# Genomic Signatures and Clinicopathological Correlation in Uterine Smooth Muscle Tumors of Uncertain Malignant Potential, Leiomyosarcoma, and Leiomyoma with Bizarre Nuclei

Ying Liu[1], Jong T Kim[2], Fabiola Medeiros[2], Bonnie L Balzer[2] Eric Vail[2], Jianbo Song[2], Kevin Baden[2], Gaurav Khullar[2], David M Engman[2], Jean R Lopategui[2]

[1]Department of Pathology and Laboratory Medicine, University of California, Davis Medical Center, Sacramento, CA 958171

[2]Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA 90048

***Background:*** Differentiating uterine smooth muscle tumors of uncertain malignant potential (STUMP), atypical leiomyoma (LEIO), and leiomyosarcoma (LMS) is challenging. In addition, prognostic genomic biomarkers are not available for these entities. Using copy number variation (CNV) chromosomal microarrays (CMA), we investigated the genomic landscape of these tumors. Our goal was to identify genetic alterations in oncogenes and tumor suppressor genes and evaluate how these genomic signatures may correlate clinicopathologically in patients with STUMP, LEIO, and LMS.

***Design:*** We retrospectively reviewed the pathology and follow up on 20 patients, including 10 STUMP, 5 LMS, and 5 LEIO, and correlated with CMA result. For each patient sample, the results were filtered to only include 720 genes from the COSMIC 2 tier cancer gene census, causally implicated in cancer. The cases were grouped by tumor type (LMS, STUMP, LEIO) and subsequently the net frequency of gene gains and losses within each group was calculated. These lists were then filtered to include genes that were lost or gained only in LMS, only in STUMP, and only in LEIO.

***Results:*** The average age at diagnosis was 66 years for LMS, 50 years for LEIO and 44.9 years for STUMP. The average size of the dominant tumor for LMS was 8.5 cm, 7.3 cm for LEIO and 5.8 cm for STUMP. TSG loss was the predominant CNV in all STUMP. Four of 10 STUMP had a unique 1p loss. Similarly, in LMS, TSG loss was the predominant CNV (CBFB, CTCF, FAT1, KLF6, LARP4B and LRP1B). TP53 loss and gain of oncogenes were only observed in LMS. One case with high nuclear grade, increased mitotic count, and coagulative necrosis had a hybrid genomic fingerprint with loss of 1p only seen in STUMP and loss of TSG CBFB and CTCF also seen in LMS. 17 patients had follow-up ranging from 2 months to 108 months with an average of 37.6 months. Four of 5 LMS patients presented with distant metastases including one who died of the disease. No metastases or death was reported among the STUMP and LEIO patients.

## Fig 1. General Parameters of LMS, STUMP and LEIO

| Parameters | LMS | STUMP | LEIO |
|---|---|---|---|
| Total No. of Cases | 5 | 10 | 5 |
| Age, Mean (yr) | 66 | 44.9 | 50 |
| Tumor Size, Largest (cm) | 8.5 | 5.8 | 7.3 |
| Followup, Mean (Range) (mo) | 20.6 (13-29) | 46.1 (0~108) | 40.3 (0-60) |
| Metastasis | 4 | 0 | 0 |
| Dead With Disease | 1 | 0 | 0* |

