Investigating the effect of DNA maintenance genes in *Drosophila melanogaster* models of Huntington's disease

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Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expanded CAG repeat tract in the huntingtin gene (*HTT*) (1). This tract encodes a polyglutamine (Q) tract.

The age at onset of HD correlates inversely with increased CAG length, accounting for 50-60% of the variance in onset, but other factors, including inherited genetic differences account for part of the variation in onset. Genome wide association studies (GWAS) have have highlighted a number of loci associated with altered age of disease onset (2,3). These loci include components of DNA repair pathways such as *MLH1* and *MSH2*, for which conserved homologs exist in Drosophila. This project aims to investigate these genetic modifiers using Drosophila as a model for HD.

Figure 1: *Drosophila* model of HD yields locomotor deficit

Full-length human *HTT* with 16 CAGs or 128 CAGs (4) was expressed in all neurons by pan-neuronal UAS driver ELAV. The locomotor phenotype was tested by rapid iterative negative geotaxis (RING) assay (5). Negative geotaxis is the average distance climbed after 4 seconds. Data were plotted as Mean±SEM. For all genotypes n=10. n=1 the average distance climbed by flies in one vial averaged over 5 technical replicates. * P=0.273, ** P=0.0082, **** P<0.0001, Dunnett's multiple comparison test.

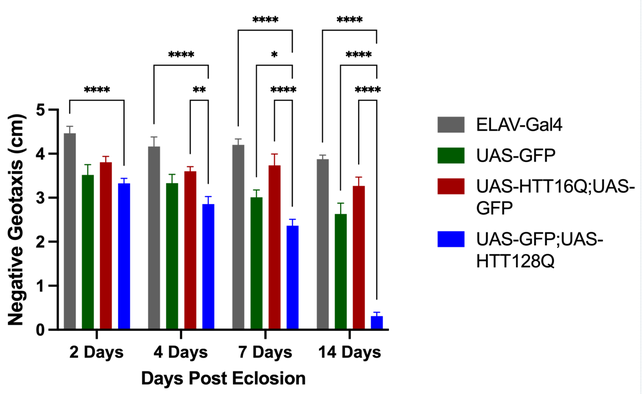


Figure 2: *MSH6* knockdown ameliorates locomotor deficit of HTT128QFL expressing flies

(A-C) The average distanced climbed by flies after 4 seconds at 2, 4 and 7 d.p.e. The flies pan-neuronally expressed an RNAi for MSH2, MSH6, EXO1 or PMS2 with a HTT128QFL background. HTT128QFL flies expressed UAS-GFP as a UAS expression control. (HTT128QFL n=15-18, MSH2 RNAi n=9-11, MSH6 RNAi n=10, EXO1 RNAi n=3-6, PMS2 RNAi n=3-6, n=1 the average distance climbed by flies in one vial averaged over 5 technical replicates). * P= 0.0198 Data are plotted as Mean ± SEM and statistical significance was calculated by One Way ANOVA and Dunnett's multiple comparison test.

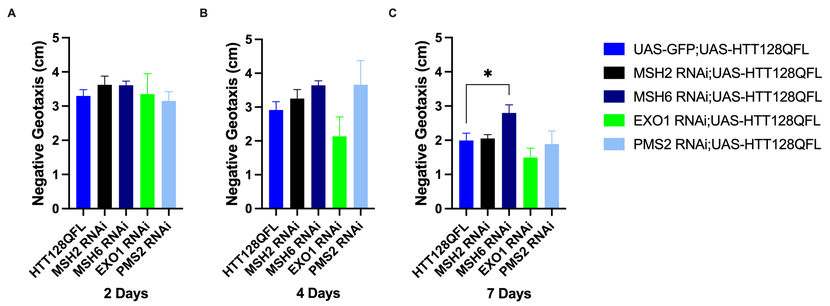


Figure 3: *MRE11* knockdown worsens locomotor phenotype of HTT128QFL expressing flies

(A-C) The average distanced climbed by flies after 4 seconds at 2, 4 and 7 d.p.e. The flies pan-neuronally expressed an RNAi for MRE11 or a heterozygous null mutant MRE11 with a HTT128QFL background. HTT128QFL flies expressed UAS-GFP as a UAS expression control. (HTT128QFL n=15-18, MRE11 RNAi n= 2-3, MRE11 mutant n=3-5, n=1 the average distance climbed by flies in one vial averaged over 5 technical replicates). Data are plotted as Mean ± SEM and statistical significance was calculated by One Way ANOVA and Dunnett's multiple comparison test.

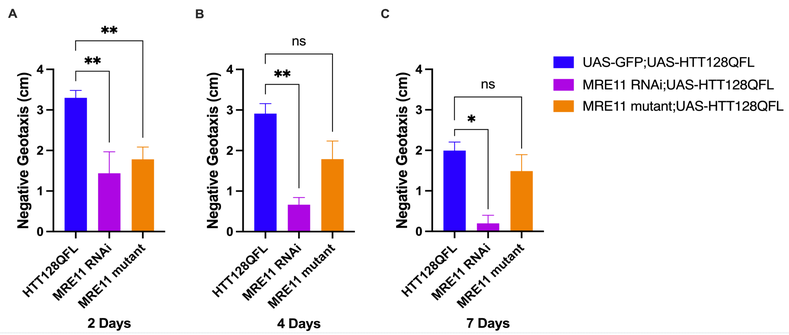
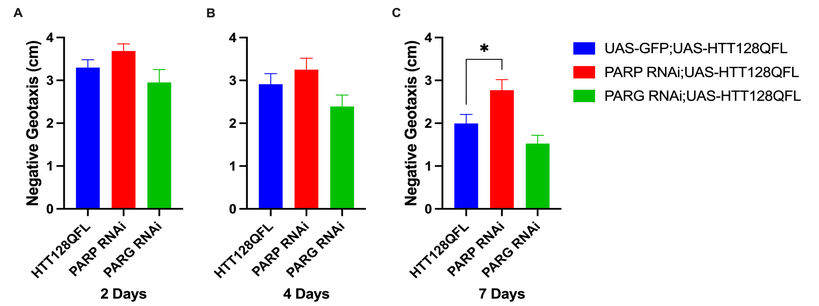


Figure 4: *PARP* knockdown rescues locomotor phenotype of HTT128QFL expressing flies

(A-C) The average distanced climbed by flies after 4 seconds at 2, 4 and 7 d.p.e. (A-C) The flies pan-neuronally expressed an RNAi for *PARP* or *PARG* with a HTT128QFL background. (HTT128QFL n=15-18, *PARP* RNAi n= 10-11, *PARG* RNAi n=7-8, n=1 the average distance climbed by flies in one vial averaged over 5 technical replicates). *, P=0.0348 Data are plotted as Mean ± SEM and statistical significance was calculated by One Way ANOVA and Dunnett's multiple comparison test.



Conclusions and Future Directions

- Neuronal expression of HTT128QFL yields a locomotor deficit
- The locomotor deficit can be rescued by PARP or MSH6 knockdown and worsened by MRE11 knockdown
- DNA maintenance genes seem to play a role in disease progression that may be unrelated to somatic instability
- PARP knockdown will be further characterized in HD fly models using RNAi and inhibitors in order to discern its role in disease progression and whether it could be potential therapeutic target for HD

References

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