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BRIEF REPORT

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Constitutional balanced translocations involving *SMARCB1*: A rare cause of rhabdoid tumor predisposition syndrome

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Abstract

Rhabdoid Tumor Predisposition Syndrome 1 (RTPS1) confers an increased risk of developing rhabdoid tumors and is caused by germline mutations in *SMARCB1*. RTPS1 should be evaluated in all individuals with rhabdoid tumor and is more likely in those with a young age at presentation (occasionally congenital presentation), multiple primary tumors, or a family history of rhabdoid tumor or RTPS1. Proband genetic testing is the standard method for diagnosing RTPS1. Most known RTPS1-related *SMARCB1* gene mutations are copy number variants (CNVs) or single nucleotide variants/indels, but structural variant analysis (SVA) is not usually included in the molecular evaluation. Here, we report two children with RTPS1 presenting with atypical teratoid/rhabdoid tumor (ATRT) who had constitutional testing showing balanced chromosome translocations involving *SMARCB1*. Patient 1 is a 23-year-old female diagnosed with pineal region ATRT at 7 months who was found to have a *de novo*, constitutional t(16;22)(p13.3;q11.2). Patient 2 is a 24-month-old male diagnosed with a posterior fossa ATRT at 14 months, with subsequent testing showing a constitutional t(5;22)(q14.1;q11.23). These structural rearrangements have not been previously reported in RTPS1. While rare, these cases suggest that structural variants should be considered in the evaluation of children with rhabdoid tumors to provide more accurate genetic counseling on the risks of developing tumors, the need for surveillance, and the risks of passing the disorder on to future children. Further research is needed to understand the prevalence, clinical features, and tumor risks associated with RTPS1-related constitutional balanced translocations.

KEYWORDS
balanced translocation, rhabdoid tumor predisposition syndrome, SMARCB1

1 | INTRODUCTION

Rhabdoid Tumor Predisposition Syndrome 1 (RTPS1, MIM# 609322) is an autosomal dominant syndrome caused by germline *SMARCB1* pathogenic variants predisposing to rhabdoid tumors, typically of the CNS or kidney, which usually develop in the first 4 years of life.[1] RTPS1 accounts for an estimated 85%–95% of RTPS cases.[2] Rhabdoid tumor predisposition syndrome 2 (RTPS2, MIM# 613325) is caused by germline *SMARCA4* pathogenic variants and accounts for an estimated 4%–15% of cases.[2,3] In RTPS1, the germline pathogenic variant represents the first of the two alterations in *SMARCB1* required for rhabdoid tumor formation. Tumor *SMARCB1* gene

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testing (typically sequencing and deletion/duplication analysis) is the gold standard to guide RTPS1 evaluation, whereby two *SMARCB1* alterations are first identified in tumor tissue, followed by targeted testing in a germline sample.[1,4]

The majority of known RTPS1-related *SMARCB1* germline variants are copy number variants (CNVs) (typically partial or whole gene deletions), followed by nonsense, frameshift, and splice site variants.[4,5] Structural variants, including reciprocal balanced and unbalanced translocations involving the *SMARCB1* locus at chromosome band 22q11.23, have been described somatically in rhabdoid tumors in isolated case reports; however, to date, none of these alterations have been reported as germline in origin.[6–14] Current tumor and germline *SMARCB1* evaluation typically does not include structural variant analysis (SVA) and, therefore, could miss such alterations.

In this study, we report two children with atypical teratoid/rhabdoid tumors (ATRT) and constitutional balanced chromosome translocations disrupting *SMARCB1*, consistent with a diagnosis of RTPS1.

