What is past is prologue

The Tempest

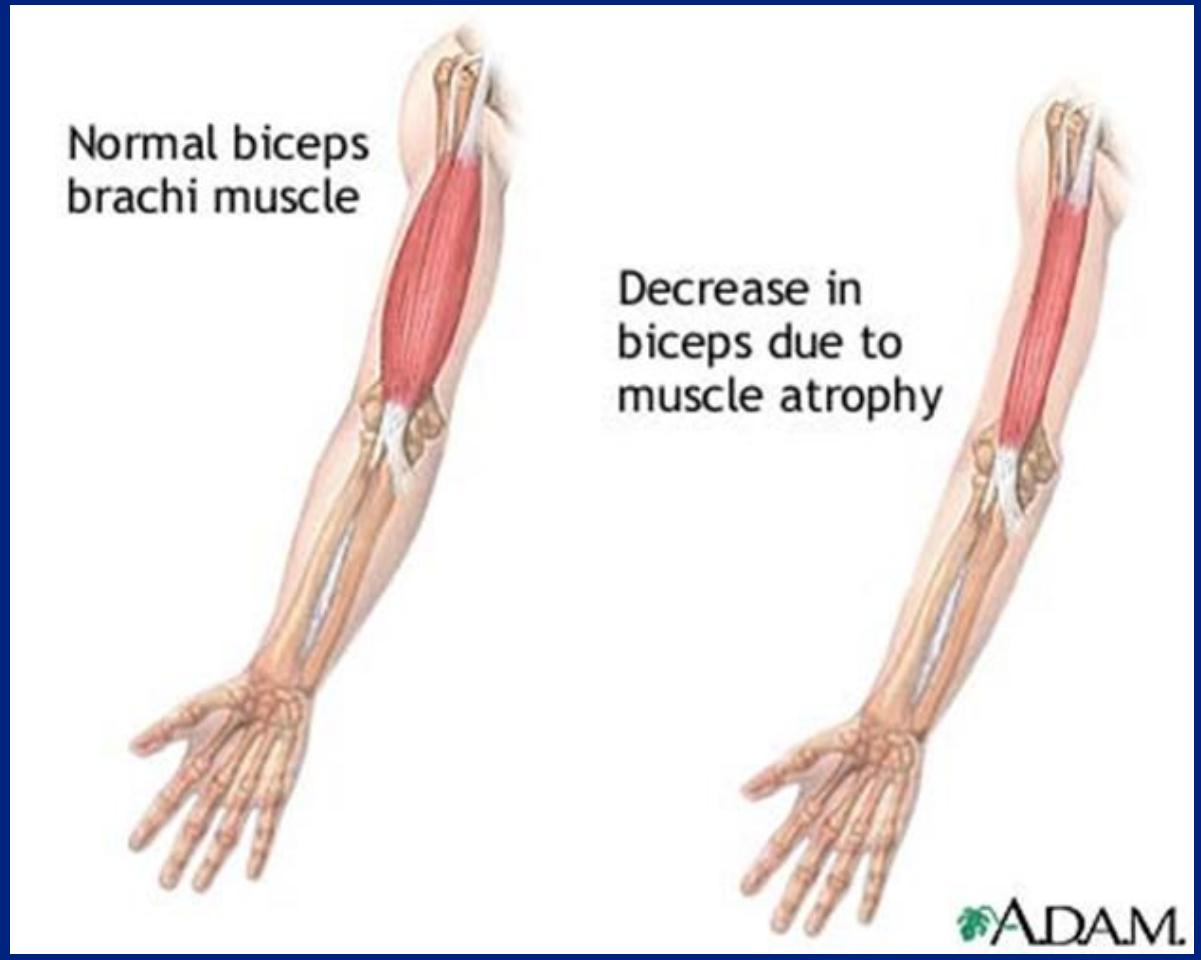
Progressive proximal spinal and bulbar muscular atrophy of late onset. A sex-linked recessive trait.

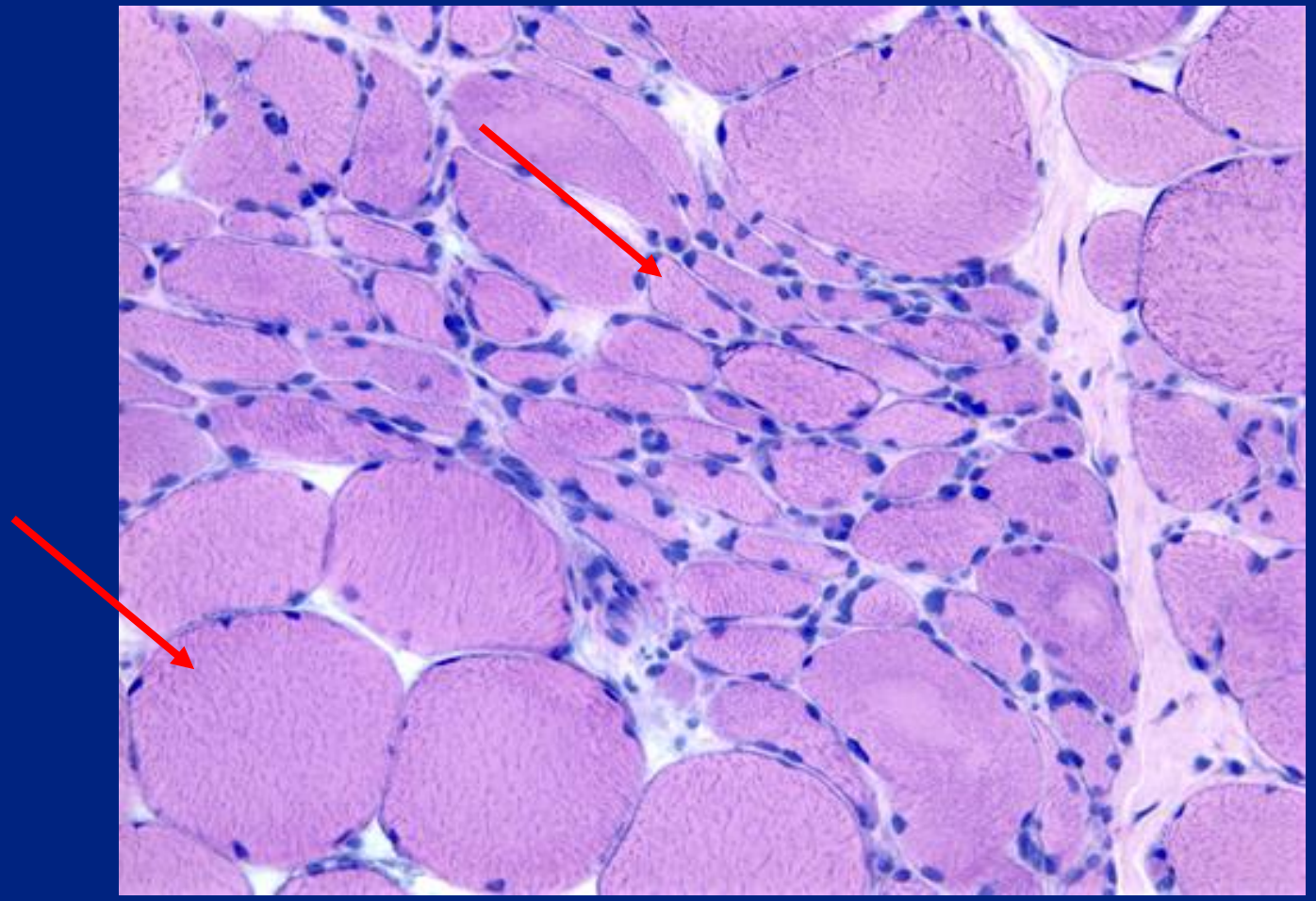
Kennedy WR, Alter M, Sung JH.

Neurology. 1968 Jul;18(7):671-80

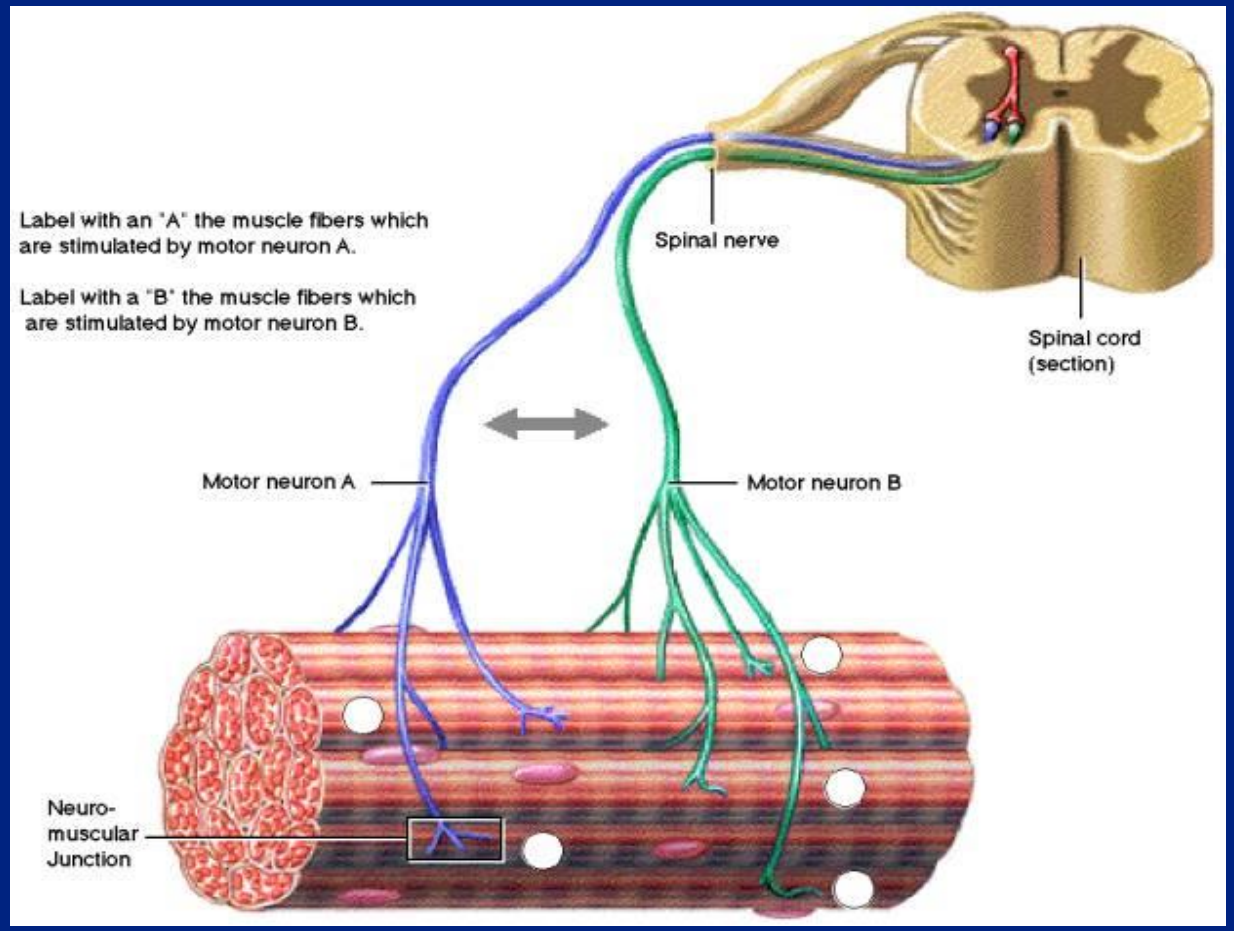
A family of progressive bulbar palsy.

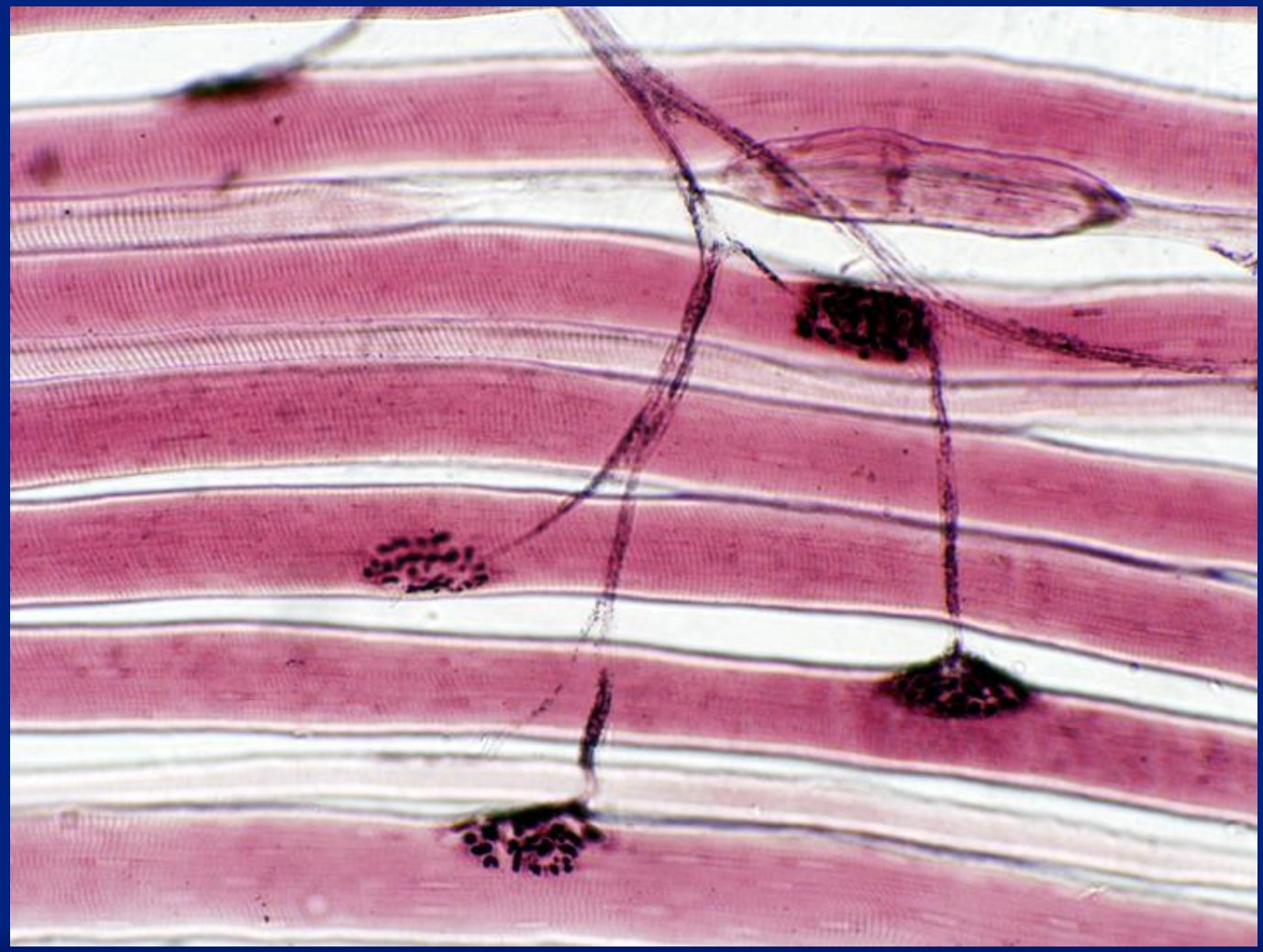
Kawahara H (1897)


Normal biceps brachi muscle
Decrease in biceps due to muscle atrophy
A.D.A.M.

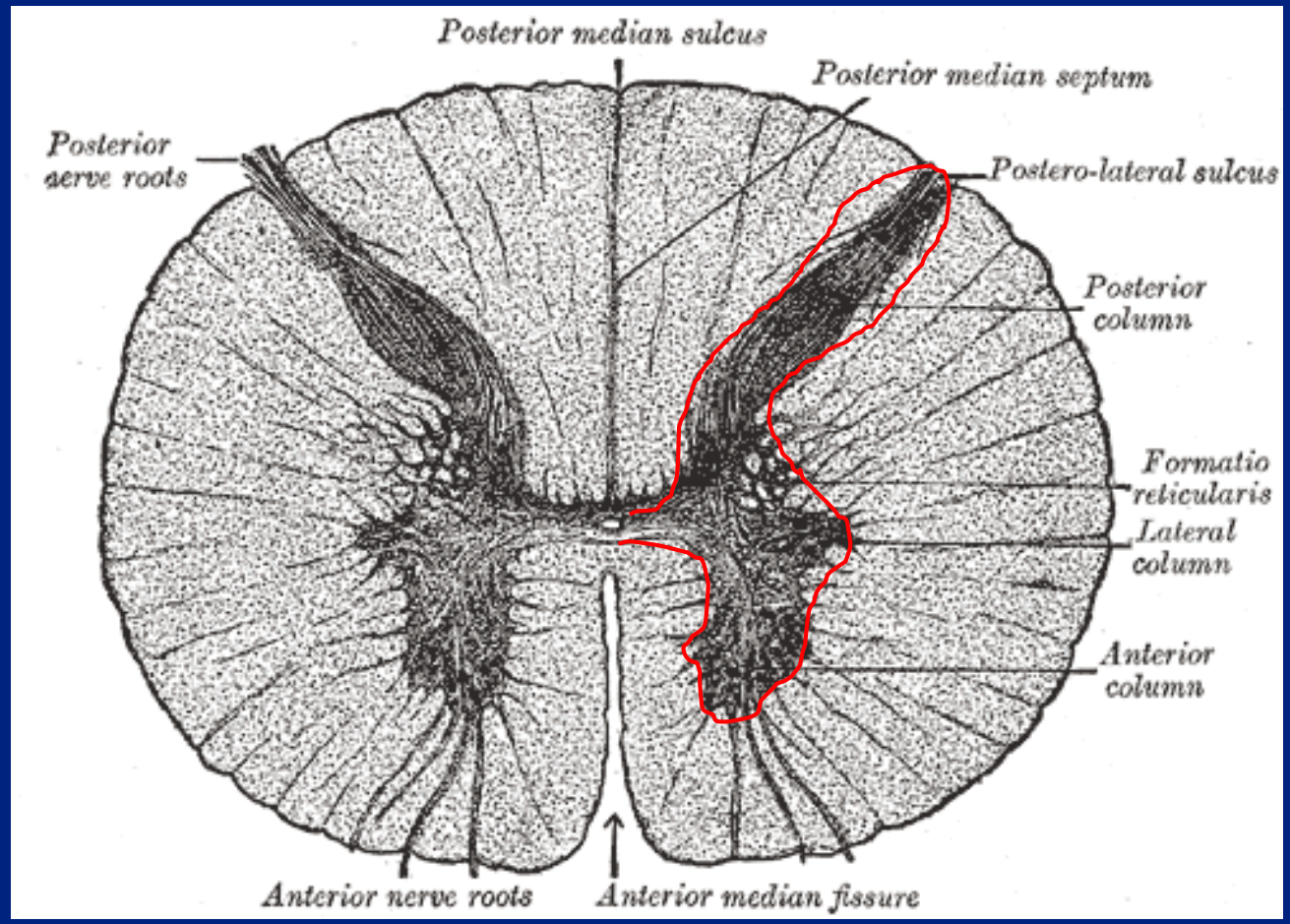


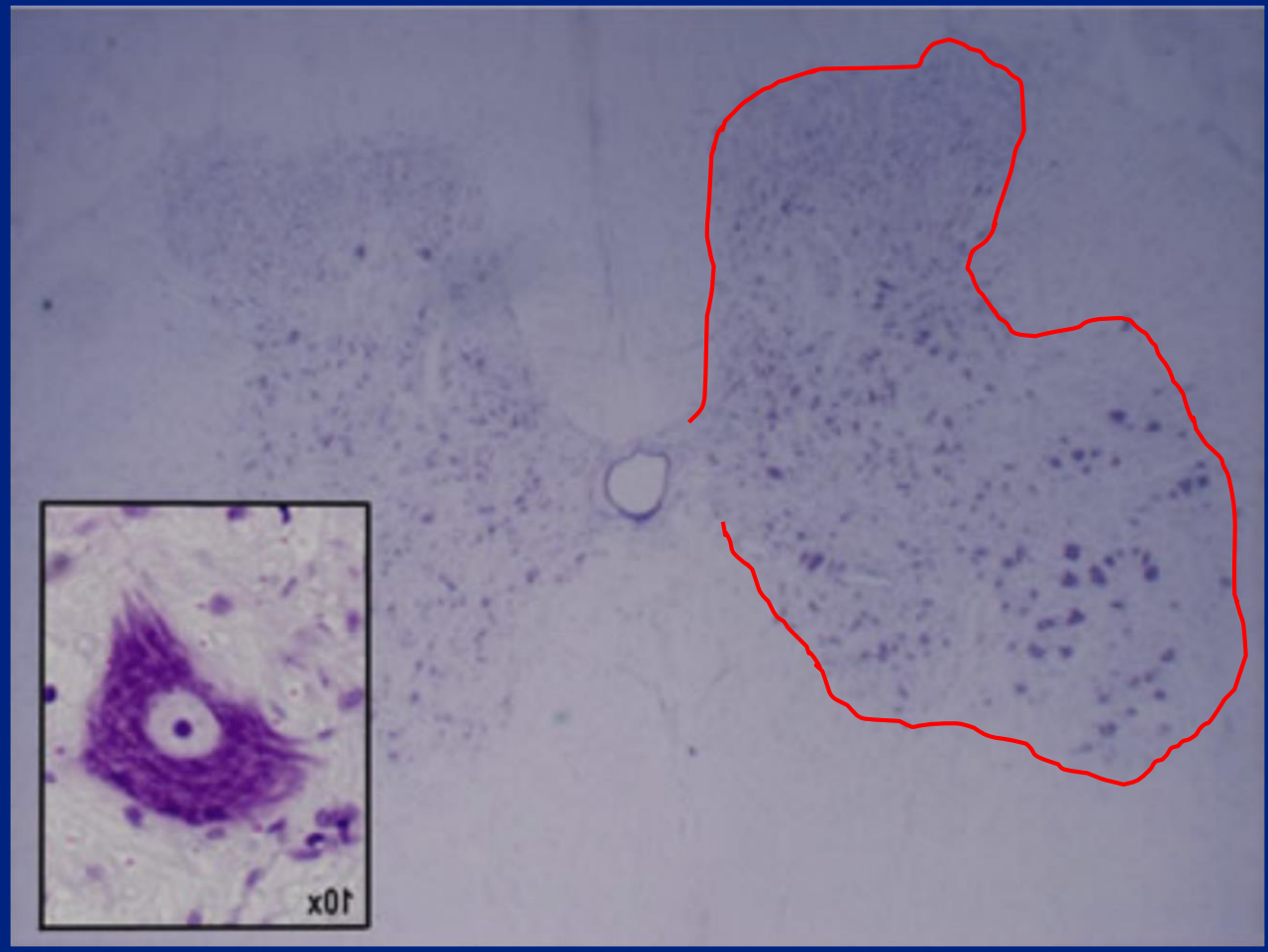
Motor Neurons





http://stevegallik.org/sites/histologyolm.stevegallik.org/htmlpages/HOLM_Chapter07_Page06.html


Posterior median sulcus
Posterior median septum
Posterior nerve roots
Postero-lateral sulcus
Posterior column
Formatio reticularis
Lateral column
Anterior column
Anterior nerve roots
Anterior median fissure


10x

Katsuno etal, Experimental Neurology 2006

Progressive proximal spinal and bulbar muscular atrophy of late onset. A sex-linked ~~recessive~~ trait.

Kennedy WR, Alter M, Sung JH.

Neurology. 1968 Jul;18(7):671-80

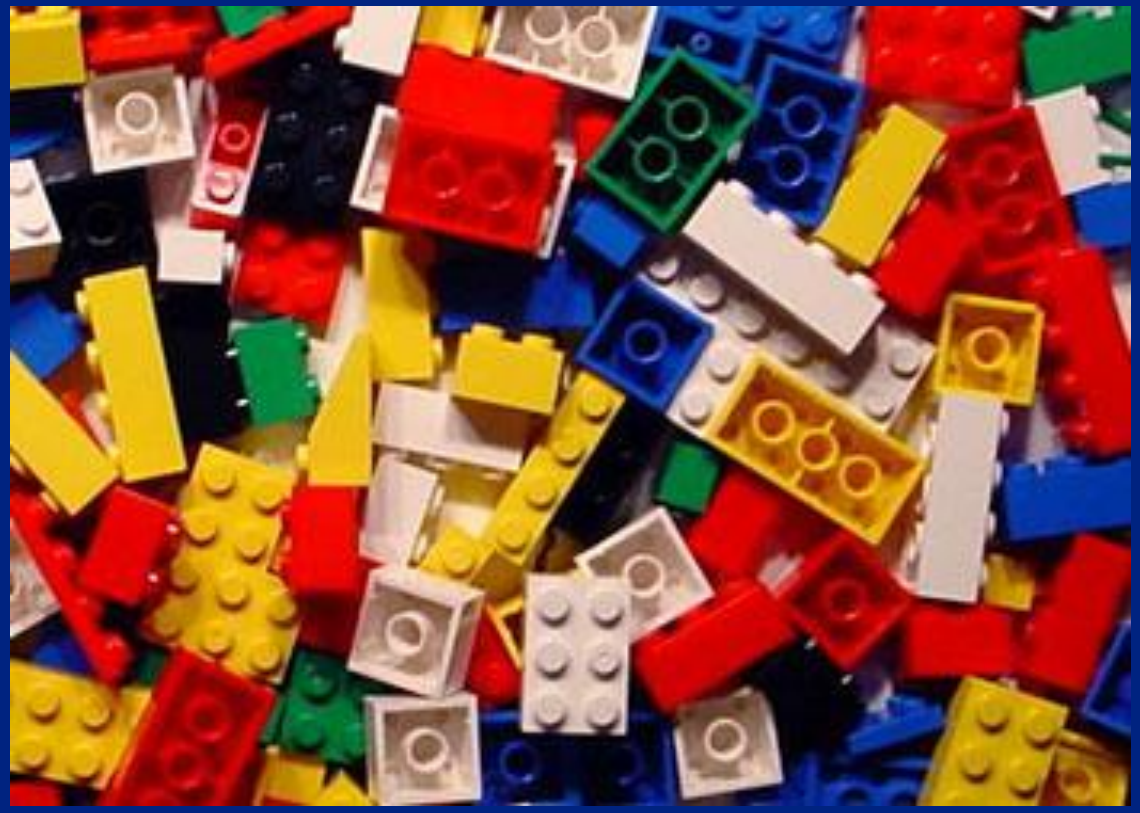
"The law of heredity is that all undesirable traits come from the other parent."

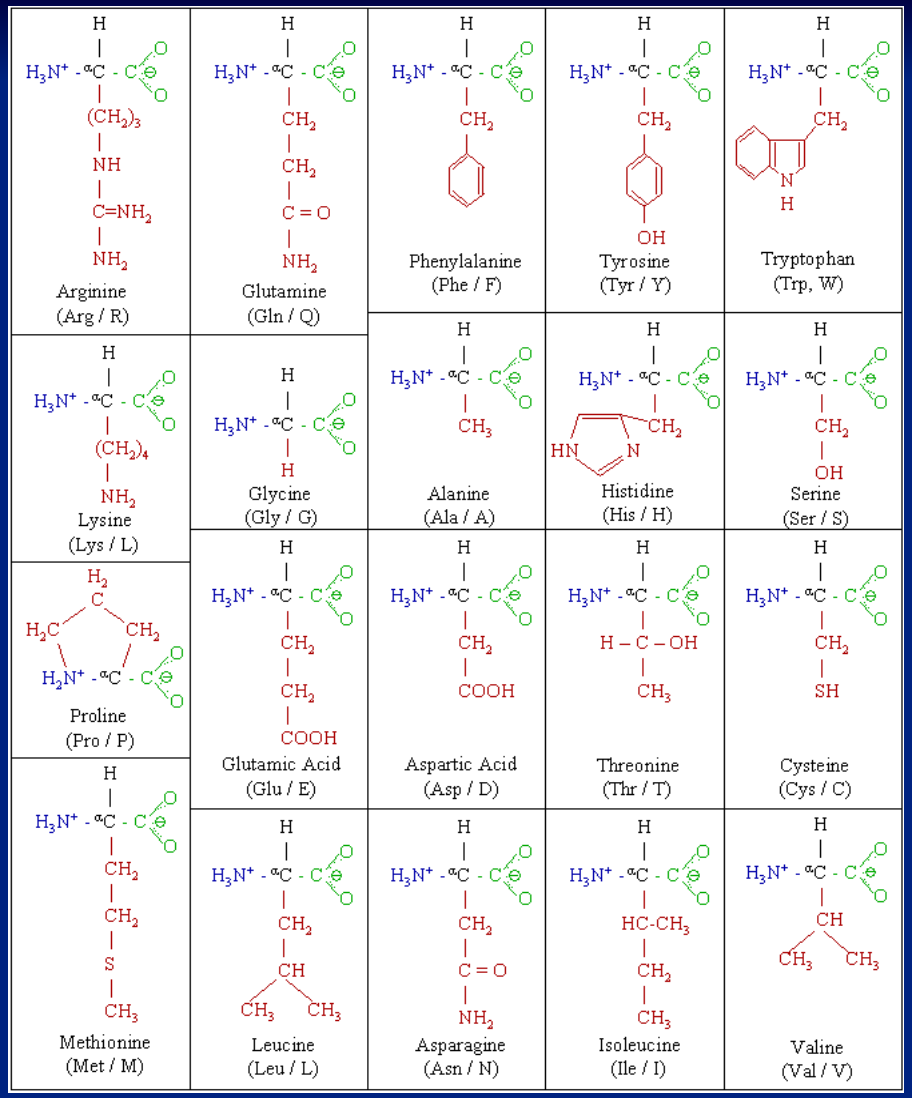
Anonymous

The only unitasker allowed in my kitchen is a fire extinguisher.

— Alton Brown —

AZ QUOTES

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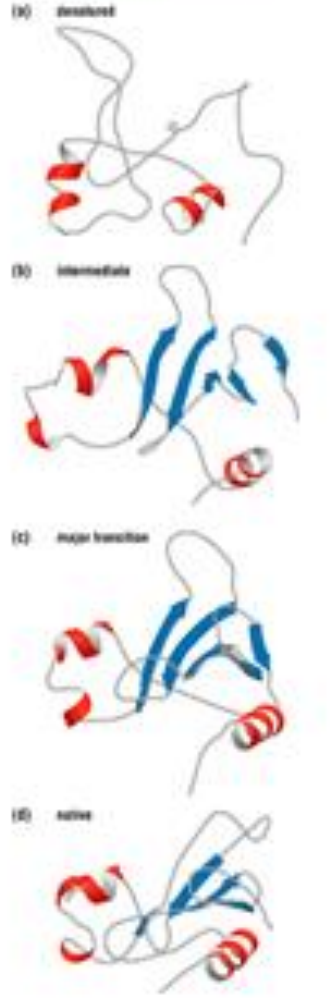
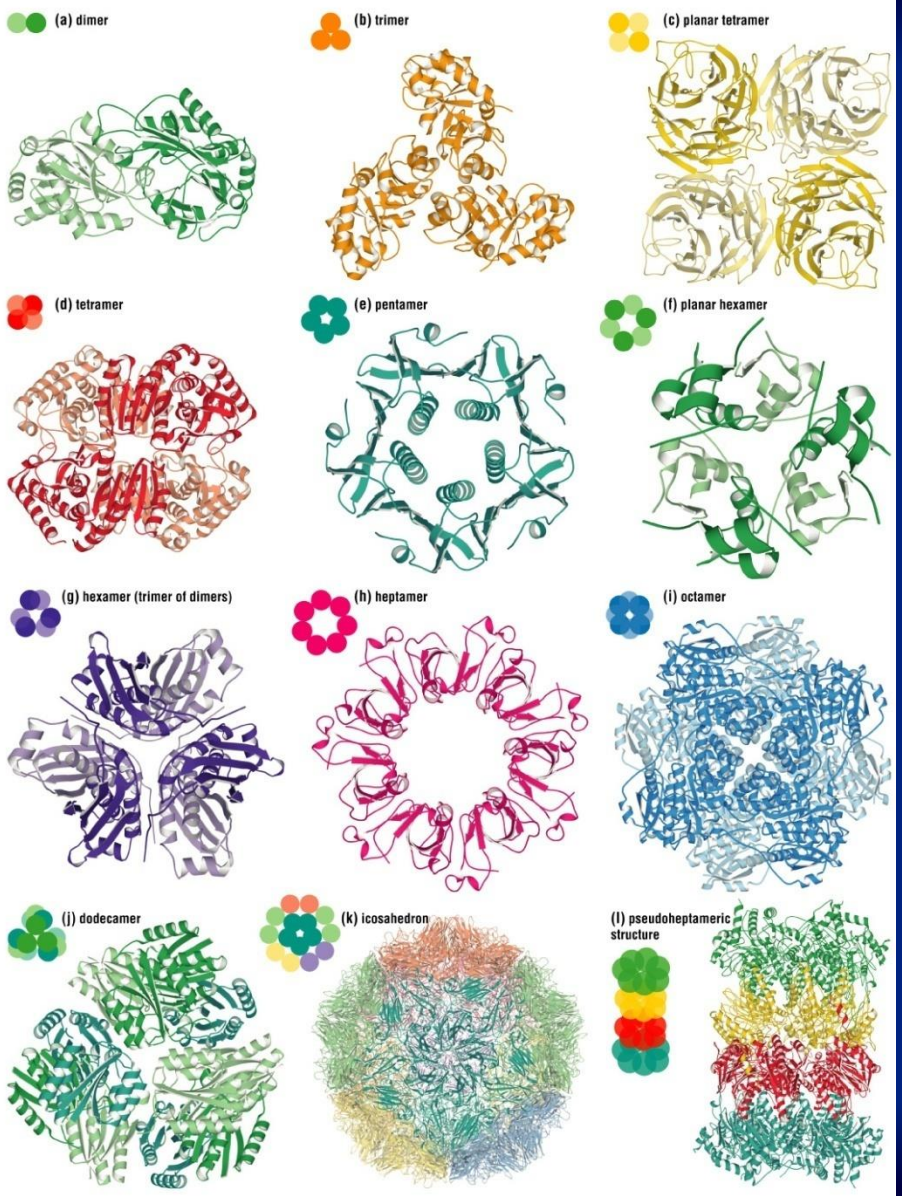
(Arg / R)
Glutamine
(Gln / Q)
Phenylalanine
(Phe / F)
Tyrosine
(Tyr / Y)
Tryptophan
(Trp, W)
Lysine
(Lys / L)
Glycine
(Gly / G)
Alanine
(Ala / A)
Histidine
(His / H)
Serine
(Ser / S)
Proline
(Pro / P)
Glutamic Acid
(Glu / E)
Aspartic Acid
(Asp / D)
Threonine
(Thr / T)
Cysteine
(Cys / C)
Methionine
(Met / M)
Leucine
(Leu / L)
Asparagine
(Asn / N)
Isoleucine
(Ile / I)
Valine
(Val / V)

From Protein Structure and Function
by Gregory A Petsko and Dagmar Ringe



From **Protein Structure and Function** by Gregory A Petsko and Dagmar Ringe



What do we have to know about proteins to pass the test?

