
# Duchenne Muscular Dystrophy

BIOC 118: Genomics and Medicine

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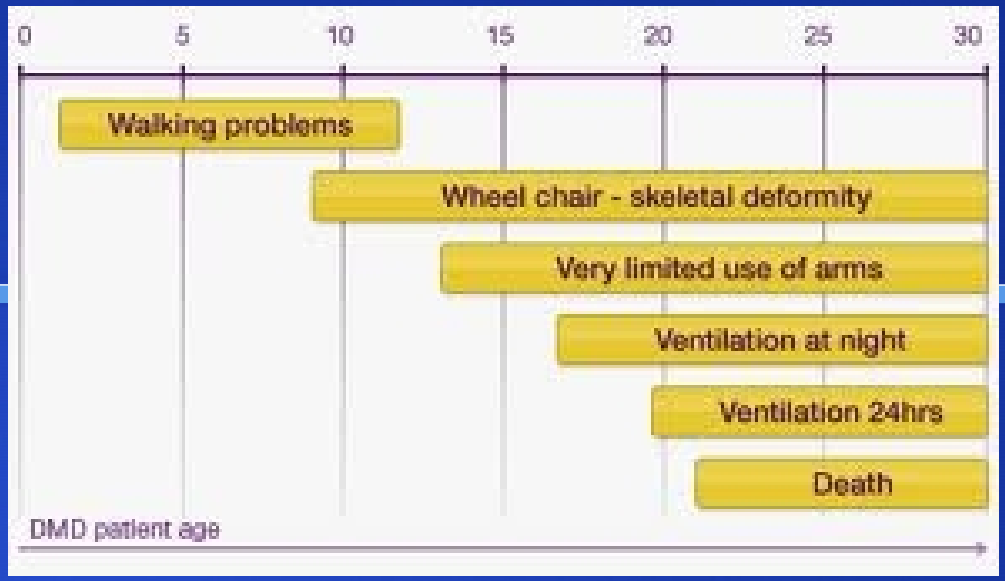
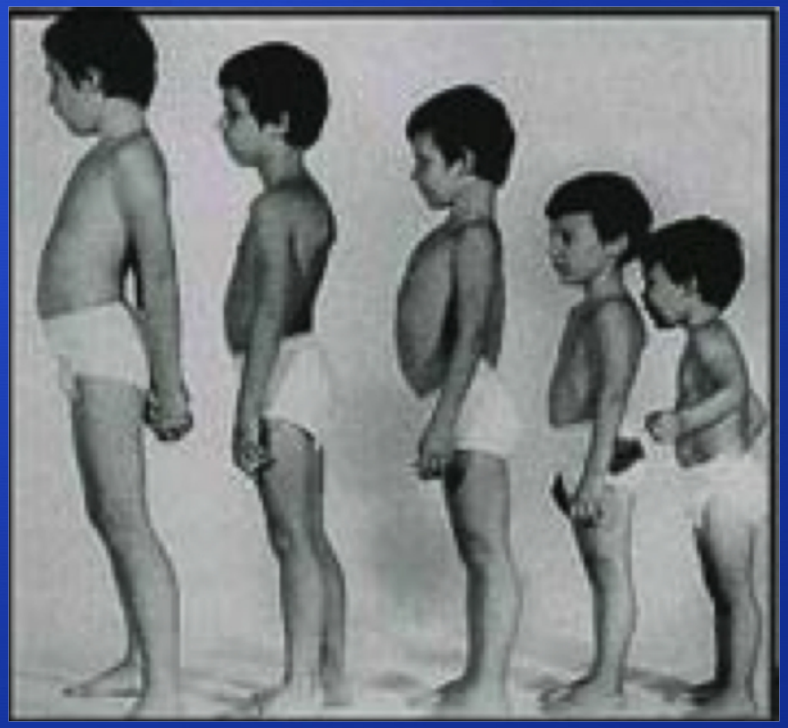
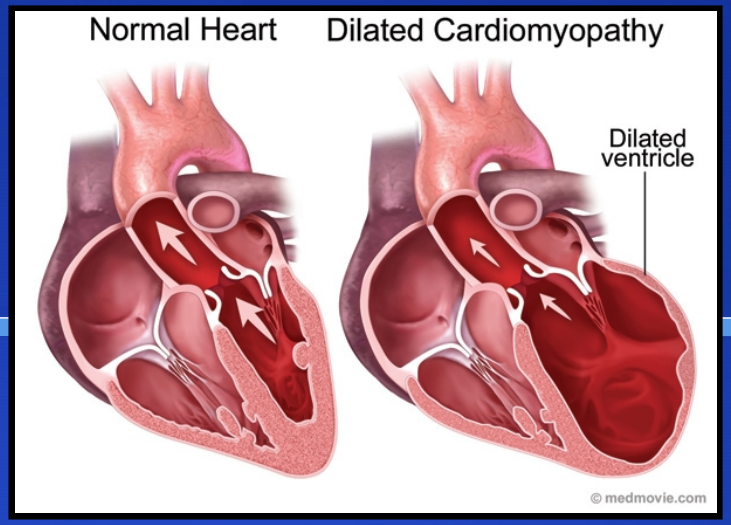
# The Basics




