

Metabolic changes in SBMA

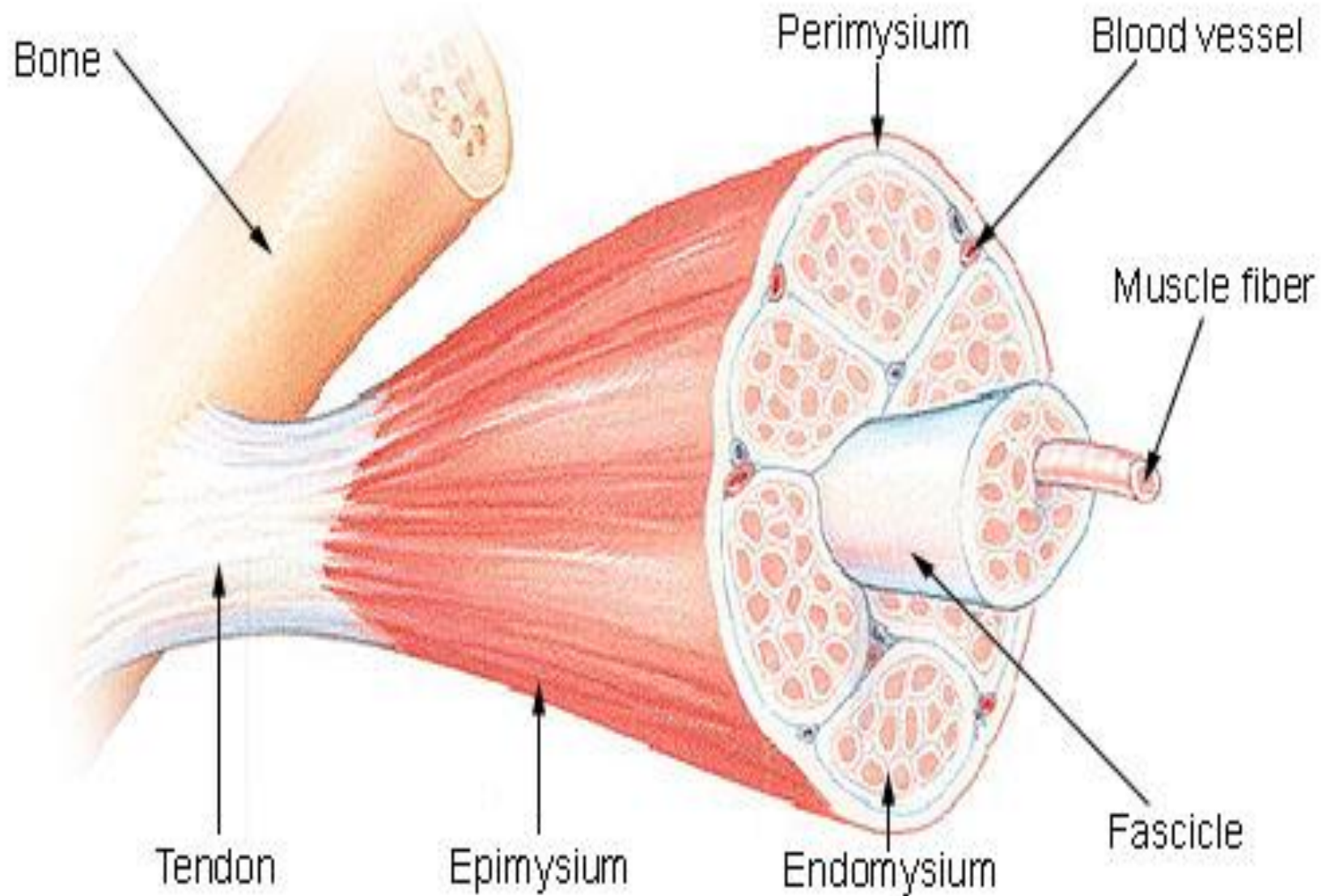
Andy Lieberman

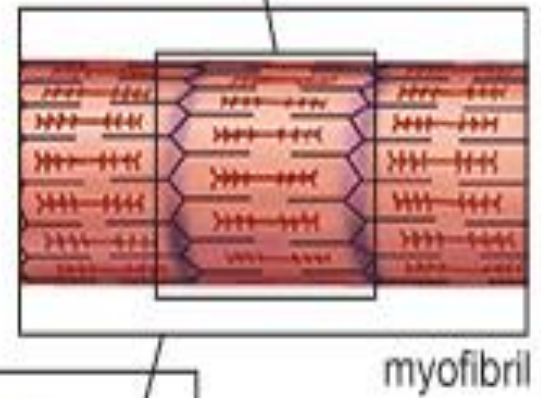
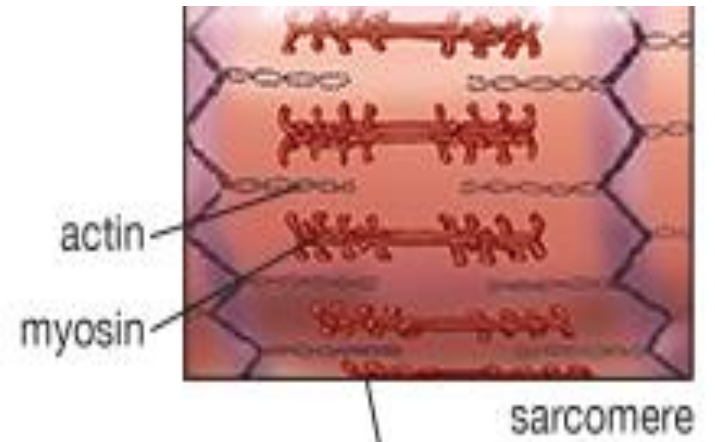
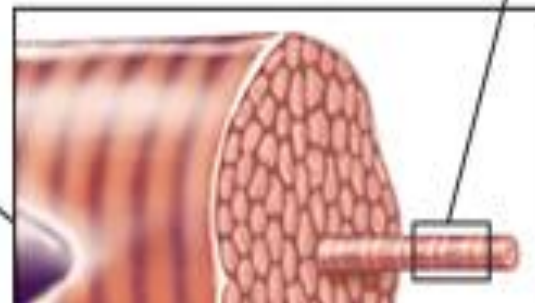
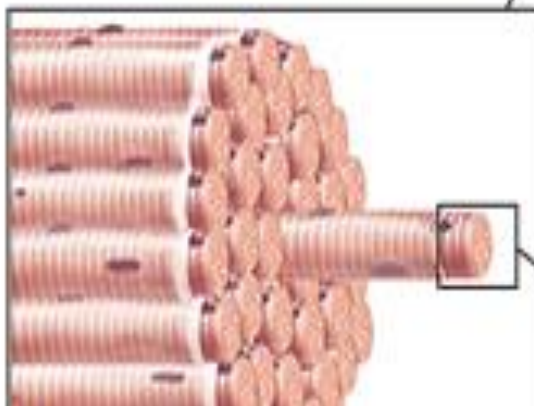
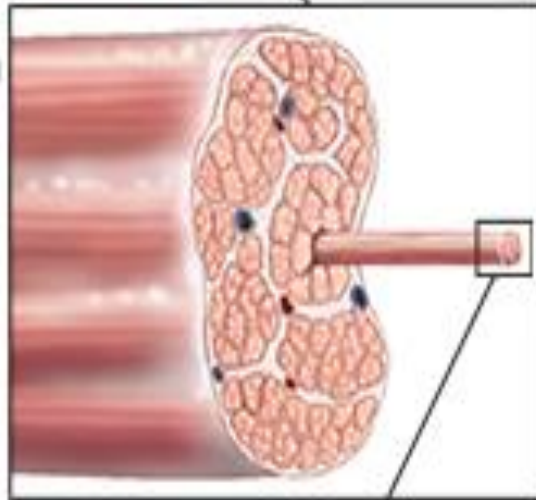
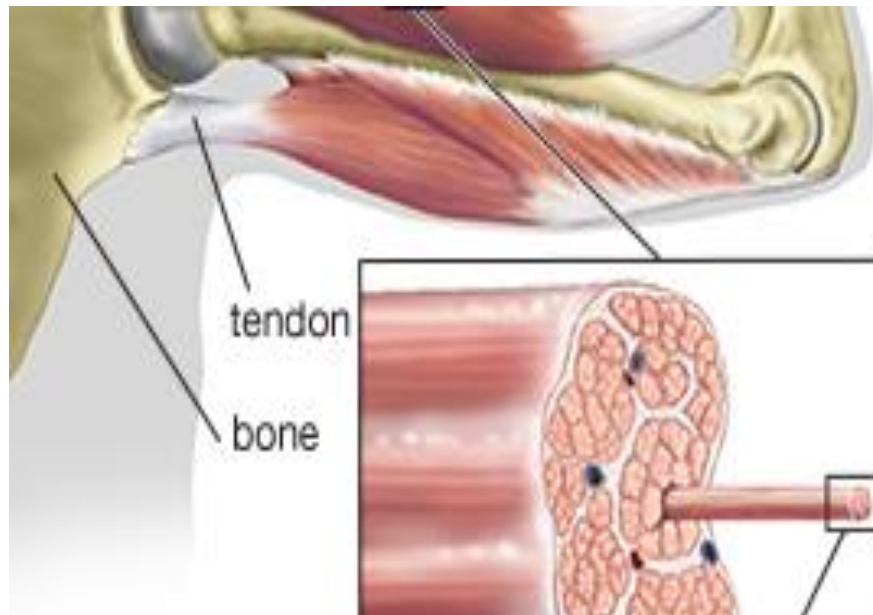
University of Michigan Medical School

