UNDERSTANDING KENNEDY'S DISEASE

CYNTHIA JORDAN

MICHIGAN STATE UNIVERSITY

KENNEDY'S DISEASE ASSOCIATION ANNUAL MEETING-NOV 9- 11, 2016

NIH definition

…progressive neurological disorders that destroy motor neurons, the cells that control essential voluntary muscle activity such as speaking, walking, breathing, and swallowing…When there are disruptions in the signals between the lowest motor neurons and the muscle, the muscles do not work properly; the muscles gradually weaken and may begin wasting away and develop uncontrollable twitching (called fasciculations) http://www.ninds.nih.gov/disorders/motor_neuron_diseases/detail_motor_neuron_diseases.htm

IN THE EYES OF NIH…
KENNEDY'S DISEASE IS A MOTONEURON DISEASE

WORKING ASSUMPTIONS

- Motoneuron death accounts for the progressive loss of motor function in motoneuron disease
- Because motoneurons die, it must be that the toxic agent acts directly in motoneurons to cause their death
- Muscle wasting in motoneuron disease accounts for the loss of muscle strength
- Loss of muscle strength is a secondary event caused by a loss of synaptic connections from motoneurons to muscle fibers

WHAT IS MY GOAL?

I want to…

UNDERSTAND WHY MOTOR FUNCTION DETERIORATES

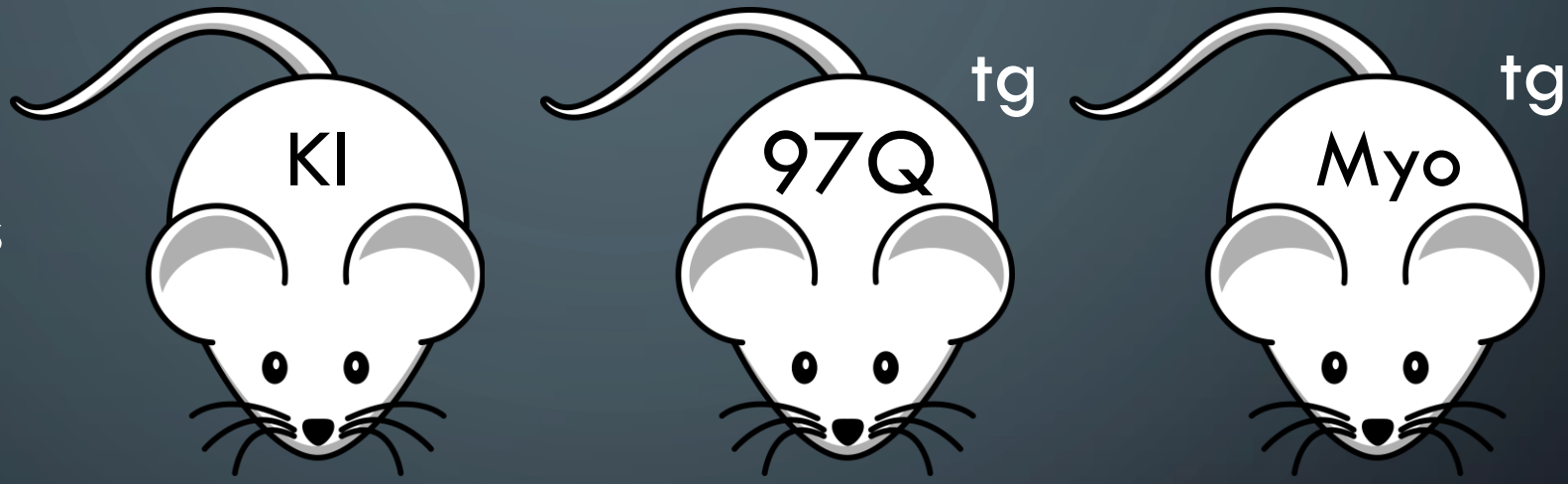
WHAT ARE THE EVENTS THAT TRIGGERS MOTOR DYSFUNCTION EARLY ON

WHAT ARE THE EVENTS BEHIND THE PROGRESSIVE WORSENING OF MOTOR DYSFUNCTION OVER TIME

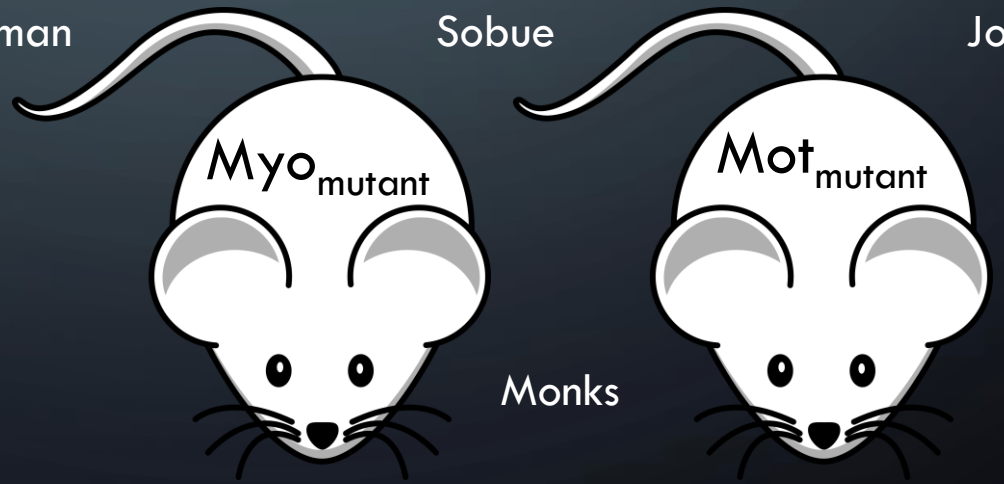
MY APPROACH?

