Twenty Years of Huntington's Disease Research at PsychoGenics

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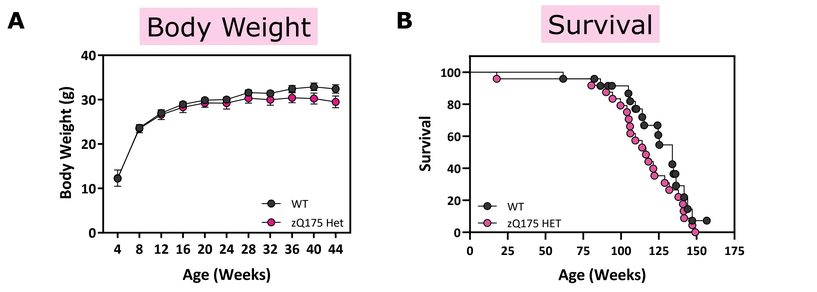
INTRODUCTION

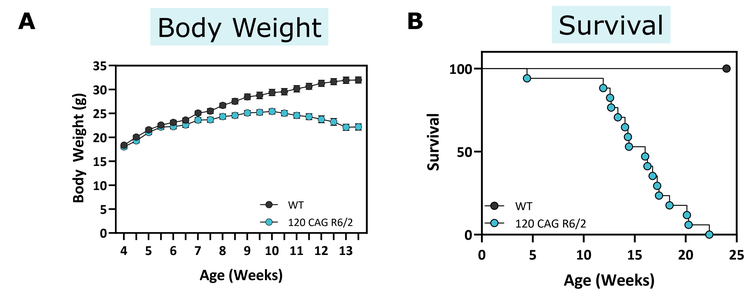
Over the course of the past 20 years, CHDI and PsychoGenics have worked closely together on characterizing mouse models of Huntington's disease. Primarily, the 120 CAG R6/2 model, the B6.Cg-Tg(HDexon1)61Gpb/J mouse line, or R6/1 model, and the zQ175 knock in model have been extensively studied at PsychoGenics. Each model carries a different modification of the huntingtin gene and/or protein and includes trinucleotide CAG repeats. While all models exhibit neurological decline, the severity and disease progression differ. In celebration of 20 years of scientific breakthroughs, here we present a side-by-side comparison of these widely used models, showcasing the main differences in behavioral, histological, and molecular readouts. Through our research, our ultimate goal is to provide validated and predictive tools for preclinical efficacy studies to support the pursuit of effective treatments for Huntington's disease.

Q175: BODY WEIGHT & SURVIVAL



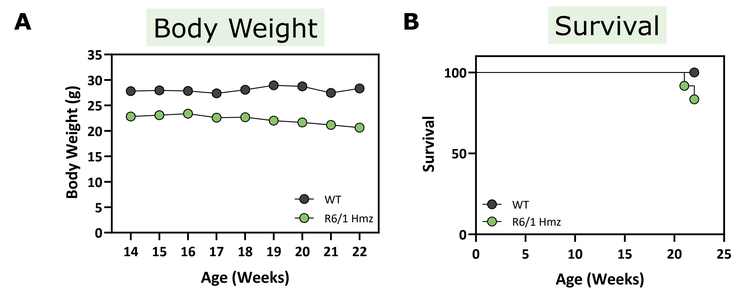
(A) Only marginal body weight loss is present in zQ175 Het mice at approximately 11 months of age. (B) zQ175 Het mice exhibit reduced survival as compared to wild type littermates.

R6/2: BODY WEIGHT & SURVIVAL



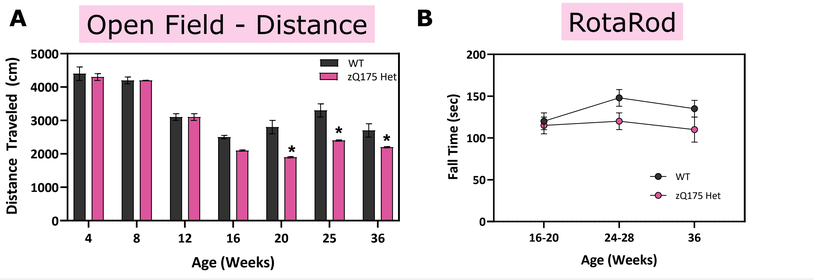
(A) R6/2 Hmz mice exhibit reduced body weight starting at 8 weeks of age. (B) R6/2 Hmz mice display reduced survival as compared to wild type littermates with a median survival of 14 weeks.

