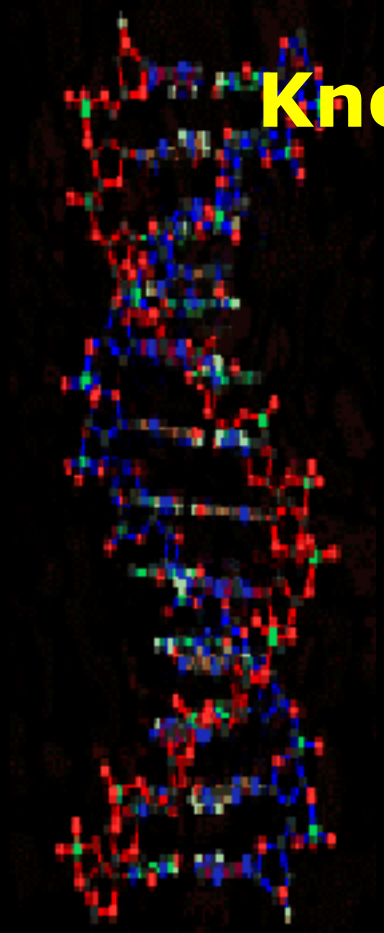
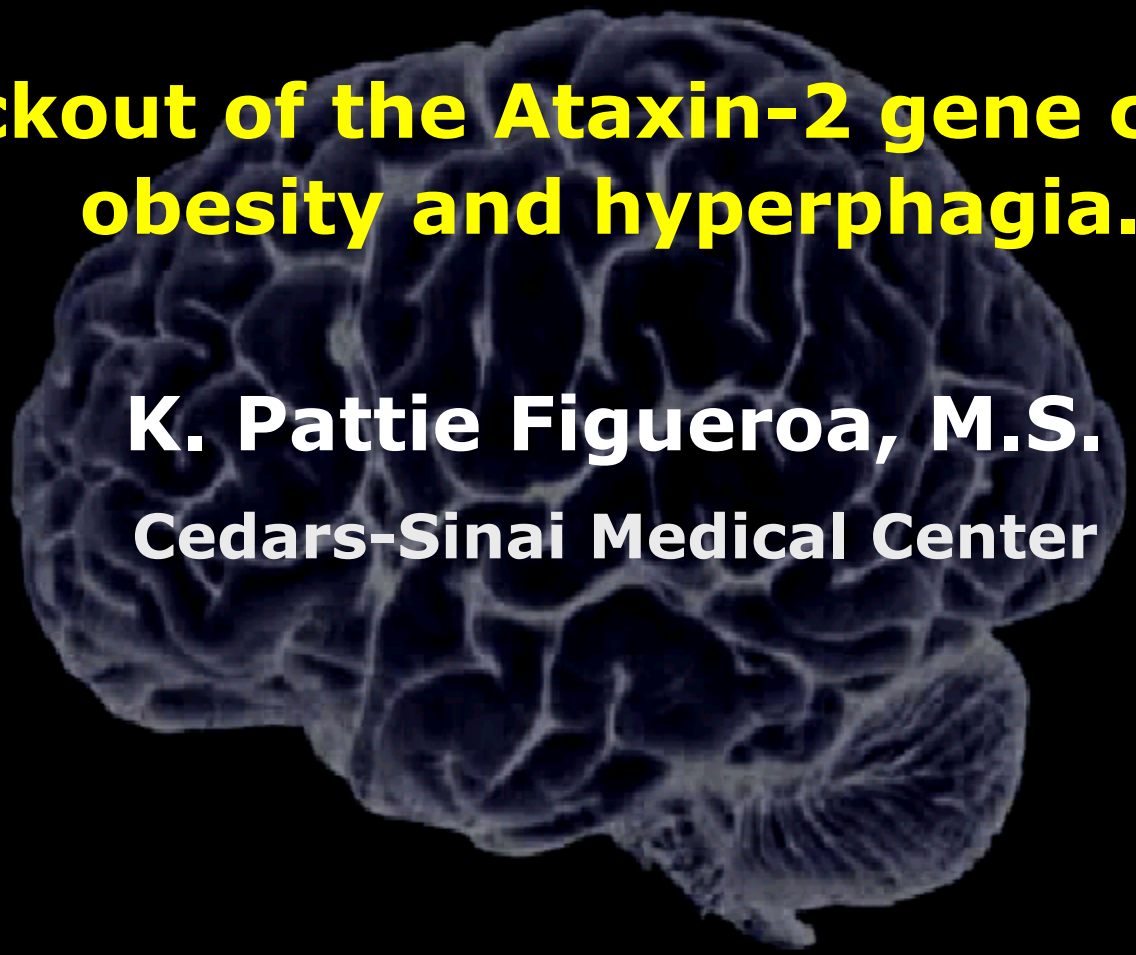
Cedars-Sinai Medical Center

Rose Moss Laboratory
for Neurogenetics,
Parkinson's and
Neurodegenerative Diseases



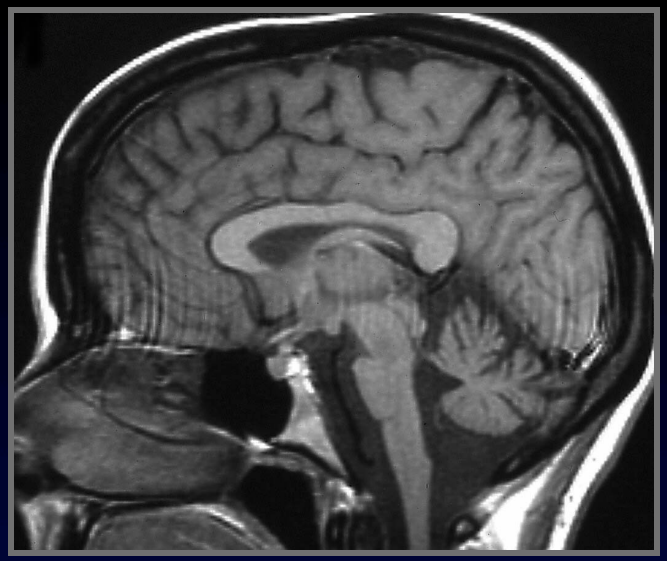
Knockout of the Ataxin-2 gene causes obesity and hyperphagia.



K. Pattie Figueroa, M.S.

Cedars-Sinai Medical Center

The SCA2 Gene



ER exit signal
CM trans Golgi

Normal: 22Q
Mutant: >33Q

- CAG Repeat codes for glutamine (Q).
- Novel Protein with Golgi localization signals.

