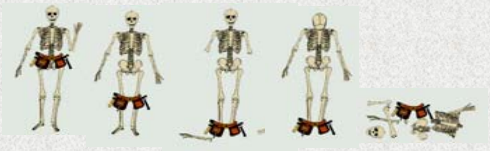
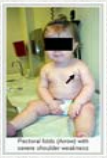
WHAT HAPPENS WHEN YOU HAVE NO MUSCLES

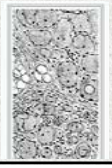


Muscular dystrophies

- Genetic disorders
- Heterogeneous
- Primarily affect the musculature
- Tend to affect the connection between the sarcomeric structure and the basement membrane, surrounding the muscle cells

Muscular dystrophies, clinical features





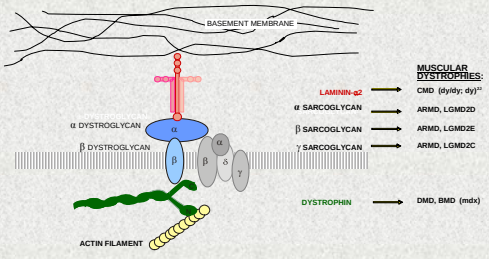
Increased endomysial connective tissue
Variable fiber size
Centrally located nuclei
Infiltration
Hypercontracted muscle fibers

Which genes are involved??

- Mutations in more than 100 genes are likely to result in myopathies
- ~40 genes have so far been identified

- **Transmembrane proteins**
- **Extracellular matrix proteins**
- Membrane-associated proteins
- Cytoplasmic proteases
- Cytoplasmic proteins associated with sarcomeres
- Protein modifying enzymes
- Nuclear membrane proteins

Transmembrane receptors in skeletal muscle



modified according to : Campbell, 1995; Worton, 1995

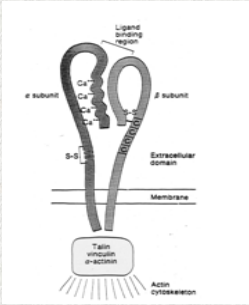
Dystrophin deficiency / Duchenne muscular dystrophy

- The most common form of muscular dystrophy in human.
- About 1 in 3000 boys is affected by the disease.
- Mutations are inherited or occur spontaneously due to the large size of the gene.
- The phenotype ranges from mild to severe.

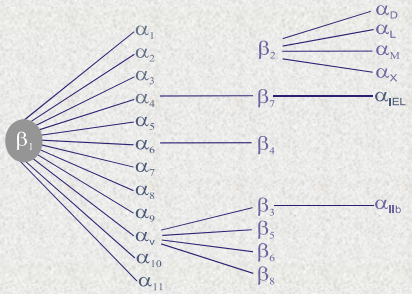
  Mild form (Becker muscular dystrophy) small in frame deletions the function of the protein is partially maintained.
  Severe form (Duchenne muscular dystrophy) complete absence of the protein. Death post-puberty.

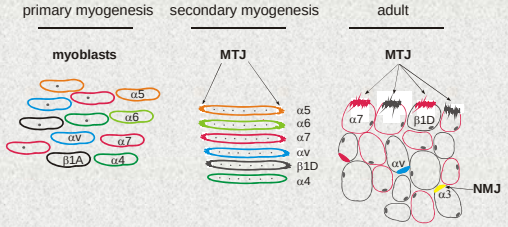
- The corresponding mouse model mdx, lacking dystrophin, develops histologically a muscular dystrophy but has a normal life span

