Myopathies and Muscular Dystrophies

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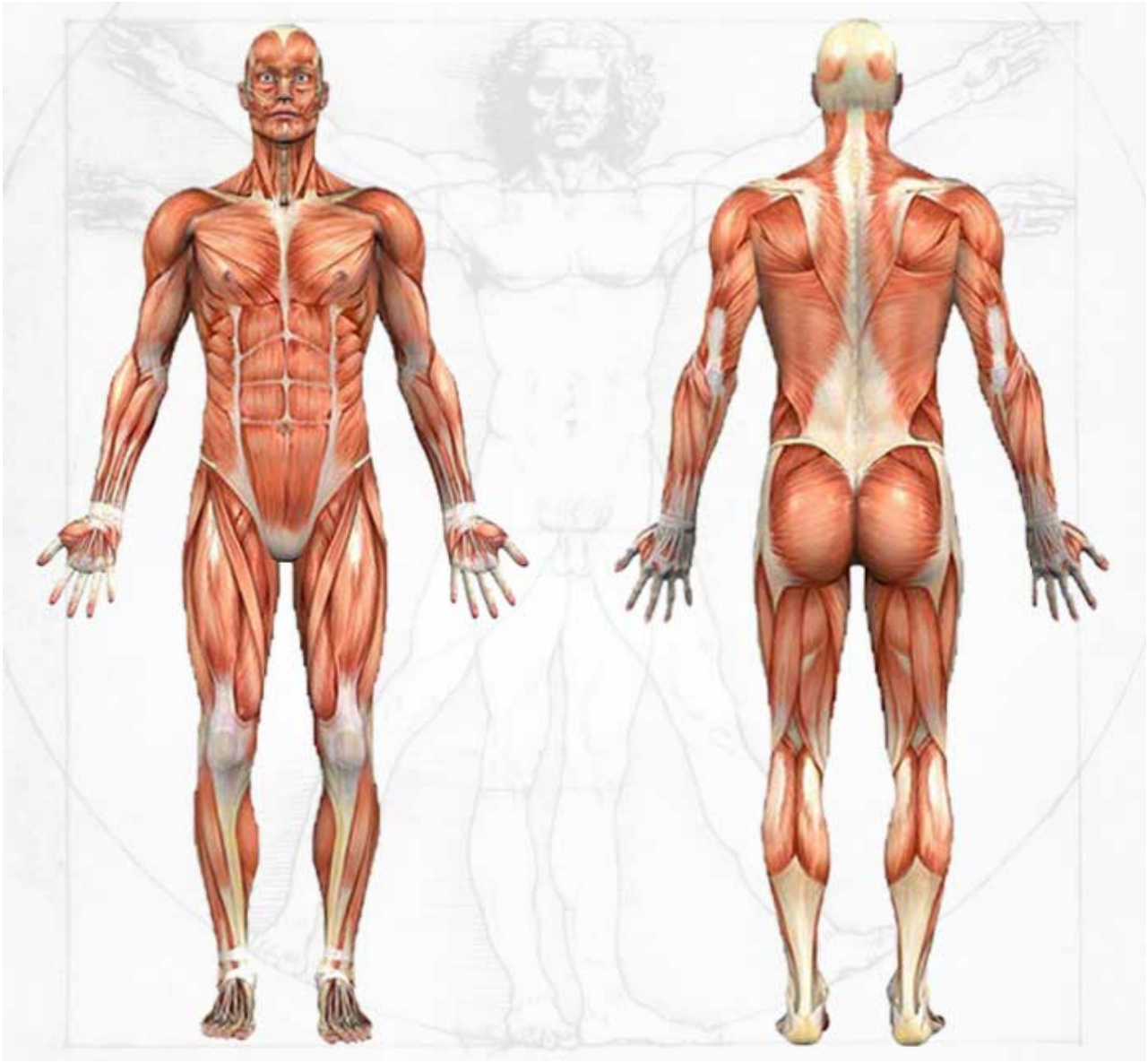
@DEVINPHYSIQUE

Skeletal Muscle

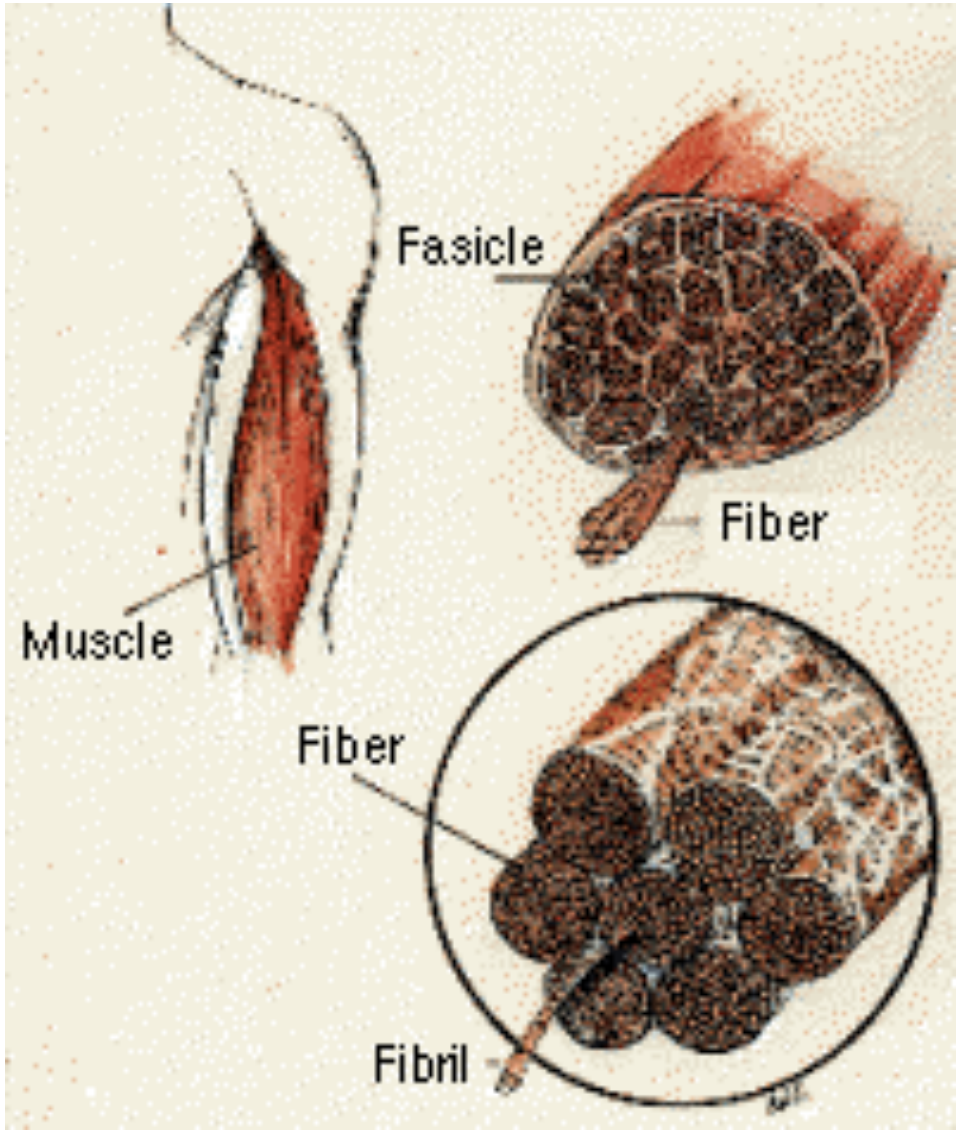
- Three types of muscle:
  - Skeletal
  - Cardiac
  - Smooth

