Duchenne Muscular Dystrophy: Mutation of DMD gene

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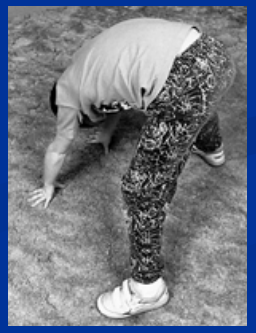
Physiology

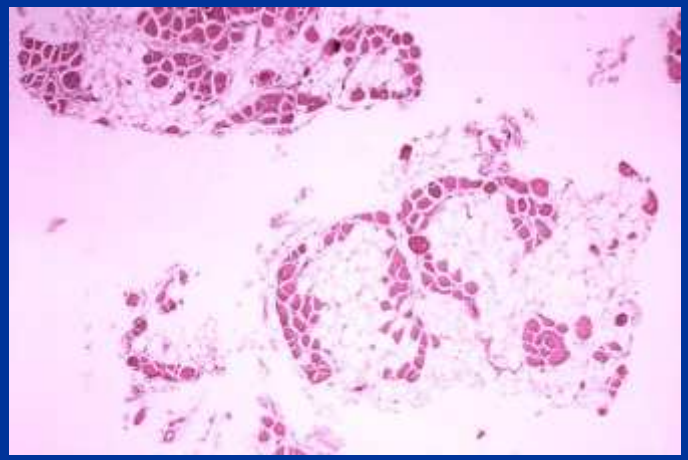
- Progressive Disease : Early onset as infant, gets worse later in life
- Muscle weakness, skeletal and cardiac
- Begins in the legs and pelvis, then arms, neck, and other areas
- Difficulty with motor skills (running, hopping, jumping)
- Frequent falls
- Ability to walk may be lost by age 12, and the child will have to use a wheelchair
- Breathing difficulties and heart disease usually start by age 20
- Low IQ around 75
- Large calves
- Gower's Maneuver

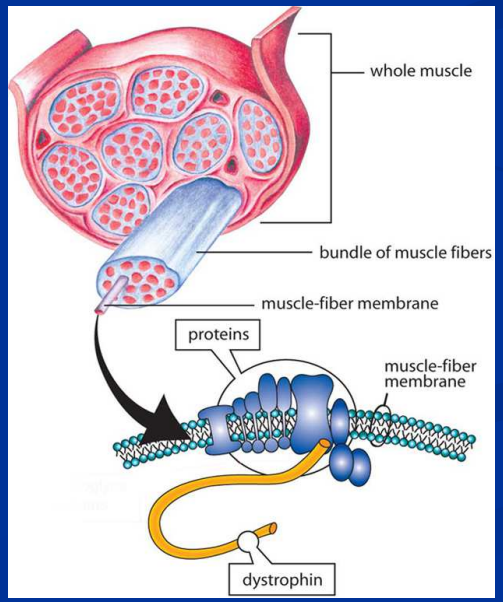


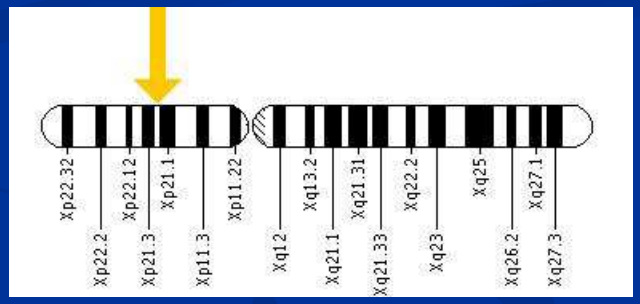



Molecular Cause

- X-linked recessive, on X-chromosome position 21.2 on short p arm
- DMD gene= largest gene we know, 79 exons, codes for dystrophin protein
- 70% of mutations are large deletions in hotspot of exons 45-53
- Mutations cause partially functioning or null phenotype of dystrophin protein
- Dystrophin + other glycoproteins form protein complex= structural stability during muscle contraction, protect muscle from injury, make muscle fibers stronger







Treatments/Limits

- Exon skipping drugs being researched
- eteplirsen shuts off exon 51 that has the mutation, so that muscle cells still have some partially functional dystrophin.
- Other names for exon skipping drugs : PROO51, PTC124
- Combination of sildenafil, spironolactone, and ibuprofen. This combination reduces the severity of Duchenne Muscular Dystrophy of mice.
- Spinal fusion surgery if spinal curve is 20 degrees
- Corticosteriods- improve muscle function
- Physical therapy: improve walking, exercise regularly
- canes, walkers, wheelchairs, strollers, ramps, and ventilators
- Limits- Aim to improve quality of life, prolong life, no cure

Proposed Cure/Limits

- Because DMD gene is so large, gene therapy does not work well with vectors
- Isis Pharmaceuticals claims to have 12 antisense mechanisms
  - Drugs can be built for any target: liver, kidney, spleen, bone marrow, and fat cells
- Antisense mechanism: RNase H, cellular enzyme
  - normally catalyzes the cleavage of RNA and in DNA replication, it also removes the RNA primer
- Antisense drugs= small DNA/RNA compound consisting of 12-21 nucleotides
- drug is complementary to the mutant mRNA, so that it can bind to the mutant mRNA
- delivery mechanism-inject drug into the bloodstream, where the drug is rapidly and easily absorbed
- Antisense drugs will bind to the target mutant mRNA, marking it for destruction by the RNase H.
- When mutant mRNA is destroyed, functional dystrophin can be made again.

References

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  Muscle picture

  https://www.google.com/search?q=dmd+muscle&aq=f&um=1&ie=UTF-8&hl=en&tbm=isch&source=og&sa=N&tab=wi&ei=ziacUZzIGuaR0QHG2oHACA&biw=1600&bih=775&sei=0SacUf-EM-fV0gHgjoHwBw#imgrc=J9AVwwAljxK8JM%3A%3BgwLORMulO428bM%3Bhttp%253A%252F%252Fwww.nature.com%252Fscitable%252Fcontent%252F35319%252FDMDtissue_MED_1.jpg%3Bhttp%253A%252F%252Fwww.nature.com%252Fscitable%252Ftopicpage%252Fsex-linked-diseases-the-case-of-duchene-800%3B335%3B223

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- CONTENT

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