Ataxia Plus
Slow saccadic eye movements

More or less pure
DOPA-responsive PD

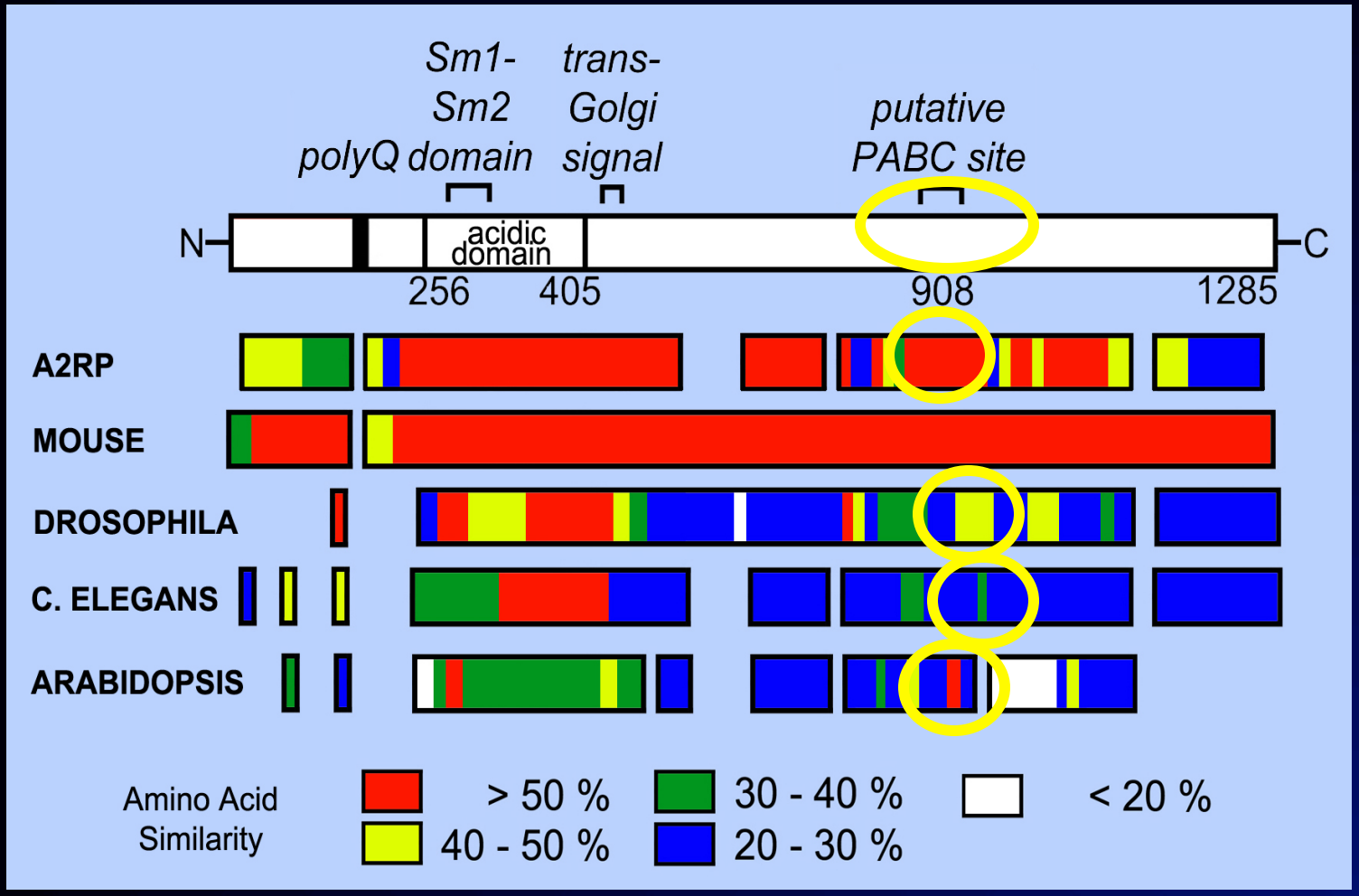
Normal:
$(CAG)_8CAA(CAG)_4CAA(CAG)_8$

Path.: (CAG)n; n>31
rare $(CAG)_{18}$ CAA $(CAG)_{16}$

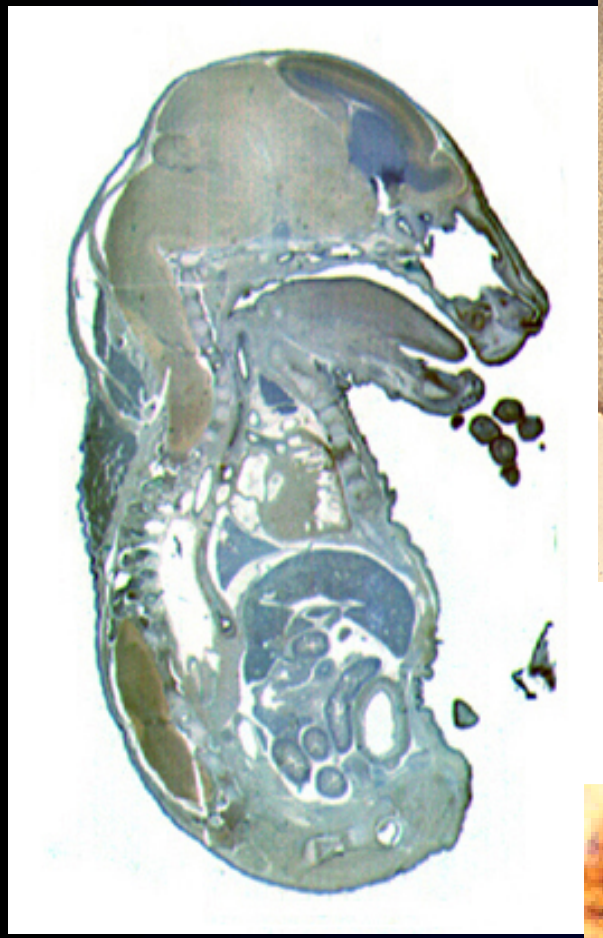
Ataxin-2 Knockout

- Does neurodegeneration in SCA2 involve any aspect of functional loss?
- Does neuronal dysfunction?
- What is normal function of ataxin-2 ?
- Ataxin-2 knockdown for therapy?

