

RESEARCH ARTICLE

Novel *SMARCA4::VEZF1* Rearrangement in Pediatric Sarcomas

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Received: 5 March 2026 | **Revised:** 21 April 2026 | **Accepted:** 27 April 2026

Keywords: molecular pathology | pediatric sarcoma | *SMARCA4::VEZF1* fusion | SWI/SNF (BAF) chromatin-remodeling complex | *VEZF1* rearrangement

ABSTRACT

The *SMARCA4* gene encodes a key ATPase subunit of the SWI/SNF (BAF) chromatin-remodeling complex, which plays an essential role in regulating transcription and cellular differentiation. Loss-of-function alterations of *SMARCA4* are common in various human cancers, including sarcomas; however, rare *SMARCA4* fusion events, presumably resulting in gain of function, have also been reported. We present two pediatric soft-tissue sarcomas harboring a novel, recurrent in-frame fusion between *SMARCA4* and *VEZF1* (Vascular Endothelial Zinc Finger 1), a transcription factor important for vascular development and angiogenesis. The predicted fusion protein contains the N-terminal QLQ protein interaction domain of *SMARCA4* and preserves most of *VEZF1*'s C2H2 zinc-finger DNA-binding domains. Interestingly, another component of the BAF complex, SS18, has also been reported to be fused to *VEZF1* in uterine sarcoma. We propose that fusion of BAF complex components to *VEZF1* leads to aberrant recruitment of chromatin-remodeling activity to *VEZF1* target loci, resulting in altered chromatin architecture, dysregulated *VEZF1*-dependent transcription, and tumorigenesis.

1 | Introduction

The mammalian SWI/SNF (mSWI/SNF, BAF) chromatin-remodeling complex is a conserved ATP-dependent machinery assembled from 12 to 15 subunits encoded by more than 29 genes [1]. It uses the energy of ATP hydrolysis to reposition, eject, or restructure nucleosomes, thereby regulating access of transcription factors and DNA repair proteins to DNA and controlling transcription, cell-cycle progression, differentiation, and DNA-damage repair [2]. mSWI/SNF complexes are classified into three related subtypes: canonical BAF (cBAF), non-canonical BAF (ncBAF/GBAF), and polybromo-associated BAF (PBAF). Each subtype contains a mutually exclusive ATPase

core, either *SMARCA4* (BRG1) or *SMARCA2* (BRM), along with a conserved scaffold composed of *SMARCB1* (INI1/BAF47), *SMARCC1* (BAF155), and *SMARCC2* (BAF170) [3].

Consistent with its central role in SWI/SNF function, the *SMARCA4* gene, located on chromosome 19p13.2, acts as a tumor suppressor by regulating transcription and facilitating DNA repair, in part through interacting with proteins like *BRCA1* [4, 5]. Genomic alterations of *SMARCA4* are found in approximately 5%–7% of human cancers, including ovarian cancer, non-small cell lung cancer, gastrointestinal cancer, thoracic sarcomas, and undifferentiated uterine sarcomas [6]. These alterations either lead to loss of *SMARCA4* expression through

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truncating mutations, deletions, or rearrangements, or to retained but dysfunctional protein through missense mutations that exert dominant-negative effects [6, 7].

The Vascular Endothelial Zinc Finger 1 (*VEZF1*) gene encodes a transcription factor containing six C2H2-type zinc finger motifs. *VEZF1* is essential for vascular development, as genetic ablation in mouse models results in embryonic lethality with profound defects in vascular remodeling and endothelial integrity [8]. At the cellular level, *VEZF1* regulates endothelial proliferation, migration, and angiogenic activity through transcriptional control of genes involved in cell-cycle progression and extracellular matrix remodeling, including *STMN1*, *EDN1*, and matrix metalloproteinases [9]. In addition, *VEZF1* exerts epigenetic control by maintaining global DNA methylation through regulation of the *de novo* DNA methyltransferase *Dnmt3b*, linking *VEZF1* to broader chromatin and gene-expression programs during vascular morphogenesis [10].

Besides its role in blood vessel biology, *VEZF1* has also been recognized as a significant transcription factor related to cancer. *VEZF1* is often overexpressed and promotes malignant transformation by activating oncogenic pathways involved in cell adhesion, invasion, and stemness. In hepatocellular carcinoma, the stabilization and O-GlcNAcylation of *VEZF1* enhanced its transcriptional activity, leading to the upregulation of pro-tumorigenic targets such as *PAQR4* and *TNS1*, thereby promoting tumor growth and metastasis [11]. In urothelial bladder cancer, *VEZF1* functioned as a tumor suppressor by directly elevating the levels of the E3 ligase *SPOP*, leading to decreased inflammatory and stemness signals driven by *STAT3* [12]. In addition, *VEZF1* fusions have been reported in various soft-tissue sarcomas. To date, seven cases of sarcomas with *VEZF1* fusion have been described in the literature [13–16], although the functional significance of these fusions remains unknown (Table 1).

