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Description of A New Oncogenic Mechanism for Atypical Teratoid Rhabdoid Tumors in Patients with Ring Chromosome 22

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Abstract

Atypical teratoid rhabdoid tumors of the central nervous system are rare, highly malignant, embryonal tumors most often occurring in children under age 3 years. Most are due to a somatic change in tumor suppressor gene *SMARCB1* followed by a second-hit, typically loss of heterozygosity, best detected on immunohistochemical staining. Despite the noteworthy genetic homogeneity of atypical teratoid rhabdoid tumors, relatively little is known about the oncogenic mechanisms that lead to biallelic inactivation of *SMARCB1*. Herein, we describe a patient with constitutional ring chromosome 22, Phelan-McDermid Syndrome and atypical teratoid rhabdoid tumor of the brain. During mitosis, sister chromatids of a ring chromosome may form interlocking and dicentric rings, resulting in chromosomal loss, complex karyotypes, and ongoing somatic variation. We hypothesized that the inherent instability of the patient's ring chromosome could lead to mosaic monosomy chromosome 22, resulting in allelic inactivation of the tumor-suppressor gene *SMARCB1* and AT/RT if a second-hit occurred. Utilizing high-density microarray technology to analyze peripheral blood and tumor tissue, we confirmed this oncogenic mechanism, previously undescribed in patients with atypical teratoid rhabdoid tumors. Our data demonstrates chromosomal loss as a consequence of ring chromosome instability serving as the first hit in oncogenesis. This rare but possibly under-recognized mechanism is important for diagnosis. Further investigation is warranted to assess if this oncogenic mechanism has health monitoring, therapeutic and/or prognostic implications.

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Keywords

atypical teratoid rhabdoid tumor; AT/RT; Phelan-McDermid syndrome; PMS; ring chromosome; *SMARCB1*; *INI1*; oncology; genetics; brain tumor

BACKGROUND

Atypical teratoid/rhabdoid tumors (AT/RT) of the central nervous system (CNS) are rare, highly malignant tumors that make up 2-3% of pediatric brain tumors and up to 20% of all CNS tumors in children less than 3 years [Packer et al., 2002]. Most are due to a somatic variant in the tumor suppressor gene *SMARCB1* (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily B, member 1; alternative symbols include *INI1*, *BAF47* and *hSNF5*), followed by a second-hit, resulting in complete loss of SMARCB1 nuclear protein [Packer et al., 2002; Biegel et al., 1999; Bourdeaut et al., 2014]. Up to 35% of patients have a constitutional pathogenic variant in tumor suppressor gene *SMARCB1* and develop AT/RT in the context of a rhabdoid tumor predisposition syndrome (OMIM# 609322) [Eaton et al., 2011]. Tumor immunohistochemical (IHC) staining is routine in pathologic evaluation of pediatric brain tumors. Loss of *SMARCB1* expression by IHC is sensitive and specific for a diagnosis of AT/RT [Biegel et al., 1999; Bourdeaut et al., 2014].

AT/RT has been previously reported in patients with ring chromosome 22 (r(22)) [Cho et al., 2014; Korones et al., 1999; Biegel et al., 1999; Rubio, 1997] and Phelan-McDermid syndrome (PMS, OMIM# 606232) [Sathyamoorthi et al., 2009; De Amorim Bernstein et al., 2013]. Herein, we report a patient with Phelan-McDermid syndrome, constitutional ring chromosome 22 and CNS AT/RT. Constitutional analysis of *SMARCB1* was normal. Immunohistochemical staining showed complete loss of SMARCB1 expression in tumor cells and preserved expression in surrounding endothelial, stromal and inflammatory cells, consistent with biallelic inactivation of tumor-suppressor gene *SMARCB1* in tumor (See Fig. 1).

