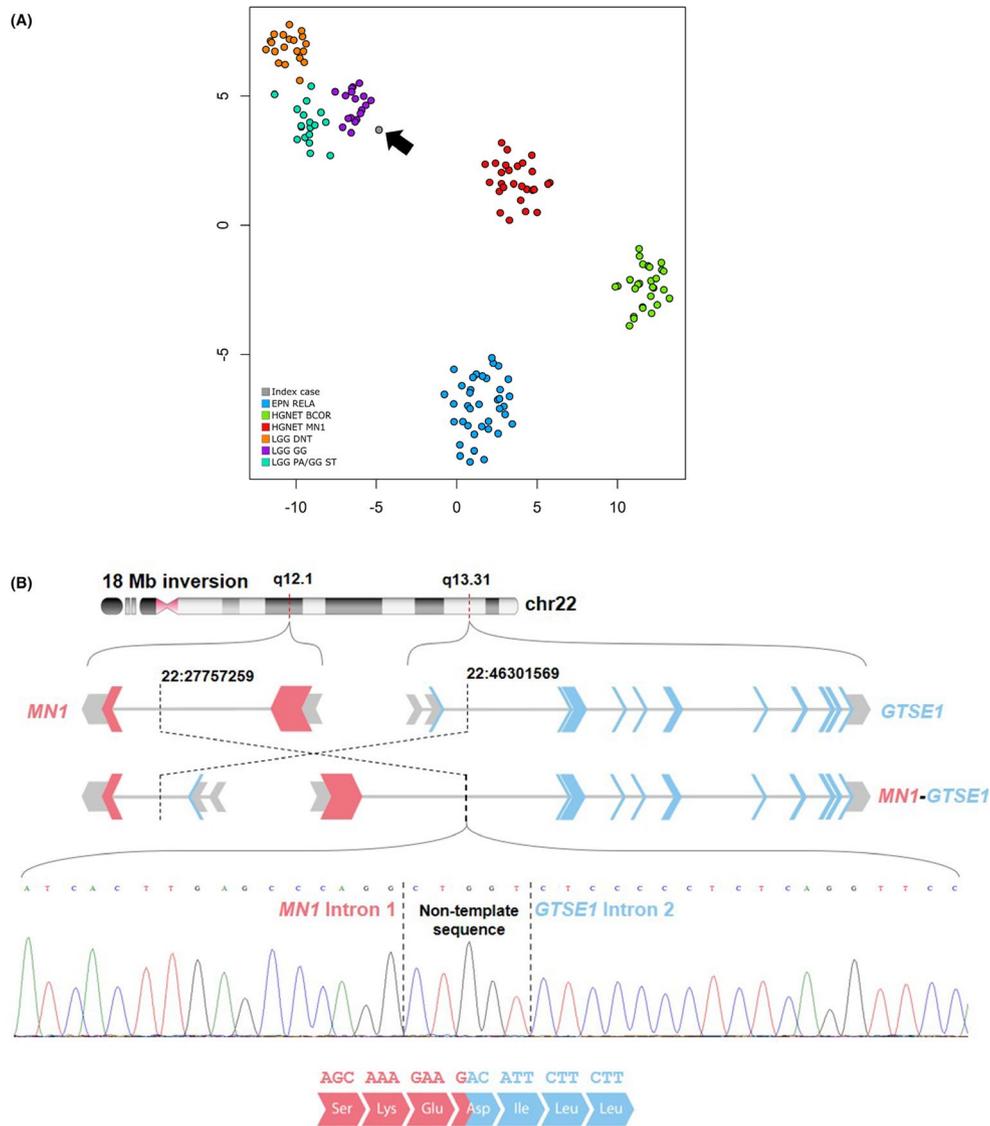


FIGURE 2 Molecular interrogation of the tumour – *MN1* fusion. (A) t-SNE (t-Distributed Stochastic Neighbour Embedding) plot based on the top 10,000 most variably methylated probes. Parameters used: perplexity = 20, theta = 0.5, dims = 2. The index case was compared with DNA methylation profiles available from DKFZ (Heidelberg Molecular Neuropathology platform, <https://www.molecularneuropathology.org/mnp>) and those held locally [24] with a confirmed molecular classification (calibrated score using MNPv11b6 >0.9). Samples are coloured according to their methylation class: HGNET BCOR: CNS high-grade neuroepithelial tumour with *BCOR* alteration; HGNET MN1: CNS high-grade neuroepithelial tumour with *MN1* alteration; EPN *RELA*: ependymoma, *RELA* fusion; LG GG: low-grade glioma, ganglioglioma; LG PA/GG ST: low-grade glioma, hemispheric pilocytic astrocytoma and ganglioglioma; LG DNT: low-grade glioma, dysembryoplastic neuroepithelial tumour. The index case is in grey (highlighted by the black arrow), and does not cluster with any of the above entities. (B) Schematic of the genomic rearrangement resulting in a novel *MN1-GTSE1* gene fusion. Whole-genome sequencing detected a somatically acquired 18 megabase (Mb) paracentric inversion on the long arm of chromosome 22, between the cytogenetic bands 22q12.1 and 22q13.31 (top image). The genomic coordinates