(yes, there is a test!)

Proteins are the ‘doers’ of a cell & required for the cell to function correctly

Proteins are composed of long, linear chains of amino acids with each protein having a unique sequence of amino acids

This sequence of aa cause the protein to fold into a unique three dimensional shape that determines the function of the protein

If a protein misfolds, the protein is dysfunctional which may cause serious consequences for the cell

All is not well; I doubt some foul play."

Hamlet

"Genes are important because they are the blueprints for proteins, but proteins are where the action is in human life and health. This ability to find links between sets of proteins involved in different genetic disorders offers a novel approach for more rapidly identifying new candidate genes involved in human diseases."

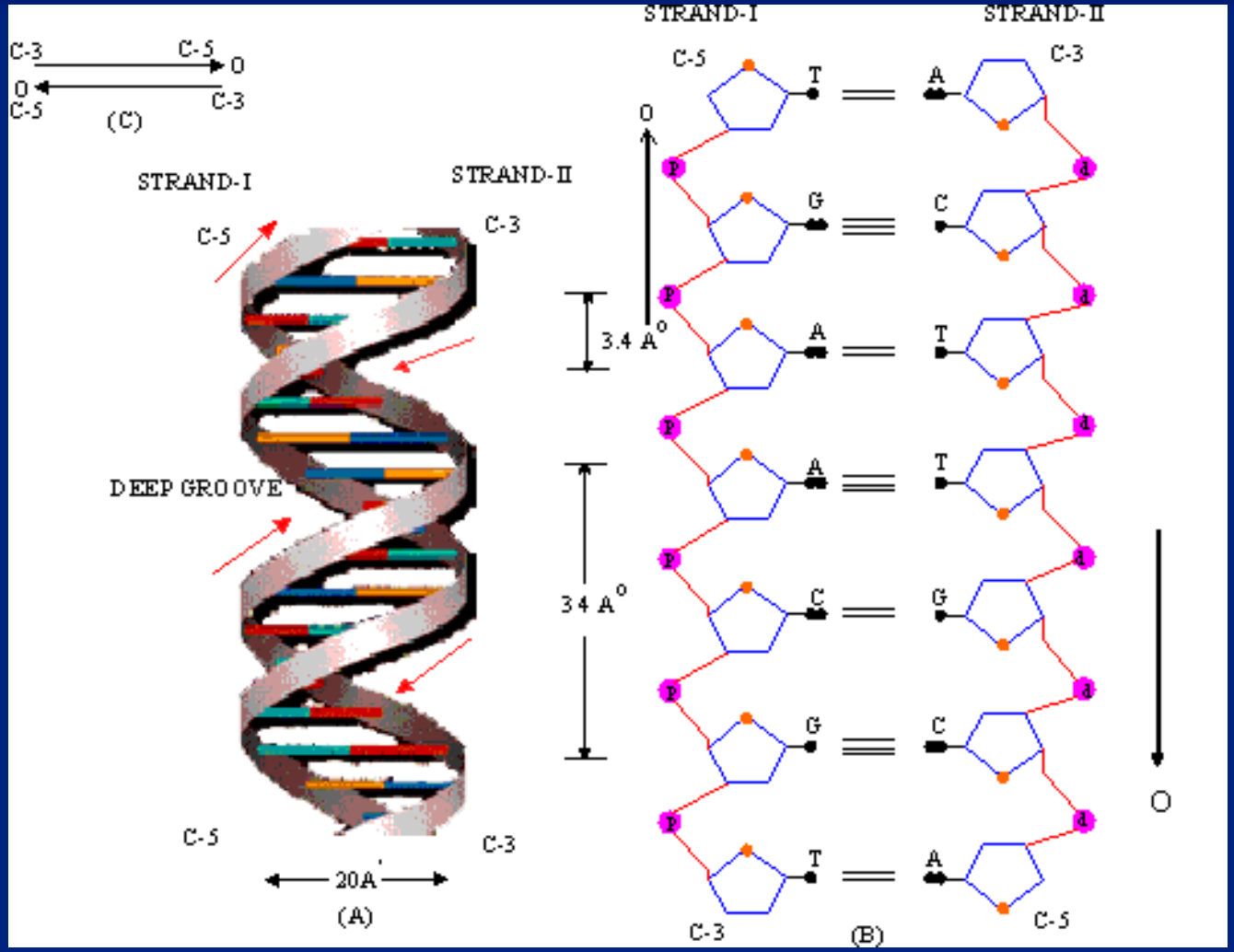
Akhilesh Pandey

What makes up a gene?

DNA

What makes up DNA?

A G C T(U)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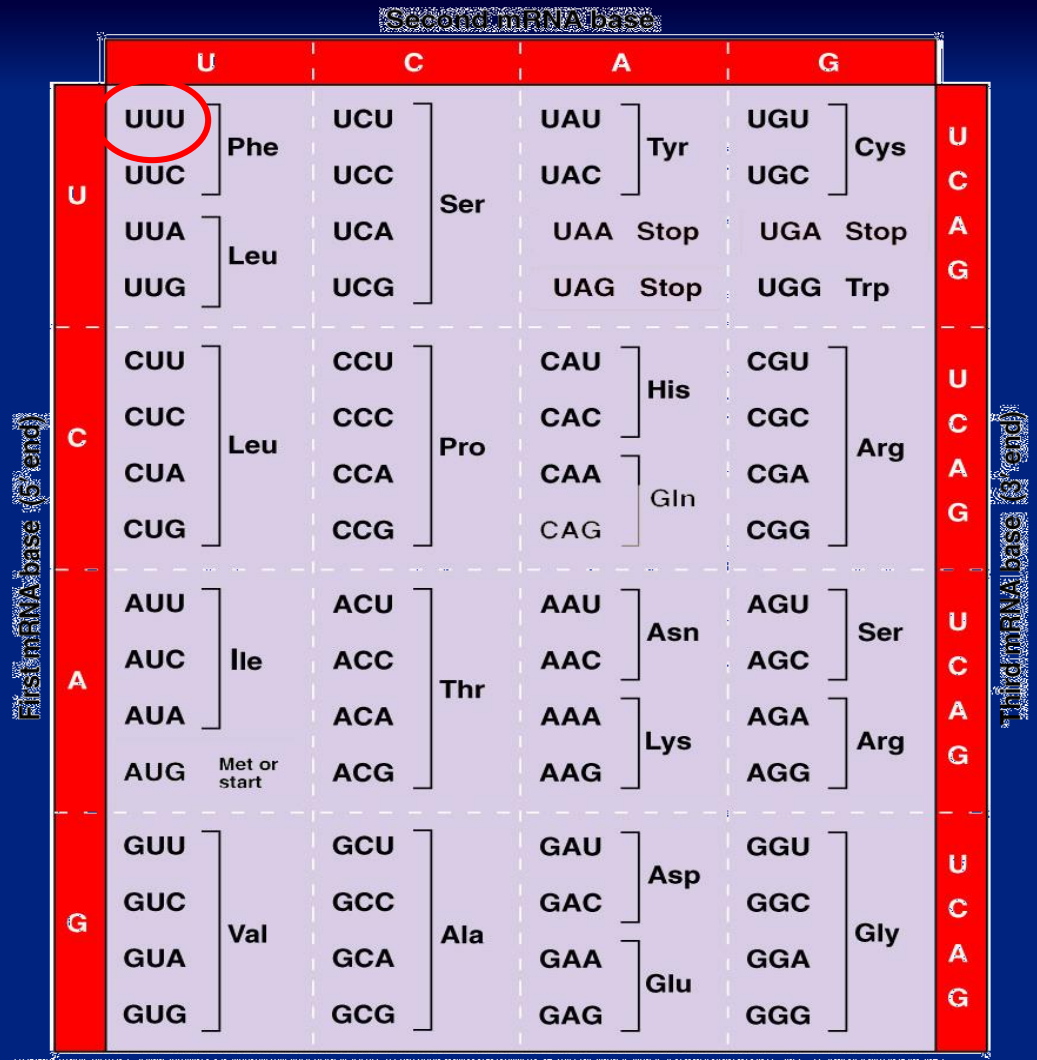
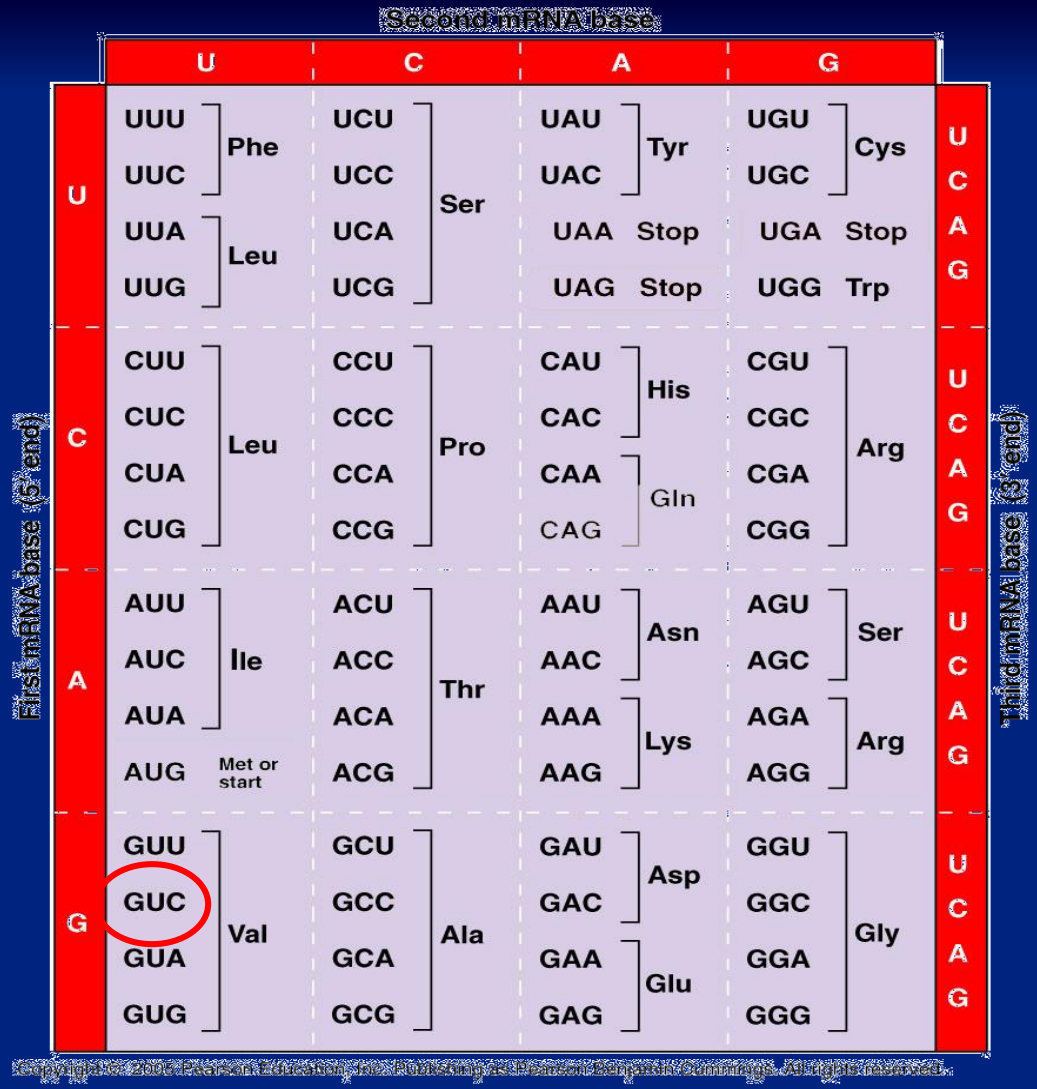
C-5
O
O
C-5
C-3
(C)
STRAND-I
STRAND-II
C-5
C-3
DEEP GROOVE
C-5
C-3
20A°
(A)
STRAND-I
STRAND-II
C-5
C-3
O
3.4 A°
34 A°
T
A
G
C
A
T
A
T
C
G
G
C
T
A
C-3
C-5
(B)
O

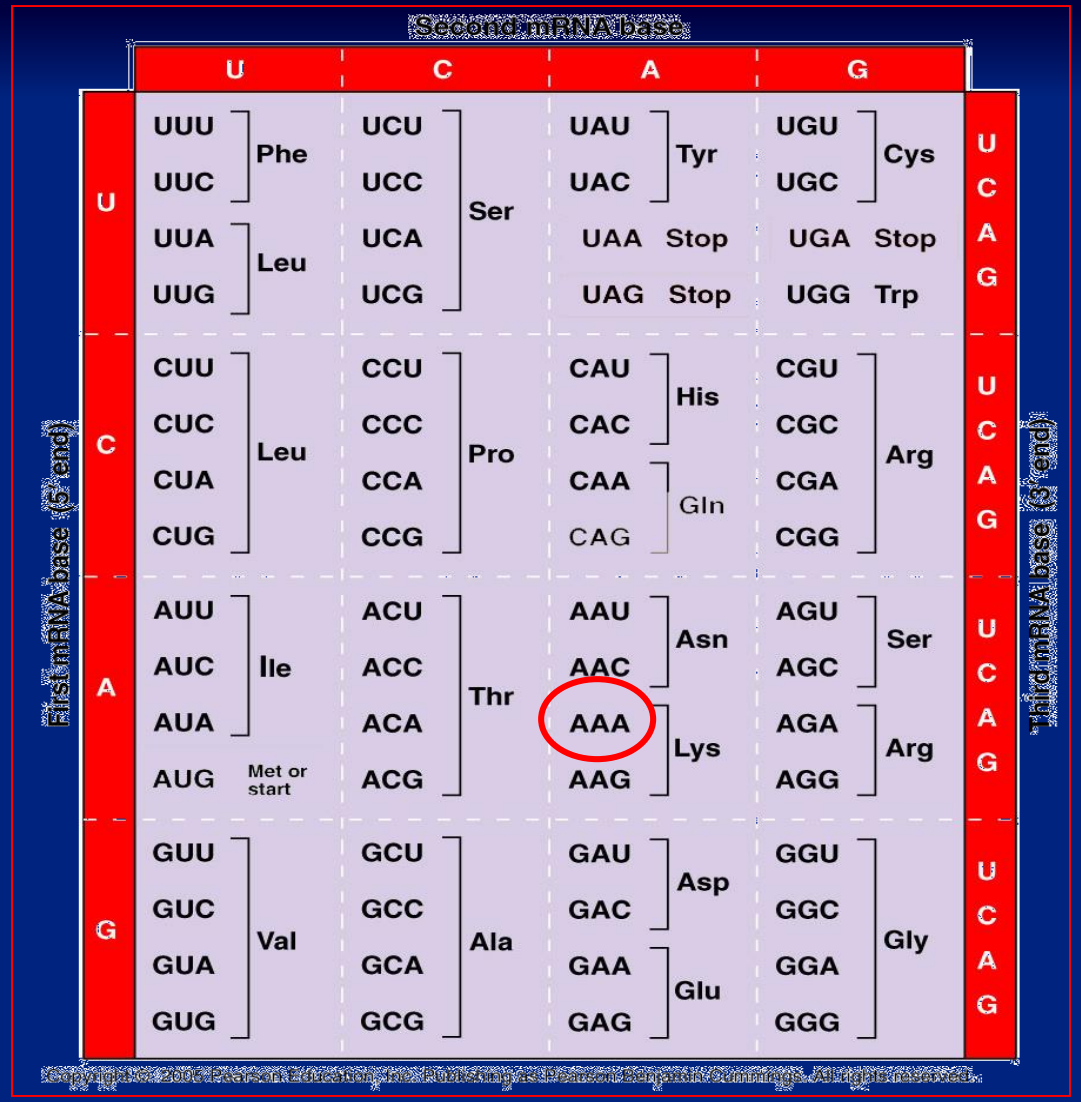
UUUGUCAAAUGA

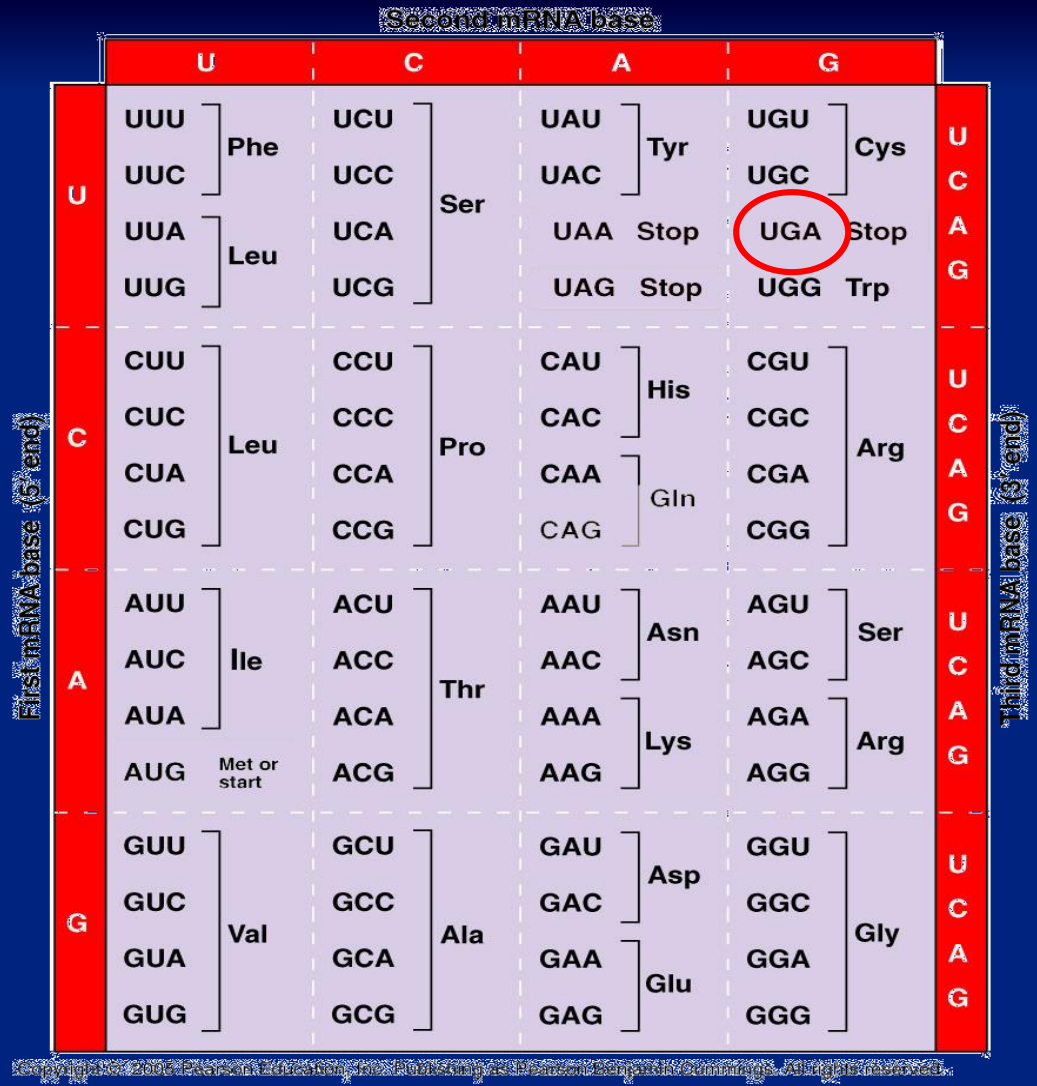
UUU GUC AAA UGA


CHEX
AGENT
www.timepassagesnostalgia.com









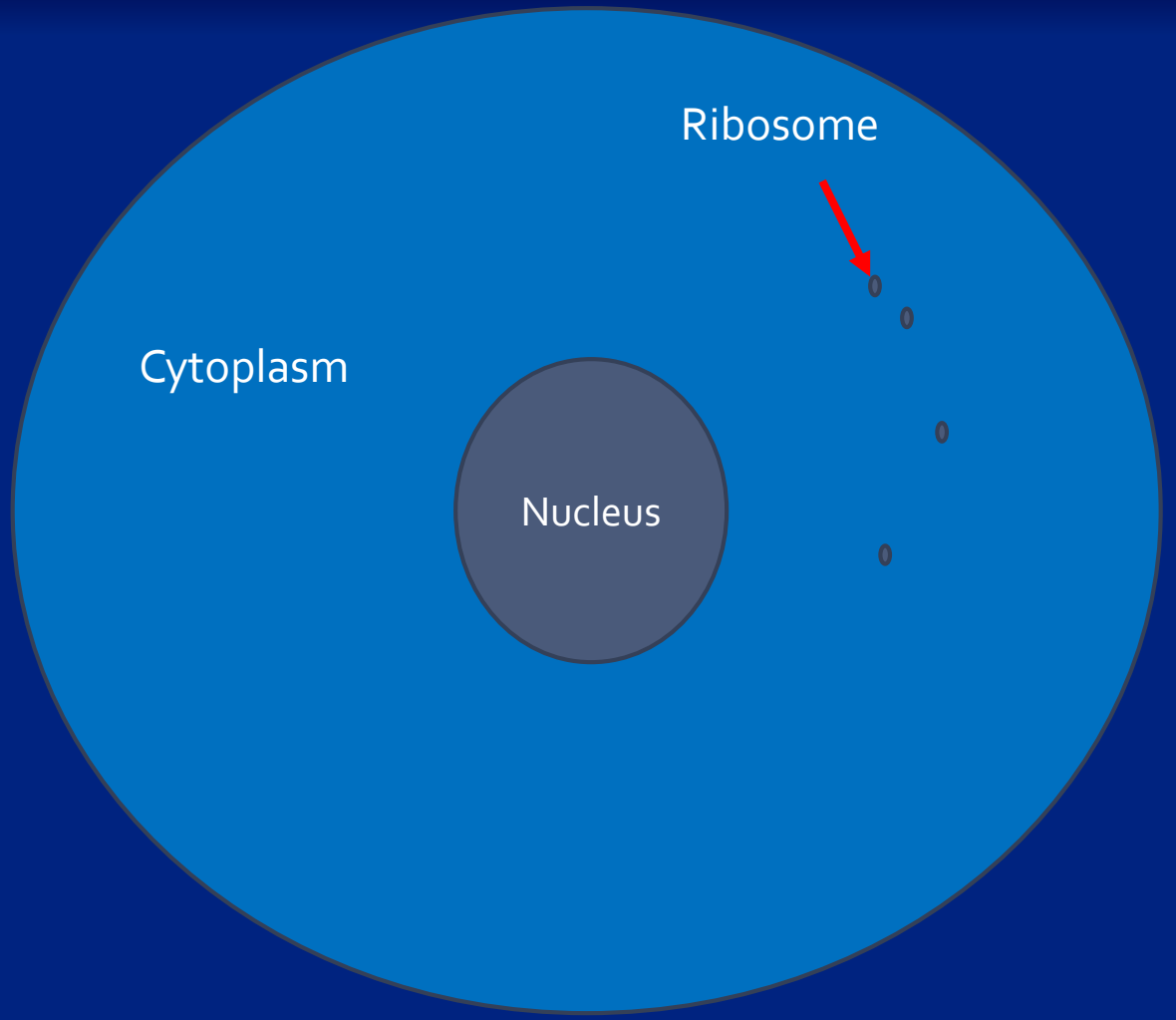
UUUGUCAAAUGA

UUU GUC AAA UGA

Phe Val Lys stop

It is one of the more striking generalizations of biochemistry - which surprisingly is hardly ever mentioned in the biochemical textbooks - that the twenty amino acids and the four bases, are, with minor reservations, the same throughout Nature.

Francis Crick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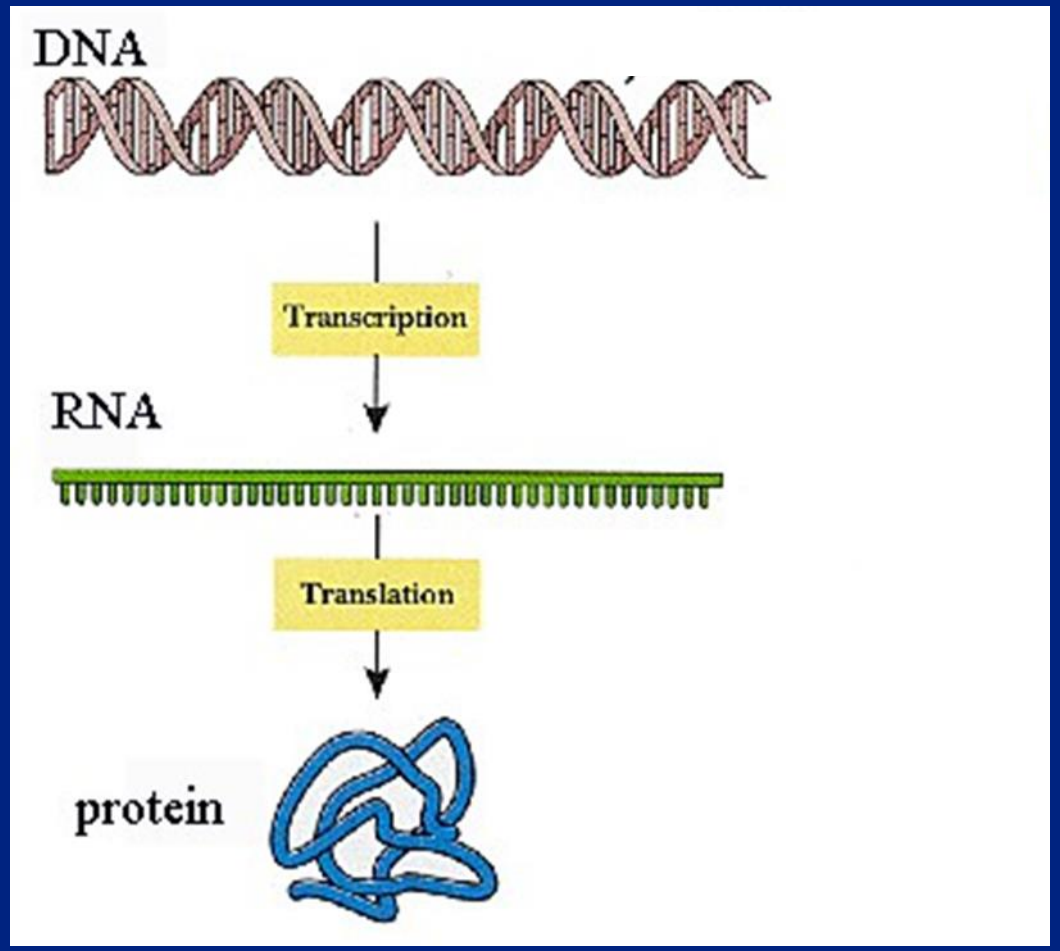
Cytoplasm
Nucleus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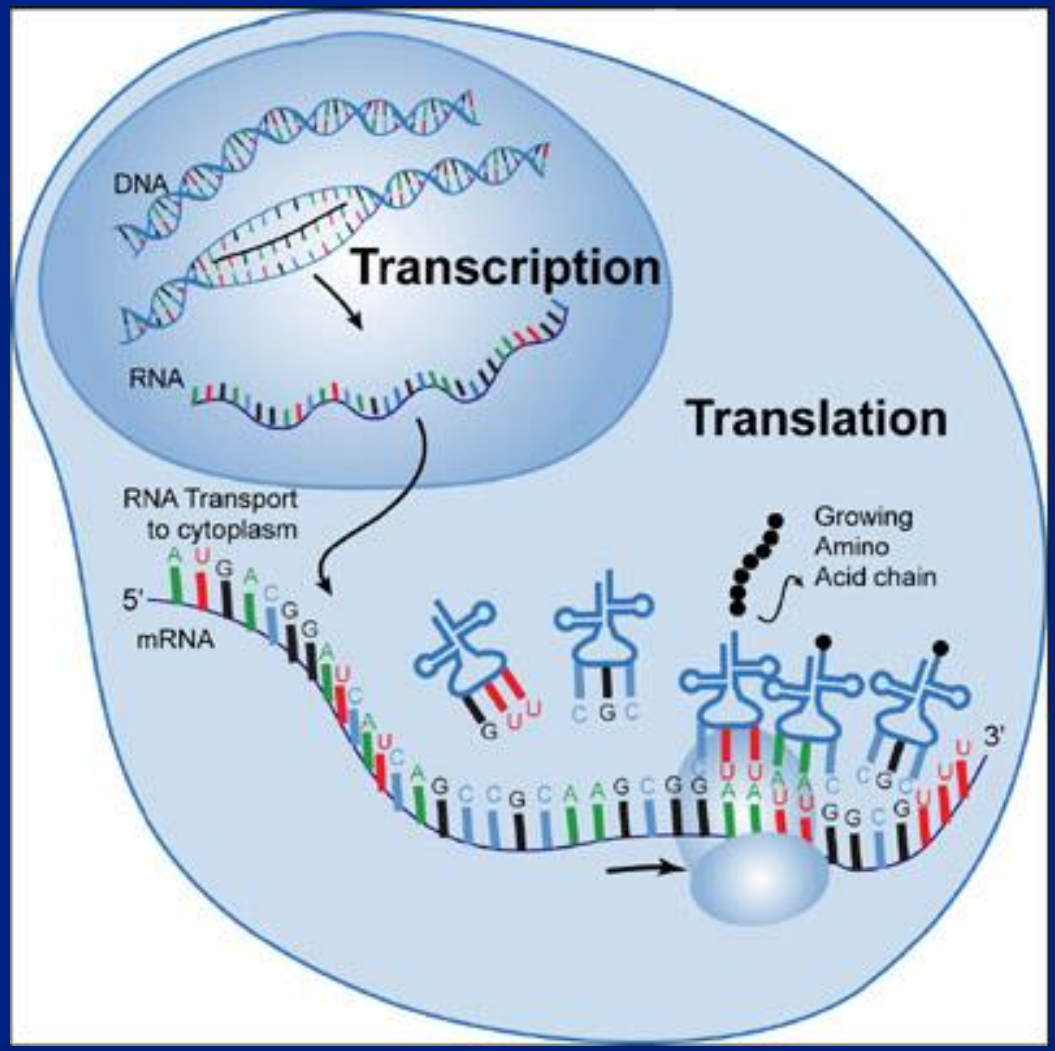
Transcription
RNA
Translation
protein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Transcription
RNA
Translation
RNA Transport
to cytoplasm
5'
mRNA
Growing
Amino
Acid chain
3'

The specific sequence of EVERY protein is coded in DNA

Proteins are made in a 2 step process, transcription(DNA to RNA) and translation (RNA to protein)

The specific piece of DNA that codes for a specific protein is a gene and this is what is inherited from your parents

DNA is composed of nucleotides and the sequence of nucleotides determines the amino acid sequence of all proteins

If the sequence of nucleotides in DNA is altered (a mutation), the protein AA sequence is altered and it may misfold

Nature hath framed strange fellows in her time.

The Merchant of Venice

So, since KD is the result of a single gene mutation and each gene contains the instructions to build a specific protein, then …

(Don’t let me down, here!)

