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“In or Out: Measure of the Malign Exon 7 in MLH3”

Introduction: Friedreich Ataxia and Huntington’s disease are progressive repeat expansion disorders. One factor affecting the rate of repeat expansion in these diseases is which isoform of the mismatch repair protein MLH3 that is expressed. Structures form during transcription that attract mismatch repair proteins that, in turn, attract MLH3. Isoform 1 of MLH3 cuts DNA in a way that leads to DNA expansion. An alternate isoform, MLH3 isoform 2, lacks exon 7 and the ability to cut DNA. Redirecting splicing to remove exon 7 slows the expansion of trinucleotide repeats and may delay the onset of symptoms. Establishing a clear measure for retention and excision of this exon will help researchers determine the efficacy of future pharmaceutical therapies.

Methods: cDNA that contained MLH3 isoforms were generated from RNA isolated from 5 cell lines consisting of human embryonic kidney, prostate cancer, and a neuroblastoma cell line. In EPI2ME Labs, wf-transcriptomes, a Docker-based Nextflow pipeline, mapped reads to the human genome using Minimap2 and then used Stringtie to differentiate isoform 1 and 2 via the supplied genome annotation we provided. Sashimi plots were generated in a Docker container version of ggSashimi. Percent retained and percent spliced out were calculated based on the output of ggSashimi.

Results and Conclusions: A baseline of MLH3 isoform expression can be established for cells or tissues. Further research on the effects of pharmaceutical treatment in vivo can determine its efficacy in changing the relative levels of MLH3 isoforms 1 and 2.