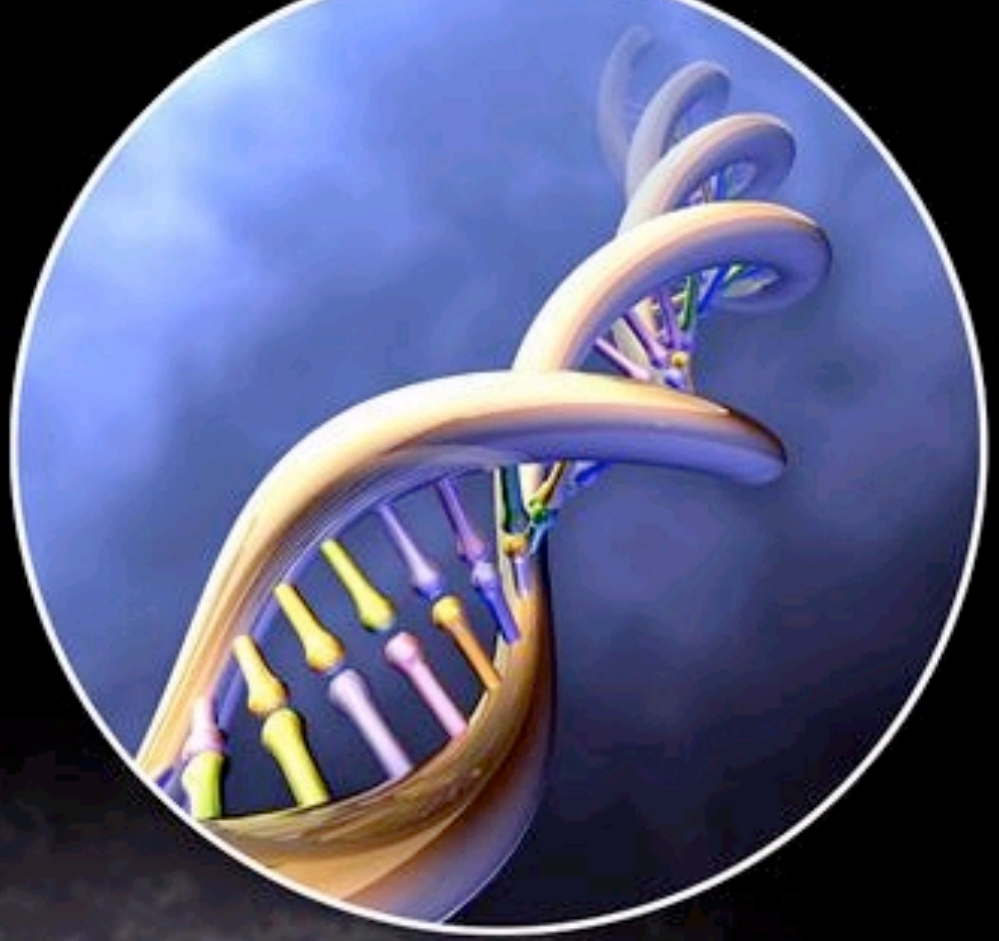
CYSTIC FIBROSIS



ARSANI
WILLIAM
BIO 118Q
21 JANUARY 2008

CYSTIC FIBROSIS

Classical Diagnosis

- Laboratory **Sweat Testing** determines the sweat chloride concentration.
- **NPD** used for Diagnostic.

- Elevated chloride concentration in sweat (1953)
- pancreatic insufficiency
- recurring pneumonia;
- progressive obstructive lung disease; chronic bacterial infection of the airways and sinuses
- male infertility due to absence of vas deferens

Genetic Diagnosis

- Autosomal recessive disease; caused by mutation of CFTR gene on **Chromosome 7** that results in defective CFTR protein (1480 a.a. long).

- Most common mutation involves a three base-pair deletion of phenylalanine at 508 position.

- CFTR protein normally regulates the transport of electrolytes, specifically chloride ion across epithelial-cell membranes.

