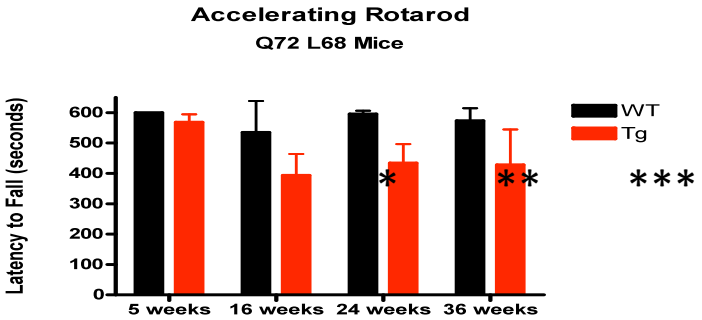
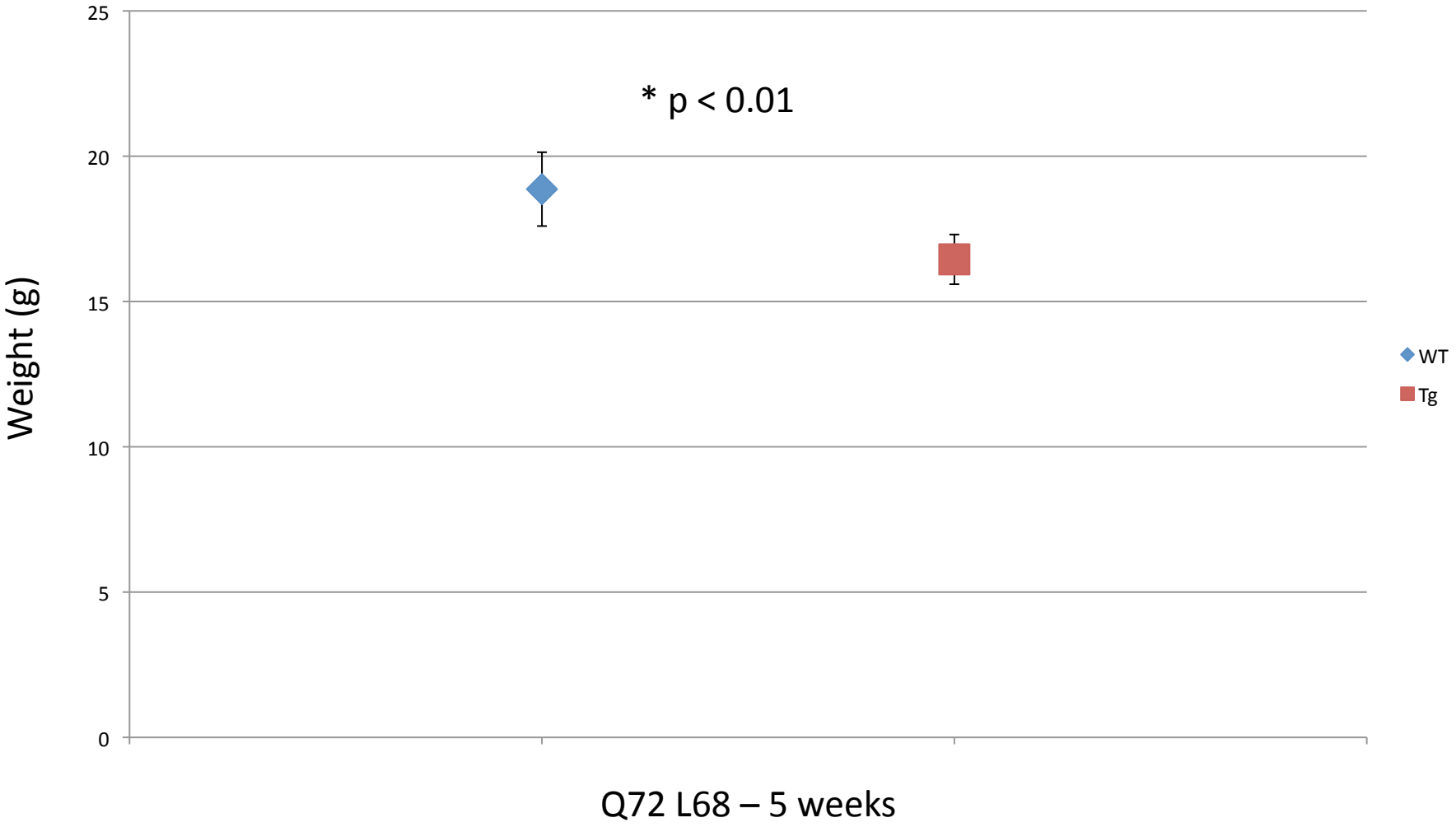