2 | MATERIALS AND METHODS

Sequencing and analysis were performed for patient 2 as previously described at St. Jude Children's Research Hospital.[15] Briefly, DNA and RNA from the formalin-fixed, paraffin-embedded (FFPE) tumor specimen were subjected to whole exome sequencing (WES) and transcriptome sequencing (RNA-Seq), respectively. The patient's germline DNA from peripheral blood was also used for WES and whole genome sequencing (WGS). The TruSeq Exome Enrichment Kit (Illumina) was employed for creating libraries from tumor and germline DNA samples for WES, while the TruSeq DNA LT PCRFree Sample Kit (Illumina) was used for WGS of germline DNA. For RNA-Seq, only the patient's tumor RNA was utilized, and the sample library was generated using the TruSeq Stranded Total RNA LT Kit (Illumina). Sequencing of the libraries was performed using HiSeq and NextSeq instruments, following a 2× 126 base pair paired-end protocol and SBS technology (Illumina). The aim was to achieve a coverage depth of 45× for 65% of bases in the WES data and 15% of bases in the RNA-Seq data in the tumor sample. For the RNA-Seq analysis, the obtained reads were aligned to the human reference genome (GRCh37) using the STAR aligner.[16] Structural variation calling was performed using CICERO,[17] which uses local assembly techniques to predict fusion events. CICERO considers factors such as allele frequency, matching length, repetitive mapping, and reading frame during the analysis.[17]

3 | CASE PRESENTATIONS

Patient 1 is currently 23 years old. At 7 months of age, she was diagnosed with a pineal region tumor and underwent subtotal resection of the tumor. A diagnosis of non-metastatic pineoblastoma was made and she underwent treatment on the PBTC01 protocol at St. Jude Children's Research Hospital with focal RT and adjuvant systemic and intrathecal chemotherapy. She developed a new metastatic lesion in the right frontal lobe at ∼1.5 years of age (Figure 1A). Tumor resection demonstrated densely packed cells with hyperchromatic, irregular nuclei, and indistinct nucleoli (Figure 1B). Some of the cells had a small amount of eccentric eosinophilic cytoplasm. The tumor cells showed strong cytoplasmic reactivity for vimentin and focal staining with epithelial membrane antigen, which had a membrane and a dot-like perinuclear pattern of staining. There was focal positivity for neuron-specific enolase, S-100 protein, and glial fibrillary acidic protein. The stains for neurofilament protein, synaptophysin, desmin, smooth muscle actin, CD99 (013), cytokeratin, and leukocyte common antigen were negative. Ki67 stain showed a markedly high proliferative index. Although there were no overt cytologic rhabdoid features, this undifferentiated small cell neoplasm with epithelial membrane antigen positivity suggested a morphologically atypical variant of ATRT. A constitutional karyotype revealed a t(16;22)(p13.3;q11.2) balanced translocation with probable disruption of *SMARCB1* in all cells

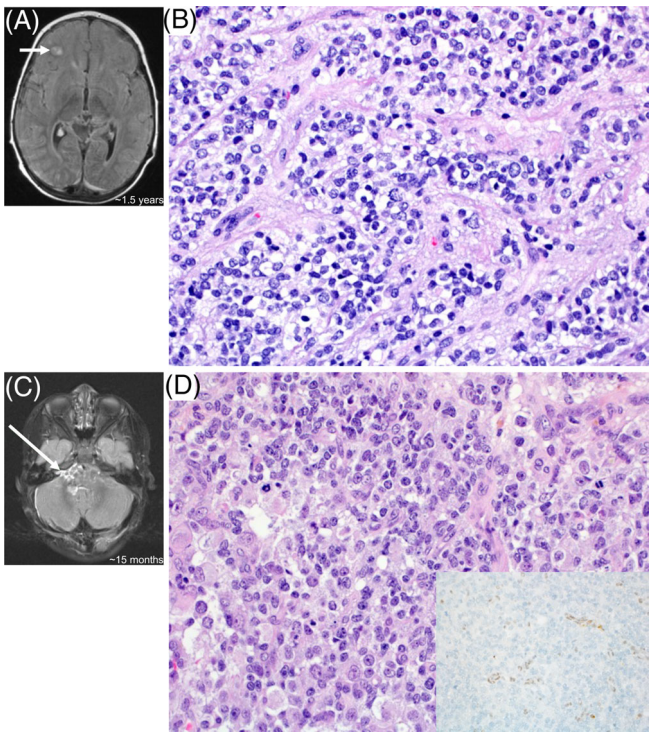


FIGURE 1 (A) Axial plane brain MRI T2-weighted- Fluid-Attenuated Inversion Recovery (FLAIR) performed on patient 1 at ∼1.5 years showing a metastatic lesion in the right frontal lobe white matter (indicated with white arrow). (B) The hematoxylin and eosin (H&E) section shows a hypercellular embryonal tumor with nuclear hyperchromasia and readily apparent mitotic activity. (C) Axial plane brain MRI with T2-weighted-FLAIR performed in patient 2 at ∼15 months of age showing a posterior fossa mass (white arrow). (D) The H&E section from patient 2 shows a hypercellular embryonal tumor. The tumor cells demonstrate variable cytologic features, ranging from small tumor cells with hyperchromatic nuclei to large tumor cells with vesicular chromatin, prominent nucleoli, and abundant pale cytoplasm. Mitotic figures are abundant. The figure inlet shows immunoreactivity for INI1 is lost among the tumor cells but retained in the non-neoplastic endothelial cells.