- Characterized by:
  - enlargement of muscles
  - rapid progression of muscle degeneration
- X-linked recessive
- One in 3,500 boys worldwide
- Onset of symptoms: infancy to age 5
- Average Life Expectancy: late teens to mid-twenties (max mid 40s) due to cardiac or respiratory failure



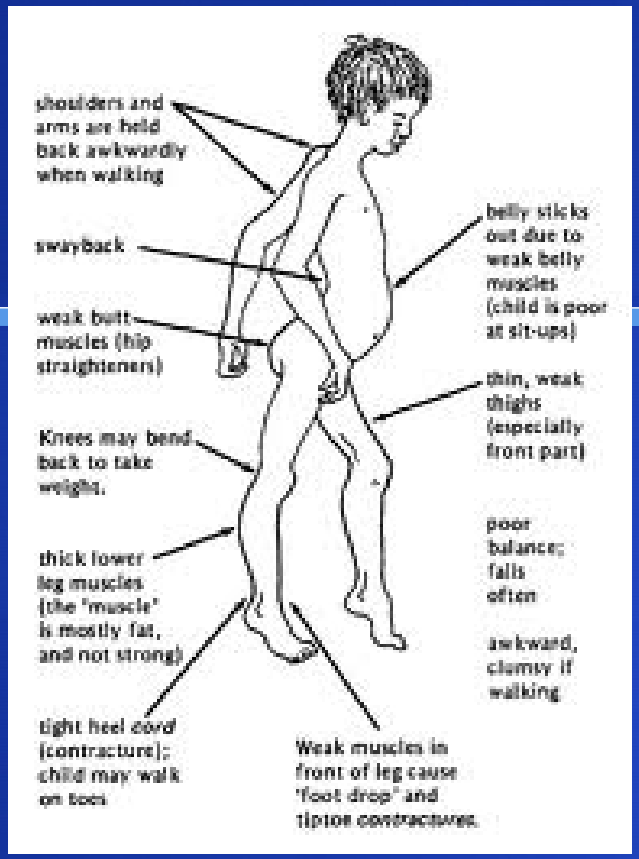



# Classical Diagnostics

- Gait difficulty beginning at age three
- Progressive muscle weakness and enlargement of the calves
- Cardiomyopathy and predisposition to respiratory illness
- Massive elevations of serum levels of creatine kinase
- Electromyography and muscle biopsy
- Biopsies taken early in the course of the disorder are prone to lead to misdiagnosis