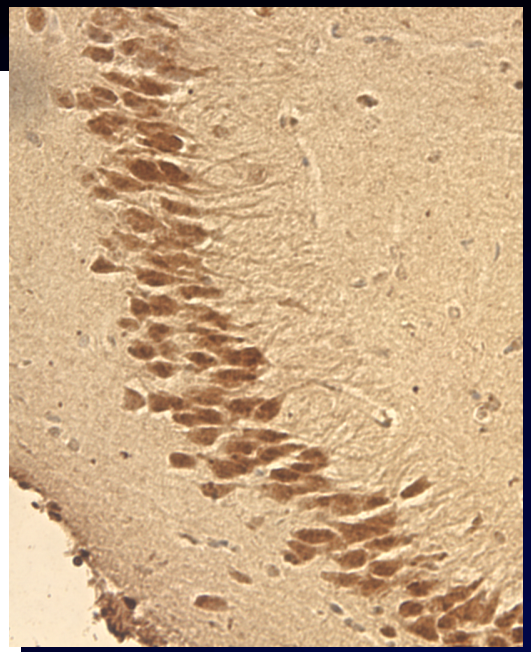
Ataxin-2 Normal Function



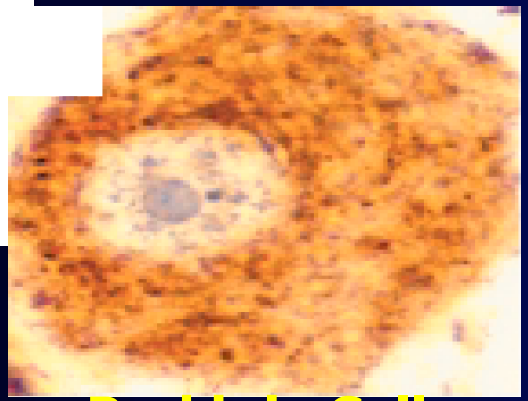
Expression of Ataxin-2



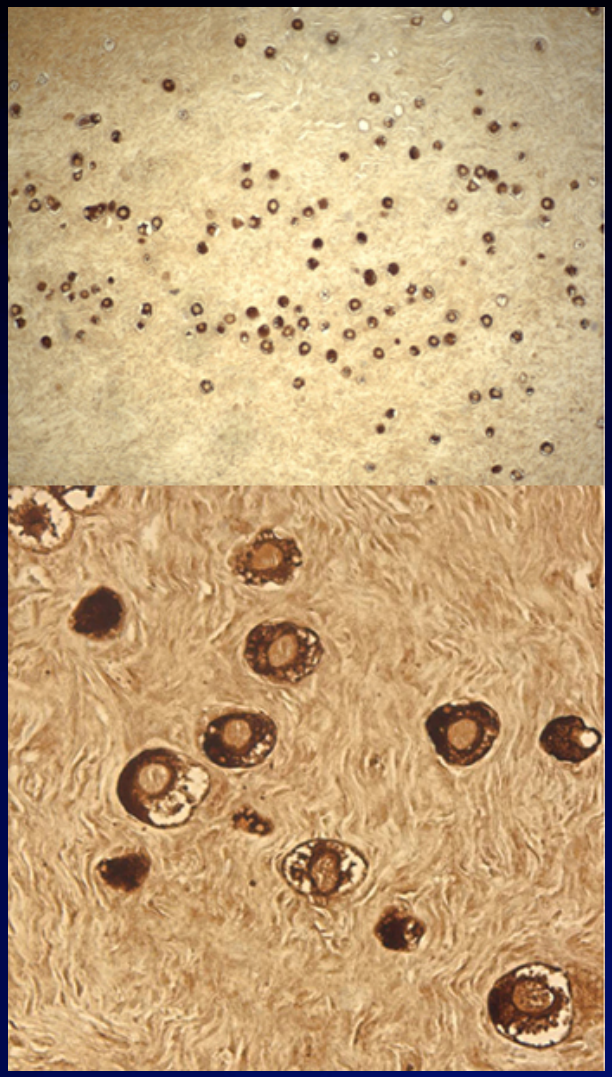
Mouse E16



Hippocampus CA3

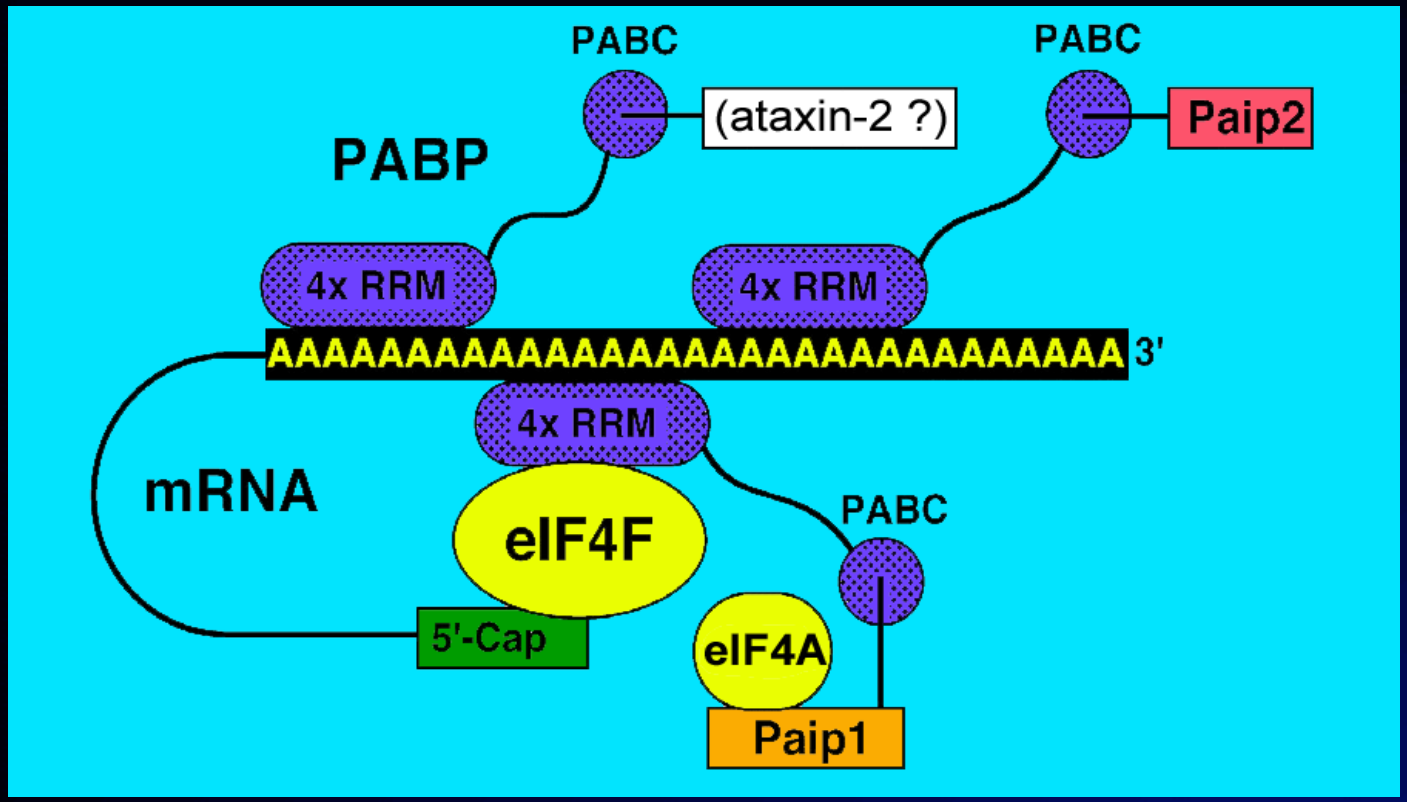


Purkinje Cell



Human Oocytes

Ataxin-2 Normal Function



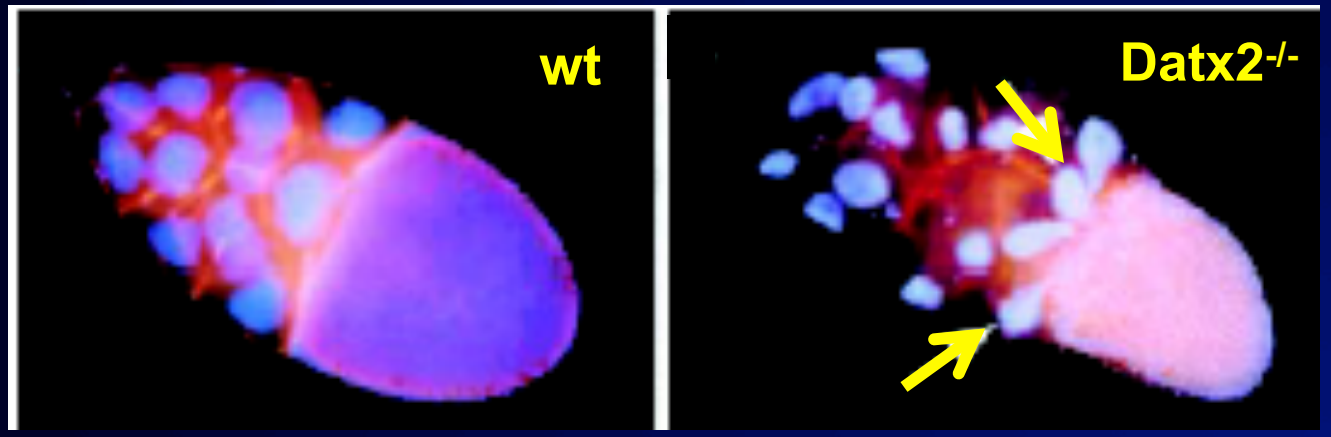
Atx-2
||
A2BP1

PABP interacting Protein1