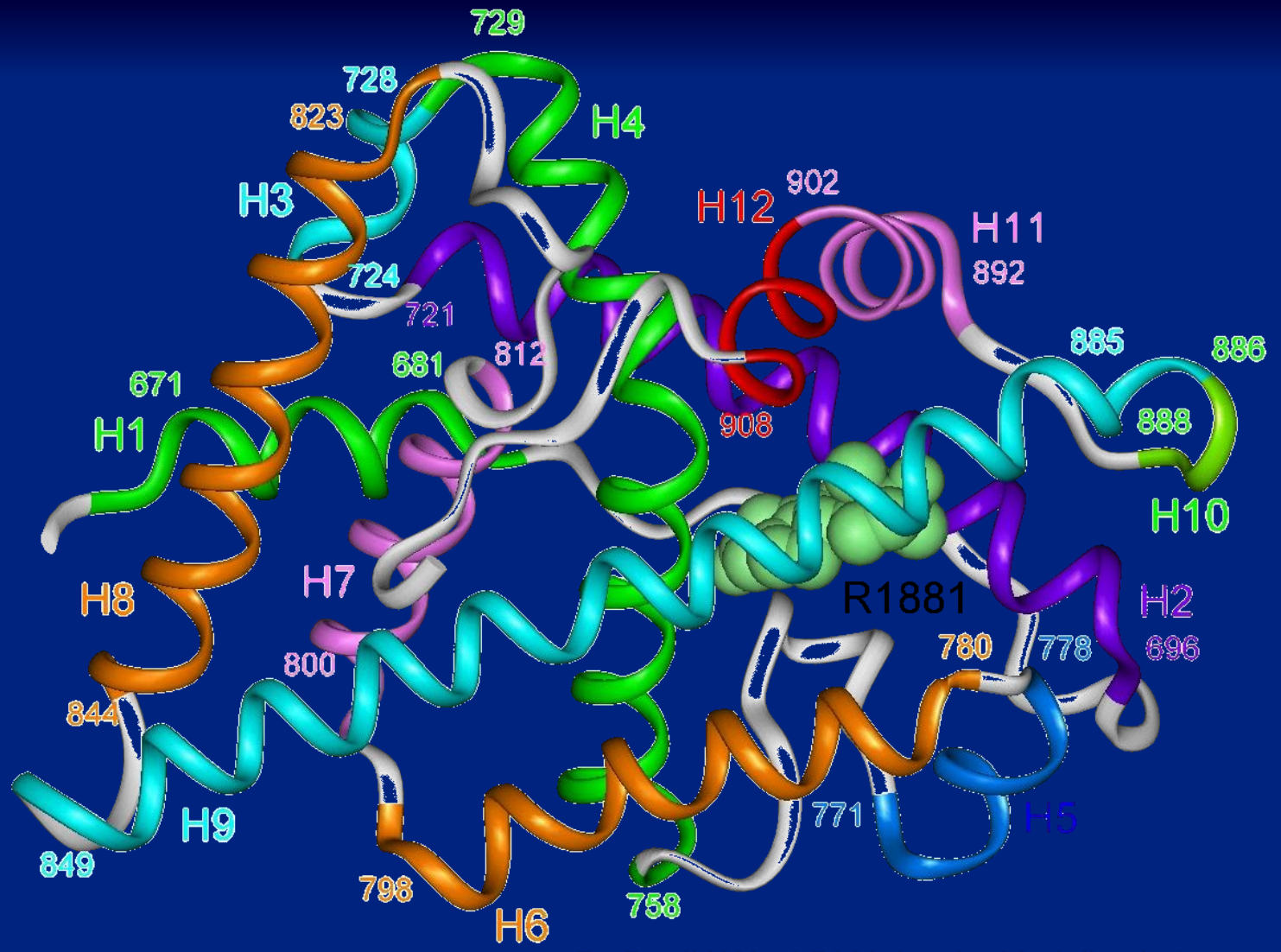
… there must be a specific protein that is the cause of KD …

There is no darkness but ignorance

The Twelfth Night

Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy.

La Spada AR, Wilson EM, Lubahn DB, Harding AE, Fischbeck KH



By Dr. JH Wu, LDI Molecular Modeling Lab.

Nucleotide Sequence of Human Androgen Receptor Gene

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Amino Acid Sequence of **Human Androgen Receptor** Protein

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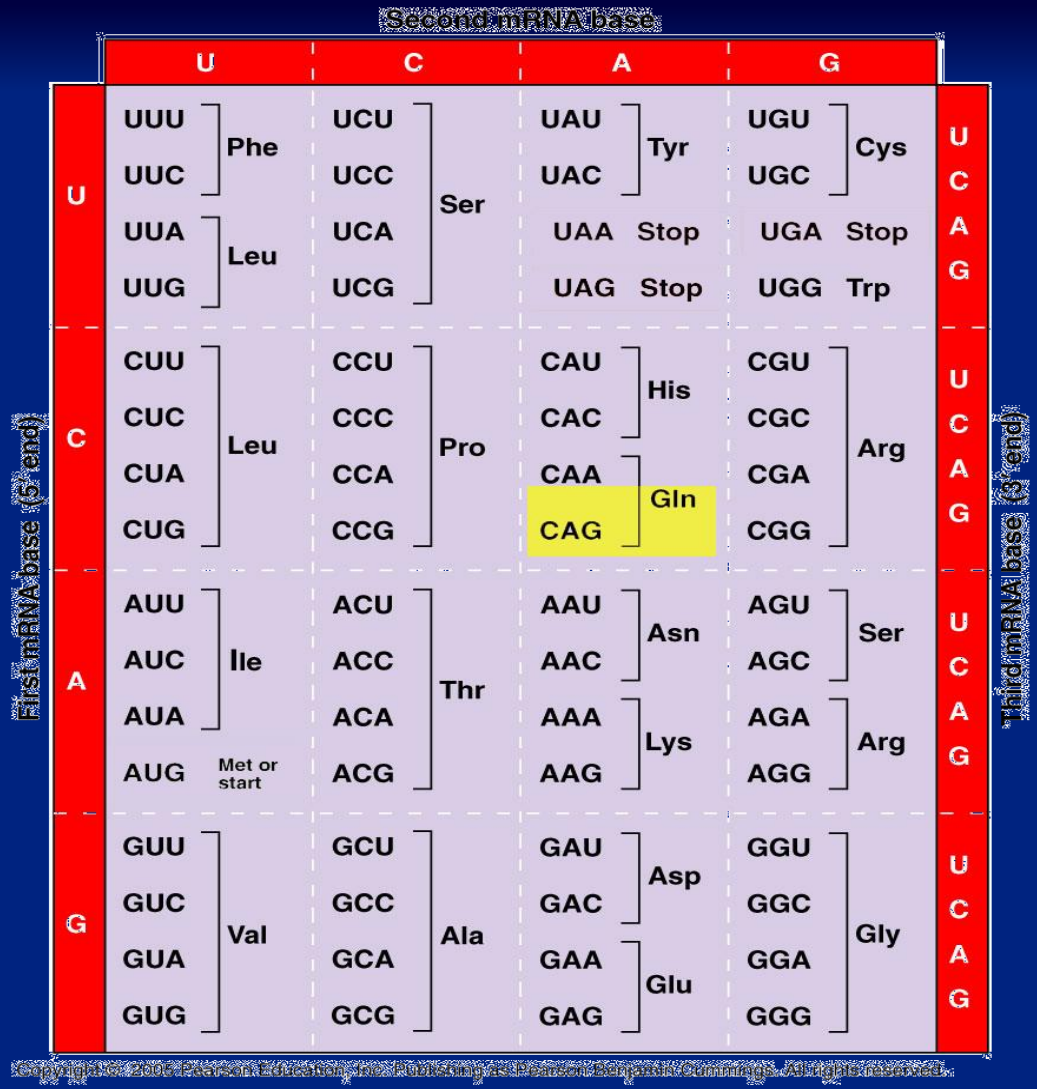

Amino Acid Sequence of Human Androgen Receptor

MEVQLGLGRVYPRPPSKTYRGAFQNLFQSVREVIQNPGPRHPEAASAAPPGASLLLLQQ
QQQQQQQQQQQQQQQQQQQQQETSPRQQQQQQGEDGSPQAHRRGPTGYLVLDE
EQQPSQPQSALECHPERGCVPEPGAAVAASKGLPQQLPAPPDEDDSAAPSTLSLLGPTFP
GLSSCSADLKDILSEAASTMQLLQQQQQEAVSEGSSSGRAREASGAPTSSKDNYLGGTSTI
SDNAKELCKAVSVSMGLGVEALEHLSPGEQLRGDCMYAPLLGVPPAVRPTPCAPLAECKG
SLLDDSAGKSTEDTAEYSPFKGGYTKGLEGESLGCSGSAAAGSSGTLELPSTLSLYKSGAL
DEAAAYQSRDYYNFPLALAGPPPPPPPPHPHARIKLENPLDYGSAWAAAAAQCRYGDLA
SLHGAGAAGPGSGSPSAAASSSWHTLFTAEEGQLYGPCGGGGGGGGGGGGGGGGGGG
GGGGEAGAVAPYGYTRPPQGLAGQESDFTAPDVWYPGGMVSRVPYPSPTCVKSEMGP
WMDSYSGPYGDMRLETARDHVLPIDYYFPPQKTCLICGDEASGCHYGALTCGSCKVFFKR
AAEGKQKYLCASRNDCTIDKFRRKNCPSCRLRKCYEAGMTLGARKLKKLGNLKLQEEGEA
SSTTSPTEETTQKLTVSHIEGYECQPIFLNVLEAIEPGVVCAGHDNNQPDSFAALLSSLNEL
GERQLVHVVKWAKALPGFRNLHVDDQMAVIQYSWMGLMVFAMGWRSFTNVNSRMLYF
APDLVFNEYRMHKSRMYSQCVRMRHLSQEFGWLQITPQEFLCMKALLLFSIIPVDGLKNQ
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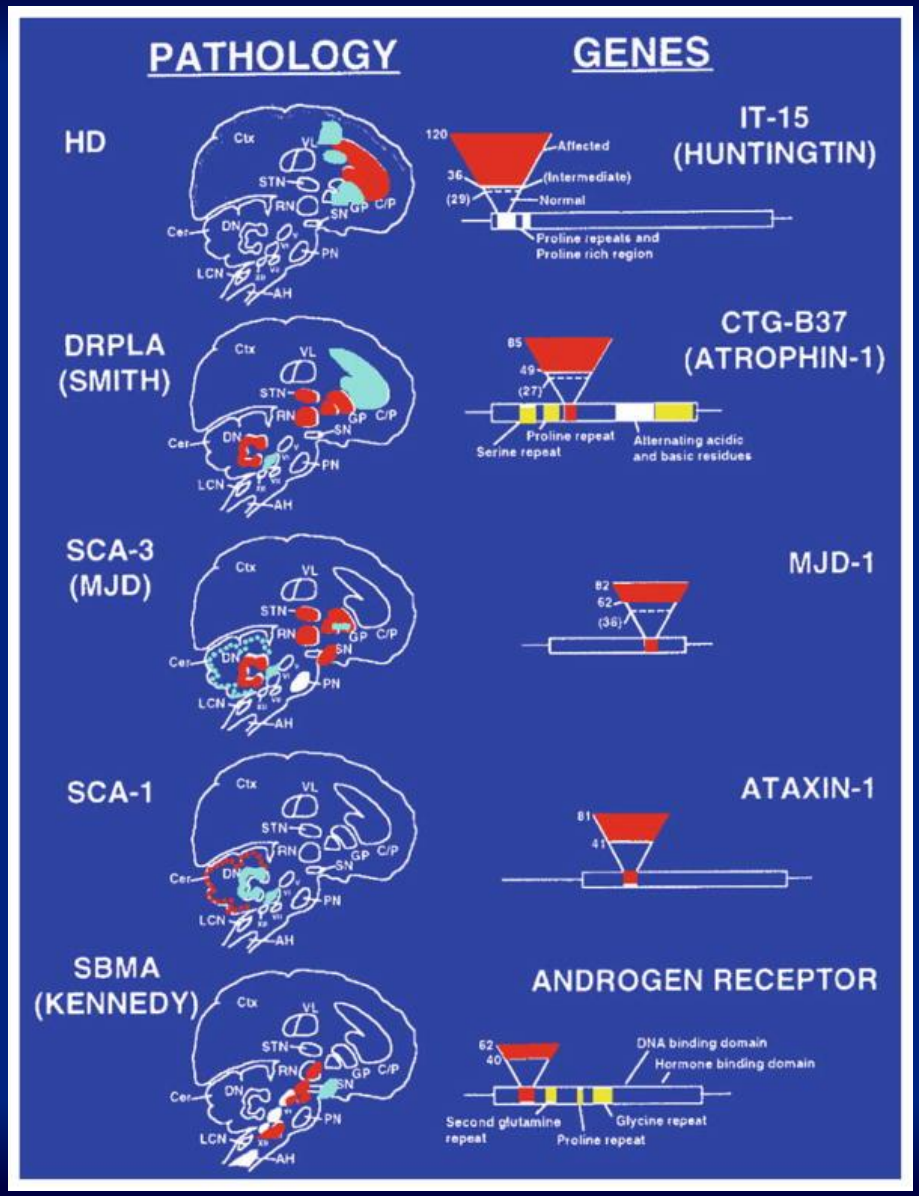
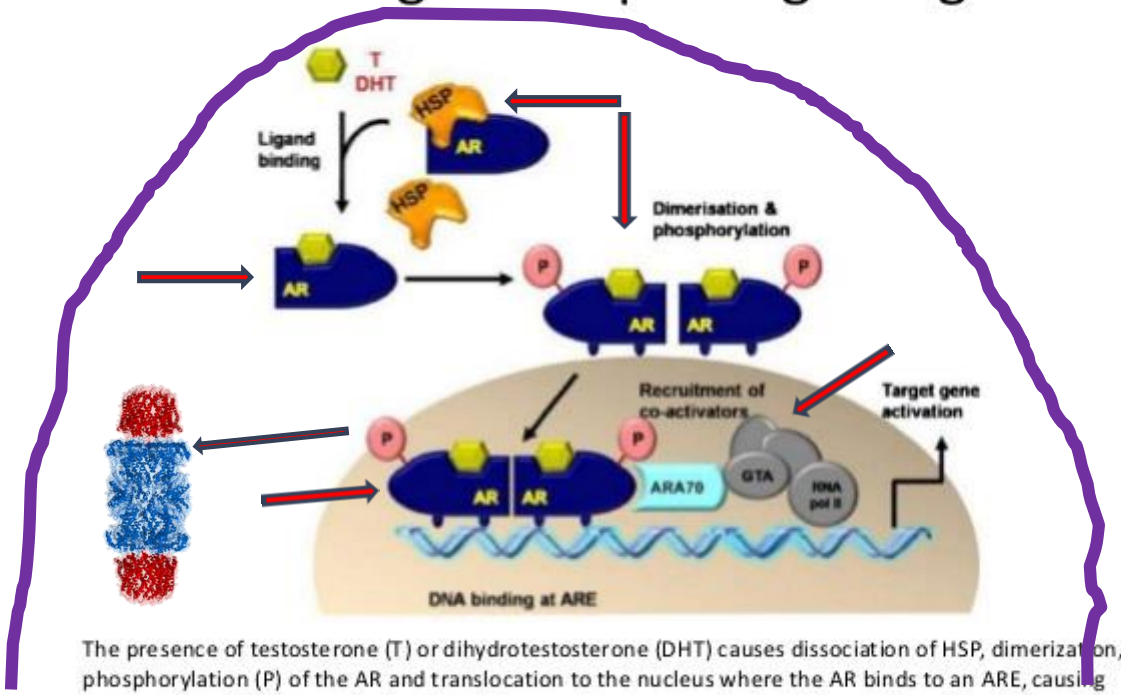
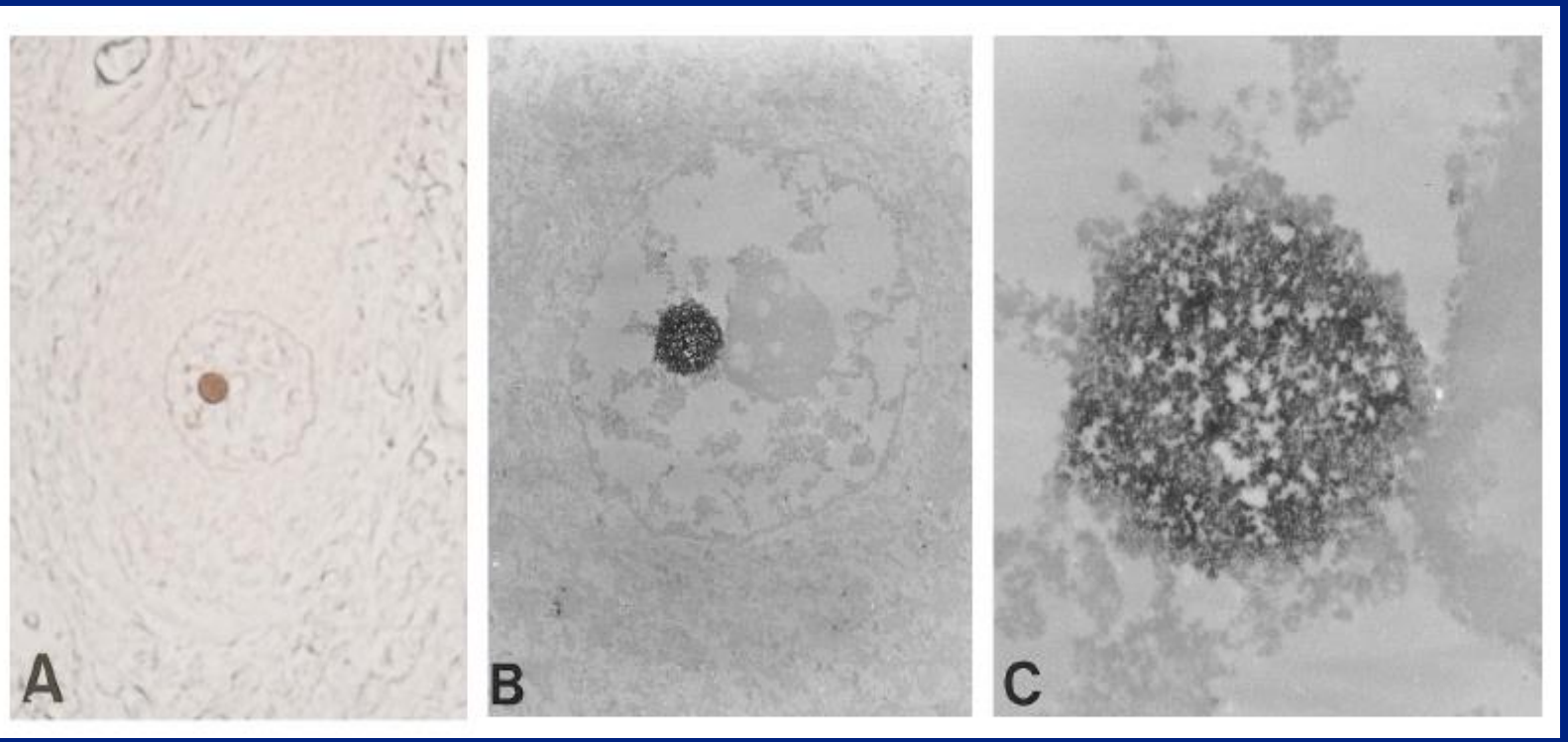

PATHOLOGY
GENES
HD
IT-15
(HUNTINGTIN)
120
Affected
36
(Intermediate)
(29)
Normal
Proline repeats and
Proline rich region
DRPLA
(SMITH)
CTG-B37
(ATROPHIN-1)
85
49
(27)
Proline repeat
Serine repeat
Alternating acidic
and basic residues
SCA-3
(MJD)
MJD-1
82
62
(36)
SCA-1
ATAXIN-1
81
41
SBMA
(KENNEDY)
ANDROGEN RECEPTOR
62
40
DNA binding domain
Hormone binding domain
Second glutamine
repeat
Proline repeat
Glycine repeat
Ctx
VL
STN
RN
SN
GP
C/P
Cer
DN
PN
LCN
AH

Androgen receptor signaling



The presence of testosterone (T) or dihydrotestosterone (DHT) causes dissociation of HSP, dimerization, and phosphorylation (P) of the AR and translocation to the nucleus where the AR binds to an ARE, causing recruitment of DNA transcriptional machinery and gene transcription. (Adapted from Li J, Al-Azzawi F. Mechanism of androgen receptor action. Maturitas 2009;63:142–8; with permission.)

Friedlander TW and Ryan CJ. Urol Clin N Am 2012; 39:453-464.



Nonneural Nuclear Inclusions in SBMA 699
AJP September 1998, Vol. 153, No. 3

Science Jargon	Meaning in English
Transcription	RNA Synthesis
Translation	Protein Synthesis
Protein Modifications	
Methylation, Phosphorylation, Acetylation	Switches on proteins
Proteasome	Protein Shredder
Autophagy	Recycler (proteins)
Co-Activators	Helpers of AR: Tugboats

KD is due to a mutation in the gene that codes for the Androgen Receptor

The AR binds to testosterone , causing the AR-T complex to move to the nucleus where it turns on transcription with the help of coactivators to make new proteins

The specific mutation in KD is an elongation of a CAG repeat in the gene

If the CAG repeat is greater than 40, then the (male) individual has KD

For the mutation to cause KD, the mutant AR must bind T and move into the nucleus.

In KD, the cell cannot adequately break down 'old' AR and that (somehow) causes the death of the cell.

Published Clinical Manifestations

Frequent
- Proximal weakness
- Proximal wasting
- Muscle cramps
- Fasciculations, twitching (perioral, tongue)
- Action tremor
- Dysarthria
- Dysphagia
- Gynecomastia (breast enlargement)

Rare
- Myalgia
- Myasthenia
- Fasciculation syndrome
- Polyneuropathy
- Post-traumatic monomelic neuronopathy
- Effort-dependent muscle intolerance
- Muscular dystrophy
- Isolated hyper-CKemia
- Under-masculinized genitalia
- Scrotal hypospadia
- Microphallus
- Decreased libido, impotence
- Oligospermia
- Laryngospasm

Questionable
- Sensory disturbances
- Impaired cognitive functions
- Increased pituitary volume
- Diabetes
- Tongue pressure
- Creatine-kinase
- Low androgens, high estrogens

Finsterer, J. & Soraru, G. J Mol Neurosci (2016) 58: 321

How to Treat KD

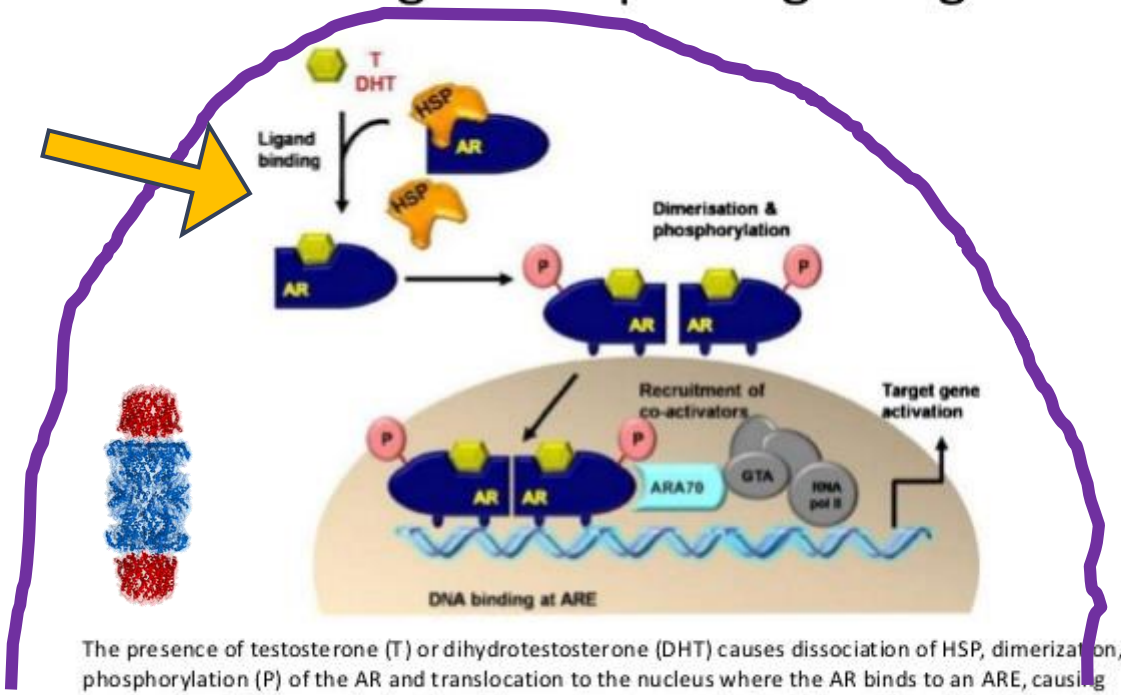
Fillet of a fenny snake,
In the cauldron boil and bake;
Eye of newt, and toe of frog,
Wool of bat, and tongue of dog,
Adder's fork, and blind-worm's sting,
Lizard's leg, and howlet's wing,
For a charm of powerful trouble,
Like a hell-broth boil and bubble.

Macbeth

How to Treat KD

1. **Prevent AR from entering nucleus**

Androgen receptor signaling



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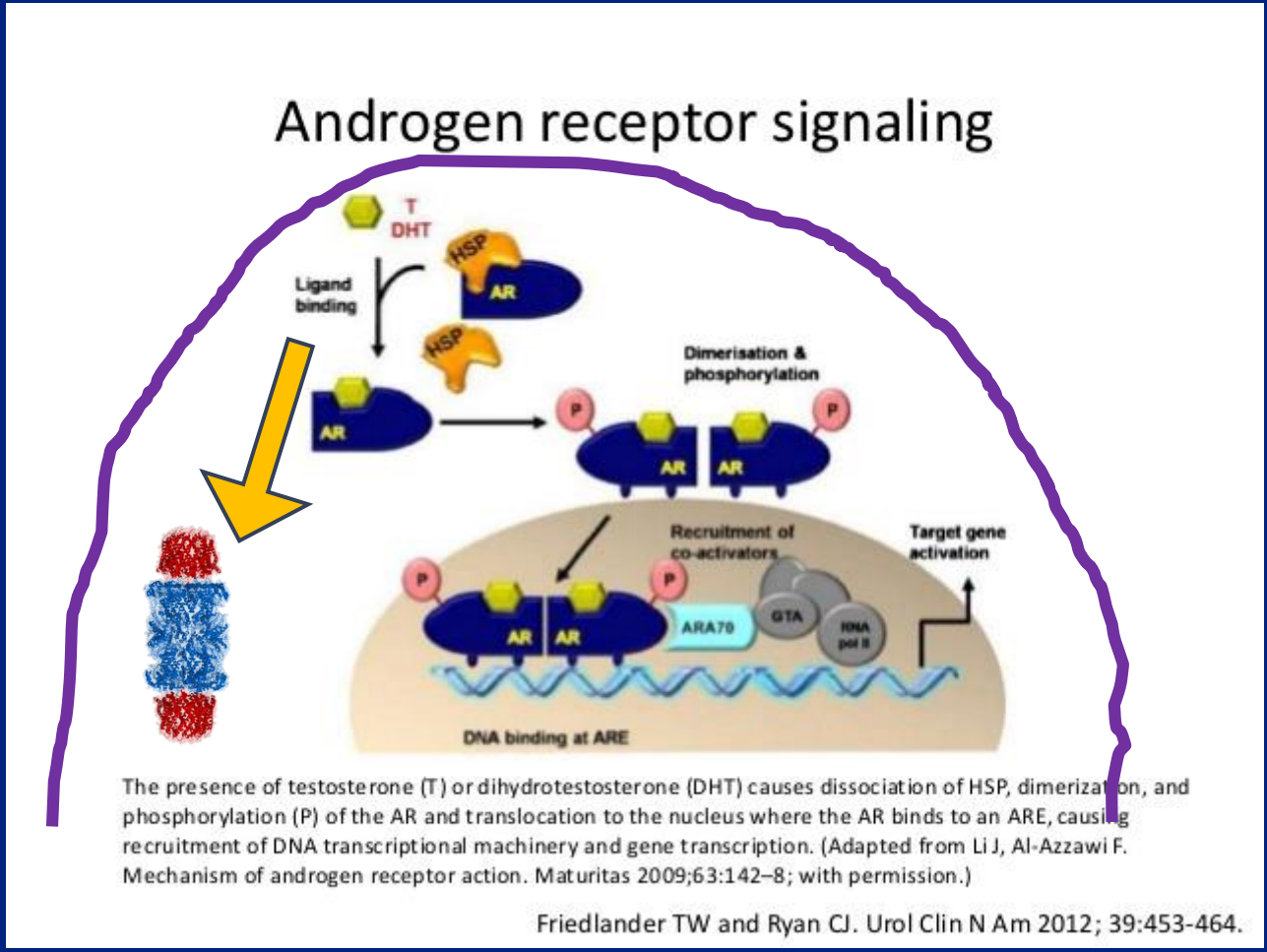
Friedlander TW and Ryan CJ. Urol Clin N Am 2012; 39:453-464.

How to Treat KD

1. **Prevent AR from entering nucleus**
2. **Find a new way to remove ‘bad’ AR**

Autophagy



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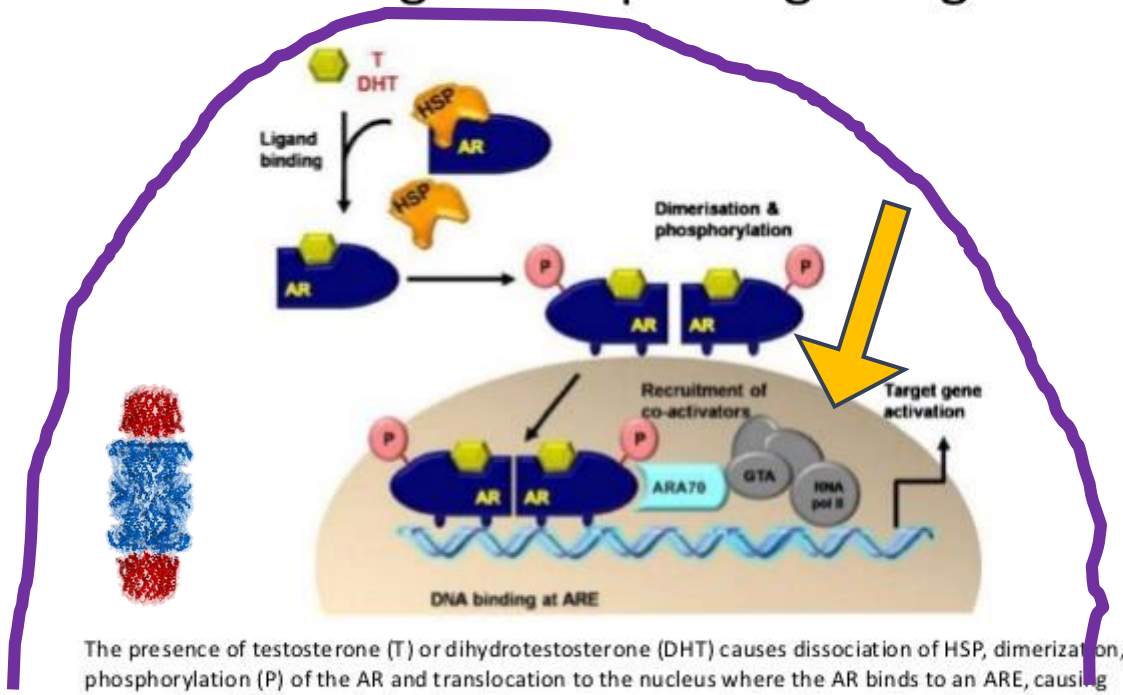
Friedlander TW and Ryan CJ. Urol Clin N Am 2012; 39:453-464.

How to Treat KD

1. **Prevent AR from entering nucleus**
2. **Find a new way to remove ‘bad’ AR**
3. **Decrease mutant AR concentration**
4. **Keep muscle cells alive and working**

Androgen receptor signaling



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Friedlander TW and Ryan CJ. Urol Clin N Am 2012; 39:453-464.

What to test?

Oft expectation fails, and most oft where most it promises; and oft it hits where hope is coldest; and despair most sits.

All's Well That Ends Well

“If we knew what it was we were doing, it would not be called research, would it?”

Albert Einstein

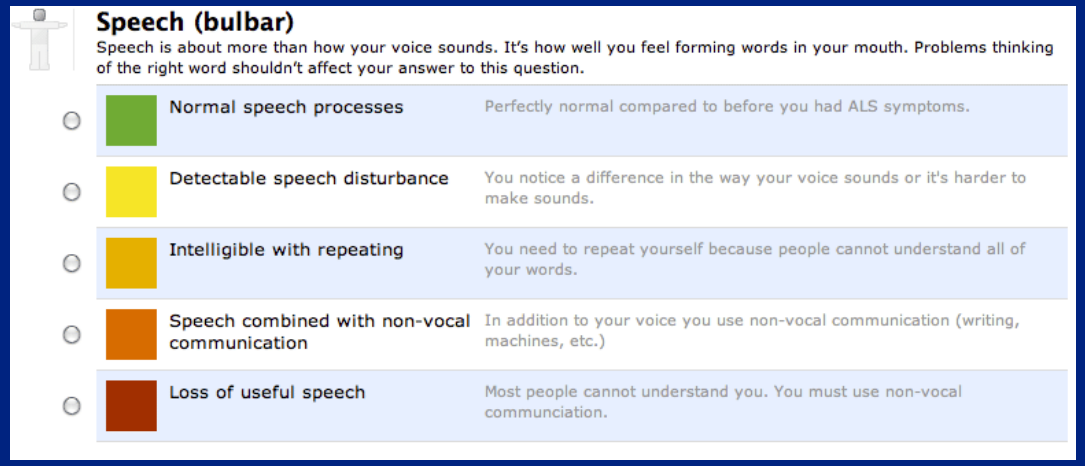
1. Anecdotal Reports/Case Studies

"I place more stock in the anecdotal reports than the clinical trial of Avodart. IMO it would be very difficult to conduct a good trail (sic) due to the nature of KD and its slow progression.

My anecdotal report is that Avodart made a significant difference to me. I was down to working half time due to fatigue and fear of not being able to get home safely after work (I had a challenging ramp to walk down at that time.) After I started to take Avodart my fatigue was greatly reduced and I return to work full time - that was six years ago and I am still working full time. My KD symptoms have continued to worsen so Avodart did not stop the progression, but I **feel** I would be much worse off if I wasn't taking Avodart."