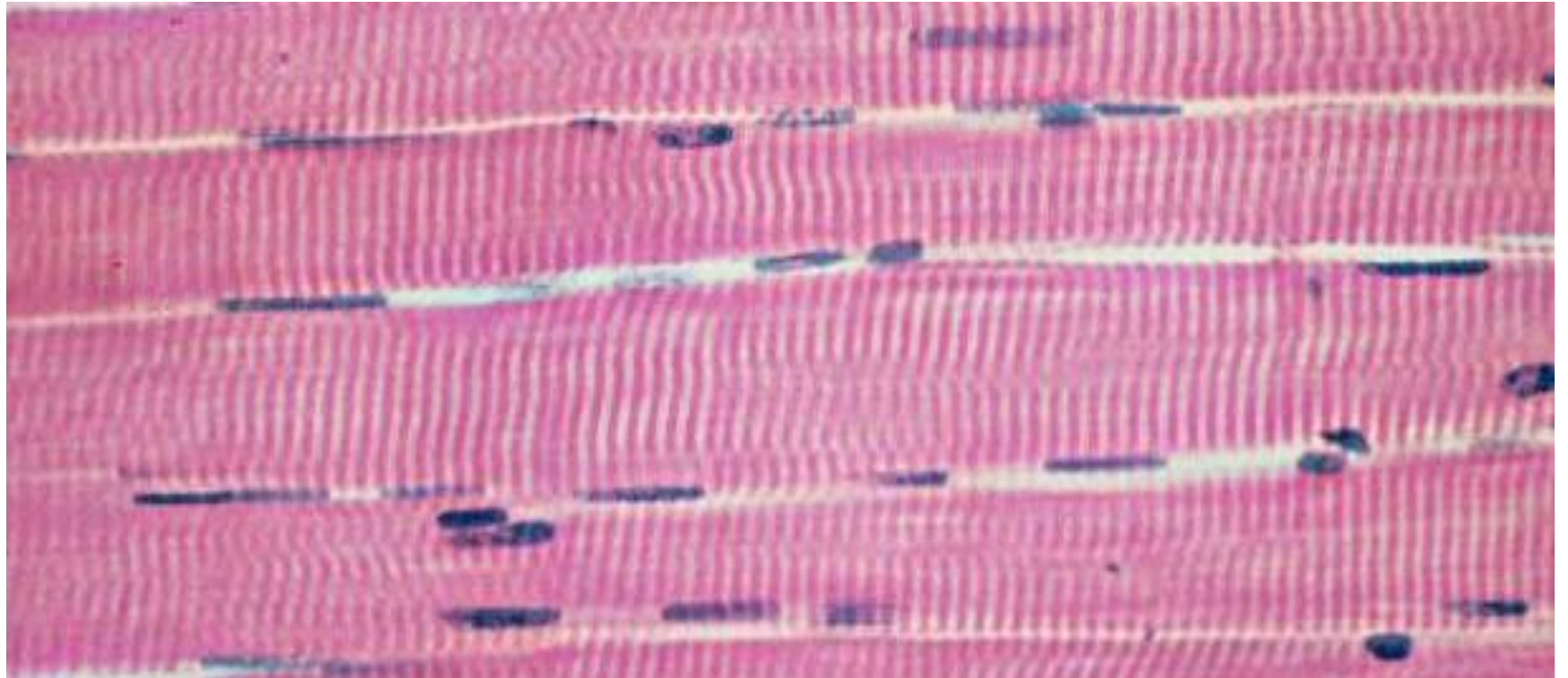
Disclosures

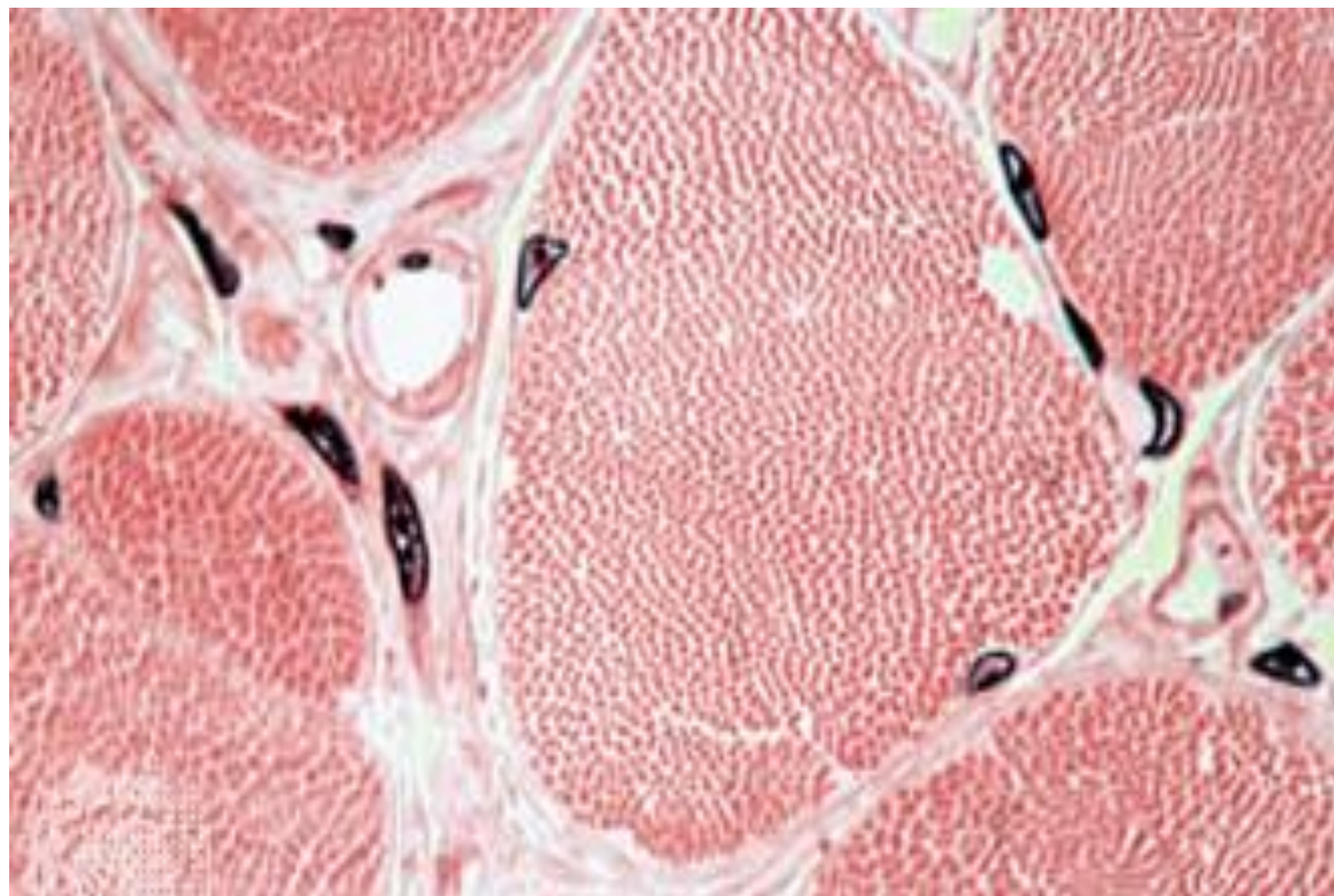
- Research funding:
NIH, MDA, APMRF
- Scientific advisory boards:
KDA, NNPDF
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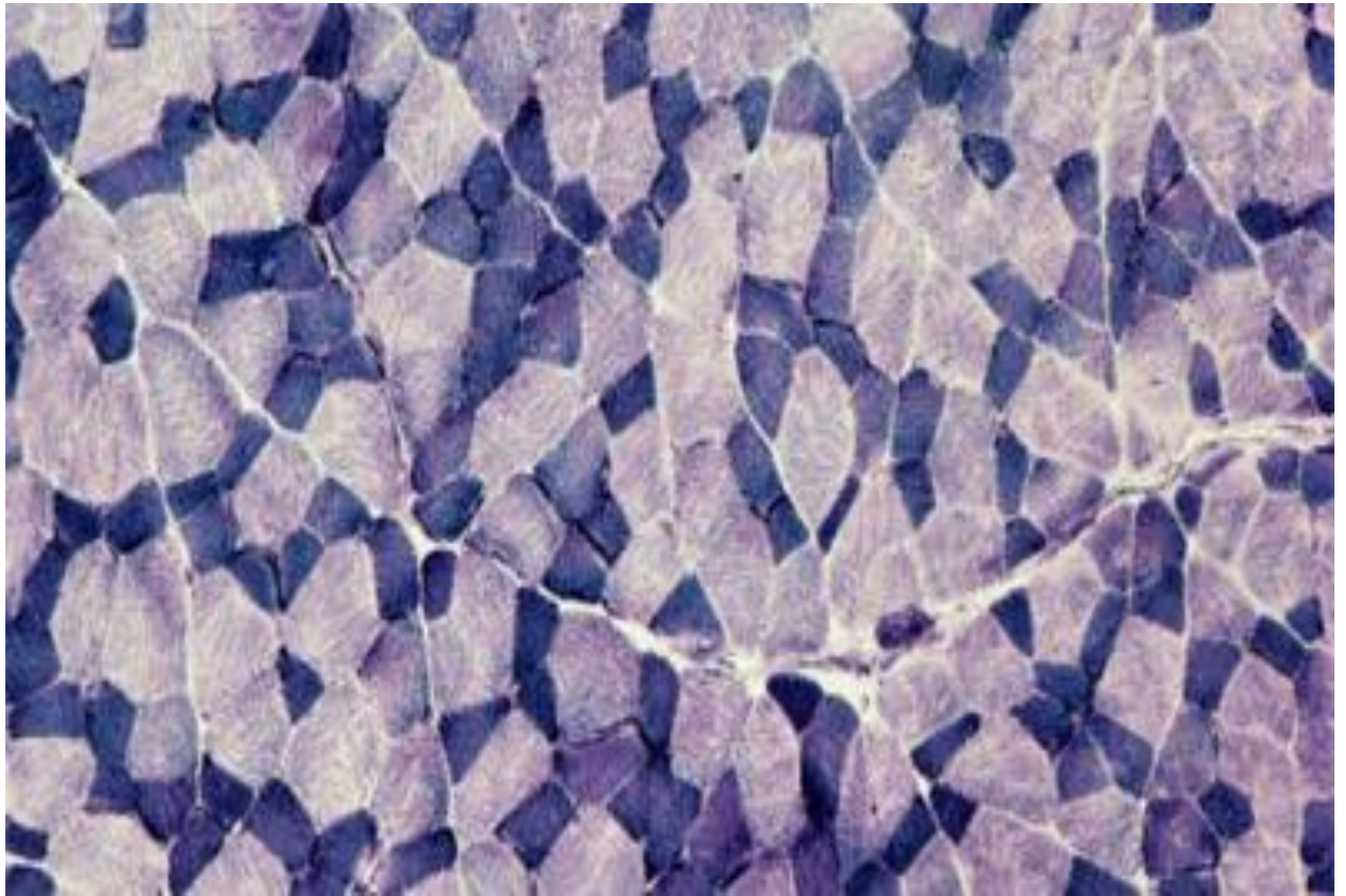
Structure of a Skeletal Muscle