- Genotyping: at least **500** CFTR mutations associated with CF

- Since **70** mutations cause **90%** of all cystic fibrosis gene dysfunction, probes are used as a genetic diagnostic

General Overview

- Dysfunction of CF transmembrane conductance regulator **(CFTR)**

- The CFTR protein is a chloride channel that controls and regulates the flow of Cl- ions, which in turn control the movement of water in tissues and across membranes; a process necessary for the production of **thin, freely flowing mucus**.

- A mutation that prevents this regulation usually results in thick and sticky mucus in the passageways of the lungs, pancreas, and other organs.

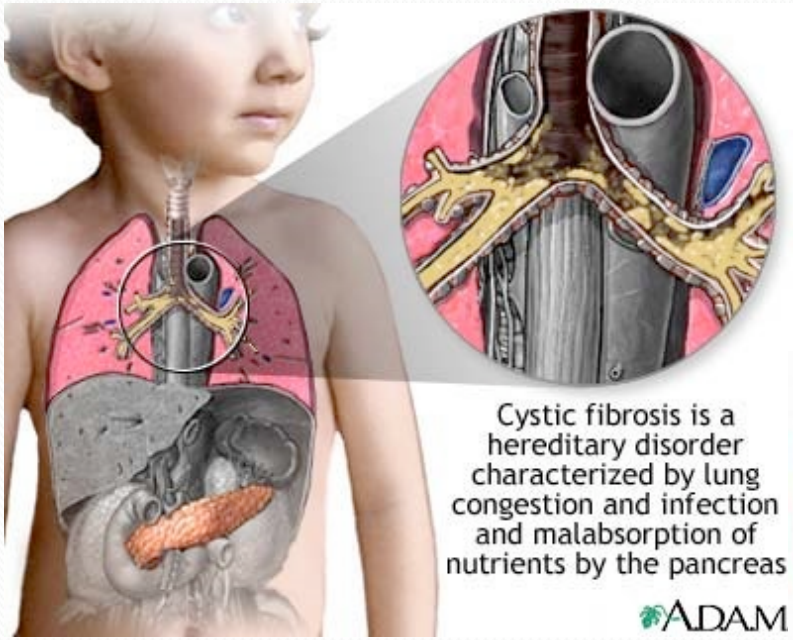
- Life expectancy= 37 years

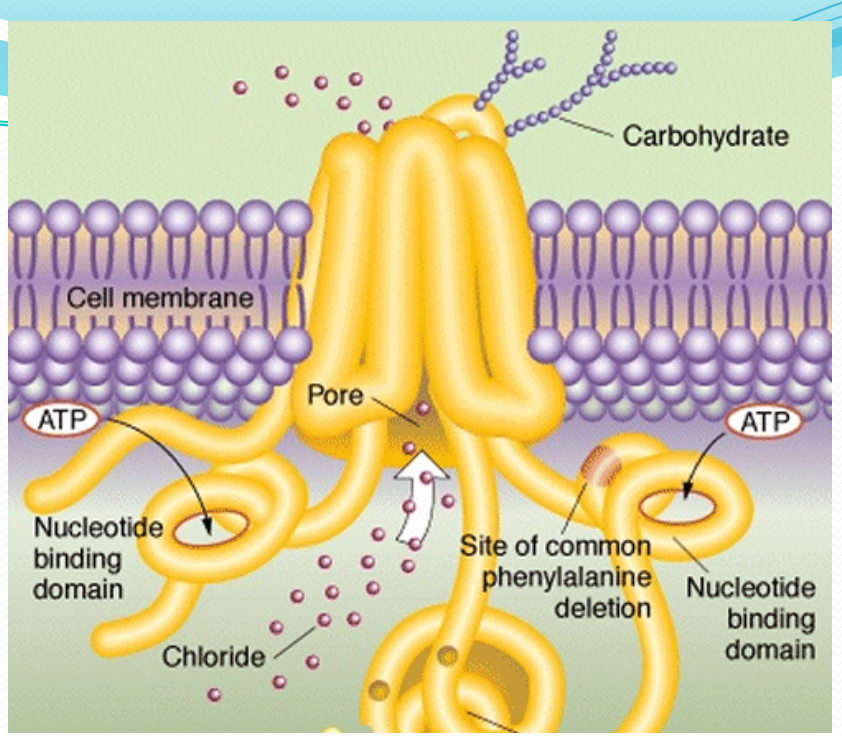
CYSTIC FIBROSIS

Symptomatic Diseases

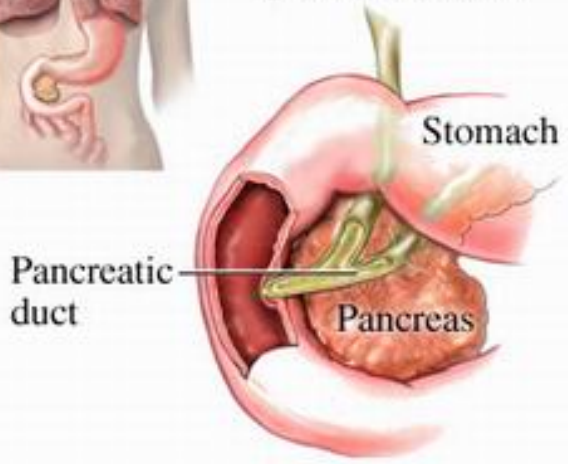