* one case dead with colonic adenocarcinoma

## Fig 2. LMS Specific CNV Frequencies

| Location | Only lost in Leiomyosarcoma | Freq lost (out of 5 cases) | Function | Only Gained in Leiomyosarcoma | Freq gained (out of 5 cases) | Function |
|---|---|---|---|---|---|---|
| 17p13 | TP53 | 5 | TSG | SSX2 | 2 | OG |
| 10p11.2 | ABI1 | 3 | oncogene, fusion | SSX4 | 2 | OG |
| 16q22 | CBFB | 3 | TSG, fusion | ARAF | 1 | OG |
| 16q22.1 | CTCF | 3 | TSG | BIRC3 | 1 | OG |
| 4q35.2 | FAT1 | 3 | TSG | TFE3 | 1 | OG |
| 10p15 | GATA3 | 3 | oncogene, TSG | CRLF2 | 1 | OG |
| 10p15 | KLF6 | 3 | TSG | TNFRSF17 | 1 | OG |
| 10p15.3 | LARP4B | 3 | TSG | EIF1AX | 1 | |
| 13q14.1 | LCP1 | 3 | | ERG | 1 | OG |
| 2q21.2 | LRP1B | 3 | TSG | FAM47C | 1 | |
| | ACBR1 | <=2 | | FLCN | 1 | TSG |
| 19q13.2 | AKT2 | <=2 | OG | GATA1 | 1 | OG |
| Xq28 | ATP2B3 | <=2 | TSG | GRIN2A | 1 | TSG |
| Xq22.1 | BTK | <=2 | OG, TSG | KDM5C | 1 | TSG |
| 4q35.1 | CASP3 | <=2 | TSG | KDM6A | 1 | OG |
| 16q24.3 | CBFA2T3 | <=2 | TSG, fusion | OLIG2 | 1 | OG |

UCDAVIS HEALTH | Department of Pathology and Laboratory Medicine

CEDARS-SINAI®

## Fig 3. STUMP Specific CNV Frequencies

| Location | Only lost in STUMP | Freq (out of 10 cases) | Function | Only Gained in STUMP |
|---|---|---|---|---|
| 1p36.13 | ARHGEF10L | 4 | TSG | CDH11 |
| 1p36.11 | ARID1A | 4 | TSG, fusion | |
| 1p13.1 | ATP1A1 | 4 | oncogene, TSG | |
| 1p36.21 | CASP9 | 4 | TSG | |
| 1p12 | FAM46Cx | 4 | TSG | |
| 1p36.12 | ID3 | 4 | TSG | |
| 1p36.11 | MDS2 | 4 | | |
| 1p36.22 | MTOR | 4 | oncogene | |
| 1p12 | NOTCH2 | 4 | oncogene, TSG | |
| 1p13.2 | NRAS | 4 | oncogene | |
| 1p36.21 | PRDM2 | 4 | TSG | |
| 1p13.3 | RBM15 | 4 | | |
| 1p22.1 | RPL5 | 4 | TSG | |
| 1p36.13 | SDHB | 4 | TSG | |
| 1p36 | SPEN | 4 | TSG | |
| 1p13 | TRIM33 | 4 | TSG, fusion | |
| 5q31 | ARHGAP26 | 3 | TSG, fusion | |
| 15q21.1 | B2M | 3 | TSG | |
| 1p22 | BCL10 | 3 | TSG, fusion | |
| 13q31.3 | GPC5 | 3 | TSG | |
| 1p35 | LCK | 3 | oncogene, fusion | |
| 1p36.2 | PAX7 | 3 | fusion | |

## *Conclusions:*

- The results of this pilot study suggest that LMS display a unique loss of TP53, loss of other TSG, and gain of oncogenes.
- STUMP is associated with a unique loss of 1p and loss of TSG.
- High grade STUMP displays loss of CBFB and CTCF observed in LMS, in addition to 1p loss typically associated with STUMP.
- Additional studies with a larger cohort and longer clinical follow-up are needed to further ascertain genomic markers of biologic behavior in uterine smooth muscle tumors.

## *References:*

- Croce S., Ducoulombier A., Ribeiro A. et al. Genome profiling is an efficient tool to avoid the STUMP classification of uterine smooth muscle lesions: a comprehensive array-genomic hybridization analysis of 77 tumors. Mod. Pathol. 2018 May;31(5):816–828.
- Zhang, Q., Ubago, J., Li, L. et al. Molecular analyses of 6 different types of uterine smooth muscle tumors: Emphasis in atypical leiomyoma. Cancer. 2014 July;120: 3165-3177.