In this report, we describe two rare pediatric sarcomas harboring a novel *SMARCA4::VEZF1* fusion. Given prior reports showing that another BAF complex component, *SS18*, can also be fused to *VEZF1*, it is likely that BAF chromatin-remodeling activity contributes to tumorigenesis in *SMARCA4::VEZF1*-driven tumors.

2 | Materials and Methods

2.1 | Patients

Two pediatric patients with soft tissue sarcomas were retrospectively identified from the pathology archives. Clinical data, including age at diagnosis, tumor site, treatment, and follow-up information, were retrieved from medical records. Tumor specimens were formalin-fixed and paraffin-embedded (FFPE) following surgical resection and used for subsequent histopathological and molecular investigations. All available histological slides were independently reviewed by experienced pathologists. Histologic assessment included evaluation of tumor morphology, mitotic activity, and the presence or absence of necrosis. The diagnosis was made according to the current

World Health Organization (WHO) Classification of Soft Tissue and Bone Tumors.

2.2 | Immunohistochemistry

FFPE tissue sections (4 μm thick) were prepared, and immunohistochemistry (IHC) staining was performed using a standardized automated platform (Benchmark GX, Ventana Medical Systems, USA). While the panel varied by cases, key antibodies evaluated included BRG1, BRM, ARID1A, CD34, pan-TRK, Desmin, SMA, and ALK. Positivity was defined as any unequivocal staining in tumor cells, and the distribution (e.g., diffuse, focal) and intensity were independently assessed by two pathologists. Nuclear staining intensity for BRG1, BRM, and ARID1A was evaluated using a three-tier system: Positive, strong nuclear staining present in >90% of tumor cells, with intensity comparable to internal control cells; complete loss, defined as definite clean absence of staining in the nuclei of tumor cells, with preserved nuclear staining in internal control cells; partial loss, defined as a mixed population of tumor cells, with a subset showing loss of nuclear staining while others retain nuclear expression.

2.3 | Next-Generation Sequencing (NGS)

Genomic DNA and total RNA were extracted from 10-μm FFPE tissue sections using the AllPrep DNA/RNA FFPE Kit (Qiagen, Germany). Targeted DNA NGS was conducted using a 638-gene panel (SANO Medical Laboratories, China) with concurrent genome-wide SNP analysis. For RNA-seq, libraries were prepared using the VAHTS Universal V8 RNA-seq Library Prep Kit (Vazyme, China), including rRNA depletion, RNA fragmentation, reverse transcription, adapter ligation, and PCR amplification. The final library was sequenced on an Illumina NextSeq 550DX platform, and gene fusions were analyzed using STAR-Fusion and Arriba software. This method provides comprehensive transcriptome coverage and was used to screen for known and novel tumor-related chromosomal rearrangements, including gene fusions.

2.4 | Reverse Transcriptase PCR and Sanger Sequencing

Total RNA was reverse-transcribed into cDNA using SuperScript IV Reverse Transcriptase (Thermo Fisher Scientific, USA) with random primers. A nested PCR approach was used to detect the *SMARCA4::VEZF1* fusion transcript. The first PCR round using primers: *SMARCA4-F* (5'-CAGATGCCAACGCTACCTCC-3') and *VEZF1-R* (5'-GTCACCTGGCATAGCTGTGGT-3'); and the second round using primers: *SMARCA4-Fnest* (5'-CTCG GTGTCCGCAACAGG-3') and *VEZF1-Rnest* (5'-TGCCC GAGGAAGATGTAGTG-3'). Both PCR conditions were as follows: 95°C for 3 min, followed by 30 cycles of 95°C for 30 s, 60°C for 60 s, and 72°C for 60 s. The PCR product was analyzed by agarose gel electrophoresis and confirmed by Sanger sequencing.

TABLE 1 | Clinicopathologic and immunophenotypic features of *VEZF1* rearranged tumors.

