



A novel type of *C11orf95-LOC-RELA* fusion in a grade II supratentorial ependymoma: report of a case with literature review

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Abstract

Background Ependymoma (EPN) is the third most common central nervous system tumor in childhood. Recent advances in the molecular classification of EPN revealed a supratentorial (ST) ependymoma subgroup characterized by *C11orf95-RELA* fusion. **Case Report** We describe a novel *RELA*-fusion composed by a chimeric transcript *C11orf95-LOC-RELA* in a supratentorial WHO grade II EPN occurring in a 4-year-old child. Metastatic loci at the brain, leptomeningeal involvement, and pulmonary nodules were identified at tumor recurrence. The child eventually died before 1 year after recurrence. **Conclusion** This index case showed aggressive behavior and nuclear accumulation of p65/*RELA*.

Keywords Ependymoma · *C11orf95-LOC-RELA* · Non-coding RNA · p65/*RELA*

Introduction

Ependymomas are rare primary central nervous system (CNS) tumors that originate from the ependymal cells and can affect either intracranial or spinal cord regions [6, 20]. Recently, it was found that supratentorial (ST), fossa posterior (PF), and spinal (SP) ependymomas represent molecularly distinct subgroups [7, 13, 15, 19]. Approximately two-thirds of ST ependymomas (ST-EPNs) are characterized by *RELA*-fusions involving *C11orf95* and *RELA* genes, which were associated with unfavorable outcome

in evidence preliminary, from retrospective series outside clinical trials, and therefore needs further prospective evaluation [13–15]. Positive *RELA*-fusion tumors are characterized by the nuclear accumulation of p65/*RELA*, which drives oncogenic transformation through NF- κ B cell signaling [2, 15, 16]. This observation is of clinical importance, since nuclear staining for NF- κ B (p65/*RELA*) in EPN cells by immunohistochemistry (IHC) has been increasingly used for the classification of ST-EPN subgroups [2, 3, 15, 16].

Different rearrangements of *C11orf95-RELA* fusion have been described in ST-EPNs, the most common involving exons 1 to 2 of *C11orf95* and exon 2 of *RELA* (*RELA* type-1), or exons 1 to 3 of *C11orf95* fused to exon 2 of *RELA* (*RELA* type-2). Contrariwise, most of the ST-EPNs lacking *RELA* fusions represent a distinct molecular subgroup that correlates with better prognosis, usually characterized by *YAPI* fusions [13]. The genetic characterization of ST-EPN still is evolving, with other fusions involving different genes/loci being rarely reported such as *C11orf95-NCOA1*, *KTNI-ALK* and *CCDC88A-ALK* [11, 16]. We describe an additional and distinct *RELA* rearrangement occurring in a WHO grade-II ST-EPN involving *C11orf95*, *RELA*, and a partial region of an uncharacterized non-coding RNA (ncRNA) from *LOC105369347* gene.

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Clinical summary

A 4-year-old male presented a 3-month history of headache and vomiting. Brain magnetic resonance imaging (MRI) depicted a solid mass at the left temporal regional, with perilesional edema. No metastatic lesions were found at image workup. The child was submitted to gross total resection of the tumor; pathological diagnosis was of a WHO grade II EPN [1]. Tumor specimen depicted an elevated cellular density at hematoxylin and eosin (H&E) (Fig. 1a-1 to a-3), low mitotic activity (Ki-67 staining—Fig. 1b-1, b-2), and rare microvascular proliferation (CD31 staining—Fig. 1c, c-2). Additionally, tumor cells showed perivascular cytoplasmic focal immunopositivity for glial fibrillary acidic protein (GFAP), epithelial membrane antigen (EMA) and vimentin, while it was negative for cytokeratin AE1/AE3 and synaptophysin (S-100) markers. The patient received local radiotherapy following surgical resection and was clinically followed. One year later, a tumor recurrence was observed at the primary site. The patient was re-operated (partial resection). New pathological exam

confirmed WHO grade II ST-EPN recurrence. He received two adjuvant cycles of chemotherapy (Ifosfamide/Etoposide/Carboplatin). Further image workup depicted fast tumor progression with metastatic lesions at the brain, leptomeningeal involvement, and pulmonary nodules. Tumor progressed despite chemotherapy and the patient eventually died from the disease 1 year after recurrence. This study was approved by the Institutional Ethics Committee (HCFM-USP Number: 1320/09).