R6/1: BODY WEIGHT & SURVIVAL



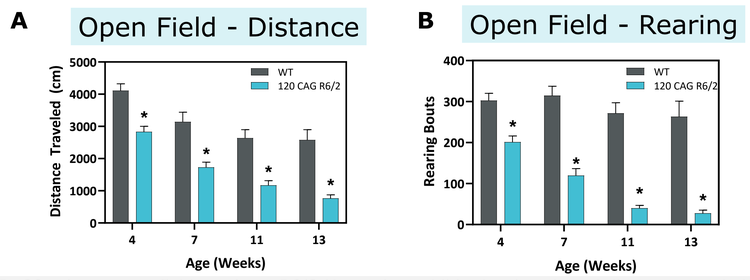
R6/1 Hmz mice exhibit reduced body weight as compared to wild type littermates starting at 9 week of age (data not shown) (A), however there are no significant differences in survival (B).

Q175: LOCOMOTOR DEFICITS



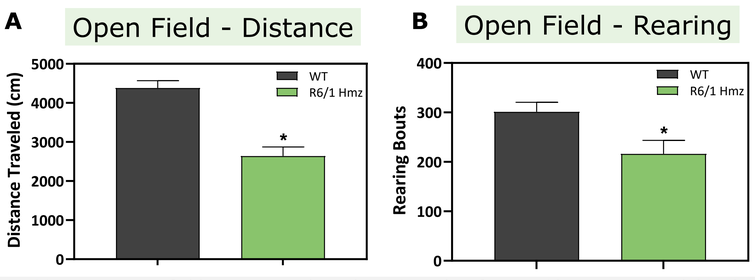
(A) Total distance traveled in 30-minute open field sessions is reduced in zQ175 Het mice starting at 20 weeks of age. (B) Latency to fall off the accelerating Rotarod in reduced in zQ175 Het mice starting around 24 weeks of age.

R6/2: LOCOMOTOR DEFICITS



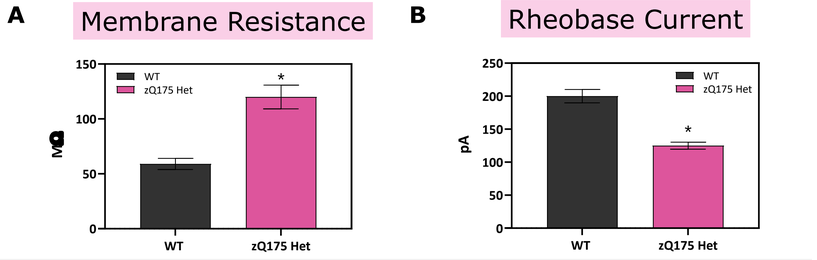
In 30-minute open field sessions, R6/2 Hmz mice exhibited reduced total distance traveled (A) and reduced rearing (B) as compared to wild type littermates, starting as early as 4 weeks of age.

R6/1: LOCOMOTOR DEFICITS



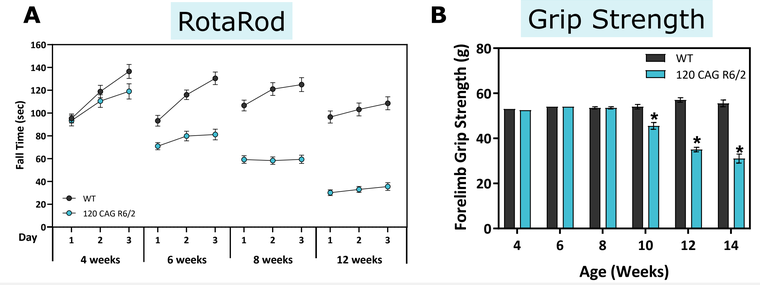
In a 30-minute open field session conducted at 16 weeks of age, R6/1 Hmz mice exhibited reduced total distance traveled (A) and reduced rearing (B) as compared to wild type littermates.