||
PolyA-Binding Protein

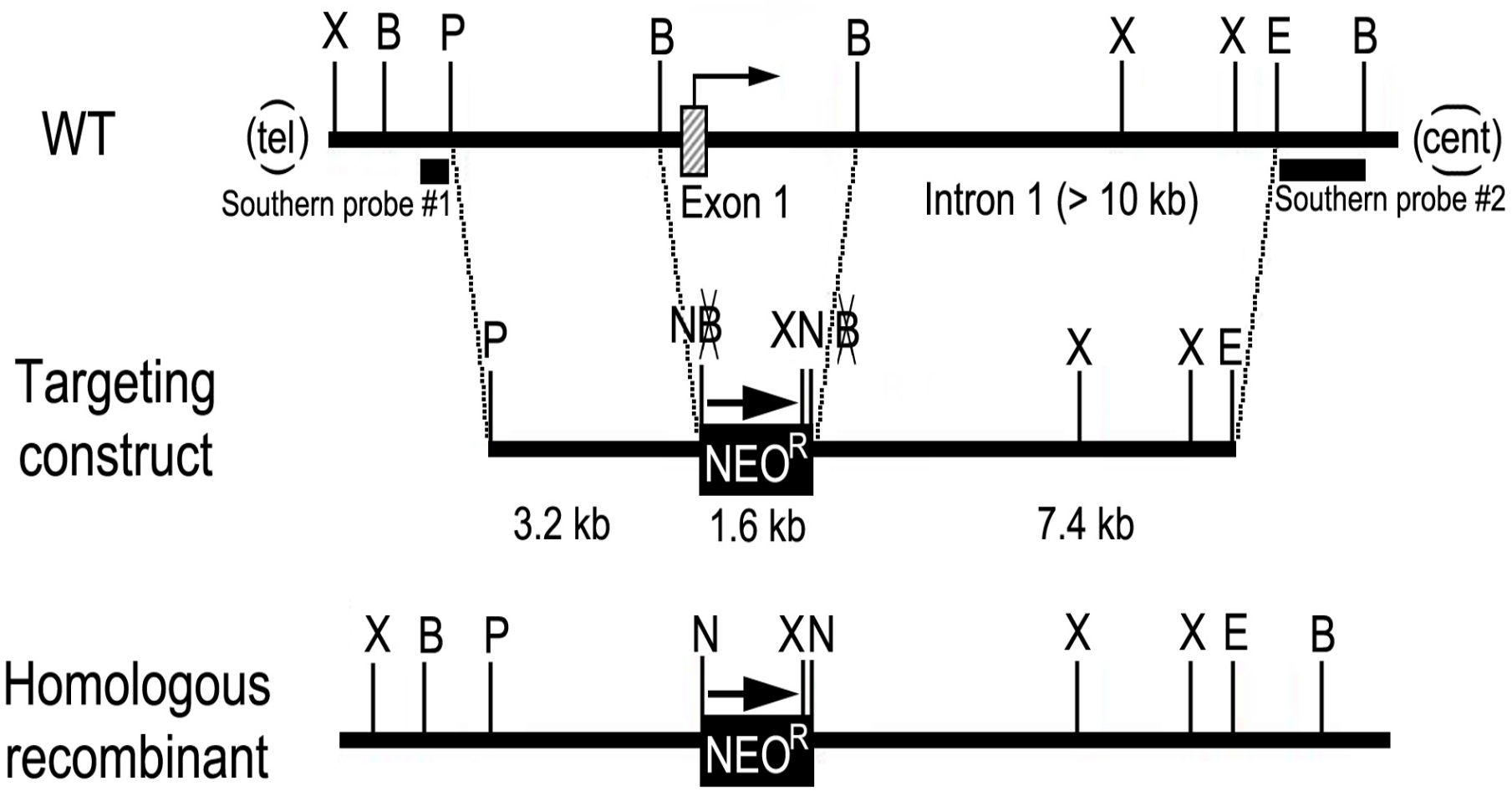
Knockout in the Fly and Worm

RNA interference (RNA)i in *C. elegans* (Kiehl et al., 2000)

Datx-2 mutants in D. melanogaster (Satterfield et al., 2002)



Targeting Strategy



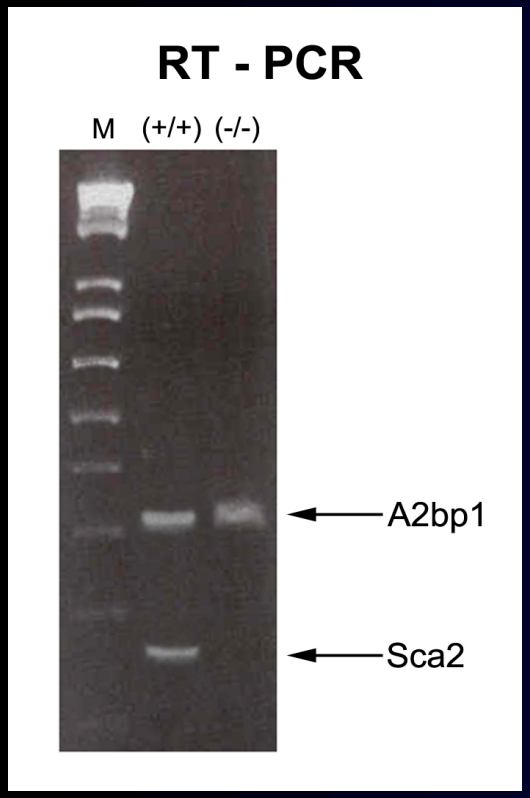
Gene Targeting Results in Lack of Ataxin-2 Expression at the RNA and Protein Level.

