Peripheral diseases and disorders (Muscle): Clinical presentation, exam, diagnosis, treatment, prognosis

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April 16, 2021

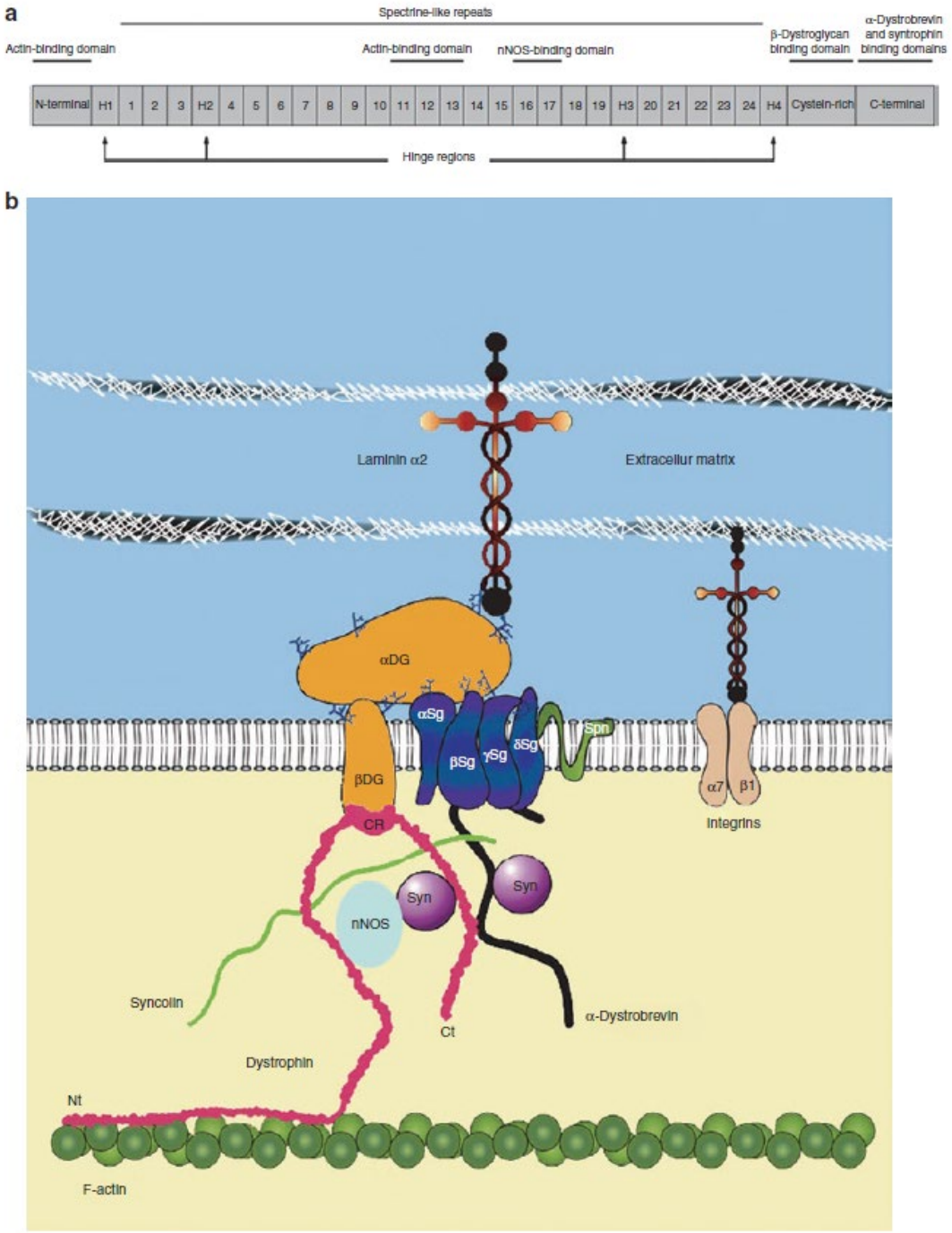
Classification of Myopathy

- Muscular dystrophy
- Channelopathy
- Inflammatory
- Congenital
- Endocrine
- Inborn errors of muscle metabolism
- Mitochondrial
- Toxic

https://neuromuscular.wustl.edu/index.html

Muscular dystrophy

- Dystrophinopathies (Duchenne; Becker)
- Emery-Dreifuss muscular dystrophy
- Myotonic dystrophy
- Facioscapulohumeral dystrophy
- Oculopharyngeal muscular dystrophy
- Distal myopathies
- Limb-girdle muscular dystrophy
- Congenital muscular dystrophy



Dystrophin is very large molecule at 479 kD and has 4 domains

- N terminus
- Central Rod with 4 hinge zones
- Cysteine rich region
- C terminus

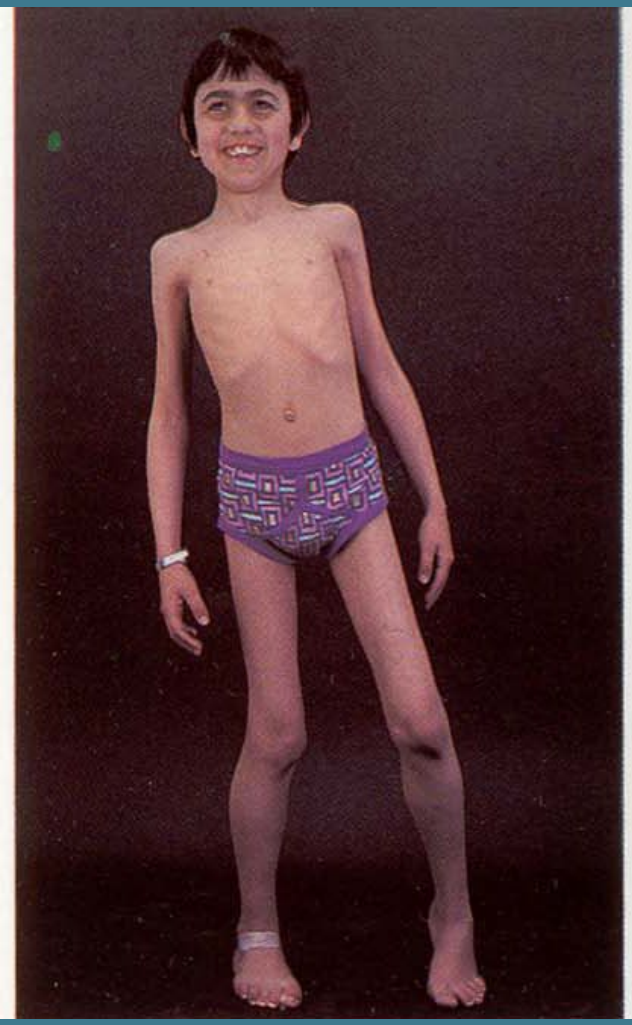
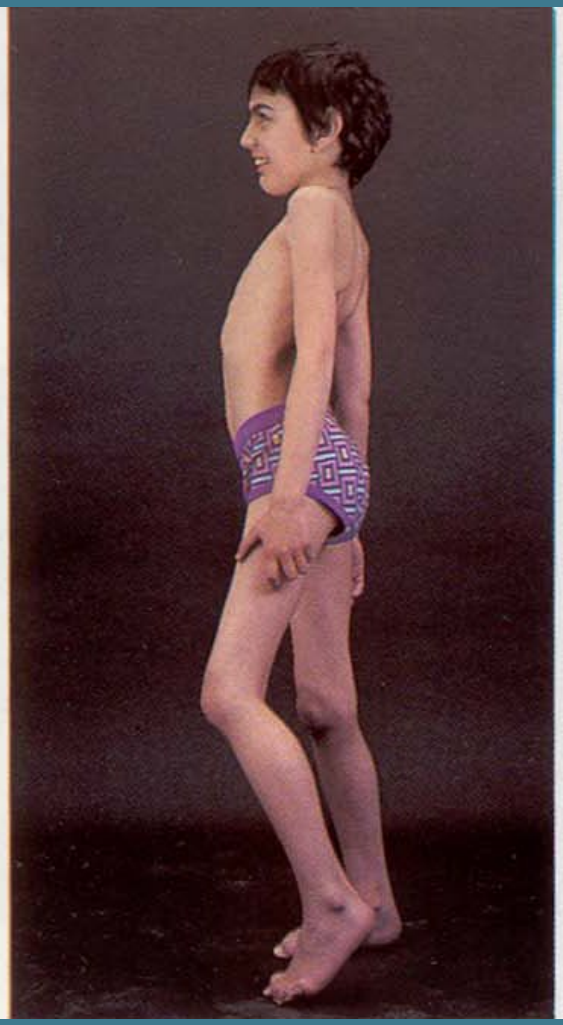
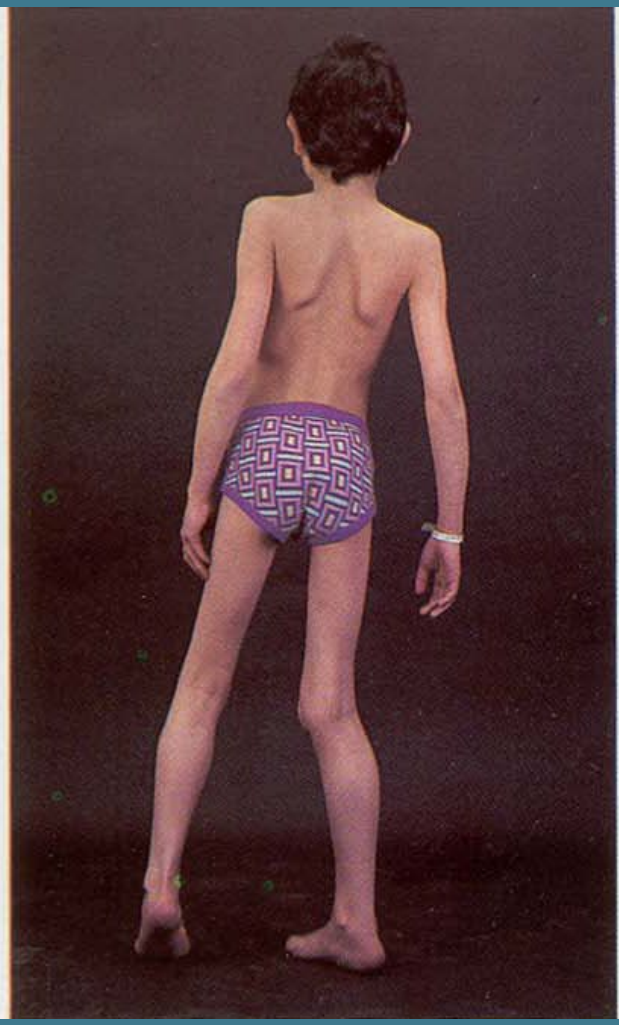
Mol Ther 5:830;2011

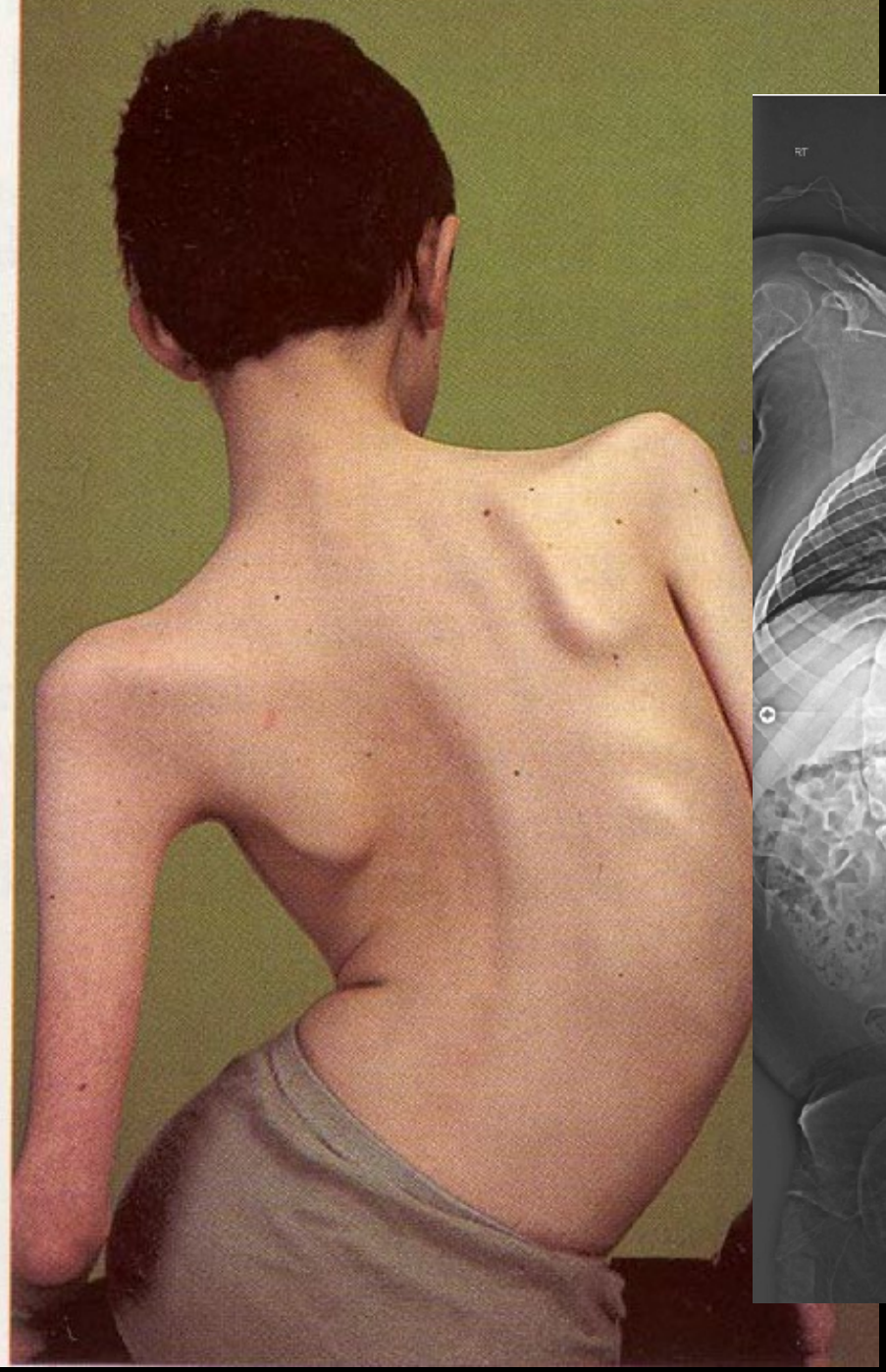
Duchenne Muscular Dystrophy

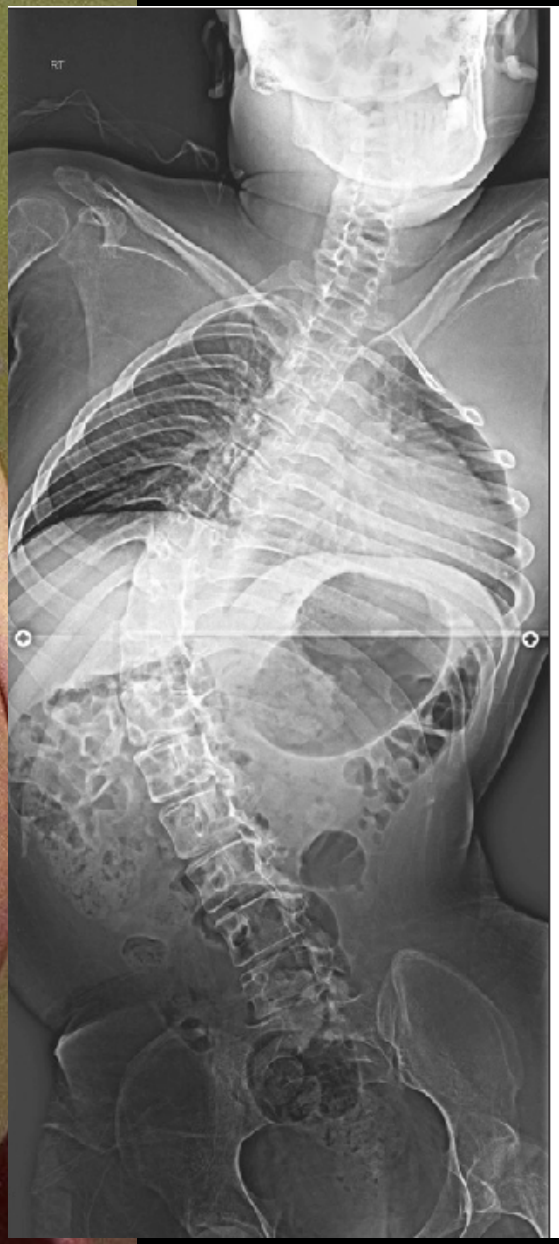
- No dystrophin present
- Onset before age 5; X-linked
- CPK 50-100 fold normal from early age
- Progressive proximal weakness
- Calf hypertrophy and lordosis
- Wheelchair bound by age 10-12
- Cardiac, GI and Pulmonary abnormalities
- Joint contractures and scoliosis are nearly universal
- 1/3 of DMD cases are new mutations

