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CASE REPORT Open Access

YAP1-MAML2 fusion in a pediatric NF2-wildtype intraparenchymal brainstem schwannoma

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Abstract

Biallelic inactivation of NF2 represents the primary or sole oncogenic driver event in the vast majority of schwannomas. We report on a four-year-old female who underwent subtotal resection of a right medullary intraparenchymal schwannoma. RNA sequencing revealed an in-frame fusion between exon 5 of *YAP1* and exon 2 of *MAML2*. *YAP1-MAML2* fusions have previously been reported in a variety of tumor types, but not schwannomas. Our report expands the spectrum of oncogenic YAP1 gene fusions an alternative to NF2 inactivation to include sporadic schwannoma, analogous to what has recently been described in NF2-wildtype pediatric meningiomas. Appropriate somatic and germline molecular testing should be undertaken in all young patients with solitary schwannoma and meningioma given the high prevalence of an underlying tumor predisposition syndrome. In such patients, the identification of a somatic non-NF2 driver alteration such as this newly described YAP1 fusion, can help ascertain the diagnosis of a sporadic schwannoma.

Keywords: Schwannoma, Pediatric, Mastermind like transcriptional coactivator 2 (MAML2), Yes1 associated transcriptional regulator (YAP1)

Background

Schwannomas are benign peripheral nerve sheath tumors that arise sporadically or in the context of inheritable tumor predisposition; i.e., neurofibromatosis type 2 (NF2) or schwannomatosis. Biallelic inactivation of *NF2* represents the primary or sole oncogenic driver event in the vast majority of schwannomas; in addition, *SH3PXD2A-HTRA1* fusions have been recently identified as an alternative oncogenic driver in a subset of sporadic schwannomas [1, 2]. Among pediatric and young adult patients with newly diagnosed solitary schwannoma, up to 30% will ultimately be diagnosed with an inheritable tumor predisposition syndrome, i.e. NF2 or less commonly, schwannomatosis. However, accurate determination of germline status can be difficult given the high prevalence of mosaicism associated with false-negative germline testing results [3].

Case presentation

A four-year-old female underwent subtotal resection of a right medullary schwannoma. The tumor was identified on magnetic resonance imaging (MRI) obtained for progressive head tilt (Fig. 1). Past medical history was notable for developmental delay and facial asymmetry (hemifacial microsomia). A prior MRI performed at age 18 months showed cerebellar hypoplasia, but no tumor. A comprehensive clinical genetic workup including targeted and whole exome sequencing of the germline was

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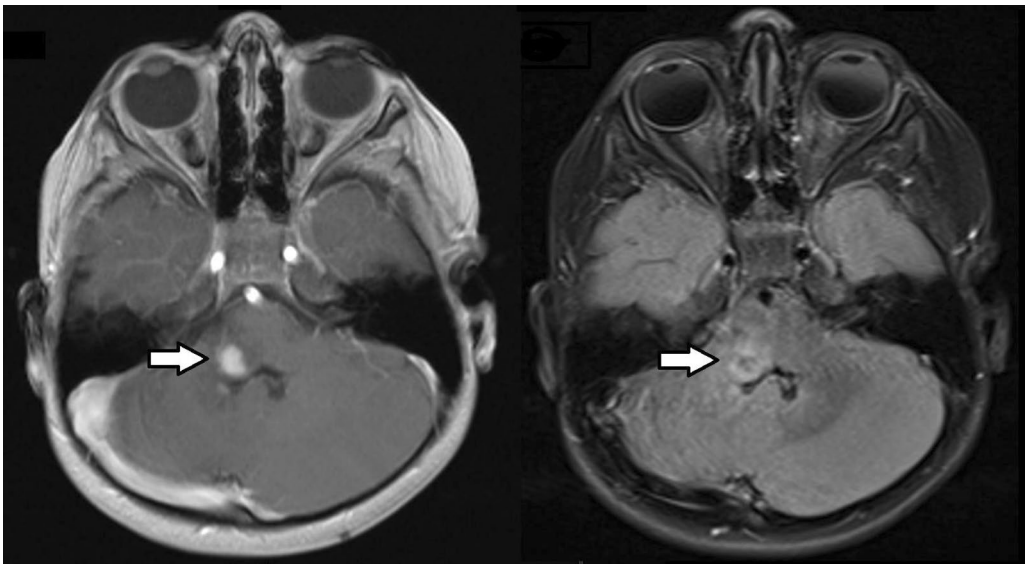


Fig. 1 T1-weighted post-contrast (left panel) and T2/FLAIR-weighted (right panel) magnetic resonance images revealing a partially contrast-enhancing intra-parenchymal right medullary tumor (arrows). The tumor involved the right lateral aspect of the inferior pons, brachium pontis and ventral cerebellum

negative. Most recent follow-up MRI of the brain eight months after diagnosis showed stable residual disease.

