Deficits in Knock in Mouse Models of Huntington’s Disease Detected Using the Tapered Balance Beam Task

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Introduction

Numerous HD mouse models have been generated to examine both the pathogenesis of the disease and to evaluate therapeutics approaches. Of these models, the most precise genetic reproductions of the human condition are the knock-in (KI) mouse models as they express the mutation in the proper genetic and protein context of the murine gene.

The CAG 140 KI mouse model carries a chimeric mouse/human exon 1 containing around 125 CAG repeats and the human polyglutamine region inserted in the murine huntingtin gene (Menalled et al., 2003; Hickey et al., 2008).

A spontaneous expansion of the CAG repeat stretch in the CAG 140 KI mouse model in the Psychogenics breeding colony has led to a new Ki line carrying around 188 CAG repeats (z_Q175 KI) in a congenic C57Bl/6 background.

While motor abnormalities displayed by CAG 140 KI mice are on the ascending rotated task are detected from as early as 4 months, deficits are not observed in CAG 140 HET KI mice until 11 months of age (Menalled et al., 2003; Hickey et al., 2008; Rising et al., 2011).

Compared to homozygous (HOMO) mice, heterozygous (HET) knock-in mice serve as a better animal model of the human disease as HD homozgyosity is very rare in humans, however, few early behavioral deficits have been revealed in knock in mouse models of HD.

The tapered balance beam test proves to be a sensitive measure of motor impairment, detecting deficits in motor skills and balance that may not be detected by other standard motor tests, such as the rotated.

The Neurocube™ platform employs computer vision to detect changes in gait geometry and gait dynamics in rodent models of neurological disorders, pain and neuromuscular diseases. Cortico-basal ganglia algorithms are utilized to detect disease phenotypes and screen compounds.

The current study compares the performance of z_Q140 KI and z_Q175 KI mice using both the tapered balance beam task and proprietary gait analysis technology developed by Psychogenics, Inc, with an emphasis on evaluating whether early deficits can be revealed in heterozygous Ki mice.

Behavioral Timeline

Tapered Balance Beam Apparatus

Methods

Subjects

The founding 140-CAG Tg line (CHDI 053) is a complex mouse/human-human-exon 1 modelized into the mouse gene by homologous targeting (Menalled et al., 2003), and HET mice in the POP colony carry around 113 KI + 124 CAG repeats. The z_Q140 KI line (CHDI 053) is a congenic mouse/human-exon 1 modelized into the mouse gene by homologous targeting (Menalled et al., 2003), and HET mice in the POP colony carry around 133.87 ± 0.62 CAG repeats. The z_175 CAG line (CHDI 053) is a congenic mouse/human-exon 1 modelized into the mouse gene by homologous targeting (Menalled et al., 2003), and HET mice in the POP colony carry around 133.87 ± 0.62 CAG repeats. The z_175 CAG line (CHDI 053) is a congenic mouse/human-exon 1 modelized into the mouse gene by homologous targeting (Menalled et al., 2003), and HET mice in the POP colony carry around 133.87 ± 0.62 CAG repeats.

Experimental Procedures.

In the Neurocube™ assessment of a z_Q140 KI mice reveals clear discrimination between both female and male z_Q140 HET and WT mice from 26 and 8wks of age, respectively, but minimal progression of gait abnormalities is observed.

Neurocube™ assessment of z_Q175 KI mice reveals a progressive decline in gait abnormalities in both female and male z_Q175 HET and WT mice from 26wks of age.

Summary and Conclusions

The spontaneous expansion of the CAG repeat stretch in the CAG 140 KI mouse model has led to a new z_Q140 KI line that carries around 188 CAG repeats.

The results of this study support the use of the tapered balance beam test and Neurocube™ gait analysis technology as sensitive measures of motor impairment in mouse models of HD and indicate that motor deficits can be detected from as early as 8 weeks of age in both z_Q140 KI and z_Q175 KI heterozygous (HET) mice.

While z_Q140 HET mice display impaired motor coordination and gait from an early age as compared to wildtype (WT) counterparts, these deficits do not reveal a robust progression, but rather remain relatively constant with age.

In contrast to the z_Q140 KI mouse model of HD, z_Q175 KI HET mice display a later onset of motor deficits as compared to WT counterparts when assessed using the tapered balance beam test and Neurocube™ gait analysis, but the decline in performance is more progressive and sexually dimorphic in nature.

The progressive decline in behavioral performance, in conjunction with the reduction of striatal volume previously observed at an early age, indicates that the z_Q175 HET KI mouse may represent a better animal model of HD as compared to the z_Q140 KI HET mouse.

Detection of early motor deficits, together with the genetic similarity to the human condition, would further support the use of heterozygous knock-in mice as a tool for examining the early mechanisms of pathophysiology of HD and for screening potential treatments.

References

B. Examples of parameters evaluated during Neurocube™ assessment

Table 2. Represents the discrimination values obtained at each age and in multiple aspects of gait performance following comparison of HET and WT mice within both z_Q140 and z_Q175 KI mouse lines. A discrimination value of 50% means that the test cannot reliably discriminate between the two genotype groups. The p values are included to show the significance of the differences between the HET and WT mice at each age and values highlighted in blue are significant at p<0.05 at least.