Case no.	1	2	3	4	5	6	7
References	Current study	Current study	Tsuda et al. [14]	Benini et al. [13]	Hodgson et al. [15]	Hodgson et al. [15]	Machadon et al. [16]
Fusion gene	<i>SMARCA4::VEZF1</i>	<i>SMARCA4::VEZF1</i>	<i>EWSR1::VEZF1</i>	<i>EWSR1::VEZF1</i>	<i>SS18::VEZF1</i>	<i>SS18::VEZF1</i>	<i>SS18::VEZF1</i>
Age/sex	0 year/F	12 years/M	12 years/F	17 years/M	42 years/F	39 years/F	53 years/F
Tumor location	Right hand	Right popliteal fossa	Calf (extraskeletal)	Right thigh (soft tissue)	Uterus	Uterus	Uterus
Tumor size (cm)	2.0 × 1.5 × 1.0	4.5 × 3.5 × 2.8	N/A	27.0	N/A	N/A	N/A
Treatment	Multiple surgical excisions, chemotherapy	Surgical excision, chemotherapy, radiotherapy	N/A	Chemotherapy, wide surgical resection	Morcellated myomectomy	Myomectomy, then hysterectomy	Surgical excision
Recurrence	Yes, multiple local recurrences	Yes	N/A	No	Yes	Yes, in abdominal scar	N/A
Metastasis	No	Yes, pulmonary metastases	N/A	No	Yes	Yes	N/A
Histological features	Monomorphic oval to short spindle cells in fascicles; moderate-to-severe atypia; conspicuous mitoses; infiltrates nerve.	Polymorphous: epithelioid, round, and spindle cells with rhabdoid features; myxoid/chondromyxoid stroma with osseous metaplasia.	Primitive round cells with increased myxoid and fibrous stroma.	High-grade spindle and round cell sarcoma; “marble-like” pattern; heterologous osteo- and rhabdomyosarcomatous differentiation.	Spindled and ovoid cells with foamy cytoplasm, irregular hyperchromatic nuclei, and prominent nucleoli in a myxoid matrix.	Recurrence: Infiltrative nodules and sex cord-like formations of uniform spindle cells in abundant myxoid stroma.	The tumor exhibited alternating hypocellular/hyalinized and hypercellular areas, composed of a monomorphic proliferation of spindle, ovoid, and epithelioid cells arranged in sheets.

(Continues)

TABLE 1 | (Continued)

Case no.	1	2	3	4	5	6	7
References	Current study	Current study	Tsuda et al. [14]	Benini et al. [13]	Hodgson et al. [15]	Hodgson et al. [15]	Machadon et al. [16]
Key immunohistochemical profile	Partial loss: BRG1, BRM, ARID1A. Positive: pan-TRK, CD34, CD99 (partial). Negative: Desmin, SMA, Myogenin, S100, ALK, EMA, pan-Cytokeratin (AE1/AE3).	Retained expression: BRG1, BRM, ARID1A. Positive: Desmin, SMA (focal), S100 (focal), CD34 (focal), EMA (partial), CD99 (partial), ALK (partial). Negative: Myogenin, pan-TRK, pan-Cytokeratin (AE1/AE3).	Negative: CD99.	Positive: Desmin (focal), Myogenin (focal), SOX10 (focal). Partial loss: H3K27me3. Negative: S100, CD99, pan-Cytokeratin (AE1/AE3).	Positive: Desmin (diffuse), Cyclin D1 (patchy), ER (patchy/diffuse), TLE1 (patchy).	Positive: Desmin (diffuse), CD10 (patchy), Cyclin D1 (patchy), ER (patchy/diffuse), TLE1 (patchy).	Positive: CD10, CD34, TLE1, estrogen and progesterone receptors. Negative: h-caldesmon, desmin, SMA, smoothelin, myosin, cyclin D1, S100, ALK, EMA, pan-TRK, and SS18-SSX.
Initial histological diagnosis	Infantile Fibrosarcoma	Undifferentiated Sarcoma; Sclerosing Epithelioid Fibrosarcoma	Round Cell Sarcoma	Malignant Peripheral Nerve Sheath Tumor (MPNST)	Symptomatic “Fibroids”	Myxoid Leiomyoma	Uterine myxoid mesenchymal tumor
Mitotic rate	10-15/10 HPF	3-15/10 HPF	N/A	N/A	1/10 HPF	20/10 HPF (recurrence)	N/A

Abbreviations: F, female; M, male; NA, not applicable or available.