Difference in chronological changes of outcome measures between untreated and placebo-treated patients of spinal and bulbar muscular atrophy.

Hashizume A, Katsuno M, Banno H, Suzuki K, Suga N, Tanaka F, Sobue G.



"In conclusion, placebo-treated and untreated SBMA patient groups demonstrated a large difference in the chronological analysis of a motor functional score, but not for an objective measure of walking capacity."

1. Anecdotal Reports/Case Studies
2. Cell & Animal Models

“If you try and take a cat apart to see how it works, the first thing you have on your hands is a non-working cat.”

Douglas Adams

UNO News

College of Business Administration

College of Education and Human Development

College of Engineering

College of Liberal Arts

College of Science

Interdisciplinary Studies

Community

Research

Student Life

Press Releases

UNO Researchers Discover Way to Delay Symptoms of Deadly Huntington's Disease

Researchers at the University of New Orleans have discovered a way to significantly delay the symptoms of Huntington's Disease in mice carrying the human Huntington's Disease gene. Huntington's Disease is an untreatable, incurable and fatal disease that causes certain nerve cells in the brain to waste away. The research is published in the online journal PLOS (Public Library of Science) ONE.

"I believe that these findings are important because they may lead to the development of the first treatment for this horrible disease," said Gerald LaHoste, associate professor of psychology.

For years, scientists have known that a mutated version of the gene known as huntingtin is present in people suffering from Huntington's Disease. UNO researchers, led by LaHoste, have identified a second gene that may be linked to the disease. Based on their findings, they believe that a class of cholesterol-lowering drugs, called statins, could greatly slow the symptoms of Huntington's Disease in humans. That research is ongoing at UNO.

The researchers studied mice that had the mutated human version of the huntingtin gene incorporated into their DNA. They discovered that the presence of another gene, called Rhes, is necessary for the symptoms of Huntington's Disease to appear. When the Rhes gene was inhibited, researchers observed a significant delay in the symptoms in the mice. Relative to the lifespan of these mice, the delay translates to about five years in

The University of New Orleans has NOT discovered a cure for Huntington's disease

The science behind an extraordinary press release claiming to have discovered 'A Way to Delay Symptoms of HD'

By Dr Ed Wild on January 28, 2013

Edited by Dr Jeff Carroll

A recent press release from the University of New Orleans (UNO) claims its researchers have discovered a "way to delay symptoms of deadly Huntington's disease". Music to the ears of HD family members everywhere. But does the science live up to the hype? The short answer, sadly, is no.

The science

The science behind the press release focuses on the protein **Rhes**. The last two letters of its name stand for 'Enriched in the Striatum', because the part of the brain where most Rhes is found is called the **striatum**.

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

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

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

Constanza J. Cortes, Shuo-Chien Ling, Ling T. Guo,3 Gene Hung, Taiji Tsunemi, Linda Ly, Seiya Tokunaga, Edith Lopez, Bryce L. Sopher, C. Frank Bennett, G. Diane Shelton, Don W. Cleveland, and Albert R. La Spada

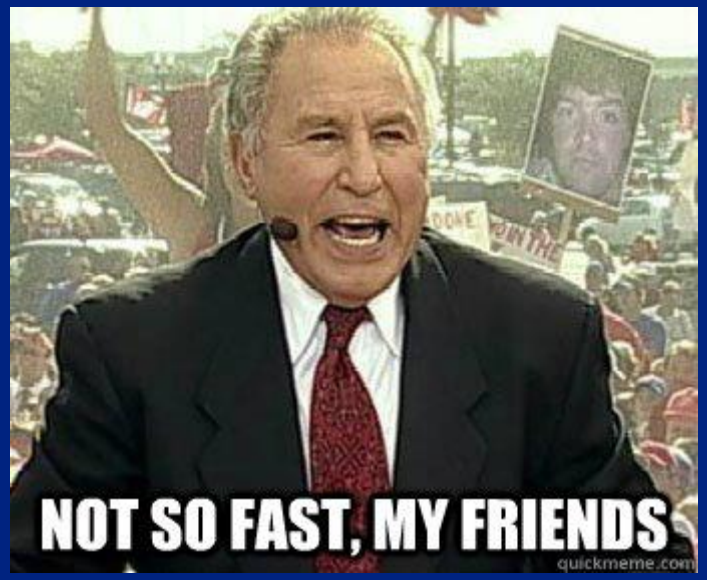
Rocchi, A., Milioto, C., Parodi, S., Armirotti, A., Borgia, D., Pellegrini, M., … Pennuto, M. (2016). Glycolytic-to-oxidative fiber-type switch and mTOR signaling activation are early-onset features of SBMA muscle modified by high-fat diet. Acta Neuropathologica, 132(1), 127–144. http://doi.org/10.1007/s00401-016-1550-4

Giorgetti, E., Yu, Z., Chua, J. P., Guan, Y., Hung, G., Lieberman, A. P., … Venneti, S. (2016). Rescue of Metabolic Alterations in AR113Q Skeletal Muscle by Peripheral Androgen Receptor Gene Article Rescue of Metabolic Alterations in AR113Q Skeletal Muscle by Peripheral Androgen Receptor Gene Silencing. CellReports, 17(1), 125–136. http://doi.org/10.1016/j.celrep.2016.08.084

Pourshafie, N., Lee, P. R., Chen, K., Harmison, G. G., Bott, L. C., Katsuno, M., … Rinaldi, C. (2016). MiR-298 Counteracts Mutant Androgen Receptor Toxicity in Spinal and Bulbar Muscular Atrophy, 24(5), 937–945. http://doi.org/10.1038/mt.2016.13

Neuromuscular junctions are pathological but not denervated in two mouse models of spinal bulbar muscular atrophy.
Poort JE, Rheuben MB, Breedlove SM, Jordan CL.
Hum Mol Genet. 2016 Aug 4.

Defects in Neuromuscular Transmission May Underlie Motor Dysfunction in Spinal and Bulbar Muscular Atrophy.
Xu Y, Halievski K, Henley C, Atchison WD, Katsuno M, Adachi H, Sobue G, Breedlove SM, Jordan CL.
J Neurosci. 2016 May 4;36(18):5094-106


NOT SO FAST, MY FRIENDS
quickmeme.com

Silencing neuronal mutant androgen receptor in a mouse model of spinal and bulbar muscular atrophy

Kentaro Sahashi, Masahisa Katsuno1, Gene Hung, Hiroaki Adachi,
Naohide Kondo, Hideaki Nakatsuj, Genki Tohnai, Madoka Iida,
C. Frank Bennett and Gen Sobue

All right, there's a thousand things that have to happen in order. We are on number eight. You're talking about number six hundred and ninety-two.

Jim Lovell

1. Anecdotal Reports/Case Studies
2. Cell & Animal Models
3. Clinical Trials

Thought are but dreams till their effects are tried.

The Rape of Lucrece

Phase I

Check a Drug's Safety: To determine if an experimental medication or treatment ***is safe***

1. Dose-limiting toxicities (DLTs) are unacceptable side effects that would force the treatment to stop (or continue at a reduced dose).
2. The maximum tolerated dose (MTD) is the largest dose that doesn't produce DLTs in a substantial number of subjects
3. Pharmacokinetics: How fast it's absorbed into the bloodstream (if it's taken orally) How fast (and by what route) it's eliminated from the body

Phase II

The next step is to find out about the drug's safety and efficacy at various doses. You may also be looking at several different dosing regimens, including the following options: What route (oral or intravenous, for example) to give the drug How frequently to give the drug For how long (or for what duration) to give the drug

Phase III

Proving that the drug works

Phase IV

Keeping an eye on the marketed drug

How Successful?

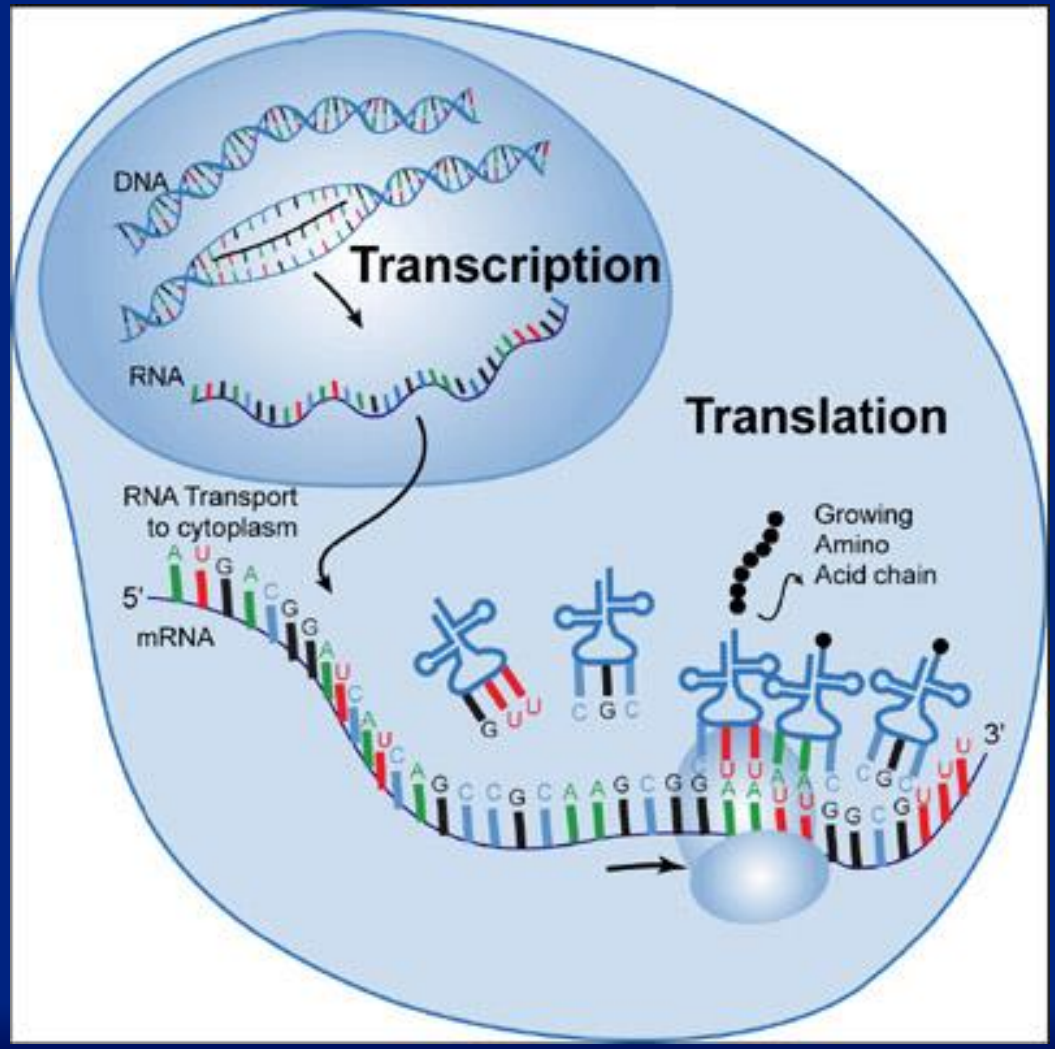
In 15 Years: 99 trials, assessing 41 compounds and 11 interventions

25% success to phase 2
19.4 % success to phase 3
14.2 % to approval
2 to phase 4

$30-40 million before approval (Phase 1+2+3)

CRISPR

Anti Sense Oligonucleotides (ASO)



Theory of mind, empathy and neuropsychological functioning in X-linked Spinal and Bulbar Muscular Atrophy: a controlled study of 20 patients

Elisa Di Rosa • Gianni Soraru ` • Johann Roland Kleinbub • Vincenzo Calvo • Antonino Vallesi • Giorgia Querin • Sonia Marcato • Irene Grasso • Arianna Palmieri

Mike, a nine-year-old boy, just started at a new school. He was in one of the cubicles in the toilets at school. Joe and Peter, two other boys, came in and were standing at the sinks talking. Joe said, "You know that new guy in the class? His name's Mike. Doesn't he look weird? And he's so short!" Mike came out of the cubicle and Joe and Peter saw him. Peter said, "Oh hi, Mike! Are you going out to play football now?"

Faux pas-related questions*	71.3	14.6	82.3	15

To sum up, in contrast with previous literature, we found executive functions apparently preserved in patients with SBMA. On the other hand, although **they had no evident cognitive impairment**, **these patients showed distinctive deficits in ToM ability, and specifically in the ability to interpret social situations by appropriately identifying other people's intentions.**

Affliction may one day smile again;
and till then, sit thee down, sorrow!

Love Labour's Lost

From this day to the ending of the world,
But we in it shall be remembered-
We few, we happy few, we band of brothers;
For he to-day that sheds his blood with me
Shall be my brother; be he ne'er so vile,
This day shall gentle his condition;
And gentlemen in England now-a-bed
Shall think themselves accurs'd they were not here,
And hold their manhoods cheap whiles any speaks
That fought with us upon Saint Crispin's day.

Henry V

Aims:

Phase II Clinical Trial to Examine the Efficacy and Safety of Dutasteride in Patients With Kennedy's Disease

Objectives:

This study will determine if the drug dutasteride can improve weakness, mobility, functioning, nerve function, and quality of life in patients with spinal and bulbar muscular atrophy

Hypotheses:

Deciding Who Will Be In the Study

Inclusion Criteria

1. Genetically confirmed SBMA
2. Neurological symptoms of SBMA
3. Ability to ambulate 100 feet with or without the use of assistive devices
4. Willingness to participate in all aspects of trial design and follow-up
5. Male sex

Exclusion Criteria

1. Age less than 18 years
2. Female sex
3. A history of hypersensitivity to dutasteride or 5 alpha-reductase inhibitors.
4. Exposure to 5 alpha-reductase inhibitors, anti-androgens, testosterone, or steroids in the preceding 6 months
5. Patients who are taking potent cytochrome P450 3A4 (CYP3A4) inhibitors for over 4 weeks
6. Patients with any pre-existing liver disease
7. Alkaline phosphatase, gamma glutamyl transferase, or direct bilirubin greater than 1.5 times the upper limit of normal
8. Alanine aminotransferase or aspartate aminotransferase greater than 1.5 times upper limit of normal in subjects with normal creatine kinase levels
9. Creatinine greater than 1.5 times the upper limit of normal
10. Platelet count, white blood cell count or hemoglobin below the lower limit of normal
11. Other clinically significant medical disease that, in the judgment of the investigators, would expose the patient to undue risk of harm or prevent the patient from completing the study

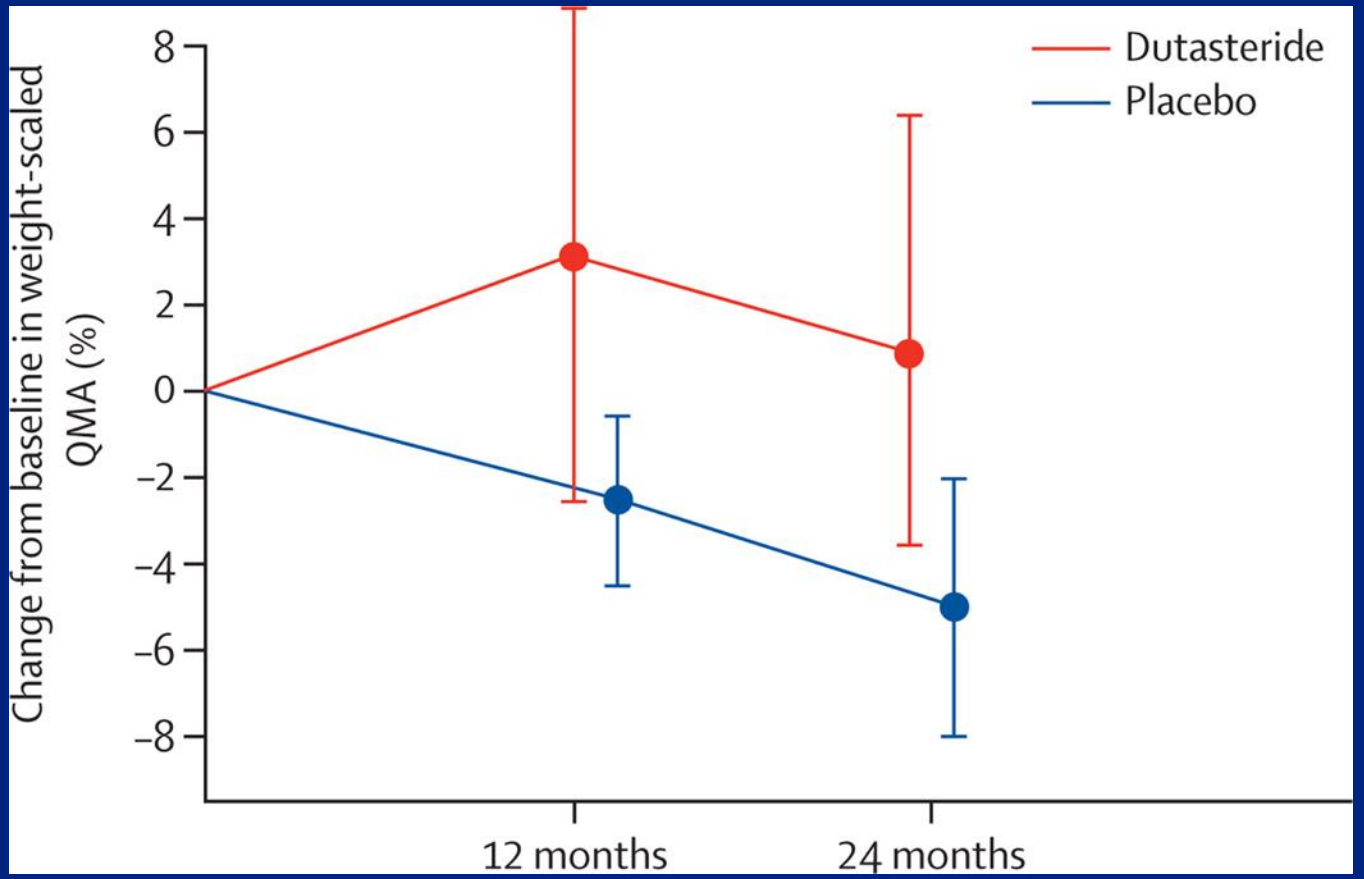
Structure of the Study

Our objective is to examine the safety and efficacy of dutasteride given at a dose of 0.5 mg a day for 2 years in an outpatient setting. This will be a randomized, double-blind, placebo-controlled trial with 25 subjects in each arm. The subjects will be evaluated neurologically and endocrinologically every 6 months at the NIH Clinical Center.

Miles from nowhere
I guess I'll take my time
Oh yeah, to reach there

Look up at the mountain
I have to climb
Oh yeah, to reach there.

Cat Stevens



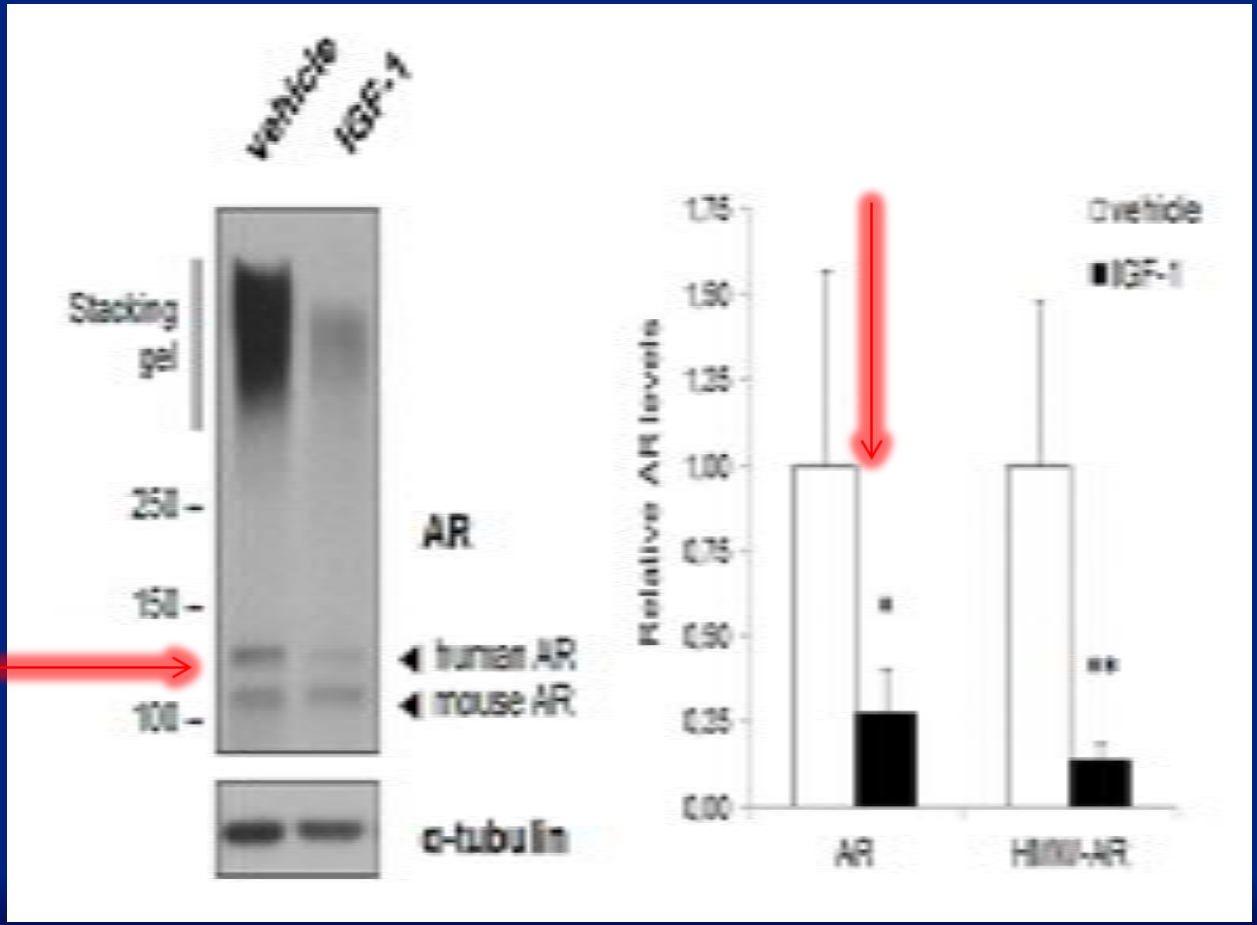
Lancet Neurol. 2011 February; 10(2): 140–147.

IGF-1 administration ameliorates disease manifestations in a mouse model of spinal and bulbar muscular atrophy

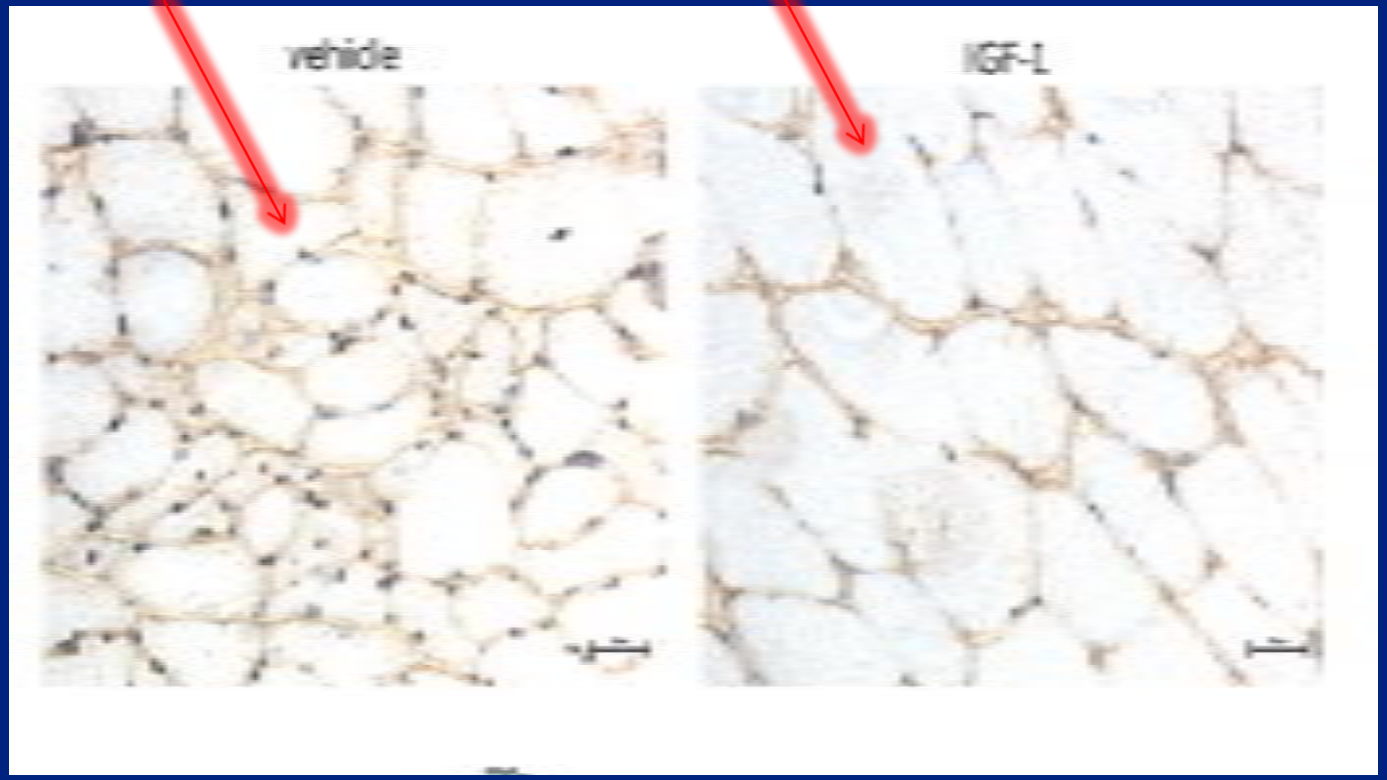
Carlo Rinaldi, Laura C. Bott, Ke-lian Chen,1 George G. Harmison, Masahisa Katsuno, Gen Sobue, Maria Pennuto, Kenneth H. Fischbeck

How does one demonstrate the IGF-1 is effective treatment for SBMA?

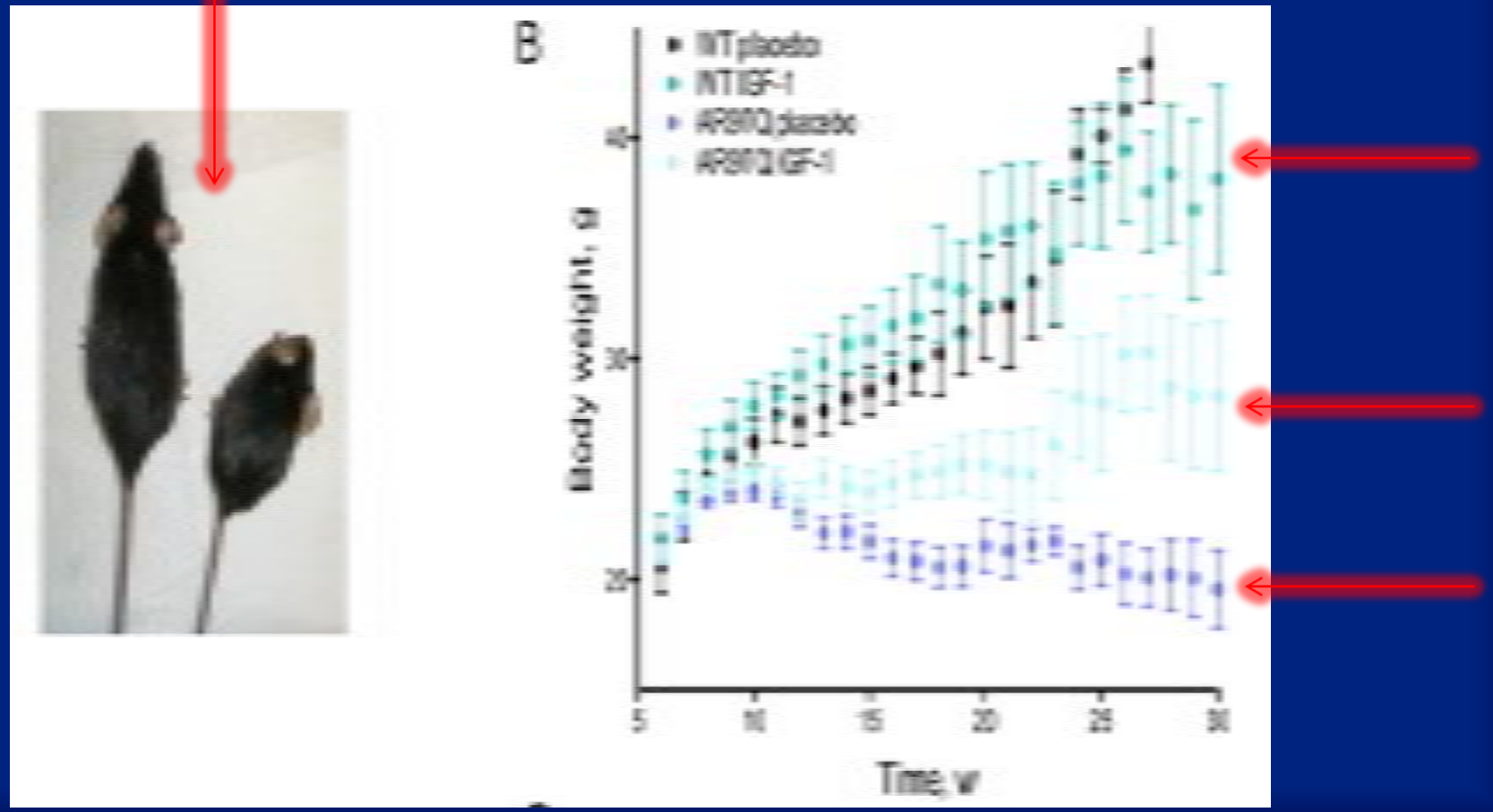
IGF-1 decreases total levels of AR in muscle cells



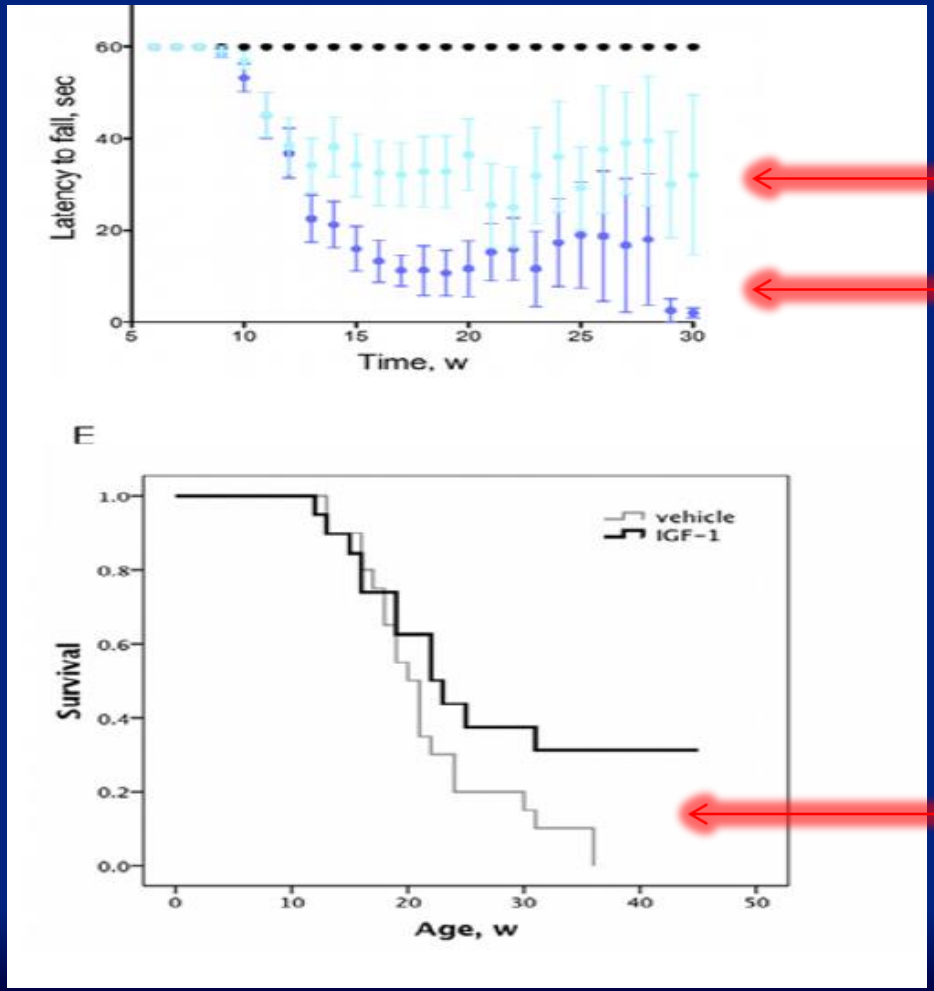
IGF-1 decreases AR localized in muscle nuclii



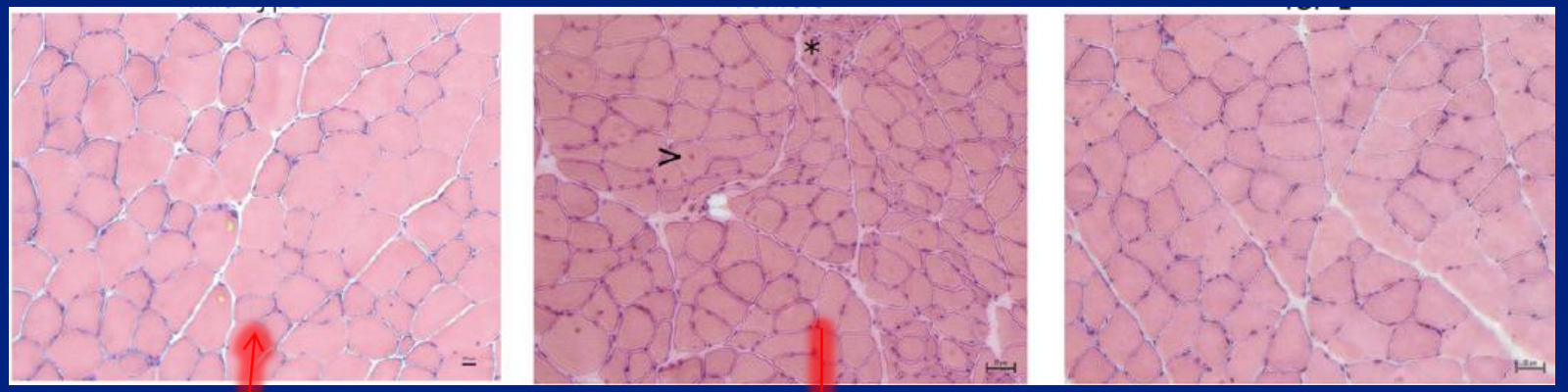
IGF-1 increases body weight of SBMA mice

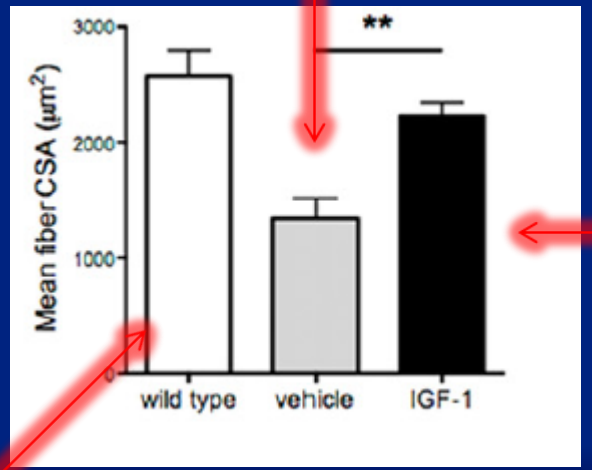


IGF-1 increases hang time and survival

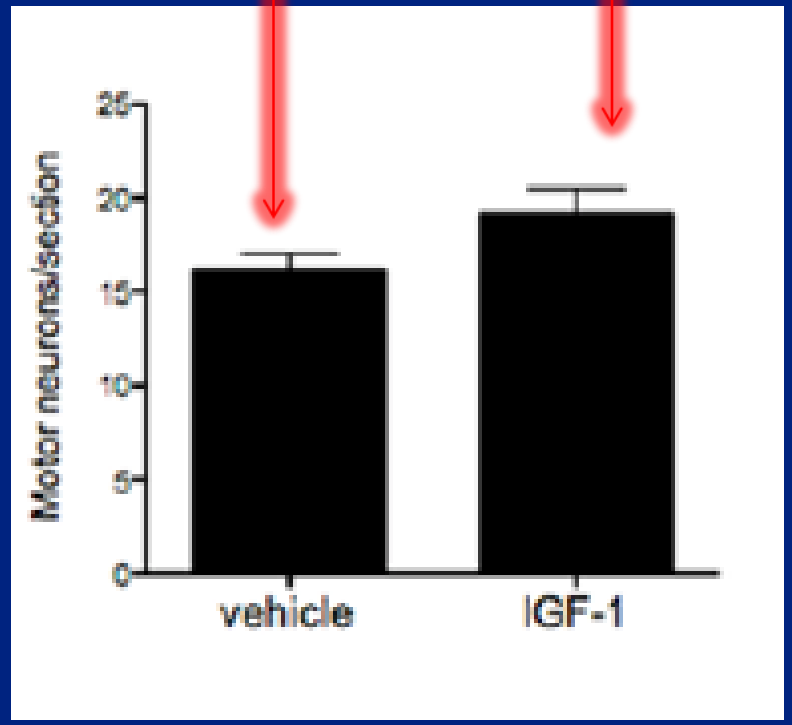


IGF-1 increases cross sectional area of muscle cells





IGF-1 increases number of motor neurons in spinal cord.