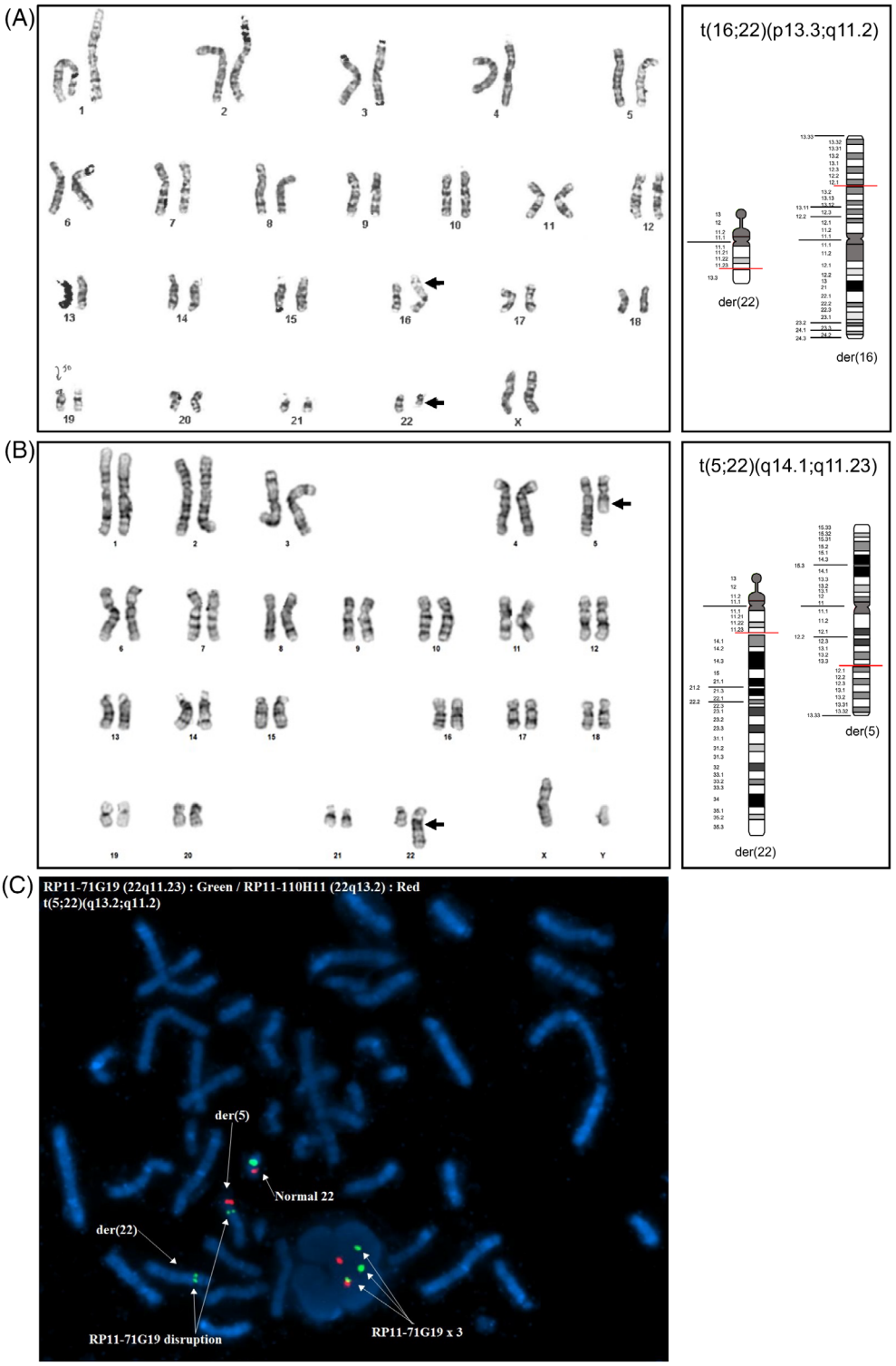


FIGURE 2 (A) Representative phytohaemagglutinin (PHA)-stimulated peripheral blood (PB) karyogram from patient 1 displaying an abnormal karyotype with a t(16;22)(p13.3;q11.2) identified in all 20 cells. An ideogram showing the derivative (der) chromosomes 16 and 22 is shown to the right of the karyogram with the breakpoint indicated with a red line. (B) Representative PHA-stimulated PB karyogram from patient 2 displaying an abnormal karyotype with a t(5;22)(q14.1;q11.23) identified in all 20 cells. An ideogram showing the derivative (der) chromosomes 5 and 22 is shown to the right of the karyogram with the breakpoint indicated with a red line. (C) Representative PB fluorescence in situ hybridization (FISH) demonstrating disruption of the RP11-71G19 probe (green) at 22q11.23 encompassing *SMARCB1* caused by t(5;22)(q14.1;q11.23) translocation. Metaphase spread on left: normal 22 chromosomes with 1 red control probe (22q13.2) and 1 green probe (arrow Normal 22). RP11-71G19 probe disruption is shown via arrows pointing to the derivative 22, der (22), and derivative 5, der (5), each containing partial RP11-71G19 probe and indicating *SMARCB1* disruption. Interphase spread at center: two normal red probes and three green probes reflecting the *SMARCB1* disruption.

analyzed (Figure 2A). Given the presence of a constitutional abnormality along with the tumor recurrence in a young patient with an aggressive course, a diagnosis of a morphologic variant of ATRT was favored. Since immunohistochemical stain for INI-1 or BRG-1 were not available at the time, these confirmatory tests could not be carried out on the tumor samples.