Histologic examination disclosed a neoplasm composed of monomorphous spindle cells in tight, interlacing fascicles (Fig. 2a), without Verocay bodies or Antoni B areas. Devoid of mitotic activity, tumor cells focally dissected into adjoining neuroparenchyma along blood vessels. Immunohistochemical studies showed the lesion to be rich in collagen IV, with tumor cells being negative for GFAP, EMA and SSTR2A, while expressing S100 protein (cytoplasmic/nuclear) and SOX10 (nuclear).

DNA methylation profiling [4] with the Heidelberg brain tumor classifier version 11b6 revealed a match to the methylation class schwannoma with a calibrated score of 0.97. Paired targeted next-generation sequencing analysis of tumor and matched normal sample [5] was negative for somatic mutations as well as structural variants, and revealed a relatively flat DNA copy number profile with focal genomic gains and losses at chromosome 11q including the *YAP1* locus (Fig. 3) [6]. RNA sequencing using Anchored Multiplex PCR [7] revealed an in-frame fusion between exon 5 of *YAP1* and exon 2 of *MAML2* (Fig. 4). *YAP1-MAML2* fusions have been reported in NF2-wild type meningioma [8] and other cancers [9], but not schwannomas. As seen in all N-terminal YAP1 fusions reported to date, the fusion detected in our patient retains

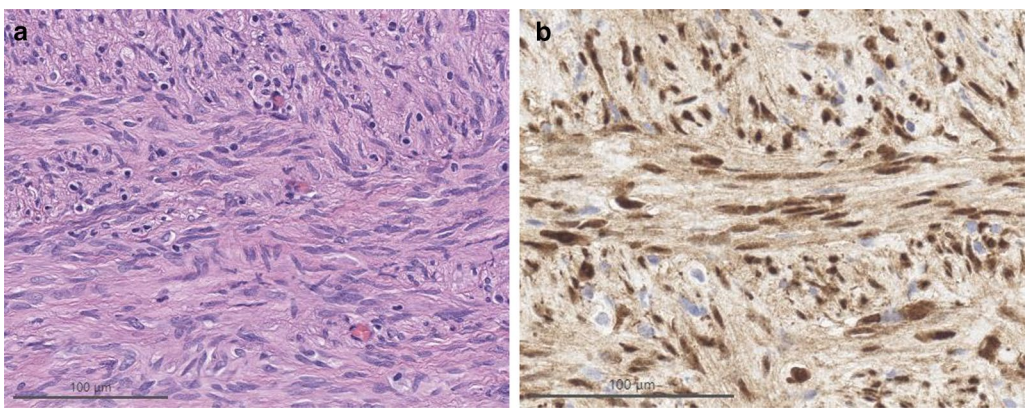


Fig. 2 Hematoxylin and eosin staining of the tumor (**a**) and immunohistochemistry for YAP1 (**b**)

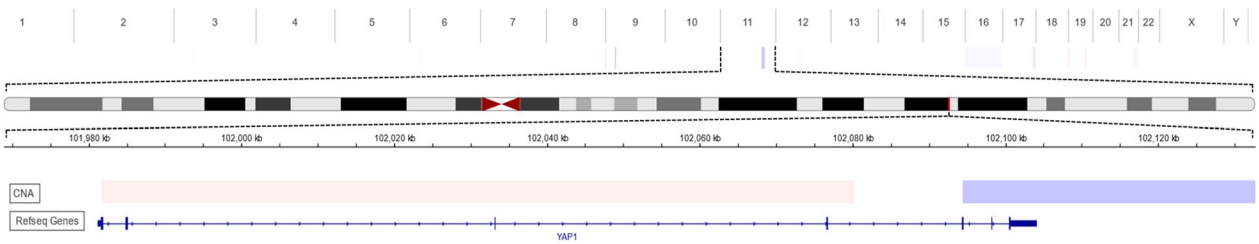
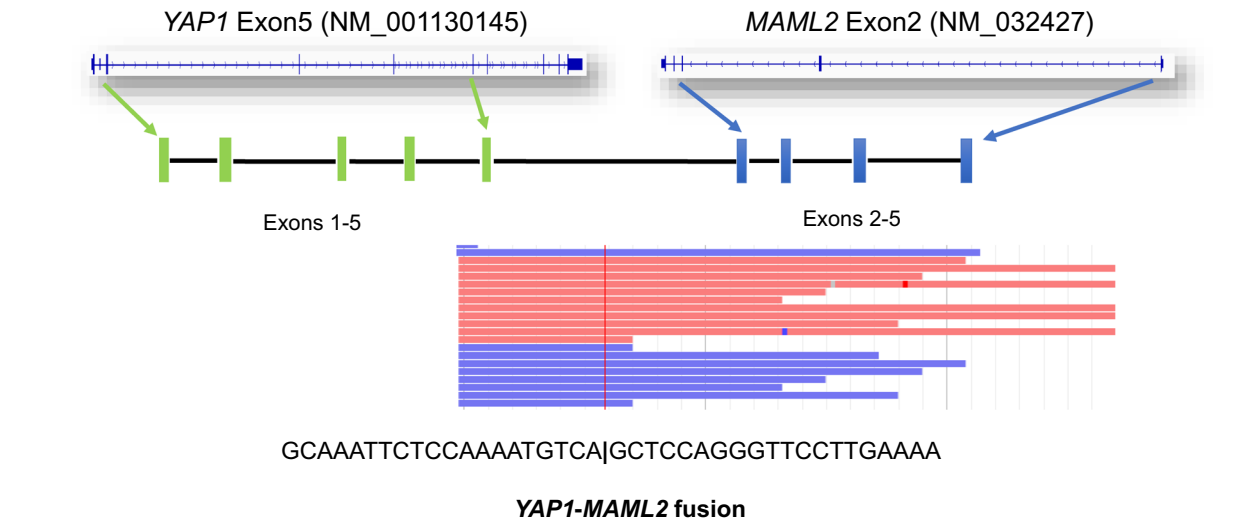