# Classical Treatment

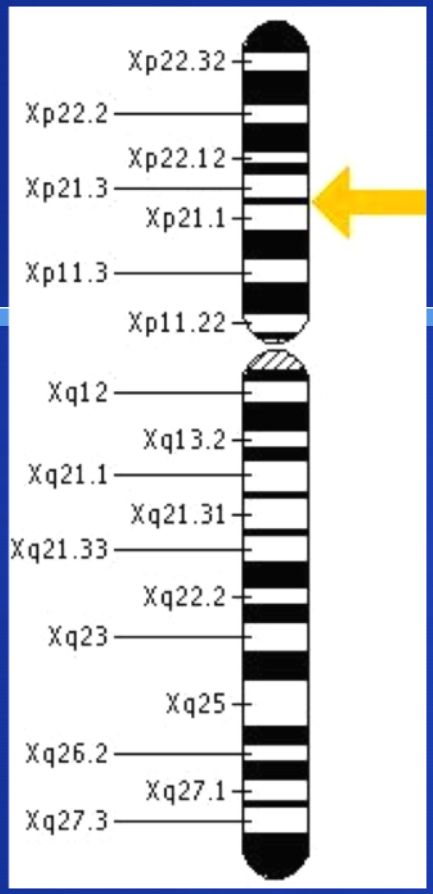
- Physical therapy
  - As muscular dystrophy progresses and muscles weaken, fixations (contractures) can develop in joints.
  - Physical therapy provides regular range-of-motion exercises to keep joints as flexible as possible, delaying the progression of contractures, and reducing or delaying curvature of your spine.
  - Hydrotherapy
- Braces (and canes, walkers, and wheelchairs)
- If respiratory muscles become weakened, using a ventilator may become necessary.




# Classical Treatment

- Medications
  - Manage myotonia: mexiletine, phenytoin , baclofen (Lioresal), dantrolene and carbamazepine.
  - Muscle deterioration: prednisone may help improve muscle strength and delay progression.
  - The immunosuppressive drugs cyclosporin and azathioprine sometimes delay damage to dying muscle cells.
- Surgery can be used to release contractures and correct curvature of the spine
- Influenza shots

# The Guilty Gene

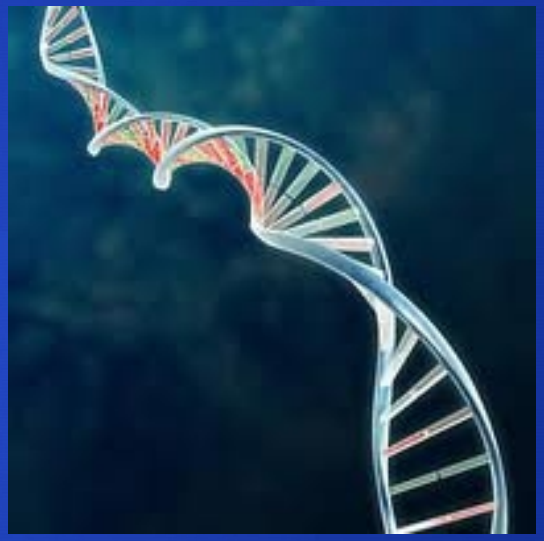



The *DMD* gene is located on the short arm of the X chromosome at position 21.2.
More precisely, the *DMD* gene is located from base pair 31,137,344 to base pair 33,357,725 on the X chromosome.

