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ETMR-like infantile cerebellar embryonal tumors in the extended morphologic spectrum of *DICER1* related tumors.

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We report for the first time *DICER1* mutations in two infantile cerebellar embryonal tumors not otherwise specified (NOS). Two girls, aged 11 months (case 1) and 8 months (case 2) presented with psychomotor delay. Both MRIs showed a midline posterior fossa tumor (Fig.1 ab). After gross total resection of the tumor, case 1 was treated with 2 cycles of etoposide/carboplatin. The controlled MRI showed spinal and leptomeningeal metastasis. After a subtotal resection, case 2 was treated according to institutional protocol for infant with high risk CNS PNET. MRI showed an increase of the residual mass during maintenance chemotherapy.

Case 1 had histological features of ETMR with an architectural pattern of embryonal tumor with abundant neuropil and true rosettes (Fig. 1fhjl). For case 2, a similar histology was seen but no true rosette was identified (Fig. 1gikm). In spite of LIN28A immunopositivity, FISH and array CGH failed to detect *C19MC* locus amplification [6]. LIN28A immunopositivity is not exclusive to ETMR, but also occurs in other tumors such as atypical teratoid/rhabdoid tumors (ATRT), ependymomas, and high grade gliomas [6]. ATRT was ruled out by INI1 and BRG1 nuclear immunopositivity in both cases. The genomic profile showed a chromosome 2 gain in both cases (Fig. 1cd): this feature is observed in

about 60% of ETMR [6]. The panel review diagnosis was ETMR NOS for case 1 and CNS embryonal tumor NOS for case 2.

Targeted gene sequencing on tumor DNA identified hotspot mutations corresponding to the RNase IIIb domain of *DICER1* in both tumors, *DICER1* c.5437G>A / p.(Glu1813Lys) and c.5113G>A / p.(Glu1705Lys) (NM_030621.4) in case 1 and 2, respectively. Germline nonsense pathogenic variants were then retrieved in both children: c.5053C>T / p.(Gln1685*) and c.1200G>A / p.(Trp400*) in case 1 and 2, respectively. Mutations in *DICER1* in other tumor types commonly follow the same pattern of one germline truncating mutation and a somatic missense mutation in the RNase IIIb domain [2, 5, 7]. No feature of *DICER1* syndrome was observed in either family, in accordance with its low penetrance (3). The tumor from case 1 also had the pathogenic variant c.134C>T / p.(Ser45Phe) in the *CTNNB1* gene. No additional alterations were observed in either tumor on our panel (Supplementary Table 1).

Germline *DICER1* pathogenic variants predispose to a broad spectrum of benign and malignant tumors [5]. Chondroid differentiation is a frequent feature in *DICER1* associated tumors such as nasal chondromesenchymal hamartoma, rhabdomyosarcoma or anaplastic sarcoma of the kidney [2, 5, 7] and was observed in case 2 (Fig. 1kl). Rare CNS embryonal tumors have been described in *DICER1* syndrome including pineoblastoma, pituitary blastoma and ciliary body medulloepithelioma [5]. The posterior fossa localization excluded these diagnoses. Interestingly, medulloepithelioma architectural pattern is one of the three architectural patterns of ETMR. This subtype is LIN28A+ and may not have *C19MC* alterations. WHO guidelines classify such tumors not as ETMR NOS but as medulloepithelioma, suggesting a different oncogenetic entity. A molecular signature still needs to be found. We hypothesize that *DICER1* mutations may have similar effects to *C19MC* amplification, in at least some medulloepitheliomas, ETMR NOS or embryonal tumors NOS. For case 2, showing a focal muscular differentiation, we considered primary intracranial spindle cell sarcoma with rhabdomyosarcoma-like features, *DICER1* mutant (SCS-RMSlike-*DICER1*), but smooth muscle actin was detected in all the 17 reported cases and was negative in our case [2]. Moreover, this sarcoma was located supratentorially in 20/22 cases with a median age of 6 years contrasting with our cerebellar infantile case [2].

Using the Heidelberg DNA methylation-based CNS tumor classifier, no class prediction was obtained with the confidence threshold of ≥ 0.9 [1]. The closest entity was ETMR with scores of 0.3 and 0.2 in case 1 and 2, respectively (Methylation data: <http://www.ncbi.nlm.nih.gov/geo> ; GSE120122). Using unsupervised t-SNE analysis, both cases were distinct from SCS-RMSlike-*DICER1* and intraocular medulloepithelioma and clustered with ETMR (Fig. 1e)[3, 4].

We recommend screening for somatic and germline *DICER1* pathogenic variants in all CNS embryonal tumors NOS, especially if they are LIN28A+, show chondroid differentiation, or are with any tumor of *DICER1* syndrome spectrum. Identification of *DICER1* mutations has implications in terms of genetic counseling and surveillance for patients and families [5].

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Legends

Figure 1: For case 1 (a) and case 2 (b), MRI showed a voluminous midline posterior fossa mass, enhancing after contrast injection. Array CGH using agilent 180k chip showed chromosome 2 gain, 4q(92,22-93,43 Mb) segmental gain and 7q(109,41-158,58 Mb) segmental loss in case 1 (c), and chromosome 2 gain in case 2 (d). t-SNE analysis (e). H&E showed small undifferentiated monotonous cells with numerous mitoses and apoptotic bodies (f: case1, g: case 2) and a biphasic histological pattern with areas of small embryonal perivascular cells and neuropil-like areas (h: case 1, i: case 2). In case 1, multilayered rosettes (left) and true rosettes (arrows) were observed (j). Foci of chondroid (left) and rhabdomyoblastic (right) differentiation were seen in case 2. Detail: desmin immunostaining (k). Strong LIN28A immunostaining: case 1 (l), case 2 (m).

Supplementary Table 1: Listing of the 78 childhood cancer genes of the targeted gene sequencing panel (Illumina_TrueSeq Custom Amplicon)