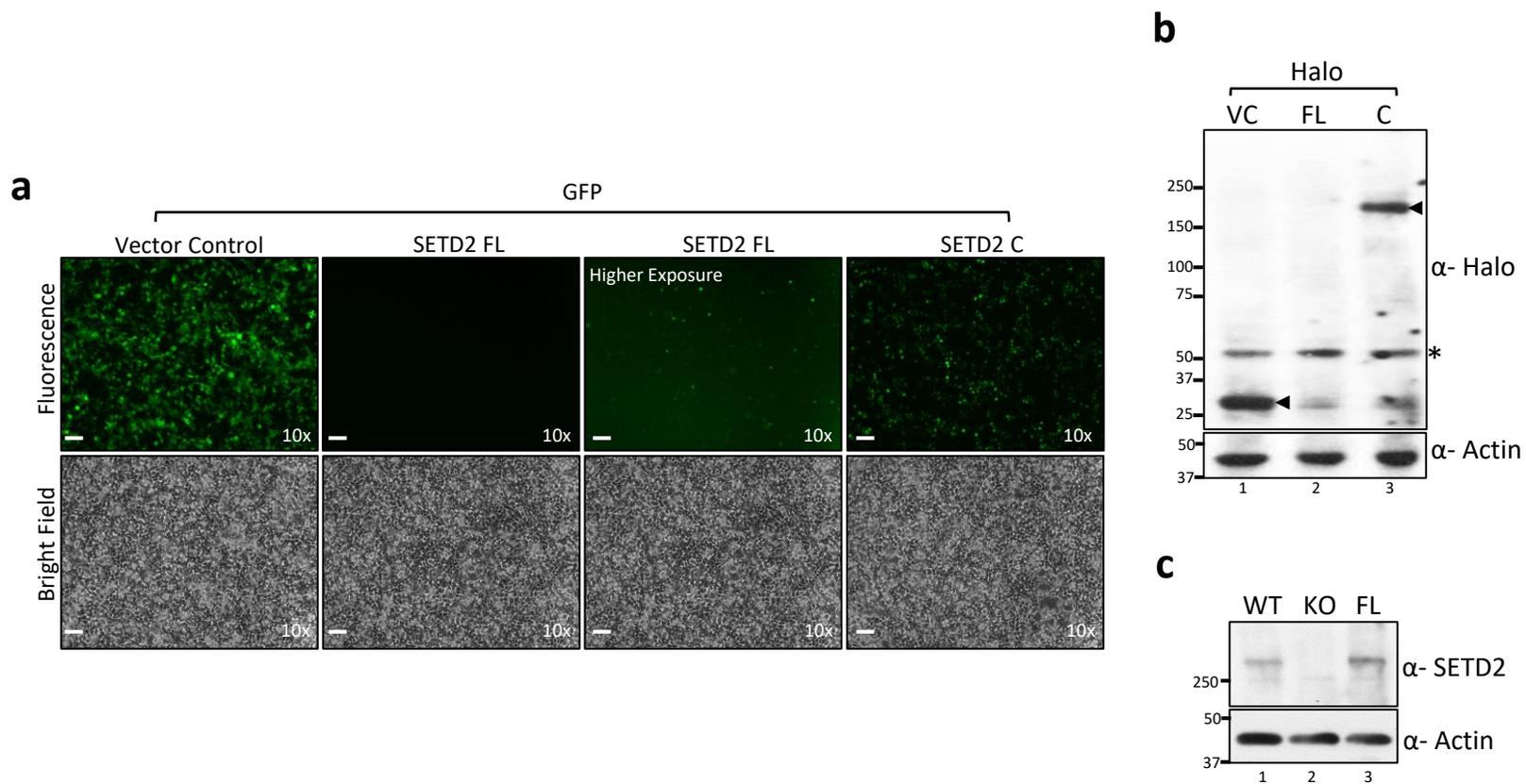
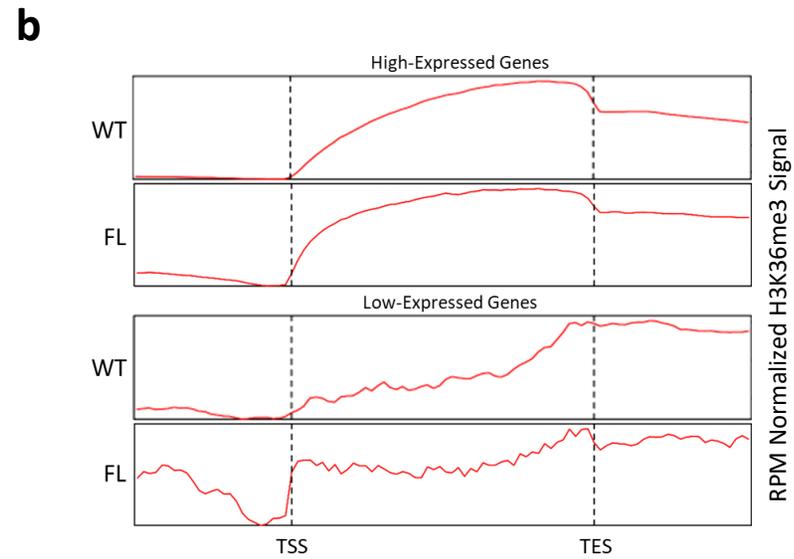
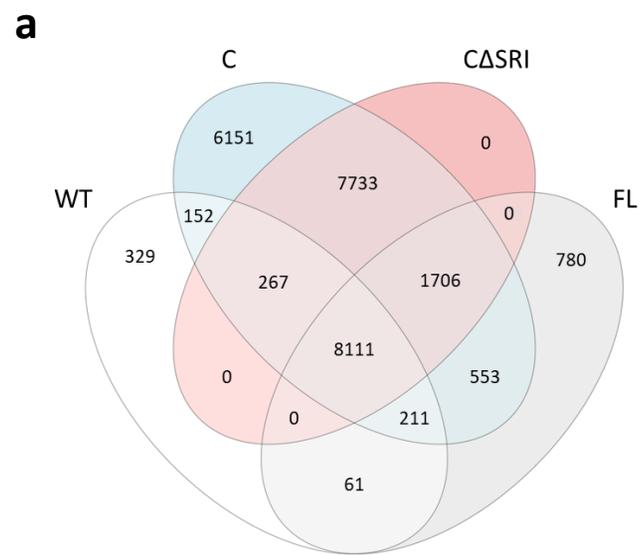