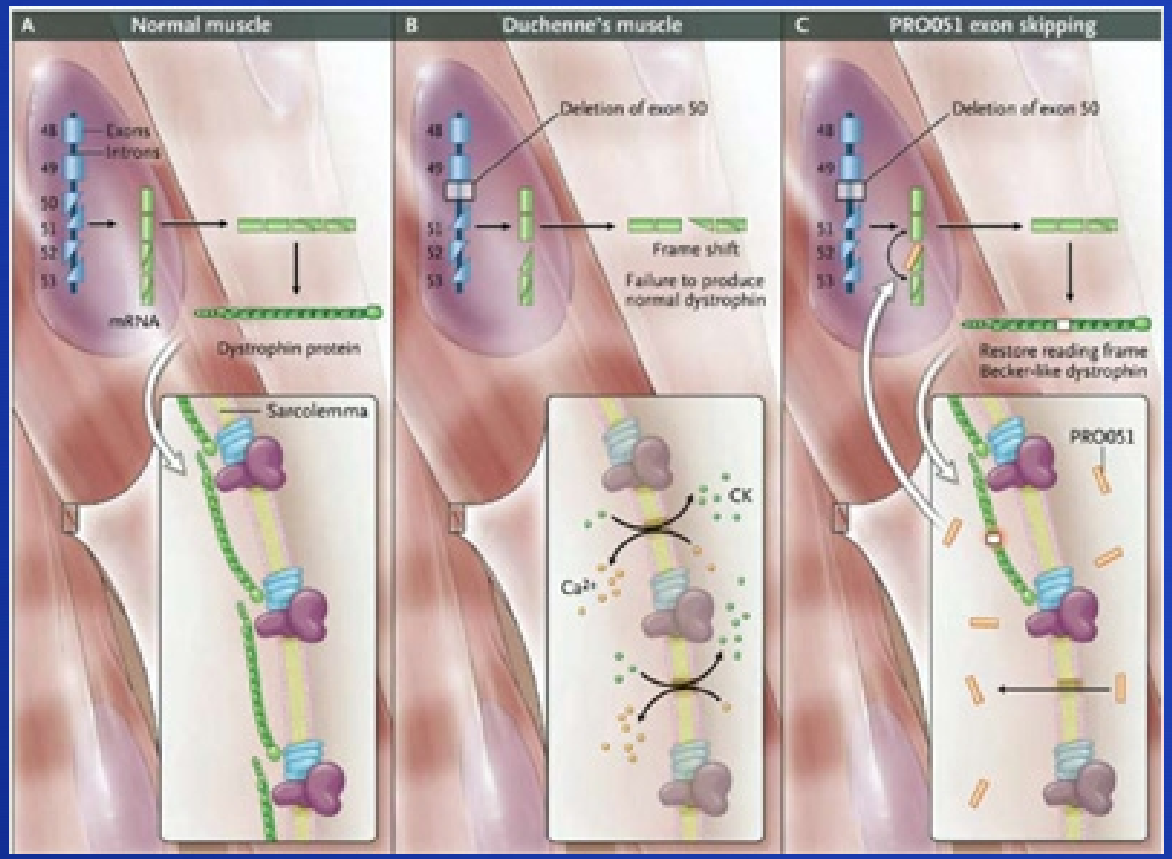
- The DMD gene is the largest known human gene
- Hundreds of mutations in the DMD gene can lead to DMD
- Codes for a protein complex called dystrophin.
  - Located in skeletal muscles and cardiac muscles
  - Small amounts are present in nerve cells in the brain
  - Strengthens muscle fibers and protects them from injury as muscles contract and relax.
  - Acts as an anchor, connecting each muscle cell's cytoskeleton with the lattice of proteins and other connective tissue that surrounds muscle cells.
  - May play a role in cell signaling
- Most are deletions that cause frame-shift mutations that prevent any dystrophin from being produced
- Muscle cells that lack enough functional dystrophin become damaged as muscles repeatedly contract and relax with use
- The damaged cells weaken and die over time, causing the characteristic muscle weakness and heart problems seen in Duchenne muscular dystrophy.
- Research suggests that the protein is important for the normal structure and function of synapses in the brain

# Genetic Diagnostics

- Composed of 79 exons
- DNA testing and analysis usually identifies the specific type of mutation or the exon or exons that are affected.
- Prenatal tests



# Mechanism of PRO051 in the restoration of Dystrophin Expression through Exon Skipping




- Correct the reading frame in 16% of patients

- Antisense oglionucleotide binds to the dystrophin mRNA.
- The modified DNA molecule allows the mRNA to skip over the affected exons, and restores the reading frame of the mRNA, for new production of dystrophin.