Q175: ELECTROPHYSIOLOGICAL PROFILES



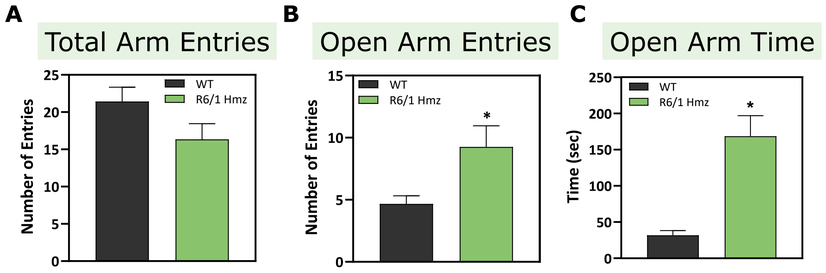
(A) MSNs in 6-month-old zQ175 Het mice exhibited elevated membrane resistance as compared to wild type littermates, rendering these cells more excitable. (B) A higher degree of excitability is further evident in the reduction of the rheobase current, which is a minimum current necessary to elicit action potentials, in zQ175 Het mice.

R6/2: MOTOR FUNCTION DEFICITS



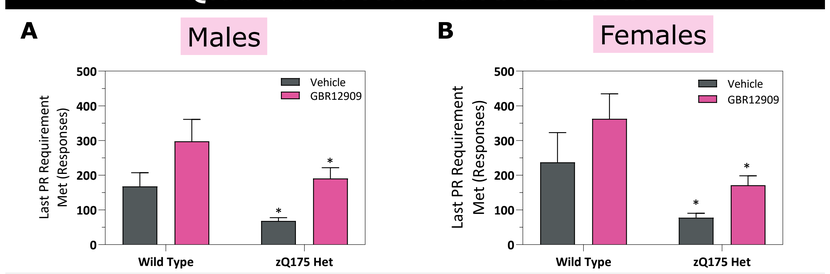
R6/2 Hmz mice exhibit reduced latency to fall off the accelerating RotaRod (A) starting at 6 weeks of age and reduced forelimb grip strength (B) starting at 10 weeks of age as compared to wild type littermates.

R6/1: REDUCED ANXIETY



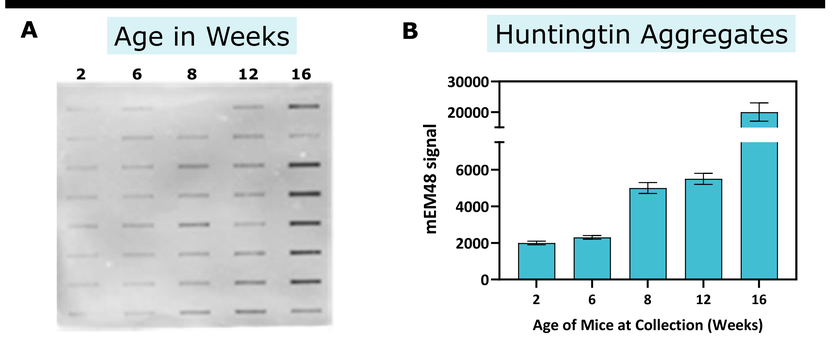
Elevated plus maze performance was assessed at 16 weeks of age. R6/1 Hmz mice did not display significantly different total arm entries (A), however, both the number of open arm entries (B) as well as the time spent in the open arms (C) was reduced as compared to wild type littermates.

Q175: COGNITION & ANHEDONIA



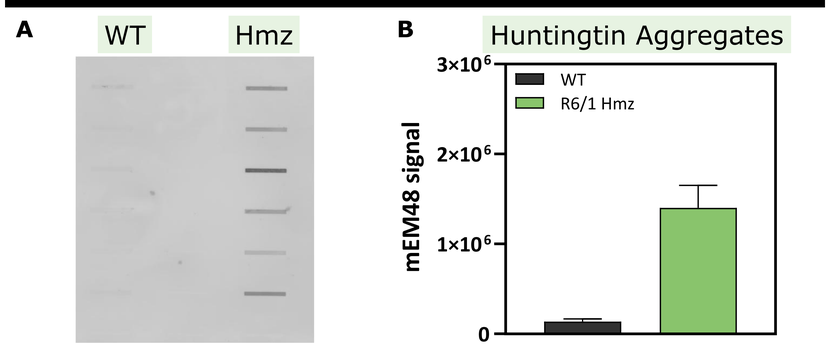
Male (A) and female (B) zQ175 Het mice aged 31-43 weeks had lower breaking points in a progressive ratio task compared to WT, suggesting that they were less willing to work for an appetitive reinforcer (access to condensed milk). The dopamine reuptake inhibitor GBR-12909 increased breakpoints in both sexes but did not interact with genotype. However, zQ175 Het mice did not differ from controls in the number of licks emitted per reinforcement opportunity (data not shown), suggesting they liked the reinforcer equally when it was available. These data suggest that symptoms of apathy and anhedonia may be separable phenomena in zQ175 Het mice.