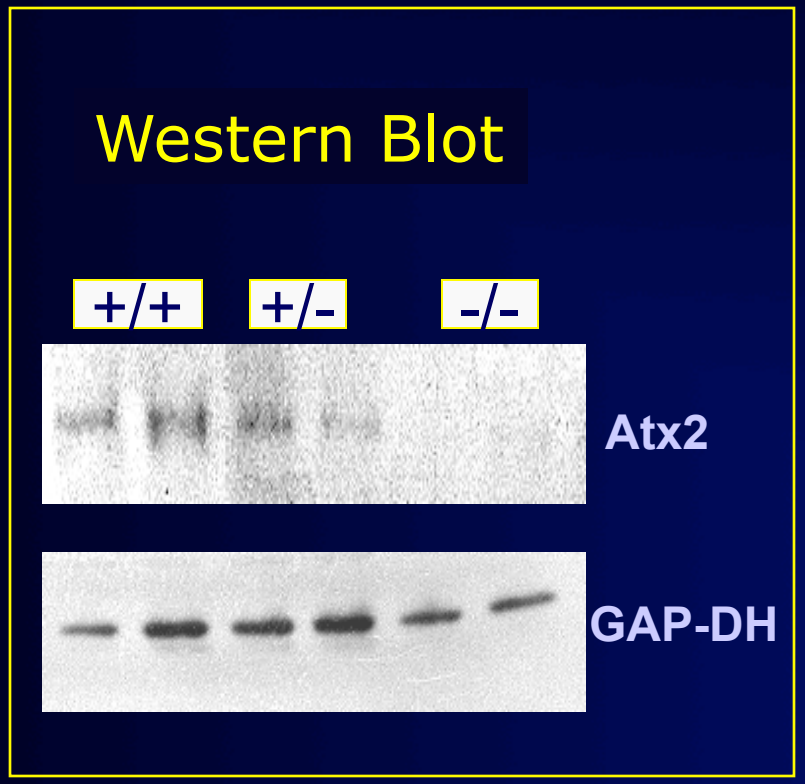
Absence of SCA2 mRNA :

- northern blot
- microarray

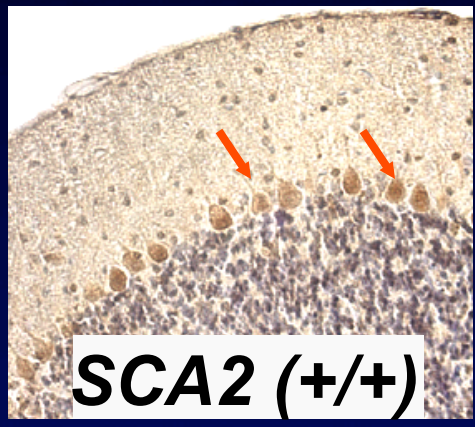
Absence of ataxin-2 :