- I am opportunistic…I study different mouse models of KD developed by different investigators

3 main models



2 new models



WORKING ASSUMPTION #1

MOTONEURON DEATH ACCOUNTS FOR THE PROGRESSIVE LOSS OF MOTOR FUNCTION IN MOTONEURON DISEASE

ALL 3 MODELS SHOW PROFOUND LOSSES IN MOTOR FUNCTION *WITHOUT* MOTONEURON LOSS

Knock-in model

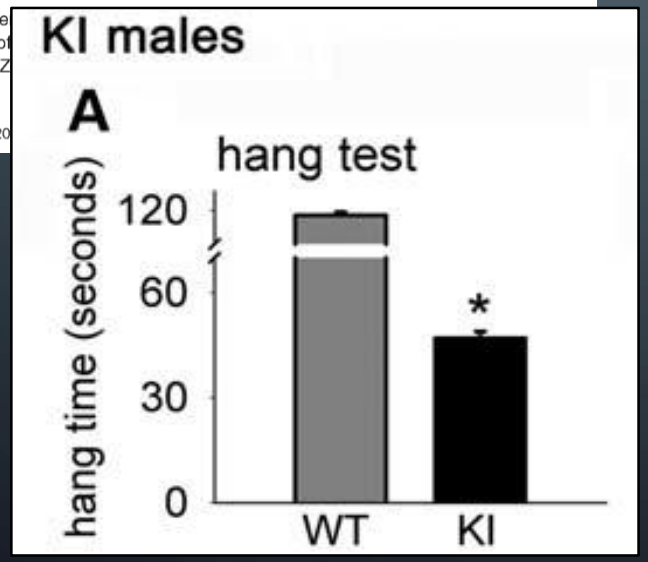
Human Molecular Genetics, 2011 **1–16**
doi:10.1093/hmg/ddr380

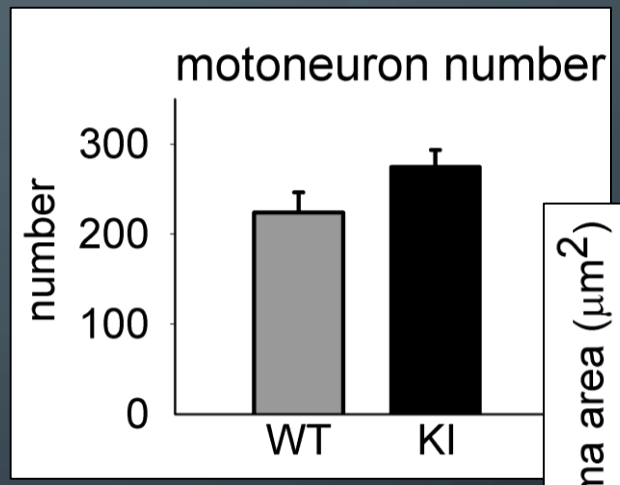
Impaired motoneuronal retrograde transport in two models of SBMA implicates two sites of androgen action

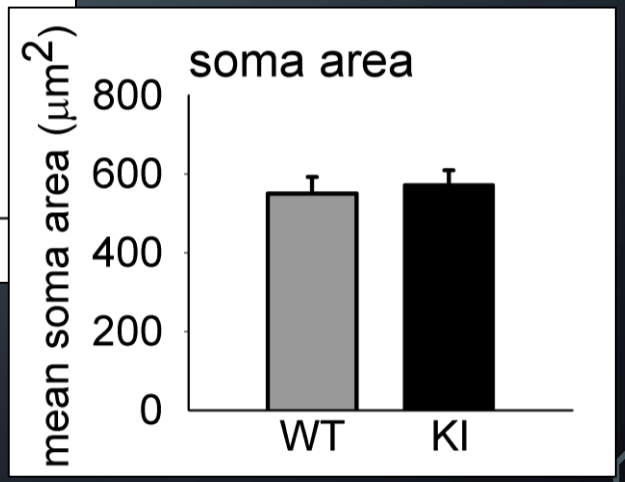
Michael Q. Kemp[1], Jessica L. Poort[1], Rehan M. Baqri[1], Andrew P. Lieberman[3], S. Marc Breedlove[1,2], Kyle E. Miller[1,4] and Cynthia L. Jordan[1,2,*]

[1]Neuroscience Program and [2]Psychology Departme
48824, USA, [3]Department of Pathology, University of
Dr., Ann Arbor, MI 48109, USA and [4]Department of Z
USA