R6/2: HUNTINGTIN PROTEIN AGGREGATE ELEVATION



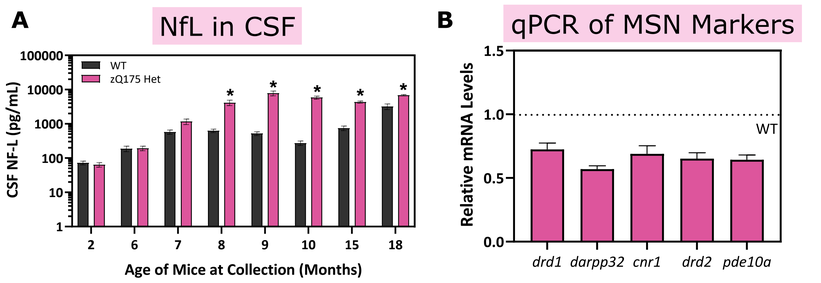
(A) Filter trap assay detected mutant huntingtin protein (HTT) aggregates in striatal protein lysate using mEM48 antibody in R6/2 Hmz mice at different ages. Each slot represents one animal. (B) HTT aggregation in R6/2 Hmz mice increases in an age dependent manner.

R6/1: HUNTINGTIN PROTEIN AGGREGATE ELEVATION



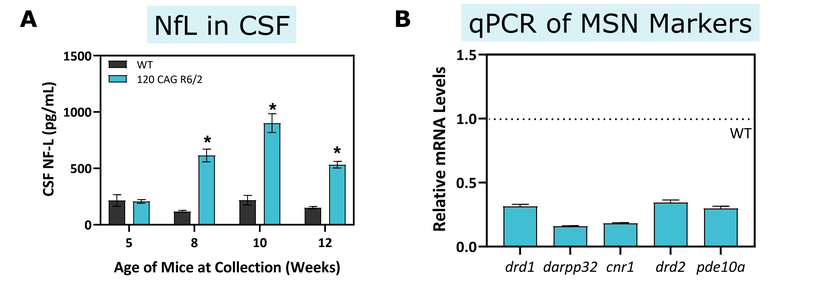
(A) Filter trap assay detected mutant huntingtin protein (HTT) aggregates in striatal protein lysate using mEM48 antibody in R6/1 Hmz mice at 22 weeks of age. Each slot represents one animal. (B) Quantification of HTT aggregation in R6/1 Hmz mice.

Q175: AXONAL DEGRADATION & MSN LOSS



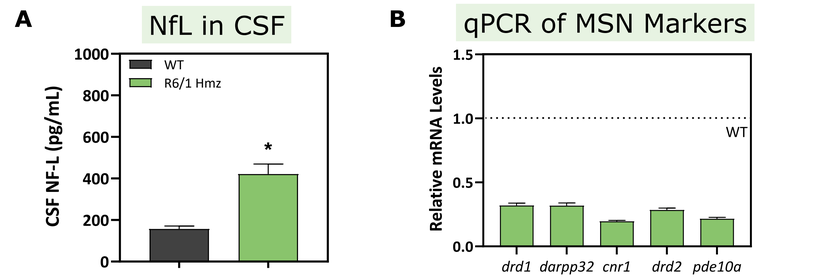
(A) Longitudinal assessment of NfL in zQ175 Het mice. NfL begins increasing starting at 8 months of age. (B) Striatal transcript levels of genes for MSN markers are reduced at 12 weeks of age, graph displays data at 30 weeks of age.

R6/2: AXONAL DEGRADATION & MSN LOSS



(A) Longitudinal assessment of NfL in R6/2 Hmz mice. NfL begins increasing starting at 8 weeks of age. (B) Striatal transcript levels of genes for MSN markers are reduced at 4 weeks of age, graph displays data at 12 weeks of age.

R6/1: AXONAL DEGRADATION & MSN LOSS



(A) NfL is elevated in R6/1 Hmz mice at 22 weeks of age as compared to wild type littermates. (B) Striatal transcript levels of genes for MSN markers are reduced by 22 weeks of age.

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