Duchenne Muscular Dystrophy

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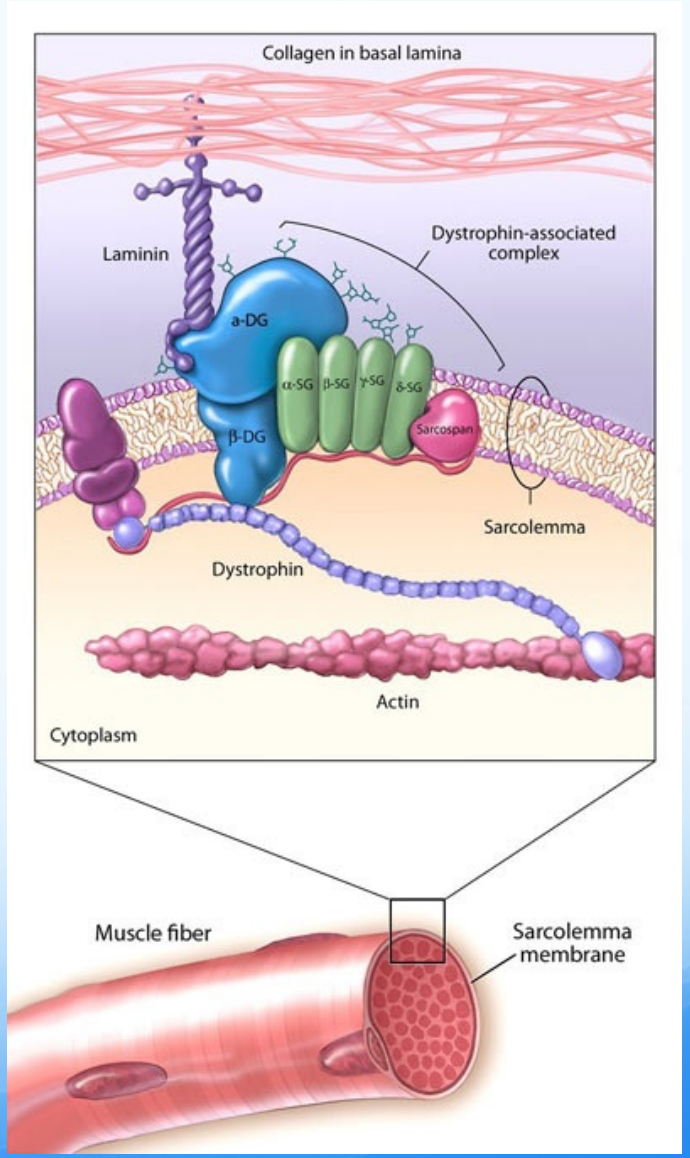
Biochem 118