During mitosis of a ring chromosome, sister chromatids may form interlocking or dicentric rings resulting in anaphase lag, unequal crossing over, complex karyotype rearrangements and mosaic aneuploidy [Cocce et al., 2011; Kistenmacher and Punnett, 1970; Zirn et al., 2012]. We hypothesized that this mitotic instability could lead to somatic mosaic aneuploidy, resulting in a heterozygous loss of *SMARCB1* and AT/RT after a second-hit. We confirmed this oncogenic mechanism through microarray analysis of tumor tissue and peripheral blood. These findings have important diagnostic implications for patients with r(22), newly diagnosed AT/RT and syndromic features. Further investigation is needed to assess if a ring chromosome, which contributes to the oncogenic mechanism of ATRT, has ongoing somatic mutation which may have prognostic and therapeutic implications.

CLINICAL REPORT

This girl was born to a 25-year-old primigravida at 38 weeks gestation after an uncomplicated pregnancy and vaginal delivery. At birth, she weighed 2,863 grams (25th-

centile). Relative right ear microtia was noted. Her head circumference measurement at birth was not recorded, but was noted to be at the 50th-centile at her 2 weeks checkup (value not recorded). She met all of her developmental milestones early: she attained a pincer grasp by 5 months and walked at 9 months of age. At six-months, hirsutism was noted on her back, axilla and pubic areas; an endocrinology evaluation was unrevealing. By 10 months, she showed subtle signs of regression. Her head circumference was now 42.6cm (-2 standard deviations (SD)). Over the following 4 months, she gradually stopped walking, signing and babbling. She developed ptosis, left facial droop, and progressive right-side weakness with eventual inability to bear weight, prompting a referral for magnetic resonance imaging (MRI) at 12 months of age. MRI revealed a 3 × 2.5 × 3 cm mass at the cerebellopontine angle. Complete surgical resection was achieved. Pathological evaluation of tumor tissue and immunohistochemistry (IHC) showed complete loss of *SMARCB1* expression, consistent with biallelic inactivation of *SMARCB1* and a diagnosis of AT/RT (see Fig. 1). Constitutional analysis of *SMARCB1* performed on a peripheral blood sample via Sanger sequencing and *SMARCB1* gene specific microarray was normal.

At 14 months (3 weeks after surgery), she underwent two cycles of induction chemotherapy consisting of vincristine, methotrexate, etoposide, cyclophosphamide and cisplatin. After completing chemotherapy, 45.92 Gray (Gy) of adjunct proton beam radiation was administered in 28 fractions over 48 days followed by three cycles of consolidation chemotherapy with thiotepa and carboplatin with peripheral blood stem cell rescue. Radiation therapy was complicated by grade I radiation dermatitis and fatigue. She tolerated her immediate treatment course without complications, and completed tumor-directed therapy at 17 months of age. Immediate post-surgical and -radiation MRIs showed the expected operative changes but were otherwise normal. Cerebral spinal fluid showed no malignant cells.

In the months following treatment, she gained strength and improved clinically. She became socially interactive again, and began to take a few steps. However, by 20 months, she stopped cruising, had difficulty holding objects and developed right-sided ptosis. Brain and spine MRI showed T2 changes and enhancement in the pons, cervical spinal cord, and splenium of the corpus callosum consistent with radiation necrosis. A SNP microarray was ordered given loss of milestones, progressive microcephaly, and microtia. Results showed a 3.1 Megabase (Mb) terminal deletion at 22q13.31q13.33 encompassing 27 OMIM-listed genes, including *SHANK3*, consistent with a diagnosis of PMS. The deletion did not include *SMARCB1*. Given that constitutional ring chromosome 22 has previously been described in patients with AT/RT and 14% of patients with PMS have r(22), a limited karyotype was performed. This confirmed a constitutional r(22) in 19 of 20 cells and a dicentric ring in 1 of 20 cells: 46,XX,r(22)(q13.1q13.3)[19/20]/46,XX,+dic r(22;22)[1/20].