She subsequently had multiple tumor recurrences and underwent several different treatment modalities. Tumor sample obtained at one of such recurrences at 5 years of age was found to have features compatible with ATRT and IHC stain for INI1 showed nuclear positivity in the non-neoplastic endothelial cells but was entirely absent in the tumor cells, confirming the diagnosis of ATRT.

Tumor and treatment-related morbidities include significant learning impairment (global developmental delay, mildly deficient cognitive function [IQ 50–69]), bilateral sensorineural hearing loss requiring hearing aids, hypothyroidism, adrenal insufficiency requiring hydrocortisone,

left eye exotropia and cataract, reduced visual acuity, and irregular menses. At 19 years, she was evaluated in the cancer predisposition clinic. Her family history was overall unremarkable, with no evidence of rhabdoid tumors, early-onset cancers, birth defects, known genetic conditions, learning disabilities, or recurrent miscarriages. Previous chromosome analysis on peripheral blood had revealed t(16;22)(p13.3;q11.2) balanced translocation. A chromosome microarray (CMA) (Ambry Genetics) was performed on the proband to evaluate for possible CNVs involving *SMARCB1* given the known (16;22)(p13.3;q11.2) translocation. CMA showed a normal result (1-22,X)x2, with no significant CNVs involving the *SMARCB1* gene and no regions of homozygosity. NGS sequence analysis (custom HaloPlex™ probe library, University of Alabama at Birmingham [UAB] Medicine) for *SMARCA4* and *SMARCB1* and deletion/duplication analysis by MLPA for *SMARCB1* were negative. The patient was unavailable for subsequent constitutional *SMARCB1* fluorescence in situ hybridization (FISH) testing. Constitutional karyotypes were performed for the proband's parents and showed a normal chromosome complement with no evidence of the (16;22)(p13.3;q11.2) balanced translocation, suggesting this was a *de novo* germline event in the proband.