3 | Results

3.1 | Clinical Information

Case 1 is a 4-month-old female infant who presented with a congenital mass at the base of the right thumb, which grew slowly to $2.0 \times 1.5 \times 1.0$ cm at diagnosis (Figure 1A). The tumor was excised, appearing margin-negative grossly but microscopically positive. Histology showed spindle to ovoid cells arranged in fascicles and diffuse sheets (Figure 1B,C). The tumor exhibited moderate to severe cytological atypia and a mitotic rate of 10–15 mitoses per 10 high-power fields (HPF), with infiltration into surrounding tissues and peripheral nerves. Notably, tumor necrosis was absent. IHC showed focal positivity for CD34 and pan-TRK (Figure 1D,E), negativity for S100 (Figure 1F), and partial loss of

core BAF proteins BRG1 (SMARCA4), BRM (SMARCA2), and ARID1A (Figure 1G–I). The initial diagnosis was infantile fibrosarcoma. The patient underwent repeated resections for local recurrences within 12 months. Following further recurrence, adjuvant chemotherapy was administered using a VAI regimen (vincristine, dactinomycin, and ifosfamide) in combination with pirarubicin, followed by an additional surgical resection. At the most recent follow-up, 5 months after the latest surgery, the patient was alive without evidence of tumor.

Case 2 is a 12-year-old male who presented with a $4.5 \times 3.5 \times 2.8$ cm mass in the right popliteal fossa, which was surgically resected via proximal right femoral tumor resection with prosthesis replacement. Histology revealed predominantly epithelioid morphology with focal rhabdoid, spindle,