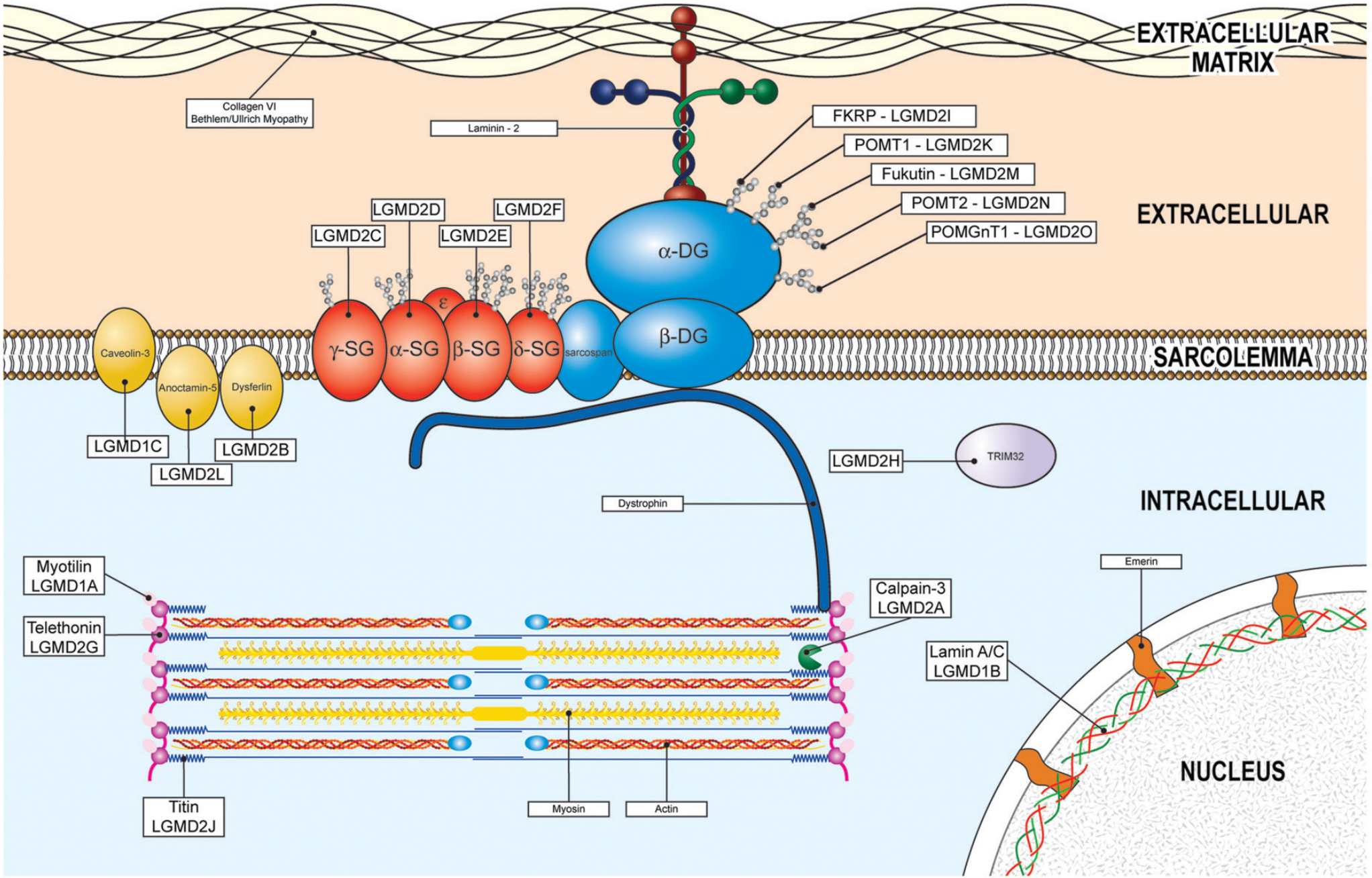
- Over 640 skeletal muscles in the human body



Anatomy of Skeletal Muscle

- Muscles
  - composed of
- Fascicles
  - which contain many
- Fibers
  - that are filled with
- Myofibrils
  - the contractile component of muscles

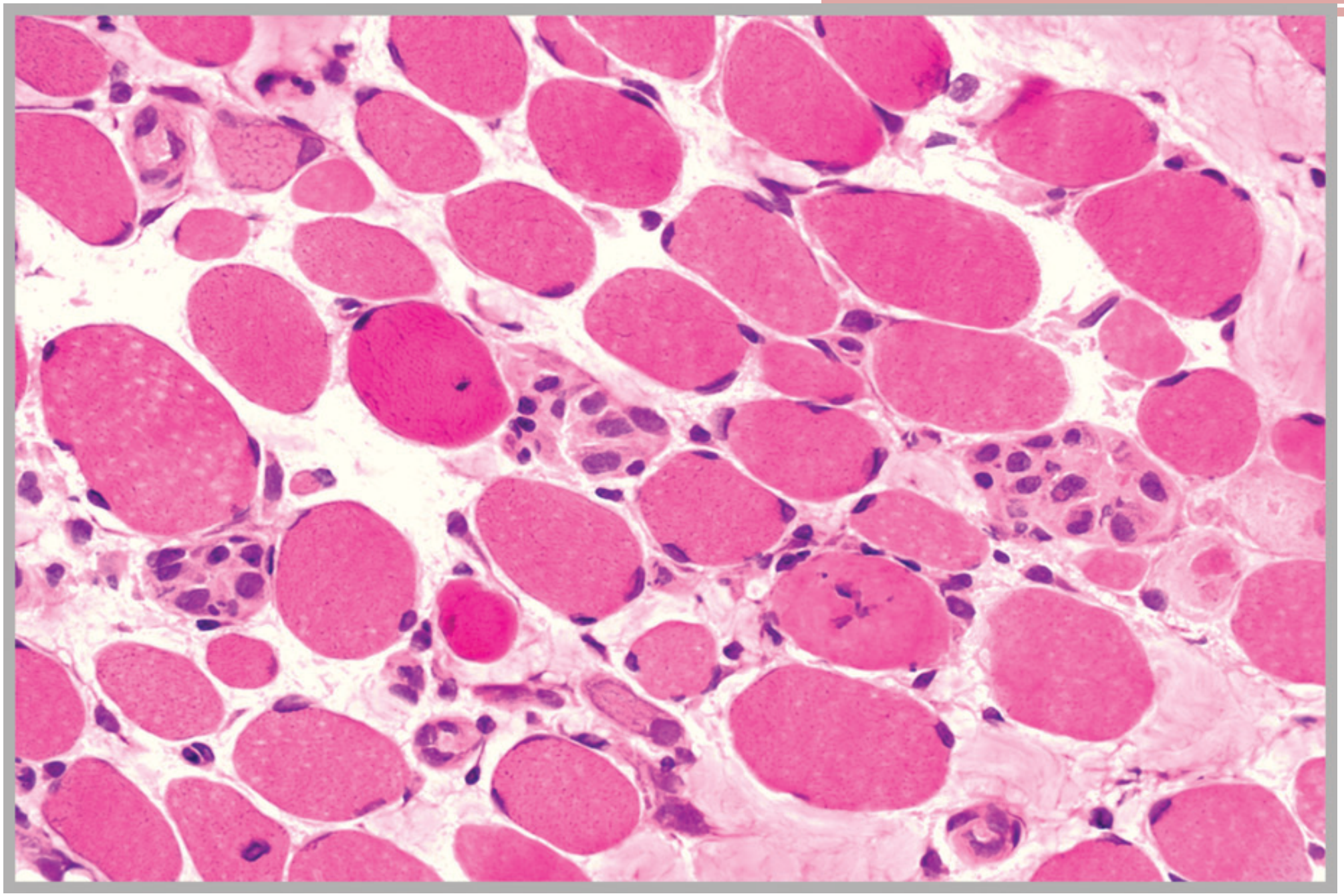



EXTRACELLULAR MATRIX
Collagen VI
Bethlem/Ullrich Myopathy
Laminin - 2
FKRP - LGMD2I
POMT1 - LGMD2K
Fukutin - LGMD2M
POMT2 - LGMD2N
POMGnT1 - LGMD2O
EXTRACELLULAR
LGMD2D
LGMD2F
LGMD2C
LGMD2E
α-DG
β-DG
γ-SG
α-SG
β-SG
δ-SG
ε
sarcospan
Caveolin-3
Anoctamin-5
Dysferlin
SARCOLEMMA
LGMD1C
LGMD2L
LGMD2B
LGMD2H
TRIM32
Dystrophin
INTRACELLULAR
Myotilin
LGMD1A
Telethonin
LGMD2G
Calpain-3
LGMD2A
Emerin
Lamin A/C
LGMD1B
Titin
LGMD2J
Myosin
Actin
NUCLEUS

Nomenclature

Definition

- Muscular dystrophies are genetic, progressive, degenerative disorders of muscle
  - Muscle weakness is the primary symptom
  - Clinical and histologic criteria have been used in the past for classification