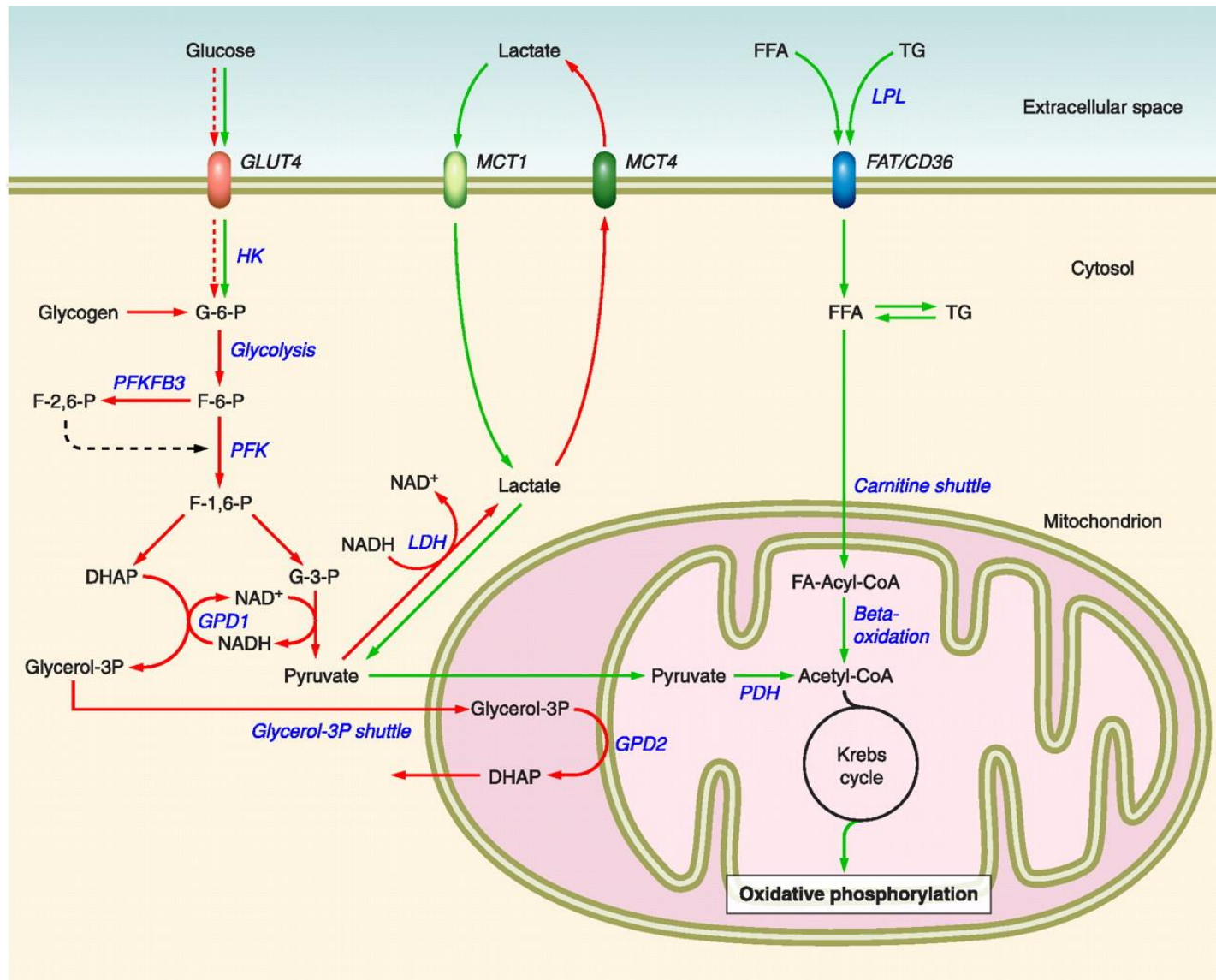












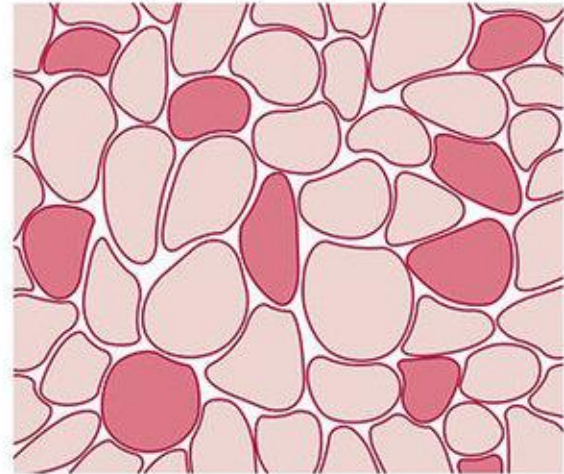
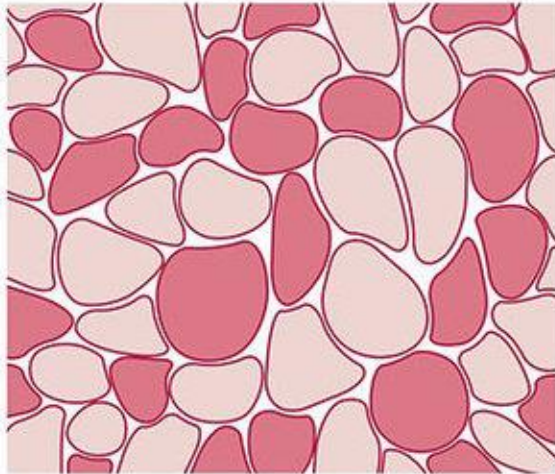
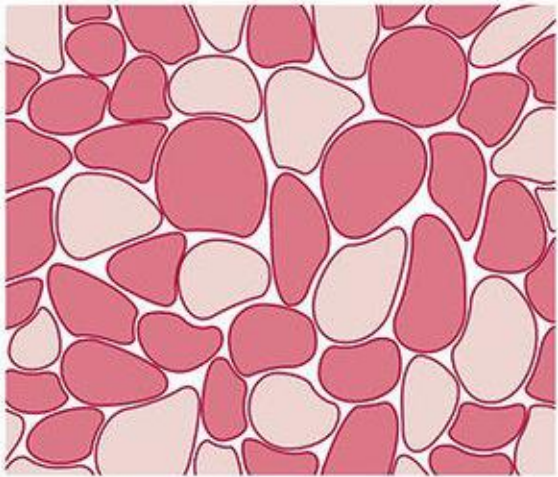
Glycolysis
Breakdown of glucose

Mitochondria
Use oxygen to make ATP

MUSCLE FIBER TYPES AND RELEVANCE:

- Skeletal muscle fibers of humans are classified into three types: (based on **physiological** **biochemical** **histological** charactersitics)..

Type I	TYPE IIA	TYPE II B
•Slow •Red oxidative fibers •Many mitochondria •Abundant myoglobin (fe++ containing protein that binds with O2 giving red color) •Energy source: primarily from aerobic oxidative phosphorylation of fatty acids . •Adapted for slow continuous contractions over prolonged periods.. As required in postural muscles..	•Fast/intermediate •Oxidative glycolytic fibers •Many mitochondria •Much myoglobin •But also considerable glycogen •Energy source – -both oxidative phosphorylation -And anaerobic glycolysis •Adapted for rapid contractions and short bursts of activity .. As required for athletics..	•Fast , white • glycolytic fibers •Fewer mitochondria •Less myoglobin •Abundant glycogen •Energy source : mainly glycolysis •Adapted for rapid contractions but fatigue quickly. •Typical in small muscles with large no of NMJ. •Muscles that move eyes and digits..
03-08-2015 Department of Orthodontics and Dentofacial Deformities, CDER, AIIMS		





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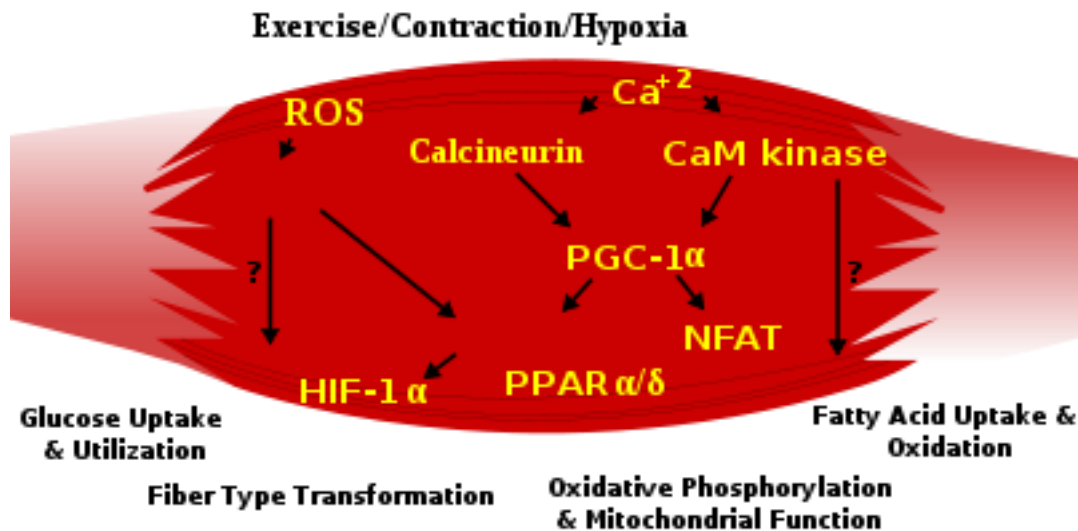
Compared elite vs trained vs untrained