Pick up the pieces you see before you
Don't let your weaknesses destroy you
You know wherever you go the world will follow
So let your reasons be true to you

Cat Stevens

And if I ever lose my legs, I won't moan, and I won't beg,
Yes if I ever lose my legs, Oh if... I won't have to walk no more.

Cat Stevens

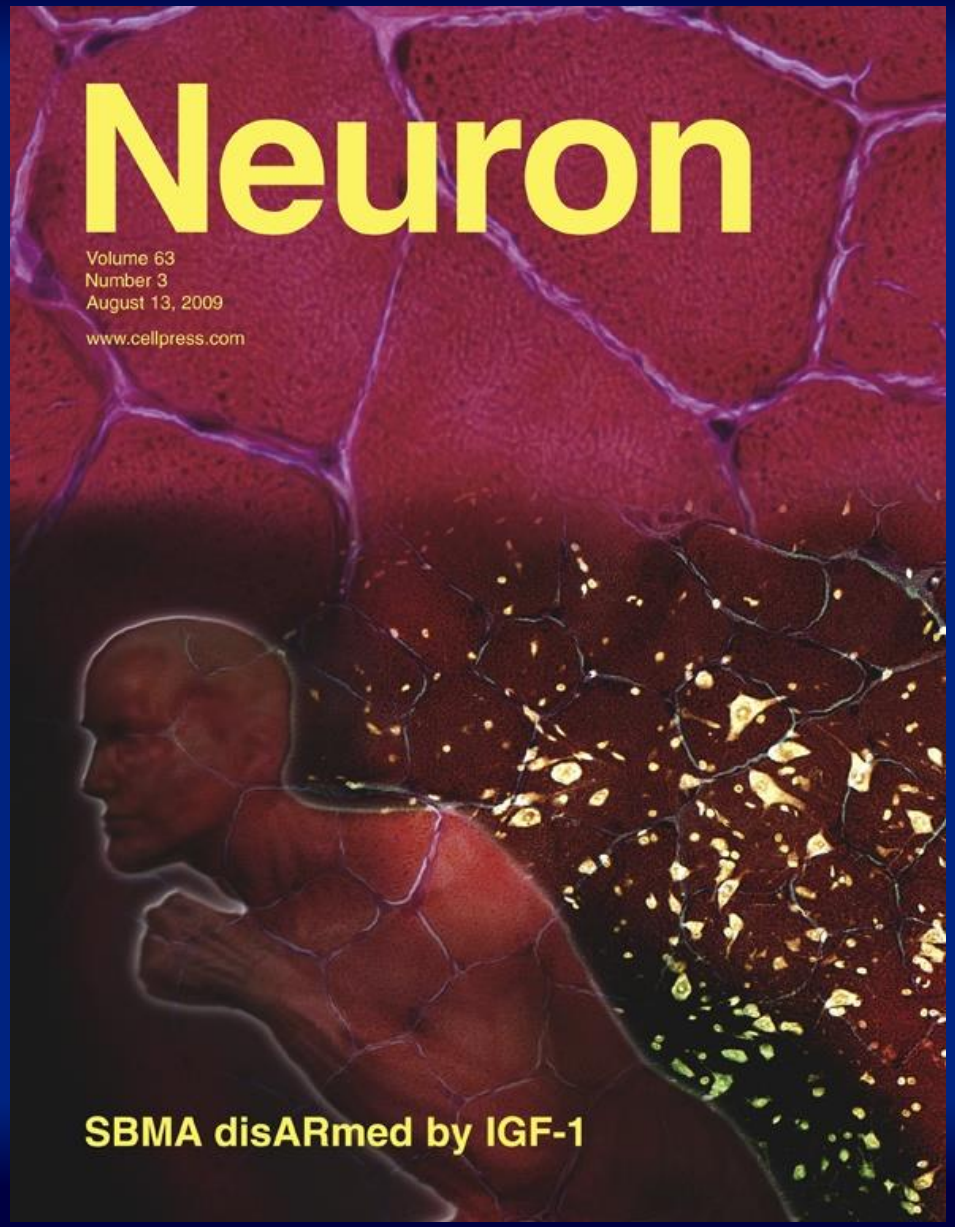
Statistics are used much like a drunk uses a lamppost: for support, not illumination.

Vin Scully

http://www.razoo.com/story/Hoya-Jack-Running-For-The-Kennedy-S-Disease-Association


SOUTH FLORIDA
OFFICIAL
GAME COIN
OFFICIAL
NFL
GAME
COIN
LIMITED
EDITION
SUPER BOWL XLIV
COLTS
SAINTS

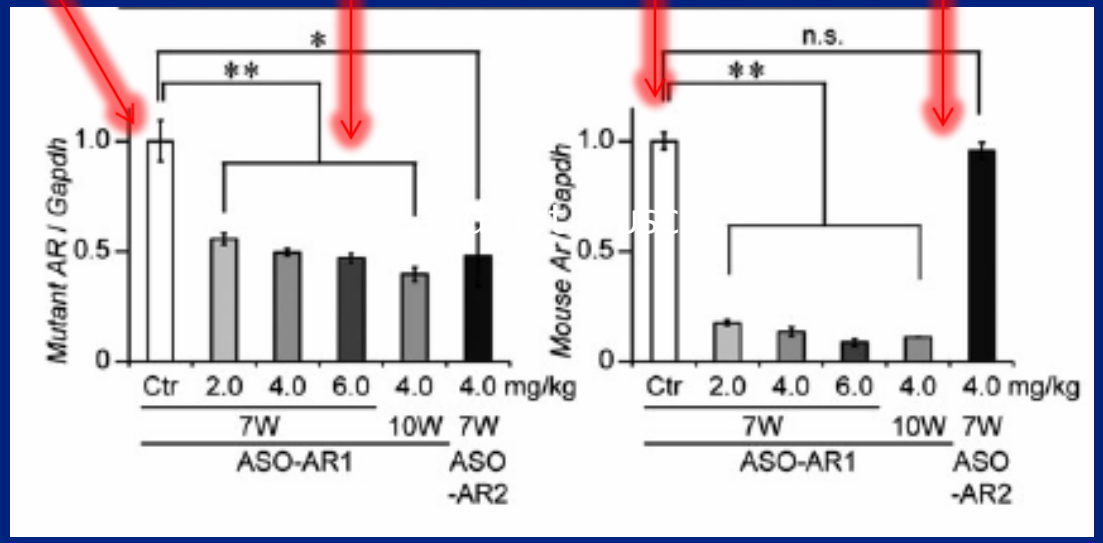

Ed R., Ed M., David R. - 9/60


Neuron
Volume 63
Number 3
August 13, 2009
www.cellpress.com
SBMA disARmed by IGF-1

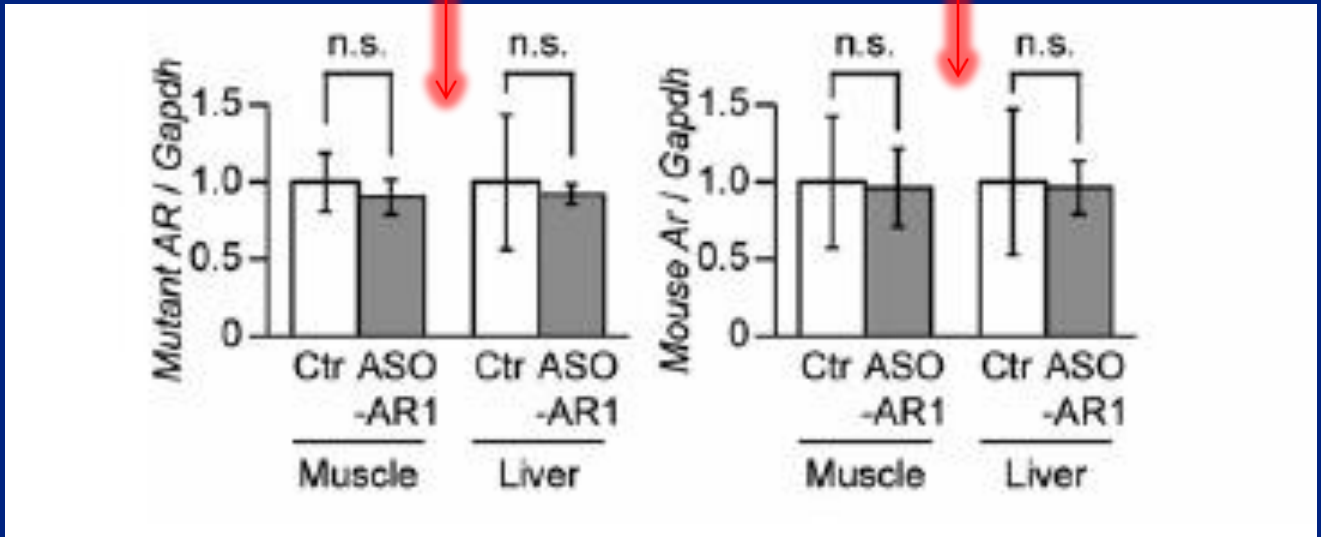
Silencing neuronal mutant androgen receptor in a mouse model of spinal and bulbar muscular atrophy

Kentaro Sahashi, Masahisa Katsuno1, Gene Hung, Hiroaki Adachi,
Naohide Kondo, Hideaki Nakatsuj, Genki Tohnai, Madoka Iida,
C. Frank Bennett and Gen Sobue

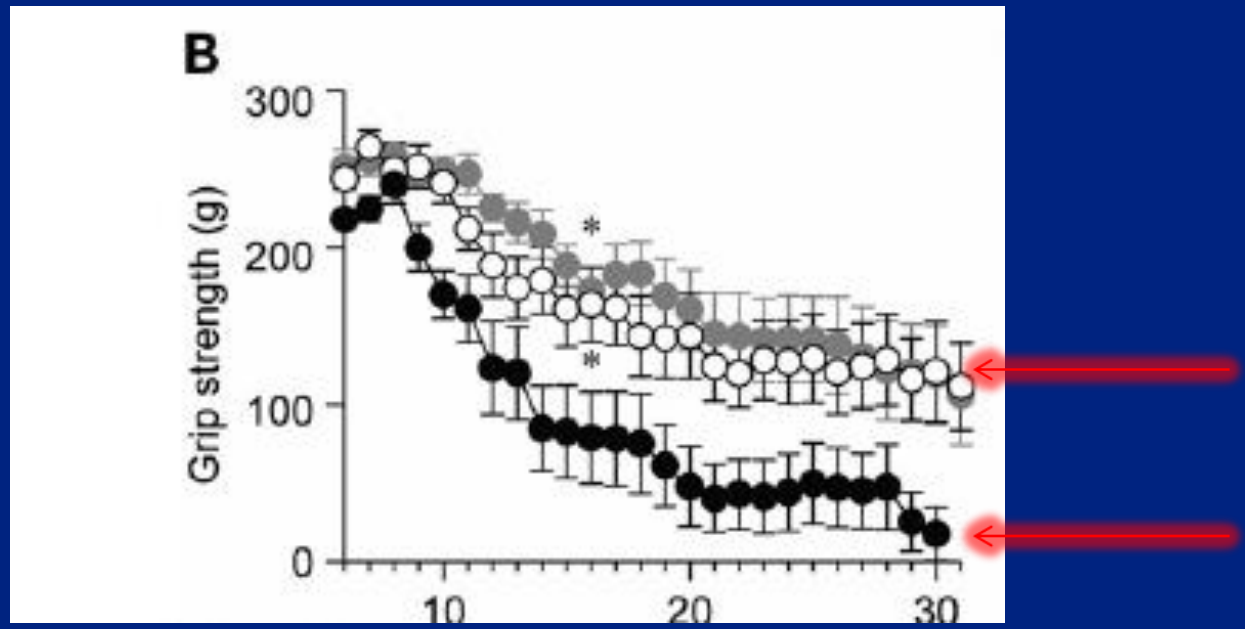
Injection of ASO nucleotide into a KD mouse model reduces the levels of human AR mRNA in spinal cord.



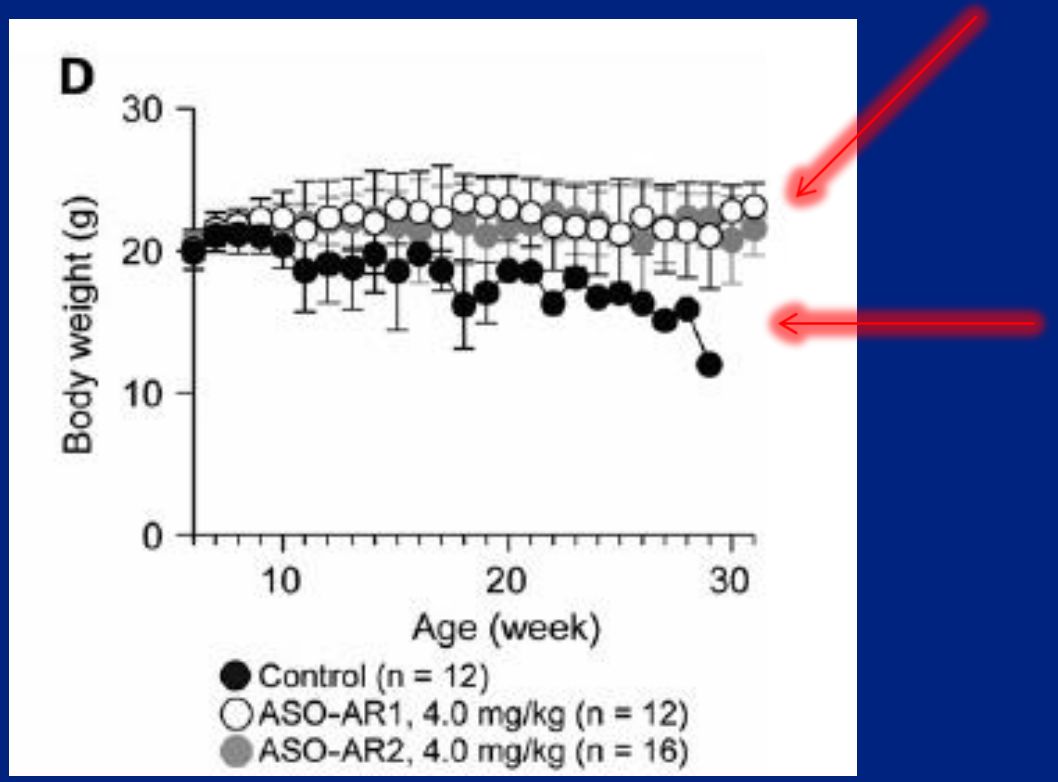
Injection of ASO nucleotide into a KD mouse model reduces the levels of human AR mRNA in brain tissue and not muscle.



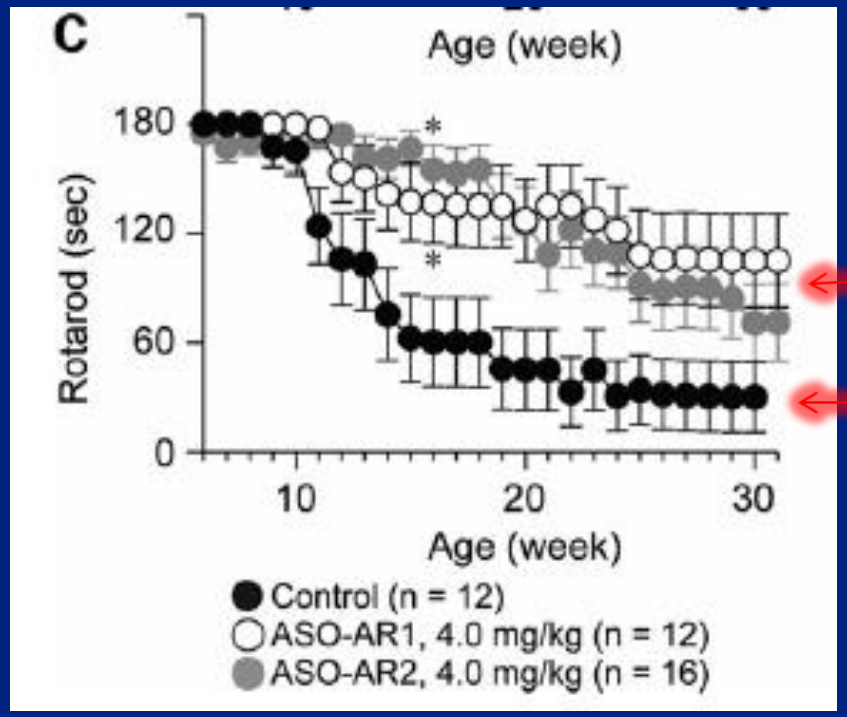
ASO treated mutant mice recovered grip strength



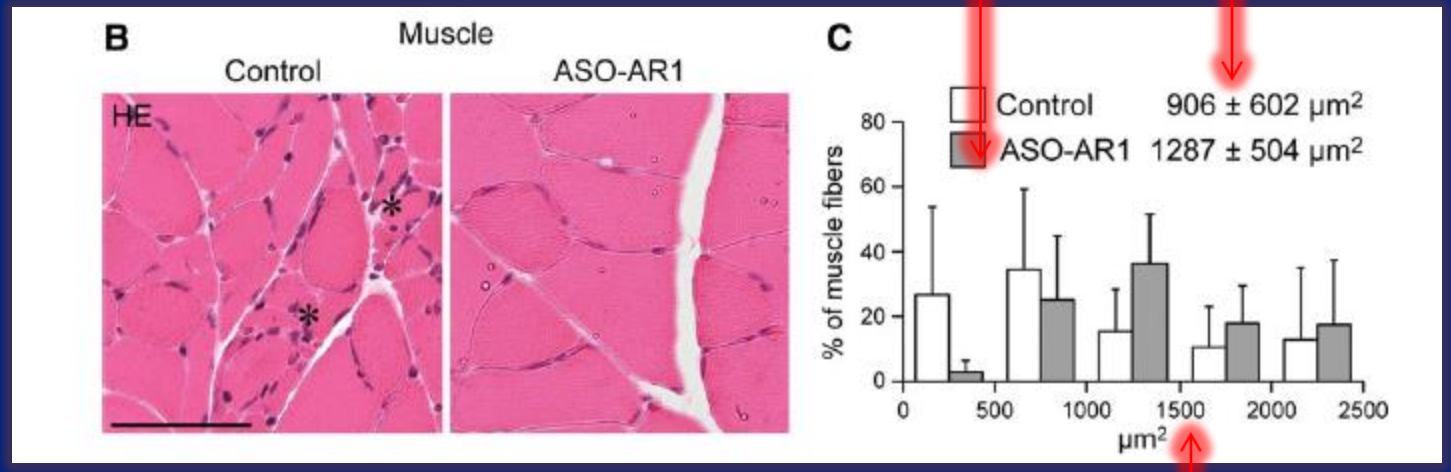
… and body weight



ASO treated mutant mice were better on the rotorod



ASO treated mutant mice had larger muscle fibers

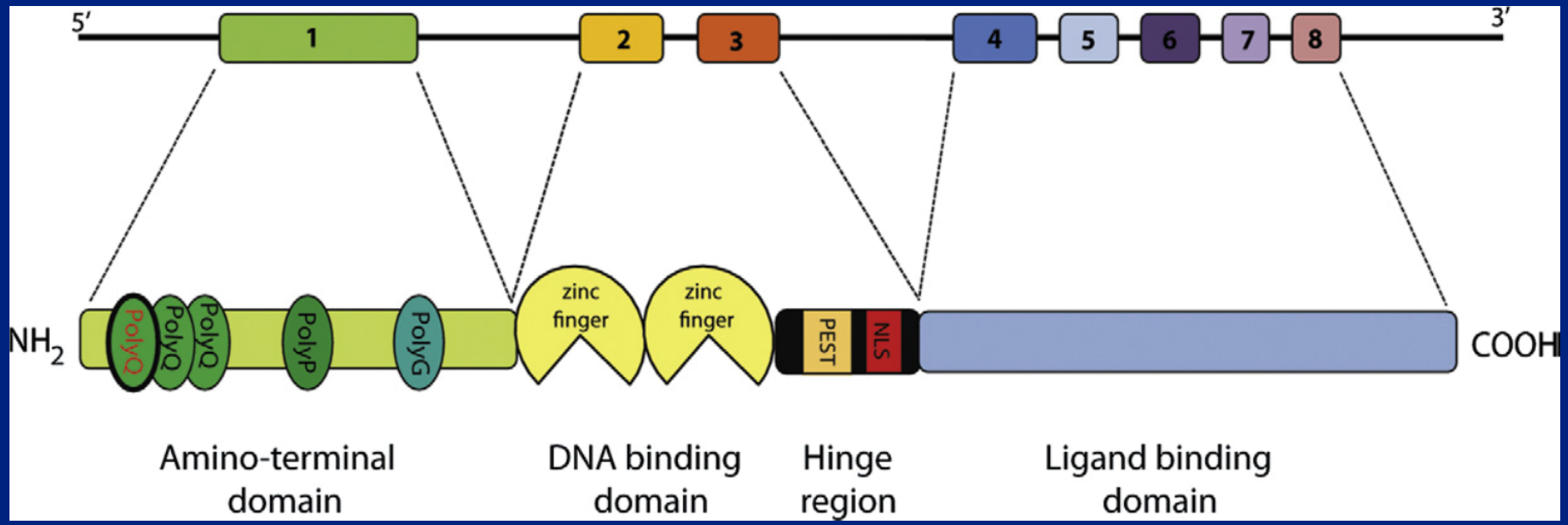


From this day to the ending of the world,
But we in it shall be remember'd;
We few, we happy few, we band of brothers;
For he to-day that sheds his blood with me
Shall be my brother; be he ne'er so vile,
This day shall gentle his condition:

Progressive proximal spinal and bulbar muscular atrophy of late onset. A sex-linked recessive trait.

Kennedy WR, Alter M, Sung JH.
Neurology. 1968 Jul;18(7):671-80

By the pricking of my thumbs,
Something wicked this way
comes.

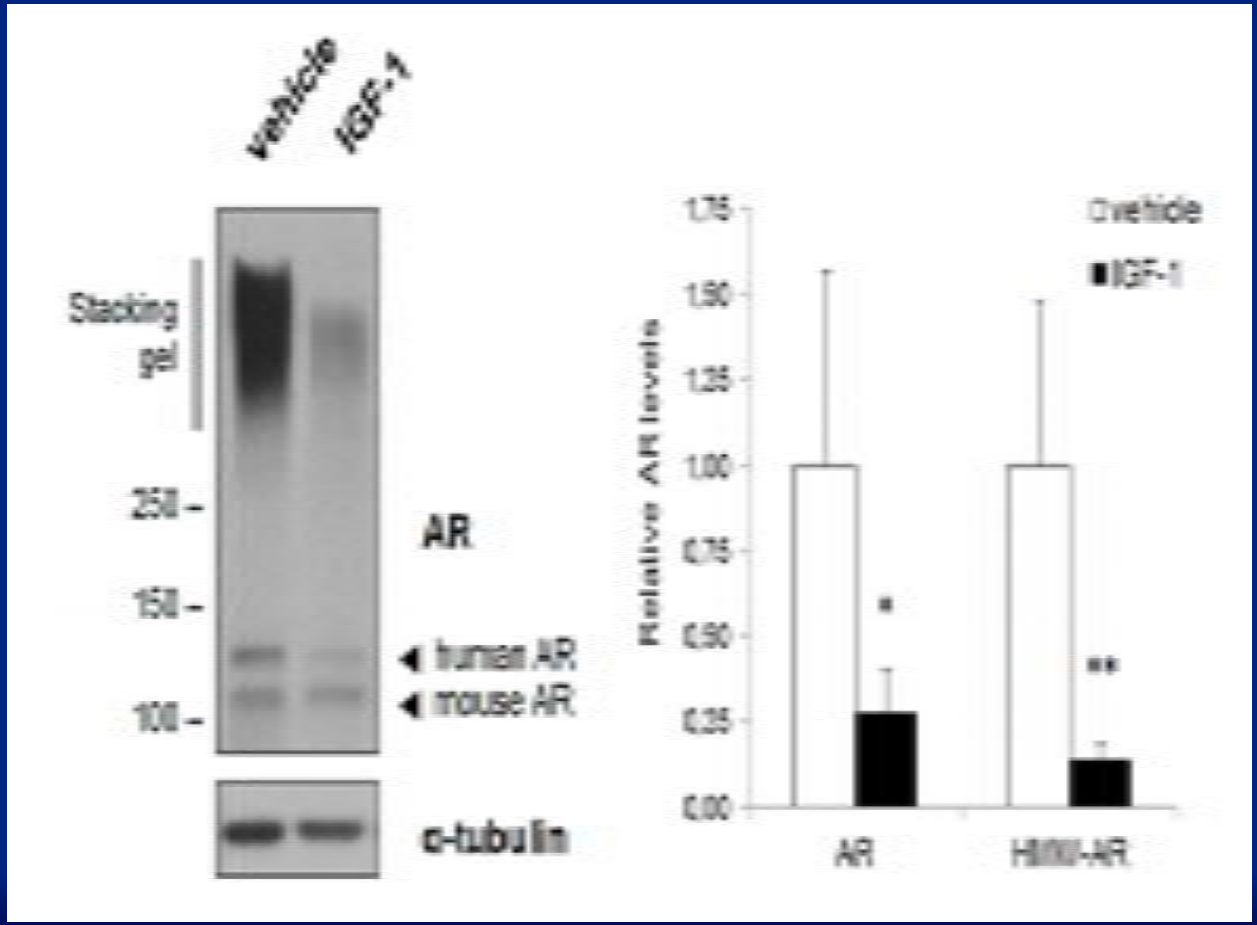

5′
3′
1
2
3
4
5
6
7
8
NH2
PolyQ
PolyQ
PolyQ
PolyP
PolyG
zinc finger
zinc finger
PEST
NLS
COOH
Amino-terminal domain
DNA binding domain
Hinge region
Ligand binding domain

IGF-1 administration ameliorates disease manifestations in a mouse model of spinal and bulbar muscular atrophy

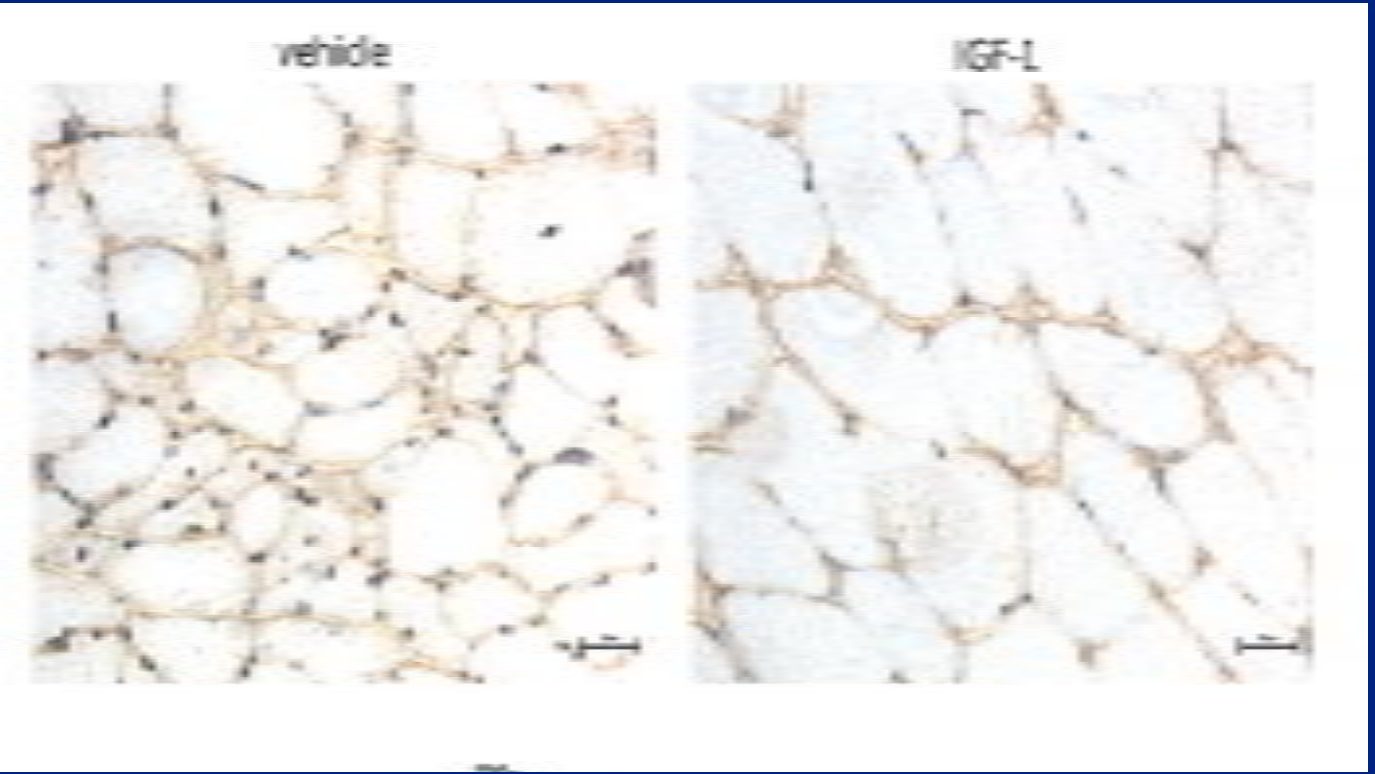
Carlo Rinaldi, Laura C. Bott, Ke-lian Chen,1 George G. Harmison, Masahisa Katsuno, Gen Sobue, Maria Pennuto, Kenneth H. Fischbeck

How does one demonstrate the IGF-1 is effective treatment for SBMA?