Received May 2, 2011; Revised and Accepted August 23, 20







ALL 3 MODELS SHOW PROFOUND LOSSES IN MOTOR FUNCTION *WITHOUT* MOTONEURON LOSS

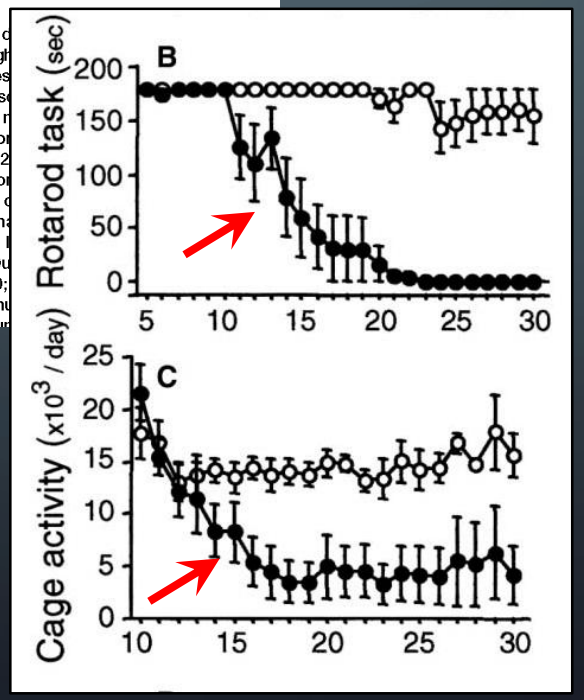
97Q model

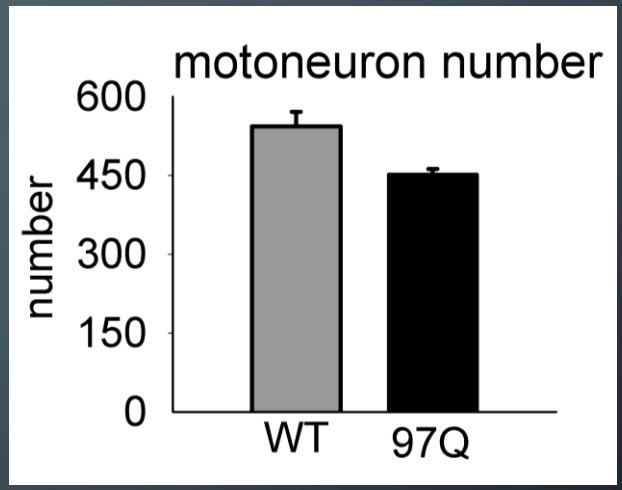
Neuron, Vol. 35, 843–854, August 29, 2002, Copyright ©2002 by Cell Press

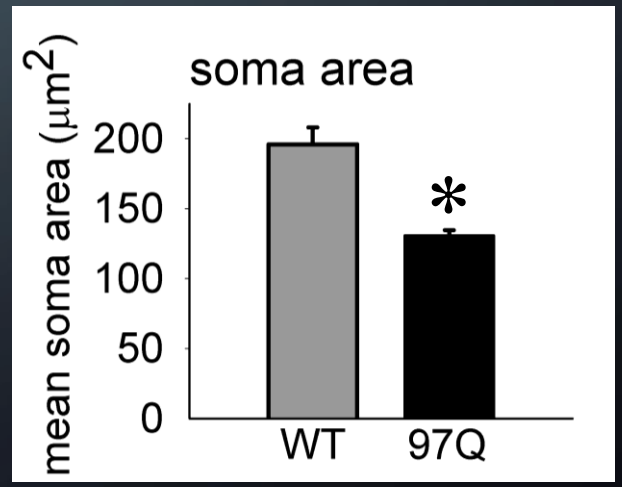
Testosterone Reduction Prevents Phenotypic Expression in a Transgenic Mouse Model of Spinal and Bulbar Muscular Atrophy

Masahisa Katsuno,[1,4] Hiroaki Adachi,[1,4]
Akito Kume,[1] Mei Li,[1] Yuji Nakagomi,[2]
Hisayoshi Niwa,[1] Chen Sang,[1] Yasushi Kobayashi,[1]
Manabu Doyu,[1] and Gen Sobue[1,3]
[1]Department of Neurology
Nagoya University Graduate School of Medicine
65 Tsurumai-cho
Showa-ku, Nagoya 466-8550
Japan
[2]Laboratory of Electron Microscopy
Aichi Medical University
21 Karimata, Yazako
Nagakute-cho, Aichi 480-1195
Japan

spinocerebellar ataxia, and c
ysian atrophy (DRPLA) (Zogh
2000). These polyQ diseases
ings such as anticipation, s
et al., 1999), and selective n
involvement despite widespr
tant gene (Zoghbi and Orr, 2
is also an inverse correlatio
size and the age at onset, c
justed by the age at examin
1992; La Spada et al., 1992;
as other polyQ diseases (Du
1993; Zoghbi and Orr, 2000;
Previously, we reported nu
taining the mutant and trun







