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Project Title: Huntington's disease skeletal muscle defects include insulin receptor aberrant splicing

Synopsis: Huntington's disease skeletal muscle defects could be attributed to the aberrant splicing of the INSR gene which codes for the insulin receptor.

Abstract: Huntington's disease (HD) is a degenerative and fatal disorder with debilitating motor and cognitive defects. The disease is caused by a CAG (polyQ) repeat in the human huntingtin gene, HTT. Generally the disease is characterized as a neurological disorder. However, our laboratory recently demonstrated that skeletal muscle fibers from a mouse model of HD exhibit physiological and mRNA splicing defects. Insulin sensitivity is known to decrease in other polyQ disorders. In this study, we investigate the aberrant splicing of INSR which codes for the insulin receptor (IR). The IR gene encodes two alternatively spliced isoforms; IR-A which excludes exon 11 and IR-B which includes exon 11. Skeletal muscle typically expresses both isoforms, but generally greater proportions of IR-A. To examine if changes in mRNA splicing in HD mice extended to the IR gene, we assessed IR-A/B splicing in R6/2 HD transgenic mice which express a mutant version of HTT. Our results reveal significant alterations in IR isoform splicing in HD compared to wild-type (WT) in the late-stage of the disease (p=0.003). Furthermore, we also found a significant difference in IR isoform splicing in mid-stage HD mice (p=0.03). However, there were no differences observed in early-stage HD mice. These results suggest there is a parallel relationship between the progression of the disease and the alterations in IR isoform splicing which could play a role in skeletal muscle defects including atrophy.