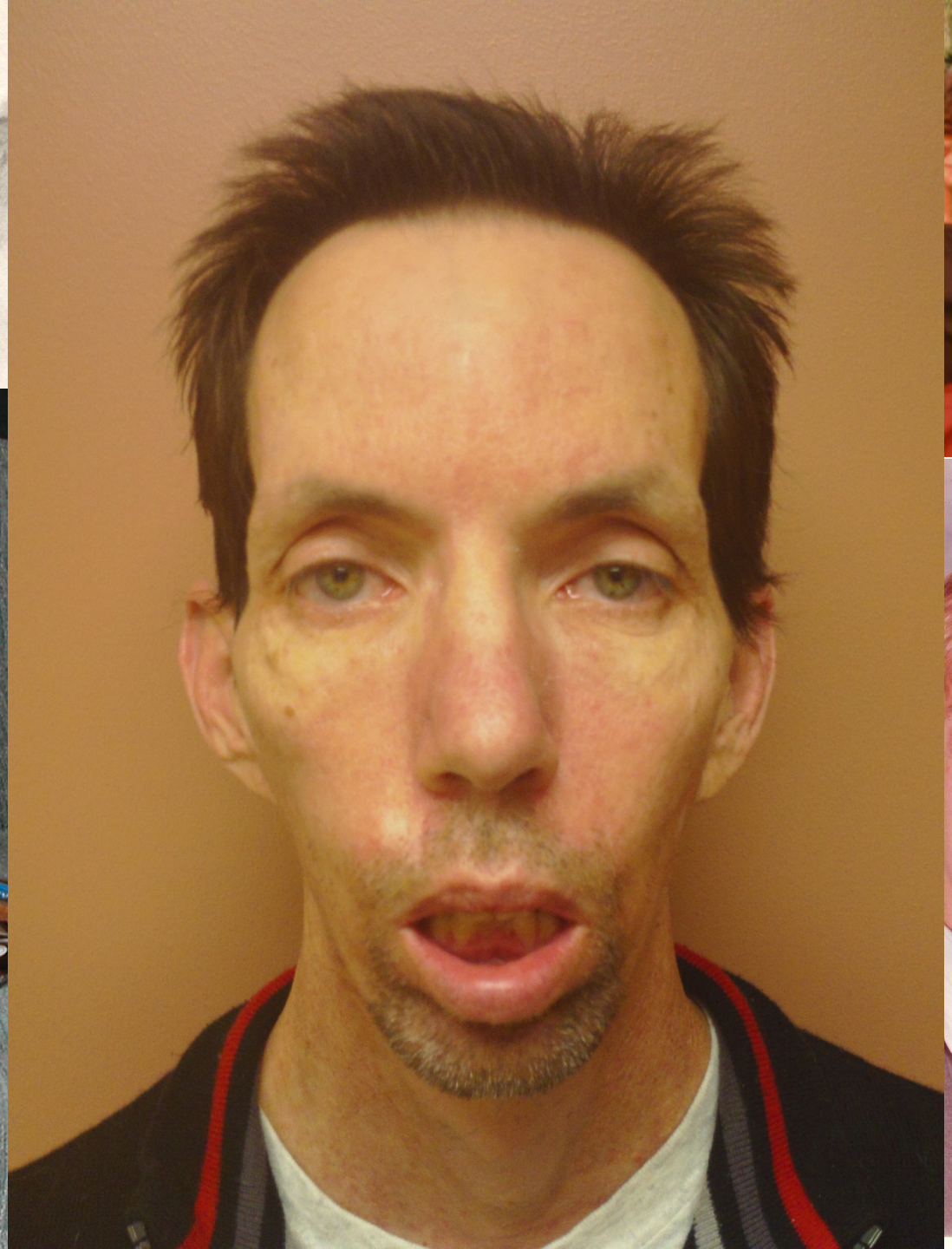


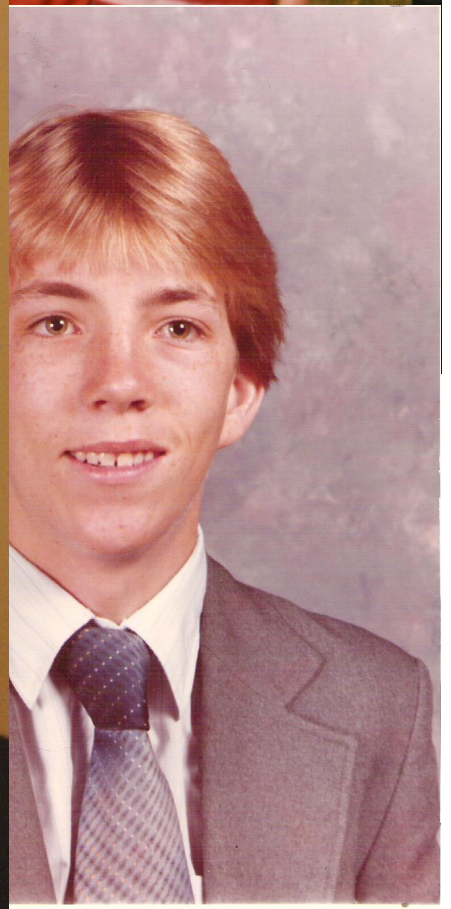
Definition

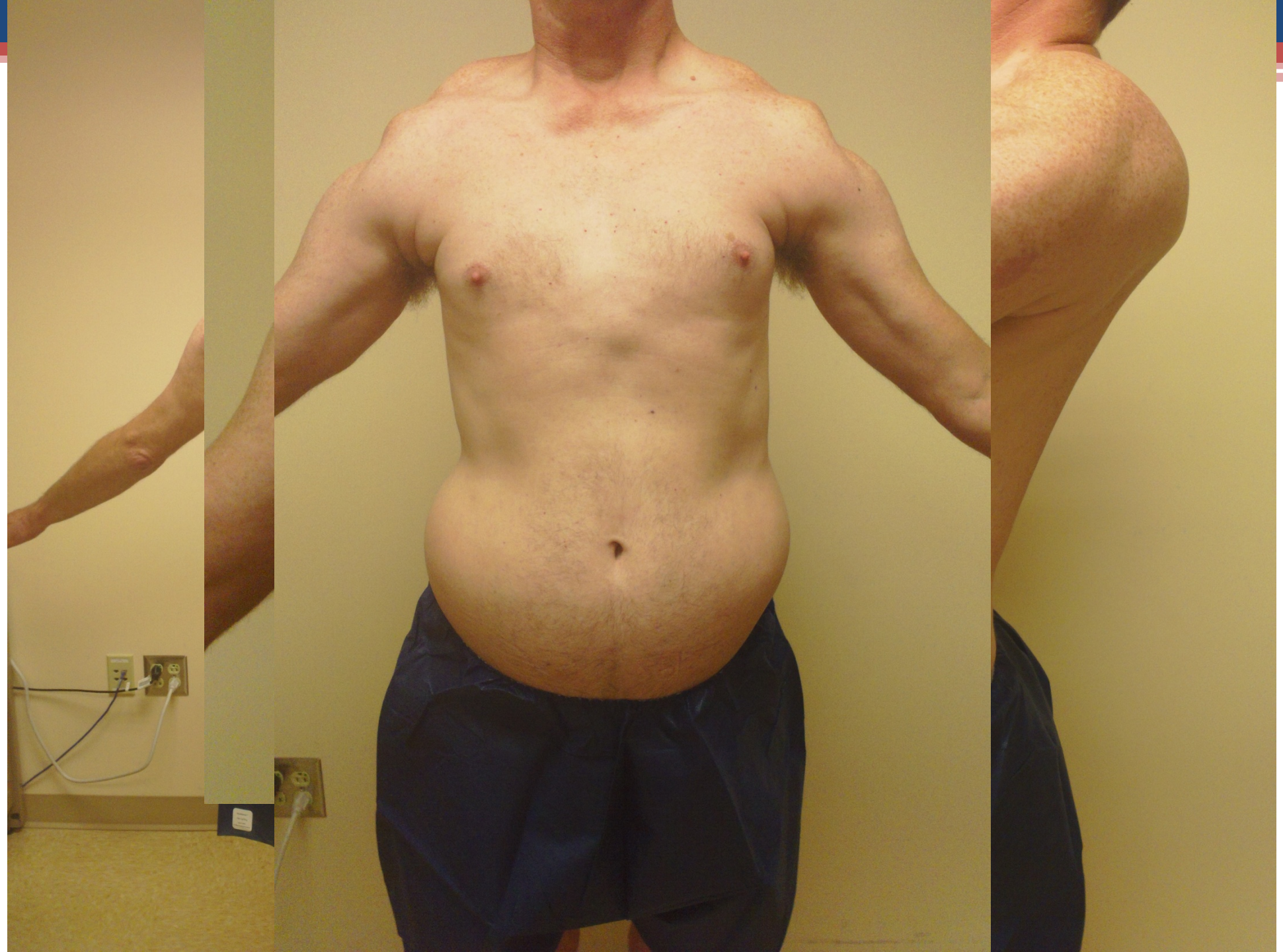
- Now muscular dystrophies are mostly classified on a genetic basis
- Thus, we often refer to them by the broader moniker of:
  - **Genetic muscle diseases**

Why Should We Care?