of the intragenic breakpoints (genome reference build 38) map to intron 1 of the *MN1* gene (NCBI Entrez Gene transcript identifier NM_016426) and intron 2 of the *GTSE1* gene (transcript NM_002430) (middle image). This inversion apposes exon 1 of *MN1* to exon 3 of *GTSE1* in the same read direction, causing an *MN1-GTSE1* gene fusion (lower image). Fluorescent sequencing analysis confirmed this fusion, which included nontemplate sequence 'CTGGT'. Upon splicing and transcription, this fusion is predicted to maintain the amino acid read frame and thus result in a novel *MN1-GTSE1* chimeric protein. Key: block arrows represent exons; grey connecting lines represent introns; grey: untranslated regions; red: *MN1* coding exons; blue: *GTSE1* coding exons; Amino acid abbreviations: Ser, serine; Lys, lysine; Glu, glutamic acid; Asp, aspartic acid; Ile, isoleucine; Leu, leucine

kidney. These observations support the functional validity of the novel *MN1-GTSE1* variant reported here. Interestingly, in this tumour, an *EWSR1* (Ewing-Sarcoma-Breakpoint-Region-1) and *PATZ1* (POZ/BTB-And-AT-Hook-Containing-Zinc-Finger-1) (*EWSR-PATZ1*)

gene fusion was also detected. This similarly involved inversion of chromosome 22 and a recent study suggests it may be consistent with a new glioneuronal tumour entity [14]. As a result of this unexpected additional finding, we explored this in more detail. Three