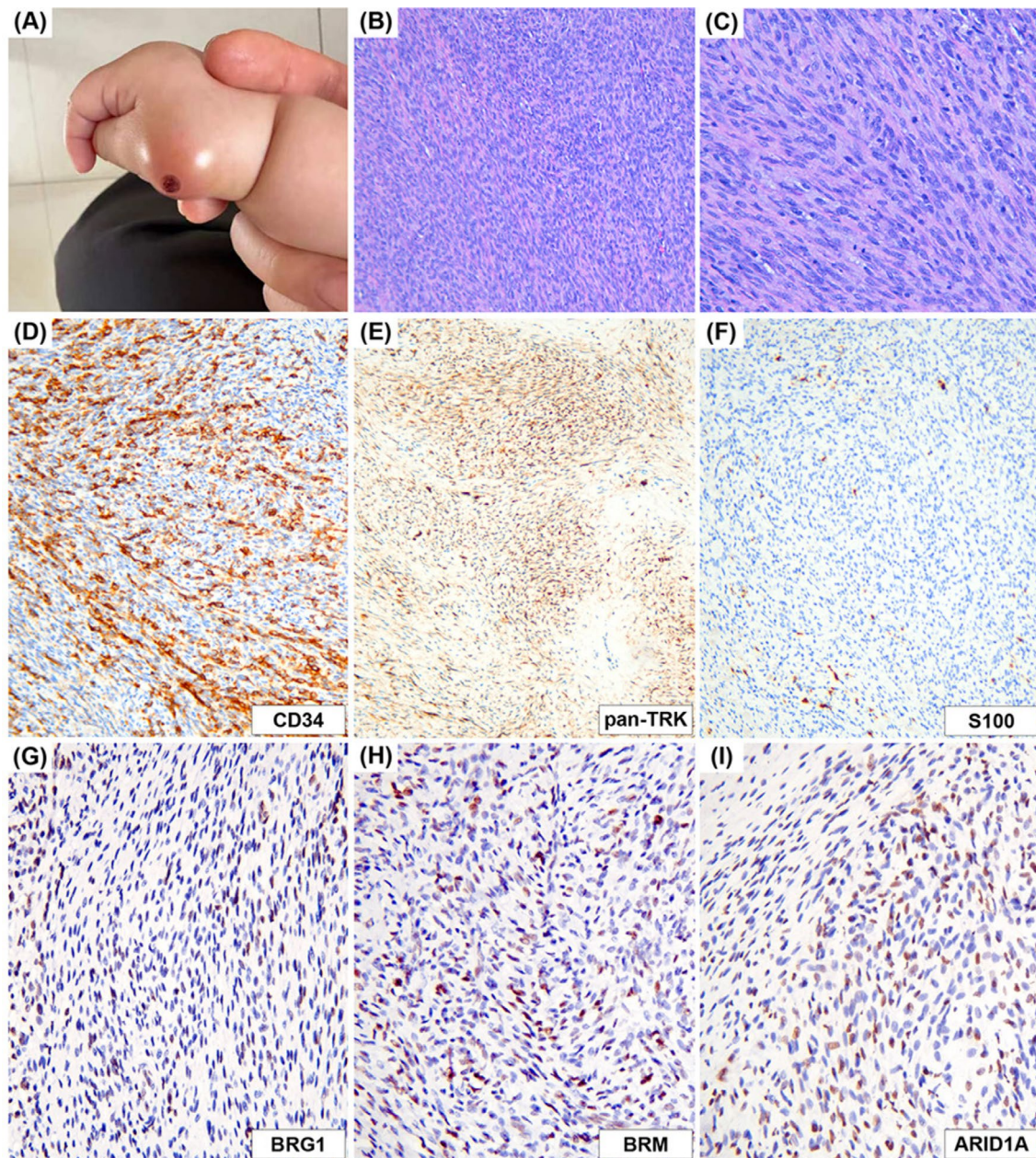


FIGURE 1 | Gross image, hematoxylin and eosin (H&E) staining, and immunohistochemistry (IHC) of Case 1 sarcomas harboring a *SMARCA4::VEZF1* fusion. (A) Clinical photograph of the tumor at diagnosis. (B, C) H&E showing fascicles of spindle cells with abundant mitotic activity. (D–I) IHC positive for CD34 and Pan-TRK, negative for S100, and partial loss of BAF complex subunits (BRG1, BRM, and ARID1A).

and small round cell features in a variably myxoid to sclerotic stroma, mimicking sclerosing epithelioid fibrosarcoma (Figure 2A–C). Assessment of the available material demonstrated overt coagulative necrosis and a mitotic rate of 3–15 mitoses per 10 HPF. IHC was focally positive for Desmin, SMA, and ALK (Figure 2D–F), with retained expression of BRG1, BRM, and ARID1A (Figure 2G–I). Following initial surgical resection, local recurrence was observed 20 months later. In addition, chest CT suggested pulmonary metastases, revealing multiple solid and ground-glass nodules in the lower lobes of both lungs. The patient subsequently received chemotherapy with a regimen consisting of vindesine, cyclophosphamide, pirarubicin, and nedaplatin combined with radiotherapy. He responded well and has since remained cancer-free for 3 years

following the completion of chemotherapy. The complete Clinicopathologic and immunophenotypic features for both cases are summarized in Table 1.

3.2 | Molecular Analysis

Genomic profiling of both tumors was performed using DNA and RNA isolated from the surgical specimens. Targeted DNA NGS covering 638 cancer-related genes, together with genome-wide SNP analysis, revealed no mutations, deletions, rearrangements, copy number variations, or loss of heterozygosity. However, transcriptome analysis identified a novel, in-frame *SMARCA4::VEZF1* fusion in both tumors. The *VEZF1*

