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CORRESPONDENCE

MN1 immunohistochemistry is a sensitive diagnostic biomarker for primitive CNS tumors with *MN1* fusion

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The diagnosis accuracy of the astroblastoma has improved significantly since its precise histomolecular definition as astroblastoma, *MN1*-altered (AB-*MN1*) in the latest World Health Organization Classification of Central Nervous System tumors (WHO CNS) [6]. This rare, circumscribed astrocytic tumor can now be more easily distinguished from other tumors with radially arranged perivascular cells, such as ependymomas (EPN), pleomorphic xanthoastrocytomas (PXA), and glioblastomas (GBM) or rare gliomas [3, 8, 10–12]. It is associated with a robust methylation signature [originally designated as CNS high-grade neuroepithelial tumors, *MN1*-altered (HGNET-*MN1*)] and characterized by specific fusions affecting the meningioma 1 (*MN1*) gene (22q12.1) and different partners. Recently, some tumors classified by DNA methylation profiling as HGNET-*MN1* were described with *EWSR1::BEND2* [7, 13] or *YAP1::BEND2* fusion [1]. MN1 is a DNA-binding protein, a transcriptional coregulator, interacting with the BAF complex [9, 14] and mutation has been initially shown in meningiomas [5, 15]. However, there is currently no validated immunohistochemical (IHC) biomarker for *MN1*-altered tumors although MN1 immunostaining has been tested successfully on *MN1::BEND2* tumors ($n=9$) [4]. The sensitivity and specificity of this biomarker remain to be evaluated.

Our study aimed to evaluate MN1 IHC on 632 well-annotated, methylation-based, or genetically proven tumor samples (adult and pediatric) across 56 different histomolecular types/subtypes according to WHO CNS 5 (Table 1).

We applied the antibody anti-MN1 (polyclonal; rabbit; 1:150 dilution; Proteintech) to 3-µm-thick sections of formalin-fixed paraffin-embedded tissue samples, using OMNIS-Automation (Omnis, Santa Clara, California, USA). IHC was performed on whole sections in 466 cases and on tissue microarrays in 166 tumors and was scored as follows: 1 for < 10% of cells with low-intensity nuclear staining; 2 for > 10% with low intensity; and 3 for > 90% of tumor cells with high intensity.

The IHC results, detailed in Table 1, showed strong nuclear labeling in all ($n=8$) but one AB with *MN1::BEND2* fusion (score 2) (Fig. 1B), but this case had been archived for over than 25 years. Astroblastomas *MN1* non-altered (with *EWSR1::BEND2* fusion) ($n=2/2$) were negative (Fig. 1D). The IHC was low in 590 other tumors, including key differential diagnosis of AB (supratentorial (ST) EPN *ZFTA::RELA*-fusion-positive, PXA, mesenchymal GBM IDH-WT) (Fig. 1H, J, L). However, strong expression was also observed in 11 other histomolecular entities ($n=31$) whose positivity was expected (meningioma; ST EPN with *ZFTA::MN1* fusion, neuroepithelial tumors with *PATZ1::MN1* fusion (Fig. 1F, P, R) but also: subependymoma; SEGA; central neurocytoma and others (Fig. 1N, T, V, X, Z). Overall, the sensitivity and specificity of MN1 IHC in diagnosing primitive CNS tumors with *MN1* fusion were 91.7% and 95.5%, respectively (AB-*MN1* as well as other tumor types with *MN1* fusion).