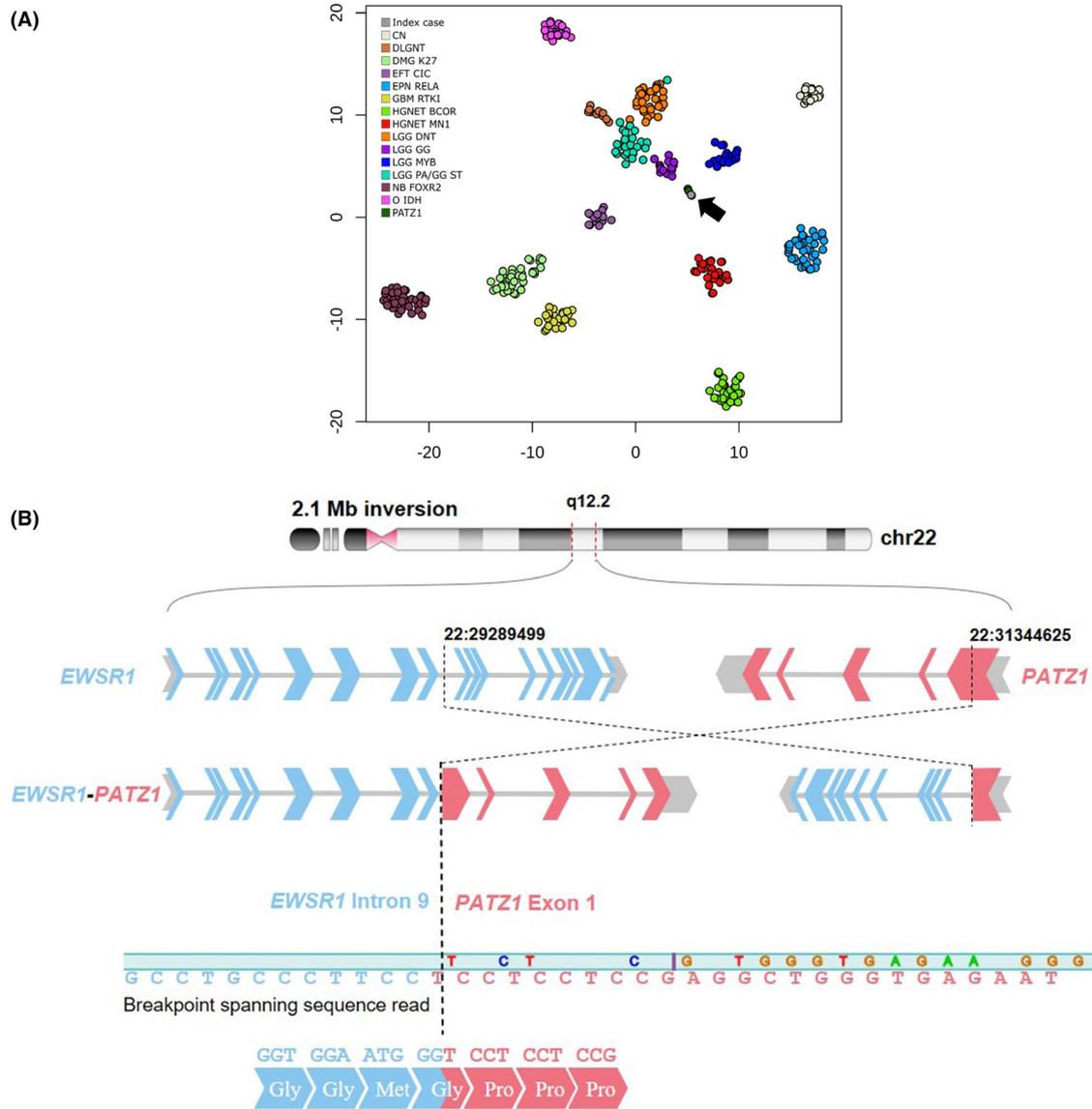


FIGURE 3 Molecular interrogation of the tumour - PATZ1 fusion. (A) t-SNE plot based on the top 10,000 most variably methylated probes, as in Figure 2A, but with additional cases including three PATZ1-fusion gliomas. Samples are coloured according to their methylation class: CN: central neurocytoma; DLGNT: diffuse leptomeningeal glioneuronal tumour; DMG K27: diffuse midline glioma with H3 K27M mutation; EFT CIC: Ewings-like family tumour with CIC alteration; EPN RELA: ependymoma, RELA fusion; GBM RTKI: glioblastoma receptor tyrosine kinase 1 group; HGNET BCOR: CNS high-grade neuroepithelial tumour with BCOR alteration; HGNET MN1: CNS high-grade neuroepithelial tumour with MN1 alteration; LGG DNT: low-grade glioma, dysembryoplastic neuroepithelial tumour; LG GG: low-grade glioma, ganglioglioma; LGG MYB: low-grade glioma MYB/MYB1; LG PA/GG ST: low-grade glioma, hemispheric pilocytic astrocytoma and ganglioglioma; NB FOXR2: neuroblastoma FOXR2-altered; O IDH: IDH glioma, 1q/19q codeleted oligodendroglioma; PATZ1: PATZ1-fusion positive cases (identified by TruSight RNA fusion panel, Illumina). The index case is in grey (highlighted by the black arrow), and clusters with the PATZ1 cases (dark green). (B) Schematic of the genomic rearrangement resulting in an EWSR1-PATZ1 gene fusion. Whole-genome sequencing detected a somatically acquired 2.1 megabase (Mb) paracentric inversion on the long arm of chromosome 22, within the cytogenetic band 22q12.2 (top image). The genomic coordinates of the intragenic breakpoints (genome reference build 38) map to intron 9 of the EWSR1 gene (NCBI Entrez Gene transcript identifier NM_013986) and exon 1 of the PATZ1 gene (transcript NM_014323) (middle image). This inversion apposes exon 9 of EWSR1 to exon 1 of PATZ1 in the same read direction, causing an EWSR1-PATZ1 gene fusion (lower image). Breakpoint spanning reads in Integrative Genomics Viewer (IGV) evidence this fusion event (paired reads: 28; split reads: 30), mapping to EWSR1 intron 9 and PATZ1 exon 1. This fusion is predicted to maintain the amino acid reading frame and thus result in a EWSR1-PATZ1 chimeric protein. Key: block arrows represent exons; grey connecting lines represent introns; grey: untranslated regions; blue: EWSR1 coding exons; red: PATZ1 coding exons; Amino acid abbreviations: Gly, glycine; Met, methionine; Pro, proline