Patient 2 is currently a 3-year-old male. He was diagnosed with posterior fossa ATRT at 14 months of age, following 2 months of persistent and worsening vomiting that was accompanied by a significant decline in his gross motor and language functioning, including difficulties walking and reduced babbling. He underwent a computed tomography (CT) scan and magnetic resonance imaging (MRI) (Figure 1C) of the head, which revealed a large posterior fossa mass and associated obstructive hydrocephalus. He underwent subtotal resection and external ventricular drain (EVD) placement. Tumor histology showed a hypercellular tumor with readily apparent mitotic activity and areas of necrosis (Figure 1D). Rhabdoid tumor cells were noted occasionally. Nuclear INI1 immunoreactivity was lost in the neoplastic cells (Figure 1D **inlet**). Many tumor cells were positive for MITF, suggesting that this tumor may be in the ATRT-Tyrosinase (TYR) molecular group. DNA methylation and copy number analysis were performed at St. Jude, and the tumor was classified as an atypical teratoid/rhabdoid tumor, subclass TYR (calibrated score 0.93/1.00, threshold 0.90). The array also showed a region of somatic copy number loss at chromosome bands 22q11.1-q13.33, including the *SMARCB1* locus. Tumor NGS testing (whole exome sequencing and whole transcriptome RNA sequencing) was performed as described above, and the structural variant pipeline showed a *SMARCB1* truncation after exon 3 (NM_003073.4) due to a t(5;22)(q14.1;q11.23) [chr22:24135876(+)::chr5:79086793(+), hg19/hGRC37].

The patient's postoperative course was complicated by posterior fossa syndrome. Cerebrospinal fluid (CSF) analysis was negative for tumor cells. A staging MRI of the brain and spine demonstrated a residual tumor in the posterior fossa and a highly suspicious metastatic lesion in the lumbar spinal area. He was consented for chemotherapy on a non-protocol treatment plan as per SJYC07,[18] as he was not eligible for any clinical trials. He went on to complete four cycles of induction therapy (high-dose systemic methotrexate, vincristine, cisplatin, and cyclophosphamide) followed by focal proton irradiation (30 fractions to a total dose of 54 cGy) to the tumor bed in the posterior fossa. Post-therapy MRI scans showed four new probable metastatic lesions in the lower spinal cord, and the patient was treated with second-line non-protocol therapy, including cyclophosphamide and topotecan, completing 6 cycles as per the SJYC07 consolidation portion. Due to further disease progression, he was then treated with tazemetostat, followed by systemic combination ifosfamide, carboplatin, etoposide (ICE) chemotherapy. He eventually received 36 Gy craniospinal proton irradiation and has been without disease at 6-months post-completion of all his therapy. Due to tumor infiltration and secondary to tumor resection, the patient continues to exhibit significant cranial nerve deficits. This has caused right vocal cord paralysis, weakness on the right side of his face resulting in an inability to close his right eye, and hearing difficulties.

The patient was seen in the cancer predisposition clinic. His available family history was unremarkable for features suggestive of a hereditary cancer-related condition, including RTPS1. A 72-hour constitutional karyotype study performed on peripheral blood from the proband at St. Jude showed a t(5;22)(q14.1;q11.2) in all 20 cells analyzed (Figure 2B). Cytogenetic testing for the *SMARCB1* locus was performed at UAB Cytogenetics Laboratory and also showed the t(5;22)(q14.1;q11.23) with sequential metaphase FISH demonstrating disruption of the *SMARCB1* locus probe at 22q11.23 (Figure 2C). The patient's mother had a normal karyotype, but his father was unavailable for testing, so the *de novo* status of this balanced translocation could not be confirmed. The patient was placed on RTPS1 tumor screening plan, which added an abdominal ultrasound every 3 months to his regular brain imaging. On a subsequent abdominal ultrasound, a right lobe liver lesion was identified and confirmed to be a fibroinflammatory liver lesion without rhabdoid morphology via ultrasound-guided core biopsy.

4 | DISCUSSION

Chromosomal rearrangements are structural changes in the genome that can be copy number neutral (balanced, e.g., translocations, inversions, and insertions) or change the dosage of chromosomal regions (unbalanced, e.g., deletions, duplications, or amplifications). CNVs are a major source of genetic diversity, accounting for about 5% of the genome, and vary widely in size.[19] Structural variants (SVs) that occur in functionally important regions of the genome, particularly those that change the open reading frame of coding genes, can impair gene function and, in the case of cancer predisposition genes, raise the risk of cancer.[19] Cancer predisposition genes are primarily tumor suppressors that require the loss of both alleles (one germline and one somatic hit) to manifest a clinical phenotype, such as tumor formation. While most heritable disease-causing mutations can be picked up by sequencing, deletion/duplication analysis, and other modalities, rarely balanced SVs may be present, which can be missed by these techniques. Advances in sequencing technologies (such as whole genome) have enabled the detection of previously undetectable SVs, broadening the spectrum of known variation in many heritable conditions.

