SMARCA4 inactivation defines a subset of undifferentiated uterine sarcomas with rhabdoid and small cell features and germline mutation association

Douglas I. Lin ^{1,*}, Justin M. Allen¹, Jonathan L. Hecht², Jonathan .K. Killian¹, Nhu T. Ngo¹, Claire Edgerly¹, Eric A. Severson¹, Siraj M. Ali¹, Rachel L. Erlich¹, Shakti H. Ramkissoon^{1,3}, Jo-Anne Vergilio¹, Jeffrey S. Ross ^{1,4} and Julia A. Elvin¹

1. Foundation Medicine Inc., Cambridge, MA. 2. Beth Israel Deaconess Medical Center, Boston, MA. 3. Wake Forest Comprehensive Cancer Center and Department of Pathology, Wake Forest School of Medicine, Winston-Salem, NC. 4. Upstate Medical University, Syracuse, NY.

A rare subset of aggressive *SMARCA4*-deficient uterine sarcomas has been recently proposed, with only a limited number of cases having been previously described. Here, we identify 16 additional cases of *SMARCA4*-deficient uterine sarcoma from the database of a large, CLIA-certified and CAP-accredited, reference molecular laboratory, and we expand on their clinicopathological and genomic features. Median patient age was 49 years (range 32-70). Most tumors were aggressive with distant metastasis. *SMARCA4*-deficient uterine sarcoma demonstrated predominantly rhabdoid or large epithelioid cells with abundant cytoplasm, but also had varying degrees of small cell and spindle cell morphology. Tumors were microsatellite stable and exhibited no other or only few co-occurring genomic alterations by comprehensive genomic profiling. We discovered one patient, who developed *SMARCA4*-deficient uterine sarcoma at age of 55, had a germline *SMARCA4* mutation, whose daughter had previously died of small cell carcinoma of the ovary, hypercalcemic type, at the age of 32. Our data support the notion that *SMARCA4* inactivation is the driver oncogenic event of a morphologically and molecularly distinct form of uterine sarcoma. Identification of *SMARCA4*-deficient uterine sarcomas may be clinically important due to their aggressive behavior, germline association and emerging targeted therapies.

Figure 2. Morphological features of *SMARCA4*-deficient uterine sarcoma.

Figure 1. Mutational landscape of *SMARCA4* across our *SMARCA4*-deficient uterine sarcoma cohort.

n	Age	Submitting diagnosis	Size (cm)	Stage	LVI	LN	Ovary	Site	Procedure
1	48	Undifferentiated sarcoma	6	IB	NA	NA	NA	Uterus	Biopsy
2	51	Undifferentiated sarcoma	14	IIIC	Pos	Pos	Neg	Uterus	TLH BSO
3	63	Undifferentiated sarcoma	4	IV	Neg	Neg	Neg	Uterus	TLH BSO
4	52	Undifferentiated sarcoma	16	IV	Pos	Neg	Pos	Uterus	TLH BSO
5	43	Undifferentiated sarcoma	Unk	IV	NA	NA	NA	Liver	Biopsy
6	51	Undifferentiated sarcoma	10.5	IIIB	Pos	Neg	Neg	Uterus	TLH BSO
7	60	Undifferentiated sarcoma	12.9	IV	Pos	NA	Neg	Uterus	TLH BSO
8	49	Undifferentiated sarcoma	6	IIB	Pos	Neg	Pos	Uterus	TLH BSO
9	33	Undifferentiated sarcoma	6	IVB	Pos	NA	Neg	Uterus	TLH BSO
10	70	HG-ESS	3.7	IIIA	Neg	NA	Pos	Uterus	TLH BSO
11	52	Undifferentiated neoplasm	5.5	IV	Pos	Pos	Neg	Uterus	TLH BSO
12	44	Undifferentiated sarcoma	6.9	IIIC	Pos	Pos	Pos	Uterus	TLH BSO
13	38	Undifferentiated sarcoma	7	IV	Pos	Pos	Neg	Uterus	TLH BSO
14	55	Undifferentiated sarcoma	Unk	IV	NA	NA	Pos	Uterus	TLH BSO
15	45	Undifferentiated sarcoma	12.2	IB	Pos	NA	Neg	Uterus	TLH BSO
16	32	Uterine adenosarcoma	17.7	III	Pos	Pos	Neg	Uterus	TLH BSO

Table 1. Clinico-pathological features of *SMARCA4*-deficient uterine sarcoma.

Figure 3. Molecular features of *SMARCA4*-deficient uterine sarcoma following comprehensive genomic profiling demonstrating none or few co-alterations. Blue rectangle: homozygous gene deletion; black square: oncogenic truncating mutation; green square: oncogenic missense mutation, red rectangle: gene amplification.

Figure 4. Case #14 with germline *SMARCA4* mutation. A. Next generation sequencing identified a 1831C>T (NM_003072), Q611*, nonsense tumor mutation that was further confirmed to be germline by genetic testing. (B) Immunohistochemistry of the patient's tumor revealed loss of BRG1 (protein encoded by *SMARCA4*) in tumor cells with appropriate labeling of benign endometrial epithelium and benign stromal cells (with BRG1 only) as internal control.

* Contact: Douglas Lin, MD.-Ph.D, dlin@foundationmedicine.com