Two-way ANOVA shows a difference between wild-type and transgenic Q72 mice (L68) at 16, 24, and 36 weeks but not at 5 weeks. Bonferroni post-hoc tests. ** $p<0.01$; *** $p<0.0001$

5 week old Q72 L68 mice showed a difference in weight



- **<u>Transgenic mouse models displaying hyperactivity</u>**:
- SCA3 – NMR spectroscopy. Increased glycolysis in the brain.
- Huntington's Disease – hyperactive (2). (caspase 6 fragment – phenotype sounds partly similar to our BAC mice; NMDA selective activation → fluctuations in intracellular Ca2+ levels and reduced AMPA receptors).
- Alzheimer's Disease – hyperactive (beta-amyloidosis).
- mGlu2R potentiators – hyperactive.
- Cav2.2 KO mice – hyperactive.
- Hermansky-Pudlak Syndrome – hyperactive (otolith defects, imbalance).

- **<u>Causes of circling behavior</u>**:
- Bronx Waltver mouse. Caused by striatal asymmetry. Model for hearing and vestibular dysfunction.
- Hypothyroid mouse with non-functioning thyroid. Affected mice had 40% fewer midbrain dopamine neurons (substantia nigra). Much slower than our mice.
- Epistatic circler mouse. Bilateral malformation of the lateral semicircular canal and duct in the inner ear. No vestibuloocular reflex.

A transgenic mouse model of spinocerebellar ataxia type 3 resembling late disease onset and gender-specific instability of CAG repeats

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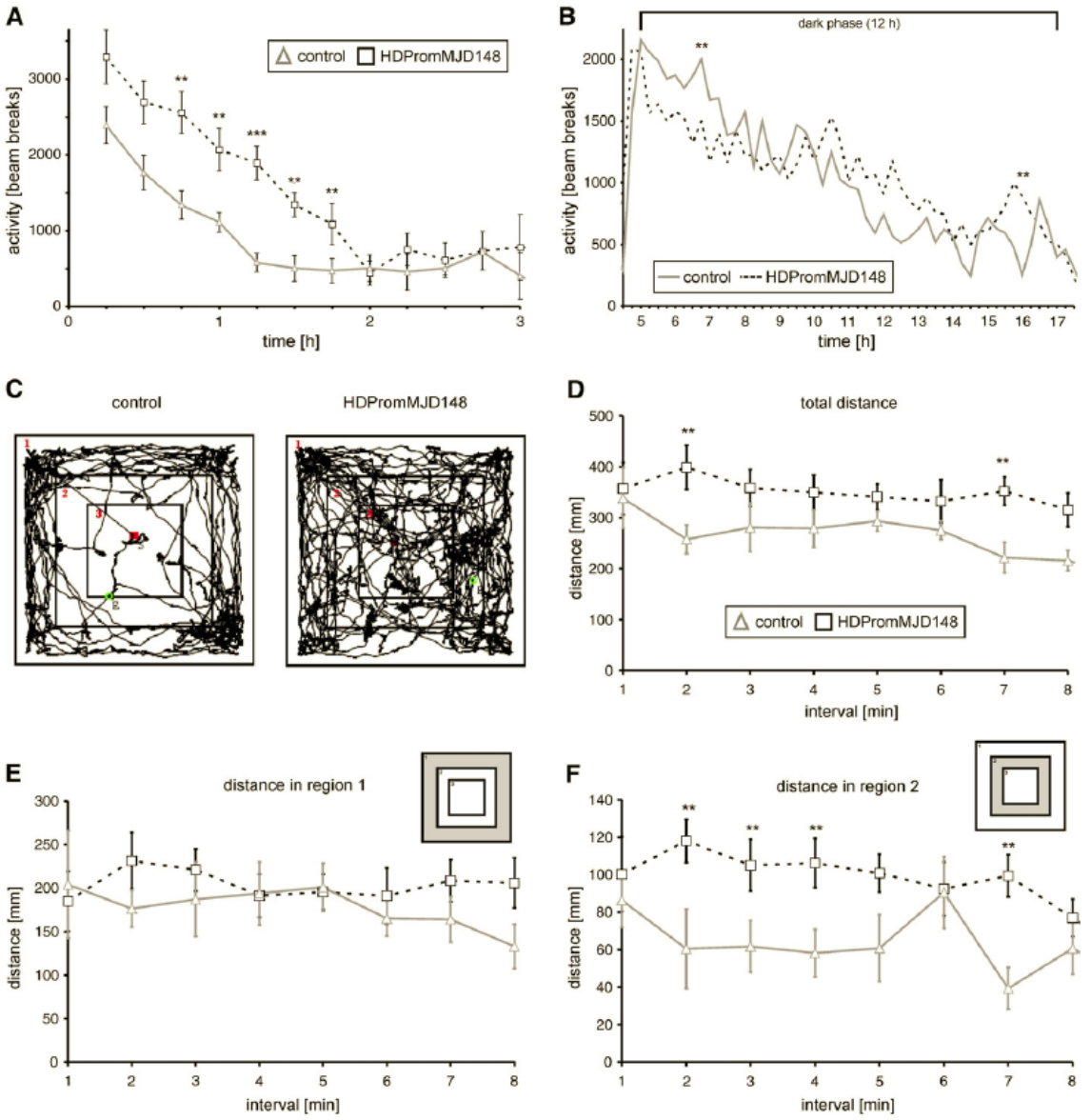