IGF-1 decreases total levels of AR in muscle cells

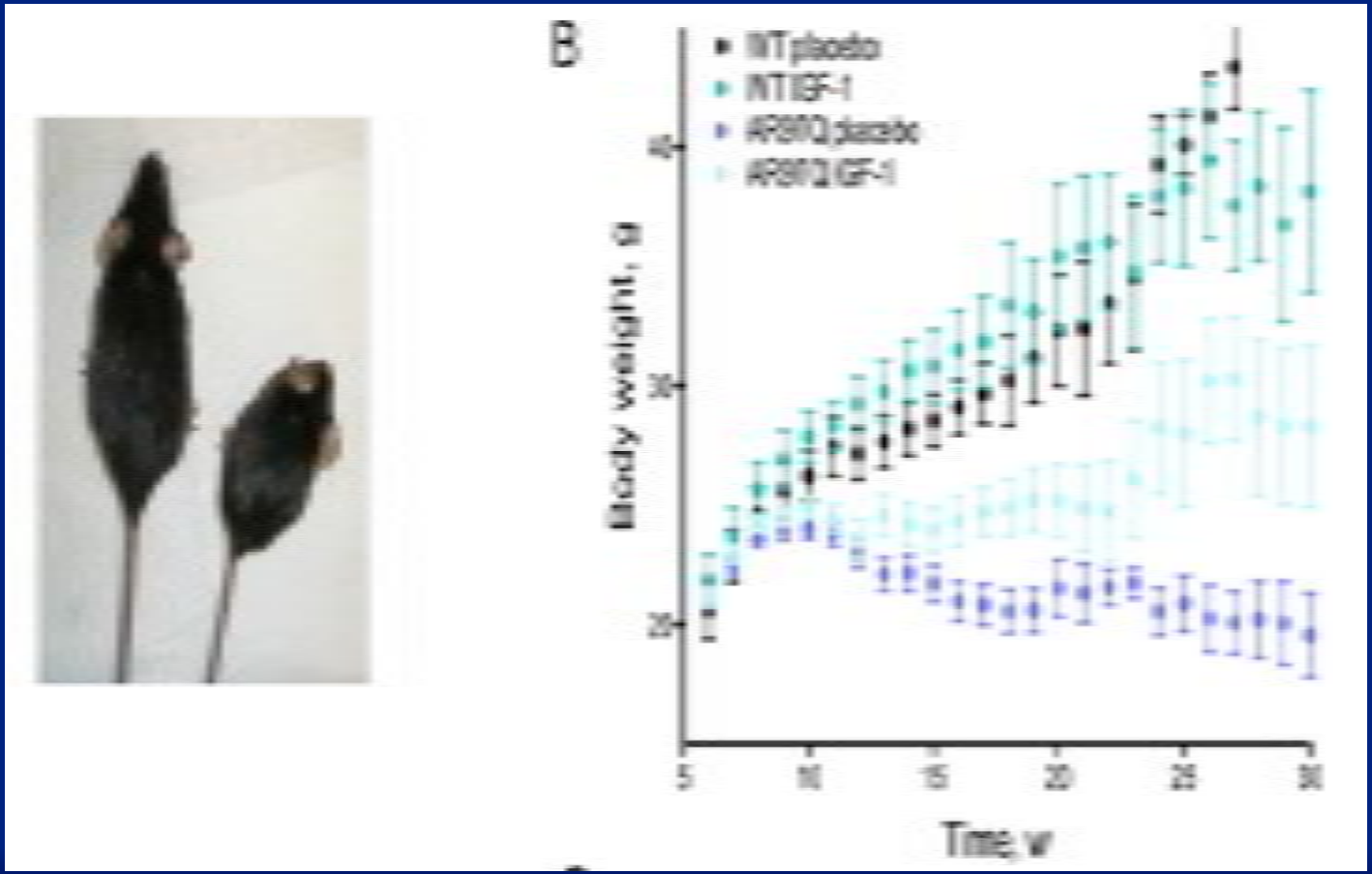


IGF-1 decreases AR localized in muscle nuclii

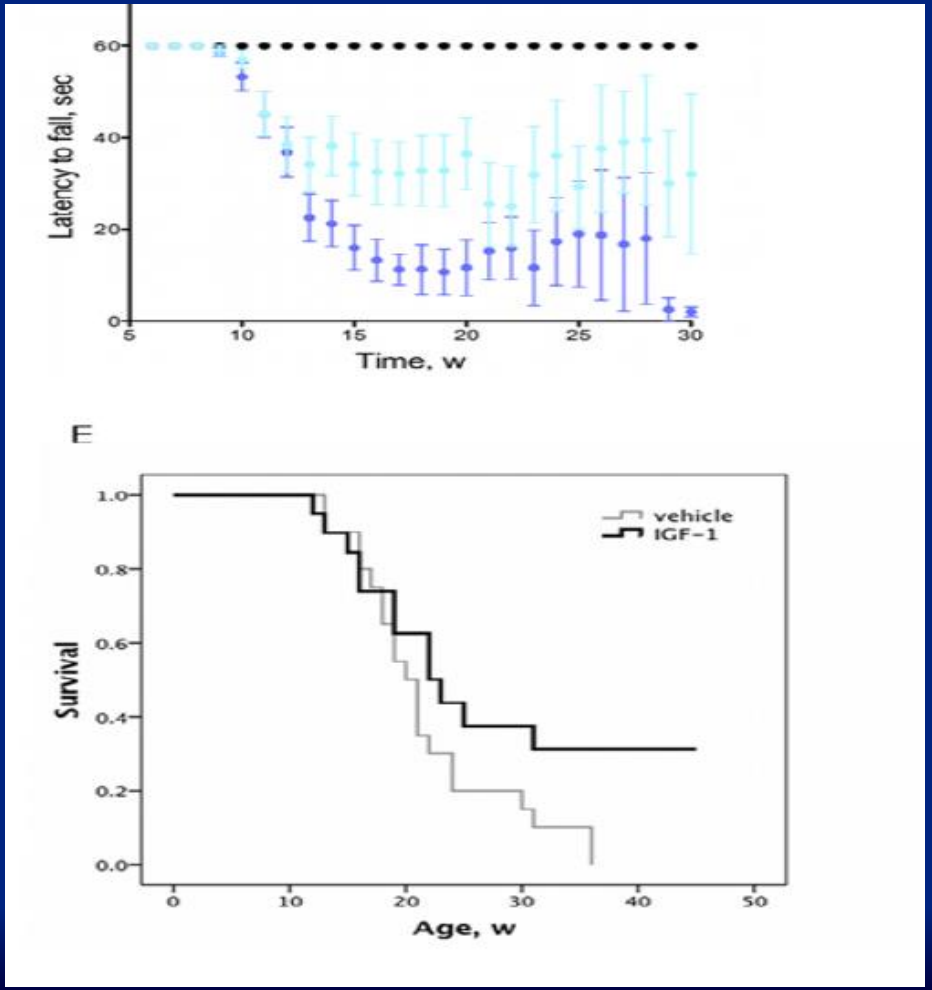



BANDIT

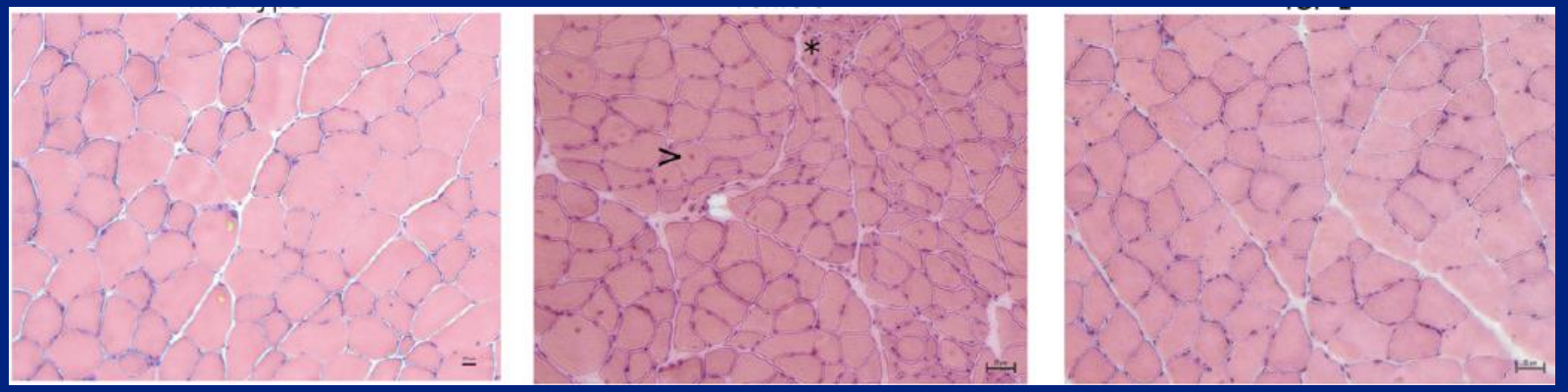
IGF-1 increases body weight of SBMA mice

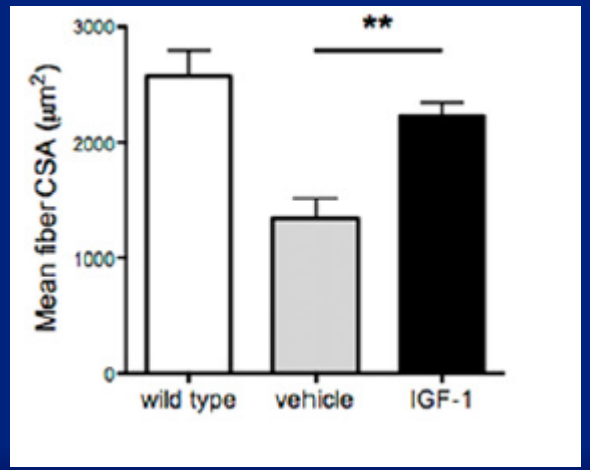


IGF-1 increases hang time and survival

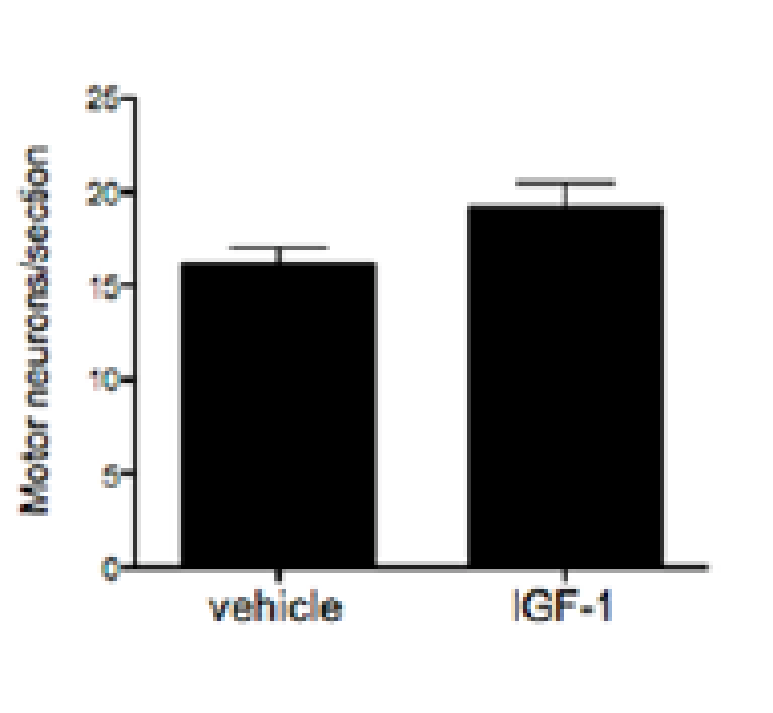


IGF-1 increases cross sectional area of muscle cells





IGF-1 increases number of motor neurons in spinal cord.



Ignorance is the curse of God; knowledge is the wing wherewith we fly to heaven.

What is past is prologue The Tempest

Nature hath framed strange fellows in her time.

To climb steep hills requires slow pace at first."
—William Shakespeare

"Oft expectation fails, and most oft where most it promises; and oft it hits where hope is coldest; and despair most sits" —William Shakespeare

"Eye of newt and toe of frog, Wool of bat and tongue of dog, Adder's fork and blind-worm's sting, Lizard's leg and owlet's wing, For a charm of powerful trouble, Like a hell-broth boil and bubble"

"Present fears are less than horrible imaginings." — William Shakespeare

"Affliction may one day smile again; and till then, sit thee down, sorrow!" — William Shakespeare

"There is a history in all men's lives." — William Shakespeare

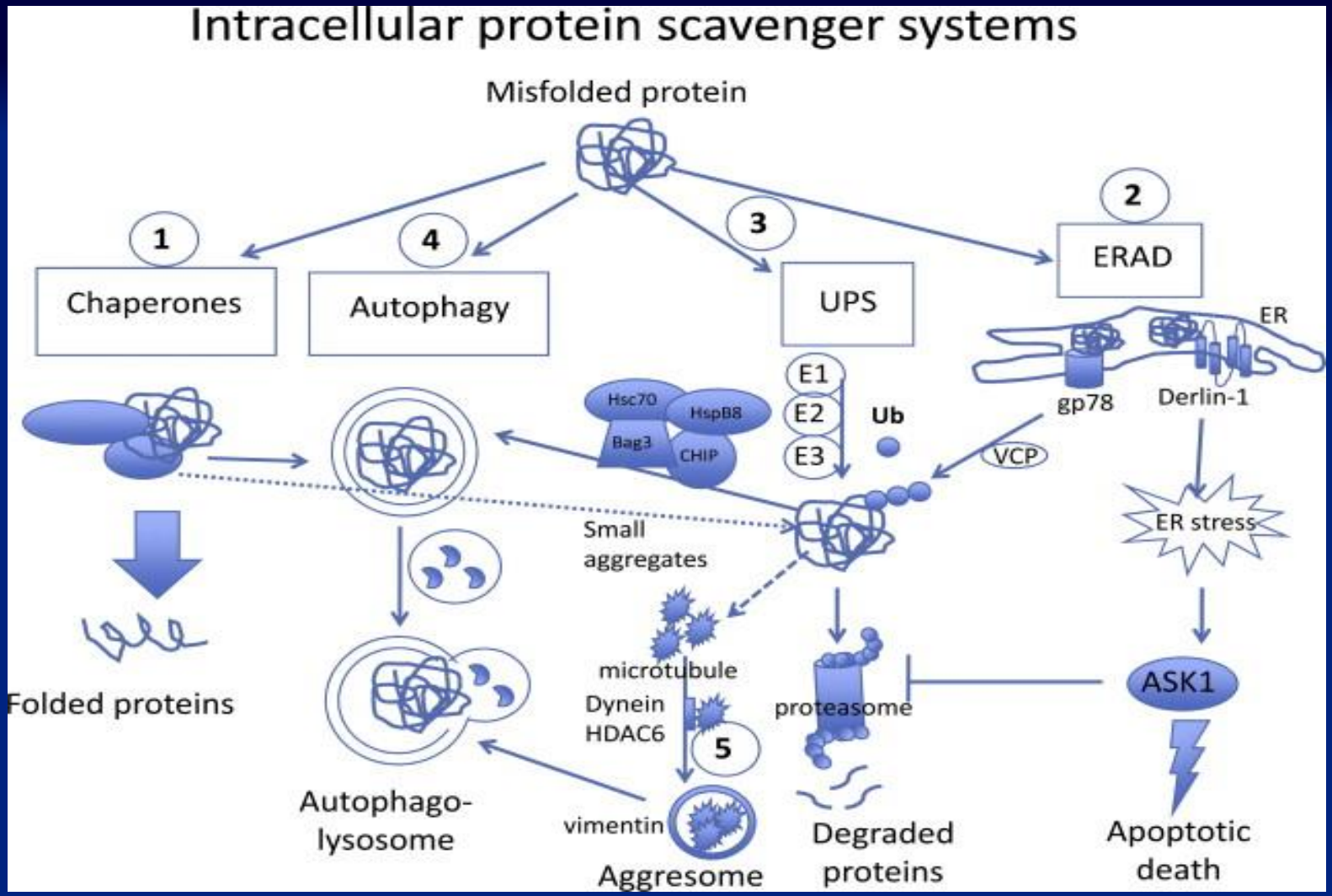
"All is not well; I doubt some foul play."

"All that glisters is not gold; Often have you heard that told"

"When you fear a foe, fear crushes your strength; and this weakness gives strength to your opponents." — William Shakespeare

"Thought are but dreams till their effects are tried." — William Shakespeare

"There is no darkness but ignorance." — William Shakespeare



Caterina Bendotti , Marianna Marino , Cristina Cheroni , Elena Fontana , Valeria Crippa , Angelo Poletti , Silvia ...

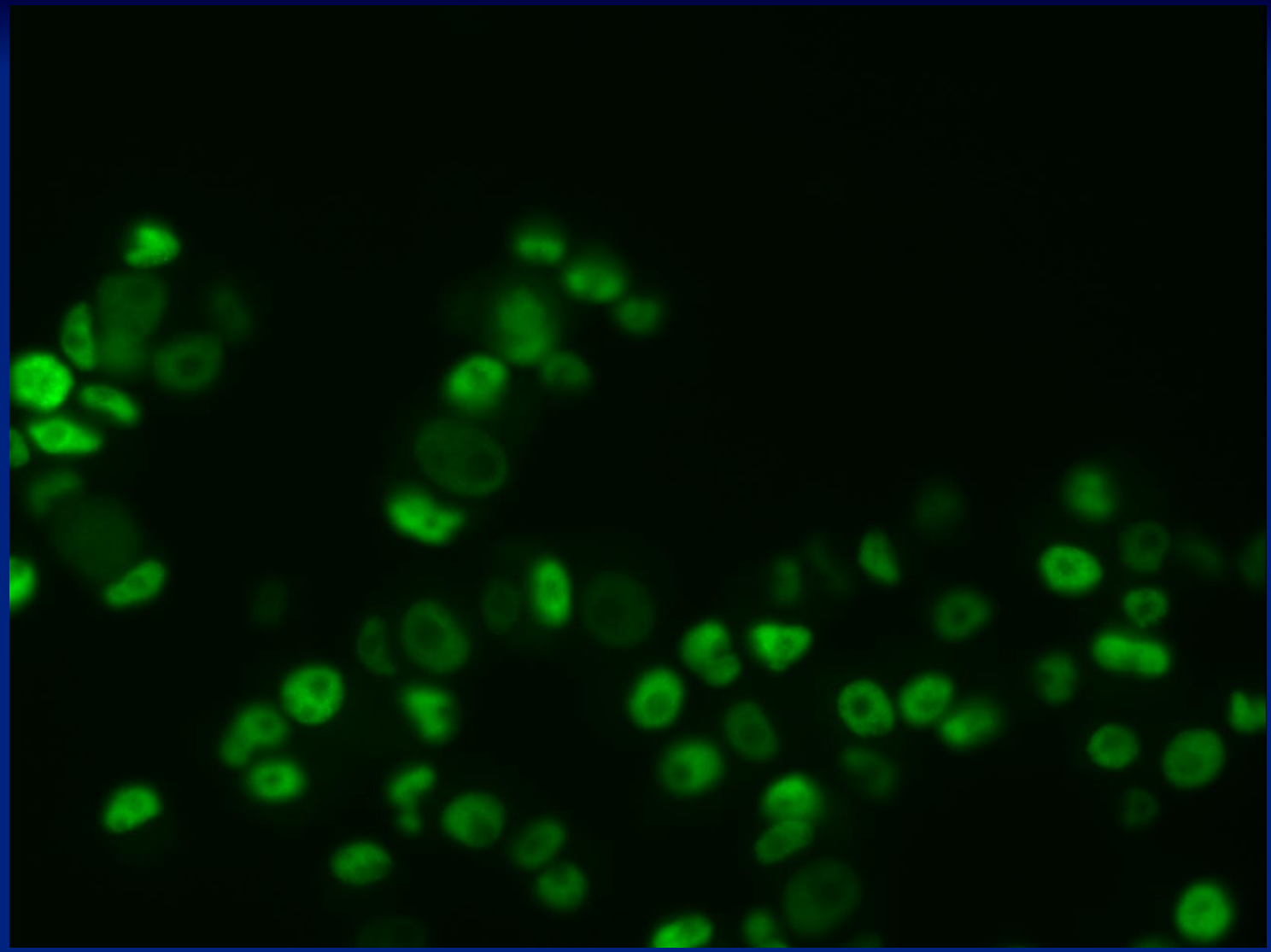
Dysfunction of constitutive and inducible ubiquitin-proteasome system in amyotrophic lateral sclerosis: Implication for protein aggregation and immune response
Progress in Neurobiology Volume 97, Issue 2 2012 101 - 126

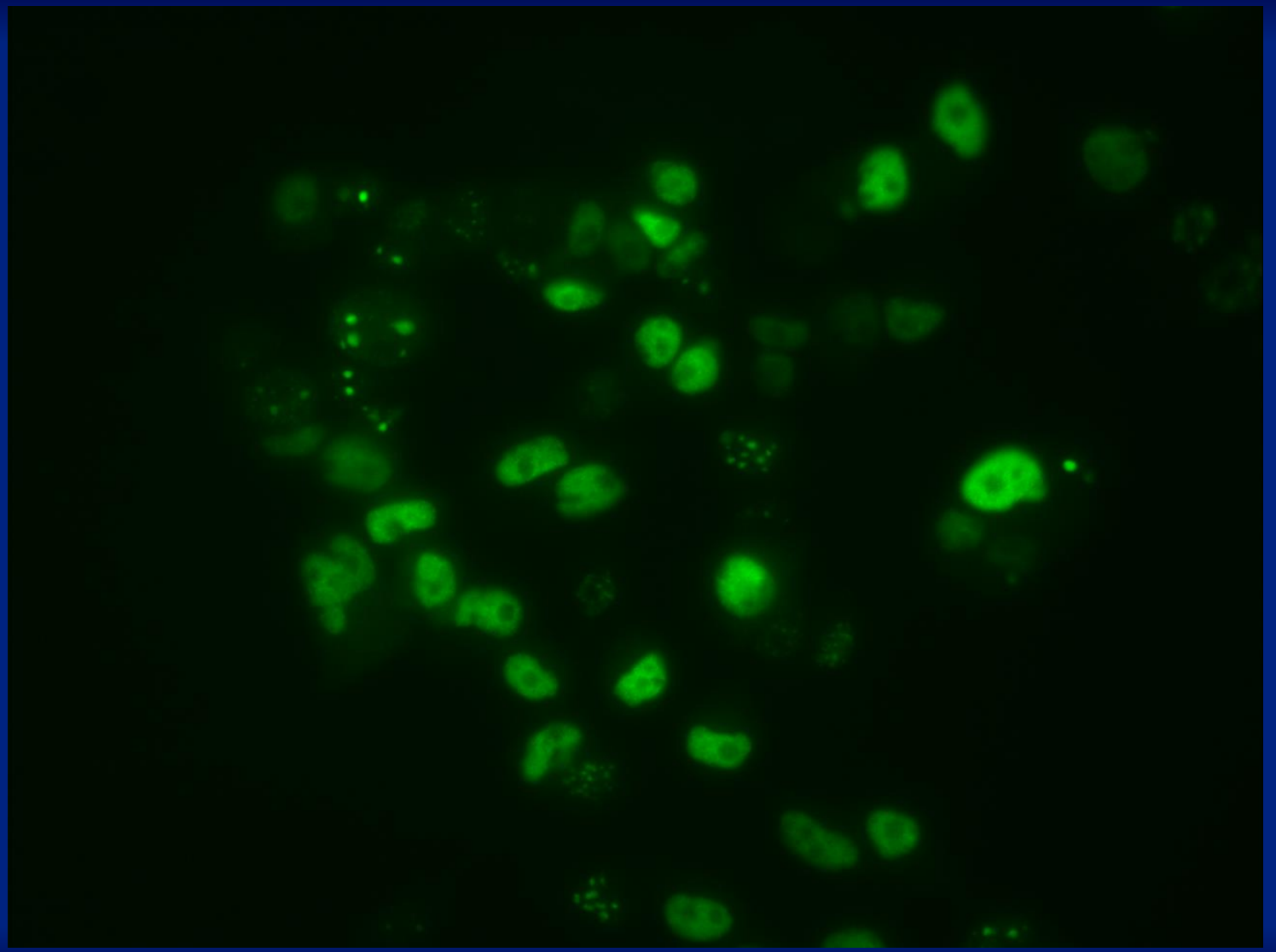
1. LBD: Ligand Binding Domain

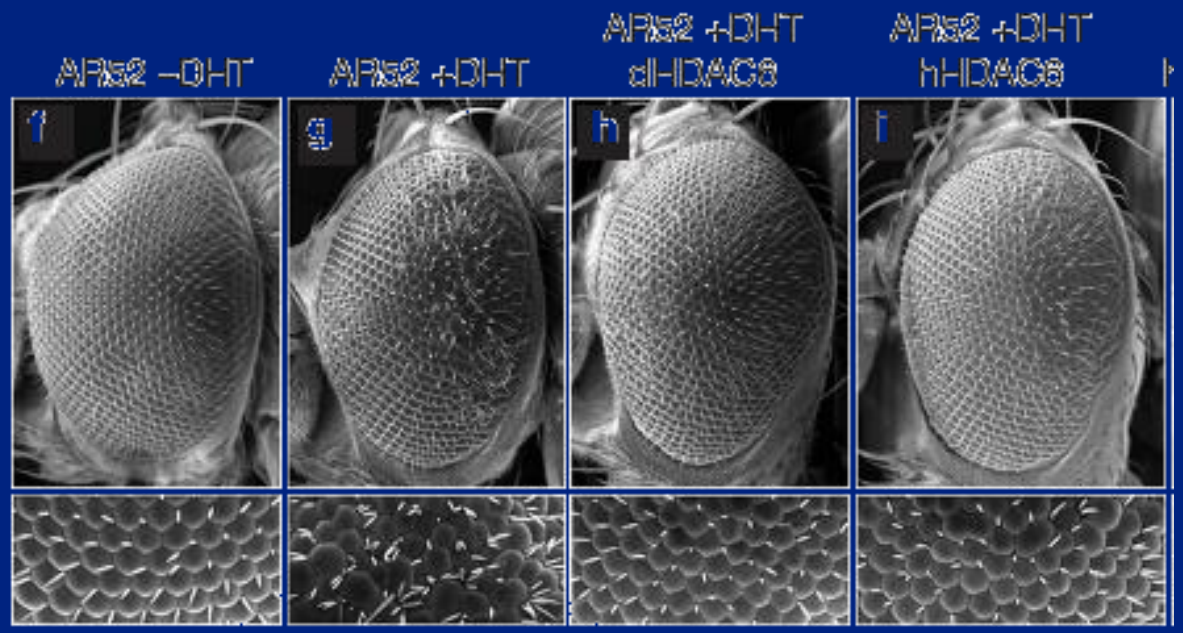
2. NLS: Nuclear Localization Site

3. DBD: DNA Binding Domain

4. AF2: Activation Site - 2





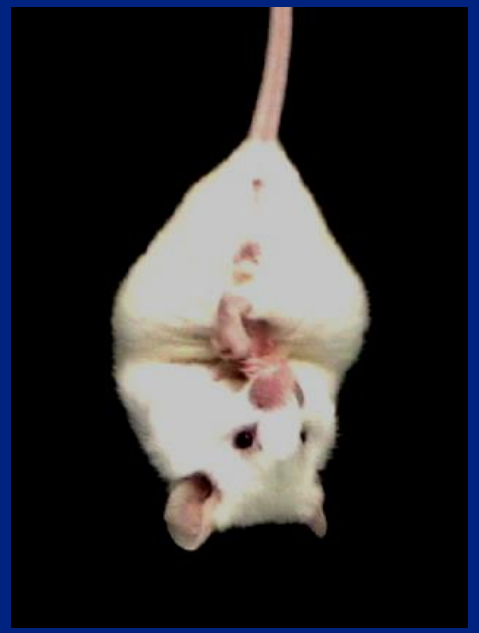


You donations at work!

Expression of Mutant Expanded AR, But Not Normal AR, Produces Neurological Disease in Transgenic Mice