MN1 IHC is homogeneously diffuse and intense, simplifying its interpretation. We recommend its routine use to quickly and inexpensively identify potential AB-*MN1* tumors, considering that morphological mimickers are negative. Most MN1 + tumors have distinct morphological features, making the positive IHC result less impactful

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Table 1 MN1 expression in 632 tumors

Tumor types	MN1 immunostaining, *n* (%)		
	Negative		Positive
	1 (< 10% of cells, low intensity)	2 (> 10% of cells, low intensity)	3 (> 90% of cells, high intensity)
Adult-type diffuse gliomas			
Glioblastoma, *IDH*-wildtype			
RTK1 subtype	11/11 (100)	0	0
RTK2 subtype	14/14 (100)	0	0
Mesenchymal subtype	36/41 (88)	5/41 (12)	0
Oligodendroglioma, *IDH*-mutant and *1p/19q*-codeleted	12/15 (80)	3/15 (20)	0
Pediatric-type diffuse high-grade gliomas			
Diffuse midline glioma, *H3 K27*-altered	11/11 (100)	0	0
Diffuse hemispheric glioma, *H3.3 G34*-mutant	14/14 (100)	0	0
Diffuse pHGG, *H3*-wildtype and *IDH*-wildtype			
RTK1 subtype	3/3 (100)	0	0
Lynch syndrome	6/6 (100)	0	0
Constitutional mismatch repair deficiency syndrome	9/9 (100)	0	0
RTK2 subtype	1/1 (100)	0	0
MYCN subtype	4/5 (80)	1/5 (20)	0
Li–Fraumeni	1/1 (100)	0	0
Infant-type hemispheric glioma	2/2 (100)	0	0
Meningioma	1/15 (7)	11/15 (73)	**3/15 (20)**
Circumscribed astrocytic gliomas			
Astroblastoma, *MN1*-altered*	0/9 (0)	1/9 (11)	**8/9 (89)**
Astroblastoma, *MN1* non-altered*	**2/2 (100)**	0	0
High-grade astrocytoma with philoid features	5/5 (100)	0	0
Pilocytic astrocytoma	17/19 (89)	2/19 (11)	0
Pleomorphic xanthoastrocytoma	12/13 (92)	1/13 (8)	0
Subependymal giant cell astrocytoma	2/10 (20)	4/10 (40)	**4/10 (40)**
Ependymal tumors			
Myxopapillary ependymoma	9/9 (100)	0	0
Posterior fossa ependymoma, group A	30/30 (100)	0	0
Posterior fossa ependymoma, group B	9/15 (60)	6/15 (40)	0
Spinal ependymoma	22/22 (100)	0	0
Supratentorial ependymoma			
YAP1-fusion-positive	6/6 (100)	0	0
***ZFTA* (non-RELA)-fusion-positive**	7/8 (87.5)	1/8 (12.5)	0
***ZFTA::MN1* fusion**	0/1 (0)	0	**1/1 (100)**
***ZFTA::RELA*-fusion-positive**	39/40 (97.5)	1/40 (2.5)	0
Subependymoma	5/14 (36)	2/14 (14)	**7/14 (50)**
Ependymoma-like tumor with *PLAGL1* fusion	0/2 (0)	2/2 (100)	0
Choroid plexus tumors			
Choroid plexus carcinoma	8/9 (89)	1/9 (11)	0
Choroid plexus papilloma	10/10 (100)	0	0
Embryonal tumors			
AT/RT MYC	7/8 (87.5)	1/8 (12.5)	0
AT/RT SHH	8/13 (62)	3/13 (23)	**2/13 (15)**
AT/RT TYR	6/6 (100)	0	0
CNS tumor with *BCOR* internal tandem duplication	7/9 (88)	2/9 (22)	0

Table 1 (continued)