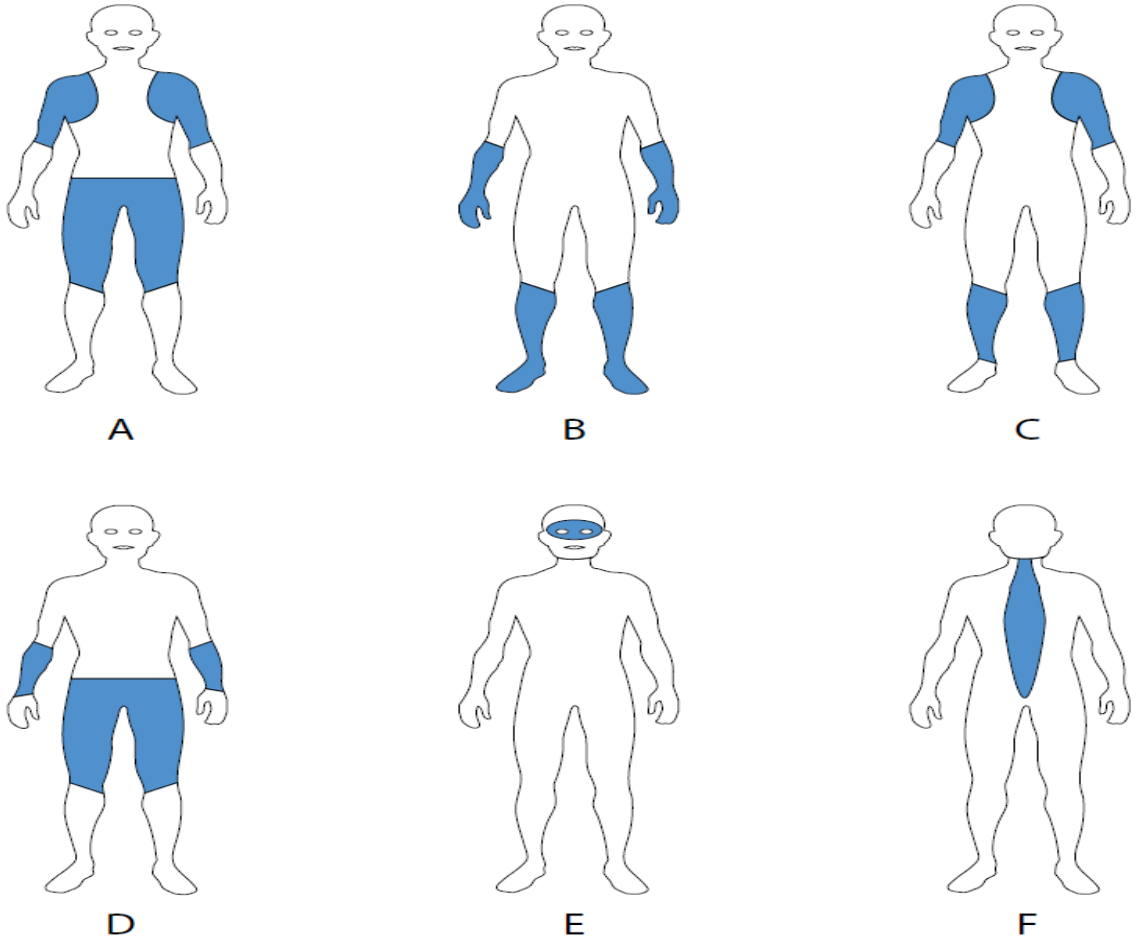
- 200+ genetic muscle diseases
- Overall minimum prevalence of symptomatic disease ~1 in 1,000 (100/100,000)
  - Similar to multiple sclerosis
  - Dystrophinopathies – 23/100,000
  - Myotonic dystrophies 1 & 2 – 14/100,000
  - FSHD – 18/100,000
  - LGMD – 7/100,000
  - All others - ~30/100,000







Pattern of Muscle Involvement Varies



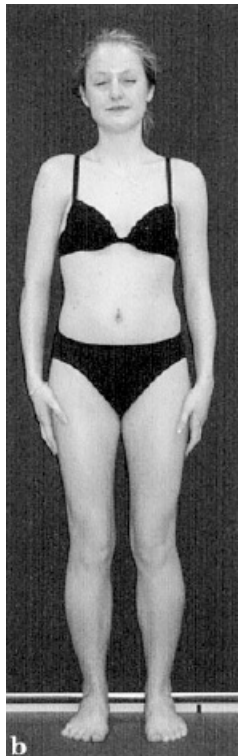
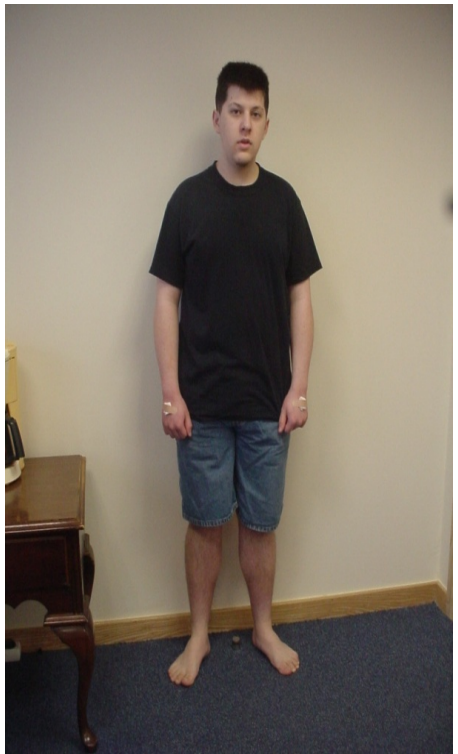
Limb Girdle Muscular Dystrophies

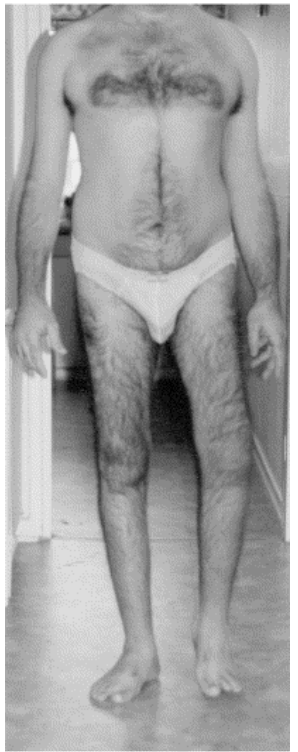
Limb Girdle Weakness

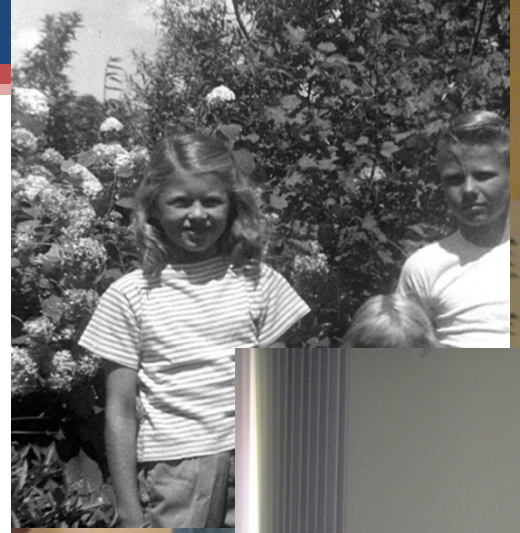
- “Post-natal onset of progressive weakness and muscle atrophy affecting proximal muscles of the upper and lower extremities”

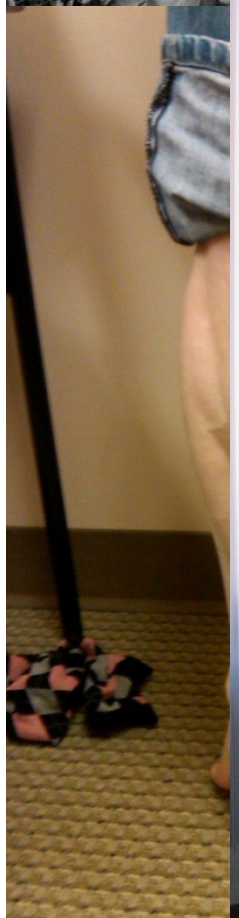
Limb Girdle Weakness

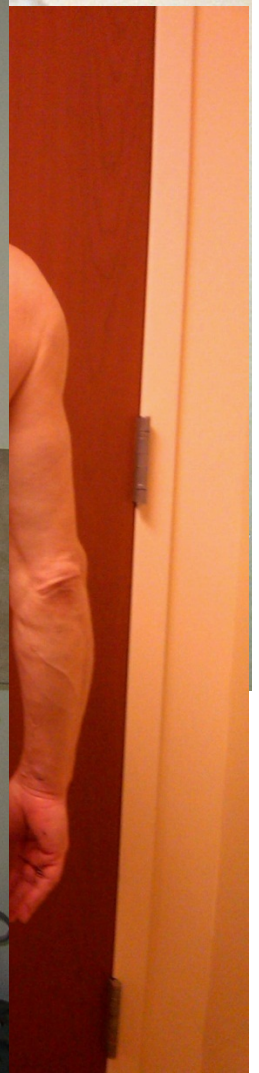
- >50 autosomal recessive LGMDs
- >10 autosomal dominant LGMDs



