Cystic Fibrosis

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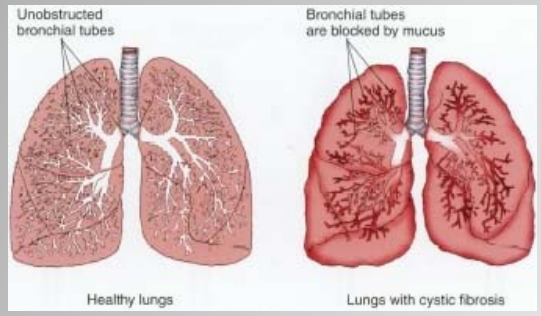
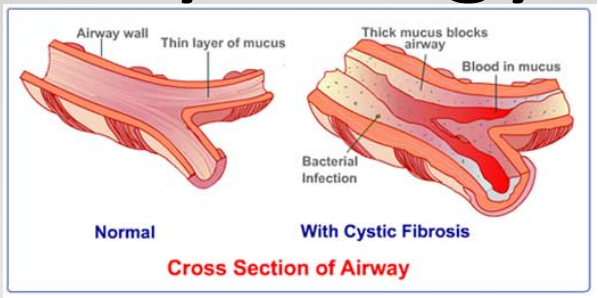
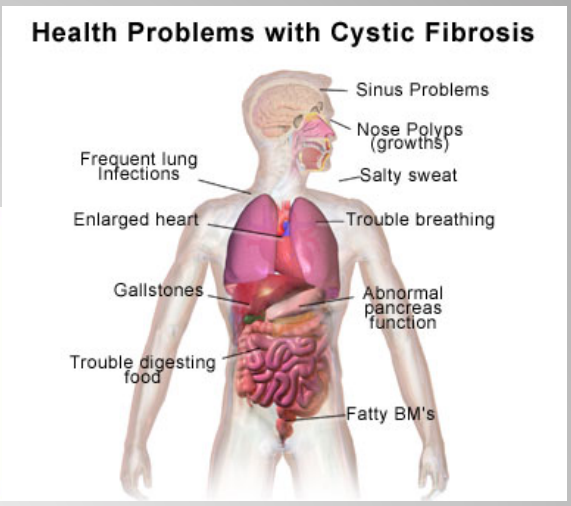
Physiology

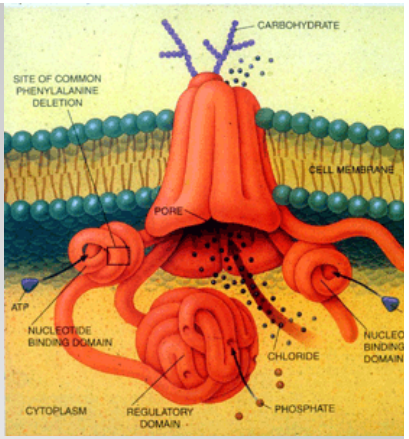


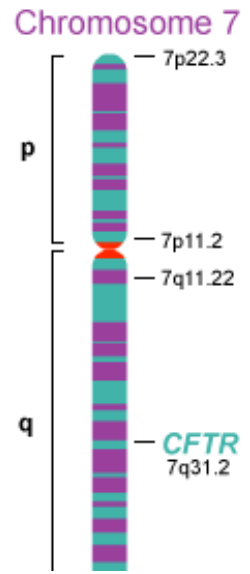




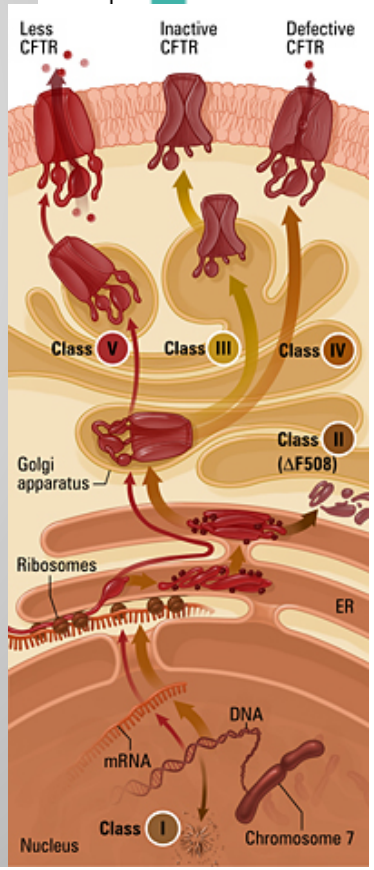
- Prenatal onset for most, although some with milder cases are diagnosed in adulthood
- Respiratory System:
  - Persistent wheezing/coughing due to thick, sticky mucus in the lungs
  - Repeated lung infections due to bacteria formation in mucus
  - Results in degradation of lungs, leading cause of death is lung failure
- Digestive System:
  - Thick mucus blocks enzymes fro traveling through ducts from pancreas to small intestine
  - Poor digestion and absorption of nutrients, affected by poor weight gain and growth
  - Thick, greasy, smelly stools result
- Reproductive System:
  - Mucus blocks the vas deferens, so even though males can ejaculate, sperm doesn't reach the semen and so they are infertile
  - Women have irregular menstrual cycles
- Sweat is salty