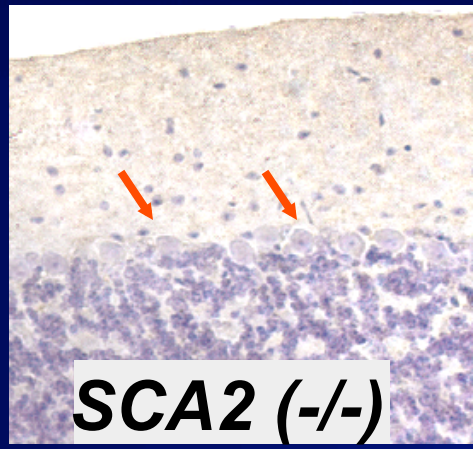
- Western blot
- immunocytochemistry





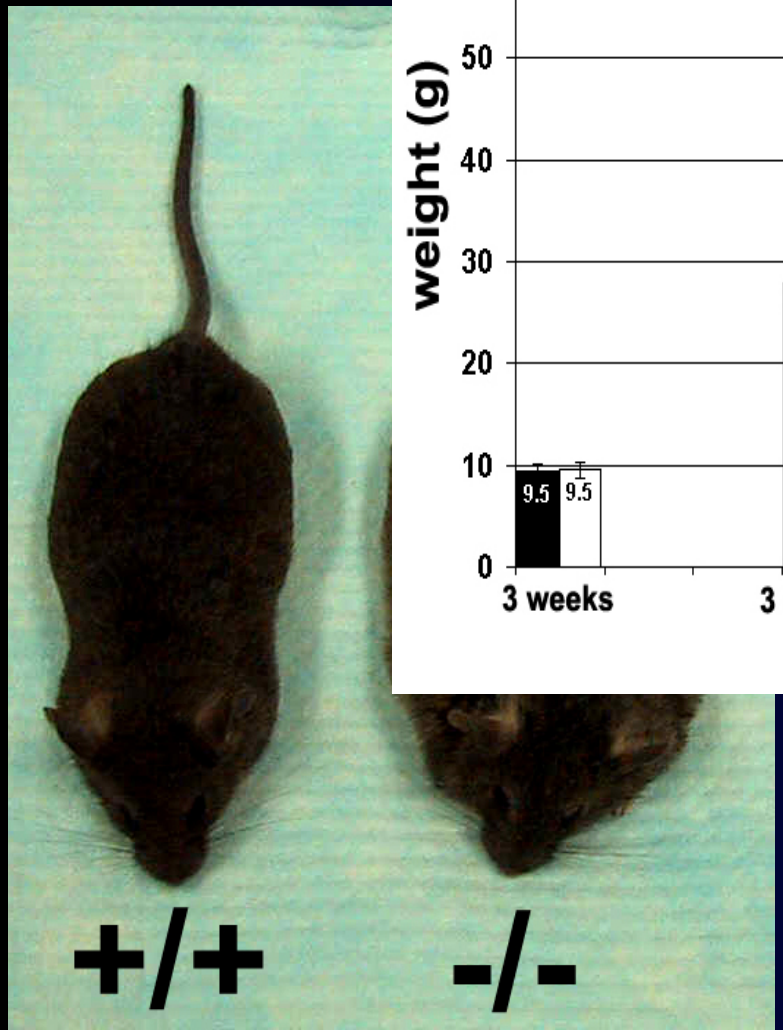
C-terminal ataxin-2 antibody

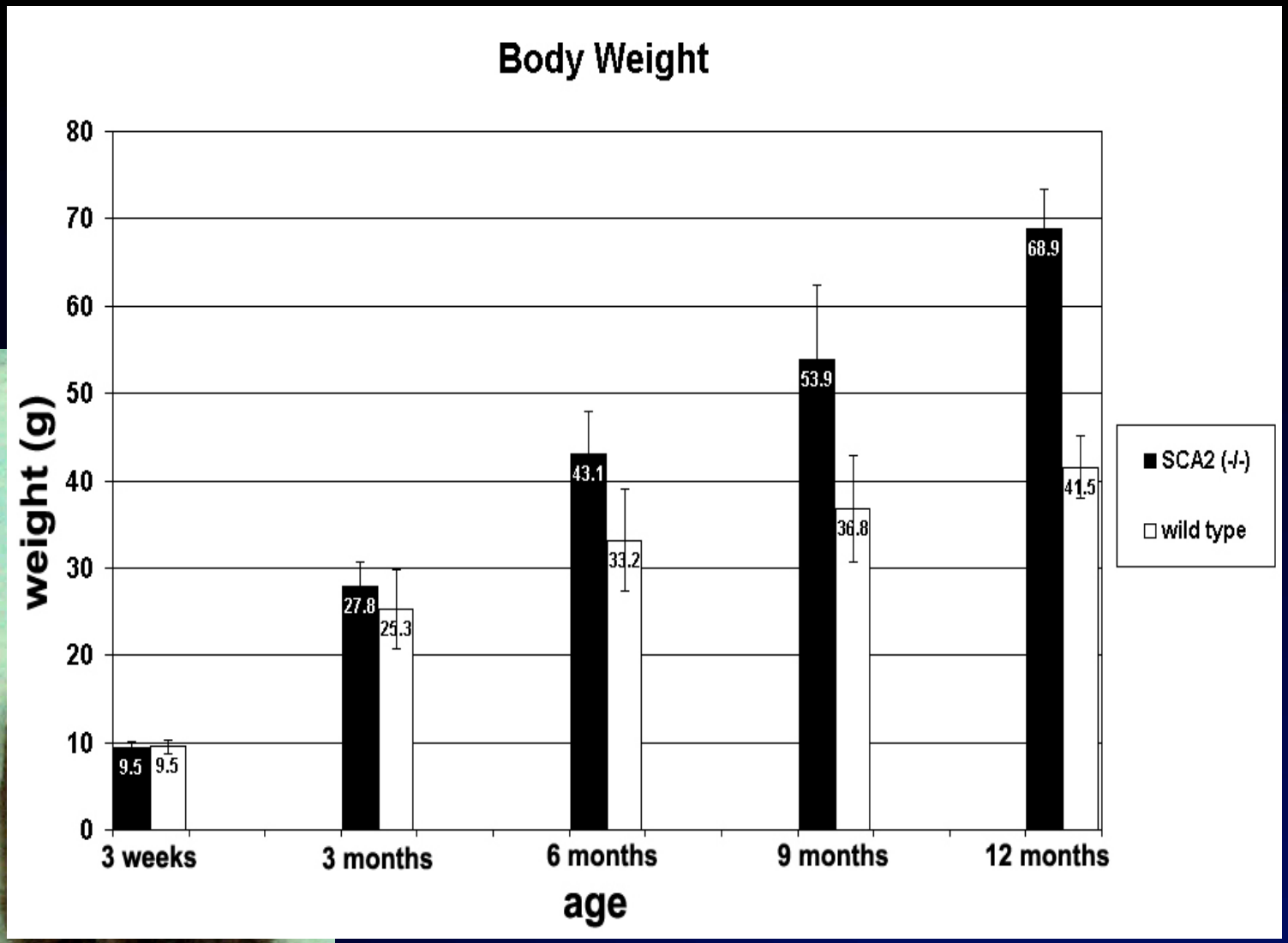




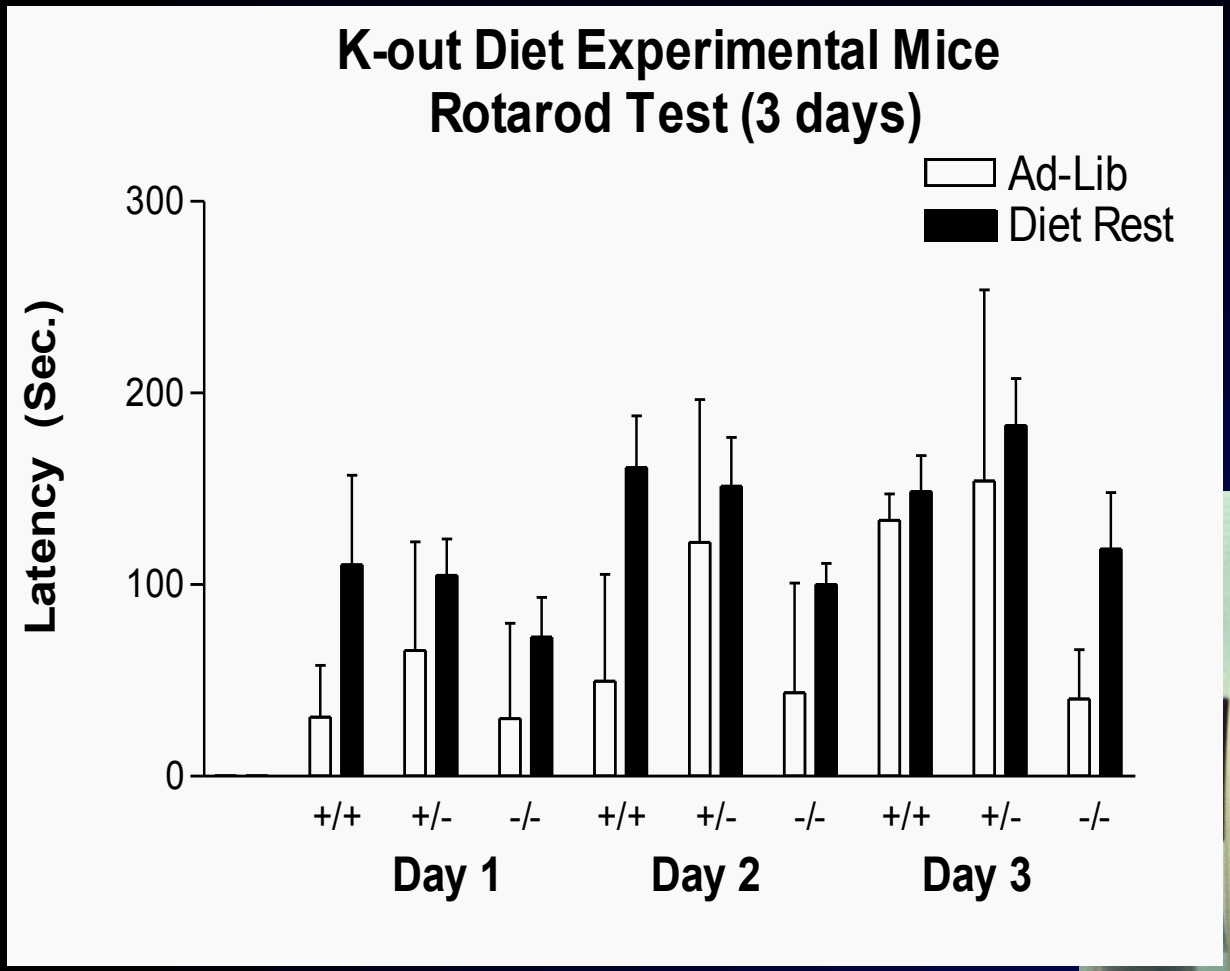
Ataxin-2 knock-out mouse

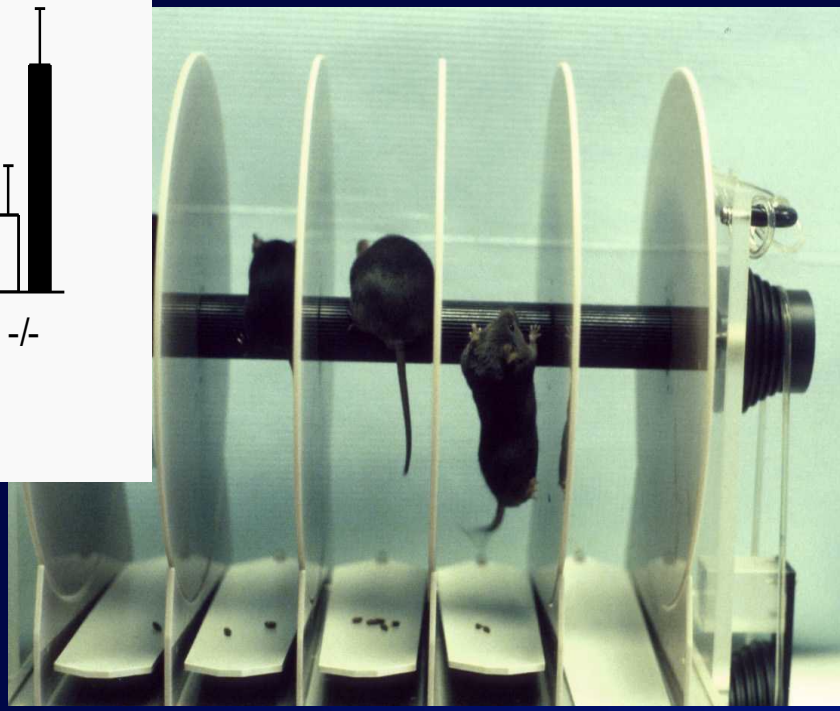
Knock out mice are near normal, and do not develop overt neurodegeneration! (at 12 months)