Molecular analysis

Total RNA was extracted from microdissected fresh-frozen tumor using *AllPrep DNA/RNA/Protein* kit (Qiagen, Valencia, CA, USA). RNA integrity was evaluated by the Agilent Bioanalyzer 2100 (Agilent Technologies, Santa Clara, USA); cDNA was synthesized using the Superscript III Reverse Transcriptase with random primers (Applied Biosystems, Foster City, USA), according to manufacturer's

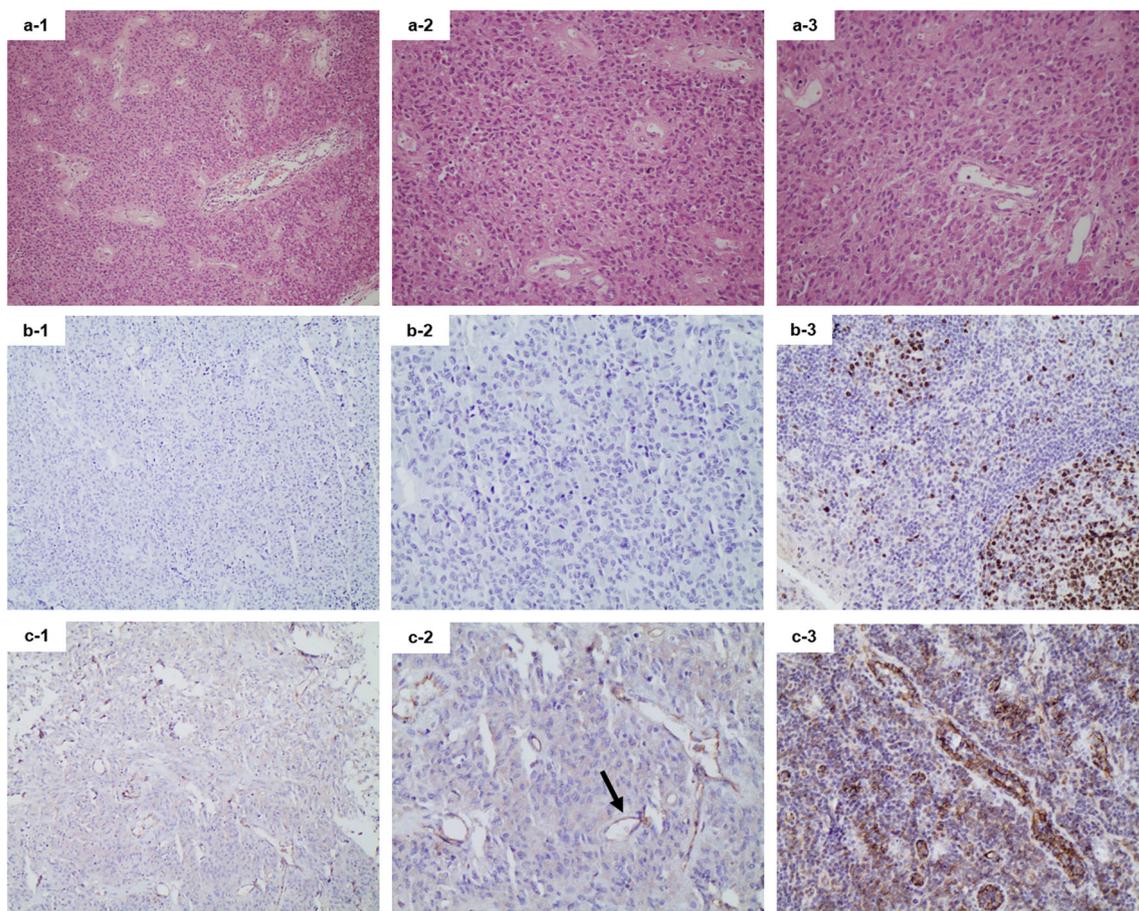


Fig. 1 Histopathological and immunohistochemistry findings. (a-1, a-2, and a-3) Elevated tumor cell density at different tumor areas by H&E ($\times 20$, $\times 40$, and $\times 40$ respectively). (b-1, b2, and b3) Low mitotic index (around 1–2%) by Ki-67 at tumor specimen (b-1 and b-2— $\times 20$ and \times

40 respectively) and positive staining control for the reaction (b-3). (c-1, c-2, and c-3) Rare vascular proliferation, arrows pointing to positive staining ($\times 20$, $\times 40$) with positive vascular staining control for CD31 (c-3)

instructions. Conventional RT-PCR was performed using a set of primers targeting ST-EPN fusions reported by Parker et al. [15], i.e., *RELA* type 1 (*C11orf95* exon 2: 5'GCGCTACT ACCACGACCACT and *RELA* exon 2: 5'GCTGCTCA ATGATCTCCACA) and *RELA* type 2 (*C11orf95* exon 3: 5' CCTGCACCTGGACGACAT and *RELA* exon 2: 5' GCTGCTCAATGATCTCCACA). PCR products were examined through a 2% agarose gel and revealed by ethidium bromide (Fig. 2a). Unexpected bands around 680 bp and 480 bp using primers *RELA* type 1 and 2 were observed, and they were submitted to Sanger sequencing, respectively. A complex fusion involving a partial region of exon 4 of the *C11orf95*, followed by a 26pb sequence of *LOC105369347* (uncharacterized non-coding RNA-ncRNA class, close to the 5' end of *RELA*) and *RELA* (partial region of exon 1) was depicted (Fig. 2b). These analyses were performed and confirmed in three independent experiments. This fusion has not been previously reported.

Immunohistochemistry for p65-RELA

Immunohistochemistry analysis was performed on serial 4- μ m-thick FFPE sections of our variant case (*C11orf95-LOC-RELA*), along with positive/negative controls using rabbit

monoclonal anti-NF- κ B antibody (clone. D14E12; dil.1:800; Cell Signaling) following routine procedures. The nuclear staining for p65-RELA on this index case was positive, with strong nuclear staining in $\geq 10\%$ tumor cells (Fig. 2c3, c4).

Discussion

Recent advances in the molecular characterization of EPNs revealed nine distinct subgroups [7, 13, 15, 19]. They are divided into three different molecular variants for each anatomical compartment: ST-EPN (*RELA* fusion and *YAP1* fusion); PF-EPN (group A and group B) and SP-EPN (myxopapillary and ependymoma). Subependymomas occurring in all three compartments are as recognized as grade I. Intracranial EPNs occurring in children are usually diagnosed within the ST-*RELA*, ST-*YAP1*, or as PF group A lesions [13]. Importantly, Parker et al. showed that around 70% of ST-EPNs present fusion on chromosome 11 involving the uncharacterized gene (*C11orf95*) and *RELA*, a transcriptional factor in the NF- κ B pathway [15].

Here, we describe a novel complex *RELA* fusion in a child with an aggressive WHO grade II ST-EPN with positive nuclear staining for p65/*RELA*. This new fusion presents an insertion region between the genes *C11orf95* and *RELA*,