Fig. 4. Activity analyses. (A and B) Home cage activity analyses revealed hyperactivity of transgenic HDPromMJD148 mice at the age of 4 to 5 months. Mice were kept for 23 h in LabMaster cages (TSE Systems) and their activity during the light and the dark phase (hour 5 to hour 17) was recorded by the number of beam breaks. Shown are the total numbers of beam breaks in 15 min intervals (A) During the first 2 h in the LabMaster cages, HDPromMJD148 mice (black squares) were significantly more active than control mice (grey triangles). (**$p<0.05$; ***$p = 0.001$). Error bars, SEM. (B) At the beginning of the dark phase, control mice (gray line) were more active than HDPromMJD148 mice (black broken line); however, their activity decreased more strongly (141 beam breaks/15 min) during the 12 h in the dark phase than the activity of HDPromMJD148 mice (88 beam breaks/15 min), resulting in a higher activity of HDPromMJD148 mice at the end of the dark phase (**$p<0.05$). Shown is the mean of 12 transgenic and 10 control mice. For clarity, no error bars are shown. (C–F) Open field analyses revealed hyperactivity and reduced anxiety in HDPromMJD148 mice at the age of 14 months (mean of 18 transgenic and 8 control mice). (C) Plot of the moved track in the arena during 15 min. Shown are two representative examples. While the wildtype mouse (control) spend most of the time in the margin area and avoided the center, the HDPromMJD148 mouse evenly moved throughout the arena without any preferences. (D) HDPromMJD148 mice moved longer distances in the open field arena during the first 8 min. The differences in interval/minute 2 and 7 are significant ($p<0.05$). (E) No difference between transgenic and control mice was observed regarding the distance moved in the margin area (region 1) of the arena. (F) Distance mice moved in the transition area between the margin and the center (region 2). HDPromMJD148 mice moved (at four intervals significantly) longer distances in the transition area, indicating frequent changes between the center and the margin.

SCA7 Knockin Mice Model Human SCA7 and Reveal Gradual Accumulation of Mutant Ataxin-7 in Neurons and Abnormalities in Short-Term Plasticity

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Table 1. Comparison between an Infantile SCA7 Patient and $Sca7^{266Q/5Q}$ Mice

Symptoms	Infantile SCA7 Patient	$Sca7^{266Q/5Q}$ Mice
Age of onset	1 month	5 weeks
Weight loss	✓	✓
Ptosis	✓	✓
Visual impairment	✓	✓
Ataxia	✓	✓
Muscle wasting	✓	✓
Kyphosis	✓	✓
Tremors	✓	✓
Death	6 months	4–5 months

Symptoms of an infantile SCA7 patient are compared with those of $Sca7^{266Q/5Q}$ mice. This patient is an individual IV-2 from BASCA kindred (Benton et al., 1998), and expanded CAG repeats from this patient were used to construct a targeting vector (see Experimental Procedures). ✓marks each symptom manifested in patient and $Sca7^{266Q/5Q}$ mice.