Becker Muscular Dystrophy

- Reduced amount of truncated dystrophin present
- Onset in first decade; X-linked
- Wheelchair bound > age 15 years
- Elevated CPK similar to DMD
- Variable course
- Calf hypertrophy
- Cardiac involvement may be paramount but often less of an issue than in Duchenne
- Can present as Limb-girdle syndrome, myalgias, or isolated cardiomyopathy as adult

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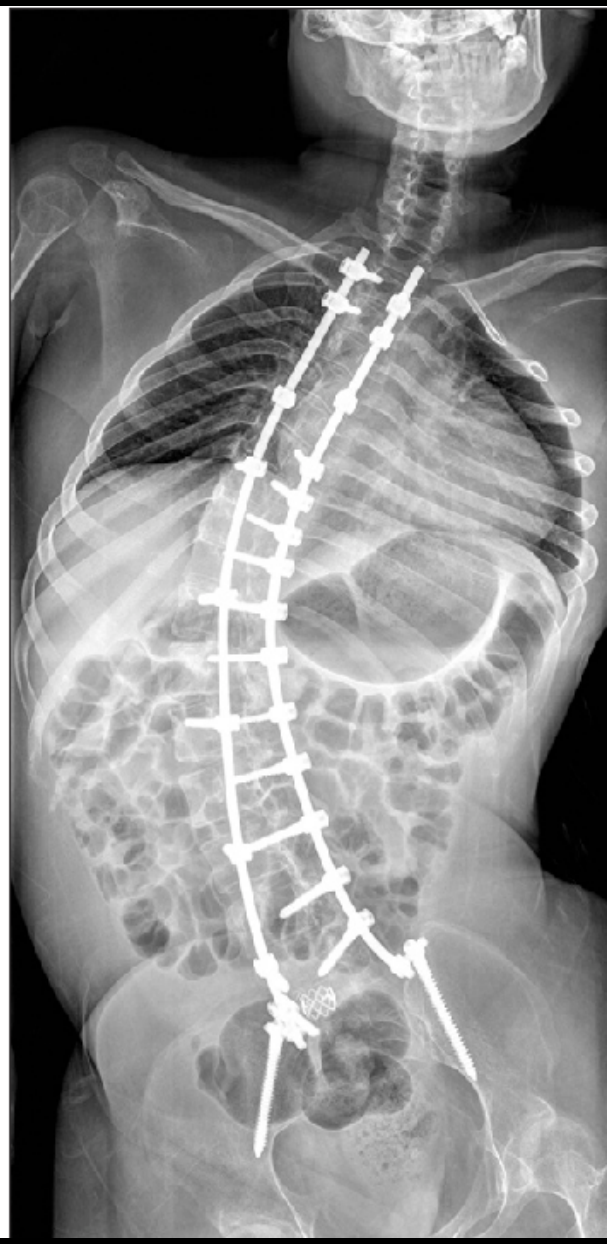
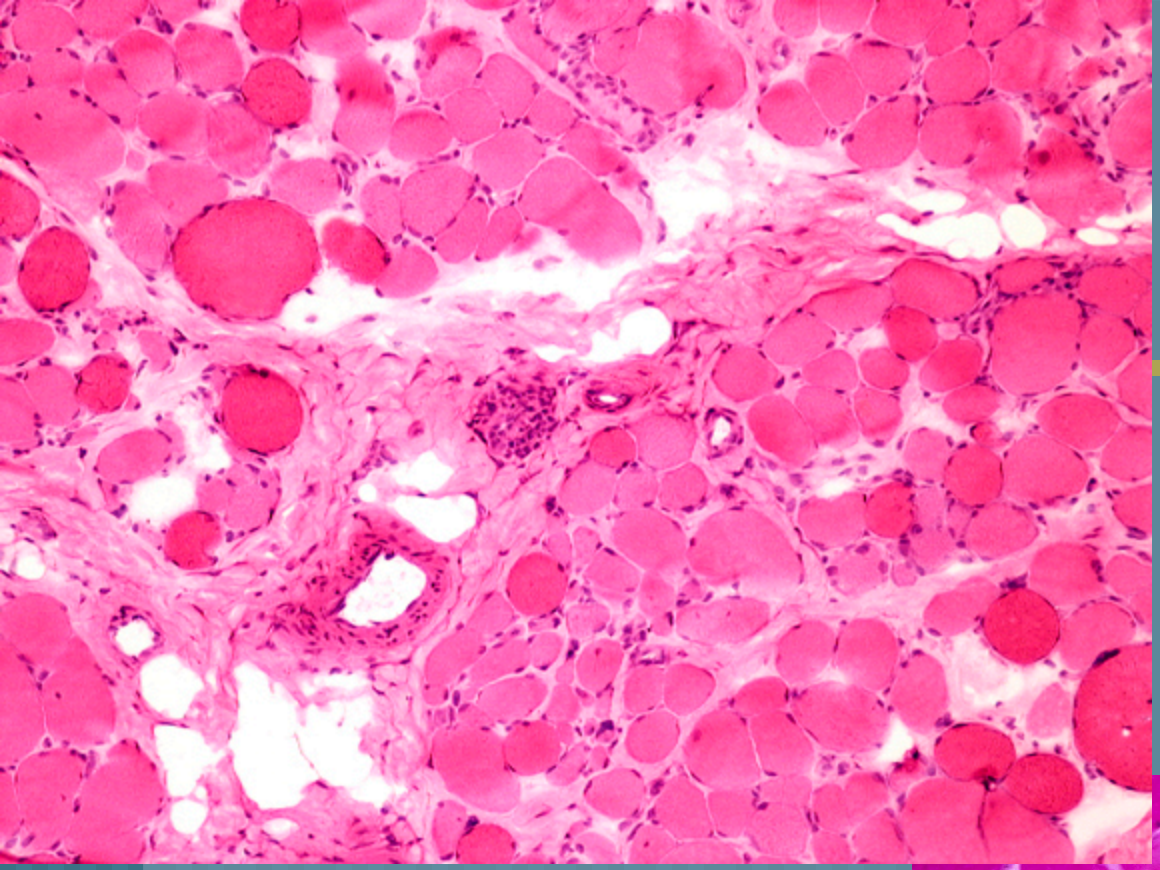
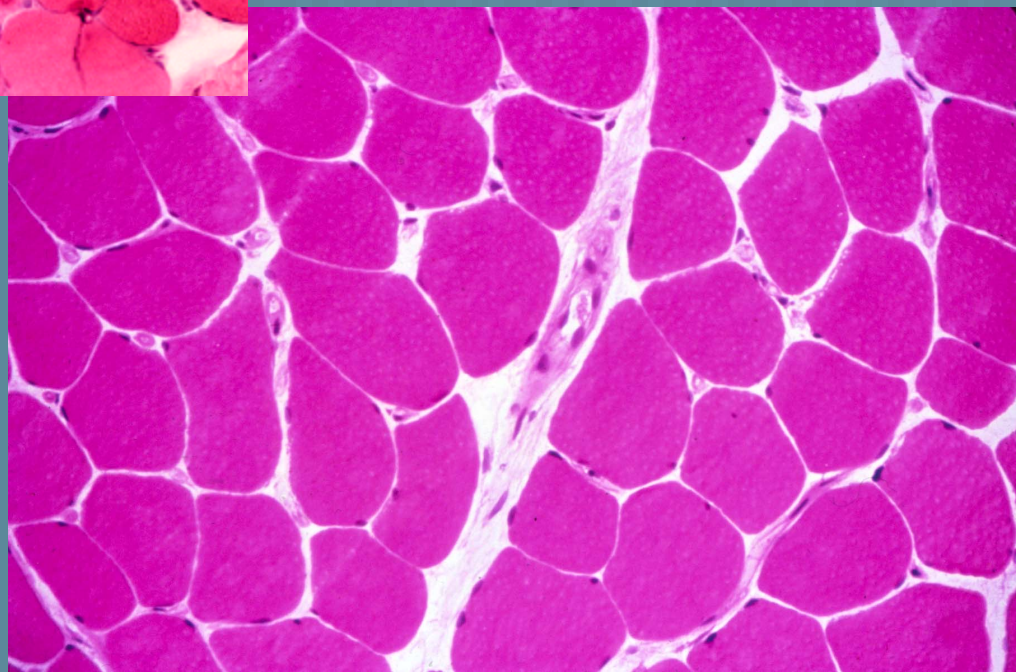
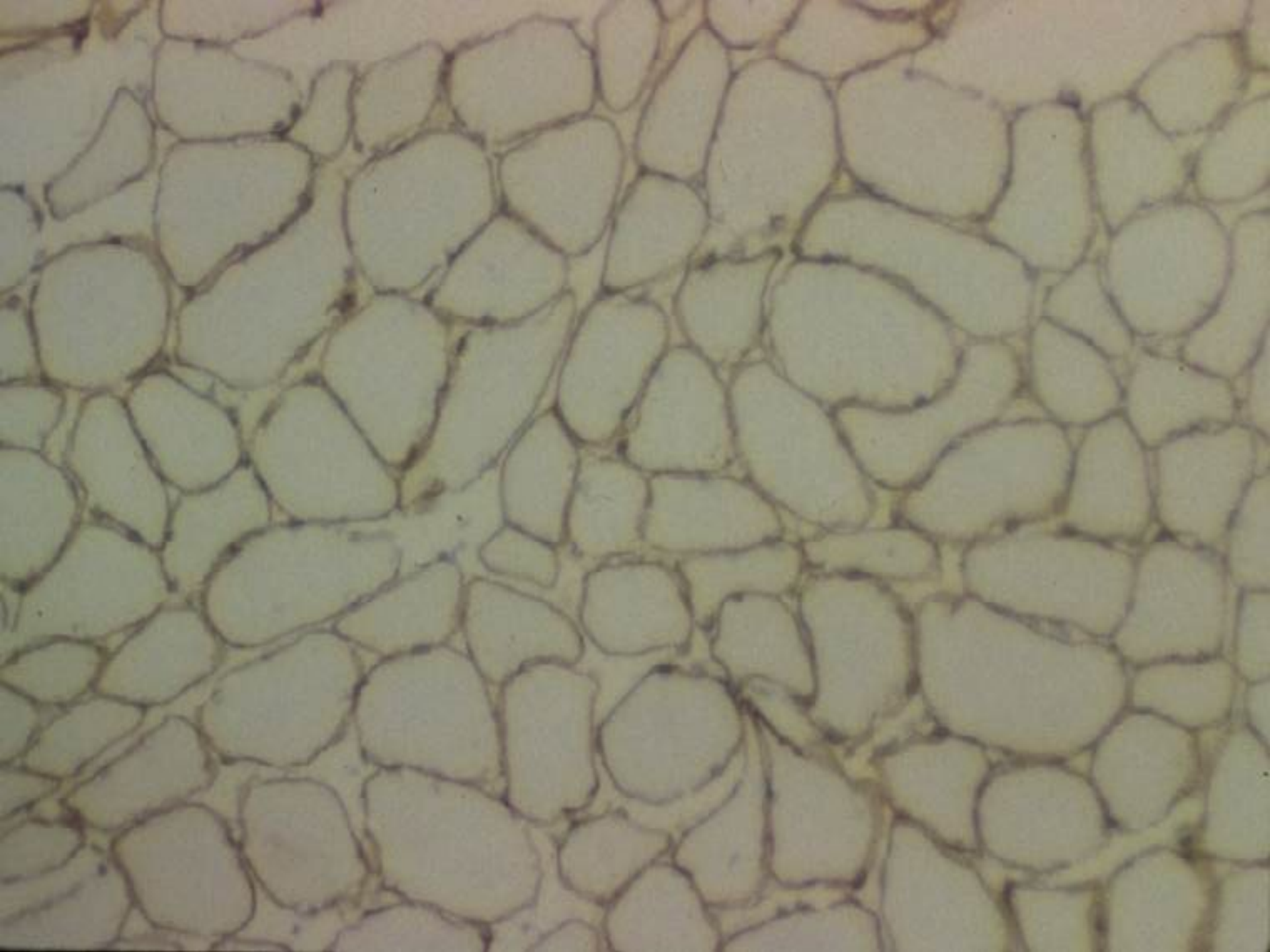




Duchenne pathology

- Fiber size variability
- Central nuclei
- Myophagocytosis
- Fibrosis
- Fatty replacement
- Fiber splitting
- Inflammation





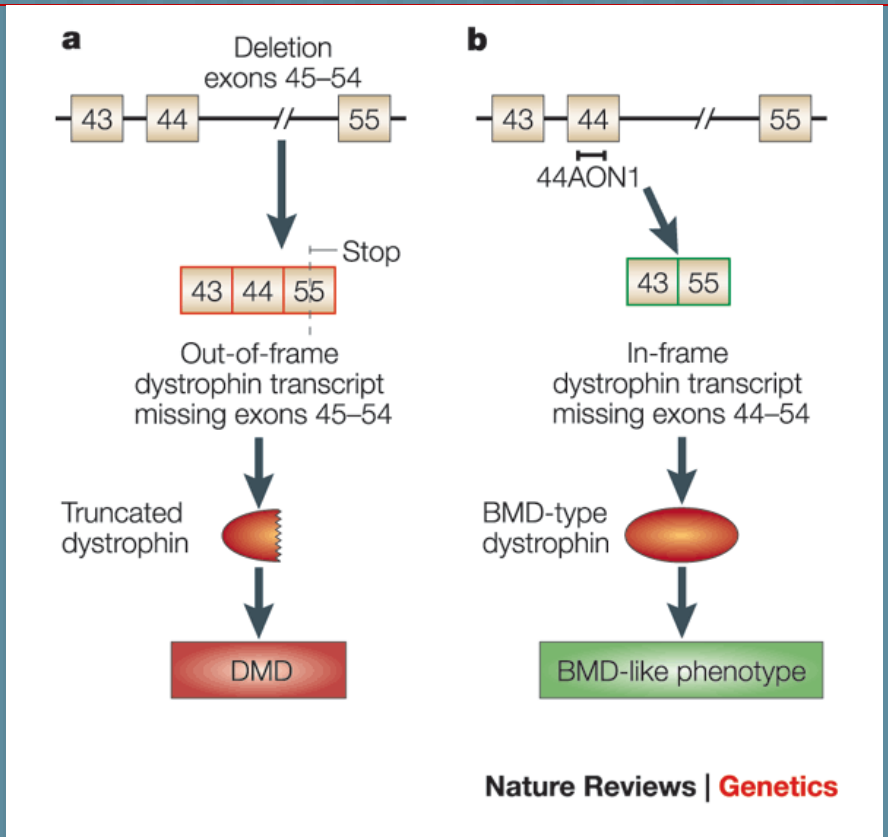
Dystrophin Mutations

- Dystrophin gene is huge
  - 2.2 million base pairs
  - 79 exons and 8 promoters
- Large deletions (>1 exon) account for 65% of DMD/BMD
- Duplications account for 5%
- Premature stop codon mutations account for 15%
- Remainder are frameshifting insertions/deletions, splice site mutations, or missense mutations.