available glioma cases known to harbour PATZ1 fusions were added to the methylation profiling comparison. Intriguingly, our astroblastoma case, with both MN1 and PATZ1 fusions, remained

distanced from the CNS-HGNET-MN1 tumours but now clustered with the three PATZ1 cases (Figure 3A). Further assessment of the EWSR1-PATZ1 fusion showed that the intragenic breakpoints were

located in intron 9 of the *EWSR1* gene and exon 1 of the *PATZ1* gene (Figure 3B). The position of the rearrangement breakpoints are consistent with those in a reported glioneuronal tumour with an *EWSR1-PATZ1* gene fusion, placing the *PATZ1* breakpoint at the same codon of exon 1, with RNA-sequencing data confirming expression of the chimeric transcript.[14] This report supports the validity of the equivalent *EWSR1-PATZ1* variant reported here. Fusion genes involving *MN1* and *PATZ1* (*MN1-PATZ1*) have also very recently been described in a malignant paediatric brain tumour [15]. We carefully explored our data for evidence of rearrangements (including translocations and tandem duplications) that could similarly adjoin *MN1* and *PATZ1* in functional orientation. We did not find evidence supporting this proposition. However, amidst the rearrangement complexity, we cannot exclude the presence of undetected cryptic events, as have been observed to generate oncogenic fusions in human cancer [16].

Astroblastomas are associated with high recurrence rates and an unpredictable biological course [5,6], with initial peri-tumoural oedema, as was present in this case, associated with early recurrence [17]. Consequently, with the molecular confirmation of an astroblastoma, the multi-disciplinary-team outcome was to undertake MRI surveillance at 3-monthly intervals for the first year of follow-up, instead of the more conservative 6-monthly scan schedule generally associated with low-grade tumours. At subsequent review, the bilateral papilloedema had resolved and there were no abnormal neurological findings on examination. All subsequent MRI scans have showed no tumour recurrence over a 36-month postoperative period, with the frequency of scans being reduced over time (3-monthly first year; 4-monthly second year; 6-monthly in the third year).

Here, we describe a patient with a rare astroblastoma, where additional molecular study assisted patient management. Neuropathologically, the differential diagnoses were an astroblastoma or glioneuronal tumour. Precise diagnosis is critical as it influences postoperative management decisions. Here, the molecular confirmation of the novel *MN1-GTSE1* gene fusion, diagnostic of astroblastoma, supported the team in recommending 3-monthly follow-up, rather than the standard 6-monthly approach which would be more typical for a glioneuronal tumour.

Astroblastomas typically arise at supratentorial sites, although occasional infratentorial cases occur [18,19]. On MRI, they appear as well-demarcated solid-cystic lesions and typically extend from cortex to periventricular regions [20]. Commonly, calcification is seen in addition to a 'bubbly' appearance, arising from signal voids due to tumour angioarchitecture [21,22]. The lesions are typically hyperintense to white matter (FLAIR/T2-weighted sequences) and show heterogeneous enhancement with rim enhancement on contrast-enhanced CT and T1-weighted MRI [9,22]. Our case showed many of these neuroradiological features (Figure 1A-C).

Histologically, astroblastomas are characterised by perivascular hyalinisation and pseudo-rosettes [8]. While these pseudo-rosettes contribute to the diagnostic criteria, they may be completely undetectable [12]. A lack of fibrillary background, hyalinised vessels, and a compressive, rather than infiltrative,

margin is also commonly observed [20]. Immunohistochemically, astroblastomas are typically positive for GFAP, vimentin and S-100 protein [20], although there is variability in staining [8]. Although there is currently no formal grading for astroblastomas (based on the 2016 WHO classification), a putative informal system has been suggested, with 'high-grade' tumours showing high cellularity, anaplastic nuclear features, vascular proliferation, high mitotic rates and necrosis [12], which may be considered for inclusion in future classifications.