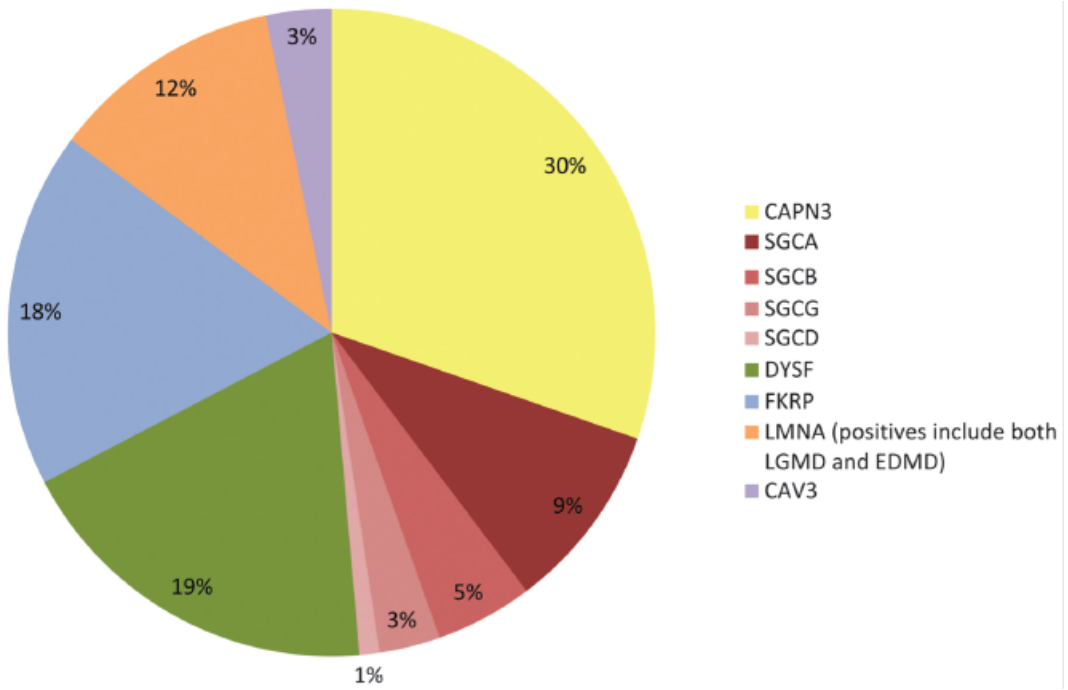




LGMD
Relative Prevalence in USA

- Calpain-3 = 15%
- Dysferlin = 10%
- Sarcoglycans = 10%
- FKRP = 10%
- Anoctamin-5 = 10%
- Lamin A/C = 5%
- *All others 40%*
  - Extracellular matrix-related proteins
  - Pompe disease
  - *VCP*
  - ***RYR1*-related myopathies**



RYR1

Not uncommon among LGMD patients

Table 1 LGMD genes[22]

Disease	Locus	Gene	No. of patients
LGMD1B	1q22	*LMNA*	3
LGMD1C	3p25.3	*CAV3*	2
LGMD2A	15q15	*CAPN3*	22
LGMD2B	2p13.2	*DYSF*	15
LGMD2C	13q12	*SGCG*	4
LGMD2D	17q21	*SGCA*	10
LGMD2E	4q12	*SGCB*	6
LGMD2G	17q12	*TCAP*	1
LGMD2H	9q33.1	*TRIM32*	1
LGMD2I	19q13.3	*FKRP*	7
LGMD2J	2q24.3	*TTN*	5
LGMD2K	9q34.1	*POMT1*	1
LGMD2L	11p13	*ANO5*	15
LGMD2M	9q31	*FKTN*	2
LGMD2N	14q24	*POMT2*	6
LGMD2R	2q35	*DES*	1
LGMD2S	4q35.1	*TRAPPC11*	2
LGMD2T	3p21	*GMPPB*	2
LGMD2V	17q25	*GAA*	10

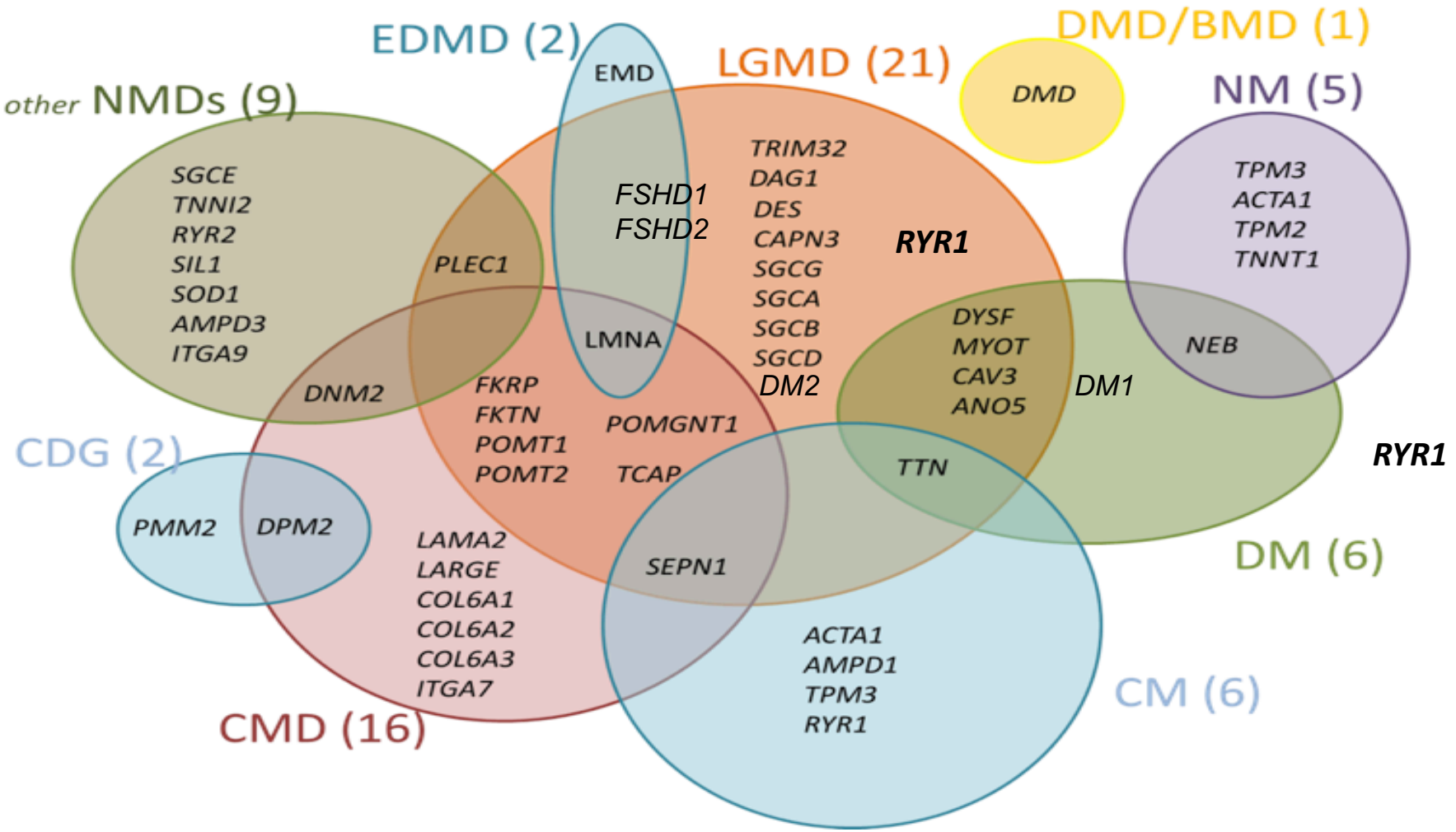
22

Table 2 Other myopathy genes

Locus	Gene	No. of patients
1q42.13	*ACTA1*	2
1p21	*AGL*	2
21q22.3	*COL6A2*	4
2q37	*COL6A3*	1
11q22.3–q23.1	*CRYAB*	1
Xp21.2	*DMD*	7
19p13.2	*DNM2*	5
Xq28	*EMD*	1
7q32	*FLNC*	4
17q25.2–q25.3	*GLA*	1
9p12	*GNE*	3
3p22.1	*GTDC2*	1
3q24	*GYG1*	1
12q13.2	*ITGA7*	2
6q22–q23	*LAMA2*	8
Xq28	*MTM1*	5
17p13.1	*MYH2*	1
14q12	*MYH7*	8
5q31	*MYOT*	1
2q23.3	*NEB*	9
11q12–q13.2	*PYGM*	3
19q13	*RYR1*	25

25

LGMD and Other Muscular Dystrophies



Multiple, overlapping phenotypes associated with numerous gene loci

Nomenclature (again)

Phenotype? Pathology? Genotype?