Flanagan KM ,et al. Hum Mutat 2009

DMD vs BMD

- Size of deletion does not correlate well with phenotype
- In-frame deletions are more likely to result in translation of a protein with partial function
  - Out-of-frame deletions are DMD ~90% of the time



READING FRAME (continued)

THE BIG RED DOG RAN AND SAT

THE BIR EDD OGR ANA NDS AT

= Duchenne muscular dystrophy

THE DOG RAN AND SAT

= Becker muscular dystrophy

If deletion/mutation/duplication is a multiple of 3 nucleic acids, reading frame preserved, translation continues and likely Beckers.
If deletion/mutation/duplication other than multiple of 3, reading frame disturbed, premature termination of translation and likely Duchenne

PATHOPHYSIOLOGY OF DUCHENNE MD

No dystrophin

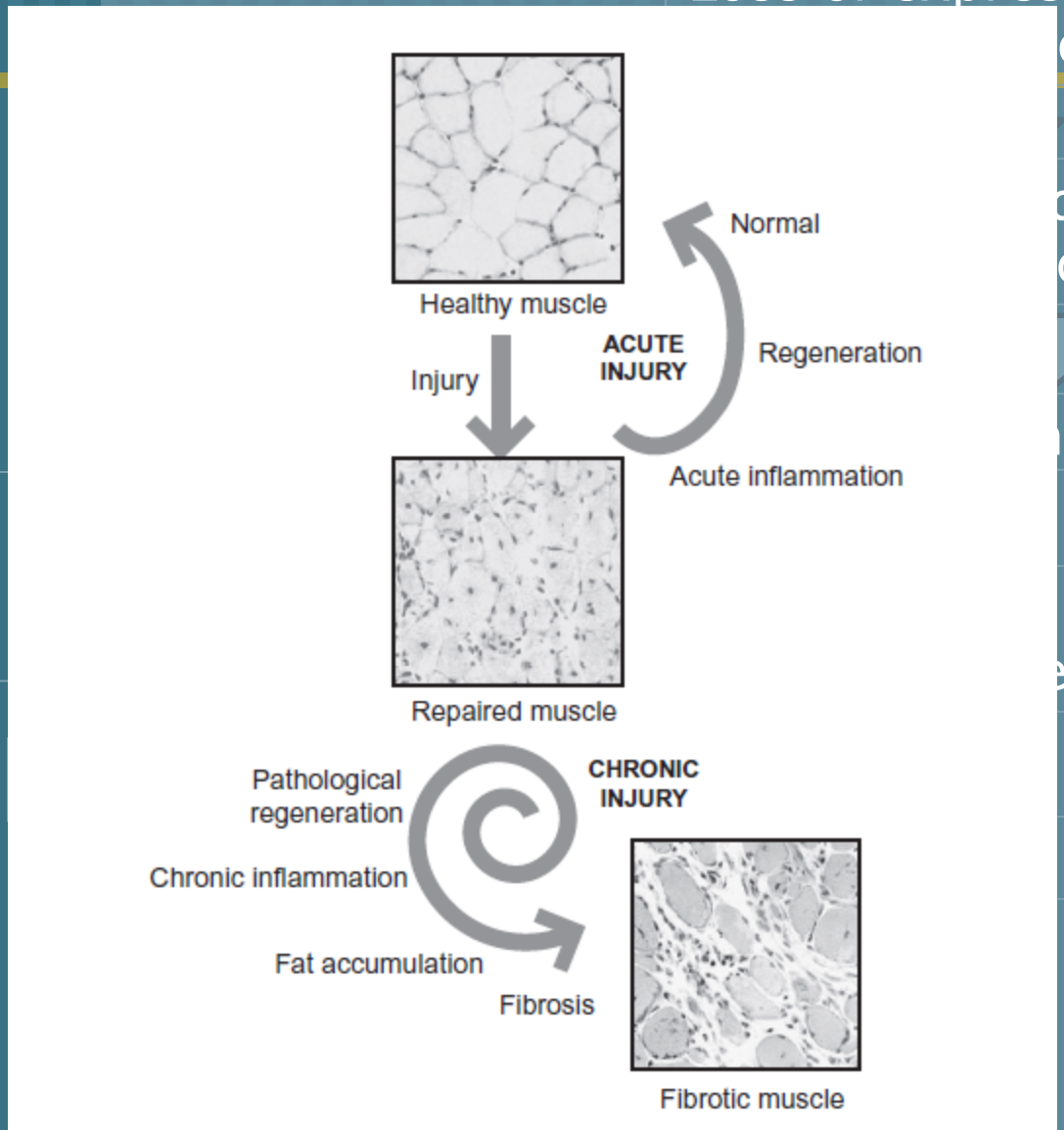
Loss of expression of other
oteins

during mechanical
on/elongation

influx

Activation of proteolytic
nzymes within muscle fiber

Cell necrosis



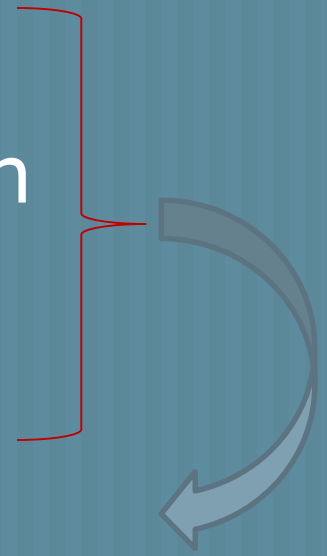
Curr Top Devel Biol
96:2011; 167.

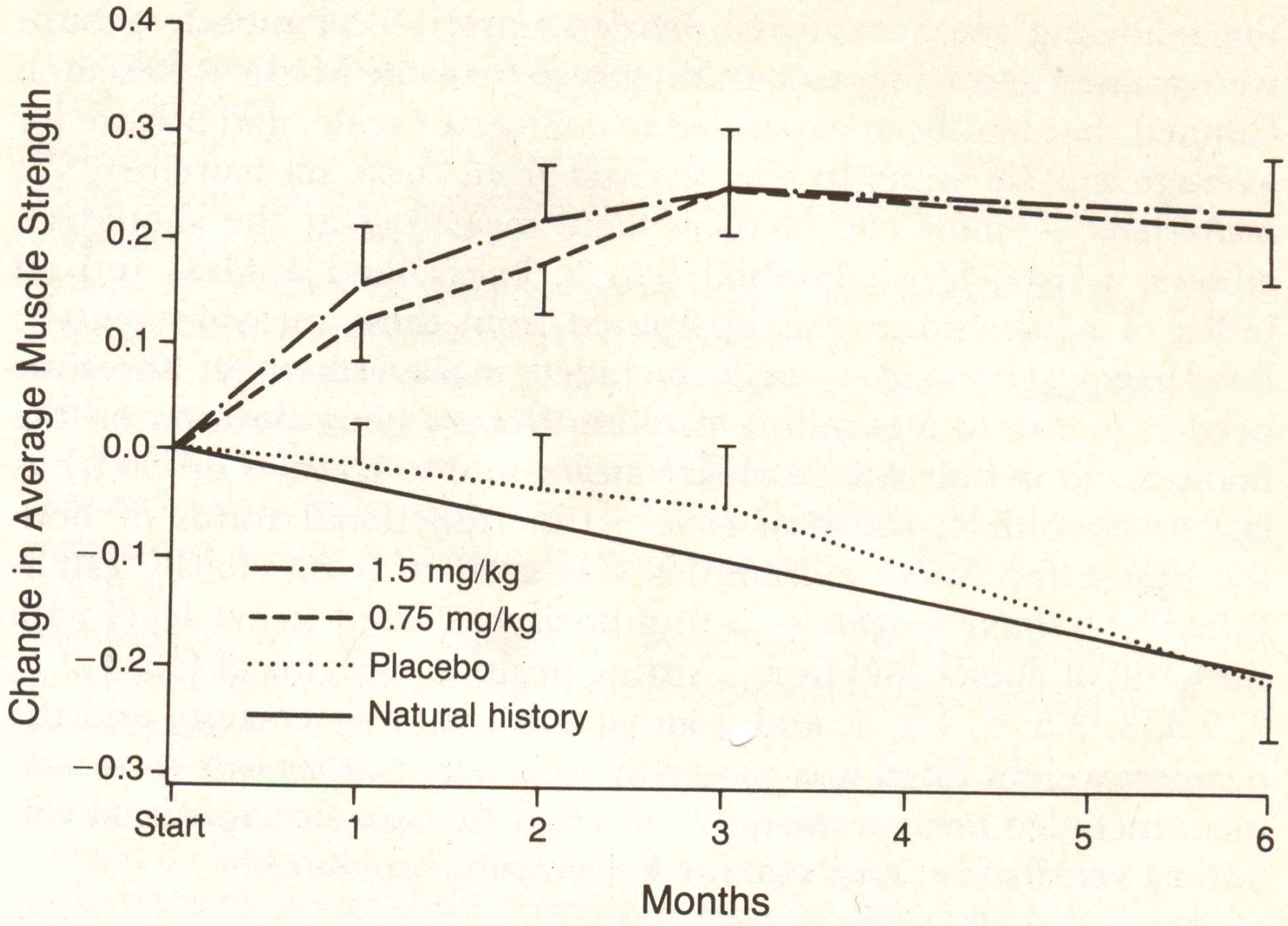
Management of DMD

- Family Planning/Genetic Counseling: prenatal testing, pre-implantation testing
- Durable Medical Equipment: bracing, wheelchairs, transfer systems, beds
- Scoliosis management
- Cardiac care: early tx vs symptomatic, heart failure
- Pulmonary: NIPPV, Tracheostomy, IPPV, cough assist, diaphragm pacing
- GI: swallow management, PEG
- Caregivers: education, respite, help, counseling

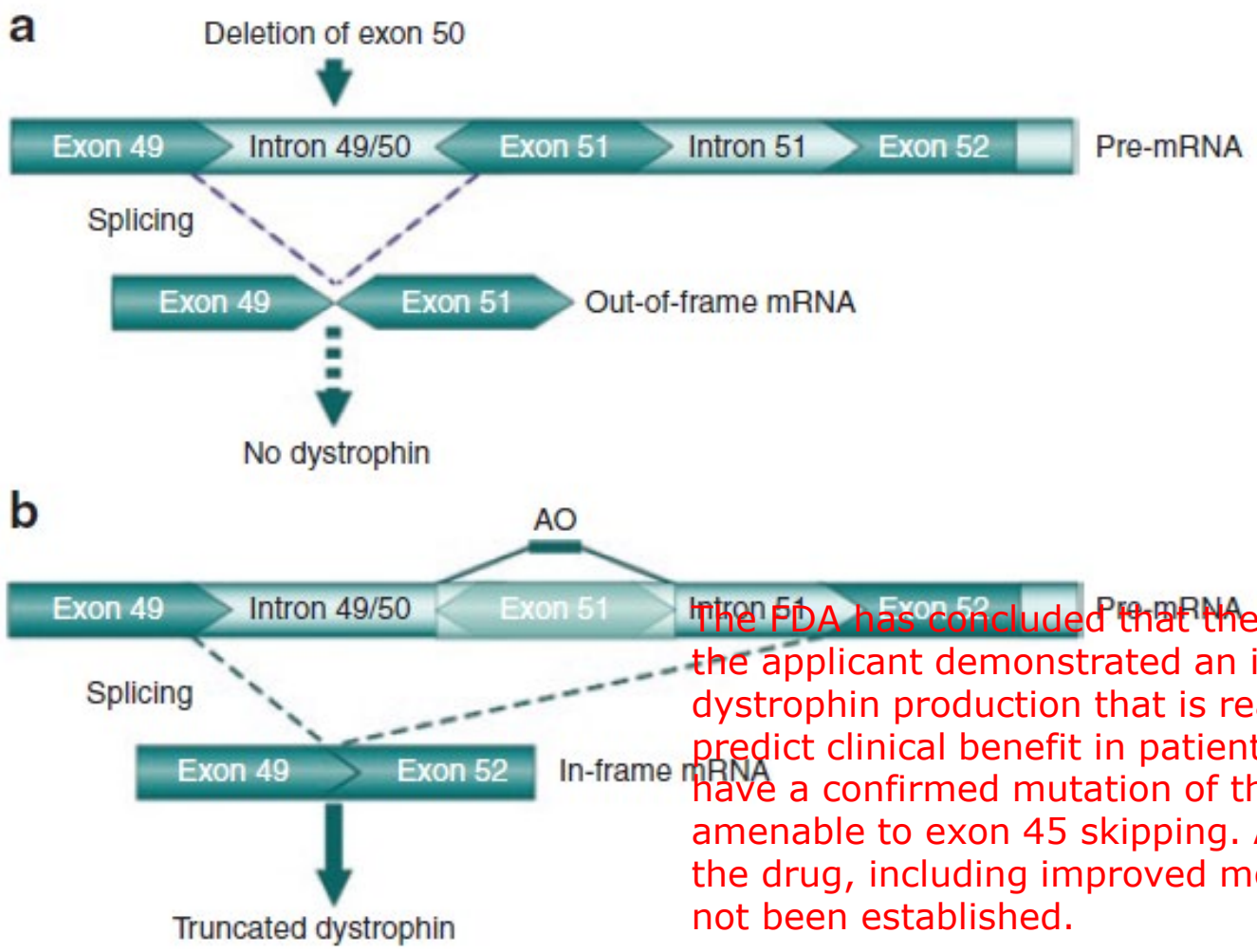
Treatment

- Steroids
- Exon skipping
- Stop-codon read through
- Gene transfer
- Utrophin upregulation
- Turn DMD into BMD
  - New born screening
  - Inhibition of fibrosis: steroids, ARB




Change in Average Muscle Strength
0.4
0.3
0.2
0.1
0.0
−0.1
−0.2
−0.3
1.5 mg/kg
0.75 mg/kg
Placebo
Natural history
Start
1
2
3
4
5
6
Months