Background

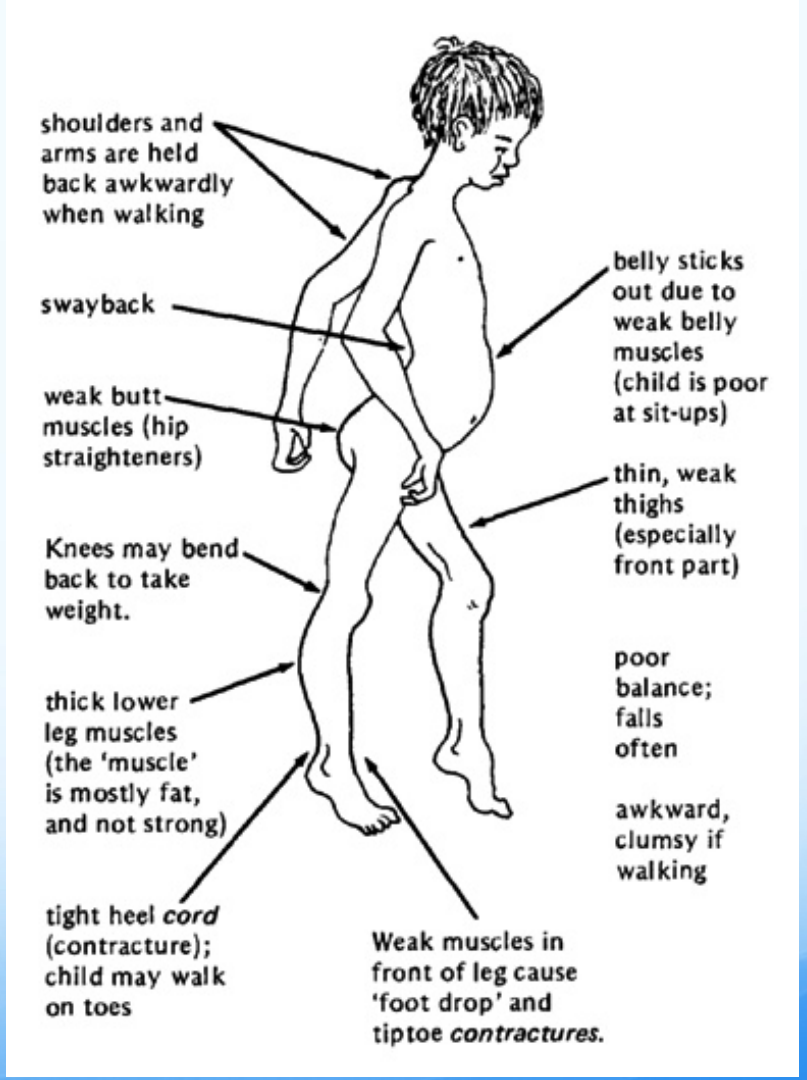
- X-linked recessive disorder
- Caused by a mutation in the gene encoding for the protein dystrophin.
- Dystrophin is found mainly in skeletal and cardiac muscle cells, and is required for structural support.
- Patients usually die in their early 20s from respiratory failure or cardiomyopathy



Kibiuk (2007)

Symptoms

- Delayed motor milestones as a child
- Steady decline in muscle function and strength from the ages of 6 to 11 years old.
- Enlargement of muscles, which begins in the lower limbs



Drugs Information Online

Classical Diagnosis

- Progressive muscle weakness starting around age 6, if not earlier.
- Muscle biopsy to measure levels of dystrophin in the muscle
- Elevated creatine kinase (CK) levels in the blood
- Family history

Classical treatment

- There is currently no effective cure. Classical treatment is just aimed at lessening the symptoms.
  - Braces are often required for walking. Eventually, most patients are confined to a wheelchair.
  - Management of breathing and cardiac disorders
    - Assistive devices for respiratory symptoms
    - Cardiac transplantation for severe cases
  - A steroid medication called prednisone is sometimes given to improve the strength of muscles and slow disease progression.