- Phenotype – what does the patient look like?
  - Malignant hyperthermia or LGMD or exercise-induced rhabdomyolysis
- Histologic features – what does the muscle biopsy look like?
  - Central core disease or multi-minicore disease or centronuclear myopathy
- Genetic – what protein or gene needs fixing???
  - Ryanodine receptor related myopathy
  - *RYR1*-associated muscle disease

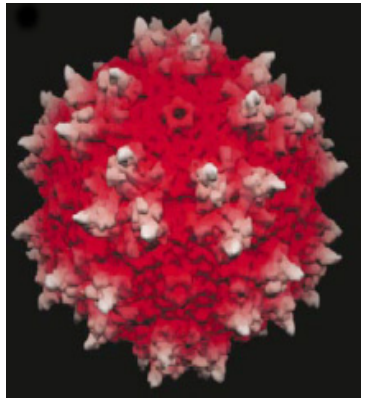
TREATMENT

=> Transition to Genetic Therapies

Successes in Genetic Therapies

- AON in DMD
- **Viral vector gene therapy (DMD, LGMD 2B, 2C, 2D, 2E, 2L)**
- Dual cassette viral vector mini-dystrophin
- Microdystrophin
  - In the GRMD model

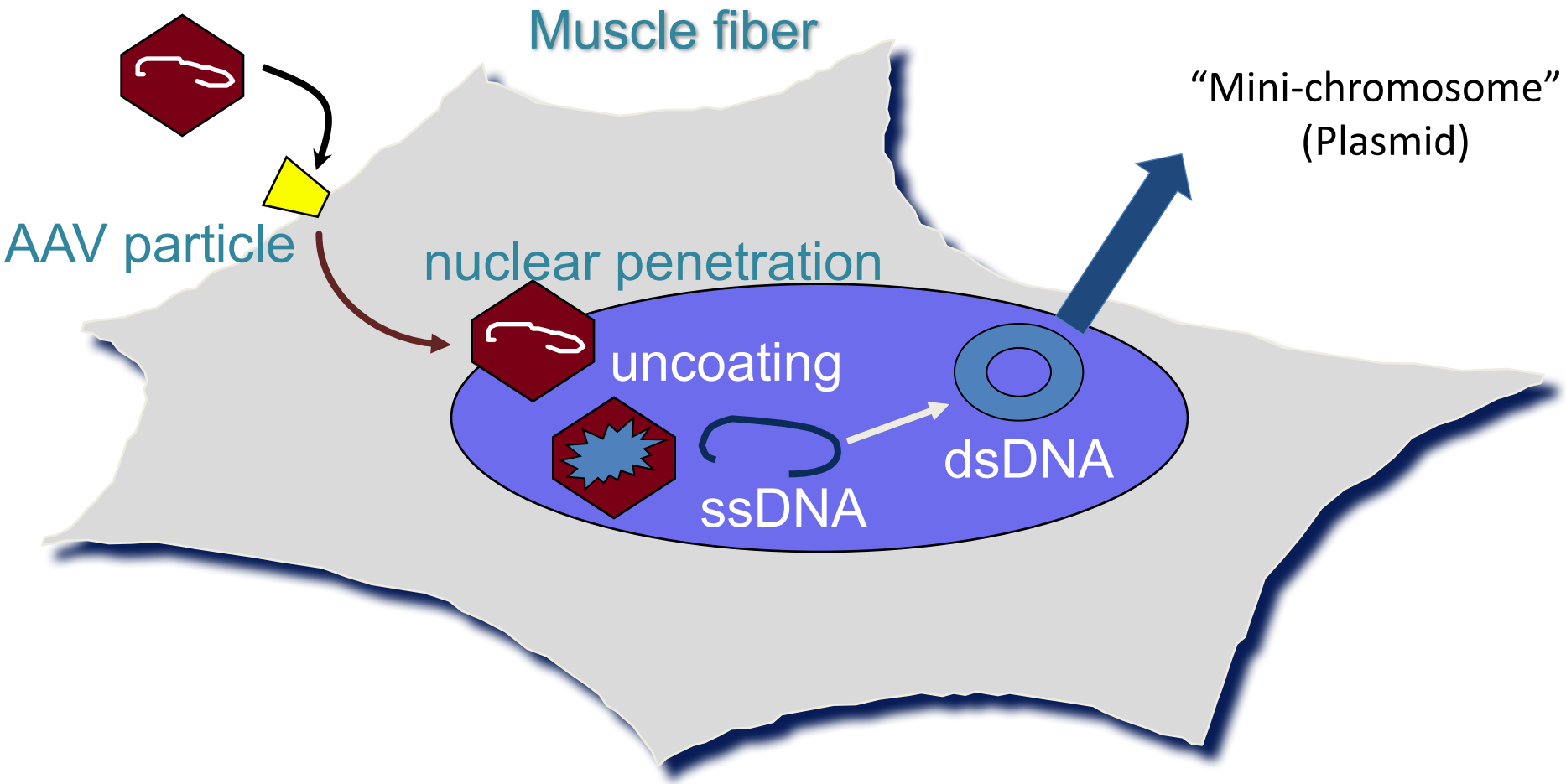
Adeno-Associated Virus (AAV)



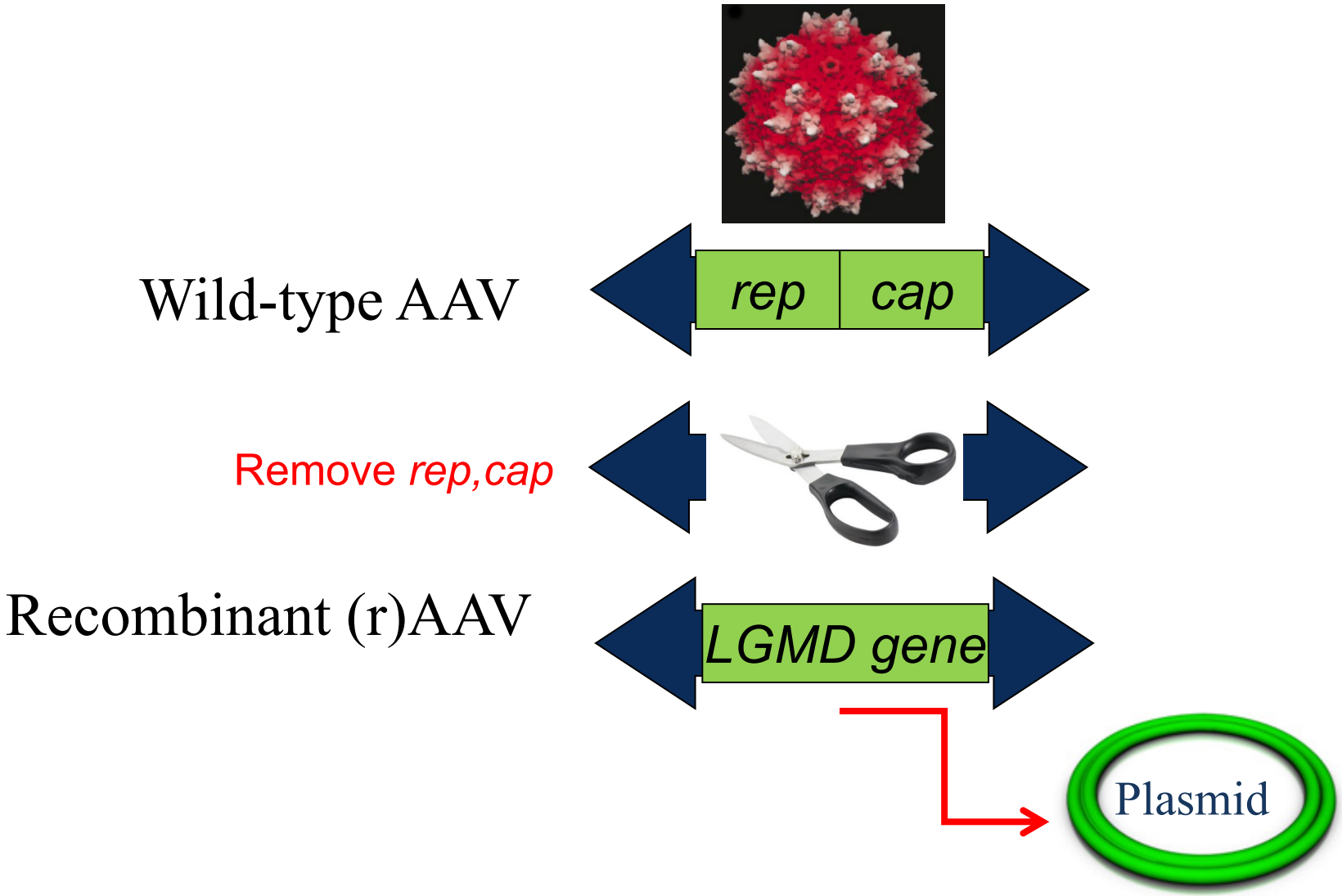
- Non-pathogenic
  - Invades cells, but no disease