However, techniques such as conventional karyotype and FISH, are still highly useful and cost-effective for identifying larger balanced translocations, which are primarily non-recurrent, as in the cases reported here.

ATRTs are heterogeneous tumors that can be difficult to distinguish based solely on histopathology,[20] as in the case of Patient 1, who was initially diagnosed with a pineoblastoma. Rhabdoid cells are the sole or predominant histopathological finding in only a minority of cases.[21] They can be extremely sparse or even absent in some cases, as in the cases described in this report. Whole transcriptome sequencing and DNA methylation profiling can be useful diagnostic aids and can be used to classify tumors into consensus molecular groups, including ATRT-TYR, ATRT-SHH, and ATRT-MYC.[22,23] These molecular groups align with differences in certain clinical characteristics, including patient age, tumor localization, and the pattern of tumor genetic alterations.[22,23] The posterior fossa tumor from Patient 2 was profiled using similar methods and found to classify with the ATRT-TYR group, which has upregulation of genes in the melanosomal pathway. Localization of tumors in this group is predominantly infratentorial, and typically occurs in the youngest age group (Patient 2 presented at 14 months; the median is 12 months).[23] *SMARCB1* is usually inactivated through a mutation in one allele and whole or partial chromosome 22 loss in the second allele, as in this case (constitutional translocation disrupting *SMARCB1* and then partial loss of chromosome 22). Further research is needed to understand the prevalence, clinical features, and tumor risks associated with RTPS1-related constitutional balanced translocations.

The gold standard for evaluating RTPS1 is through tumor *SMARCB1* gene testing, which typically involves sequencing and deletion/duplication analysis. The first step in this process is identifying alterations in tumor tissue, which is then followed by targeted testing in the germline sample for all patients with rhabdoid tumor.[1] The risk of germline mutations ranges from 26% to 41% in *SMARCB1*-deficient tumors[4,18,24–26] and for RTPS2, may be considerably higher in *SMARCA4*-deficient tumors (6/7 or ~86%).[27] One study found that *de novo* mutations account for two-thirds of all germline mutations.[4] Unaffected adult carriers[4,26,28,29] as well as parental gonadal mosaicism[26,30–32] are well documented in RTPS1. Most known RTPS1-related *SMARCB1* germline variants are CNVs, with single nucleotide variants and indels being slightly less common.

Large deletions and duplications that disrupt *SMARCB1* have been identified in several patients with RTPS1 in the literature. Rhabdoid tumors presenting in patients with additional syndromic features such as dysmorphic features, cleft palate, congenital cardiovascular defects, and developmental delay may be suggestive of 22q11.2 distal deletion syndrome (MIM# 611867), which is distinct from DiGeorge syndrome (DGS; MIM# 188400) and velocardiofacial syndrome (VCFS; MIM# 192430).[33–35] While the previously discussed testing modalities confirm a diagnosis in the majority of cases, there are still cases with SMARCB1-deficient tumors where the underlying biallelic mutations cannot be identified. With advances in molecular technologies, including the widespread utilization of next-generation sequencing and introduction of optical genome mapping (OGM) and long-read sequencing, additional rarer mechanisms of structural gene disruption have been identified including retrotransposon insertions (SINE-VNTR-Alu, subfamily E [SVA-E] element and AluY element).[36,37] However, it is important to note that structural variant analysis (conventional karyotype and NGS-based structural variant analysis) is not typically included in tumor and germline evaluations, nor is it considered standard of care based on current recommendations.[1] Though there have been rare case reports of translocations involving the *SMARCB1* locus at 22q11.23 in rhabdoid tumors, none of these translocations have been shown to be germline, to our knowledge. The two cases reported here had a very early presentation of ATRT, raising the risk of germline alterations, and were appropriately referred for genetic screening. These novel cases suggest that structural variants should be considered in the evaluation of children with rhabdoid tumors to provide more accurate genetic counseling for patients and families on risk for additional primary tumors, appropriate tumor surveillance, and recurrence risk for future children.

CONFLICT OF INTEREST STATEMENT

The authors have no relevant conflicts of interest.

DATA AVAILABILITY STATEMENT

All of the relevant patient variant/alteration and phenotype data used in this study have been provided in the manuscript or figures.

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