Fig. 3 DNA copy number profile derived from paired targeted next-generation sequencing analysis of tumor and matched normal sample, revealing a relatively flat DNA copy number profile with focal genomic gains (depicted in red) and losses (depicted in blue) at chromosome 11q including the *YAP1* locus. CNA: copy number alterations



Gene 1	Gene 2	Position 1	Position 2	Transcript 1	Exon No. 1	Transcript Strand 1	Transcript 2	Exon No. 2	Transcript Strand 2	Fusion Junction sequence	Frameshift class
YAP1	*MAML2*	chr11: 102076805	chr11: 95826681	NM_001130145	5	+	NM_032427	2	-	GCAAATTCTCC AAAATGTCA|GC TCCAGGGTTCC TTGAAAA	In frame

Fig. 4 RNA sequencing using Anchored Multiplex PCR revealing an in-frame fusion between exon 5 of YAP1 and exon 2 of MAML2

the TEAD transcription factor binding domain of YAP1, along with the nuclear localization sequence and transactivation domain of MAML2. The resulting fusion protein is resistant to inhibitory signaling of the Hippo tumor suppressor pathway by constitutive nuclear localization and resistance to proteasomal degradation [10]. In keeping with these observations, we confirmed strong nuclear localization of YAP1, as well as weaker cytoplasmic labelling in our patient's tumor by immunohistochemistry (Fig. 2b).

Discussion and conclusions

Our finding of an oncogenic *YAP1-MAML2* fusion in an NF2 wild-type schwannoma supports the notion that canonical Hippo signaling through the effectors YAP/TAZ is required for schwannomagenesis [11]. Intraparenchymal schwannomas including brainstem schwannomas are rare, and molecularly not well characterized [12].

Among pediatric and young adult patients with solitary schwannoma or meningioma, up to 30% and 50%, respectively, will have an identifiable genetic predisposition, most commonly NF2 [3]. Accordingly, appropriate clinical screening examinations and molecular genetic testing of tumor and germline are recommended for all young patients with solitary schwannoma or meningioma. However, a diagnosis of NF2 or schwannomatosis can be difficult to rule out in patients with negative germline testing due to the high prevalence of mosaicism [13]. In such patients, the identification of a somatic

non-NF2 driver alteration such as a *YAP1* fusion, can help ascertain the diagnosis of a sporadic schwannoma or meningioma with confidence, and may obviate the need for further genetic or clinical testing to rule out an inheritable tumor predisposition syndrome.

Abbreviations
EMA: Epithelial membrane antigen; GFAP: Glial fibrillary acidic protein; HTRA1: HtrA serine peptidase 1; MAML2: Mastermind like transcriptional coactivator 2; MRI: Magnetic resonance imaging; NF2: NF2, moesin-ezrin-radixin like (MERLIN) tumor suppressor; S100: S100 calcium binding protein; SH3PXD2A: SH3 and PX domains 2A gene; SOX10: SRY-box transcription factor 10; SSTR2A: Somatostatin receptor subtype 2A; YAP1: Yes1 associated transcriptional regulator.

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Author contributions
Conceptualization, MAK; Sample and/or data acquisition, all authors; data analysis: MAK, BL, JJY, JKB, TAB, MKR. Manuscript writing and approval of the final version, all authors. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
The patient's legal guardian signed informed consent under a research protocol approved by the MSK Institutional Review Board.

Consent for publication
The patient's legal guardian signed informed consent under a research protocol approved by the MSK Institutional Review Board.

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

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