# Other Prospects…

- Adeno-associated viruses carrying micro-dystrophins into dystrophic muscles
- Resulted in a striking reversal of histopathologic features of the disease
- Difficult to produce

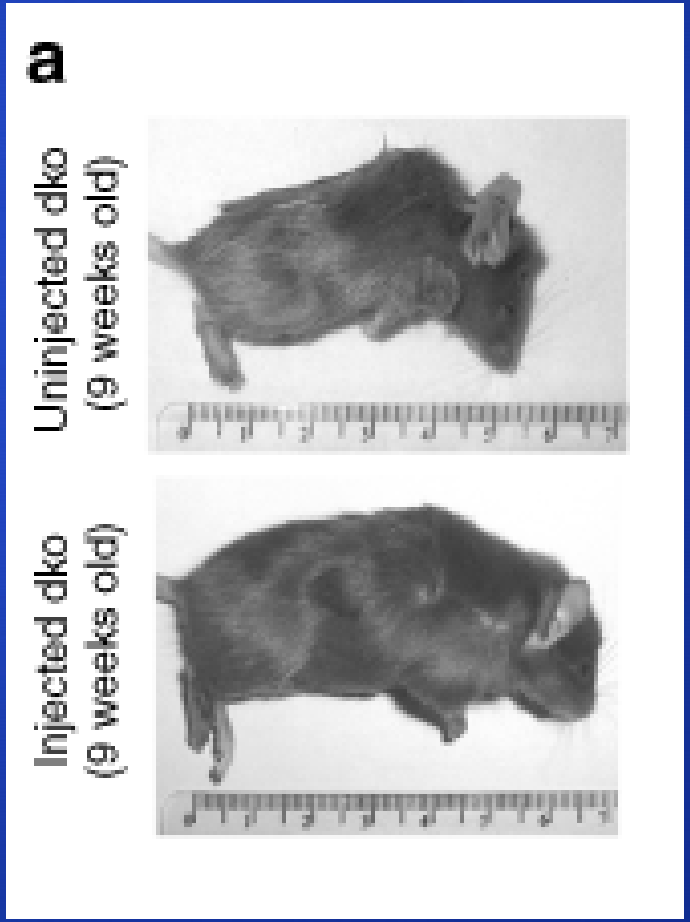


Table 1 | **Overview of strategies for Duchenne muscular dystrophy gene therapy**

| Strategy | Action/effect | Advantages | Disadvantages | Prospects |
|---|---|---|---|---|
| Adenoviral vectors | Full-length dystrophin cDNA transfer | High transduction levels in regenerating muscle, expression of fully functional dystrophin | Viral immune response, limited persistence of transgene expression, maturation dependent | ++ |
| Herpes simplex viral vectors | Full-length dystrophin cDNA transfer | High transduction levels in regenerating muscle, expression of fully functional dystrophin | Viral toxicity and immune response, limited persistence of transgene expression, maturation dependent | + |
| Plasmid vectors | Full-length dystrophin cDNA transfer | Synthetic, non-infectious, relatively safe, flexible, simple engineering | Large molecule, delivery requires efficient transfection method | ++ |
| Myoblast transplantation | Introduce dystrophin-producing cells | Non-infectious, relatively safe | Low efficiencies, immune suppression required | + |
| Stem-cell therapy | Introduce dystrophin-producing cells | Conventional treatment, relatively safe | Low efficiencies, immune suppression required | ++ |
| Chimeric oligonucleotides | Correction of mutation at the DNA level | Cumulative, permanent effect | Low *in vivo* efficiencies | + |
| Gentamicin therapy | Ribosomal read-through of stop codons in mRNA | Conventional drug | Low reproducibility, risk of nonspecific adverse effects | + |
| rAAV vectors* | Mini- or micro-dystrophin cDNA transfer | High transduction efficiencies in muscle, non-pathogenic minimal immune responses | Unable to deliver full-length dystrophin, laborious production systems | +++ |
| Antisense oligonucleotides* | Splicing modification of pre-mRNA | Synthetic, small-molecule drug, relatively safe, restores all isoforms | Repeated administrations and (targeting) delivery reagent needed, mutation specific | +++ |
| Utrophin upregulation* | Replacement of dystrophin | Small-molecule drug, no immune response, relatively safe | No effective specific compound identified as yet | ++ |

*These three relatively new strategies are most likely to lead to an effective treatment for Duchenne muscular dystrophy. The symbols in the prospects column indicate a subjective assessment of the probability of a particular strategy leading to an effective treatment, ranging from low (+) to high (+++). rAAV, recombinant adeno-associated virus.

# Questions?