- Of over 100 AAV serotypes
  - Only ~6 widely used (AAV1, AAV5, AAV6, AAV8, AAV9, **AAVrh74**)

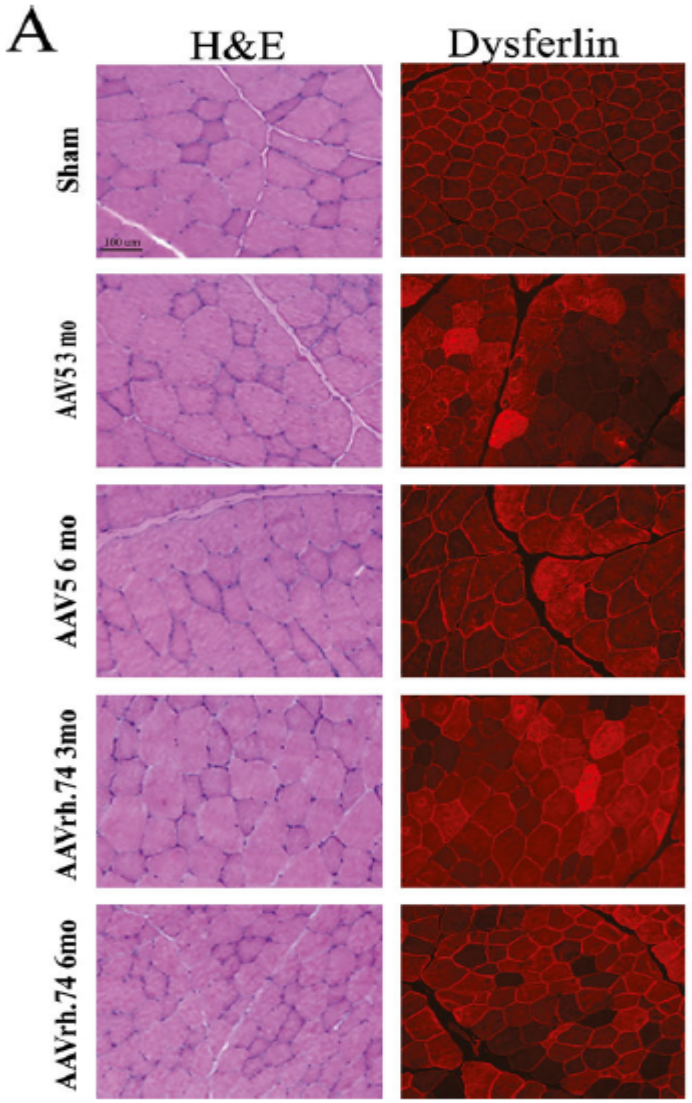
Adeno-associated Virus (AAV) is a Delivery Vehicle



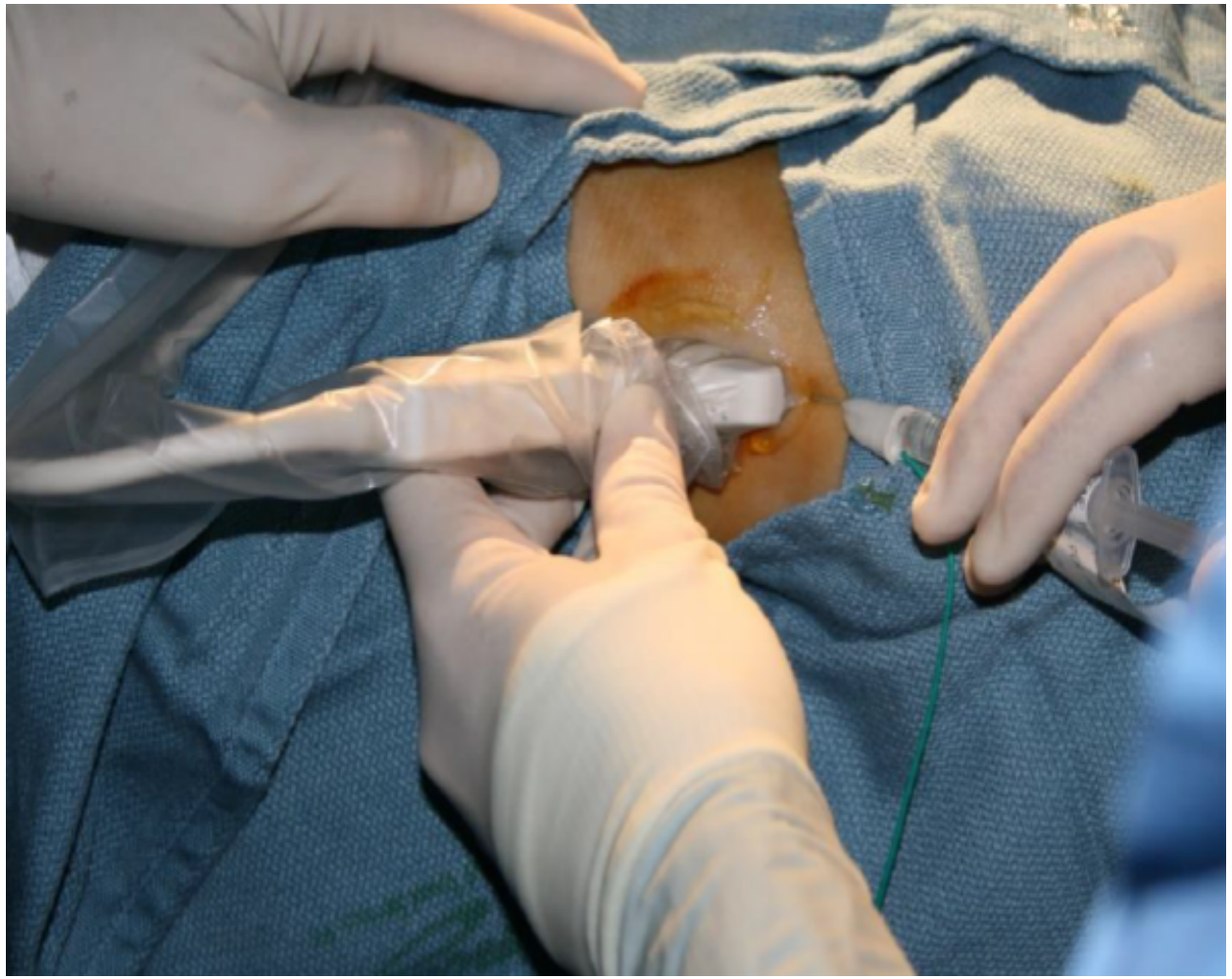
Viral Genes are Removed From AAV

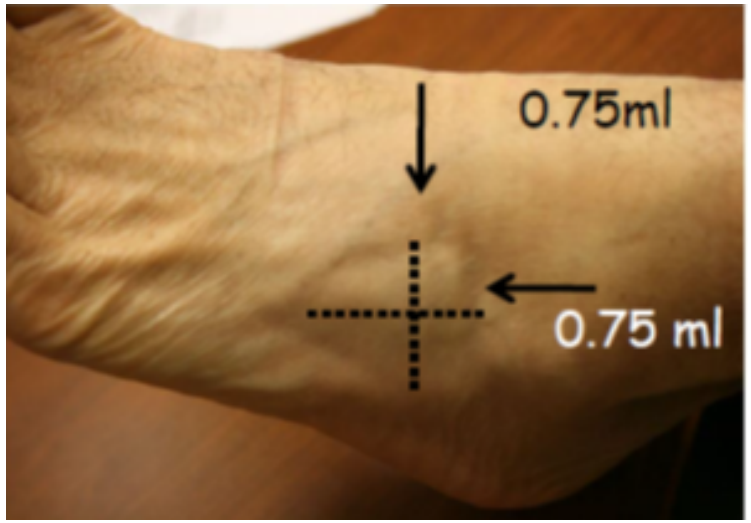


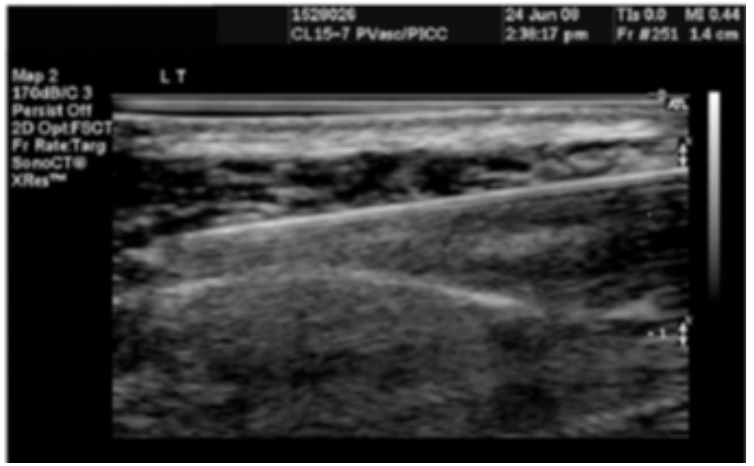
Non-Human Primate - Intramuscular



Sondergaard, P. C., Griffin, D. A., Pozsgai, E. R., Johnson, R. W., Grose, W. E., Heller, K. N., ... & Sahenk, Z. (2015). AAV. Dysferlin overlap vectors restore function in dysferlinopathy animal models. Annals of clinical and translational neurology, 2(3), 256-270.