NON-TRANSGENIC

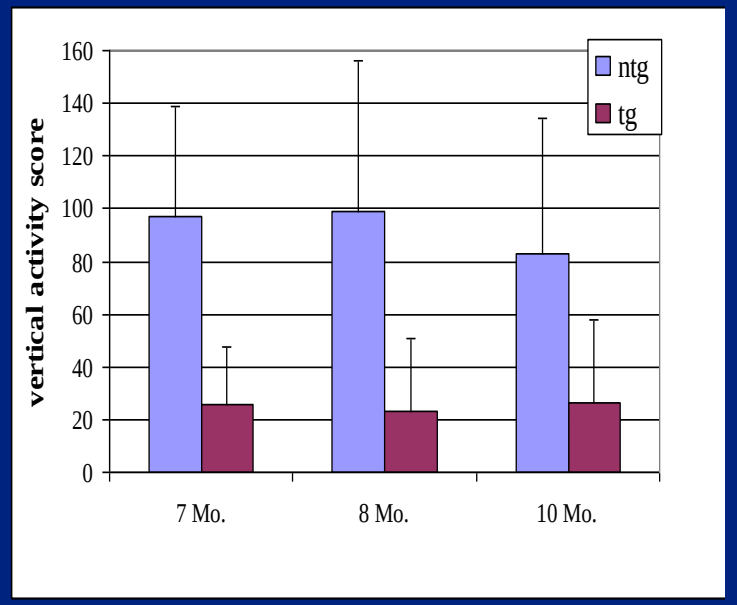
TEN-MONTHOLD TRANSGENIC



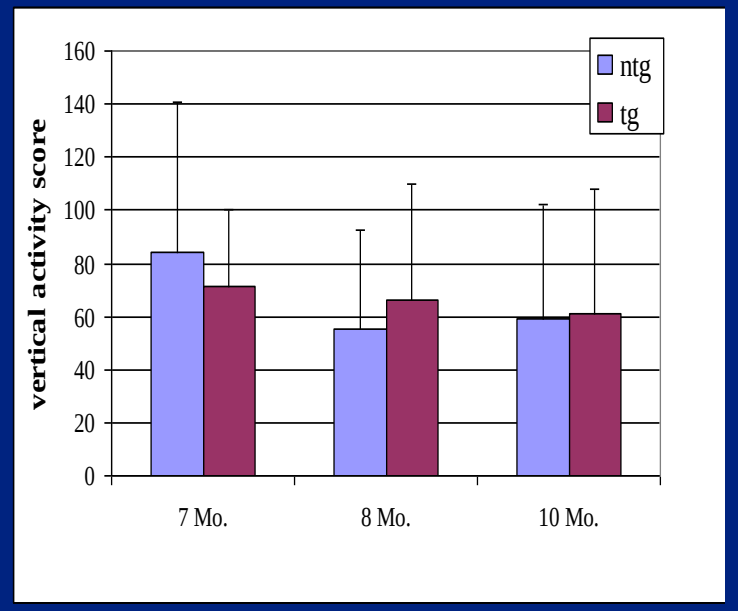

D
Ntg
Male
Tg
112Q
Male

Males Show Decreased Rearing

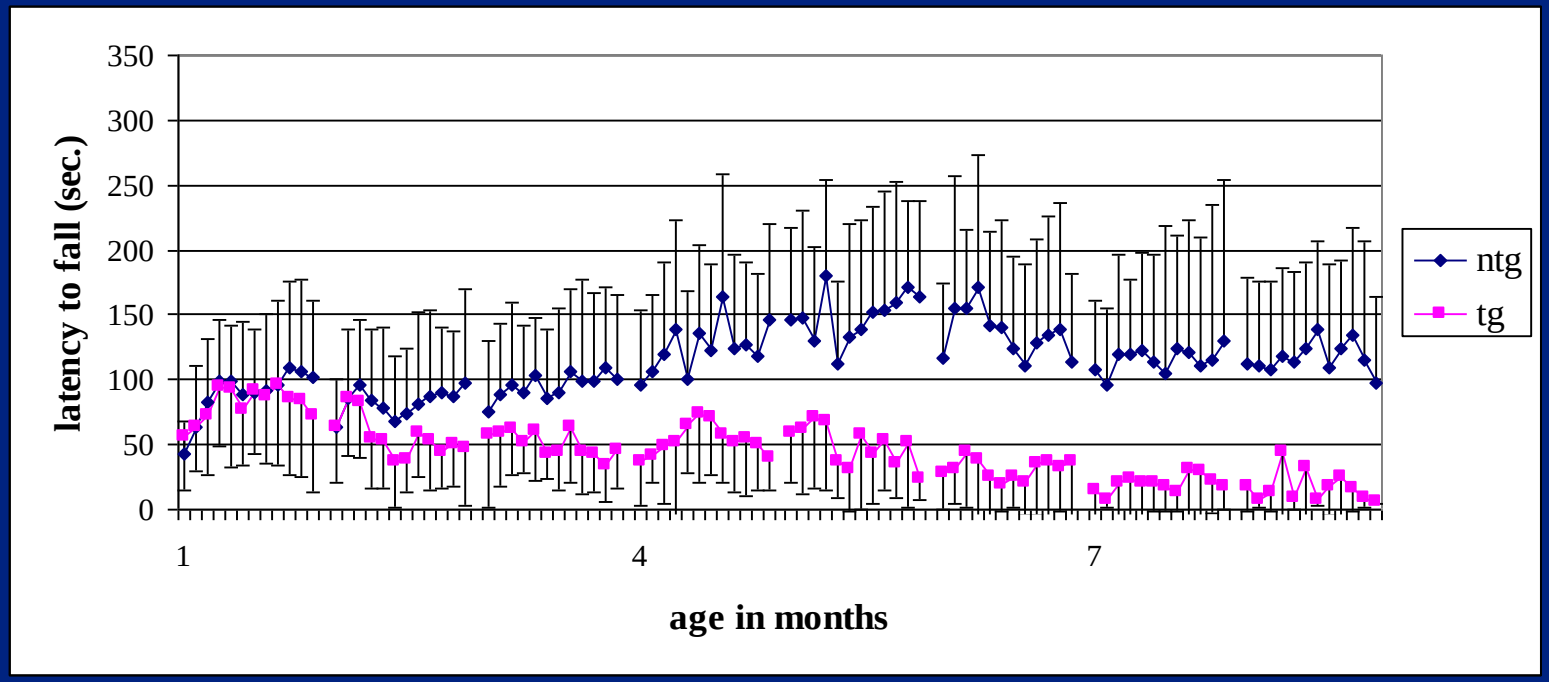
Males



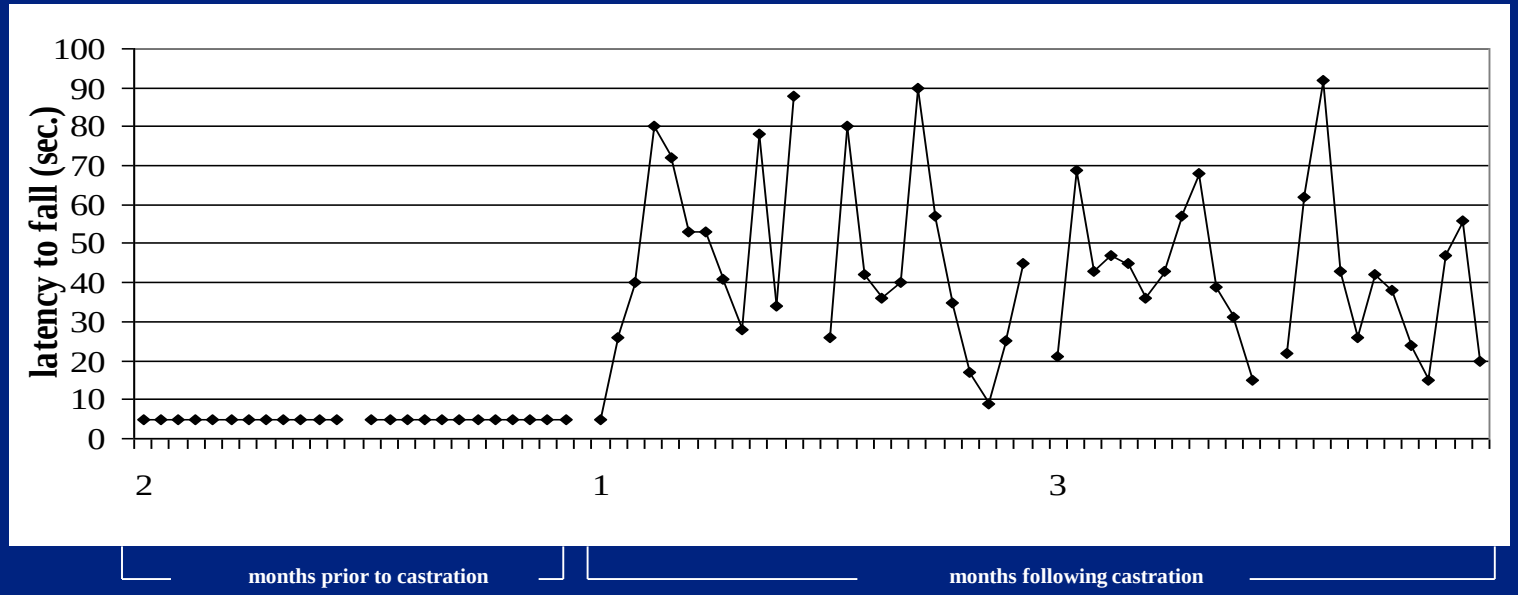
Females

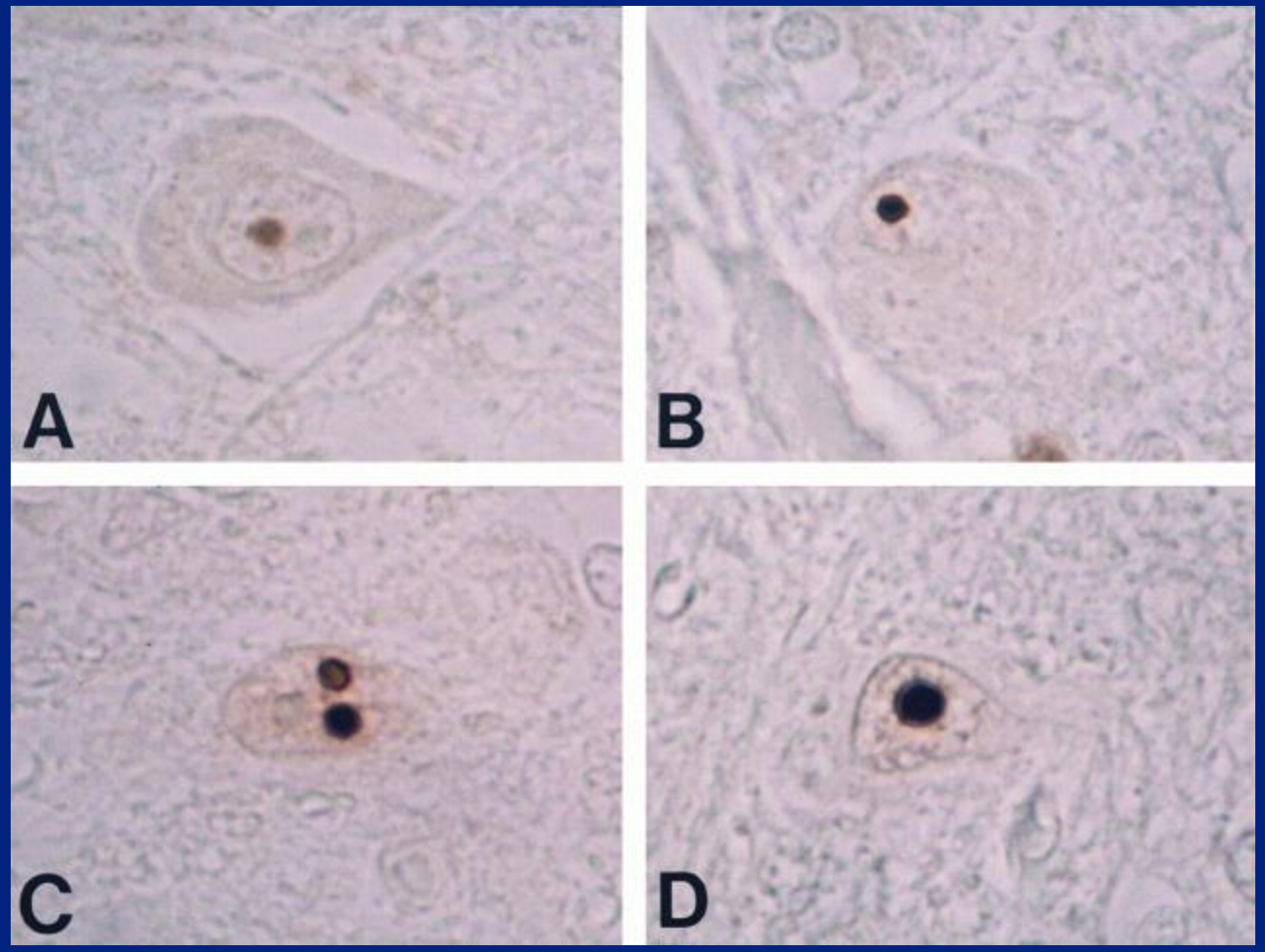


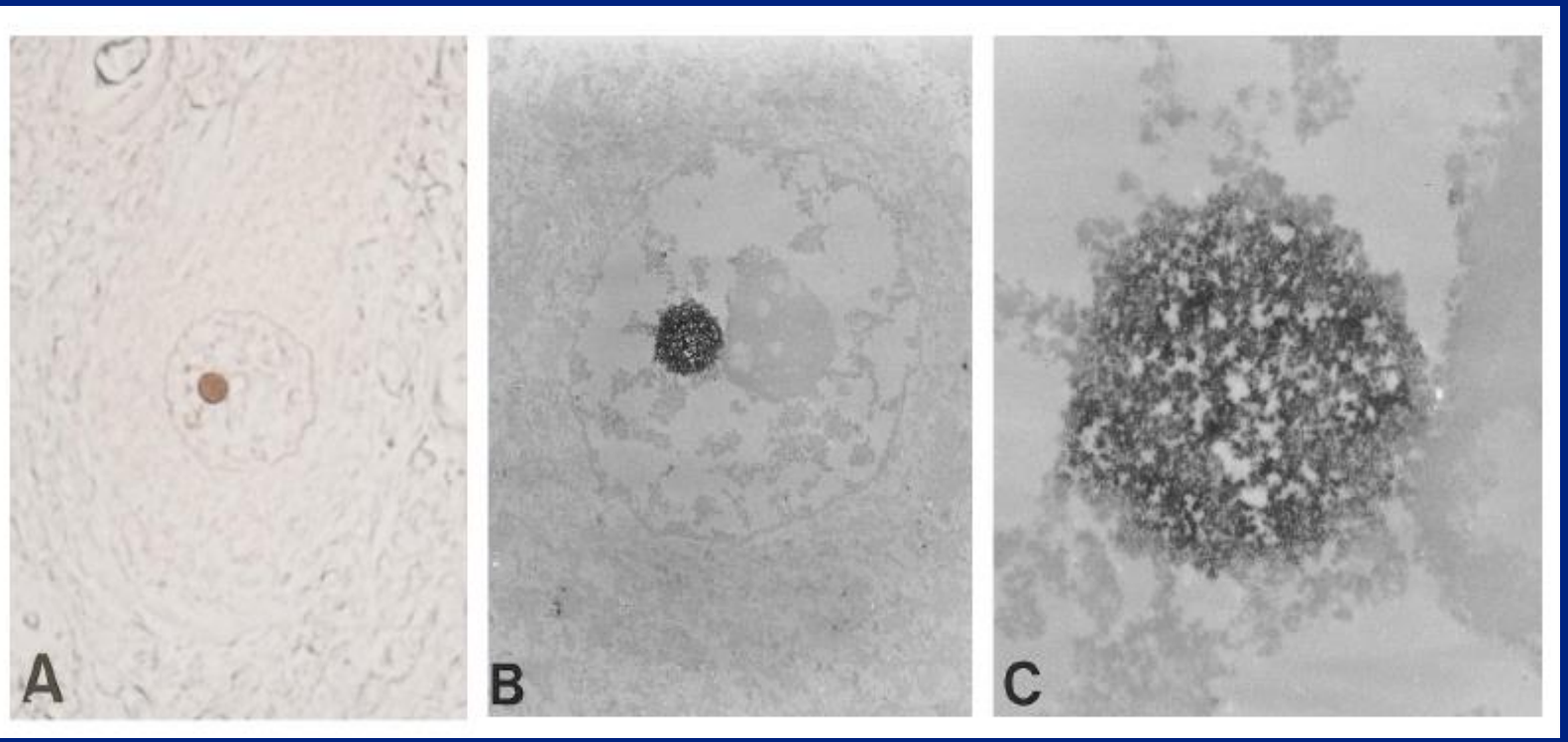
Motor Deficits Represented by Poor Performance on Accelerating Rotarod



Castration Restores Motor Function to 18 Month-Old Males



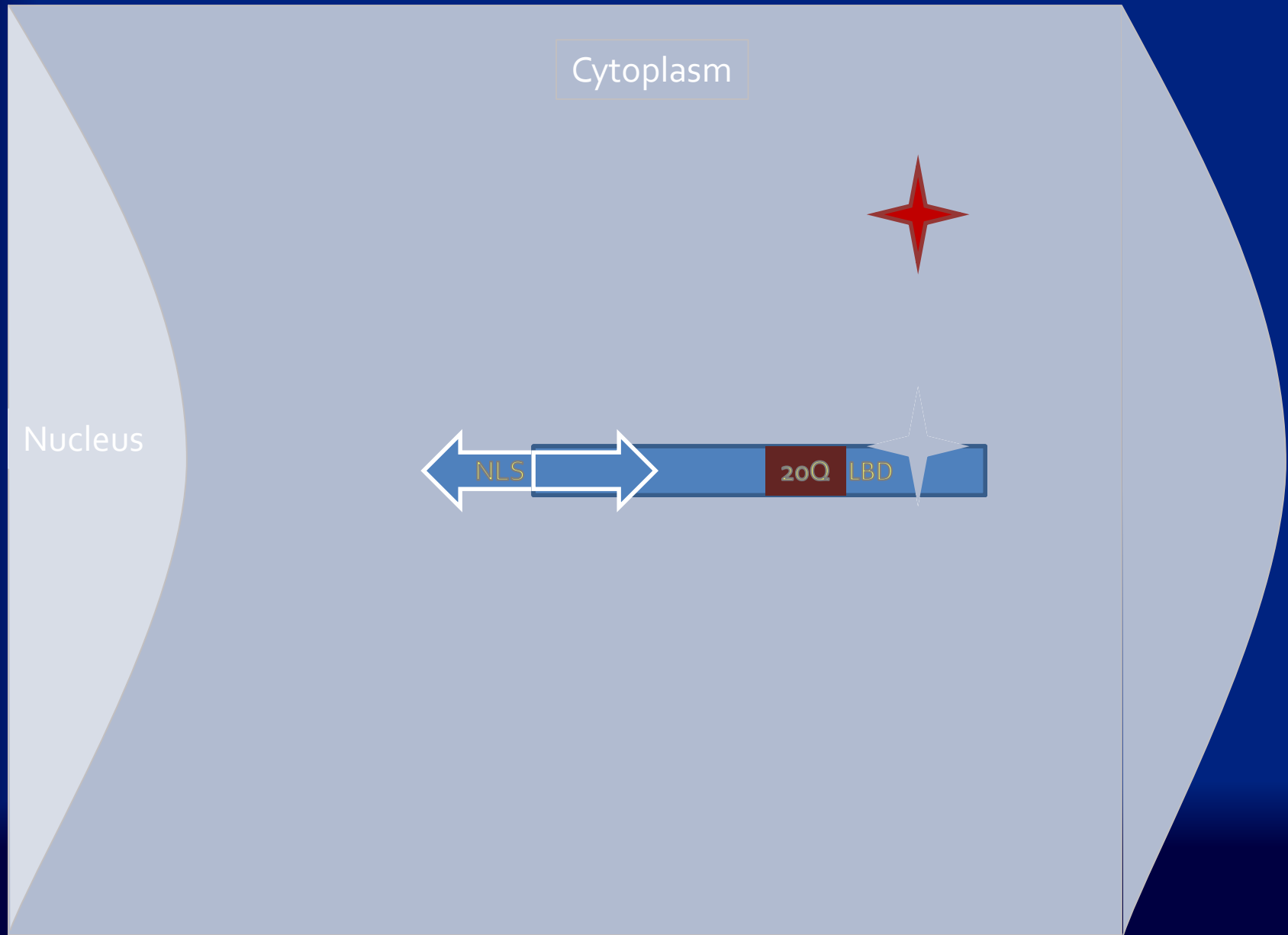

A
B
C
D



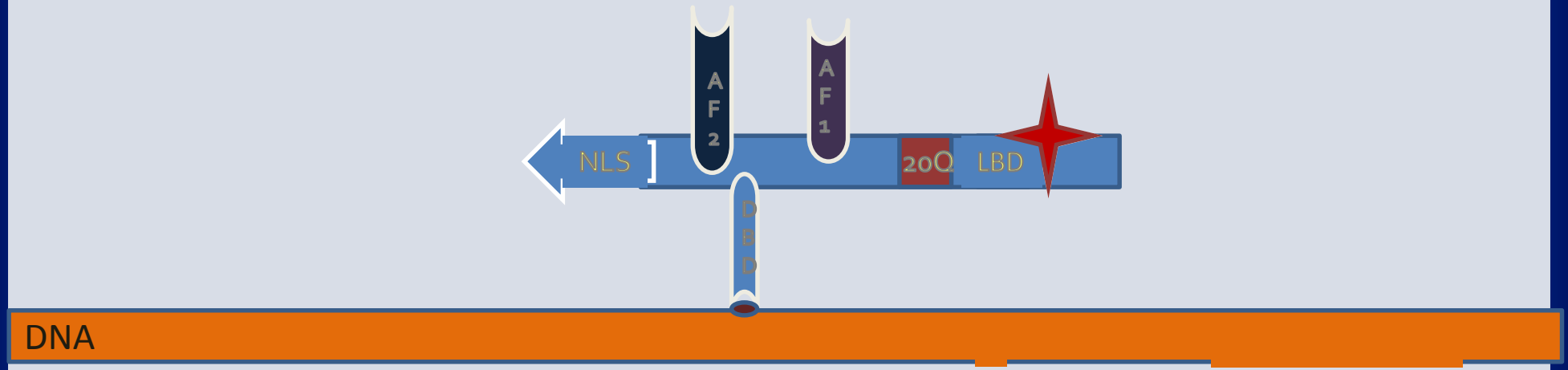
Nonneural Nuclear Inclusions in SBMA 699
AJP September 1998, Vol. 153, No. 3

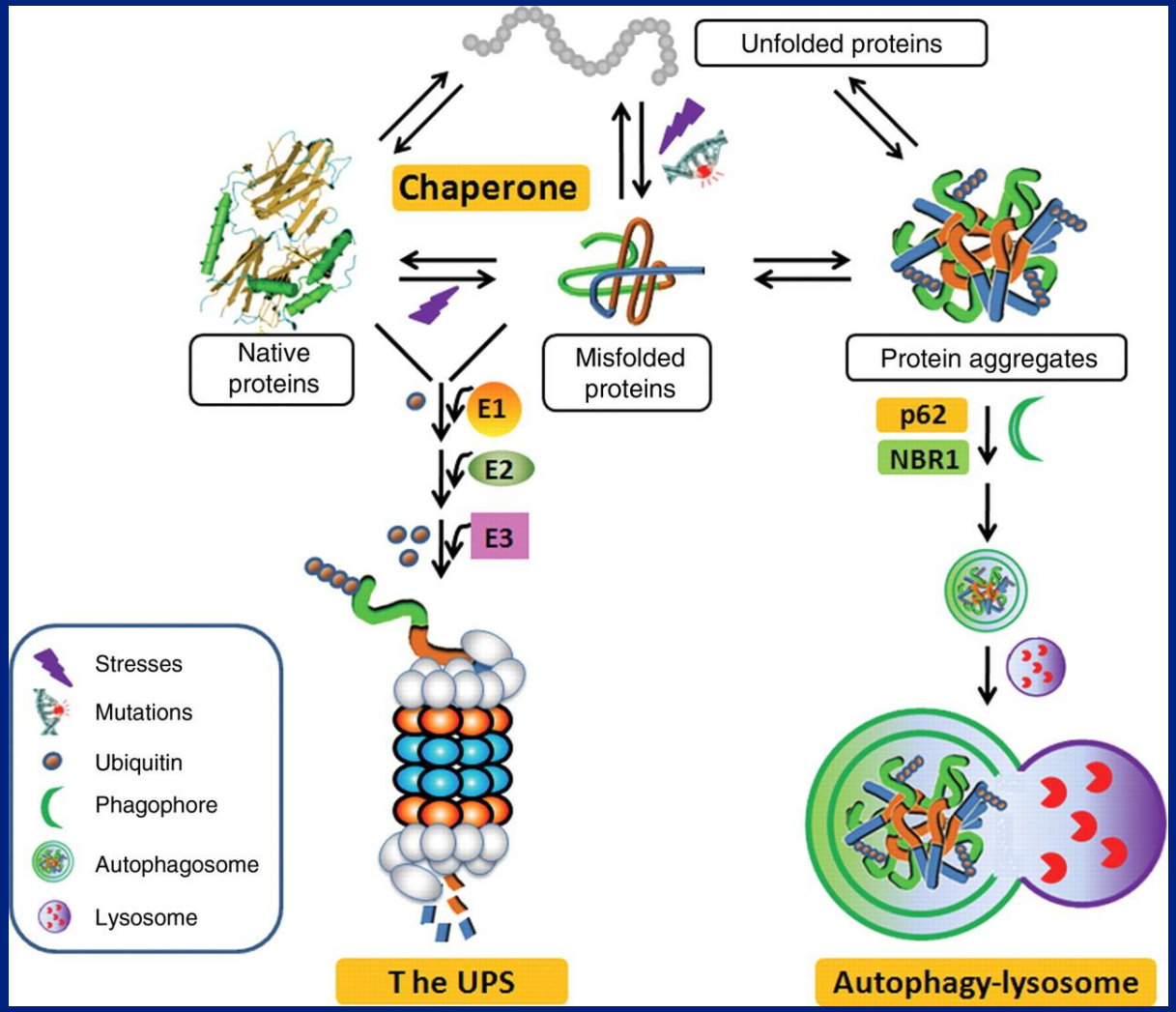
Why do you build me up (build me up)
Buttercup, baby
Just to let me down (let me down)and
mess me around

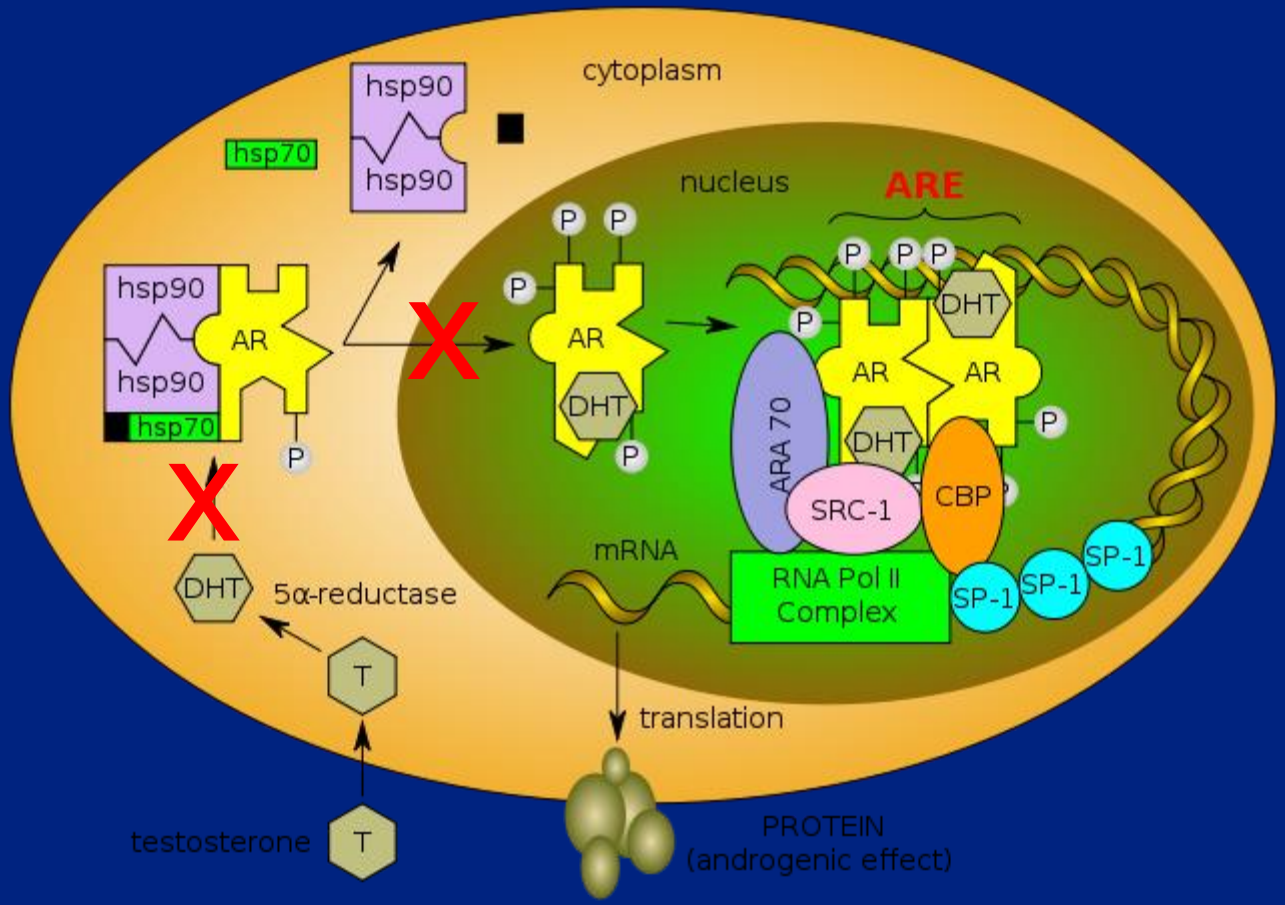
The Foundations


Cytoplasm
Nucleus
NLS
20Q
LBD

Nucleus




Unfolded proteins
Chaperone
Native proteins
Misfolded proteins
Protein aggregates
E1
E2
E3
p62
NBR1
Stresses
Mutations
Ubiquitin
Phagophore
Autophagosome
Lysosome
T he UPS
Autophagy-lysosome


cytoplasm
nucleus
ARE
hsp90
hsp90
hsp70
AR
DHT
P
ARA 70
SRC-1
CBP
SP-1
RNA Pol II Complex
mRNA
translation
PROTEIN
(androgenic effect)
5α-reductase
T
testosterone

Chain, chain, chain, chain, chain, chain
Chain, chain, chain, chain of fools

Aretha Franklin

Table 1 Trinucleotide repeat diseases that are caused by a CAG/polyglutamine repeat expansion in the relevant protein. The presence of intracellular inclusions detected in brains of patients is listed

Disease	*Normal range (CAG repeats)*	*Disease range (CAG repeats)*	*Presence of inclusions*
Huntington's disease (HD)	6-35	36-121	Yes
Dentatorubral-pallidoluysian atrophy (Haw River syndrome/DRPLA)	3-35	49-85	Yes
Spinobulbar muscular atrophy (Kennedy's/SBMA)	11-33	38-62	Not assessed
Spinocerebellar ataxia 1 (SCA1)	6-44	40-81	Yes
Spinocerebellar ataxia 2 (SCA2)	15-29	35-59	Not assessed
Spinocerebellar ataxia 3 (Machado-Joseph disease/SCA3)	12-41	55-84	Yes
Spinocerebellar ataxia 6 (SCA6)	4-17	20-30	Not assessed
Spinocerebellar ataxia 7 (SCA7)	4-35	37→200	Yes