ST fibers in gastroc: 79% vs 61% vs 57%

Maximal O₂ uptake is more important

Factors that influence skeletal muscle fiber type

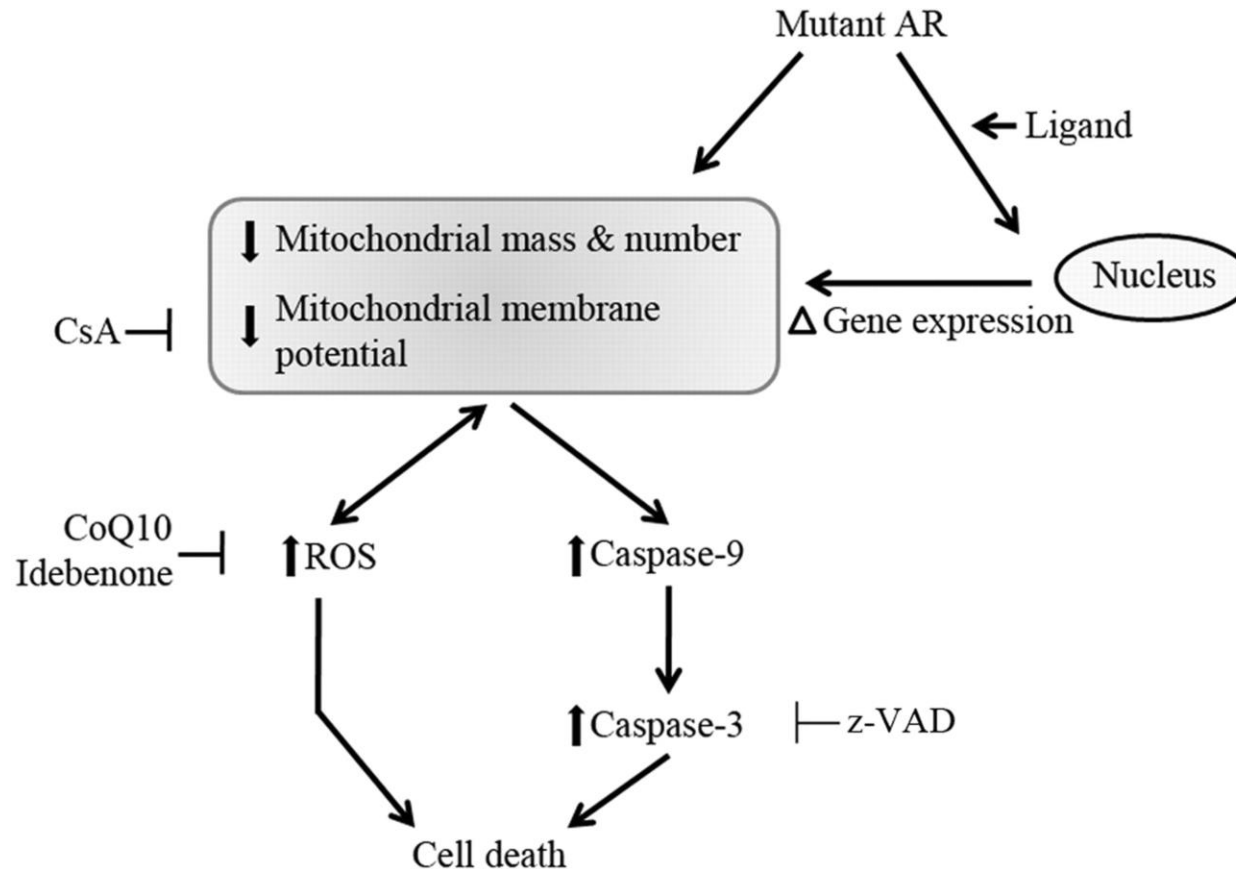
Nerve stimulation of muscle



Diabetes, aging, physical inactivity

Oxidative/slow to glycolytic/fast shift

Mitochondrial abnormalities in SBMA models



From: Mitochondrial abnormalities in spinal and bulbar muscular atrophy

Hum Mol Genet. 2008;18(1):27-42. doi:10.1093/hmg/ddn310

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Glycolytic-to-oxidative fiber-type switch and mTOR signaling activation are early-onset features of SBMA muscle modified by high-fat diet

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Rescue of Metabolic Alterations in AR113Q Skeletal Muscle by Peripheral Androgen Receptor Gene Silencing

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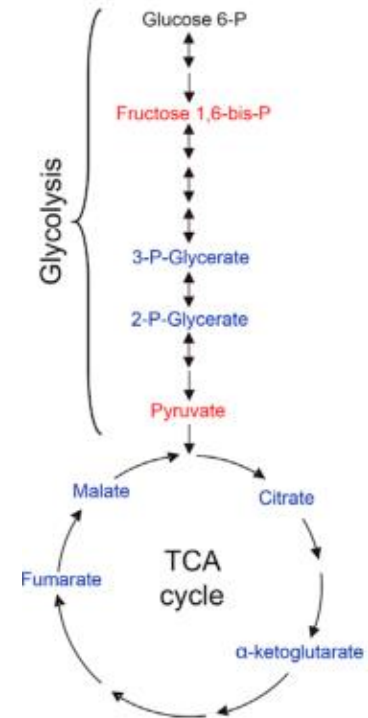
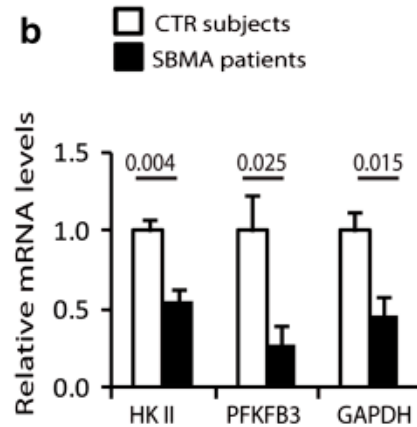
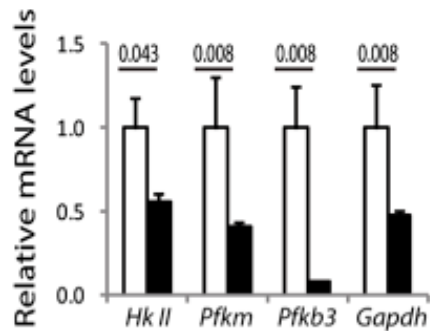
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⁶Lead Contact

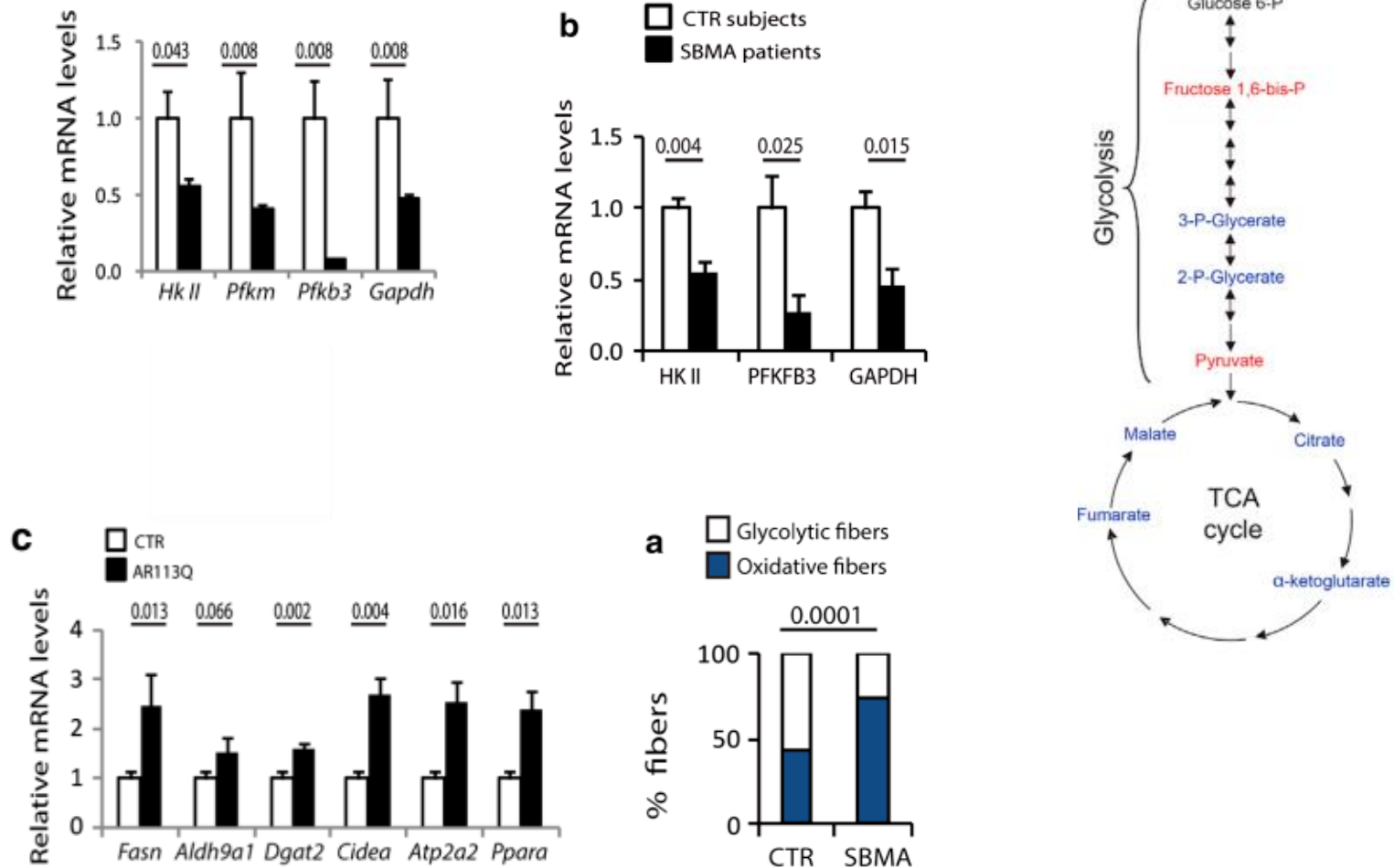
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<http://dx.doi.org/10.1016/j.celrep.2016.08.084>