- CFTR mRNA transcripts were expressed highly in nasal, tracheal, and bronchial epithelial cells (Trapnell, 1991). Liver and Pancreatic expression was also frequent.
- Lung disease results from a buildup of mucous along the airway tubes, leading to inflammation , pneumonia, bacterial infection, and chronic difficulty in breathing.
- The pancreas loses ability to regulate, resulting in thickened secretions that disrupt proper flow of gastrointestinal enzymes, and lead to inflammation and pancreatic damage.
- Infertility: 97% of men with CF are sterile.
- These mucosa secretions of the liver cause scarring (cirrhosis)
- Abnormal chloride movement out of the cell → thickened secretions→ blockage of narrow passageways→ infection & organ failure.

CYSTIC FIBROSIS





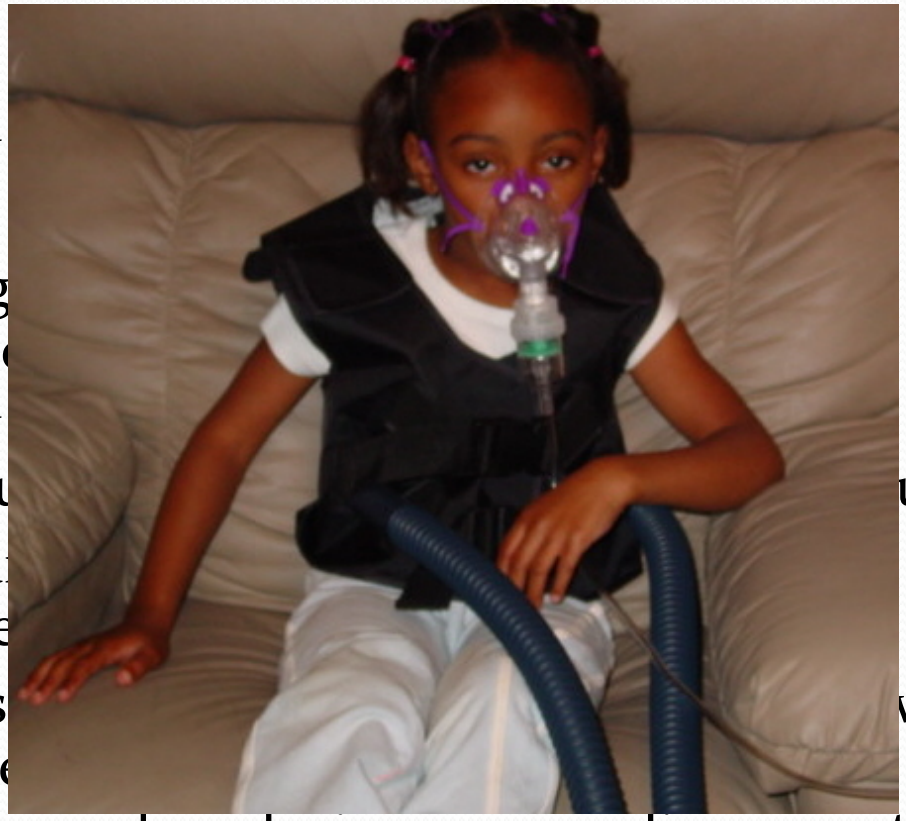
Mucus blocks air sacs (alveoli) in the lungs