ALL 3 MODELS SHOW PROFOUND LOSSES IN MOTOR FUNCTION *WITHOUT* MOTONEURON LOSS

Myo model

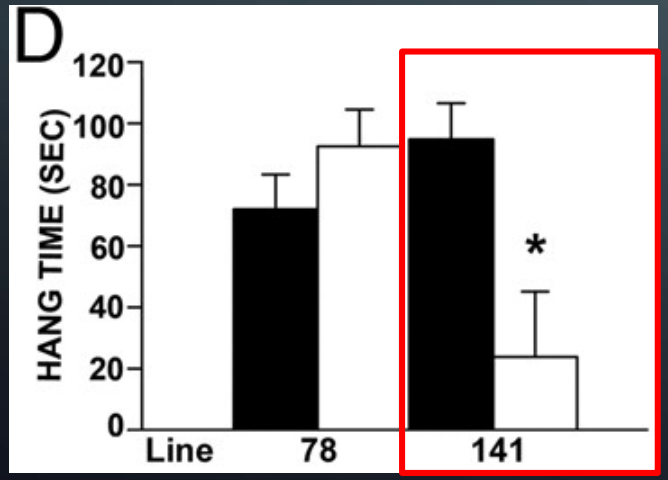
PNAS

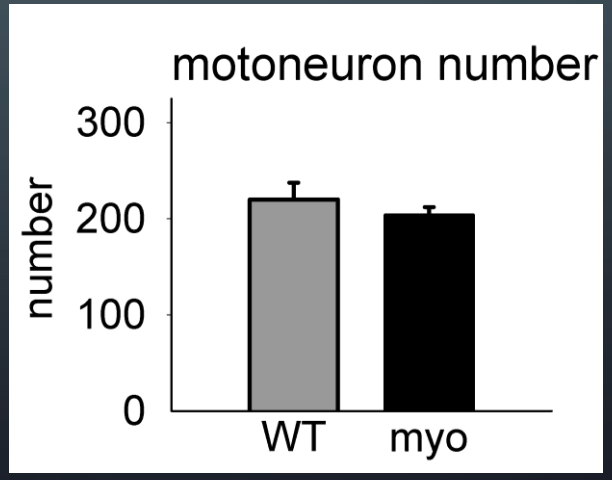
Overexpression of wild-type androgen receptor in muscle recapitulates polyglutamine disease

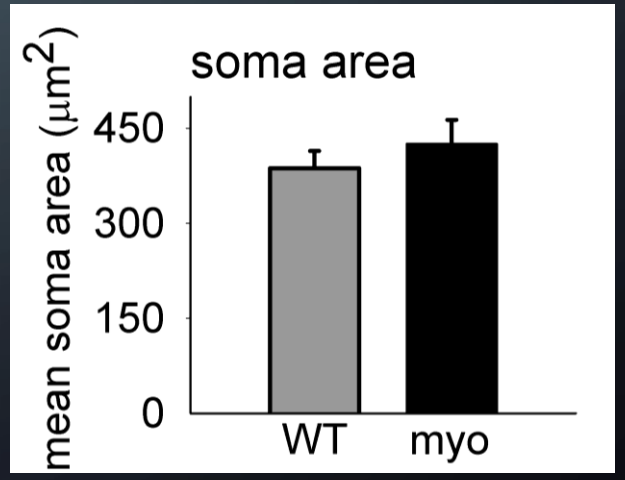
Douglas Ashley Monks*†‡, Jamie A. Johansen*, Kaiguo Mo‡, Pengcheng Rao‡, Bryn Eagleson§, Zhigang Yu¶, Andrew P. Lieberman¶, S. Marc Breedlove*†, and Cynthia L. Jordan*†‖

*Neuroscience Program and †Department of Psychology, Michigan State University, East Lansing, MI 48824; ‡Department of Psychology and Institute of Medical Science, University of Toronto, Mississauga, ON, Canada L5L 1C6; §Van Andel Institute, Grand Rapids, MI 49503; and ¶Department of Pathology, University of Michigan, Ann Arbor, MI 48109

Edited by Joshua R. Sanes, Harvard University, Cambridge, MA, and approved September 26, 2007 (received for review June 12, 2007)







CONCLUSION?

MOTONEURON DEATH *PER SE* DOES NOT CAUSE THE LOSS IN MOTOR FUNCTION

even though it may contribute to the worsening symptoms over time

WORKING ASSUMPTION #2

WHEN MOTONEURONS DIE, IT MUST BE THAT THE TOXIC AGENT ACTS DIRECTLY IN MOTONEURONS TO CAUSE THEIR DYSFUNCTION AND DEATH

SO…
WHILE WE THINK MOTONEURON DEATH DOES *NOT* TRIGGER (AND MAY NOT UNDERLIE) MOTOR DYSFUNCTION…

WE CAN STILL ASK…

DO MUTANT ANDROGEN RECEPTORS ACT IN MOTONEURONS TO CAUSE THE LOSS OF MOTOR FUNCTION?

WELL…APPARENTLY NOT

Neuron
Article

Muscle Expression of Mutant Androgen Receptor Accounts for Systemic and Motor Neuron Disease Phenotypes in Spinal and Bulbar Muscular Atrophy

Constanza J. Cortes,[1] Shuo-Chien Ling,[2,11] Ling T. Guo,[3] Gene Hung,[4] Taiji Tsunemi,[1,12] Linda Ly,[1] Seiya Tokunaga,[2] Edith Lopez,[1] Bryce L. Sopher,[5] C. Frank Bennett,[4] G. Diane Shelton,[3] Don W. Cleveland,[2,6] and Albert R. La Spada[1,2,6,7,8,9,10,*]

OPEN ACCESS

Cell Reports
Article

Peripheral Androgen Receptor Gene Suppression Rescues Disease in Mouse Models of Spinal and Bulbar Muscular Atrophy

Andrew P. Lieberman,[1,*] Zhigang Yu,[1] Sue Murray,[2] Raechel Peralta,[2] Audrey Low,[2] Shuling Guo,[2] Xing Xian Yu,[2] Constanza J. Cortes,[3] C. Frank Bennett,[2] Brett P. Monia,[2] Albert R. La Spada,[3,4] and Gene Hung[2,*]

CONCLUSION?