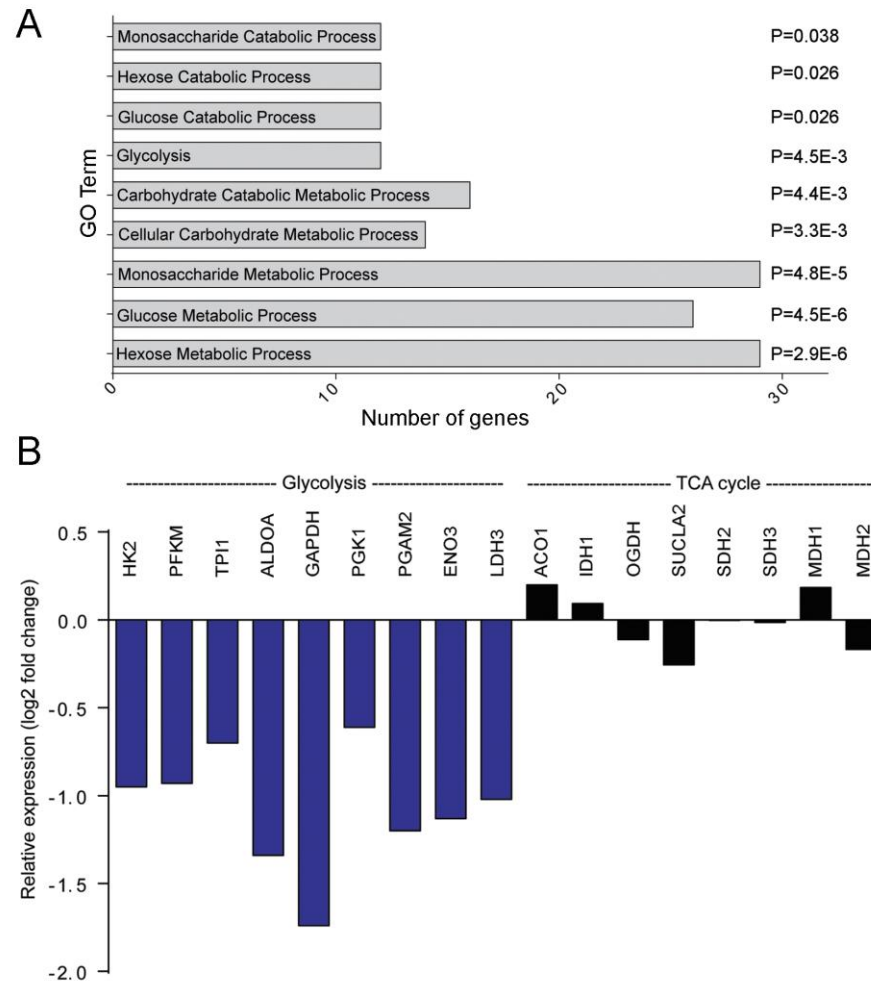
Glycolytic to oxidative switch in SBMA muscle



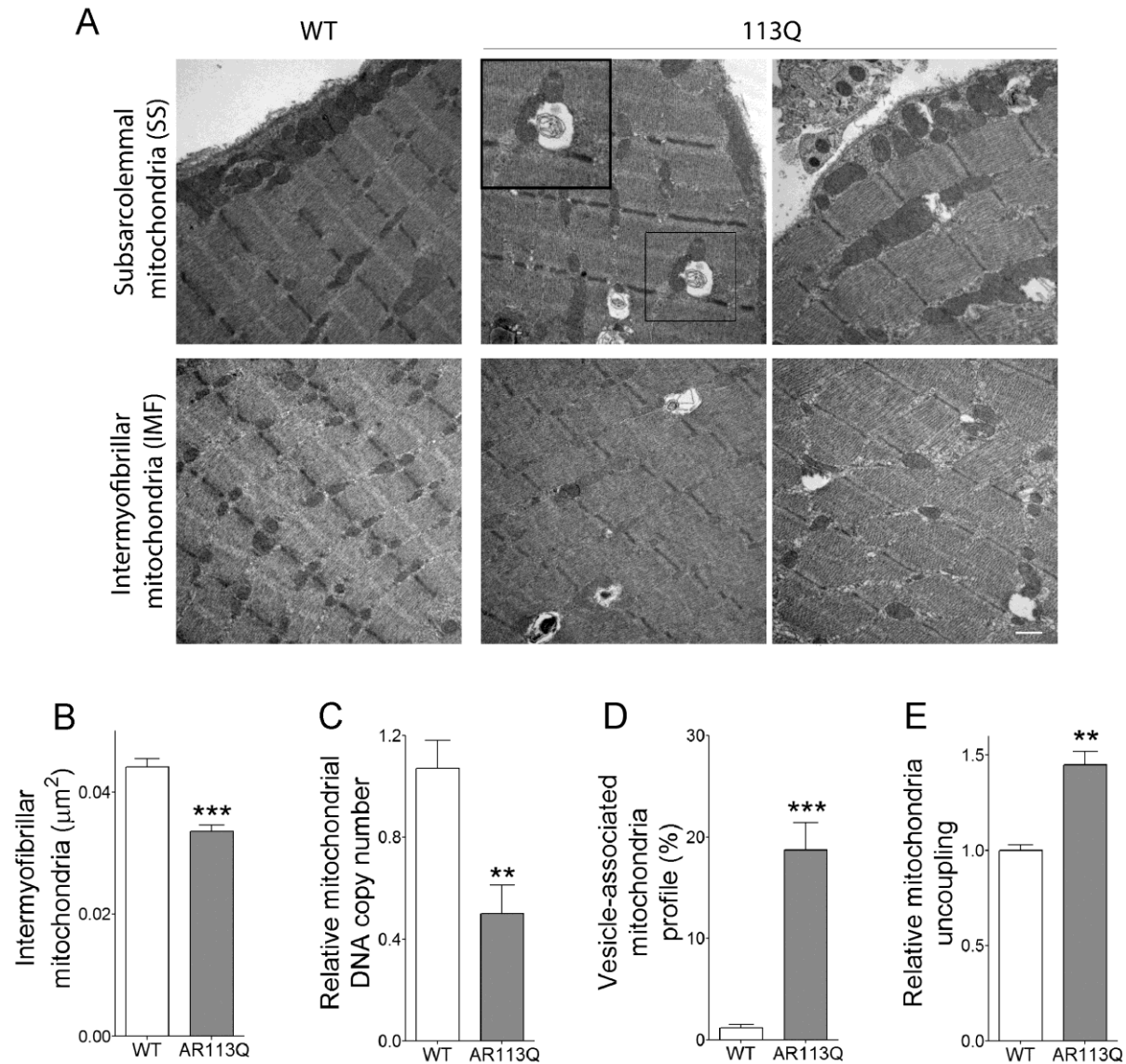
Glycolytic to oxidative switch in SBMA muscle