At 22 months, the patient developed acute right-sided paralysis, right-sided neglect and global hypotonia. Repeat MRI showed mild cerebral volume loss in addition to previous findings. She was started on dexamethasone for suspected radiation necrosis with no clinical improvement. At 23 months, she developed acute encephalopathy and dysautonomia with intermittent bradycardia, hypotension, and hypopnea. At 2 years of life, she stopped verbalizing. Repeat brain and spine MRI showed enlargement of the pontine lesion and a

new area of diffusion restriction in the internal capsule. At age 2.5 years, MRI showed diffuse volume loss in bilateral cerebral hemispheres and brainstem, myelomalacia in the cervical spinal cord and multiple foci of diffusion restriction, consistent with progression of brainstem necrosis.

We hypothesized that mitotic instability of r(22) led to somatic, mosaic monosomy chromosome 22, followed by a second-hit that resulted in *SMARCB1* loss of function (Figure 1b). To investigate, we extracted DNA from frozen tumor and peripheral blood and performed array comparative genomic hybridization to detect copy number variation using a 4x180K oligonucleotide array (180,000 probes, average probe spacing 16 kb, Agilent Technologies, Santa Clara, CA). Chromosomal microarray results of blood confirmed a heterozygous 3.1-Mb terminal deletion at 22q13.1q13.3, consistent with the patient's known diagnosis of Phelan-McDermid syndrome (Fig. 2a). Hybridization of tumor to blood revealed loss of the proximal 48-Mb of chromosome 22 in tumor, consistent with loss of the r(22) (Figure 2c). Heterozygous loss of the r(22) from all cells would result in a $\log_2$ ratio of -1.0; an average $\log_2$ ratio of -0.5 across the 48-Mb region suggests a mosaic loss of the ring chromosome or, more likely, contamination of tumor tissue with normal cells. No other copy number alterations were identified in the tumor sample compared to blood DNA (data not shown). Full Sanger sequencing of exons and intron-exon boundaries was performed on DNA isolated from tumor. No sequencing alterations were detected. Methylation, structural rearrangements, or variants in promoters or enhancers distant from *SMARCB1* were not assessed.

DISCUSSION

In this report, we evaluate a patient with Phelan-McDermid syndrome, constitutional r(22) and AT/RT. Tumor IHC was consistent with biallelic inactivation of *SMARCB1;* germline *SMARCB1* sequencing and deletion/duplication analysis was negative. Using microarray, we confirmed our hypothesis that inherent instability of the constitutional r(22) led to monosomy 22 in AT/RT tumor that was not present in peripheral blood. This confirmed oncogenic mechanism has diagnostic implications and potentially identifies an important subgroup. Additional investigation is warranted.

Extensive genetic analysis in patients with AT/RT has shown a remarkable lack of genomic alteration [Bourdeaut et al., 2014; Biegel et al., 1999]. Recurrent variants have only been reported in *SMARCB1* and rarely, *SMARCA4* [Lee et al., 2012; Hasselblatt et al., 2014; Biegel et al., 1999; Coccé et al., 2012]. Survival has improved with better recognition and aggressive therapies, though mortality remains high. Much effort has been dedicated to recognition of clinicopathologic markers for therapeutic and prognostic indicators [Bourdeaut et al., 2014; Johann et al., 2016]. The majority of patients with AT/RT have biallelic variants/deletions in SMARCB1 leading to inactivation of the tumor suppressor gene, best detected on IHC [Biegel et al., 1999; Coccé et al., 2012; Kordes et al., 2010]. IHC is considered the most sensitive method to detect loss of function in SMARCB1; a substantial subset of patients with loss of SMARCB1 expression on IHC have no or only a heterozygous *SMARCB1* sequencing variant or deletion detected in tumor tissue [Kordes et al., 2010; Tsai et al., 2012; Johann et al., 2016]. Various hypotheses have been suggested for

this; better understanding of the molecular profile and oncogenic drivers in this aggressive cancer is an active area of research [Tsai et al., 2012; Zirn et al., 2012; Bourdeaut et al., 2014; Johann et al., 2016]. Johann et al. [2016] showed that methylation patterns in AT/RT primary tumors can vary widely and may be a way to further characterize these aggressive tumors. Methylation as a somatic second-hit, resulting in the inactivation of a tumor suppressor gene has been shown in other cancers, such as colorectal cancer [Valo et al., 2015]. Analysis of alternative inactivating mechanisms, such as methylation, structural variants, or variants in non-coding regions, promoters or enhancers, was beyond the scope of this study.