CYSTIC FIBROSIS

Current Treatments

- Treatment is completely
  lifetime.
- Treatment includes drug
  tract, but is merely aime
- Transplantation is many
  damaged by thick mucou
  ure.
- Oral antibiotics are requ
  treatment using nebulise
- Aerosolized medications
  wn
  the DNA in sputum to d
  increase size of small airways by relaxing surrounding smooth
  muscle



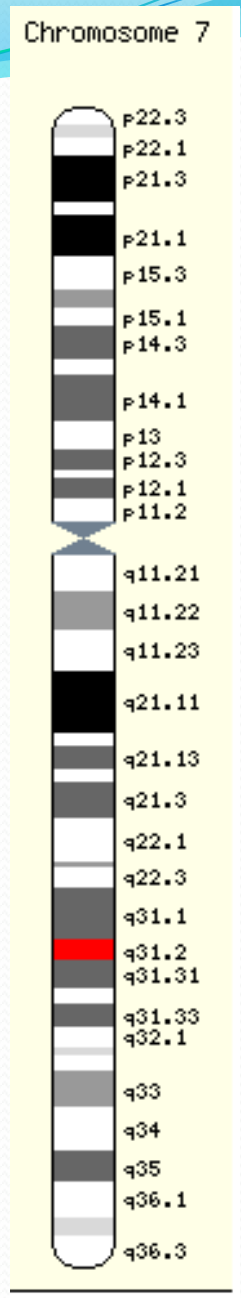
CYSTIC FIBROSIS

Gene Therapy

- strong candidate for potentially successful gene therapy.
- Placement of normal CFTR copy gene into affected cells
- 5-10% of normal CFTR needed to prevent symptoms
- Liposomes, viral vectors
- Problems subsist in how cDNA can recombine efficiently in cells

Natural Selection

- the 508 mutation is estimated to be 52,000 years old.
- Heterozygote advantage
- Normal CFTR proteins are entry way for typhoid; mutation resistant to typhoid fever.
- Some resistance to TB.



CYSTIC FIBROSIS

Mutation	Relative Frequency	Mutation Functional Class [1]
ΔF508	66.0%	II
G542X	2.4%	I
G551D	1.6%	III
N1303Lys	1.3%	II
W1282X	1.2%	I
R553X	0.7%	I
621+1G>T	0.7%	I
1717-1G>A	0.6%	I
R117H	0.3%	IV
R1162X	0.3%	Not clear [4]

Population Group	Approximate Carrier Frequency
Ashkenazi Jewish	1:29
North American Caucasian	1:28
African American	1:61

CYSTIC FIBROSIS

TESTING

-Two quantitative tests:
-*pilocarpine iontophoresis* sweat chloride values (>6o mEq/L)

-transepithelial nasal potential difference (NPD) measurements characteristic of CF.

-*Testing of relatives at risk:* sweat chloride testing of sibs and mothers of affected individuals to determine if they may have mild or not yet symptomatic forms of CF.

Prenatal testing is available for pregnancies at increased risk for *CFTR*-related disorders if the disease-causing mutations in the family are known.

Newborn screening. Newborn screening using immunoreactive trypsinogen (IRT)

Treatment and Management

CPT is typically performed in conjunction with administration of any inhaled medications that have been prescribed, given in a standard sequence:

Before CPT
1. Bronchodilator
2. Hypertonic saline
3. DNase

After CPT
4. Inhaled corticosteroids and/or long-acting beta-agonist
5. Inhaled antibiotics

Acknowledgements

- GeneReviews. CFTR-Related Disorders. http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=cf 2/19/2008.

- OMIM. John Hopkins University. CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR; CFTR. http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=602421. 10/22/2008

- Wikipedia. Cystic Fibrosis. http://en.wikipedia.org/wiki/Cystic_fibrosis. 20/1/2009.

- Moss, RB. Infection, Inflammation, and the Downward Spiral of Cystic Fibrosis Lung Disease. Pubmed. 20/1/2009.