Tumor types	MN1 immunostaining, *n* (%)		
	Negative		Positive
	1 (< 10% of cells, low intensity)	2 (> 10% of cells, low intensity)	3 (> 90% of cells, high intensity)
CNS tumor with *EP300::BCOR* fusion	2/5 (40)	1/5 (20)	**2/5 (40)**
Embryonal tumor with multilayered rosettes	12/12 (100)	0	0
CNS neuroblastoma, *FOXR2*-activated	2/2 (100)	0	0
Medulloblastoma, group 3	30/30 (100)	0	0
Medulloblastoma, group 4	30/30 (100)	0	0
Medulloblastoma, *SHH*-activated and *TP53*-wildtype	30/30 (100)	0	0
Medulloblastoma, *WNT*-activated	13/13 (100)	0	0
CNS embryonal tumor with *PLAGL1* amplification	0/1 (0)	1/1 (100)	0
Pineal tumors			
Pineoblastoma	13/14 (93)	1/14 (7)	0
Mesenchymal tumors			
***CIC*-rearranged sarcoma**	4/7 (57)	2/7 (29)	**1/7 (14)**
Rhabdomyosarcoma	2/2 (100)	0	0
Ewing sarcoma	3/4 (75)	0	**1/4 (25)**
Intracranial mesenchymal tumor, *FET::CREB* fusion-positive	2/6 (33)	2/6 (33)	**2/6 (33)**
Primary intracranial sarcoma, *DICER1*-mutant	2/2 (100)	0	0
Glioneuronal and neuronal tumors			
Desmoplastic infantile ganglioglioma/desmoplastic infantile astrocytoma	10/10 (100)	0	0
Diffuse leptomeningeal glioneuronal tumor	6/6 (100)	0	0
Dysembryoplastic neuroepithelial tumor	15/15 (100)	0	0
Ganglioglioma	14/14 (100)	0	0
Central neurocytoma	1/8 (12.5)	1/8 (12.5)	**6/8 (75)**
Papillary glioneuronal tumor	3/3 (100)	0	0
Rosette-forming glioneuronal tumor	7/7 (100)	0	0
Neuroepithelial tumors with *PATZ1* fusion			
PATZ1::EWSR1 fusion	0/1 (0)	1/1 (100)	0
***PATZ1::MN1* fusion**	0/2 (0)	0	**2/2 (100)**

AT/RT, atypical teratoid/rhabdoid tumor; *ZFTA::RELA*, Supratentorial ependymoma *ZFTA::RELA*-fusion-positive. *ZFTA::MN1*, Supratentorial ependymoma *ZFTA* (non-RELA)-fusion-positive. *PATZ1::MN1*, Neuroepithelial tumor with *PATZ1* fusion; CNS, central nervous system. Bolded groups represent differential diagnoses, critical information, or unexpected findings

*All cases of astroblastomas were both confirmed by DNA methylation profiling and RNA sequencing analyses

diagnostically. Interestingly, central neurocytoma, subependymoma and SEGA share a common subependymal location, a similar potential cell of origin (radial glial-like cell) and a MAPkinase/AKT pathway activation (for SEGA and central neurocytoma) [2]. However, information about the function of *MN1* gene and its regulation are currently too limited to understand its causal or non-causal relationship.

Overall, MN1 IHC shows good sensitivity for diagnosing primitive CNS tumors with *MN1* fusion and should be included in routine IHC panels though molecular studies must support the final diagnosis.