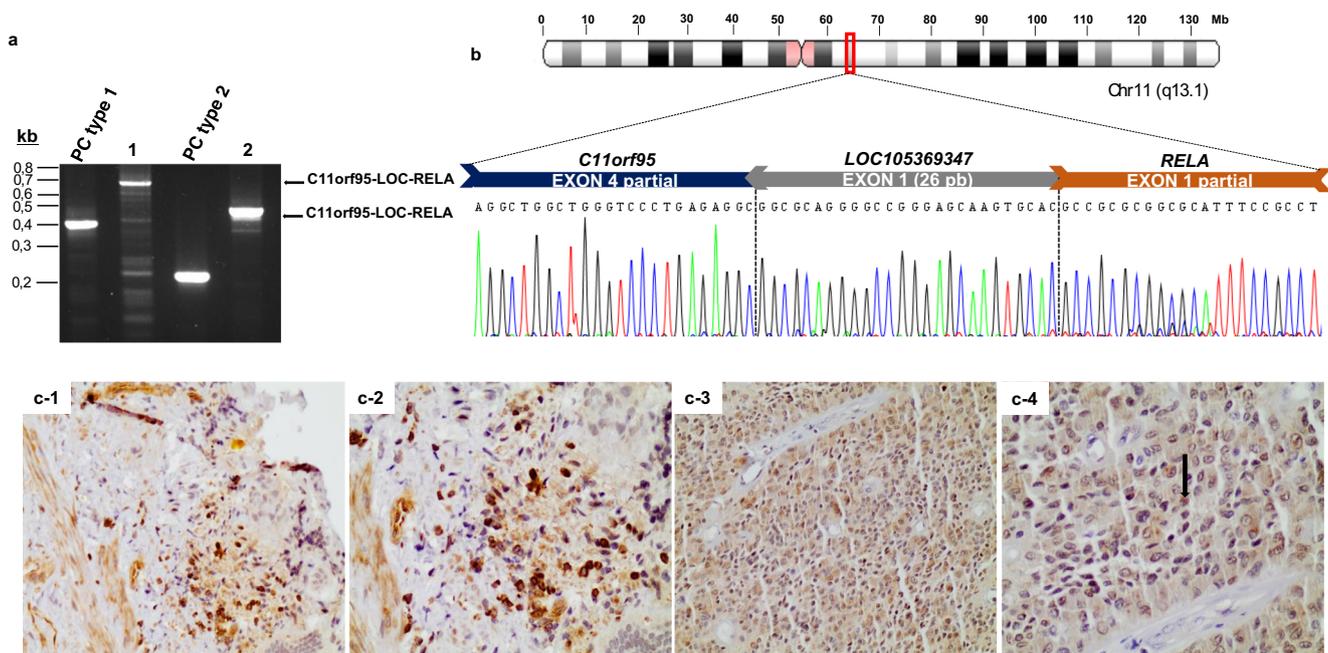


Fig. 2 *C11orf95-LOC-RELA* fusion detected in a supratentorial ependymoma tumor tissue by RT-PCR. Sanger sequencing and p65/*RELA* immunohistochemistry staining. (a) Reverse transcription PCR products detected in this case with both primers as has been view in lane 1: primers *RELA* type 1 and lane 2: primers *RELA* type 1.1 Kb DNA ladder. PC, positive control using cDNA from a *C11orf95-RELA* type 1 and 2 fusion-positive ependymoma tissue (Kindly provided by Dr. Kristian W. Pajtler). (b) Representative electropherograms with mapping

position on chromosome showing the *C11orf95-LOC-RELA* fusion sequencing. (c) Representative immunostaining of *C11orf95-LOC-RELA* fusion. (c-1 and c-2) Immunostaining using p65/*RELA* of the positive control: chronic cholecystitis, $\times 20$ magnification and $\times 40$ magnification, respectively. (c-3 and c-4) *C11orf95-LOC-RELA* corresponding to p65/*RELA* immunohistochemistry results (arrows pointing to positive nuclear staining), $\times 20$ magnification and $\times 40$ magnification, respectively

Table 1 Summary of all distinct fusion genes involving *RELA* gene in ST-EPN reported to date (including the current case) that included p65/*RELA* IHC staining and references

