Brain tumor with an ATXN1-NUTM1 fusion gene expands the histologic spectrum of NUTM1-rearranged neoplasia

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We report a novel ATXN1-NUTM1 gene fusion in a primitive brain tumor (Fig 1a). A 21-year-old woman was seen in an emergency department for symptoms of increased intracranial pressure, visual disturbance and right hemiparesis. She reported unusual headaches for the past 3 weeks. MRI showed a frontal tumor with intratumoral hemorrhage (Fig. 1b). The entire tumor was surgically removed. The patient did not receive any additional treatment. 16 months after surgery, the patient was symptom-free and MRI showed no recurrence of the tumor.

Histological features were characterized by a fascicular architectural pattern and chondro-myxoid areas (Fig. 1c, d, e, f). Neuron-like tumor cells were apparent (Fig. 1c). Mitotic activity was overall low but increased in some foci (Fig. 1d). Strong GFAP staining led to an initial diagnosis of an unclassified glioneuronal tumor in spite of olig2 and PS100 negativity (Fig. 1g). Microscopically, the tumor was well circumscribed (Fig. 1h). p53 was accumulated (Fig. 1i). CD56 was strongly expressed. TTF1, chromogranin, synaptophysin, CD34, p63, CK5/6 and smooth muscle actin were negative. ATRX, INI1 and BRG1 expression was maintained. Using the Heidelberg DNA methylation-based CNS tumor classifier, no class prediction was obtained with a greater than ≥0.9 confidence threshold [1]. The closest entity was the CNS Ewing Family Tumor CIC group with a score of 0.235 (Additional file 1: Table S1) (Case methylation data: http://www.ncbi.nlm.nih.gov/geo; GSE138550). This tumor group is associated to the CIC-NUTM1 gene fusion [6]. We observed strong homogeneous nuclear staining with an anti-NUT antibody, suggesting the presence of a CIC-NUTM1 fusion (Fig. 1j). RNA sequencing using the Illumina TruSight RNA Fusion panel and Manta for fusion calling revealed a novel ATXN1-NUTM1 fusion. A CIC-NUTM1 fusion was not detected. ETV4 was overexpressed as in CIC-fused sarcomas [4, 6]. No pathogenic variants were observed in tumor DNA using a 571-gene targeted sequencing panel (Additional file 2: Table S2).

The fusion gene transcript encompassed almost all of the ATXN1 coding sequence and the entire exon 6, 7 and 8 regions of NUTM1. The most common NUTM1 breakpoints map between exon 1 and 2, but breakpoints at the distal end of exon 5 have also been described in some CIC-NUTM1 sarcomas [4].

Initially associated with NUT midline carcinomas, NUTM1 fusions have now been described in a broad spectrum of tumors ranging from carcinoma to sarcoma and leukemia [2, 3, 7]. The most common fusion partner gene in carcinoma and sarcoma is BRD4 followed by BRD3 and NSD3. Various new partners have been recently described [2, 3, 5]. The prognosis of these tumors is generally poor, although NUT-associated leukemias appear to be associated with a better prognosis and YAP1-NUTM1 is associated with benign skin adnexal gland tumors [3, 5].

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CIC rearranged sarcomas are often fused to DUX4 and less frequently to NUTM1 [4, 7]. All CIC re-arranged tumors irrespective of their location or their fusion partner gene share the same transcriptomic profile defining a molecular subgroup distinct from NUT carcinoma [4, 7]. Interestingly, ATXN1 codes for ataxin1 which forms a transcriptional repressor complex with CIC. They are both part of the CIC-ATXN1-ATXN1L mitotic cell cycle regulator axis [8]. Excluding CIC-NUTM1 fused tumors, only one NUTM1 rearranged brain tumor has been previously reported, namely a cytokeratin negative BRD4-NUTM1 PNET-like parietal lobe tumor in a 3-year old boy with GFAP and synaptophysin positivity. On methylation profiling, this neoplasm did not cluster with tumors of the CNS Ewing Family Tumor CIC group [2].

**Fig. 1** ATXN1-NUTM1 gene fusion, confirmed by RT-PCR and Sanger sequencing (a). MRI identified a frontal mass. Enhancement after contrast injection (T1) (b). Representative histopathology. On the left, loose area with neuron-like tumor cells (*detail). On the right, increase in cell density (c). Fascicular architecture with three mitoses (arrows) (d). Chondroid-like, myxoid and hyalinized areas were observed (e). Undifferentiated cells with large nucleoli in a chondromyxoid background (f). Strong GFAP staining was observed. Tumor showed vascular proliferation (g). Neurofilament staining circumscribed the tumor mass with no significant staining within the tumor (h). p53 accumulated in tumor nuclei (i). Anti-NUT antibody staining showing homogeneous intranuclear expression (j).
Myxoid and chondroid differentiation has been reported in NUTM1-rearranged sarcomas but is unusual in primary glioneuronal tumors. Whether the strong GFAP positivity of our specific case is indicative of a glial tumor or of a sarcoma with myoepithelial differentiation cannot be assessed due to the lack of positive staining and specificity for other markers tested. GFAP positivity has been described in 3 out of 4 NUTM1-rearranged soft tissue or visceral sarcomas, this is in contrast to the CNS Ewing Family Tumor CIC group which fails to express any differentiation markers [2, 6]. We recommend performing NUT immunohistochemistry followed by RNA sequencing to identify any potential NUTM1 fusion partner genes in GFAP+/olig2- unclassified glioma, particularly those with myxoid and/or chondroid features. The ATXN1-NUTM1 fusion gene may define a novel group of rare primary brain tumors. The prognostic influence of NUTM1 fusion partners and the brain localization of NUTM1-rearranged tumors warrant further investigation.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s40478-019-0870-8.

Additional file 1: Table S1. Results of the Heidelberg DNA methylation-based CNS tumor classifier (entities and scores).
Additional file 2: Table S2. List of the 517 childhood cancer genes in the dragon targeted gene sequencing panel (Illumina TruSeq Custom Amplicon).

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Authors’ contributions
AS, FT, FB, EUC were major contributors in writing the manuscript. JMP, GP, YN, BMO carried out the molecular genetic studies. AS, SP, EUC characterized the histological features. YN, CD carried out the sequence alignment. FER, DLC, MG, IC contributed to the data collection. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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