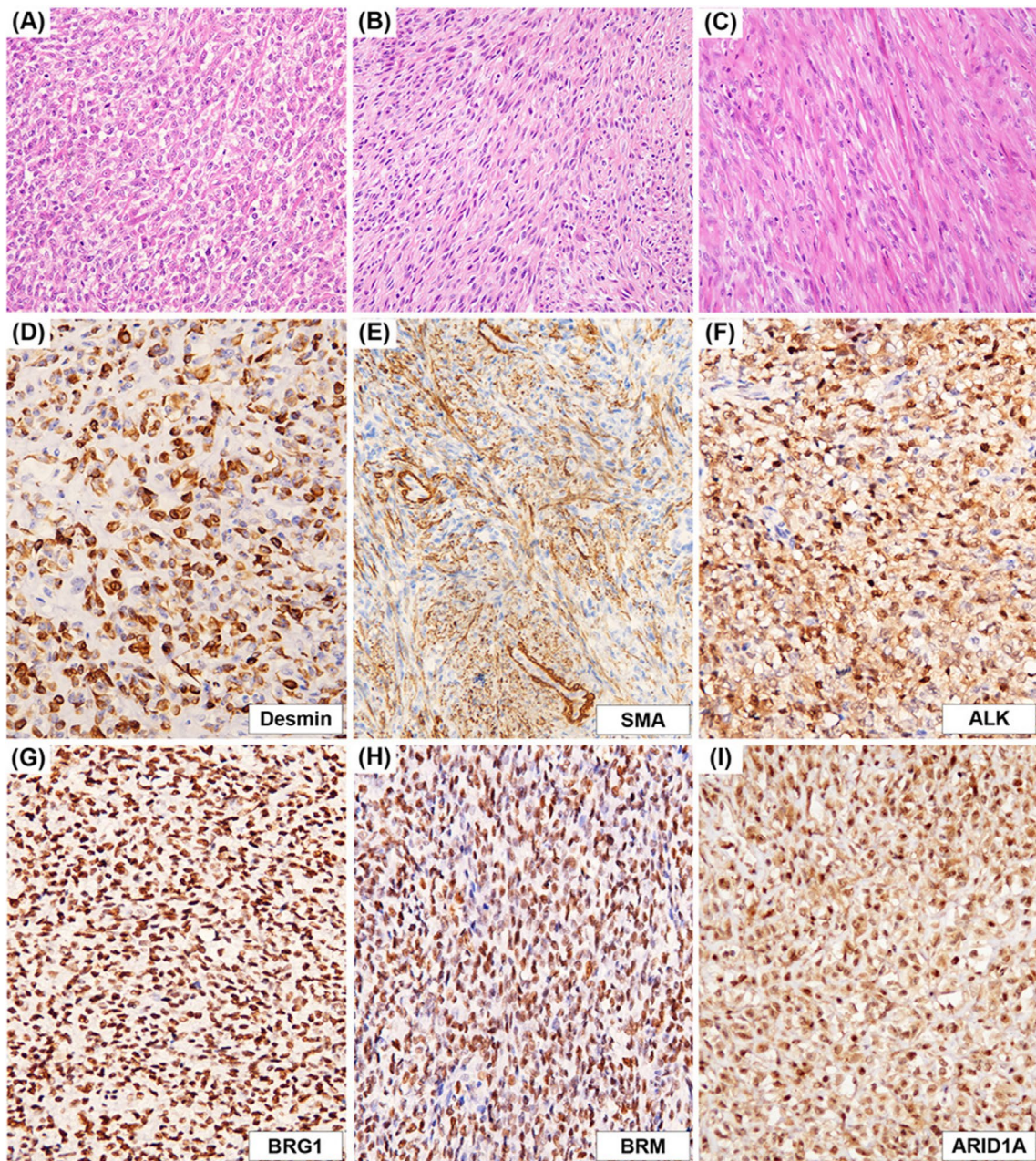


FIGURE 2 | Histopathological and immunophenotypic features of Case 2 sarcoma harboring a *SMARCA4::VEZF1* fusion. (A–C) H&E showing a tumor with predominantly epithelioid morphology, with focal spindle and small round cell features, and sclerotic stroma. (D–I) IHC positive for Desmin, SMA, ALK, and retained expression of BRG1, BRM, and ARID1A.

breakpoint was identical in both cases at exon 2, whereas the *SMARCA4* breakpoints differed, localizing to exon 4 in case 1 and exon 5 in case 2 (Figure 3A). The predicted fusion protein retained most of *VEZF1*, including five of its six C2H2 DNA-binding domains, fused to the QLQ protein–protein interaction domain of *SMARCA4* (Figure 3A). The fusion transcript was further confirmed in case 1 by RT-PCR using *SMARCA4*- and *VEZF1*-specific primers, followed by direct Sanger sequencing (Figure 3B). Unfortunately, no material was available to confirm the fusion in case 2.

4 | Discussion

SMARCA4 is mainly considered a tumor suppressor, and loss-of-function alterations in *SMARCA4*, together with those in another BAF complex component, *SMARCB1*, define a group of tumors characterized by BAF complex deficiency [17]. These tumors occur across a wide spectrum of epithelial and mesenchymal malignancies arising in diverse anatomic sites, including the central nervous system, kidney, thoracic cavity,

gastrointestinal and pancreatobiliary tract, sinonasal region, gynecologic organs, and soft tissues [17–21]. *SMARCA4*/*SMARCB1*-deficient tumors are typically poorly differentiated or undifferentiated, exhibit aggressive clinical behavior, and are often resistant to conventional chemotherapy, resulting in an overall poor prognosis [6].

Although *SMARCA4* rearrangements have been observed in a variety of tumors, they are generally believed to result in gene truncation and loss of function rather than gain of function [6]. For example, one reported case described an undifferentiated sarcoma in a 15-year-old female harboring an out-of-frame *SMARCA4::THOPI* fusion together with a splice-site mutation in *SMARCA4*, leading to biallelic *SMARCA4* inactivation and complete loss of *SMARCA4* protein expression [22].