Molecular Cause

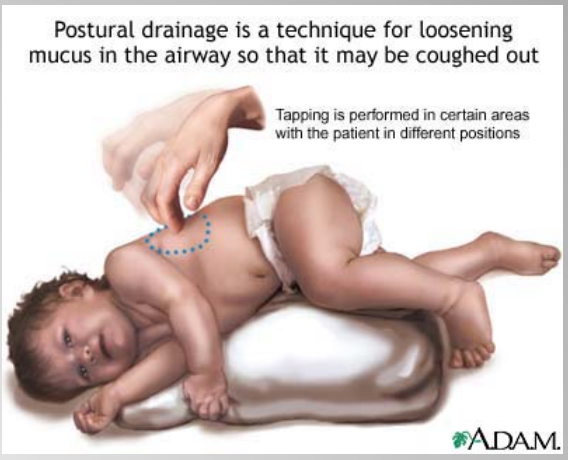




- Autosomal recessive
- Chromosome 7, position 7q31.2, mutation in protein CFTR (cystic fibrosis transmembrane conductance regulator)
- CFTR is an ATP-binding transporter class ion transport channel
- ATP binds to the binding domain, which opens the channel and allows chloride ions to move across the cell membrane
- This causes a hypotonic solution outside the cell, so water diffuses out of the cell
- F508del, the most common mutation, which accounts for 70% of CF patients, is a deletion of phenylalanine at position 508 in the protein that causes the protein to misfold
- This causes the protein to be degraded by the ER, and so it is not able to reach the cell membrane
- Over 1000 other mutations have been observed as well
- Mutations divided into five main classes



Treatment/Risks and Limits



- ACTs (airway clearance techniques) allow the patient to clear their lungs of mucus
- Bronchodilators open the airways for easier breathing and clearing of mucus
- Mucus thinners thin mucus
- In hypertonic saline therapy, patients inhale saline solution so that their lung mucus will contain more salt and water will diffuse out of the cell
- These can be used in conjunction with each other since they have complementary effects
- They are only temporary solutions and do no address the causes of the disease, and so symptoms continue
- Antibiotics are used to fight lung infections due to the build up of bacteria
- This may cause bacteria to mutate into super germs, which are resistant to antibiotics
- Double lung transplant can be performed, and an allocation system gives lungs to those most in need
- The body must be put on immunosuppressant drugs so that it will not reject the foreign matter, which opens the body to invasion by pathogens, and the body can still reject the lungs

Proposed Cure/Limits

- Currently, trials are underway to test the cationic liposome GL67A with the plasmid DNA expressing CFTR pGM169
  - The negatively charged plasmid is combined with a positively charged liposome and then aerosolized, so that patients can breath in a fine mist with a nebulizer
  - This is taken into the lung cells, and the plasmid is brought to the nucleus where it starts to express normal CFTR proteins
- When the F508del CFTR protein is in the ER, the ER continually marks it for refolding to try to make it fold correctly by binding it to a chaperon protein, which prevents the CFTR protein from moving form the ER to the Golgi body
  - After prolonged association with chaperon proteins, the CFTR protein is sent for ER associated degradation (ERAD)
  - As an alternative, if proteins are folded correctly, they are bound to cargo proteins for sorting into COPII (coat protein II) vesicles, which take the protein on to the Golgi body
  - To prevent the F508del CFTR protein from being degraded, it will be bound to a cargo protein for export out of the ER and on to the Golgi, so that it can eventually move to the cell membrane
  - Limits: current technology is not able to attach cargo proteins to proteins in the ER

References

Physiology Slide:

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Proposal Slide:

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