EXON SKIPPING THERAPY

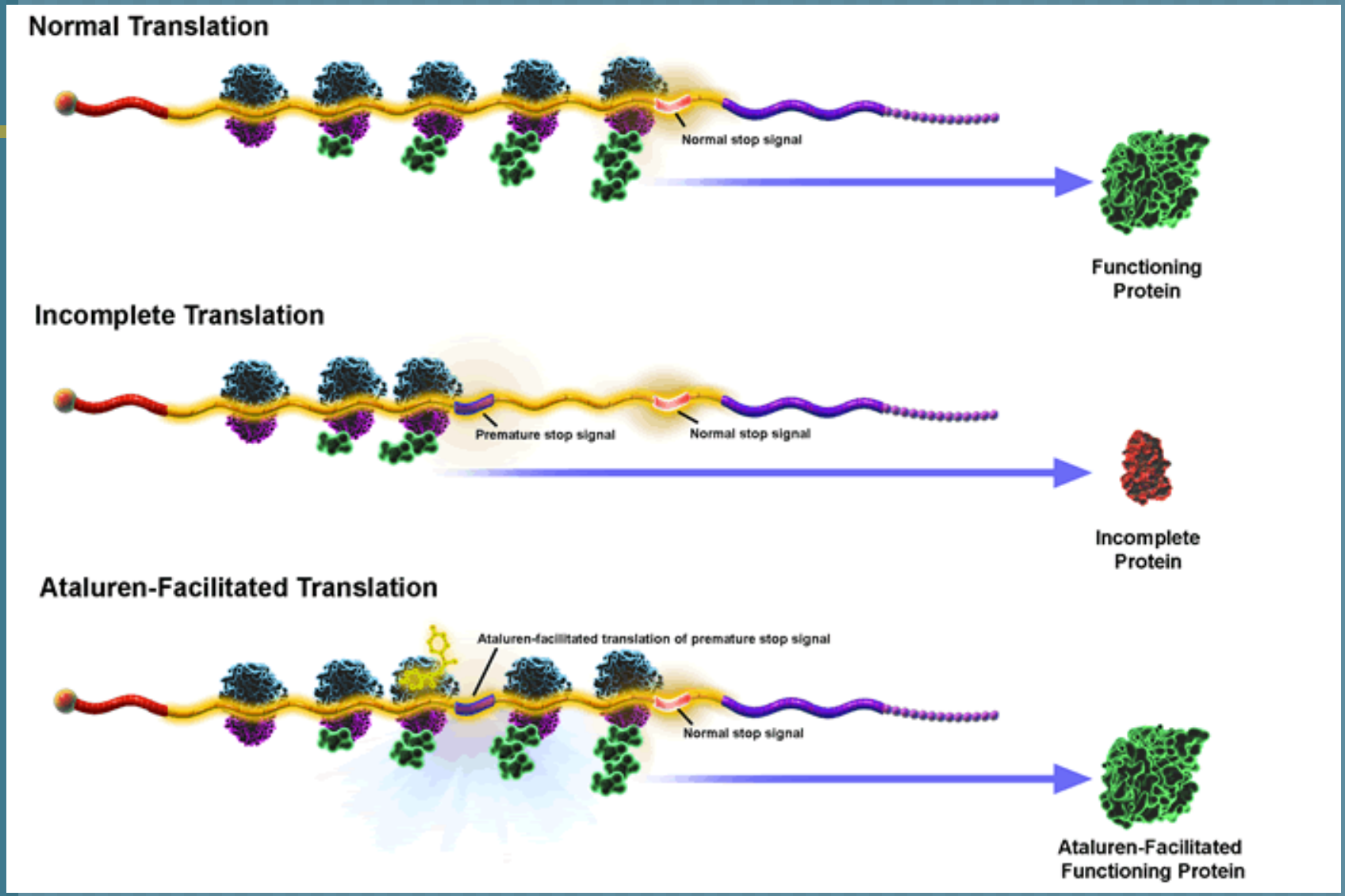


The FDA has concluded that the data submitted by the applicant demonstrated an increase in dystrophin production that is reasonably likely to predict clinical benefit in patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 45 skipping. A clinical benefit of the drug, including improved motor function, has not been established.

Etelirpsen FDA approved for Exon 51 DMD
Vyondys FDA approved for Exon 53 DMD
Amondys FDA approved for Exon 45 DMD

Mol Ther 19;830: 2011

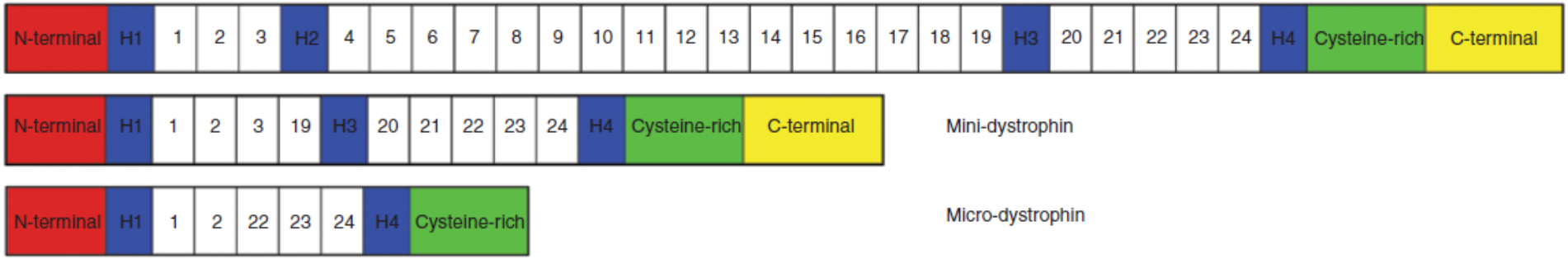
STOP CODON READ-THROUGH



Ataluren in talks with FDA for nonsense mutations in DMD

Ptcbio.com

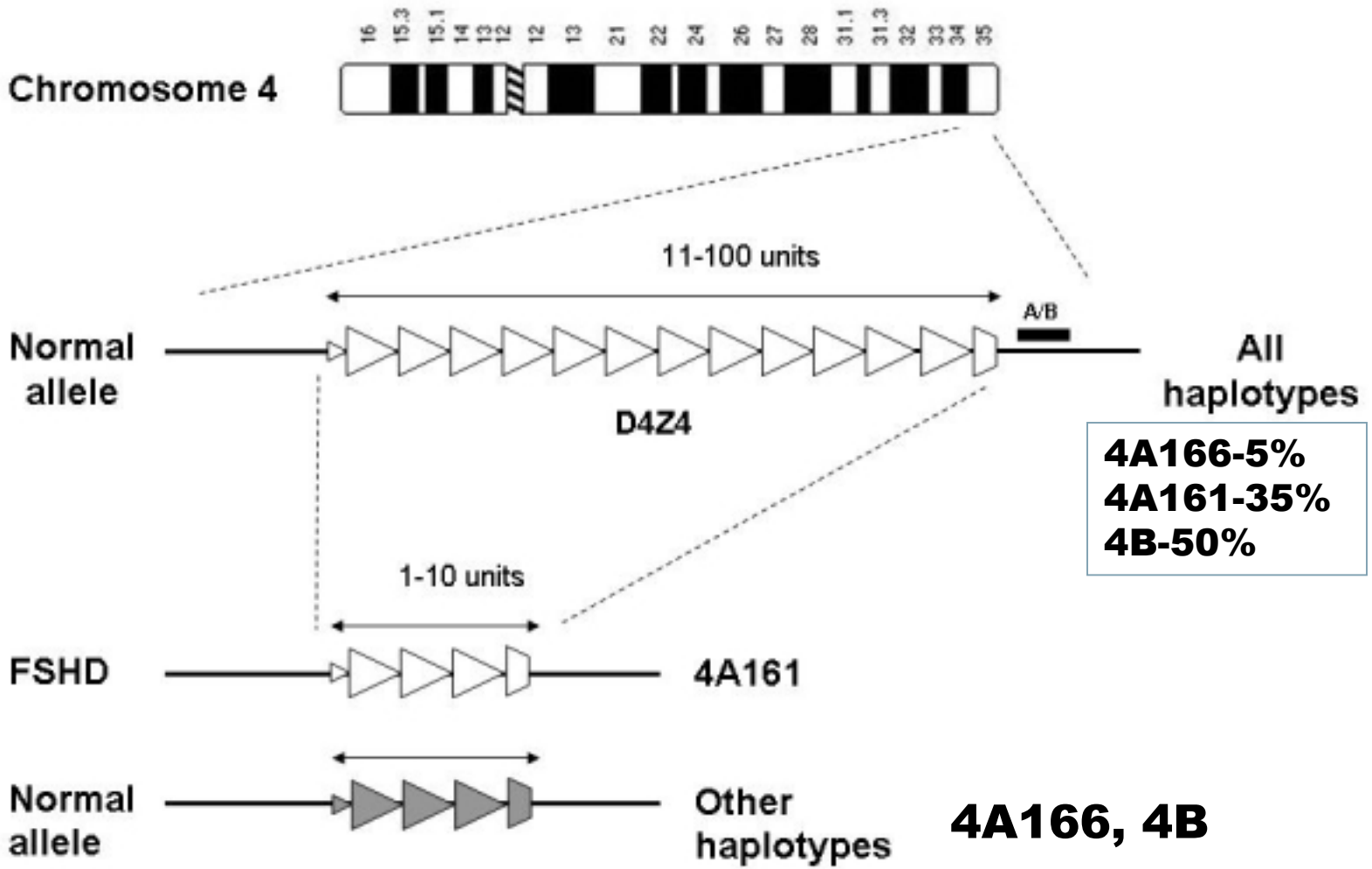
VIRAL GENE REPLACEMENT THERAPY



Mol Ther 19;830: 2011

Facioscapulohumeral Muscular Dystrophy

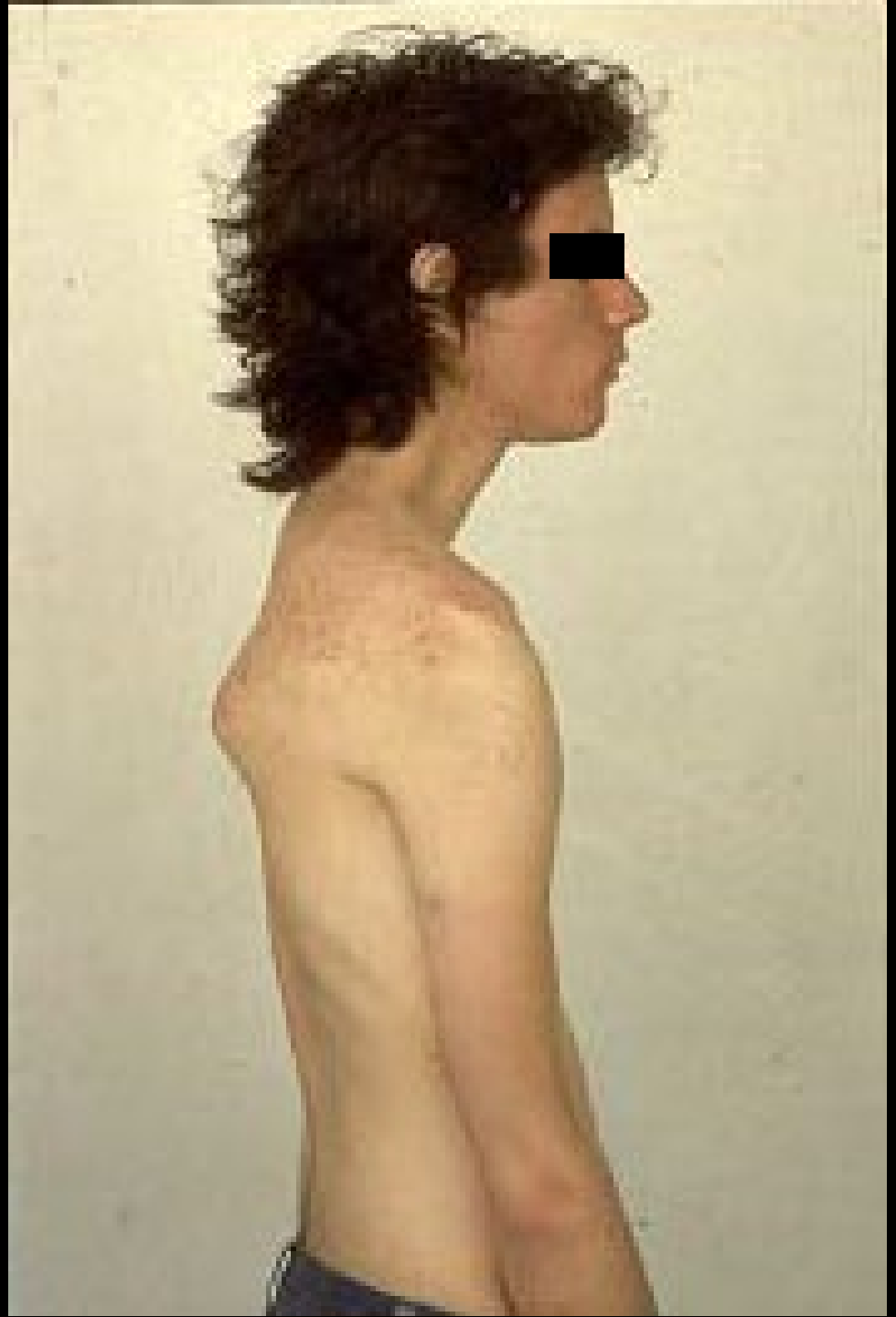
- Variable onset: earlier onset = worse course
- Facial, shoulder girdle weakness
- Legs, distal>proximal, can also be weak
- Autosomal dominant
- 95% have genetic defect on 4q35
- Deletion of copies of D4Z4: disease is <10, normal 11-100