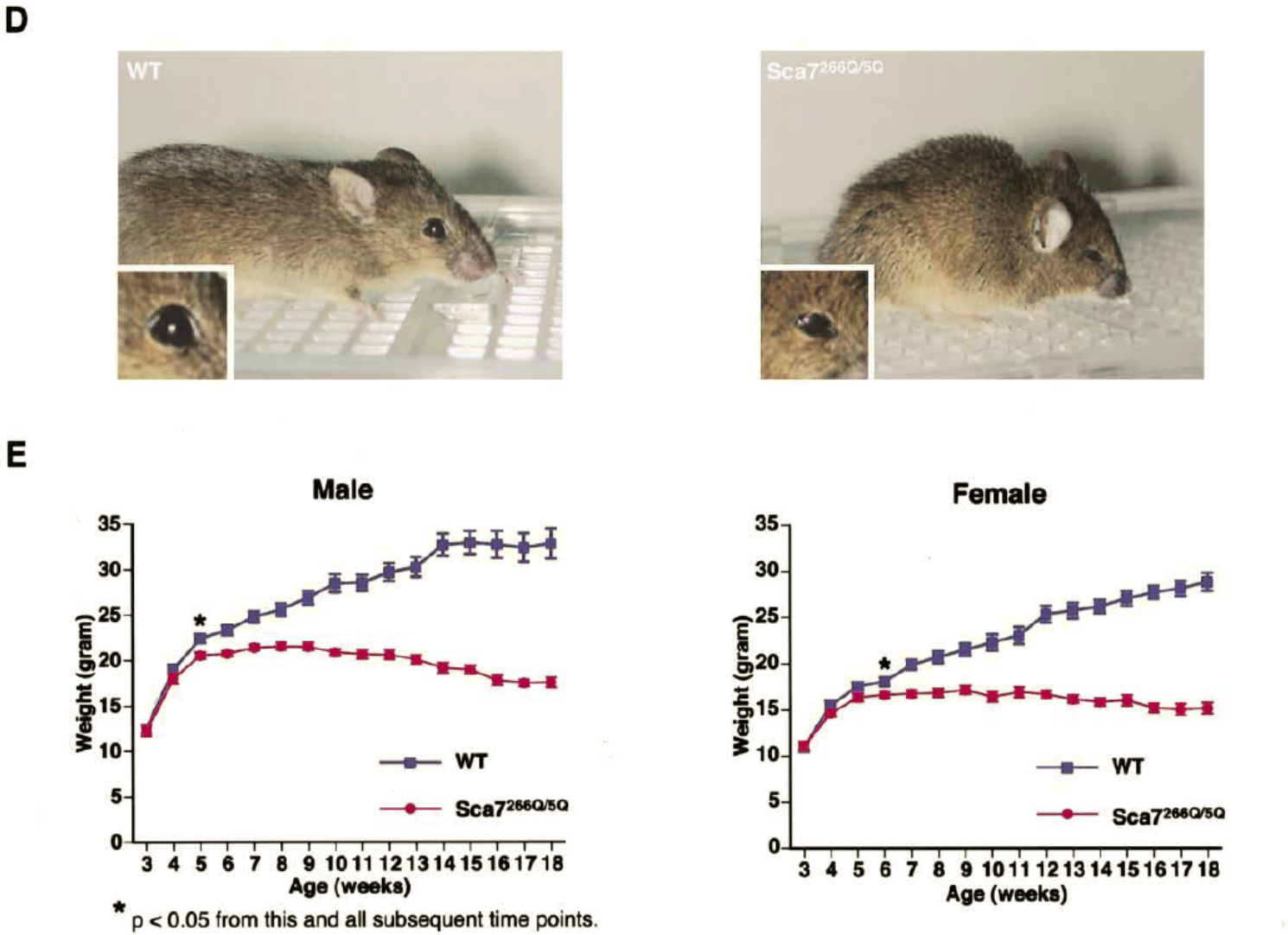

Figure 1. Generating Sca7$^{266Q/5Q}$ Mice

(A) Targeting scheme. The top diagram shows a simplified version of mouse *Sca7* locus near exons 3 and 4. Targeting construct introduced 266 CAG repeats (inverted triangle) and flanking regions from human *SCA7* into exon 3, obtaining a targeting frequency of 4%. Electroporation of Cre recombinase into the positive ES clones allowed the excision of the *Neomycin (Neo)/Thymidine kinase (Tk)* selection cassette (shown as an open box) from the targeted locus. P indicates a probe used for Southern analysis. Red arrowheads indicate *lox*P sites. Abbreviations are as follows: 3, exon 3; 4, exon 4; 3^e, engineered exon 3 with 266 CAG repeats; RV, EcoRV; RI, EcoRI; S, ScaI; and B, BamHI.

(B) Germline transmission of a targeted allele. Southern analysis of EcoRI-digested tail DNA revealed 15.2 kb wild-type and 10.3 kb mutant bands in Sca7$^{266Q/5Q}$ mice. Only the 15.2 kb band was detected from wild-type (WT) mice.

(C) Ataxin-7 is predominantly nuclear in the cerebellum, and expanded ataxin-7 is expressed in vivo. Both wild-type and mutant