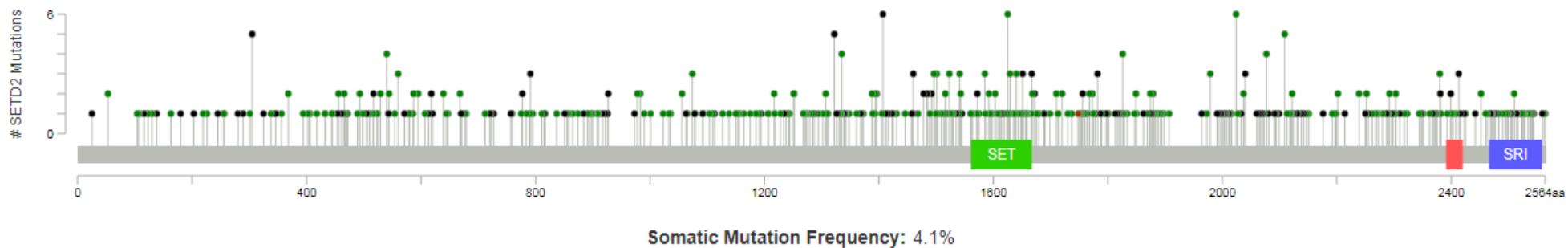
# Supplementary Information



**Figure S1:** (a) Microscopy images showing the expression of GFP-SETD2 constructs in 293T cells. (b) Western blot of whole-cell lysates probed with the depicted antibodies. *setd2* $\Delta$  293T (KO) cells were transfected with Halo-vector control (VC), SETD2 full-length (FL), or SETD2 C (C) and lysates were prepared 72 hrs post-transfection. \* denotes non-specific band. The expected bands for the target are depicted by arrows. (c) Western blot of whole-cell lysates probed with the depicted antibodies. In FL, *setd2* $\Delta$  293T (KO) cells were transfected with GFP-SETD2 full-length and lysates were prepared 72 hrs post-transfection. WT is Wild Type.



**Figure S2:** (a) Venn diagram showing the overlap of H3K36me3 peaks between different samples. (b) Metagene plots depicting the normalized distribution of H3K36me3 in WT and SETD2 FL-expressing KO cells.



375 Missense   
 193 Truncating  
1 Inframe   
 20 Other

<http://www.cbioportal.org>

**Figure S3:** Cartoon depicting the location of various mutations found in SETD2 gene of cancer patients that may result in the generation of truncated forms of SETD2 with altered half-lives.

Oligo	Sequence (5'-3')
MMP12_F	AACCAACGCTTGCCAAATCC
MMP12_R	TTTCCCACGGTAGTGACAGC
MMP13_F	CATGAGTTCGGCCACTCCTT
MMP13_R	CCTCGGAGACTGGTAATGGC
NEAT1_F	TCGACCCCTATCACATTGCC
NEAT1_R	CTCAGCAGTCTGCAGACC
GAPDH_F	TTCGACAGTCAGCCGCATCTTCTT
GAPDH_R	CAGGCGCCAATACGACCAAATC

**Figure S4:** Sequence of oligos used to perform qPCR.