Although *VEZF1* is not considered a common cancer driver gene, its overexpression has been observed in several malignancies and has been shown to promote malignant cellular behavior. To date, five cases of *VEZF1* rearrangements have been reported. Three involved *SS18::VEZF1* fusions, all in adult

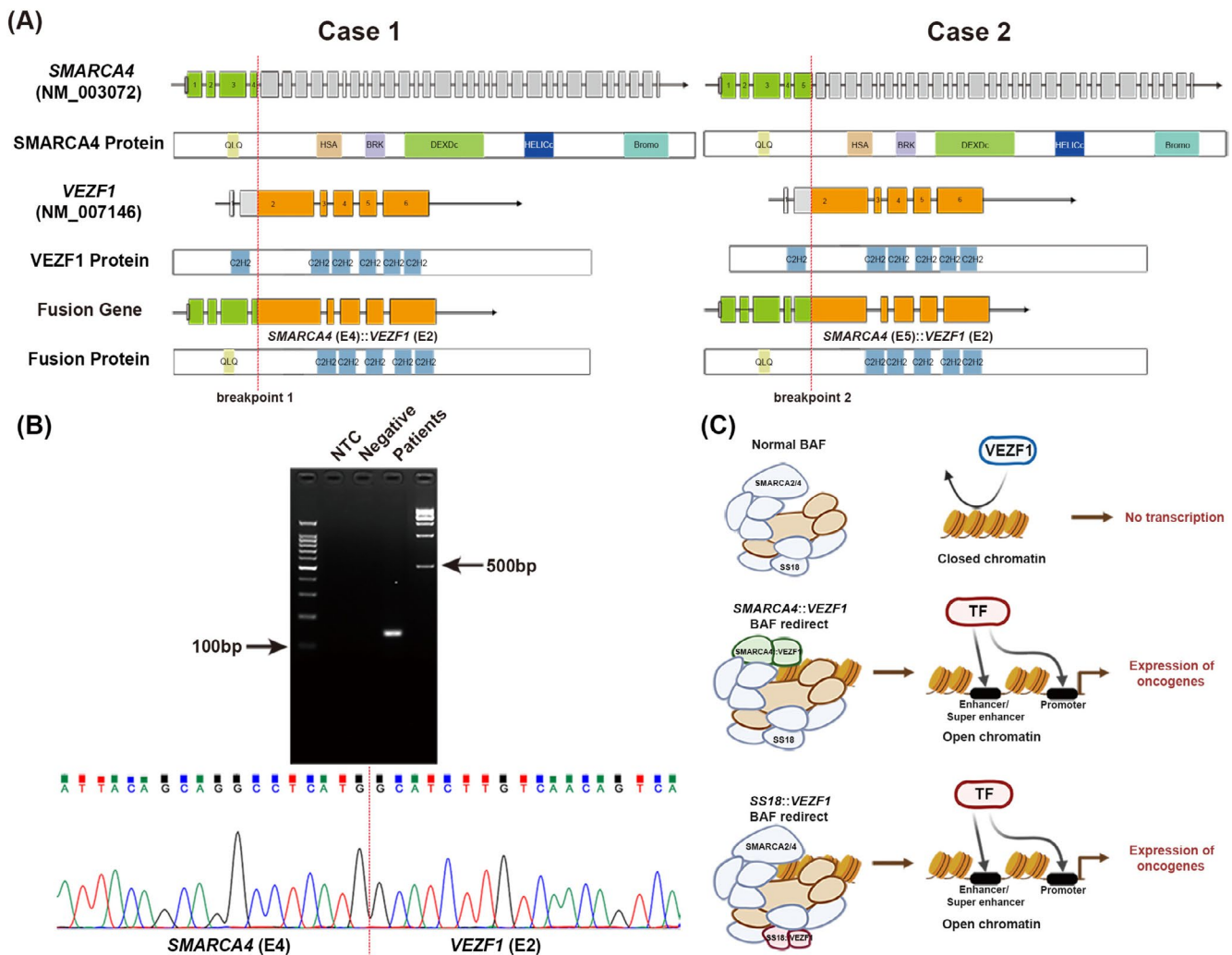


FIGURE 3 | Genomic characterization of the *SMARCA4::VEZF1* fusion. (A) Schematic illustration of the exons and functional domains of wild-type *SMARCA4*, *VEZF1*, and the *SMARCA4::VEZF1* fusion. (B) Validation of the *SMARCA4::VEZF1* fusion by RT-PCR and Sanger sequencing in case 1. NTC, no-template control. (C) Hypothetical oncogenic mechanism in *VEZF1*-rearranged sarcomas: The BAF chromatin-remodeling complex is recruited to *VEZF1*-target genes, leading to chromatin-opening and aberrant expression of *VEZF1*-regulated genes.