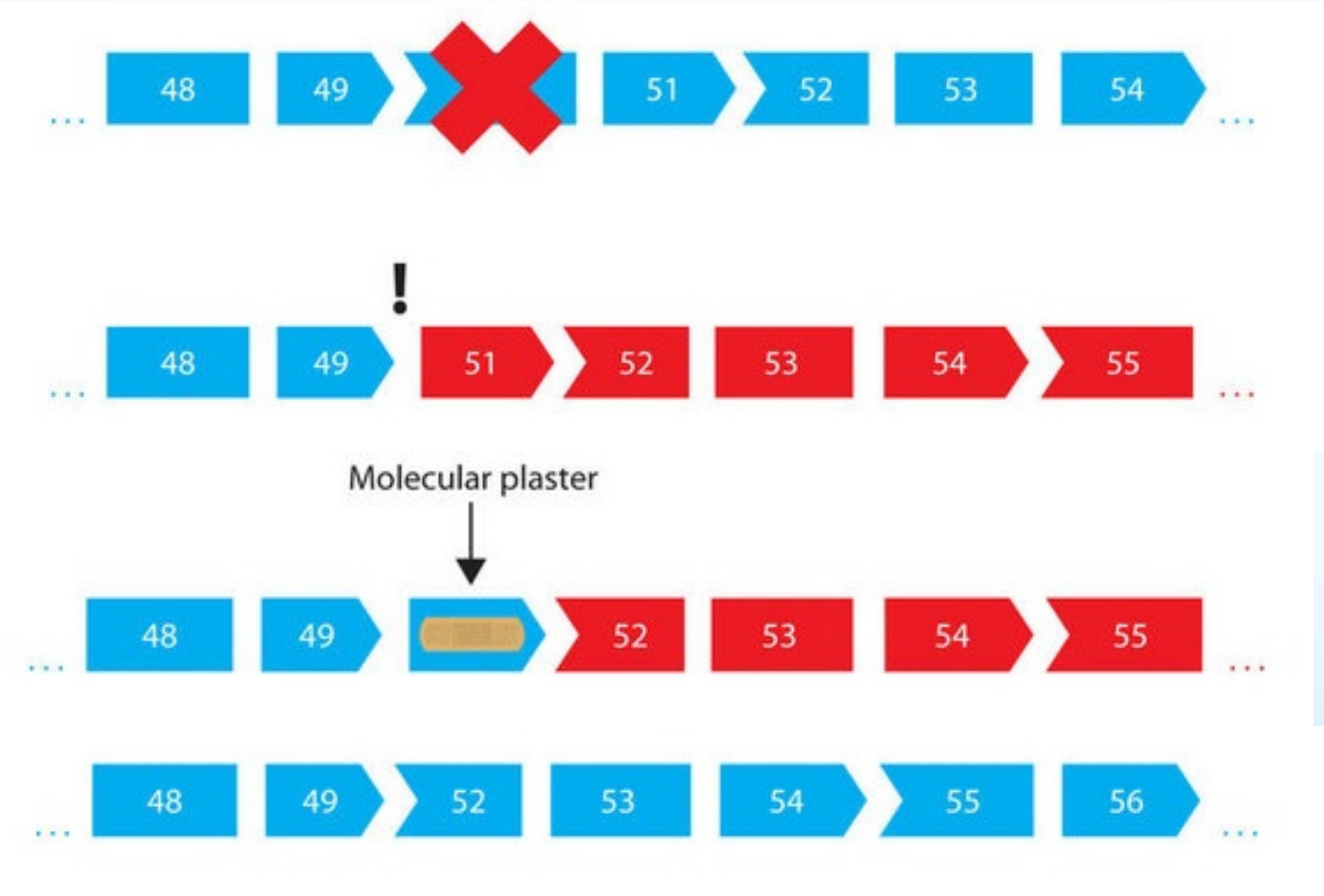
Novel Diagnostic Methods

- Genetic testing for large deletions and duplications
  - Multiplex ligation probe amplification (MLPA)
  - Array comparative genomic hybridization (CGH)
- Mutation scanning for point mutations
  - SCAIP (single condition amplification/internal primer)

Gene Therapy

- Using adenovirus (Ad) or adeno-associated viral (AAV) vectors for the delivery of dystrophin.
  - AAV have reduced immune responses compared to Ad
  - However, AAV have a small cloning capacity, and can't hold a full-length dystrophin cDNA.
- Creation of mini- and microdystrophin genes that can be delivered by an AAV capsid
  - Not as effective in producing dystrophin as the full-length gene.

Exon skipping



Muscular Dystrophy Campaign

Utrophin

- Distrophin and utrophin are 74% similar at the amino acid level, and have very similar structure.
- Mouse models have shown that when utrophin is overexpressed in muscle fibers, it can compensate for the absence of dystrophin.
- Utrophin is unlikely to elicit an immune response because it is naturally expressed in fetal muscle and some non-muscle tissues in adults.
- Upregulation of utrophin by utrophin promoters like nabumetone.

Chakkalakal (2005)

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