Dose escalation in 6 non-ambulatory LGMD2B patients

Mendell, J. (2008). Gene Therapy for Muscular Dystrophy, A Decade of Research and Challenges.

LGMD2E Gene Therapy- Gene Replacement for Beta Sarcoglycan

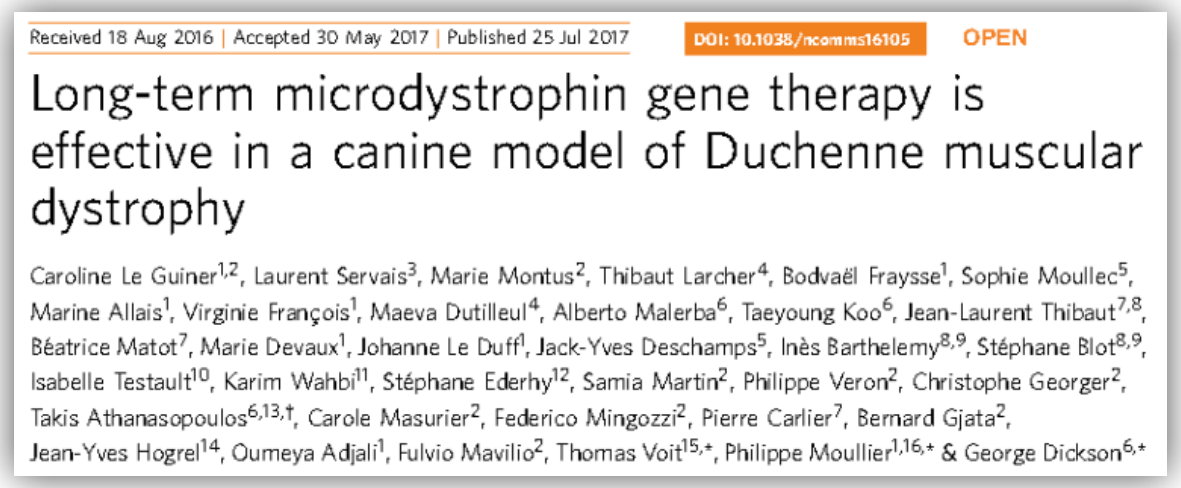
Human Phase 2 Systemic Therapy Trial Underway

=> 2 subjects dosed

83-98% transfection rates

Successes in Genetic Therapies

- AON in DMD
- Viral vector gene therapy (DMD, LGMD 2B, 2C, 2D, 2E, 2F)
- Dual cassette viral vector mini-dystrophin
- Microdystrophin
  - In the GRMD model



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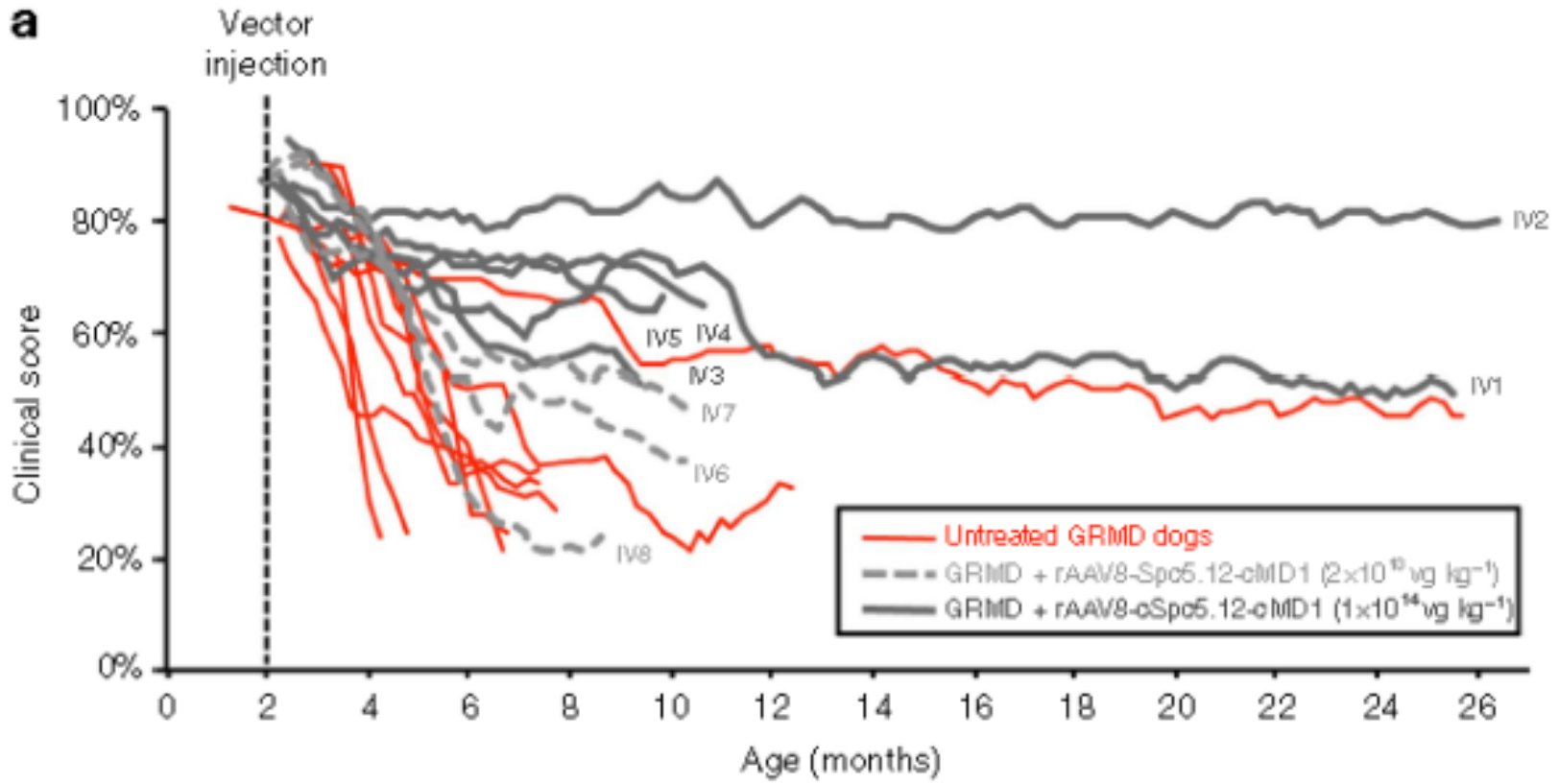
Long-term microdystrophin gene therapy is effective in a canine model of Duchenne muscular dystrophy

Caroline Le Guiner[1,2], Laurent Servais[3], Marie Montus[2], Thibaut Larcher[4], Bodvaël Fraysse[1], Sophie Moullec[5], Marine Allais[1], Virginie François[1], Maeva Dutilleul[4], Alberto Malerba[6], Taeyoung Koo[6], Jean-Laurent Thibaut[7,8], Béatrice Matot[7], Marie Devaux[1], Johanne Le Duff[1], Jack-Yves Deschamps[5], Inès Barthelemy[8,9], Stéphane Blot[8,9], Isabelle Testault[10], Karim Wahbi[11], Stéphane Ederhy[12], Samia Martin[2], Philippe Veron[2], Christophe Georger[2], Takis Athanasopoulos[6,13,†], Carole Masurier[2], Federico Mingozzi[2], Pierre Carlier[7], Bernard Gjata[2], Jean-Yves Hogrel[14], Oumeya Adjali[1], Fulvio Mavilio[2], Thomas Voit[15,*], Philippe Moullier[1,16,*] & George Dickson[6,*]

Nat. Commun. 8, 16105 doi: 10.1038/ncomms16105 (2017)

Microdystrophin Gene Therapy



Microdystrophin Gene Therapy

Le Guiner C, Servais L, Montus M, et. al. NATURE COMMUNICATIONS | 8:16105 | DOI: 10.1038/ncomms16105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