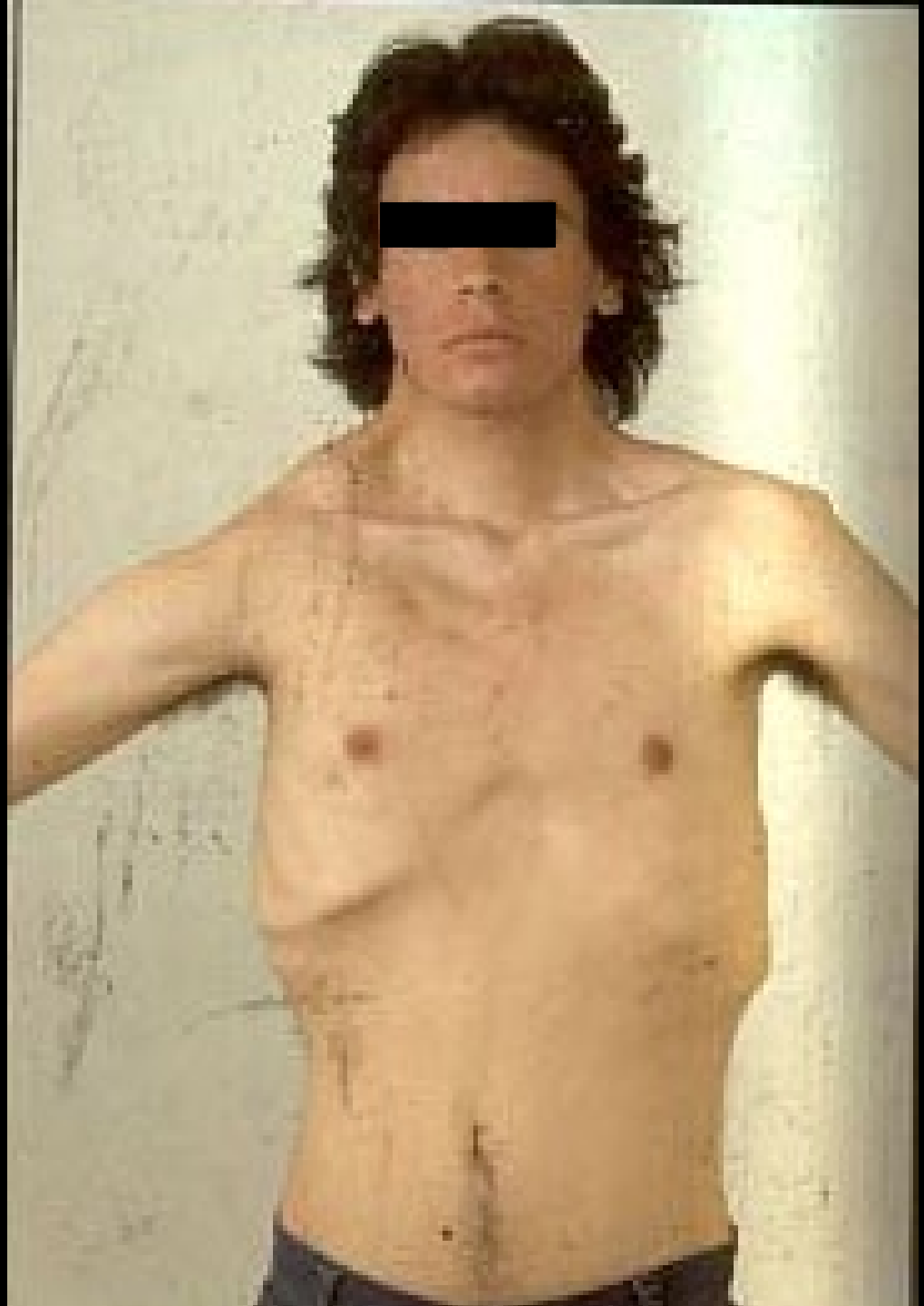


Causes chromatin relaxation and de-repression of DUX4 gene

Lemmers, van der Maarel.Gene Reviews 2014

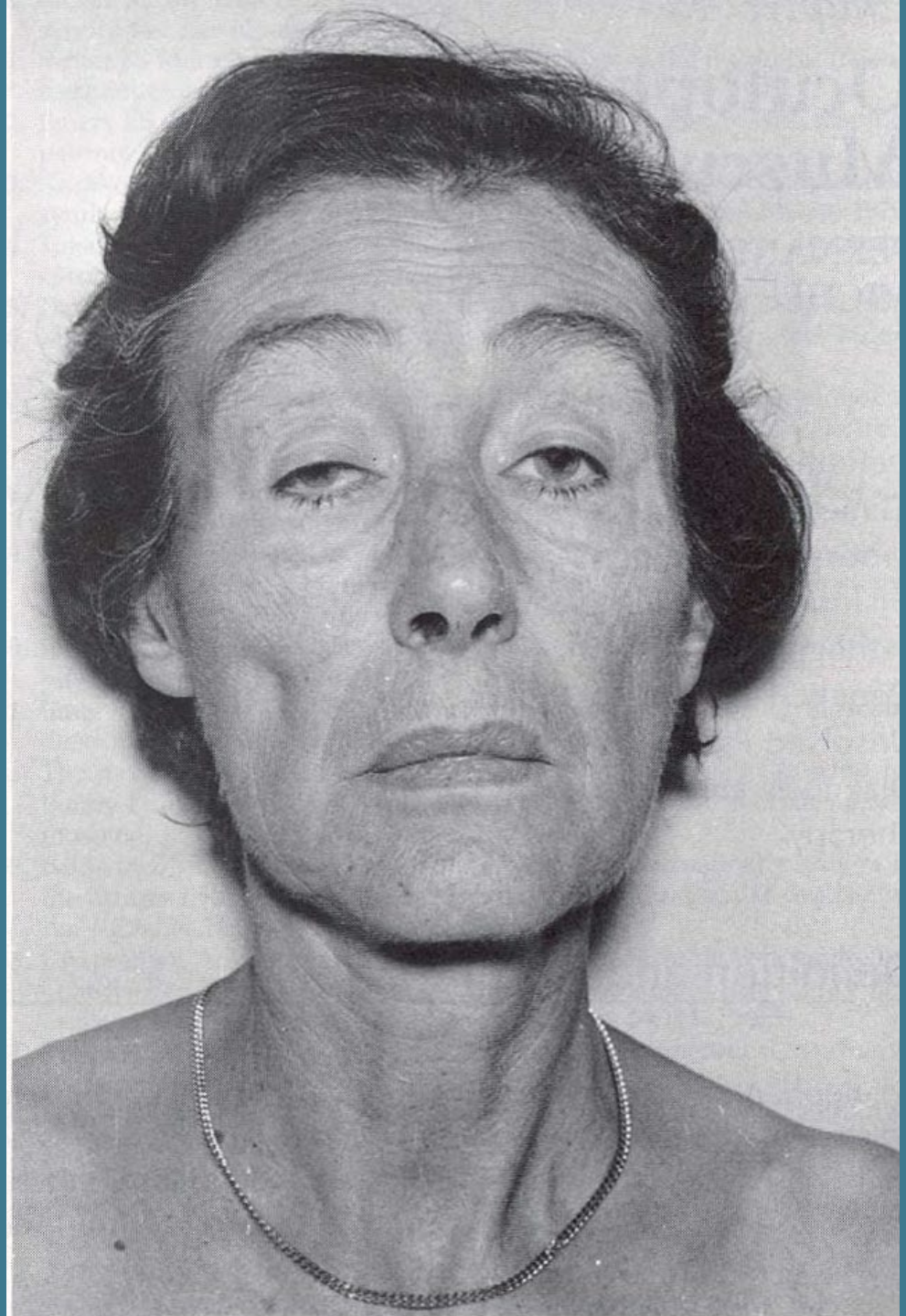
FSHD2, pathogenic variants in the chromatin modifier *SMCHD1* (Chr 18)cause the chromatin relaxation at D4Z4.





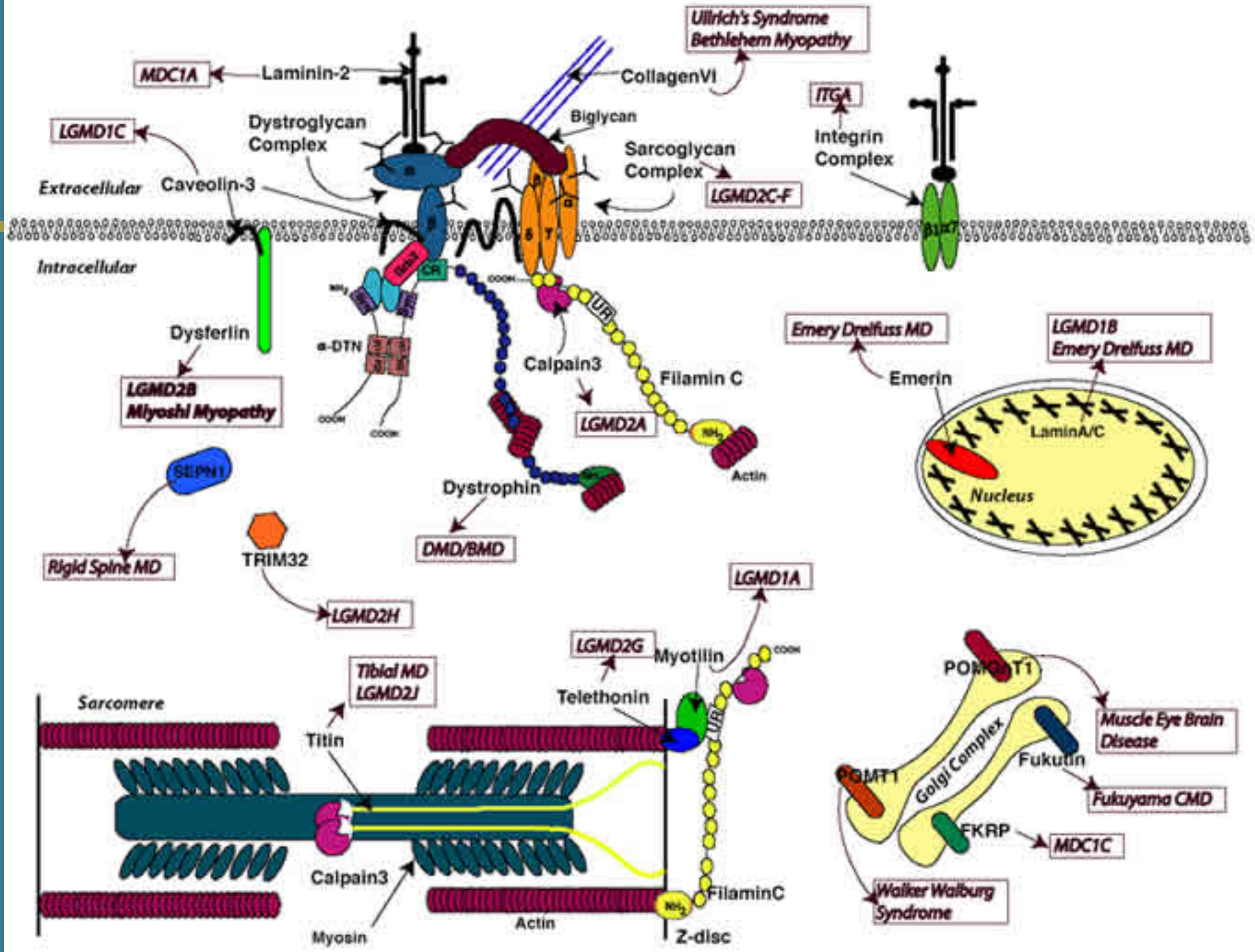
Oculopharyngeal Muscular Dystrophy

- Onset in 4th-5th decade, slowly progressive
- Ptosis, dysphagia are hallmarks
- Less commonly, limb weakness
- Non-fatal if nutrition maintained
- Autosomal dominant, chr. 14
- Triplet repeats: normal GCG_{6}; Abnormal $GCG_{8\text{-}13}$
- French-Canadian; Spanish American



Limb-girdle Muscular Dystrophy

- Onset in late teens, twenties
- Progressive proximal weakness
- Several genetic isoforms
- Some manifest in childhood as Duchenne-like syndrome, often due to null or nonsense mutations
- Autosomal recessive 95%


Ullrich's Syndrome
Bethlehem Myopathy
MDC1A
Laminin-2
CollagenVI
ITGA
Biglycan
LGMD1C
Dystroglycan
Complex
Integrin
Complex
Sarcoglycan
Complex
LGMD2C-F
Extracellular
Caveolin-3
Intracellular
Dysferlin
LGMD2B
Miyoshi Myopathy
α-DTN
Calpain3
Filamin C
LGMD2A
Actin
Dystrophin
DMD/BMD
Emery Dreifuss MD
LGMD1B
Emery Dreifuss MD
Emerin
LaminA/C
Nucleus
SEPN1
Rigid Spine MD
TRIM32
LGMD2H
LGMD1A
LGMD2G
Myotilin
Telethonin
Tibial MD
LGMD2J
Titin
Sarcomere
Calpain3
Myosin
Actin
FilaminC
Z-disc
POMGnT1
Muscle Eye Brain
Disease
Golgi Complex
Fukutin
POMT1
Fukuyama CMD
FKRP
MDC1C
Walker Walburg
Syndrome

Limb-girdle Muscular Dystrophy-Dominant

	LOCUS	GENE	PRODUCT
LGMD 1A	5q31	MYOT	Myotilin
LGMD 1B	1q21	LMNA	Lamin A/C
LGMD1C	3p25	CAV3	Caveolin-3
LGMD1D	7q	DNAJB6	DNAJB6
LGMD 1E	2q35	Desmin	Desmin
LGMD 1F	7q32	TNPO3	Transportin 3
LGMD 1G	4q21	HNRPDL	HNRPDL protein
LGMD 1H	3p23		
LGMD 1I	15q15.1	CAPN3	Calpain 3

Bethlem	21q22, 2q37		Collagen VI

Limb-girdle Muscular Dystrophy

AR LGMD	LOCUS	GENE	PRODUCT	
2A	15Q15	CAPN3	Calpain-3	12%
2B	2q13.1	DYSF	Dysferlin	18%
2C	13q12	SGCG	γ-sarcoglycan	
2D	17p21	SGCA	α-sarcoglycan	
2E	4q12	SGCB	ß-sarcoglycan	15%
2F	5q33	SGCD	δ-sarcoglycan	
2G	17q11-12	TCAP	Telethonin	
2H	9q31-33	TRIM32	tripartite-motif 32	
2I	19q13.3	FKRP	FKRP	15%
2J	2q31	TTN	Titin	
2K	9q34	POMT1	Protein O-mannosyltransferase 1	
2L	11p14.3	ANO5	Anoctamin 5	
2M	9q31	FCMD	Fukutin	
2N	14q24	POMT2	Prot O-man…. 2	
2O	1p34	POMGnT1	Prot O-…beta 1,2-N-acetylglucosaminyl transferase 1	

Limb-girdle Muscular Dystrophy

AR LGMD	LOCUS	GENE	PRODUCT
2P	3p21	DAG1	Dystrophin-assoc glycop 1
2Q	8f2q		Plectin
2R	2q35		Desmin
2S	4q35	TRAPPC11	Transport protein particle
2T	3p21	GMPPB	Mannose1phosphate Guanyltransferase beta
2U	7p21	ISPD	
2V	17q25	GAA	Acid Maltase (Pompe)
2W	2q14	LIMS2	Lim senescent cell Ag-like
2X	6q21	POPDC1	Popeye domain-contain 1
2Y	1q25	TOR1AIP1	Torsin A-interacting
2Z	3q13	POGLUT1	Protein 0-glucosyltransferase

Myotonic dystrophy types

Type 1

- Chr. 19, DMPK gene coding for DM protein kinase
- CTG repeats: nl <34.
- Autosomal dominant
- Distal weakness
- Congenital form, almost exclusively inherited from mother.
- Anticipation, due to expansion of unstable repeats

Type 2

- Chr 4, CNBP (ZNF9) gene coding for Zinc finger 9 protein
- CCTG repeat: nl < 26
- Complex repeat
- Autosomal dominant
- Proximal weakness
- No congenital form
- Repeat number ≠ severity

Myotonic Dystrophy type 1

Phenotype	Clinical signs	CTG repeat size	Age at onset	Age at death
Pre-mutation	none	35-49	NA	NA
Mild	Cataracts Mild myotonia	50-150	20-60 yrs of age	60 years to normal lifespan
Classic	Cataracts Myotonia Distal weakness Frontal balding Cardiac arrhythmia Sleep apnea Insulin resistance Others	100-1000	10-30 yrs of age	45-55 years of age
Congenital	Infantile Hypotonia Mental Retardation Respiratory insufficiency Joint contractures Classis signs as adult	>2000	Birth to 10 years	<45 years of age

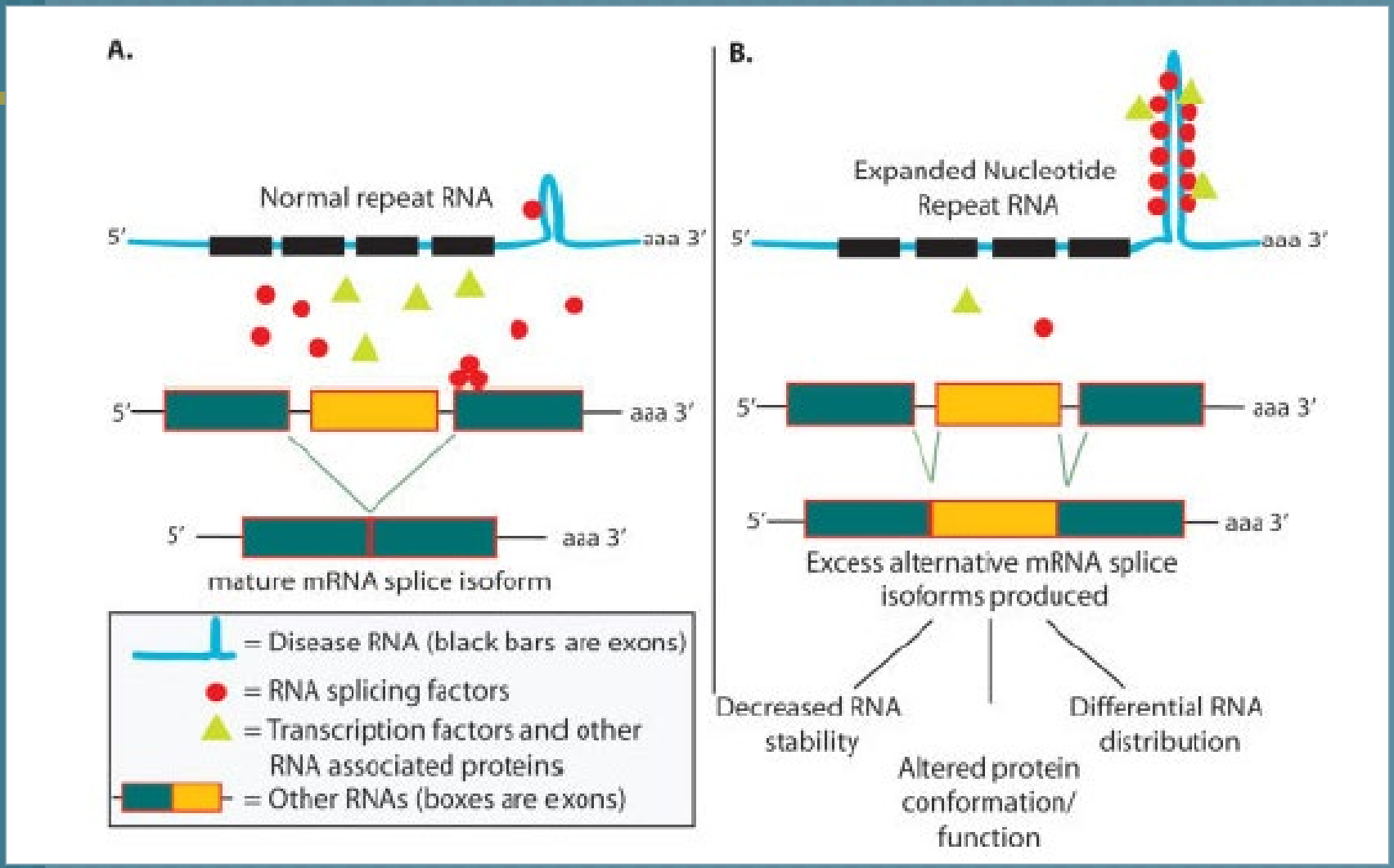
Bird T, Gene Reviews, 2007

Myotonic dystrophy type 2

Phenotype	Clinical signs	Repeat size	Age at onset	Age at death
Normal		11-26		
Pre-mutation	Never seen	177-376	NA	NA
Adult	Myotonia, Proximal weakness, Muscle pain, stiffness, Cataracts, Cardiac conduction, Insulin insensitivity, Gonadal failure in males	>376	3rd-4th decade	