NOT ONLY DOES MOTONEURON DEATH NOT ACCOUNT FOR THE LOSS IN MOTOR FUNCTION

BUT

THE MUTANT ANDROGEN RECEPTOR DOES NOT APPEAR TO ACT IN MOTONEURONS TO CAUSE MOTOR DYSFUNCTION

WORKING ASSUMPTION #3

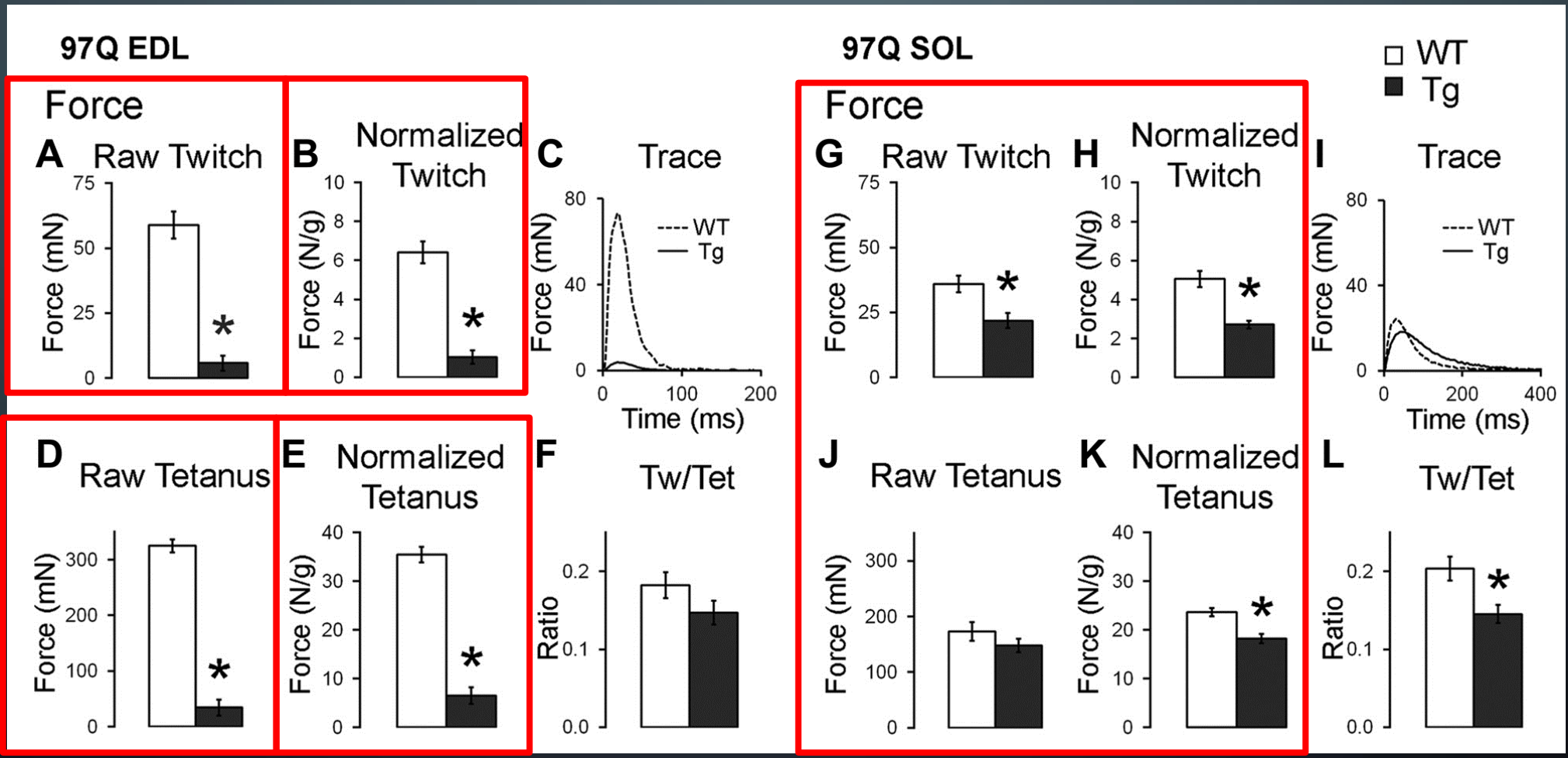
MUSCLE WASTING IN MOTONEURON DISEASE ACCOUNTS FOR THE LOSS OF MUSCLE STRENGTH

Contractile dysfunction in muscle may underlie androgen-dependent motor dysfunction in spinal bulbar muscular atrophy

Kentaro Oki, Katherine Halievski, Laura Vicente, Youfen Xu, Donald Zeolla, Jessica Poort, Masahisa Katsuno, Hiroaki Adachi, Gen Sobue, Robert W. Wiseman, S. Marc Breedlove and Cynthia L. Jordan

J Appl Physiol 118:941-952, 2015. First published 5 February 2015;
doi:10.1152/japplphysiol.00886.2014