Ring chromosome 22 is an extremely rare chromosomal anomaly. It has a broad clinical phenotypic spectrum, related to the size and location of the accompanying deletion, the underlying stability of the ring, and the ongoing propensity for the ring to be lost during subsequent mitosis [Guilherme et al., 2014]. Recurrent breakpoints associated with the formation of a ring chromosome 22, ring instability or oncogenic risk is unknown [Bonaglia et al., 2011]. To date, four patients with AT/RT and r(22) have been described [Rubio, 1997; Biegel et al., 1999; Korones et al., 1999; Cho et al., 2014]. The patient described by Cho et al. [2014] had a 3.5-Mb deletion at 22q13.31q13.33; deletion breakpoints were either not investigated or noted for other cases [Bonaglia et al., 2011]. Clearly, not every patient with r(22) develops AT/RT [Guilherme et al., 2014]. Investigation into breakpoints in similar patients, though challenging, may inform prognostic ring instability and/or oncogenic risk [Bonaglia et al., 2011]. By confirming the oncogenic mechanism of allelic SMARCB1 inactivation in this patient, we demonstrate the finding of r(22) in a patient with AT/RT is nonrandom, laying groundwork for future investigation.

AT/RT is a rare tumor, making it difficult to assemble a cohort. To date, all children reported with AT/RT and r(22) or AT/RT and PMS have had a poor outcome [Rubio 1997; Biegel et al., 1999; Korones et al., 1999; Sathyamoorthi et al., 2009; De Amorim Bernstein et al., 2013; Cho et al., 2014]. However, given the high mortality in all patients with AT/RT – most of who do not have a constitutional chromosomal abnormality – assessing the prognostic contribution of r(22) or PMS is difficult. Noting underlying chromosomal abnormality in patients with AT/RT in published cohorts may elucidate potential therapeutic and/or prognostic implications.

The tumorigenic mechanism we describe – biallelic loss of a tumor suppressor gene due to somatic aneuploidy of r(22) followed by a second-hit – has been previously reported in patients with r(22) and neurofibromatosis type 2 (NF2, OMIM # 607379) [Tsilchorozidou et al., 2004; Zirn et al., 2012]. *NF2* is located just upstream of *SMARCB1.* Zirn et al. [2012] have put forward monitoring recommendations for children with r(22), including neurological evaluation and brain imaging, though these are specifically designed to assess for NF2 [Zirn et al., 2012]. This tumorigenic mechanism has also been described for other ring chromosomes, including neurofibromatosis type 1 (NF1, OMIM# 162270) and ring chromosome 17 and Wilms tumor (OMIM# 194070) and ring chromosome 11 [Havlovicova et al., 2007]. In each case, the oncogenic mechanism was confirmed in a fashion similar to the method we describe. These individuals continued to accumulate lesions with age,

consistent with ongoing, dynamic somatic change, though this finding is based on a small number of patients [Tsilchorozidou et al., 2004, Havlovicova et al., 2007].