Integrins



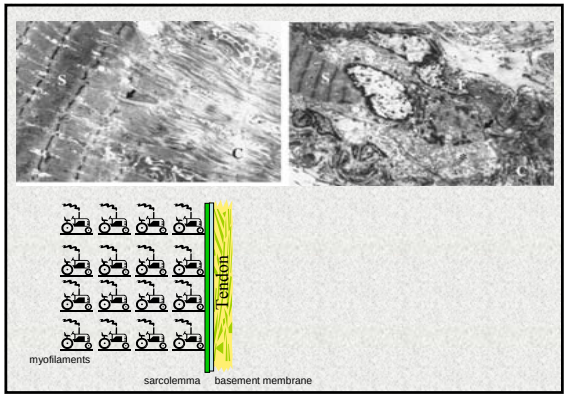
The Integrin Super-Family

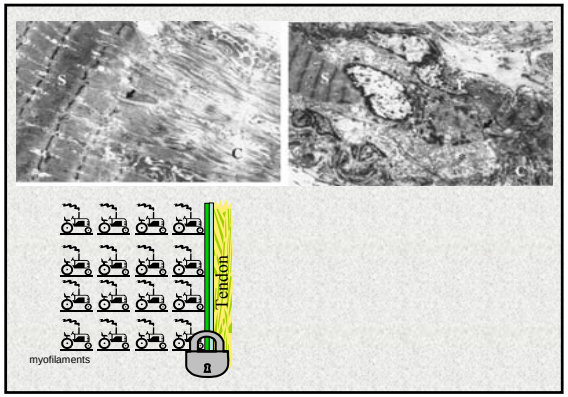


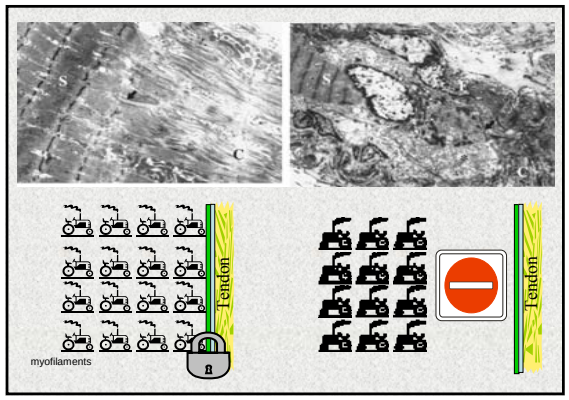


α7β1 INTEGRIN

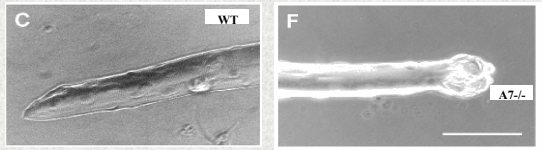
- specific laminin receptor
- two extracellular (X1, X2)
  two intracellular splice variants (A, B)
- associates with β1D in skeletal and cardiac muscle
- mainly expressed in skeletal and cardiac muscle
  but also found in smooth muscle, neurons, melanocytes
- deficiency of the α7 subunit leads to a
  muscular dystrophy in human and mice



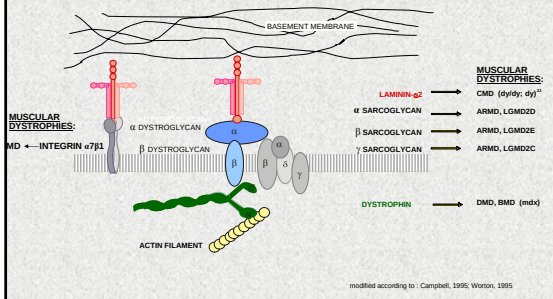


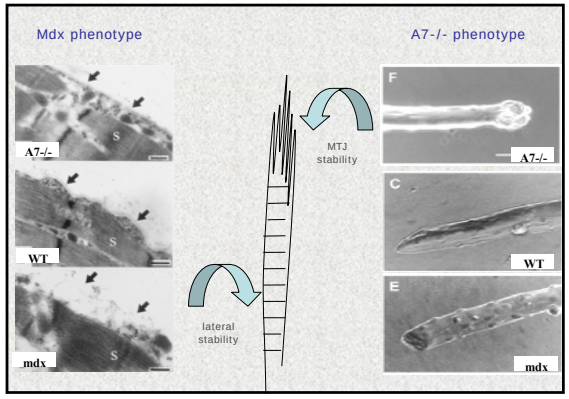


Myotendinous junctions phenotype in integrin α7 null mice

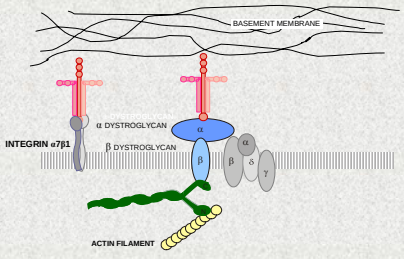


Transmembrane receptors in skeletal muscle





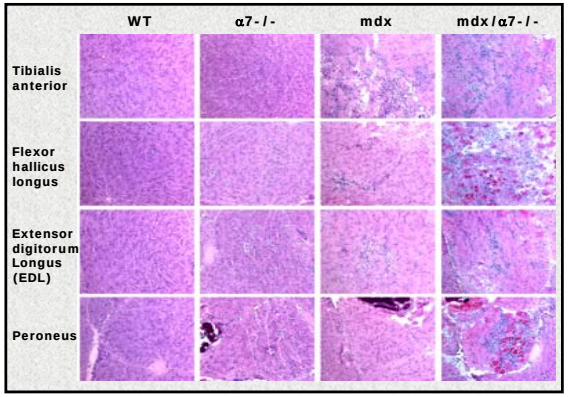
Transmembrane receptors in skeletal muscle



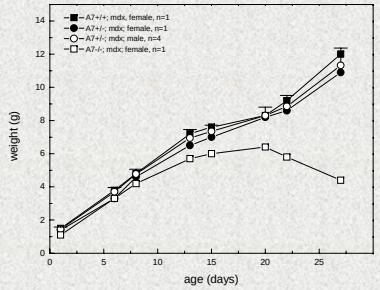
Integrin α7-/- mice

X

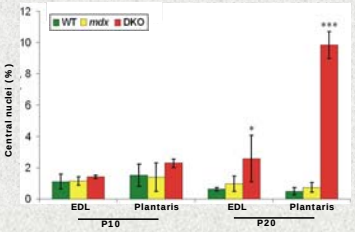
mdx mice (dystrophin-deficient)