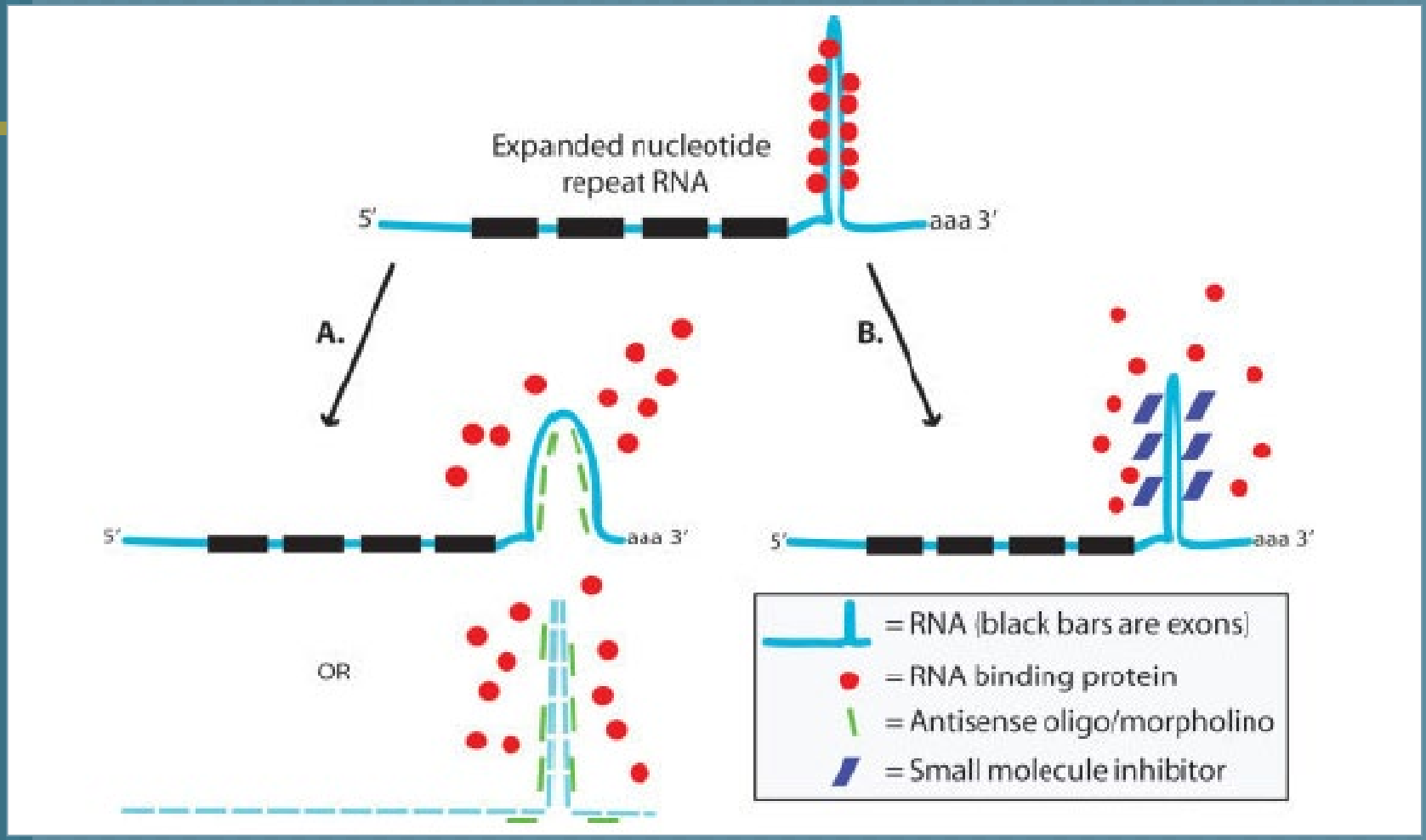
Dalton, Ranum, Day, Gene Reviews, 2007

Sequestration hypothesis of RNA-dominant disorders



Todd, Paulson, Ann Neurol 2010

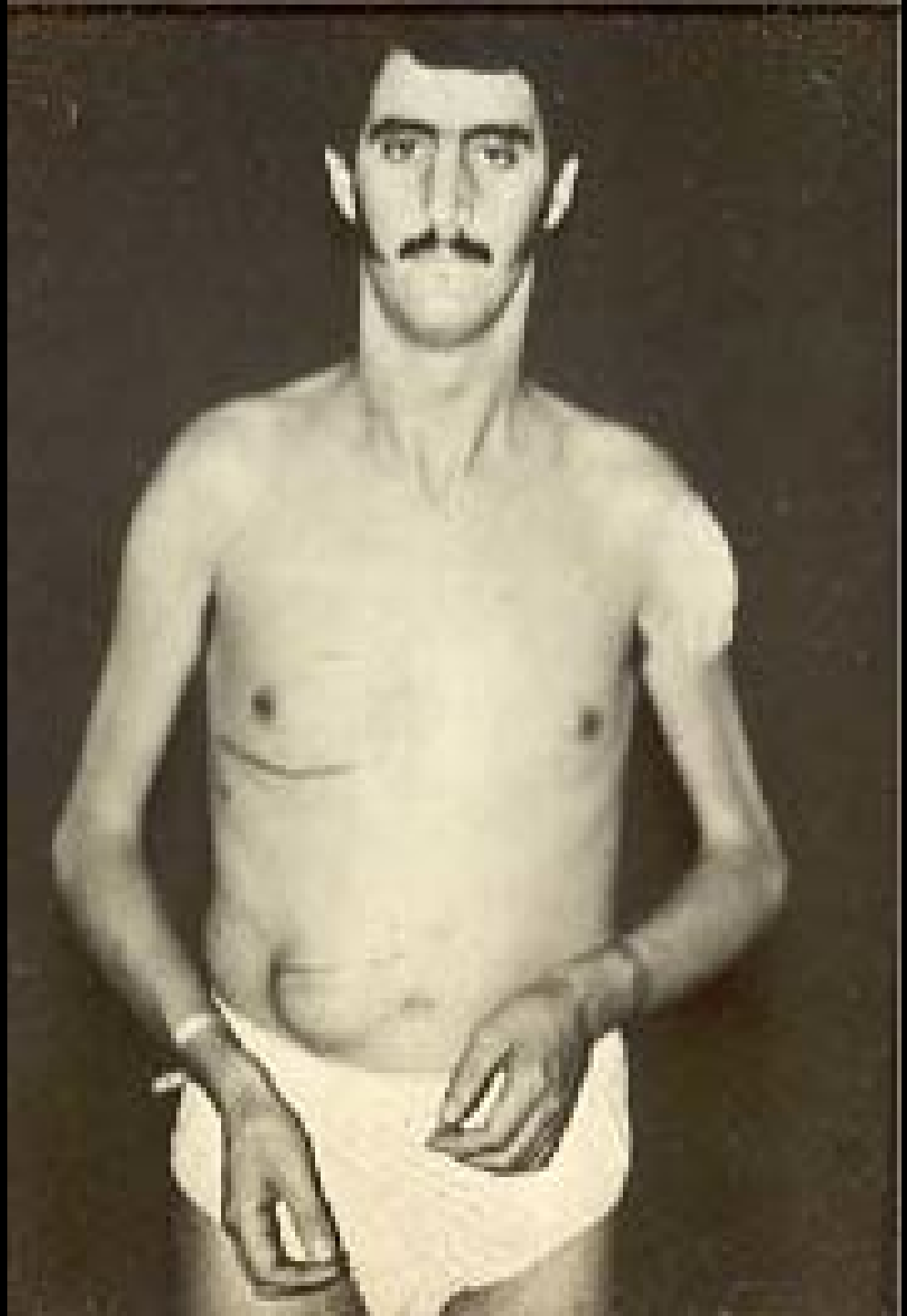
Therapeutic approaches to myotonic dystrophy 1 and 2



Todd, Paulson, Ann Neurol 2010

Emery-Dreifuss Muscular Dystrophy

- Onset in early childhood
- Humeral-peroneal weakness and atrophy
- Early and unusual contractures: elbow, neck
- Cardiac conduction defects: atrial standstill
- X-linked (Emerin-defective protein)



Congenital Muscular Dystrophy

- Various syndromes, all with onset at birth
- Without cerebral involvement has variable course

  (despite abnormal brain MRI)
- With cerebral involvement (e.g. Fukuyama) : progressive, fatal within few years
- Autosomal recessive

Distal Myopathies

	Nonaka	*Miyoshi*	*Laing*	*Welander*	*Markesbery Griggs*	*VCPMD*
Inheritance	AR sporadic	AR sporadic	AD	AD	AD	AD
Gene Loci	9p1 – q1	2p12 - 14	14q11	2p13	2q31 - 33	5q31
Onset Age	20 - 30	15 - 30	4 - 25	> 40	> 35	25 – 50
Onset Site	Anterior Legs	Posterior Legs	Legs	Hands	Anterior Legs	Hands, feet, VC
Rim vacuoles TF Inclus	Yes	None	None	Yes	Yes	Yes
Allelic disorders	Hereditary IBM	LGMD 2B			Tibial/ Udd	LGMD1A

Channelopathies

Myotonia congenita	AD, AR not weak, Cl- channel
Hyperkalemic periodic paralysis	AD, myotonia, Na+ channel
Hypokalemic periodic paralysis	AD, Ca++ channel
Paramyotonia congenita	AD, Na+ channel, worsened by cold
Malignant Hyperthermia	Ryanodine receptor, Ca++ ch.

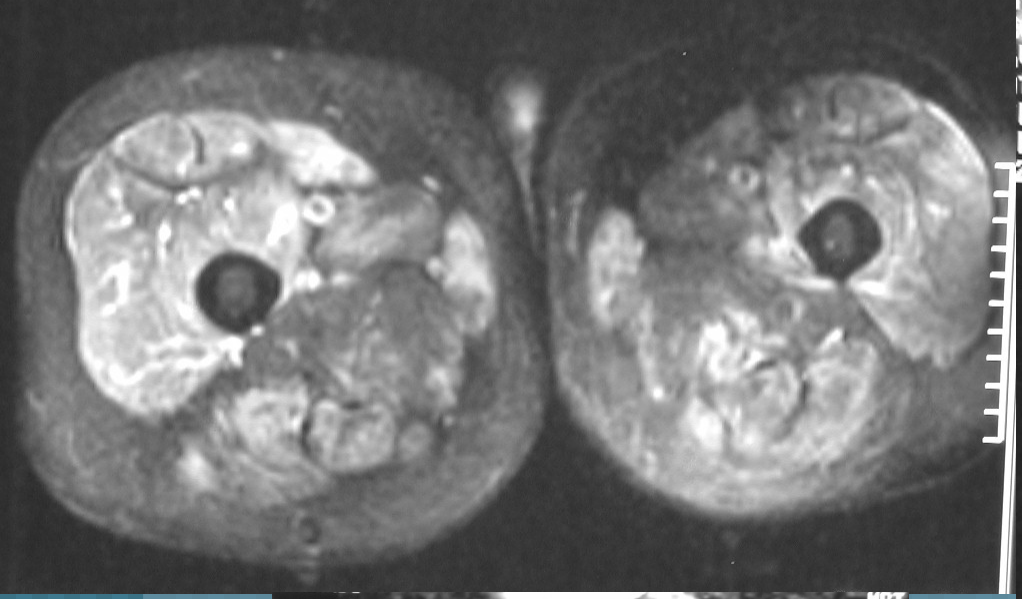
Inflammatory myopathies

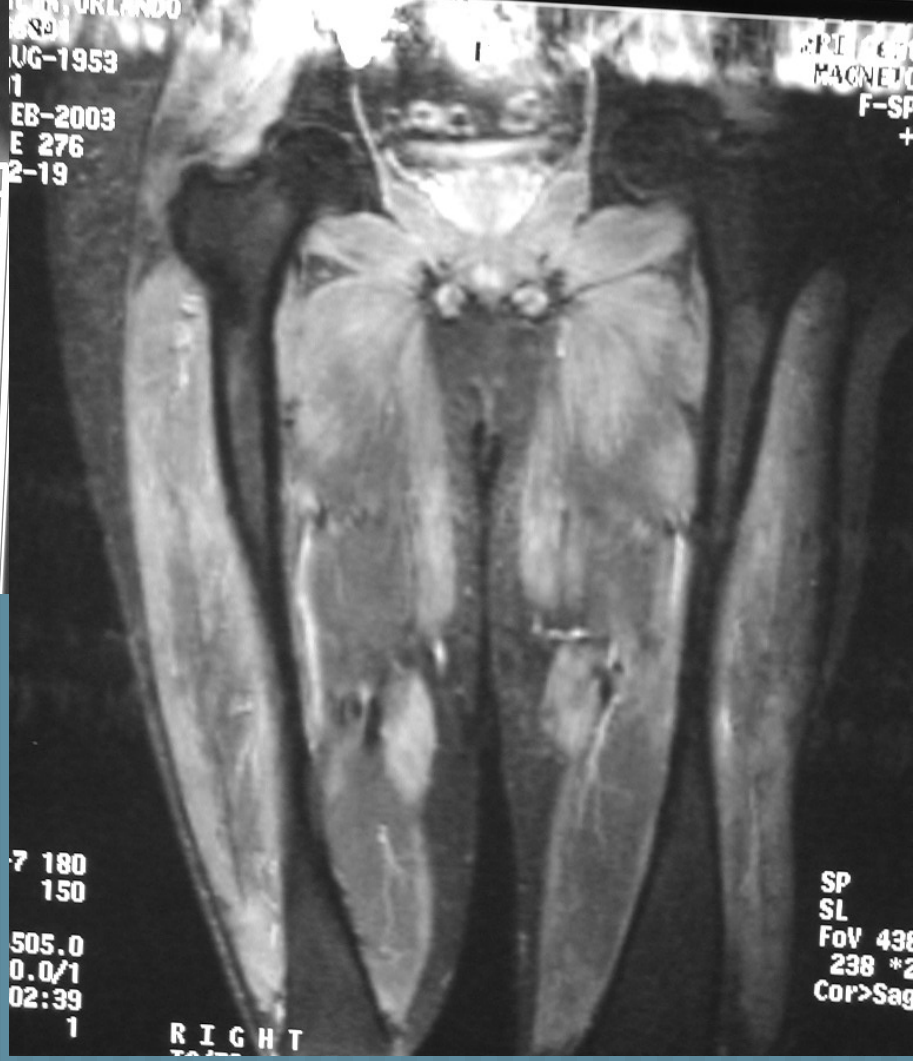
- Polymyositis
- Dermatomyositis
- Immune-mediated necrotizing myopathy (anti SRP, anti HMGCR)
- Inclusion body myositis
- Acute viral myositis
- Parasitic myositis
- Miscellaneous
- Sarcoidosis