To our knowledge, this is the first reported case of a patient with a constitutional ring chromosome receiving radiation. The therapeutic goals of proton-beam radiation therapy are to cause cell death in the area of the tumor resection bed (or tumor if surgical resection is incomplete) to prevent recurrence. This therapeutic mechanism takes advantage of the intrinsic differences in how malignant and healthy cells repair damage, with malignant cells doing so more slowly than surrounding healthy cells. However, mitosis of a ring chromosome can be chaotic and delayed. The patient initially tolerated radiation therapy well. She developed radiation necrosis within a similar timeframe seen in other patients with AT/RT and radiation complications on the same therapeutic protocol (unpublished data). What differed was that the radiation necrosis in our patient continued to progressively worsen: within six months she was profoundly disabled; within 12 months she was unable to handle her own secretions; and within 18 months she was ventilator dependent. While it is biologically plausible that a ring chromosome may compromise tissue regeneration, information is insufficient to draw a conclusion. The progression and severity of her radiation necrosis could have been due to the location of her radiation necrosis, independent of an underlying chromosomal anomaly. Outcomes data in patients with a constitutional ring chromosome receiving radiation therapy would be helpful to assess if a constitutional ring chromosome is a risk factor for complications of radiation therapy.

In conclusion, we confirm an alternative diagnostic oncogenic mechanism in patients with r(22) and AT/RT and identify a potentially important subgroup of patients with AT/RT. Medical genetics consultation should be considered in all patients with AT/RT [Eaton et al., 2011]. Up to 35% of patients with AT/RT have rhabdoid tumor predisposition syndrome due to a germline pathogenic variant in *SMARCB1*, which has important prognostic and familial implications [Kordes el al., 2010]. All patients with PMS should have a limited karyotype to evaluate for r(22). Additional research is warranted to assess if this tumorigenic mechanism has therapeutic and prognostic implications.

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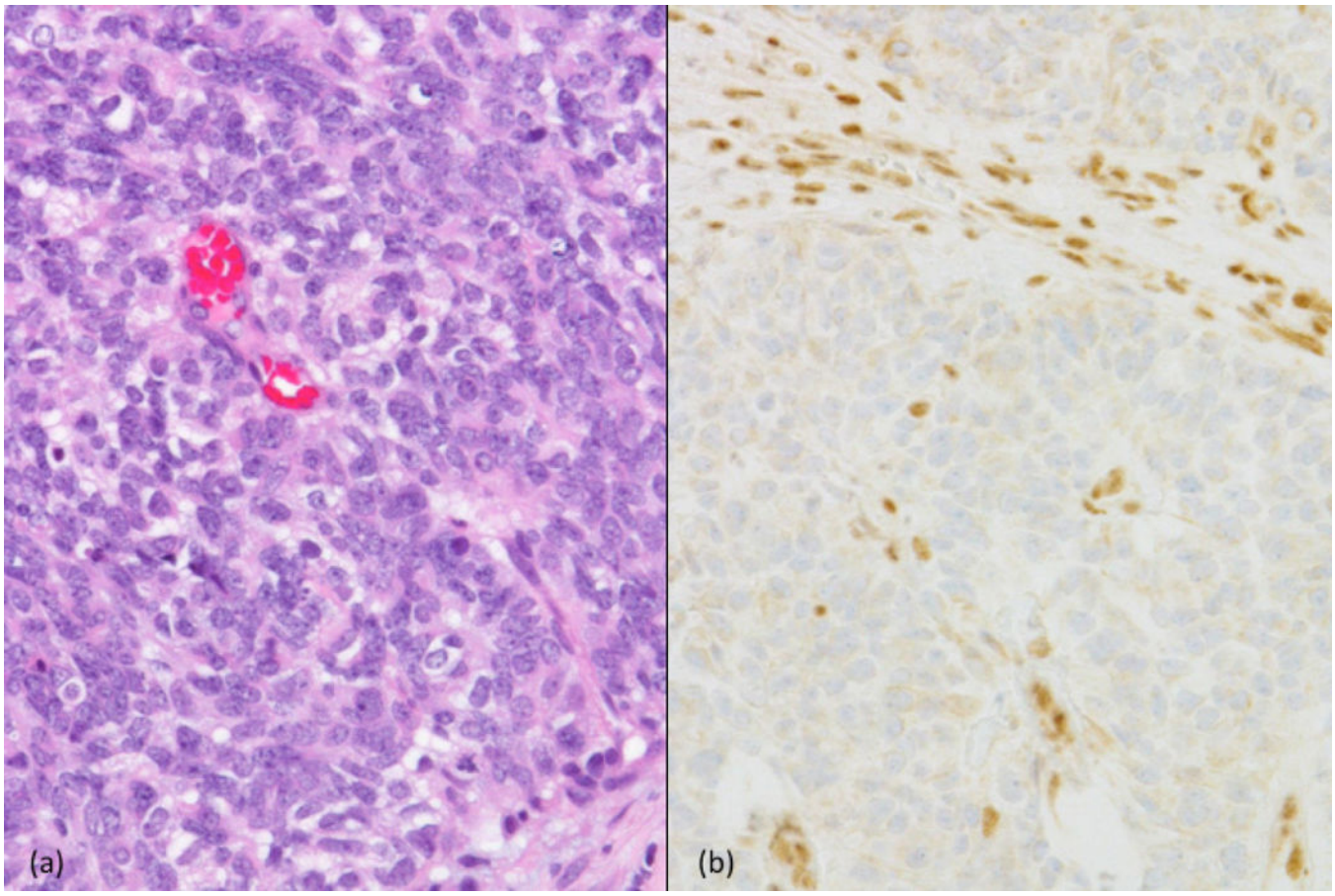