LOSS OF MUSCLE CONTRACTILE FORCE OCCURS *INDEPENDENT* OF MASS



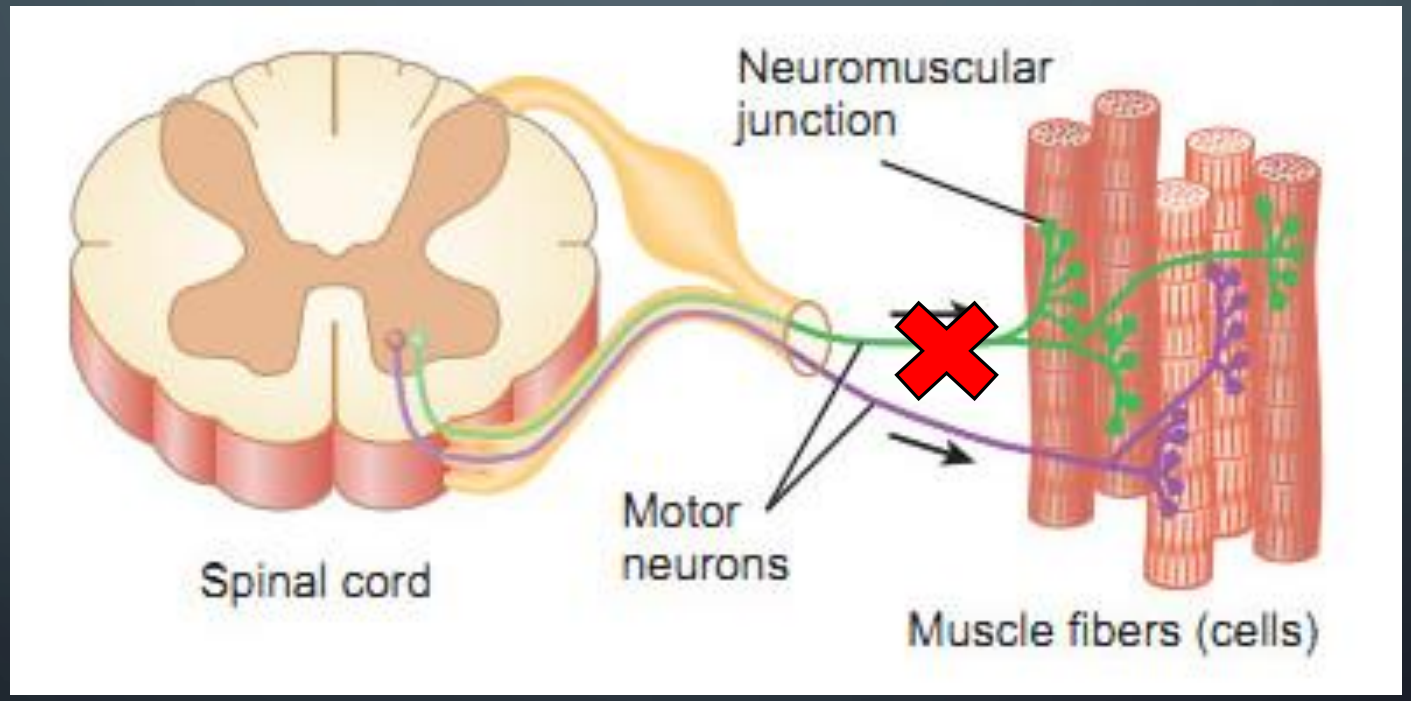
CONCLUSION?

MUSCLE WASTING DOES NOT EXPLAIN THE LOSS OF MUSCLE STRENGTH

(even though wasting can and may contribute significantly to lost muscle strength in the later stages)

WORKING ASSUMPTION #4

LOSS OF MUSCLE STRENGTH IS A SECONDARY EVENT CAUSED BY DENERVATION OF MUSCLE FIBERS



Muscle denervation = loss of synaptic inputs

NEUROMUSCULAR JUNCTIONS *ARE* PATHOLOGICAL BUT *NOT DENERVATED* IN SMBA MOUSE MODELS

HMG Advance Access published August 18, 2016

OXFORD

Human Molecular Genetics, , Vol. 0, No. 0 1–16

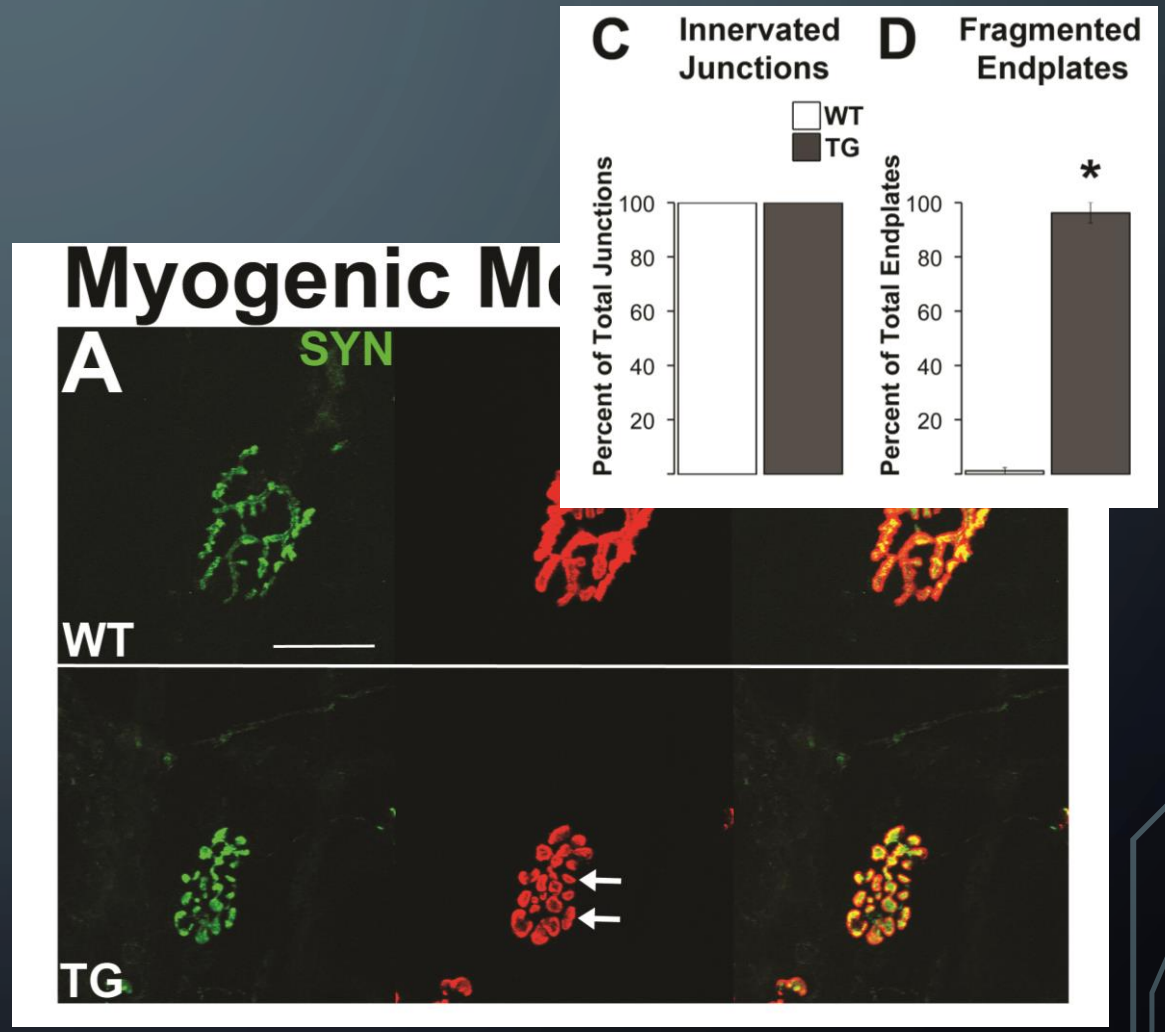
doi: 10.1093/hmg/ddw222
Advance Access Publication Date: 4 August 2016
Original Article

