METHYLATION QTL IN HUNTINGTON'S DISEASE LINKED WITH EARLIER AGE OF ONSET.

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Huntington's disease (HD) is a devastating neurodegenerative disease caused by an expanded CAG trinucleotide repeat in the *huntingtin* gene on chromosome 4. CAG repeat length is correlated with age of onset and disease severity however it does not account for the total variation observed. There is even variation in identical twins implying that there are other genetic or epigenetic modifiers in disease pathogenesis. In this study, we investigated relative differences in methylation, in a genome wide analysis, comparing post-mortem HD cases with controls (using tissue sourced from the middle frontal gyrus). The analysis was undertaken using Illumina Human Methylation 450K bead arrays. This resulted in the discovery of 15 significant differentially methylated disease associated loci (FDR corrected). The most statistically significant of these was a predicted enhancer region adjacent to the SMYD2 gene. We then took a subsample (n=15: 7 control and 8 HD cases) and tested the relative expression levels of SMYD2, we found a significant decrease in SMYD2 transcription in HD cases versus controls. We then tested the potential age of onset effect of methylation at this locus (net methylation array probe binding) after adjustment for CAG repeat and found a significant difference with more binding related to an earlier age of onset (P= 0.0197). This led us to consider whether there was any sequence variation at this locus that may contribute to either the affinity of the probe binding or methylation. We found a polymorphism at this site; the resulting SNP rs957454 CG>CA alters the CpG methylation target of DNA methyltransferases and inhibits methylation at this locus (MeQTL activity).

We are currently investigating the magnitude of this effect, the potential association of the underlying SNP with variance in age of onset and whether this MeQTL offers a plausible gene-editing target for HD.