FIG. 1.

Pathologic analysis of tumor tissue: (a) H&E staining of neoplastic cells display the typical primitive small round blue cell appearance. Rare cells have eccentric nuclei and eosinophilic cytoplasm characteristic of rhabdoid morphology. (b): By SMARCB1/INI-1 immunohistochemical staining, the tumor cells demonstrate a loss of nuclear immunoreactivity; endothelial, stromal, and inflammatory cells retain normal nuclear staining.

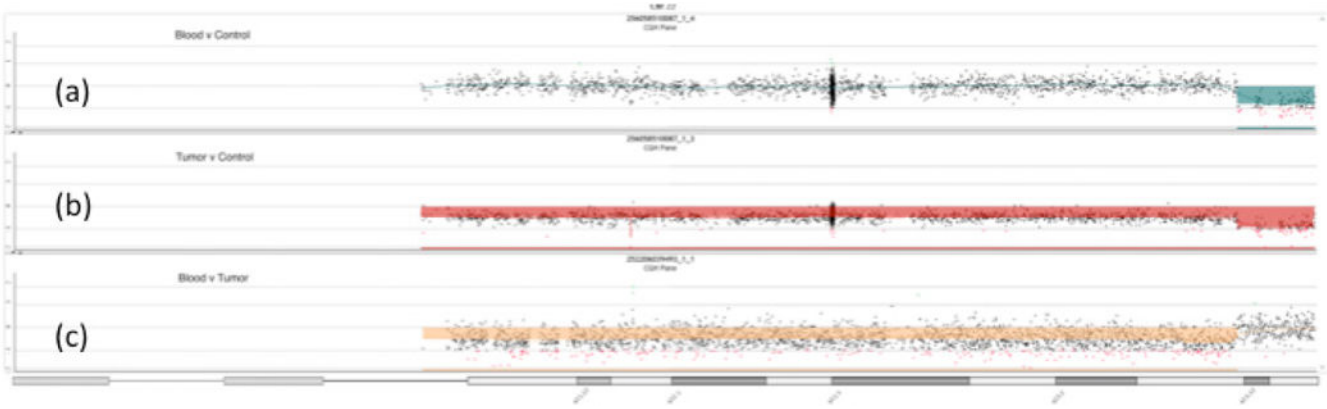

FIG. 2.

Chromosomal microarray comparing normal control to (a) peripheral blood and (b) patient tumor. Plot (c) compares the patient's peripheral blood to tumor. Patient tumor and blood samples confirm a 3.1-Mb terminal deletion, 22q13.3q13.3, consistent with the patient's known diagnosis of Phelan-McDermid syndrome. Mosaic monosomy 22 is seen in tumor tissue but absent in peripheral blood (b and c).