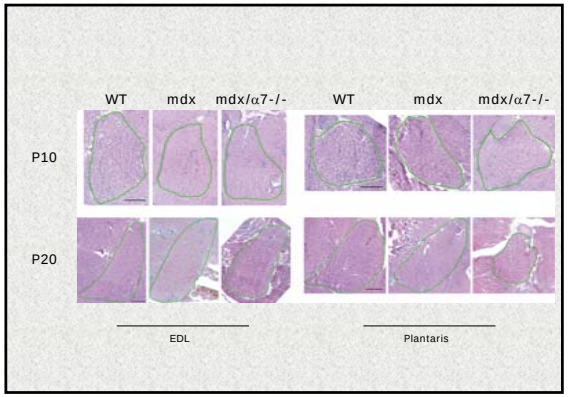


Integrin α7/mdx double-mutant mice gain less weight than controls

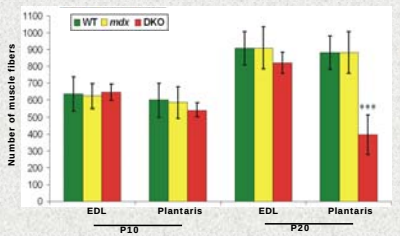


The number of fibers with centrally located nuclei is low

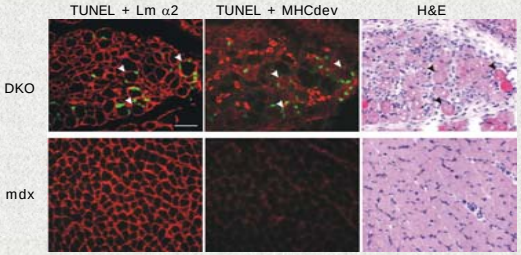




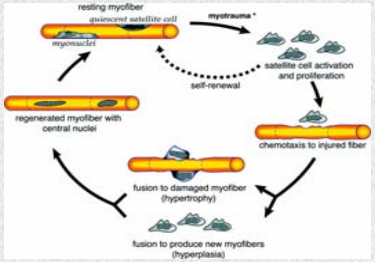
The number of muscle fibers is reduced



Apoptosis is not prominent

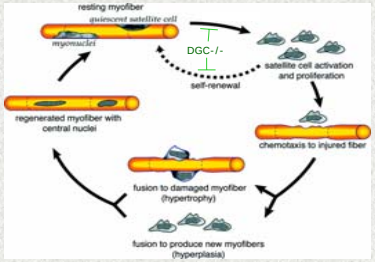


Satellite cell activation and function



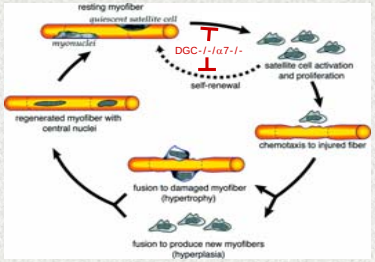
adapted from Hawke and Garry, 2001

Satellite cell activation and renewal is impaired in integrin α7 / mdx double-mutant mice

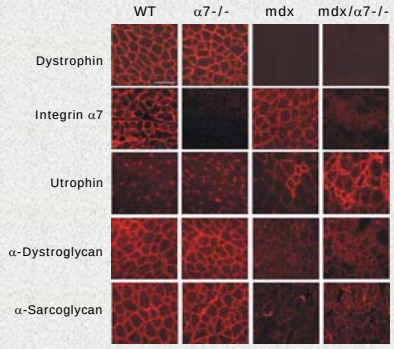


adapted from Hawke and Garry, 2001

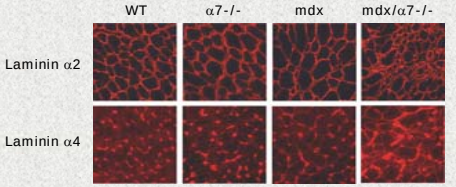
Satellite cell activation and renewal is impaired in integrin α7 / mdx double-mutant mice



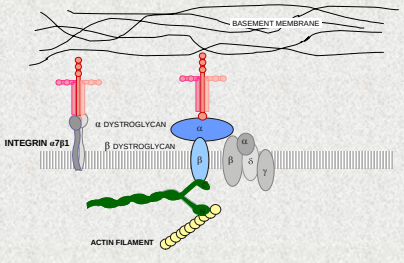
adapted from Hawke and Garry, 2001



The laminin α2 chain is unaltered in double-mutant mice

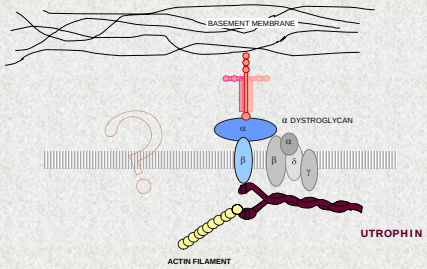


Transmembrane receptors in skeletal muscle



modified according to : Campbell, 1995; Worton, 1995

Transmembrane receptors in integrin α7 / mdx double-mutant mice



The phenotype of Integrin α7/mdx double-mutant mice closely resembles Duchenne muscular dystrophy

Could integrin α7 be a therapeutic target for DMD?