ORIGINAL ARTICLE

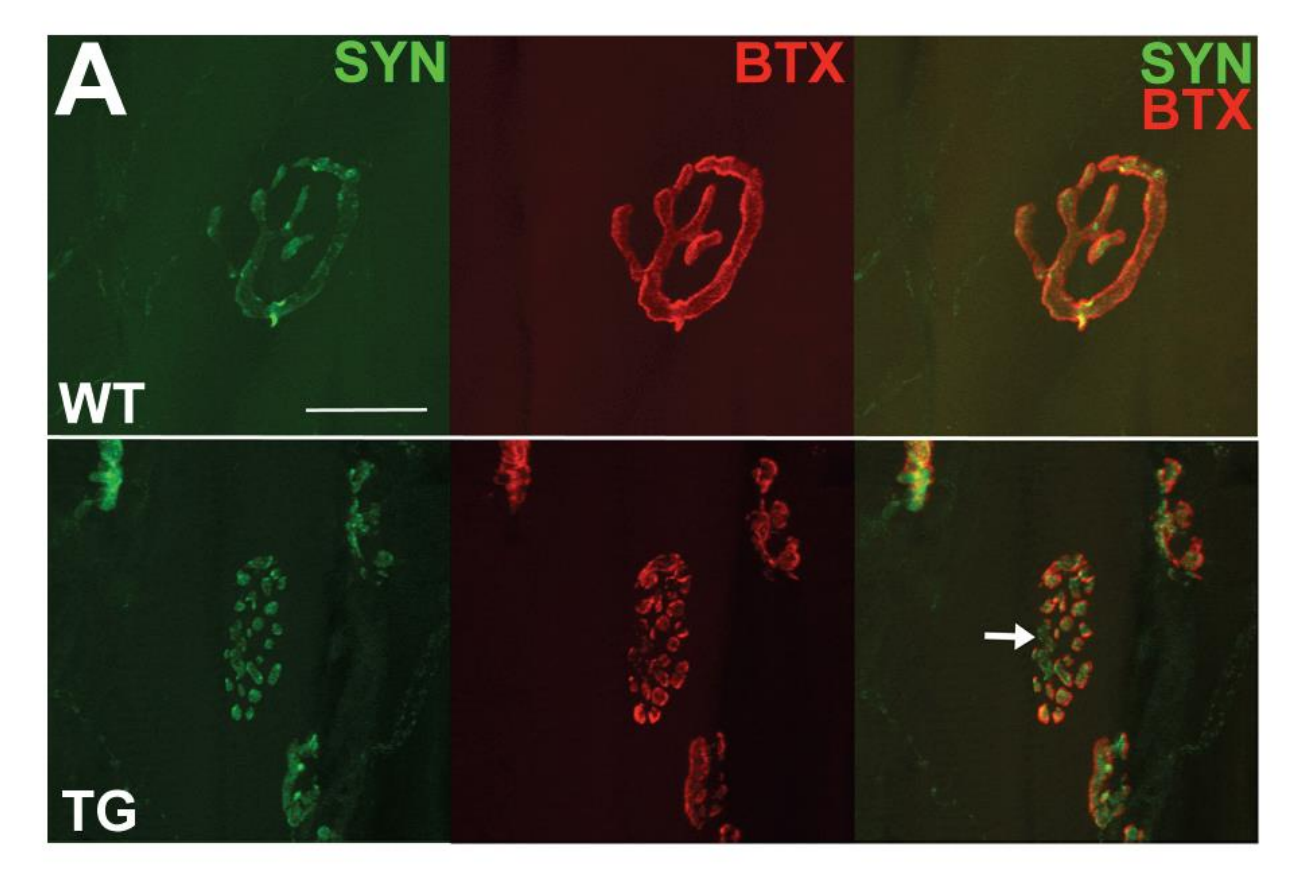
Neuromuscular junctions are pathological but not denervated in two mouse models of spinal bulbar muscular atrophy