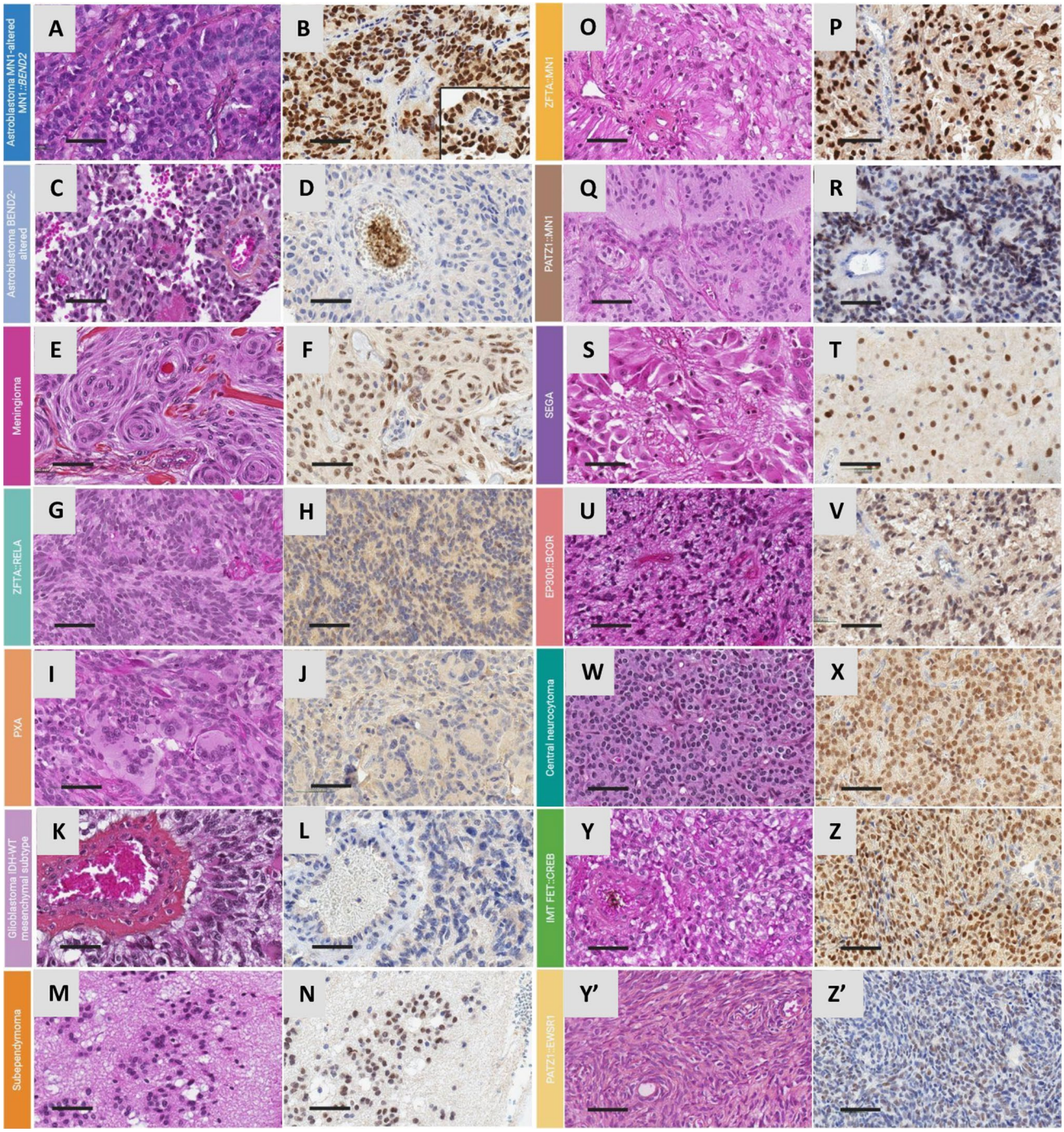

Fig. 1 Expression of MN1 in primitive CNS tumors, comparing hematoxylin phloxine saffron staining with MN1 IHC. There is diffuse and strong MN1 expression in tumors with *MN1* fusion, particularly astroblastoma, *MN1::BEND2*-fused (B), *ZFTA::MN1* (P), *PATZ1::MN1* (R), as well as meningioma (F) and in unexpected tumors with no *MN1* fusion like SUBEPN (N), SEGA (T), tumors with *EP300::BCOR* (V), central neurocytoma (X) and IMT FET::CREB (Z). Conversely, no MN1 expression is observed in tumors like astroblastoma *BEND2*-altered (D), *ZFTA::RELA* (H), PXA (J), glioblastoma IDH-WT mesenchymal subtype (L) and *PATZ1::EWSR1* (Z'). Scale bars: 50 µm

Author contributions RD and PV conducted the molecular studies, analysis, interpretation of the IHC data, and drafted the manuscript. ATZ generated the cohort, ATZ and AM helped in the writing of this manuscript. RD, CB, NP, JL, conducted the immunohistochemical techniques. RD and AC conducted the search for blocks.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest directly related to the topic of this article.