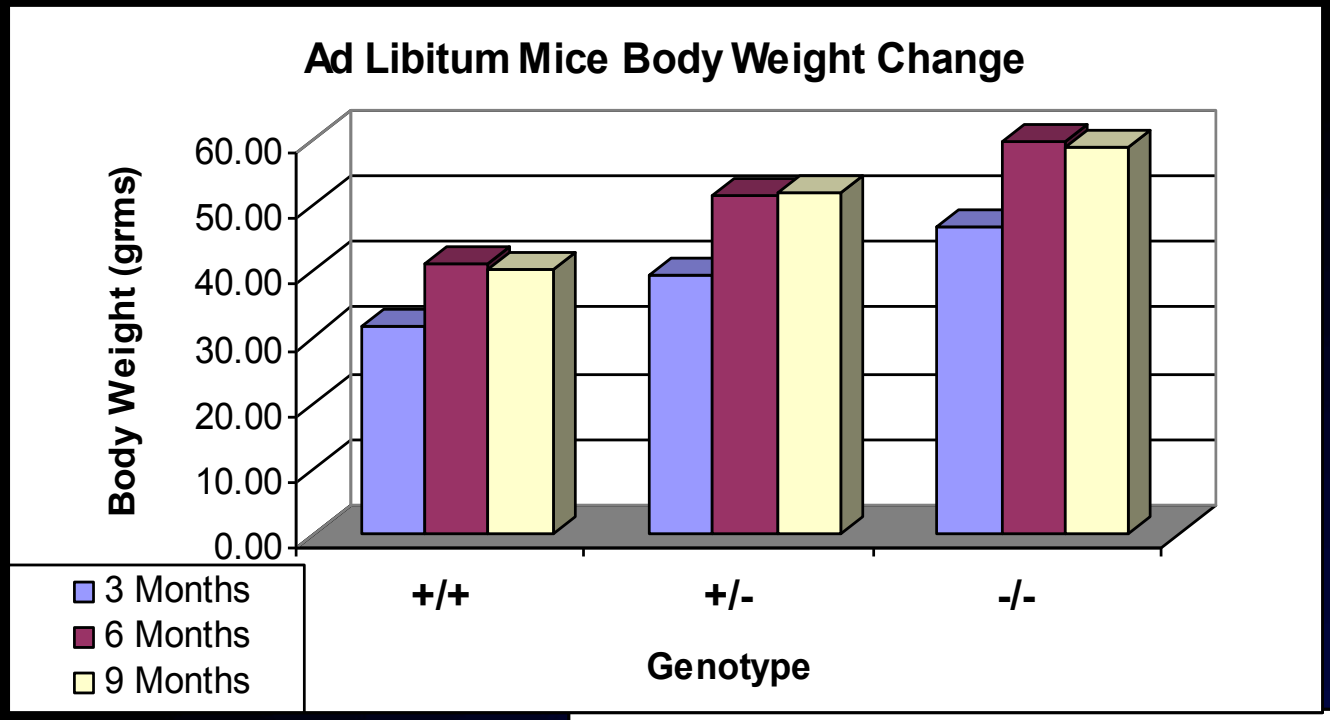

+/+
-/-


Body Weight
weight (g)
80
70
60
50
40
30
20
10
0
9.5
9.5
27.8
25.3
43.1
33.2
53.9
36.8
68.9
41.5
3 weeks
3 months
6 months
9 months
12 months
age
SCA2 (-/-)
wild type