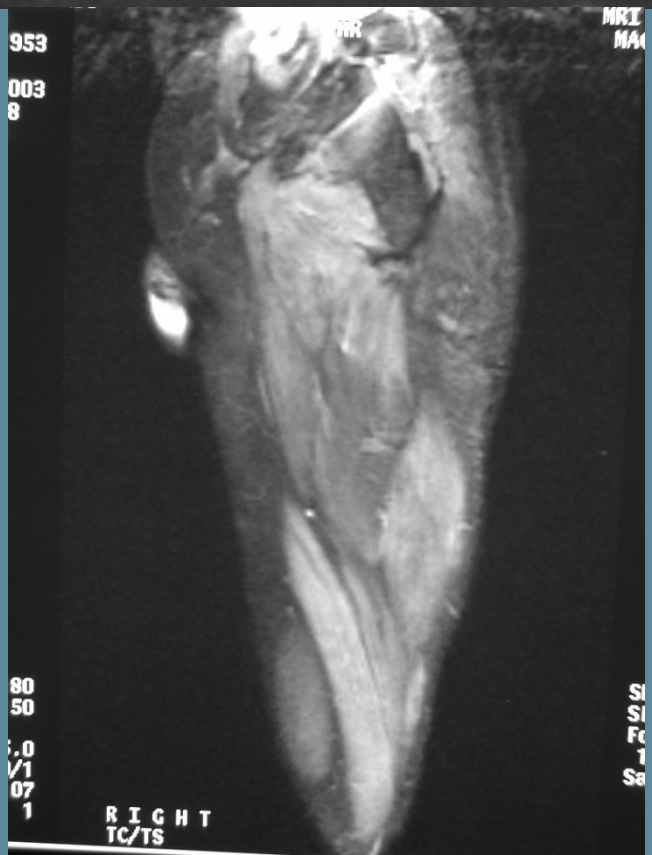
Polymyositis

- Adult onset (> 40), females more common
- Often associated with CTD.
- Proximal weakness, high CK, abnl EMG and inflammation on biopsy
- cytotoxic T-cell attack on muscle fibers
- Steroids: 1-2 mg/kg, 4-6 months

TABLE. CLINICAL ROLE OF ANTIBODIES IN IMMUNE-MEDIATED MYOPATHIES		
Antibodies	**Clinical characteristics and other associated syndromes**	**Treatment response and prognosis**
Dermatomyositis		
Anti-Mi-2	Subacute onset of classic dermatomyositis, typical skin involvement	Good response to corticosteroids, which may be sufficient alone
Anti-MDA5	Severe skin involvement, can present as amyopathic form, rapidly progressive interstitial lung disease (ILD), vasculopathy (digital ulcerations)[3]	Poorest survival of all DM types due to ILD, avoid methotrexate (pulmonary toxicity), annual pulmonary function test (PFT), chest CT if suspicion of ILD
Anti-NXP-2	Mild-to-moderate weakness, classic skin rash, calcinosis, increased malignancy risk	Good response to treatment,[4] monitor for malignancy
Anti-SAE	Mild-to-moderate muscle involvement and typical skin findings	Monitor for malignancy
Anti-TIF1-γ	Severe skin manifestations (hyperkeratotic papules, hypopigmentation, telangiectasia) greatly increased malignancy risk	Monitor for malignancy
Myositis overlap syndromes		
Antisynthetase (Jo-1, PL-7, PL-12)[5]	ILD, nonerosive arthritis, Raynaud's phenomenon, mechanic's hands, fever, occasional rash, no known increased malignancy risk[6]	Often requires 2nd-line agent, avoid methotrexate (pulmonary toxicity); anti-Jo associated with lower likelihood of treatment-free remission; obtain annual PFT, chest CT if clinical suspicion of ILD
Anti-La, PM-Scl, Ro, Ku, U1-RNP	Myositis overlap syndromes; also associated with Sjögren's syndrome, systemic lupus erythematosus (SLE), scleroderma, mixed connective tissue disease (MCTD), rheumatoid arthritis (RA)	Typically responds well to immunotherapy
Immune-mediated necrotizing myopathy		
Anti-SRP	Immune-mediated necrotizing myopathy (IMNM), aggressive disease, severe weakness, pulmonary involvement, dysphagia, axial muscle weakness, more cardiac complication risk with earlier onset, not associated with malignancy[7]	Poor response to corticosteroids, consider 2nd-line agent at presentation; consider rituximab early for those unresponsive to combination of corticosteroids and 2nd-line agents
Anti-HMGCR	IMNM, prior statin exposure (60%), potentially increased malignancy risk, HMGCR-myopathy can mimic limb-girdle muscular dystrophy (LGMD)[8]	Poor response to corticosteroid, consider 2nd-line agent at presentation or in 1st month, consider intravenous immunoglobulin (IVIG) at presentation, add IVIG at 6 months if no response to monotherapy[9]
Inclusion body myositis		
Anti-cN1A	Inclusion body myositis (IBM; 70% of patients); also associated with Sjögren's syndrome or SLE; rarely found in persons with dermatomyositis or polymyositis and healthy people	Positive test result may preclude need for muscle biopsy; no response to current clinically available immunomodulatory treatment



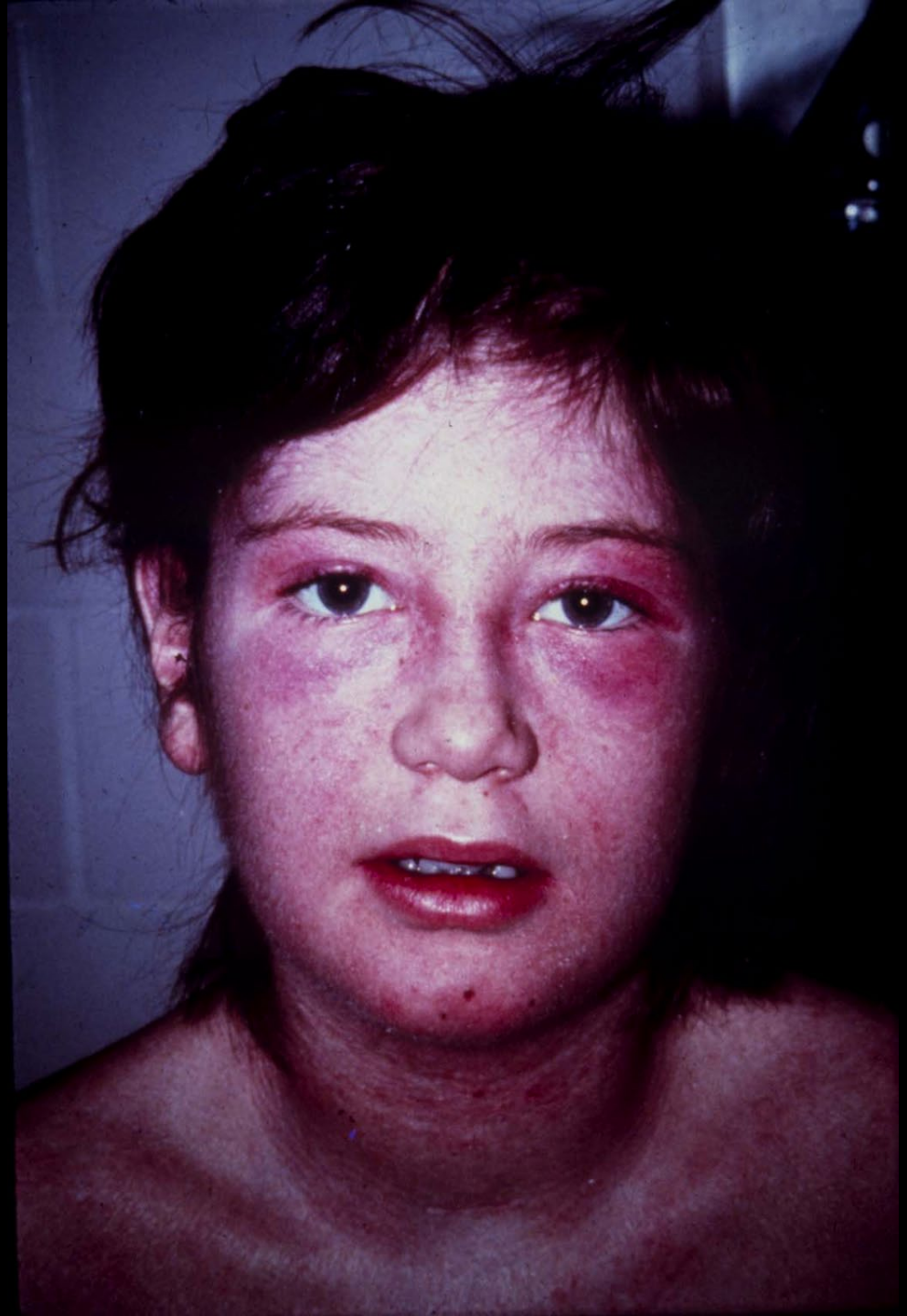




Fat-saturated T2 images

Dermatomyositis

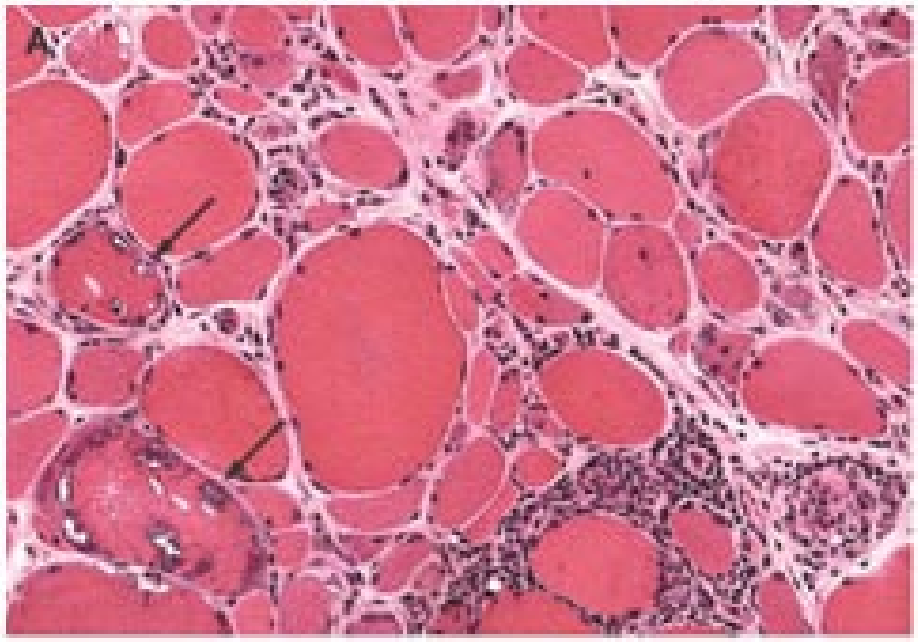
- All ages, female
- Rash but otherwise similar clinical syndrome and testing
- Humoral, antibody attack on capillaries: complement membrane attack complex
- Increased risk of malignancy, adults > 40.
- Steroids: high dose, long time (4-6 months)



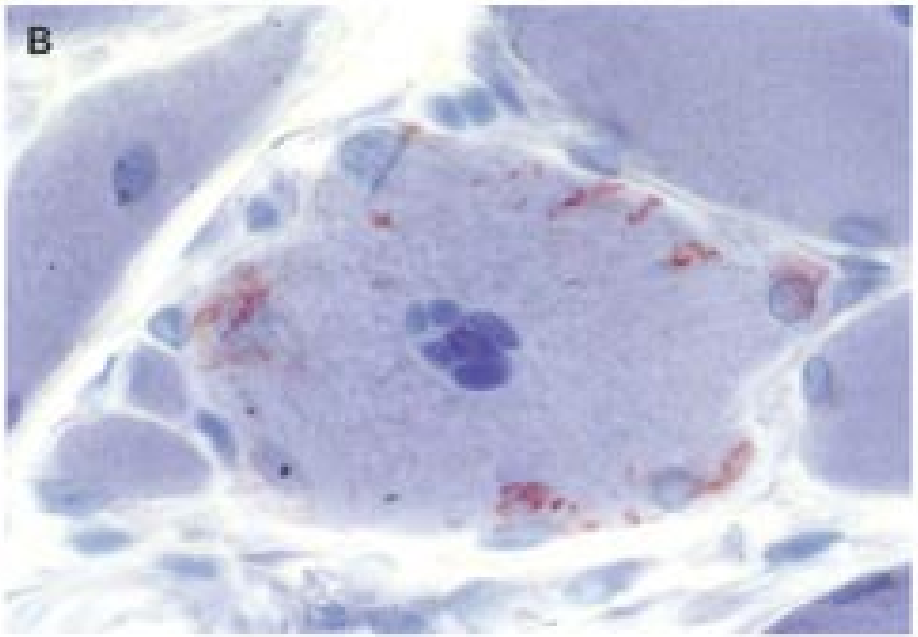
Inclusion Body Myositis

- >50 years of age, male
- Most common myopathy>50 years
- "Alzheimers" disease of muscle
- No association with malignancy or CTD
- Forearm flexors, Quad weakness and atrophy are characteristic
- mild CK rise, abnl EMG, characteristic bx.
- Anti-cytosolic 5'-nucleosidase 1A (cN1A) autoantibodies in 50%
- 15-18 nm filaments in inclusions
- Slow progression.
- No response to treatment

H&E



Crystal violet stain of amyloid



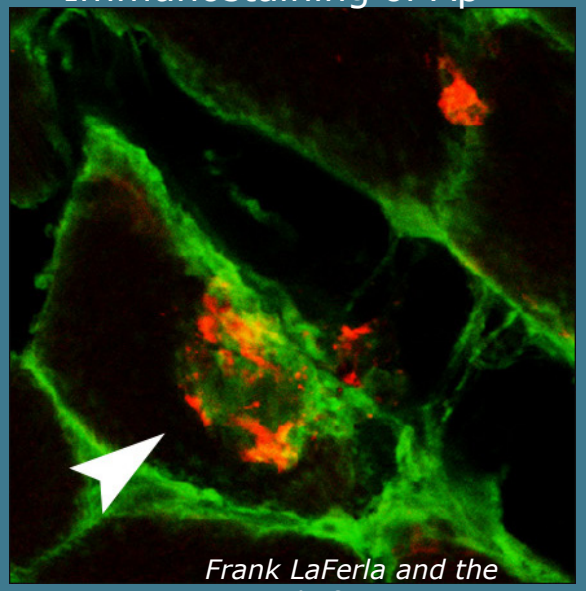
Nature Clinical Practice Neurology (2006) **2**, 437-

Disease	N	Frequency of anti-NT5c1A (%)	Odds ratio	95% confidence interval	*p*-Value*
sIBM	43	21 (48.8)	–	–	–
IIM	142	10 (7.0)	0.08	0.03, 0.19	<0.0001
SLE	199	27 (13.6)	0.16	0.08, 0.34	<0.0001
SSc	50	3 (6.0)	0.07	0.02, 0.25	<0.0001
OA	47	5 (10.6)	0.12	0.04, 0.38	0.0001
NMD	13	2 (15.4)	0.19	0.04, 0.96	0.03
RA	27	0 (0.0)	–	–	<0.0001
SjS	19	0 (0.0)	–	–	0.0002
JDM	40	0 (0.0)	–	–	<0.0001
HC	78	4 (5.1)	0.06	0.02, 0.18	<0.0001

**p-Value for two-sample test of proportions compared against sIBM, p < 0.05 considered to be statistically significant. HC, healthy controls; IIM, inflammatory immune myopathies; JDM, juvenile dermatomyositis; NMD, neuromuscular/metabolic disorders; OA, osteoarthritis; RA, rheumatoid arthritis; sIBM, sporadic inclusion body myositis; SjS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.*