thecatatetheratend

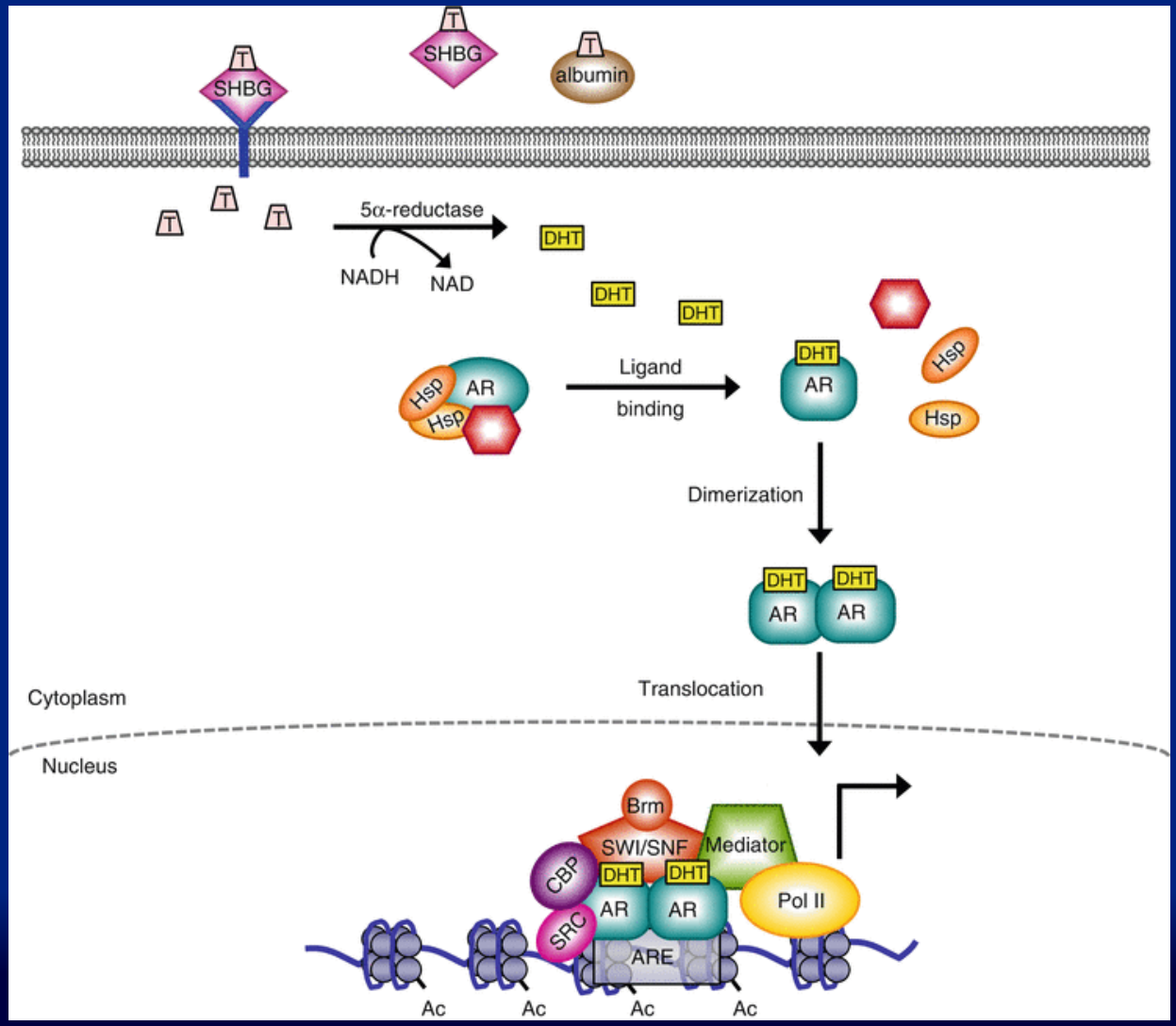
thebatatetheratend

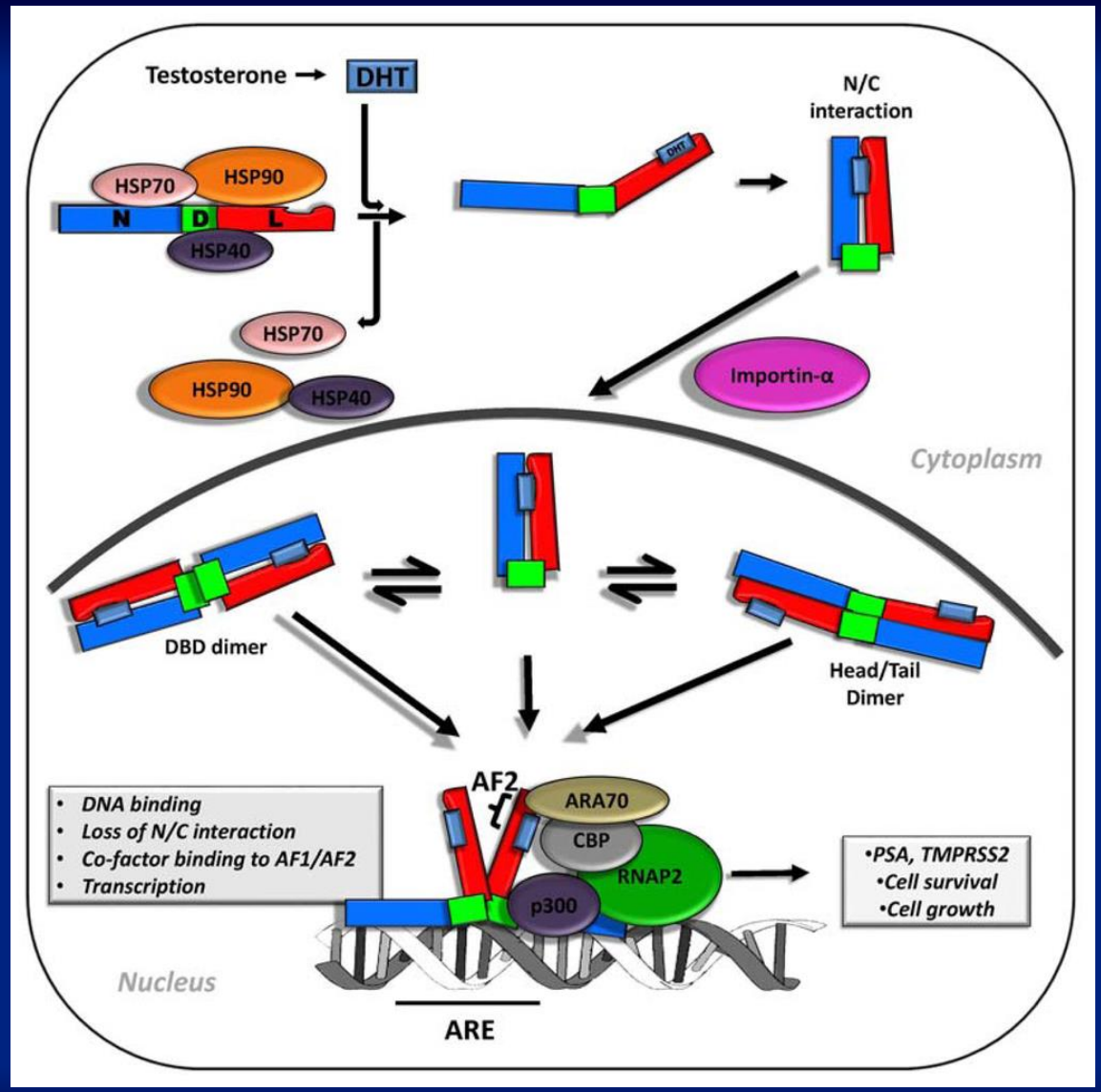
thekatatetheratend

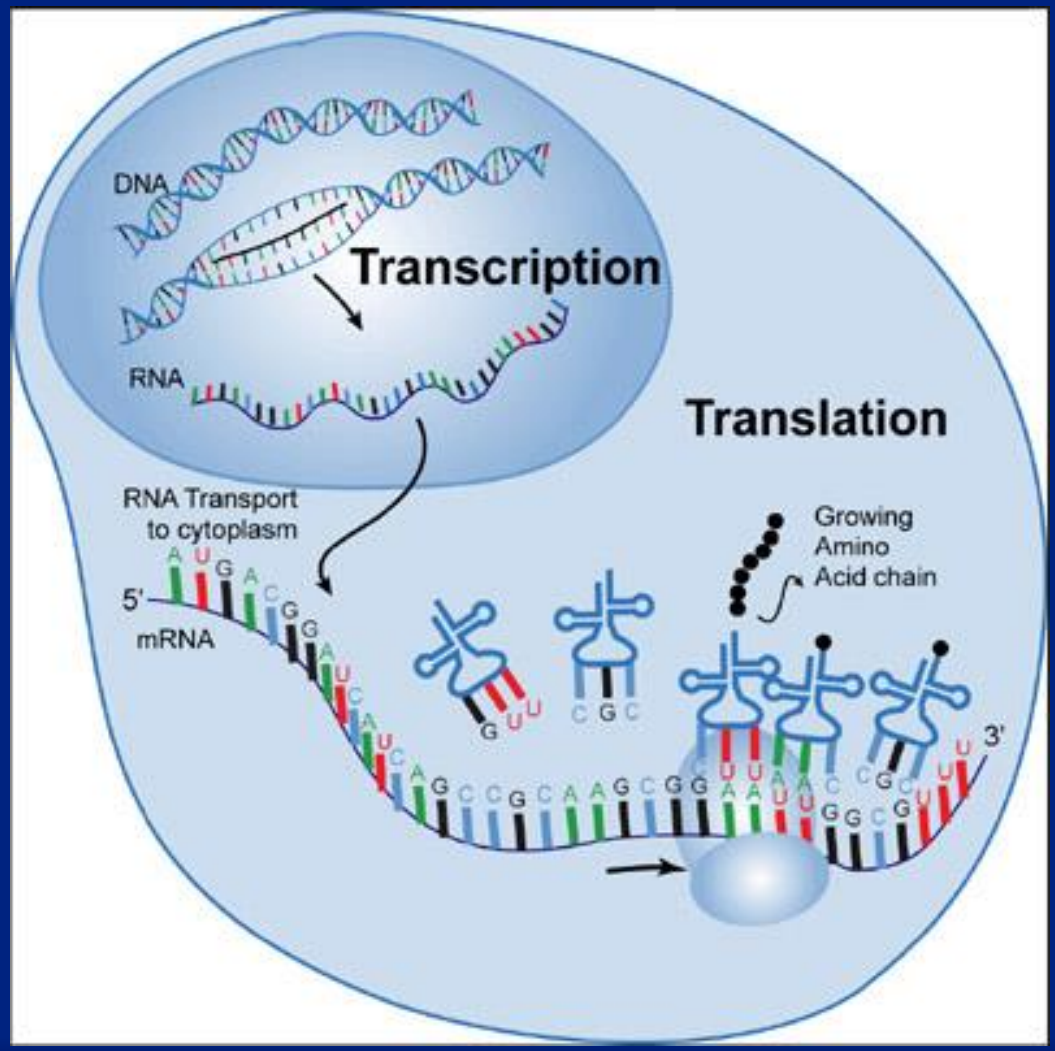
theatatetheratend

theqatatetheratend

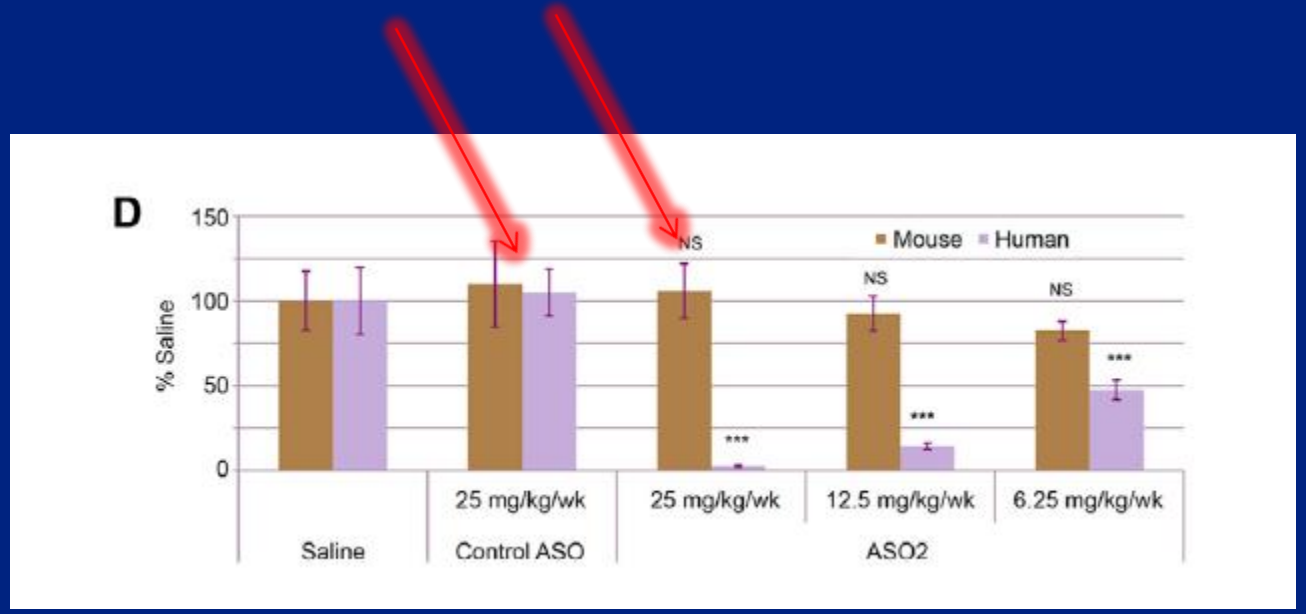
thechatatetheratend


SHBG
SHBG
albumin
T
5α-reductase
NADH
NAD
DHT
Hsp
AR
Ligand
binding
Dimerization
Translocation
Cytoplasm
Nucleus
Brm
SWI/SNF
Mediator
CBP
SRC
Pol II
ARE
Ac

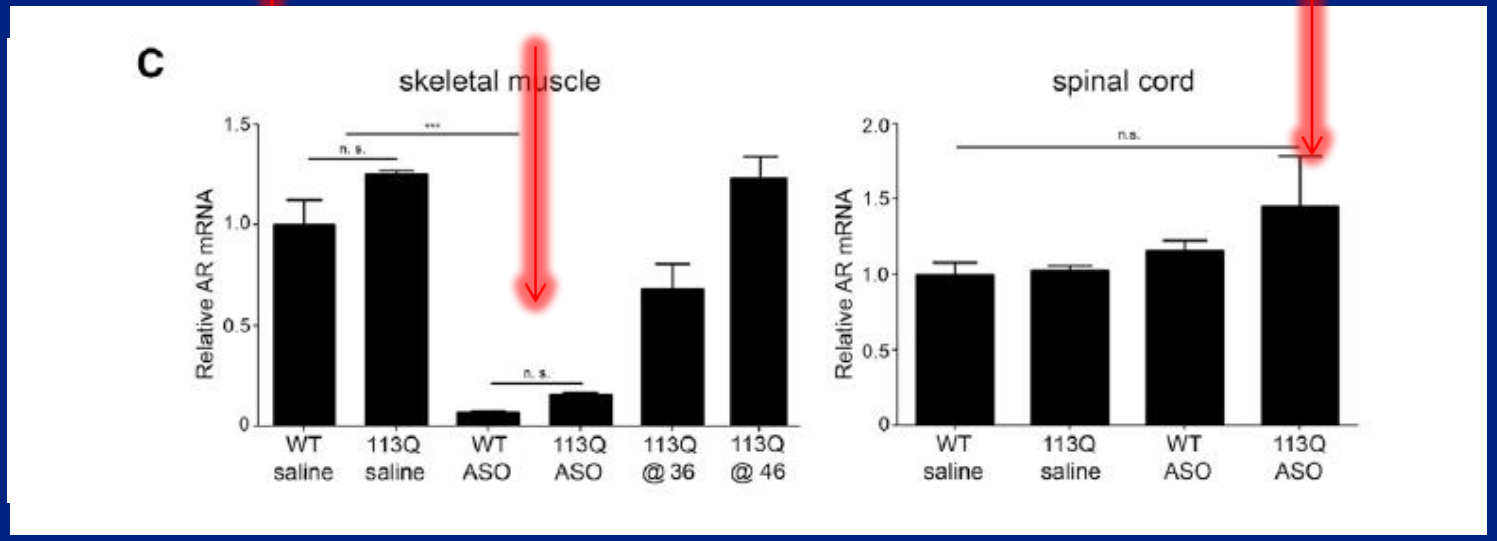

Testosterone
DHT
N/C
interaction
HSP70
HSP90
N
D
L
HSP40
HSP70
HSP90
HSP40
Importin-α
Cytoplasm
DBD dimer
Head/Tail
Dimer
AF2
ARA70
CBP
RNAP2
p300
• DNA binding
• Loss of N/C interaction
• Co-factor binding to AF1/AF2
• Transcription
•PSA, TMPRSS2
•Cell survival
•Cell growth
Nucleus
ARE


DNA
Transcription
RNA
Translation
RNA Transport
to cytoplasm
5'
mRNA
Growing
Amino
Acid chain
3'

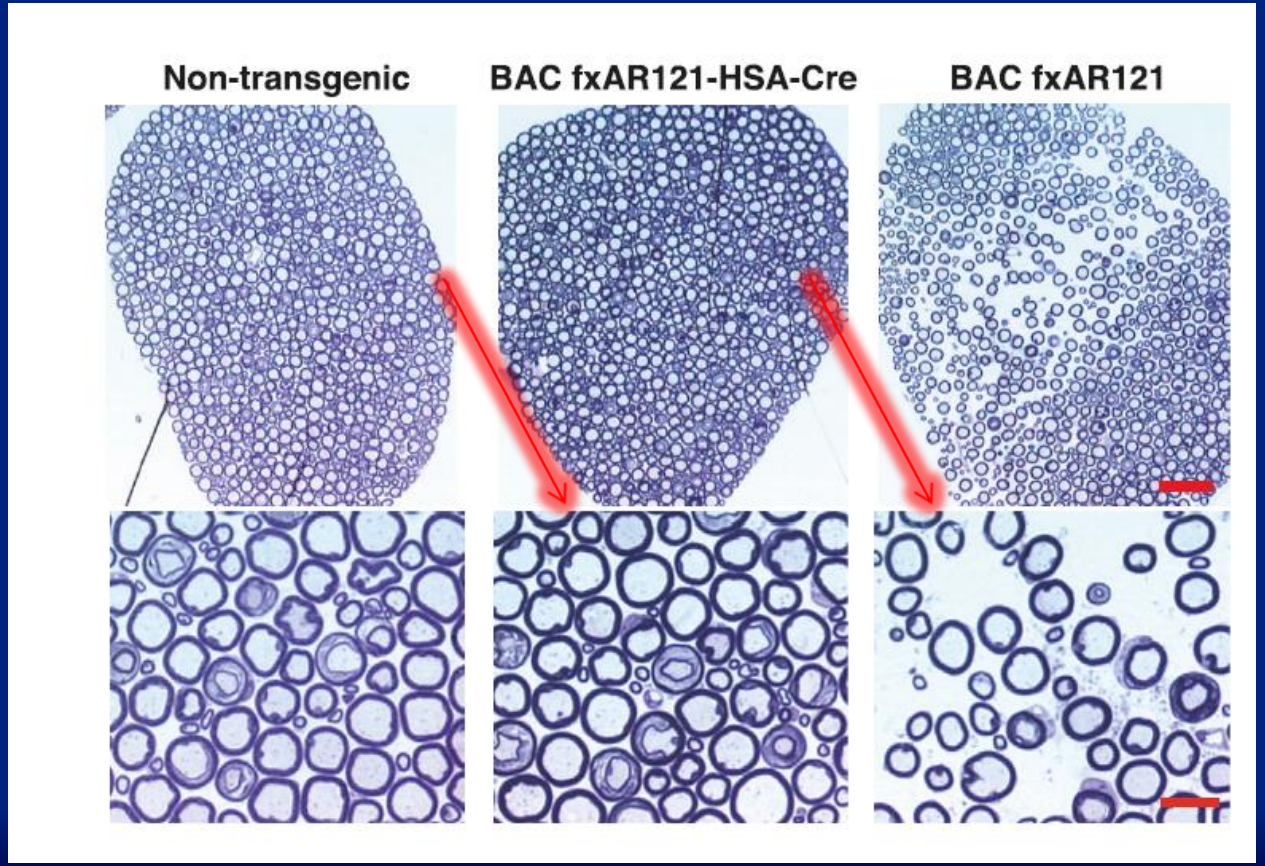
Injection of ASO nucleotide into a KD mouse model reduces the levels of human AR mRNA in muscle tissue.



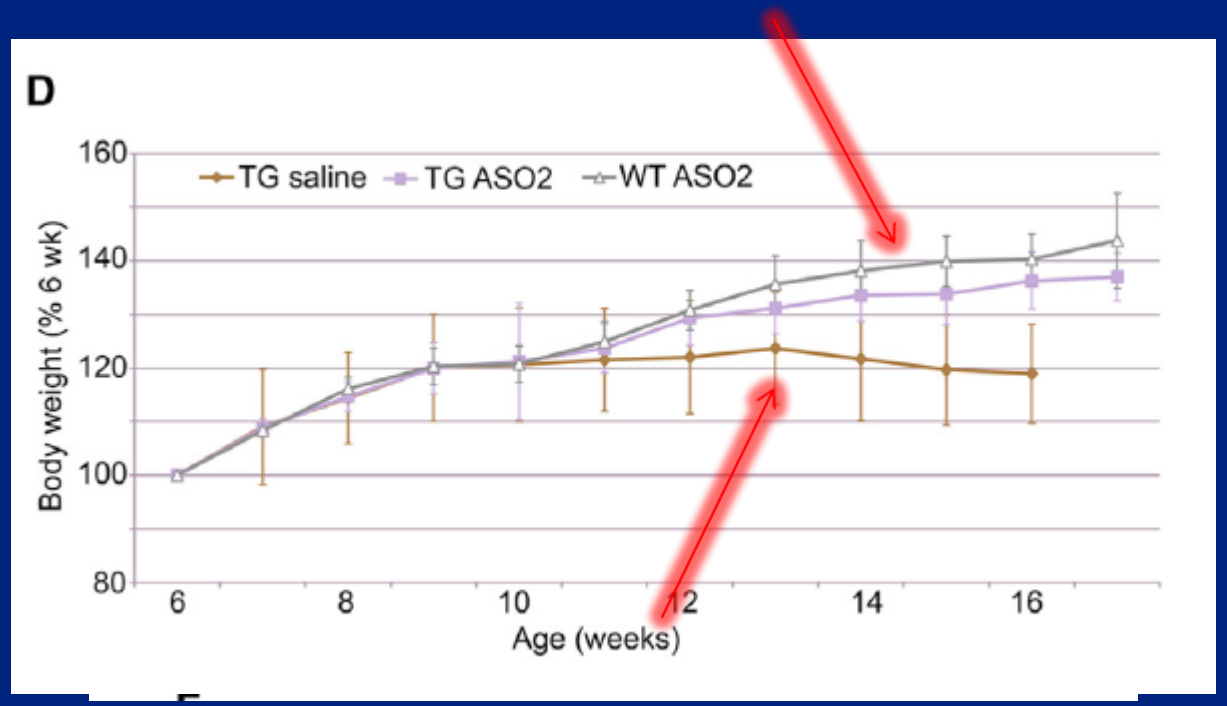
Injection of ASO nucleotide into a KD mouse model reduces the levels of human AR mRNA in muscle tissue and not brain.



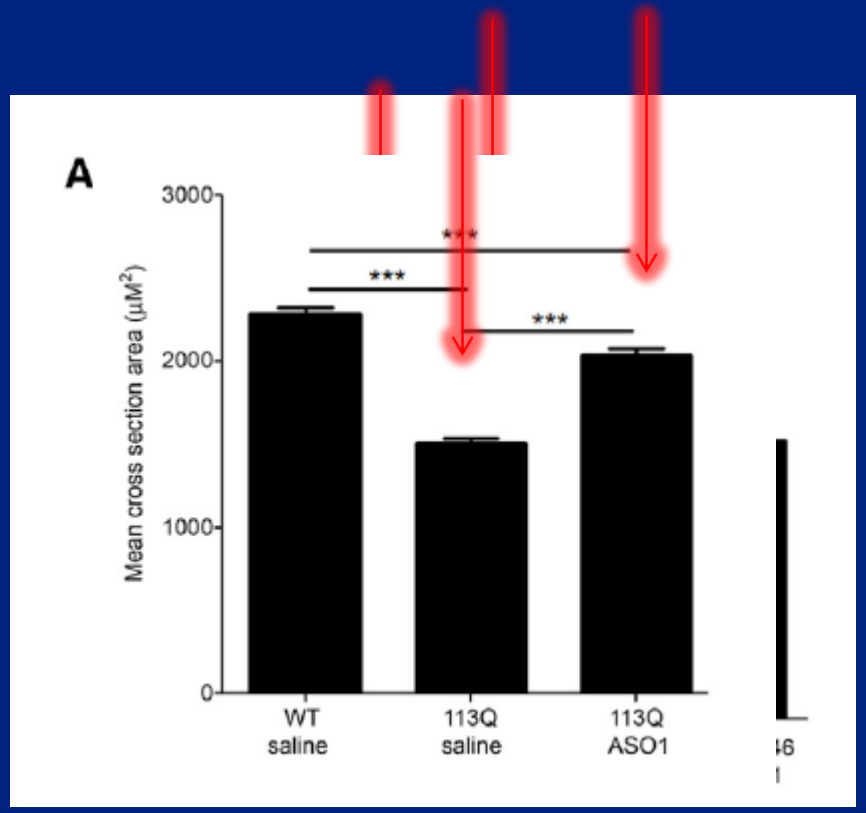
Motor degeneration is prevented by lack of mutant AR in muscles alone!!!



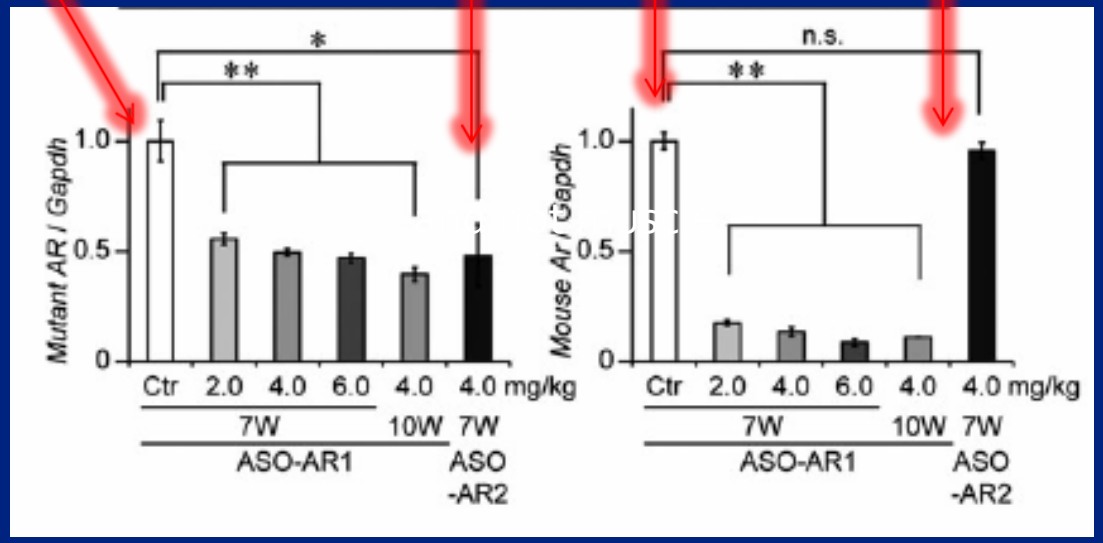
KD mice show improvement in grip strength and body weight
When AR in muscles only is reduced.



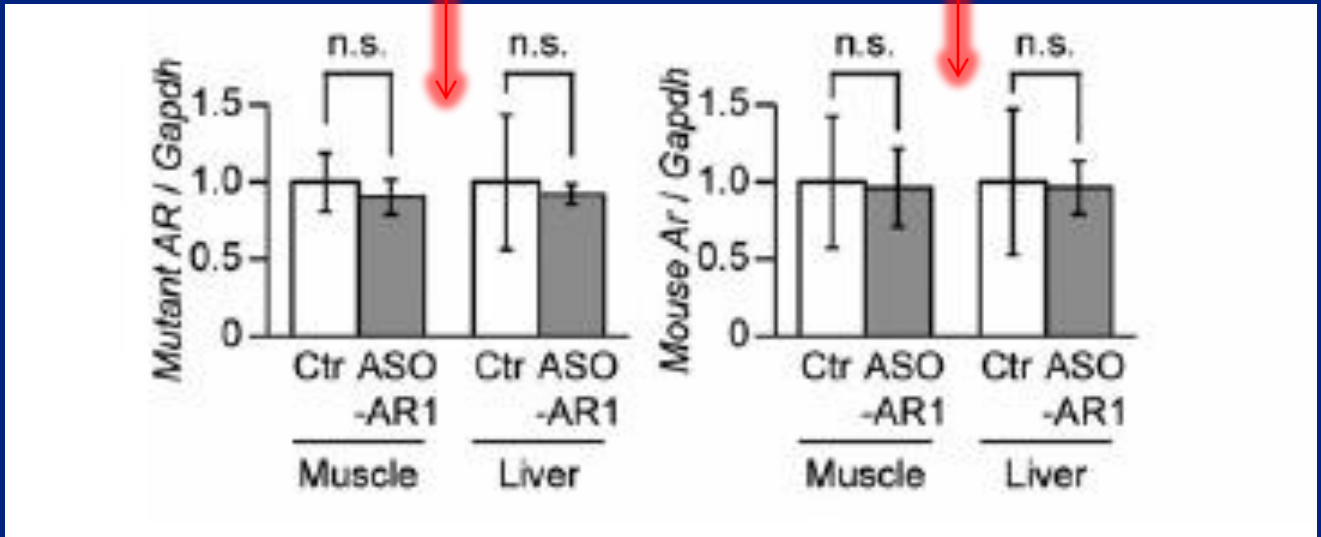
Muscle atrophy of KD mouse is reversed with ASO



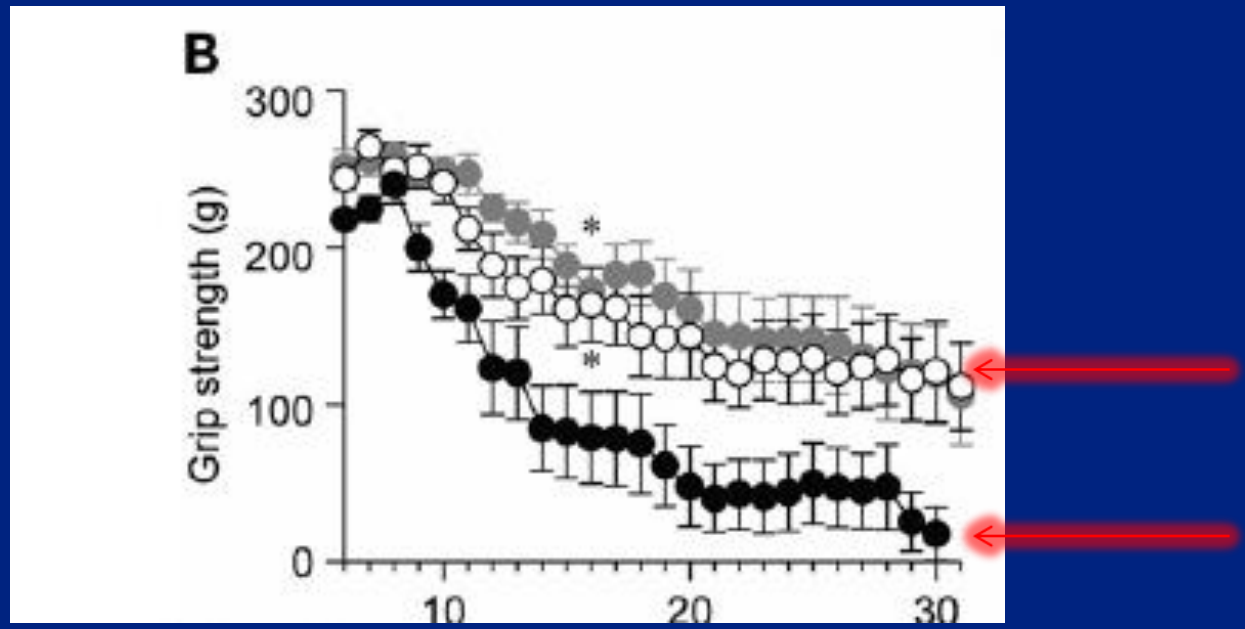
Injection of ASO nucleotide into a KD mouse model reduces the levels of human AR mRNA in spinal cord.



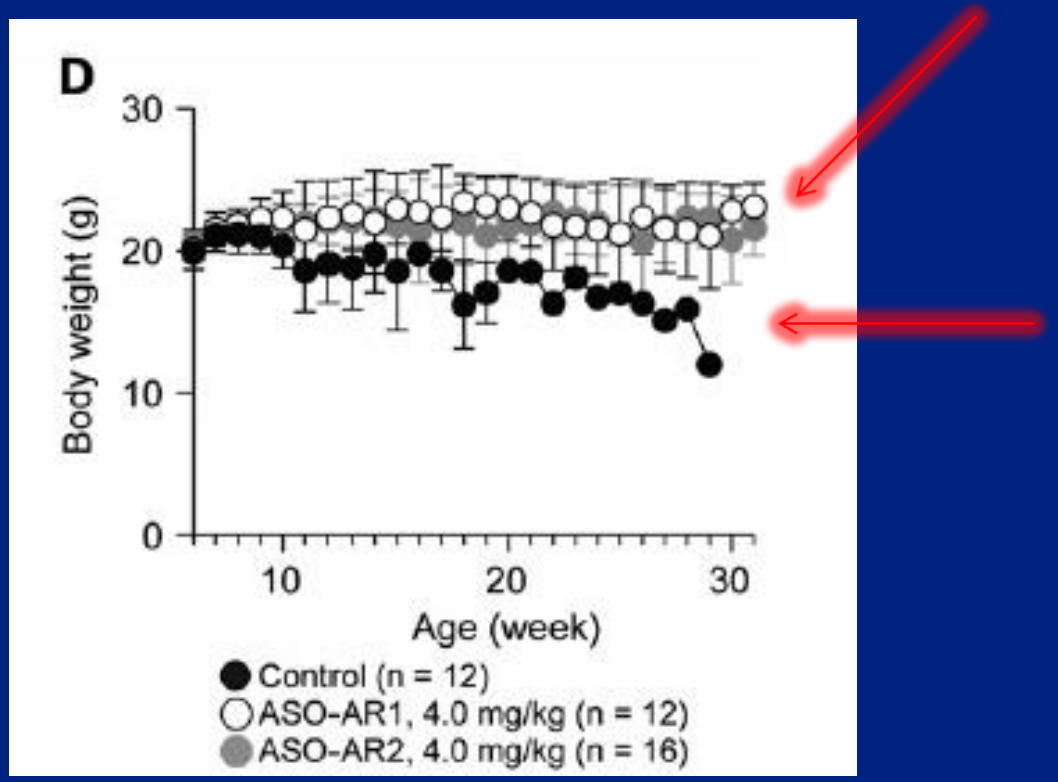
Injection of ASO nucleotide into a KD mouse model reduces the levels of human AR mRNA in brain tissue and not muscle.



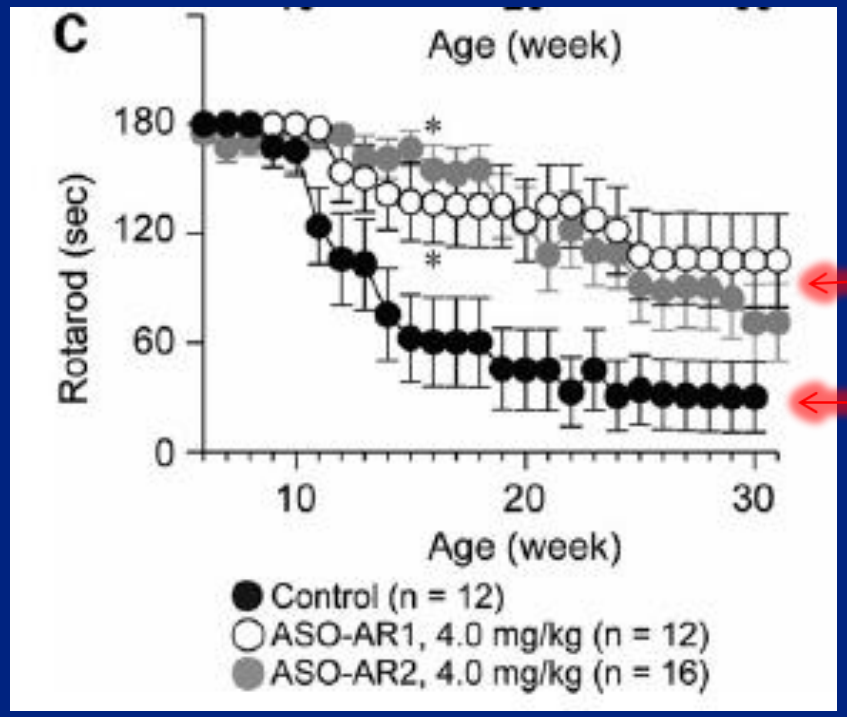
ASO treated mutant mice recovered grip strength



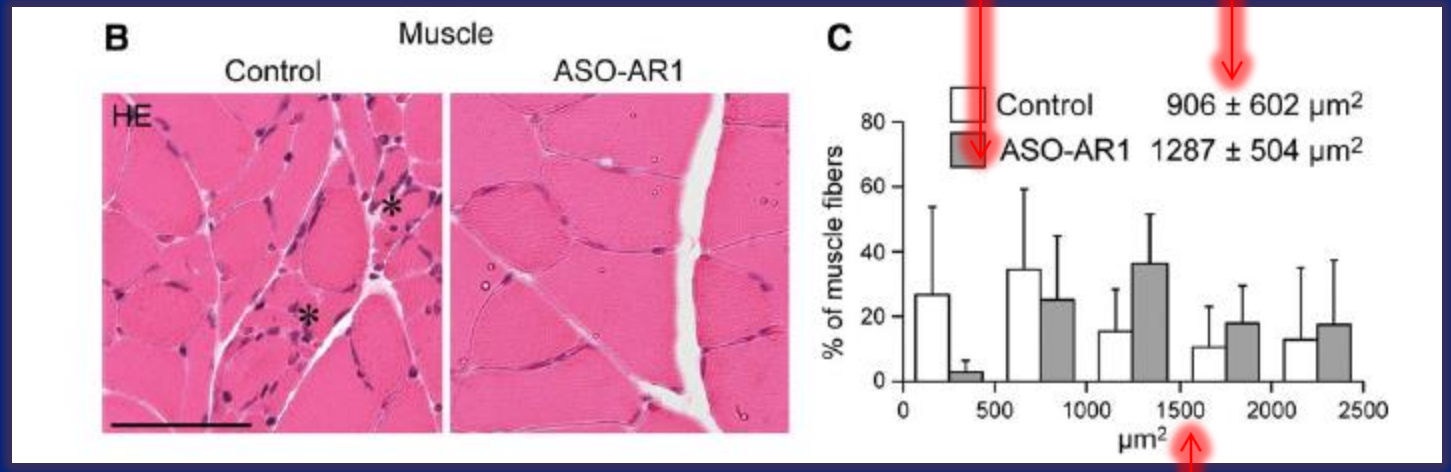
… and body weight



ASO treated mutant mice were better on the rotorod



ASO treated mutant mice had larger muscle fibers



Meriggioli, M. N., & Rowin, J. (2003). Fatigue and abnormal neuromuscular transmission in Kennedy's disease. *Muscle and Nerve*, *27* (February), 249–251.

It is not clear whether repeated bouts of exercise of this severity would eventually result in (or accelerate) muscle fiber denervation. Our patient's signs and symptoms have remained remarkably stable for over 3 years. He continues to run competitively and is resolute in his desire to pursue this activity. However, the electrophysiological findings and the points raised in this article may argue in favor of a milder conditioning program.