Decreased glycolytic enzymes in AR113Q muscle



Mitochondrial abnormalities in AR113Q muscle

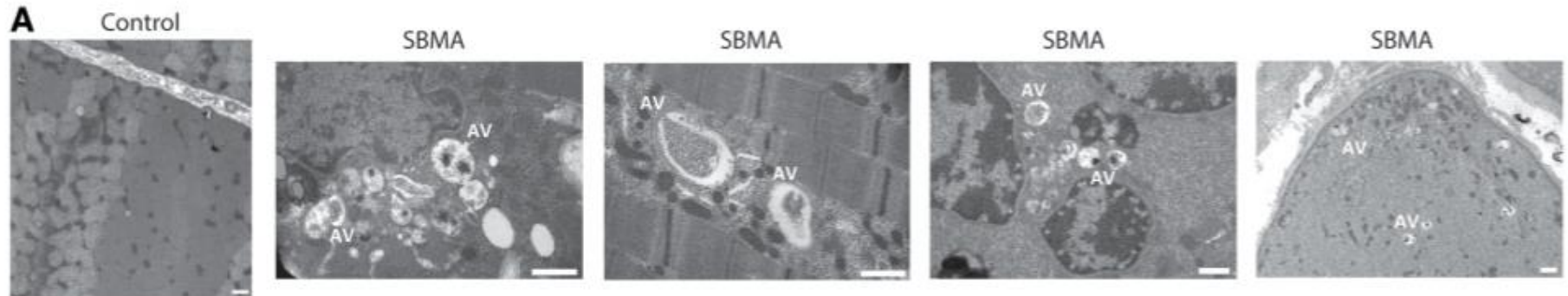


Mitochondrial abnormalities in SBMA muscle

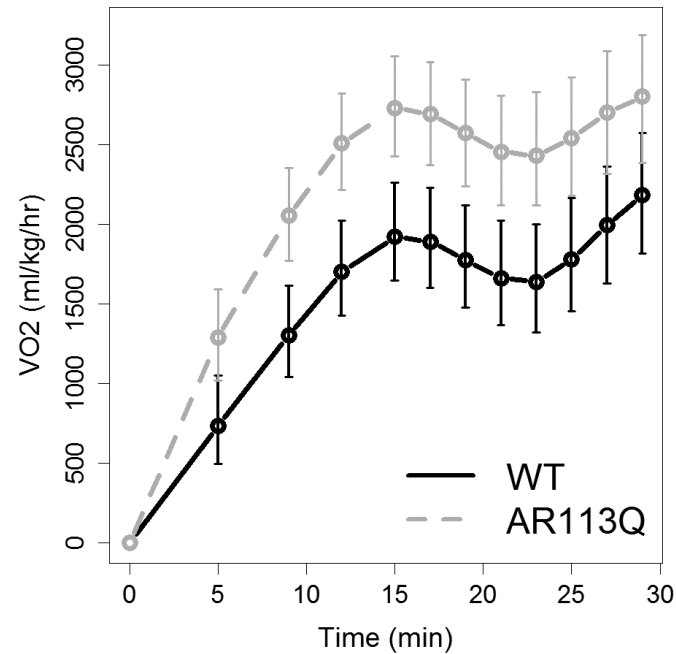
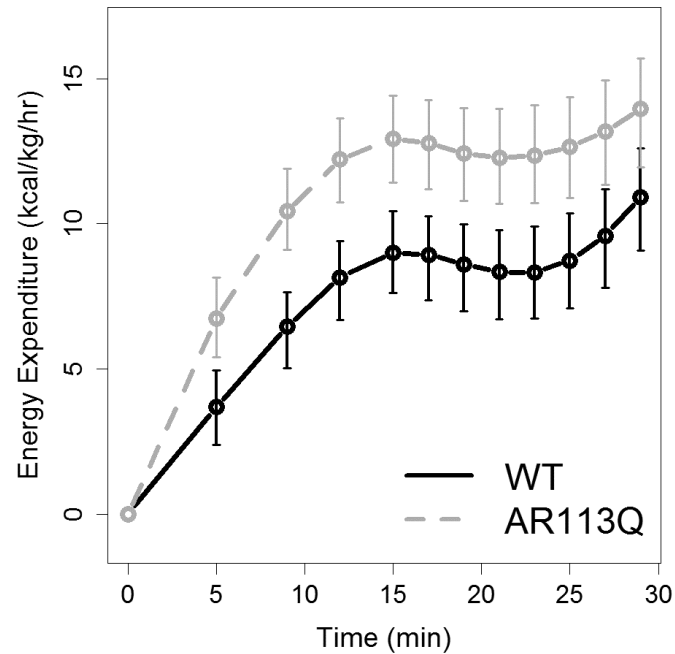
ORIGINAL ARTICLE

Increased mitophagy in the skeletal muscle of spinal and bulbar muscular atrophy patients

Doriana Borgia¹, Adriana Malena¹, Marco Spinazzi², Maria Andrea Desbats³, Leonardo Salviati³, Aaron P. Russell⁴, Giovanni Miotto^{5,6}, Laura Tosatto⁷, Elena Pegoraro¹, Gianni Sorarù¹, Maria Pennuto^{7,*} and Lodovica Vergani^{1,*}



AR113Q mice use more energy and consume more oxygen to complete exercise



Published online: March 27, 2015

Research Article



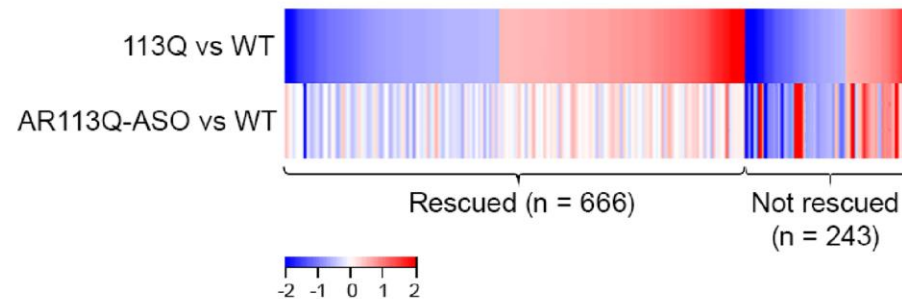
EMBO
Molecular Medicine

A metabolic switch toward lipid use in glycolytic muscle is an early pathologic event in a mouse model of amyotrophic lateral sclerosis

