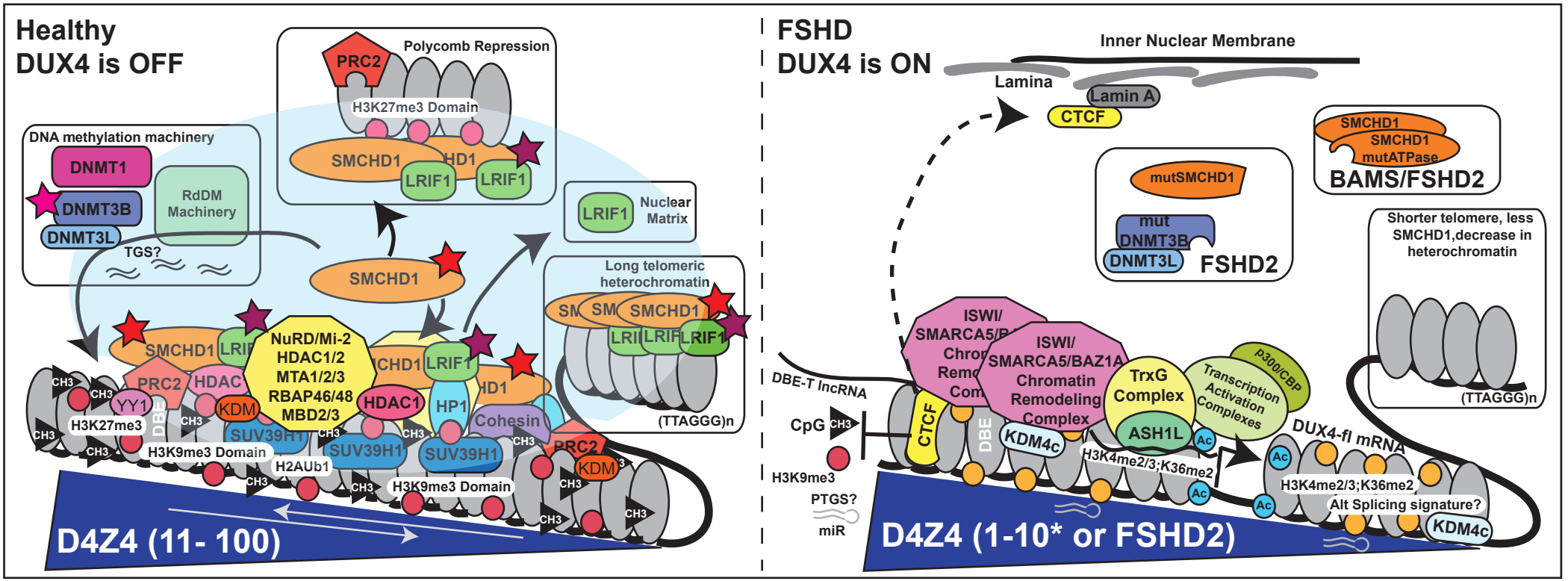
Model for FSHD2

FSHD1 and FSHD2 are caused by genetic changes that affect epigenetic repression of the chromosome 4 D4Z4 array resulting in aberrant expression of the *DUX4* gene from within the array.



(Left panel) Healthy-sized D4Z4 arrays are recognized by the cell's mlecular machinery to be transcriptionally silenced (OFF) in skeletal muscle cells and thus recruit transcriptional repressor proteins and establish an OFF epigenetic state. (Right panel) However, in FSHD2, you have a mutation in one of the genes known to cause FSHD2 (★*SMCHD1*, ★*DNMT3B*, or ★*LRIF1)*. All three genes encode proteins that function in repressing the healthy chromosome 4 D4Z4 arrays (and chromosome 10s) to keep the arrays silent and to keep DUX4 expresion OFF. When mutated, *DUX4* becomes expressed.