Fusion gene	p65/ <i>RELA</i> IHC	Molecular characteristics	Authors
<i>C11orf95-RELA</i> *	Positive	NA	Pietsch et al. 2014 [16]; Figarella-Branger et al. 2016 [2]
<i>C11orf95-RELA type 1</i>	Positive	<i>C11orf95</i> exon 2 and <i>RELA</i> exon 2	Parker et al. 2014 [15]; Gessi et al. 2017 [3]; Nambirajan et al. 2016 [10]; Pagès et al. 2018 [12]
<i>C11orf95-RELA type 2</i>	Positive	<i>C11orf95</i> exon 3 and <i>RELA</i> exon 2	Parker et al. 2014 [15]; Gessi et al. 2017 [3]; Pagès et al. 2018 [12]
<i>C11orf95-RELA type 3</i>	NA	<i>C11orf95</i> exon 3 and <i>RELA</i> exon 3	Parker et al. 2014 [15]
<i>C11orf95-RELA type 4</i>	NA	<i>C11orf95</i> exon 2 and <i>RELA</i> exon 3	Parker et al. 2014 [15]
<i>C11orf95-RELA type 5</i>	NA	<i>C11orf95</i> exon 4 (partial) and <i>RELA</i> exon 1 (inverted partial)	Parker et al. 2014 [15]
<i>C11orf95-RELA type 6</i>	NA	<i>C11orf95</i> exon 4 (partial) and <i>RELA</i> exon intron 1-2	Parker et al. 2014 [15]
<i>C11orf95-RELA type 7</i>	NA	<i>RELA</i> exon 1 (inverted partial) and <i>RELA</i> exon 3	Parker et al. 2014 [15]
<i>C11orf95-RELA variant case</i>	Positive	<i>C11orf95</i> exon 4 and <i>RELA</i> intron 3	Gessi et al. 2017 [3]
<i>C11orf95-LOC-RELA</i>	Positive	<i>C11orf95</i> exon 4, <i>LOC105369347</i> , and <i>RELA</i> exon 1	Current case

*Not available specific subtypes of the *RELA* fusion; NA data not available

belonging to the ncRNA *LOC105369347*. Distinct tumors have already occurred with gene fusions around non-coding RNAs [4, 8]. In B cell lymphoma, a fusion involving the Bcl-6 proto-oncogene and the non-coding gene *GAS5* was identified [9]. Tomlins et al. identified the recurrent occurrences of the *ETV1* gene fused with 5' untranslated regions of genes *TMPRSS2*, and *SLC45A3* in prostate cancer [18]. In these fusions, the ncRNAs and untranslated regions can become gene-coding and functionally relevant, contributing to the expression of aberrant proteins [5, 17]. It is known that chromothripsis events on 11q13.1 may result in formation of different fusion genes in the neighborhood between *C11orf95* or *RELA*; *LOC105369347* is located close to the 5' of *RELA*. During chromosomal rearrangement that originated the fusion, a segment of this ncRNA gene was probably retained [15]. Yet, the actual functional role of the chimeric transcript involving *LOC105369347* needs further clarification and was beyond the scope of this descriptive report.

In total, eight different fusions involving *RELA* genes were described in ST-EPNs. Table 1 summarizes these fusions and their reported frequencies. Gessi et al. also identified a unique variant case involving *C11orf95* exon 4 and 15 bp of *RELA* intron 2 upstream *RELA* exon 3 [3]. Similarly, to what we observed, their case also retained positivity for p65/*RELA* staining, suggesting that the activation of NF- κ B pathway is a key element shared by many *RELA*-fused ST-EPNs. This finding reinforces the role of p65-*RELA* IHC for the classification of different *RELA* rearrangements in ST-EPNs. Nevertheless, careful IHC

evaluation of new *RELA* gene fusions may be advisable to ensure conserved positivity for p65-*RELA* outside the more common *RELA*-1 and 2 fusion subtypes.

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Compliance with ethical standards

This study was approved by the Institutional Ethics Committee (HCFM-USP Number: 1320/09).

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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