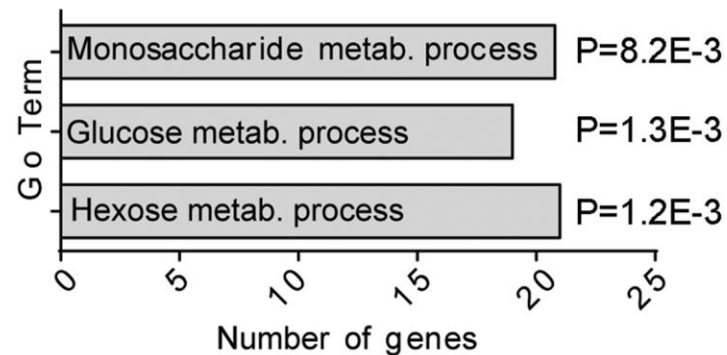
Lavinia Palamiuc^{1,2}, Anna Schlagowski^{3,4}, Shyuan T Ngo^{5,6}, Aurelia Vernay^{1,2}, Sylvie Dirrig-Grosch^{1,2}, Alexandre Henriques^{1,2}, Anne-Laurence Boutillier⁷, Joffrey Zoll^{3,4}, Andoni Echaniz-Laguna^{1,2,8}, Jean-Philippe Loeffler^{1,2,*} & Frédérique René^{1,2,**}

Antisense oligonucleotides rescue changes in metabolic gene expression

A



B



Nerve

Impaired
neuromuscular
communication

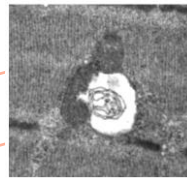
Muscle

↓ glycolytic genes

↑ fat utilization by
muscle mitochondria

Mitochondrial damage

Mitophagy



Effect of aerobic training in patients with spinal and bulbar muscular atrophy (Kennedy disease).

[Preisler N](#)¹, [Andersen G](#), [Thøgersen F](#), [Crone C](#), [Jeppesen TD](#), [Wibrand F](#), [Vissing J](#).

OBJECTIVE:

We examined the effect of aerobic exercise in patients with spinal and bulbar muscular atrophy (SBMA). SBMA is caused by a defect androgen receptor. This defect causes motor neuron death, but considering the important function of androgens in muscle, it is possible that muscle damage in SBMA also occurs independently of motor neuron damage.

METHODS:

Eight patients with SBMA engaged in regular cycling exercise for 12 weeks. Maximum oxygen uptake ($Vo(2max)$), maximal work capacity ($W(max)$), muscle morphology, citrate synthase (CS) activity, body composition, EMG, static strength measurements, lung function, plasma proteins, and hormones were evaluated before and after training. Evaluation of improvements in activities of daily living (ADL) was conducted after training.

RESULTS:

$W(max)$ increased by 18%, and CS activity increased by 35%. **There was no significant change in $Vo(2max)$ or any of the other variables examined before and after training, and the patients with SBMA did not feel improvements in ADL.**

CONCLUSIONS:

Frequent, moderate-intensity aerobic conditioning is of little beneficial effect in patients with spinal and bulbar muscular atrophy (SBMA). High levels of plasma creatine kinase and muscle regeneration indicate a primary myopathic affection, which, in parallel with the motor neuron deficiency, may attenuate the response to exercise training in patients with SBMA.

Details

Observational study

12 wks on stationary bike, at a heart rate $\sim 70\%$ VO2 max

2x/wk in wks 1 -2

3x/wk in wks 3 -4

5x/wk in remaining wks

Primary outcomes: VO2 max and ADL

Result: No improvement in VO2 max or ADL

A randomized controlled trial of exercise in spinal and bulbar muscular atrophy

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Annals of Clinical and Translational Neurology 2015; 2(7): 739–747

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^aThese two authors contributed equally to this work.

Abstract

Objective: To determine the safety and efficacy of a home-based functional exercise program in spinal and bulbar muscular atrophy (SBMA). **Methods:** Subjects were randomly assigned to participate in 12 weeks of either functional exercises (intervention) or a stretching program (control) at the National Institutes of Health in Bethesda, MD. A total of 54 subjects enrolled, and 50 completed the study with 24 in the functional exercise group and 26 in the stretching control group. The primary outcome measure was the Adult Myopathy Assessment Tool (AMAT) total score, and secondary measures included total activity by accelerometry, muscle strength, balance, timed up and go, sit-to-stand test, health-related quality of life, creatine kinase, and insulin-like growth factor-1. **Results:** Functional exercise was well tolerated but did not lead to significant group differences in the primary outcome measure or any of the secondary measures. The functional exercise did not produce significantly more adverse events than stretching, and was not perceived to be difficult. To determine whether a subset of the subjects may have benefited, we divided them into high and low functioning based on baseline AMAT scores and performed a post hoc subgroup analysis. Low-functioning individuals receiving the intervention increased AMAT functional subscale scores compared to the control group. **Interpretation:** Although these trial results indicate that functional exercise had no significant effect on total AMAT scores or on mobility, strength, balance, and quality of life, post hoc findings indicate that low-functioning men with SBMA may respond better to functional exercises, and this warrants further investigation with appropriate exercise intensity.

Details

Randomized controlled trial

Functional exercises were designed to resemble activities typically performed in daily life

54 pts were randomized to functional exercise program or stretching

Exercise started at one set performed on 2 consecutive days/wk at 50% baseline number of repetitions

Increased to 3x/wk at 70% baseline

Primary outcome: Adult Myopathy Assessment Tool and endurance tests

Result:

Functional exercise well tolerated

No benefit in primary outcome measure

Post hoc subgroup analysis suggests benefit to subject with lower baseline AMAT scores

Non-neural phenotype of spinal and bulbar muscular atrophy: results from a large cohort of Italian patients

Giorgia Querin,¹ Cinzia Bertolin,¹ Elisa Da Re,¹ Marco Volpe,¹ Gabriella Zara,¹ Elena Pegoraro,¹ Nicola Caretta,² Carlo Foresta,² Maria Silvano,³ Domenico Corrado,³ Massimo Iafrate,⁴ Lorenzo Angelini,⁴ Leonardo Sartori,⁵ Maria Pennuto,⁶ Alessandra Gaiani,¹ Luca Bello,¹ Claudio Semplicini,¹ Davide Pareyson,⁷ Vincenzo Silani,⁸ Mario Ermani,¹ Alberto Ferlin,² Gianni Sorarù,¹ on behalf of the Italian Study Group on Kennedy's disease

Table 1 Biochemical profile of patients with spinal and bulbar muscular atrophy

	Mean±SD (range; median)	Reference range	Out of reference range	
			High	Low
Biochemical analyses				
Haematocrit (%)	0.43±0.02 (0.37–0.50; 0.43)	0.41–0.507	1/73	0/73
Creatine kinase (U/L)	1095.8±823 (119–4406; 823)	20–180	68/73	0/73
Fasting glucose (nmol/L)	5.9±1.7 (3.7–14.1; 5.4)	3.7–5.6	29/73	0/73
Glycated haemoglobin (nmol/L)	38.9±8.2 (25–75; 37)	20–38	25/73	0/73
Triglycerides (mg/dL)	1.94±1.26 (0.51–9.28; 1.66)	<2.11	35/73	–
Total cholesterol (nmol/L/L)	5.3±1.0 (3.32–8; 5.33)	<5.18	40/73	–
High-density lipoprotein (nmol/L)	1.42±0.5 (0.32–2.86; 1.34)	>1.55	–	50/73
Low-density lipoprotein (nmol/L)	3.3±0.87 (1.78–4.68; 3.2)	<3.34	29/73	–
Prostate-specific antigen (µg/L)	1.17±1.18 (0.11–21.7; 0.5)	<4	3/73	–

Summary

Metabolic changes in SBMA mouse model indicate diminished glycolysis and increased utilization of fats as an energy source in muscle

Mitochondrial damage may lead to increased clearance of mitochondria, with functional consequences impairing exercise function

Similar changes involving glycolytic gene expression and mitochondria are seen in muscle biopsies from SBMA patients

Significant benefits from exercise have not been demonstrated in SBMA patients...

But functional exercise is safe and well tolerated, may have improved performance in individuals with low function at entering the trial, and importantly, may have many other beneficial effects

Additional clinical experience is needed to understand the best exercise protocols for SBMA subjects at different stages of disease