Molecular data for astroblastomas are limited [23]. This is consistent with methylation profiling being uninformative in this case, despite its overall utility for paediatric brain tumours [24]. Interestingly, despite re-running the classifier again in 2020, the calibration score of 0.0764 was again too low for reliable classification. DNA methylation studies on CNS high-grade neuroepithelial tumours (CNS-HGNETs) revealed a distinct methylation cluster of recurrent meningioma-1 (*MN1*) gene rearrangements on chromosome 22q. The majority of astroblastomas matched the CNS-HGNET-*MN1* tumour cluster (not seen here; Figure 2A) and approximately 40% of the CNS-HGNETs with *MN1* alteration showed histological features of astroblastomas. Furthermore, RNA sequencing revealed two inter-chromosomal gene fusions involving the *MN1* gene (*MN1-BEND2* and *MN1-CXXC5*) [11,12]. Thus, it is plausible that the genetic basis of astroblastomas may involve *MN1* rearrangement with fusion partner genes, such as *BEND2*, *CXXC5* and other unidentified genes [12]. This is supported by another study showing *MN1* alterations in four of eight tumours diagnosed histologically as astroblastomas [25]. In our patient, we confirmed a novel *MN1-GTSE1* gene fusion, which to our knowledge, is the first such description in an astroblastoma. Interestingly, we also observed an *EWSR1-PATZ1* fusion generated through the rearrangement complexity emanating on chromosome 22, which has been described in glioneuronal tumours and sarcoma [14,26]. Whilst it is unusual to find two oncogenic gene fusions in the same tumour, this is not unprecedented [27]. It may represent the development of two parallel clones with uniform (i.e. nonbiphasic) histology or a double hit within the same clone.

From a diagnostic perspective, our observation of two fusions in this case are intriguing, as without WGS neither fusion would have been detected and our retrospective, integrated interpretation, requiring up-to-date molecular subtyping for context, was critical, despite the astroblastoma histology. We believe that this case is unlikely to represent a typical CNS-HGNET-*MN1* tumour, due to the dissimilarity in methylation profile compared with reference HGNET-*MN1* cohorts, the similarity with *PATZ1*-fusion cases and the intact X chromosome seen here (frequently disrupted in HGNET-*MN1* tumours). Such questions will be answered more definitively in time, as our diagnostic services move away from single-gene testing to WGS and other NGS sequencing technologies, alongside methylation profiling, for CNS tumours. Single-gene testing for *MN1* (e.g. break-apart FISH or PCR) is not available via our standard clinical practices, despite *MN1* FISH data being described in the literature. However, in England, all children with CNS tumours are now eligible

for commissioned WGS via Genomics England. We would therefore expect to identify gene fusions and their variants via this route.

In conclusion, astroblastomas are rare brain tumours with an unpredictable biological course and recurrence pattern, that present potential diagnostic challenges. Despite noninformative methylation studies, this case highlighted a novel *MN1-GTSE1* gene fusion detected on WGS, in keeping with other studies of *MN1* gene alterations in astroblastomas and supported increased frequency of standard MRI surveillance. The additional detection of a second *EWSR1-PATZ1* fusion highlights the complexity of such cases. Recent expansion of high-resolution genomic and other molecular profiling for paediatric brain tumours is likely to continue to lead to improved diagnostic and prognostic techniques, with consequent positive impacts on patient management.

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CONFLICTS OF INTEREST

TSJ is Editor-in-Chief of the journal. All other authors have no conflicts to declare. The Editors of Neuropathology and Applied Neurobiology are committed to peer-review integrity and upholding the highest standards of review. As such, this article was peer-reviewed by independent, anonymous expert referees and the authors (including TSJ) had no role in either the editorial decision or the handling of the paper.

AUTHOR CONTRIBUTION

Study concept: KA, MJM; Methodology: KC, JCP, SB, TSJ, KA, MJM; Data analysis and interpretation: KC, JCP, SB, TSJ, JT, PT, KA, MJM; Literature Review: KC, KA, MJM; Figure acquisition/production: DS, JCP, TSJ, JT, PT, KA, MJM; Clinical input: KH, DS, AD, KA, MJM; Manuscript writing: KC, KA, MJM; Manuscript revision and approval: KC, KH, DS, AD, JCP, SB, TSJ, JT, PT, KA, MJM.

DATA AVAILABILITY STATEMENT

Data available upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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