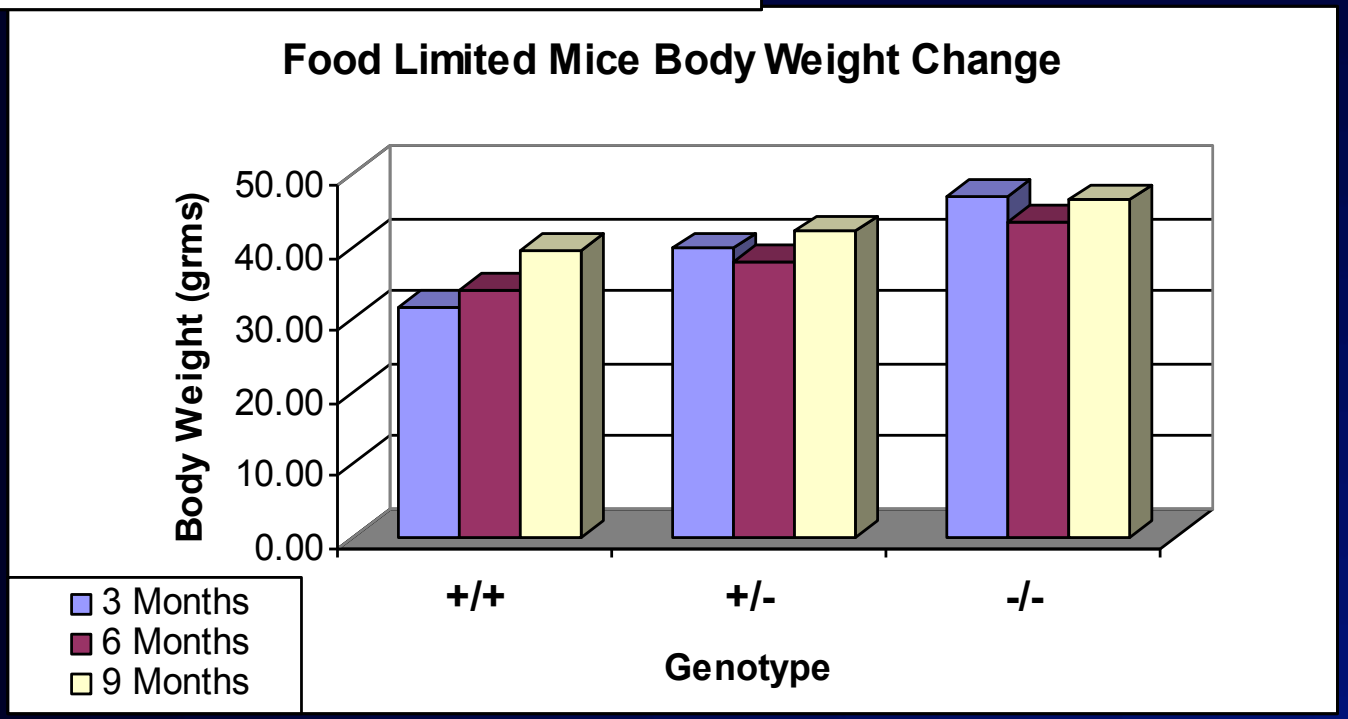
Motor Performance



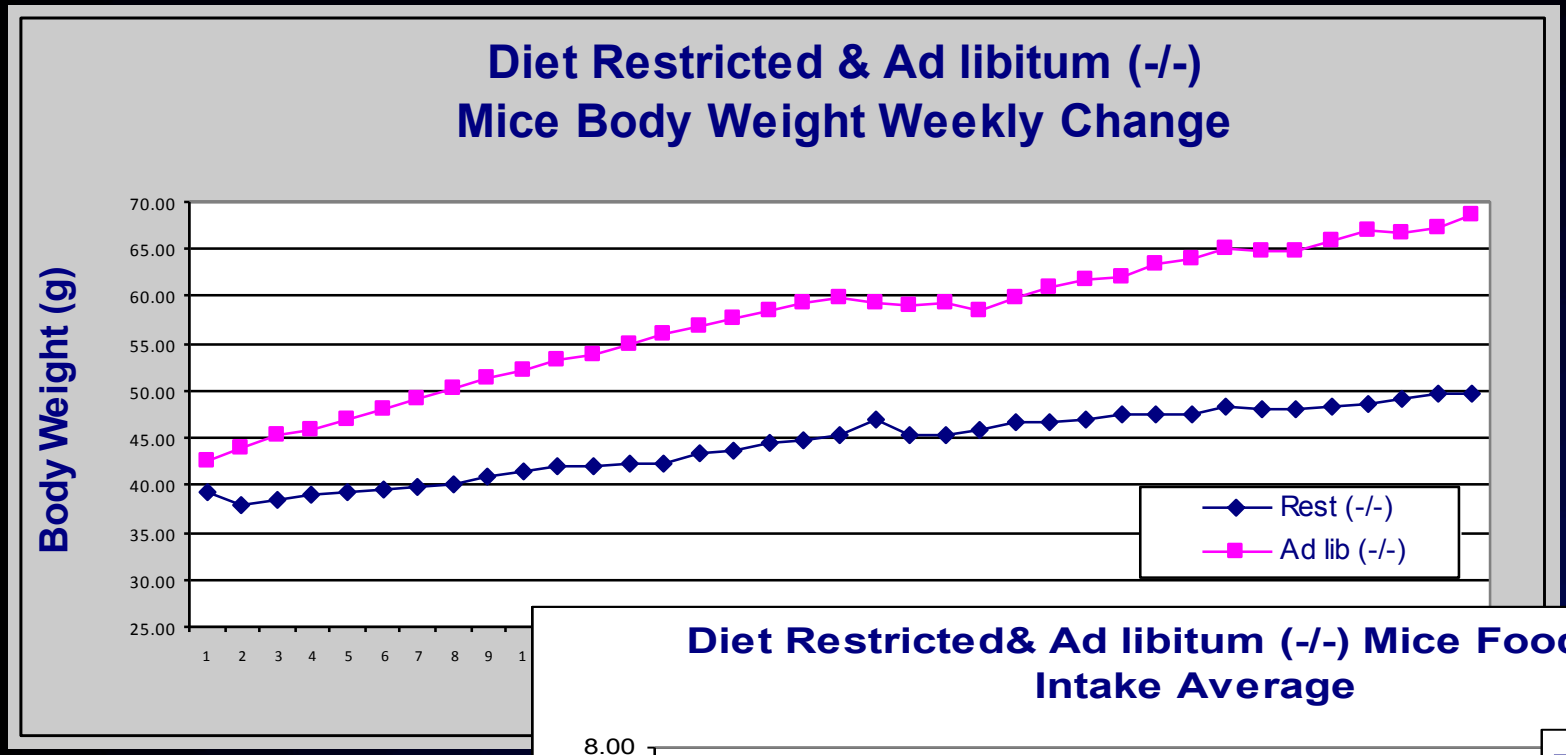


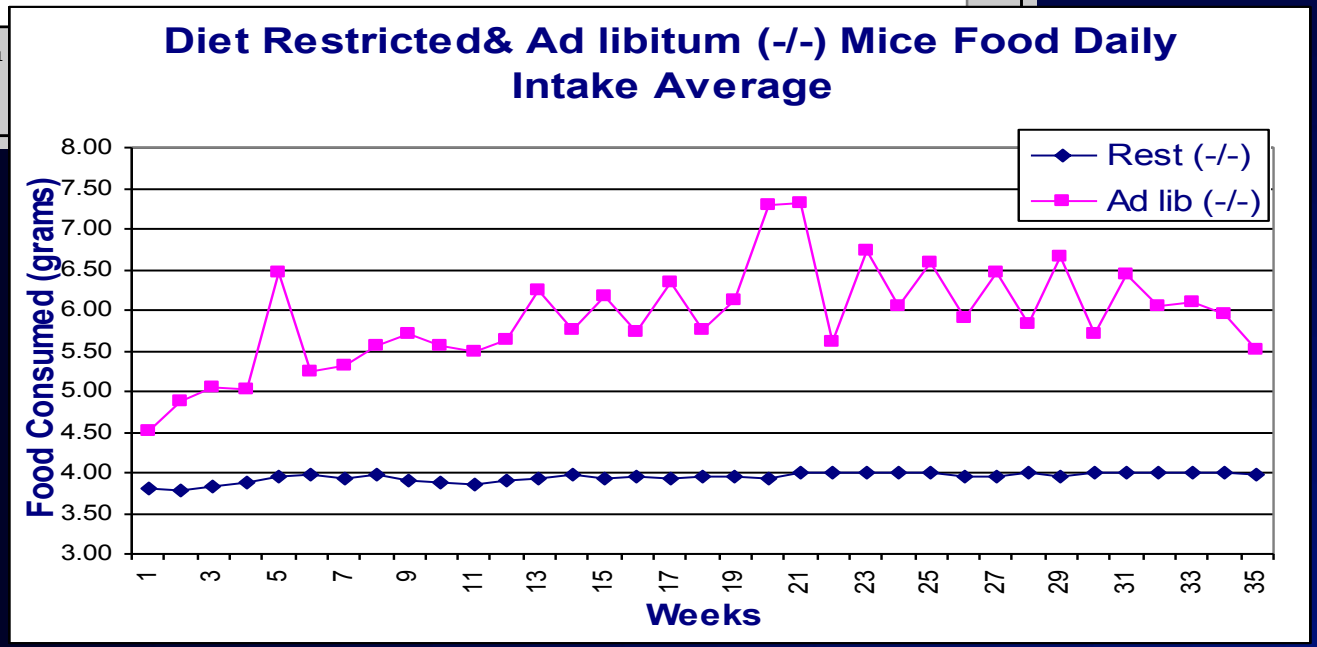


Ataxin-2 deficiency causes hyperphagia



Food restriction limits obesity





Normal anatomy of arcuate and paraventricular nuclei

Conclusions

- In contrast to invertebrates, ataxin-2 deficient mice are viable and fertile.
- Knockout animals do not have grossly visible malformations at birth.
- The CNS is normal by light microscopy.
- Rotarod performance is normal.
- $Sca2^{+/-}$ and $SCA2^{-/-}$ mice are obese.
- Obesity is caused by hyperphagia.
- A study of weight in SCA2 patients is warranted.
- The SCA2 gene represents a reasonable target for mutation analysis in humans with morbid obesity.