patients, and two harbored *EWSR1::VEZF1* fusions, both in pediatric patients. All three *SS18::VEZF1* cases arose in the uterus [15, 16], whereas the two *EWSR1::VEZF1* tumors were located in the right thigh and calf, respectively [13, 14]. The reported histopathologic diagnoses of the *SS18::VEZF1* tumors included uterine myxoid mesenchymal tumor, myxoid leiomyoma, and symptomatic fibroids. In contrast, the *EWSR1::VEZF1* tumors were classified as malignant peripheral nerve sheath tumor (MPNST) and round cell sarcoma (Table 1). Our two cases, both harboring *SMARCA4::VEZF1* fusions, occurred in pediatric patients and were histologically diagnosed as infantile fibrosarcoma and sclerosing epithelioid fibrosarcoma, respectively. Despite sharing the same *SMARCA4::VEZF1* fusion, the two tumors displayed divergent histology and immunophenotype, likely reflecting genetic promiscuity. Alternatively, the phenotypic differences may be attributable to their distinct *SMARCA4* breakpoints. The loss of exon 5 in the Case 1 fusion may create a structurally unstable protein with a dominant-negative effect that promotes complex degradation, while its retention in Case 2 could allow for a more stable complex, resulting in the different BAF expression patterns. All reported *VEZF1* fusions share a common breakpoint within exon 2 of *VEZF1*, regardless of fusion partners, preserving most of the *VEZF1* coding sequence. This recurrent structural feature suggests that retention of *VEZF1* functional domains is critical for the oncogenic activity of *VEZF1* fusion proteins.

Diagnostically, *SMARCA4::VEZF1* fusion sarcomas may present with pediatric onset, aggressive local infiltration, rapid recurrence, and striking morphological heterogeneity. Histologically, these tumors can exhibit a mixture of epithelioid, spindle, and focal rhabdoid cells within a diverse myxoid or sclerotic stroma arranged in a lobular architecture. Immunophenotypically, these tumors demonstrate multidirectional differentiation (e.g., CD34, Desmin, SMA) and the expression of receptor tyrosine kinases (RTKs, including pan-TRK and ALK), coupled with a highly unusual partial or retained expression of SWI/SNF proteins (BRG1, BRM, ARID1A) (Table 1). This distinctive combination of aggressive behavior, complex morphology, and discordant SWI/SNF staining should raise suspicion for a *SMARCA4::VEZF1* fusion-associated sarcoma, necessitating molecular testing for definitive confirmation. While assessing *VEZF1* expression by immunohistochemistry would be diagnostically valuable, a highly specific, clinically validated commercial *VEZF1* antibody for FFPE tissue is currently unavailable, precluding its evaluation in this study. The future development and validation of robust *VEZF1* antibodies will be crucial to further characterize the protein expression profiles and diagnostic utility of these tumors.

An interesting observation is that 2 of the reported fusion partners of *VEZF1* (*SMARCA4* and *SS18*) are core components of the SWI/SNF (BAF) chromatin-remodeling complex. Because of its central role in gene-expression, it is not surprising that BAF alterations are found in many cancers, with deregulation observed in approximately one-quarter of all malignancies. Among its components, *ARID1A* is the most frequently mutated. Our laboratory was the first to report *ARID1A* alterations in breast and lung cancers [23]. Subsequent studies have shown *ARID1A* mutations in a wide spectrum of tumor types. Most BAF alterations result in loss of function, disrupting

the balance between the chromatin-opening BAF and the chromatin-closing Polycomb (PRC2/EZH2) complexes and leading to the downregulation of tumor suppressor genes. In this study, we describe an alternative oncogenic mechanism: the mislocalization of BAF through fusion of a BAF subunit with the DNA-binding protein *VEZF1*. This fusion likely re-directs BAF activity to *VEZF1* target sites, thereby activating *VEZF1*-regulated genes (Figure 3C).

In summary, we describe two pediatric patients harboring a novel *SMARCA4::VEZF1* fusion. We propose that fusion of a BAF complex component to *VEZF1* leads to aberrant recruitment of chromatin-remodeling activity to *VEZF1* target loci, resulting in altered chromatin architecture, dysregulated *VEZF1*-dependent transcription, and tumorigenesis. Further functional studies are warranted to define the molecular consequences of this fusion, including the genes it dysregulates and the downstream oncogenic signaling pathways it activates.

Author Contributions

L.F., R.M., and S.X. designed the project. L.F., C.Z., and F.Y. drafted the manuscript. L.F., R.M., S.X., and D.Z. performed pathological diagnoses and collected clinical and pathological data. L.F. and R.M. evaluated clinical data. C.Z. and S.C. conducted molecular analyses. All authors contributed to data interpretation and participated in discussions of the results.

Funding

The authors have nothing to report.

Ethics Statement

This study was conducted on retrospectively collected, anonymized patient samples and associated clinical data. All procedures were carried out in accordance with institutional guidelines and the principles outlined in the Declaration of Helsinki. Identifiable personal information was not included in the analysis.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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