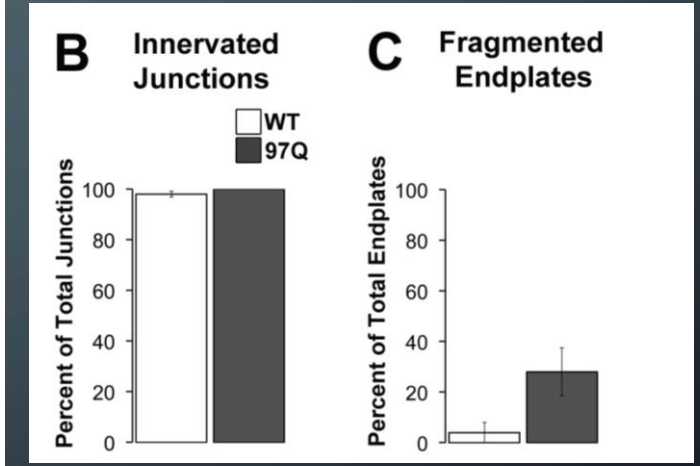
Jessica E. Poort[1], Mary B. Rheuben[1], S. Marc Breedlove[1] and Cynthia L. Jordan[1,*]

NEUROMUSCULAR JUNCTIONS ARE *NOT* DENERVATED IN DISEASED KI OR MYO MICE



NEUROMUSCULAR JUNCTIONS ARE *NOT* DENERVATED IN DISEASED 97Q MICE





CONCLUSION?

MUSCLE DENERVATION DOES NOT EXPLAIN THE LOSS IN MUSCLE STRENGTH AND MASS

(even though denervation may contribute to the worsening of symptoms as the disease progresses)

ARE THERE DEFECTS IN SYNAPTIC FUNCTION THAT COULD EXPLAIN THE LOSS OF MOTOR FUNCTION?

5094 • The Journal of Neuroscience, May 4, 2016 • 36(18):5094–5106

Neurobiology of Disease

Defects in Neuromuscular Transmission May Underlie Motor Dysfunction in Spinal and Bulbar Muscular Atrophy

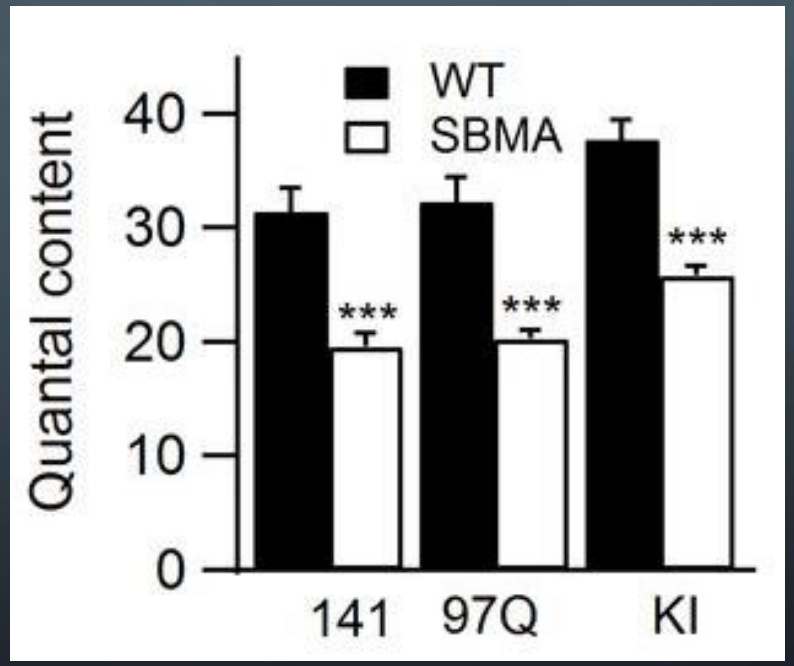
Youfen Xu,[1] Katherine Halievski,[1] Casey Henley,[1] William D. Atchison,[1] Masahisa Katsuno,[2] Hiroaki Adachi,[3] Gen Sobue,[2] S. Marc Breedlove,[1] and Cynthia L. Jordan[1]

[1]Neuroscience Program, Michigan State University, East Lansing, Michigan 48824, [2]Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan, [3]Department of Neurology, University of Occupational and Environment Health School of Medicine, Fukuoka 807-8555, Japan

YES, THERE ARE DEFECTS IN SYNAPTIC FUNCTION

Weaker synapses in motor-impaired mice:

They release less excitatory juice (acetylcholine) to stimulate muscle contraction



OVERALL CONCLUSION?

A LOSS OF MOTOR FUNCTION IS LIKELY DUE TO:

1. Primary defects in muscle function
2. Secondary defects in synaptic function

WHAT IS BEHIND THE DISCREPANCY? MODELS VS PATIENTS

NEXT TALK…

THEME: NOT ALL MUSCLES ARE CREATED EQUALLY

BDNF helps some muscles but not others

ACKNOWLEDGEMENTS

The founders!

Ashley Monks

Jamie Johansen

Weak muscles

Ken OKi

Disrupted NMJs

Jessica Poort

Youfen Xu

AR
(working in muscle)

Weak synapses

Deficit in muscle BDNF mRNA

Kathy Halievski

Mike Kemp

Impaired retrograde transport

THANK YOU!