References

1. Cuoco JA, Williams S, Klein BJ, Borowicz VM, Ho H, Stump MS et al (2024) Astroblastoma with a novel YAP1::BEND2 fusion: a case report. J Pediatr Hematol Oncol 46:e313–e316. https://doi.org/10.1097/MPH.0000000000002885
2. Lee Y, Chowdhury T, Kim S, Yu HJ, Kim K-M, Kang H et al (2024) Central neurocytoma exhibits radial glial cell signatures with FGFR3 hypomethylation and overexpression. Exp Mol Med 56:975–986. https://doi.org/10.1038/s12276-024-01204-3
3. Lehman NL (2023) 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 161:425–439. https://doi.org/10.1007/s11060-022-04222-1
4. Lehman NL, Spassky N, Sak M, Webb A, Zumbar CT, Usubalieva A et al (2022) Astroblastomas exhibit radial glia stem cell lineages and differential expression of imprinted and X-inactivation escape genes. Nat Commun 13:2083. https://doi.org/10.1038/s41467-022-29302-8
5. Lekanne Deprez RH, Riegman PH, Groen NA, Warringa UL, van Biezen NA, Molijn AC et al (1995) Cloning and characterization of MN1, a gene from chromosome 22q11, which is disrupted by a balanced translocation in a meningioma. Oncogene 10:1521–1528
6. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D et al (2021) The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol 23:1231–1251. https://doi.org/10.1093/neuonc/noab106
7. Lucas C-HG, Gupta R, Wu J, Shah K, Ravindranathan A, Barreto J et al (2022) EWSR1-BEND2 fusion defines an epigenetically distinct subtype of astroblastoma. Acta Neuropathol 143:109–113. https://doi.org/10.1007/s00401-021-02388-y
8. Mhatre R, Sugur HS, Nandeesh BN, Chickabasaviah Y, Saini J, Santosh V (2019) MN1 rearrangement in astroblastoma: study of eight cases and review of literature. Brain Tumor Pathol 36:112–120. https://doi.org/10.1007/s10014-019-00346-x
9. Riedel SS, Lu C, Xie HM, Nestler K, Vermunt MW, Lenard A et al (2021) Intrinsically disordered Meningioma-1 stabilizes the BAF complex to cause AML. Mol Cell 81:2332-2348.e9. https://doi.org/10.1016/j.molcel.2021.04.014
10. Sari R, Altinoz MA, Ozyar E, Danyeli AE, Elmaci I (2021) A pediatric cerebral tumor with MN1 alteration and pathological features mimicking carcinoma metastasis: may the terminology "high grade neuroepithelial tumor with MN1 alteration" still be relevant? Childs Nerv Syst 37:2967–2974. https://doi.org/10.1007/s00381-021-05289-3
11. Sturm D, Orr BA, Toprak UH, Hovestadt V, Jones DTW, Capper D et al (2016) New brain tumor entities emerge from molecular classification of CNS-PNETs. Cell 164:1060–1072. https://doi.org/10.1016/j.cell.2016.01.015
12. Tauziède-Espariat A, Pagès M, Roux A, Siegfried A, Uro-Coste E, Nicaise Y et al (2019) Pediatric methylation class HGNET-MN1: unresolved issues with terminology and grading. Acta Neuropathol Commun 7:176. https://doi.org/10.1186/s40478-019-0834-z
13. Tsutsui T, Arakawa Y, Makino Y, Kataoka H, Mineharu Y, Naito K et al (2021) Spinal cord astroblastoma with EWSR1-BEND2 fusion classified as HGNET-MN1 by methylation classification: a case report. Brain Tumor Pathol 38:283–289. https://doi.org/10.1007/s10014-021-00412-3
14. van Wely KHM, Molijn AC, Buijs A, Meester-Smoor MA, Aarnoudse AJ, Hellemons A et al (2003) The MN1 oncoprotein synergizes with coactivators RAC3 and p300 in RAR-RXR-mediated transcription. Oncogene 22:699–709. https://doi.org/10.1038/sj.onc.1206124
15. Zhang X, Jia H, Lu Y, Dong C, Hou J, Wang Z et al (2014) Exome sequencing on malignant meningiomas identified mutations in neurofibromatosis type 2 (NF2) and meningioma 1 (MN1) genes. Discov Med 18:301–311