Amlani et, Front Immuno 2019

Immunostaining of Aβ



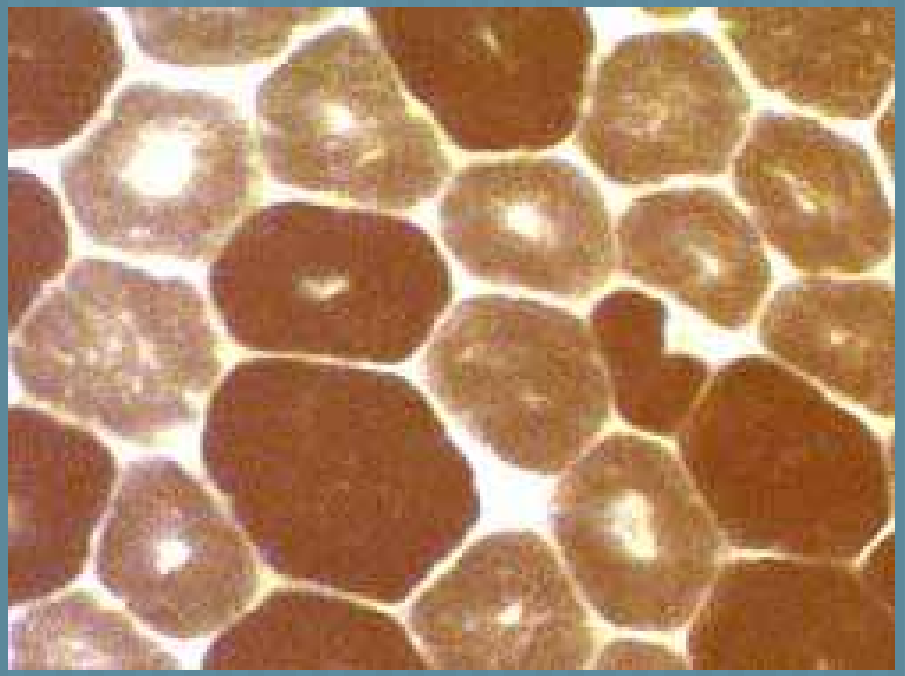
Frank LaFerla and the Journal of Neuroscience

Congenital myopathies

- Often hereditary
- Often relatively benign, with stable weakness, hypotonia
- Infantile = severe; childhood = moderate; adult = mild course
- Thought secondary to one-time disruption of muscle development

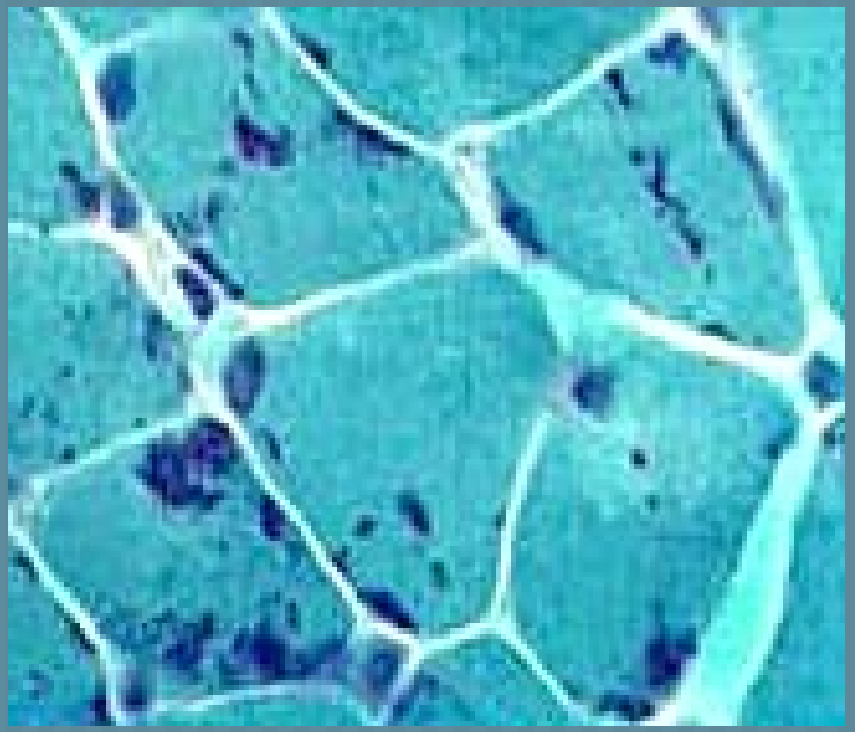
Central core disease

- AD: 19q
- Associated with malignant hyperthermia
- Somatic defects



Nemaline myopathy

- AD or AR
- Severe in infants, uncommon and variable in adults
- Adults associated with respiratory weakness



Endocrine myopathies

- Thyroid: hypo-and hyper-thyroid
- Adrenal: steroid myopathy, adrenal insufficiency
- Parathyroid: hyper- and hypo-parathyroid
- Acromegaly

Inborn errors of muscle metabolism

- Glycogen storage disease
- Carnitine Palmitoyltransferase deficiency
- Lipid myopathy
- Malignant hyperthermia
- Myoadenylate deaminase deficiency
- Myoglobinuria

Pompe Disease
(nee acid maltase deficiency; GSD type II)

- Deficiency of acid α-glucosidase (GAA)
- First described in 1932: 7 month old girl died of cardiomyopathy
- 1960's, 70's: milder, later onset phenotypes described
- 1:138,000 has infantile-onset form
- 1:57,000 has late-onset form
- Both types are fatal, with late onset usually from respiratory failure
- GAA enzyme analysis by dried blood spot
- Confirmed by blood or tissue analysis, or GAA gene sequencing

Pompe Disease characteristics

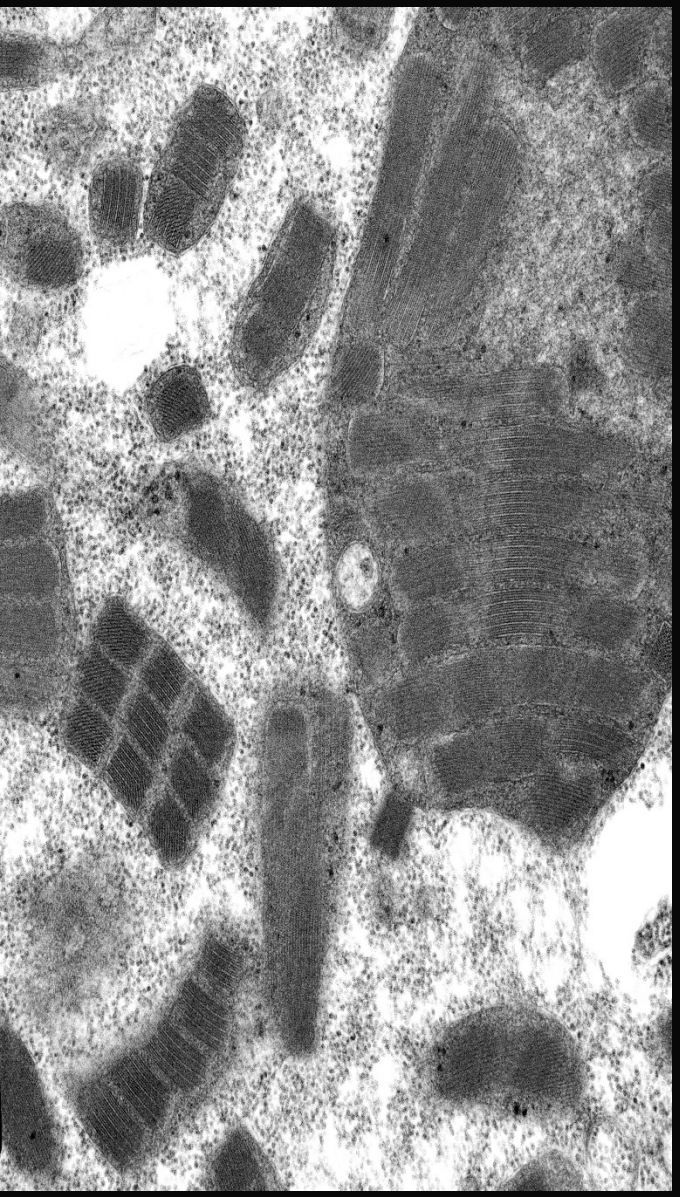
- Multi systemic, particularly infantile form:
  - Hepatomegaly, splenomegaly, cardiomyopathy, tongue hypertrophy
- Late onset form:
  - Slowly progressive proximal weakness
  - Electrical myotonia
  - Early diaphragmatic involvement
  - Prominent axial muscle weakness
  - Myotonia on EMG

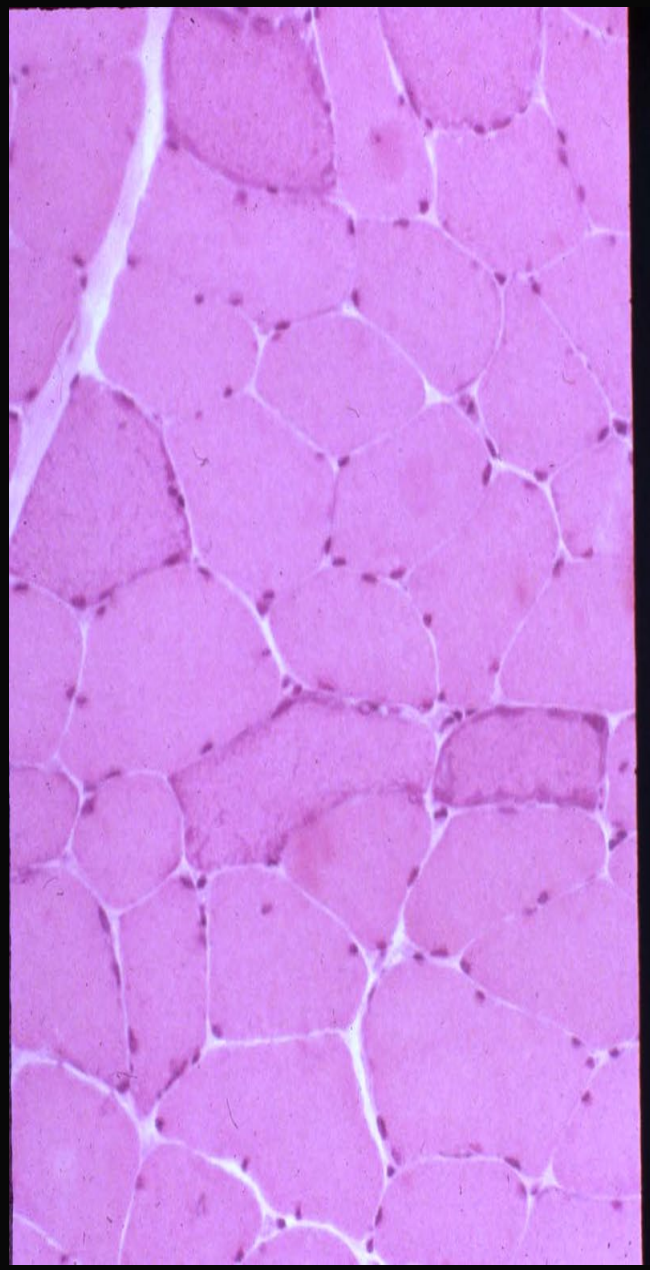
Pompe Disease
Enzyme Replacement Therapy

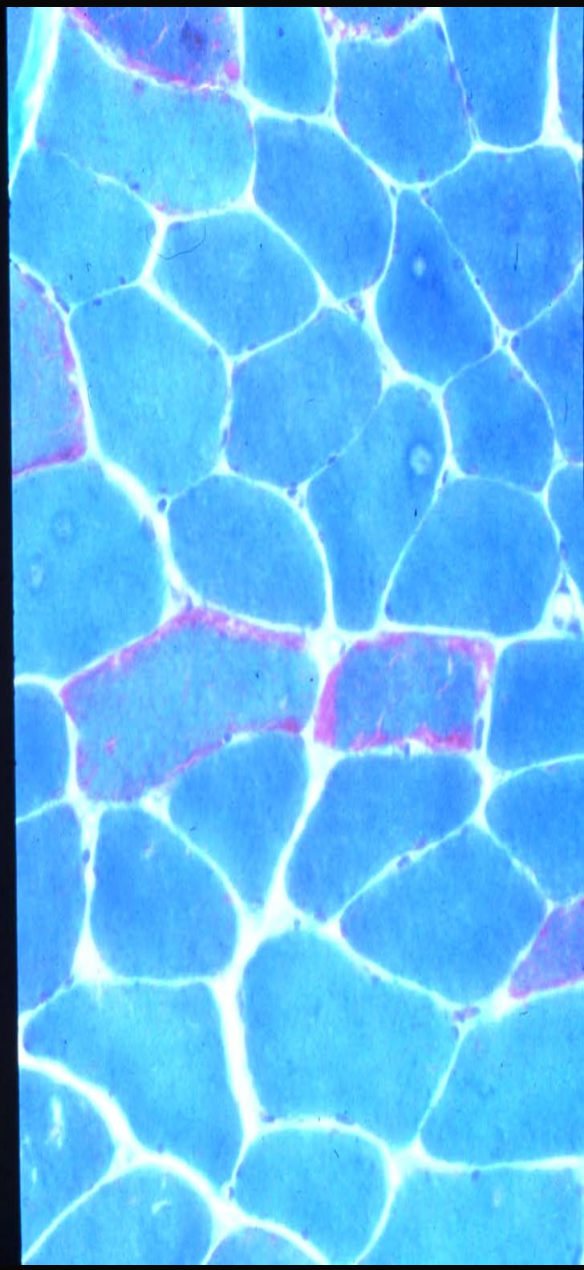
- Recombinant human acid α-glucosidase (rhGAA)
  - IV infusions 20-40 mg/kg each or every other week
  - Myozyme approved for infantile onset 2006
  - Lumizyme approved for late onset 2010
- Infantile onset treatment
  - Risk of death reduced 99% in infants
  - 13/18 had motor/functional gains; 7/18 walking
- Late onset treatment
  - 90 patients-6 min walk test increased 28 m, FVC increased 3.4%
  - Anaphylactic, allergic reactions in 5-8% (IgE ab to GAA)

Mitochondrial encephalomyopathies

- 15% of mitochondrial proteins encoded by mitochondrial genome
- Deletions, mutations result in defective respiratory chain
- Mitochondrial inheritance
- MELAS, MEERF, Kearns-Sayre, NARP, CPEO are common syndromes







Toxic

- Ethanol
- CLAM
- Chloroquine
- Colchicine
- Zidovudine
- L-tryptophan
- Propofol
- Corticosteroids
- Immune Checkpoint Inhibitors

Ethanol myopathy

- Acute necrotizing myopathy: high CPK, heavy alcoholic (binging) or withdrawal, weeks to months to recovery
- Chronic myopathy: muscle atrophy, proximal weakness
- Cardiomyopathy: 40% mortality, chronic alcoholics

Cholesterol lowering agent myopathy (CLAM)

- Fibrates (gemfibrizol, clofibrate)
- HMG CoA reductase inhibitors (statins)
- Myalgias common, CK often normal, biopsy-few necrotic fibers. Recovery days to months
- Myopathy-1 in 10,000.
- Rhabdomyolysis onset weeks to months; rapid improvement after drug stopped
- Predisposing:higher dose, liver, renal disease, niacin, gemfibrizol, cyclosporine

Statin-associated myopathy: a spectrum

- mild persistent CK ↑ w/o symptoms (≈ 1%)
- myalgia with and without ↑ CK (9-20%)
- persistent myalgias and ↑ CK after statin withdrawal
- myopathy (CLAM; SAM)can progress to rhabdomyolysis (0.4 per 100,000)
- Persistent, necrotizing myopathy can be associated with anti-HMGCR ab