CYSTIC FIBROSIS:

- Typically presents in childhood
- Most common lethal inherited disease
- Autosomal recessive
  - > Carrier frequency 4%
  - > Single gene disease **(CFTR gene)**
    - Protein located in glandular apical epithelium

GENETIC MUTATIONS IN CF:

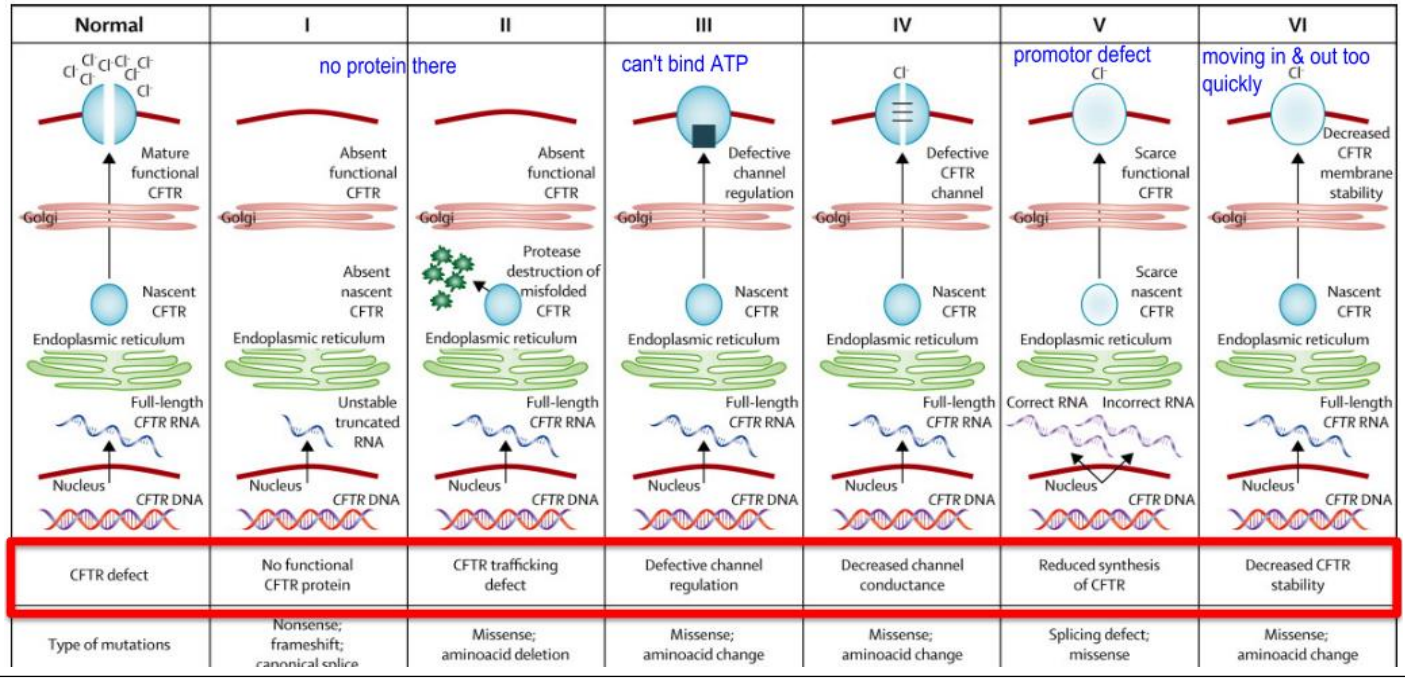
- Most common mutation (70%): 3 base pair deletion → absence of PHENYLALANINE at position 508 of the CFTR
- Large number (>1000) of relatively uncommon mutations (2%)

CLASSIFICATION OF CF:

Classic	Non-classic
• Chronic cough (may be productive) • Chronic bacterial infection of airways & sinuses • Poor growth/weight gain IN SPITE of good appetite • Meconium ileus (obstructed bowel) at birth • Fat maldigestion, due to pancreatic exocrine insufficiency = GREASY, BULKY, FLOATING STOOL • Infertility in males due to obstructive azoospermia • ELEVATED CONCENTRATIONS OF CHLORIDE IN SWEAT	• Partial CFTR function • Respiratory dysfunction but no/minimal maldigestion

GENE MUTATIONS: can change the QUANTITY of CFTR protein or change the FUNCTION of CFTR protein

- ALL CLASSES: respiratory insufficiency
- CLASS 1-3: "severe" mutations = pancreatic insufficiency with decreased survival
- CLASS 4 – 5: "mild" mutations = pancreatic sufficiency



(NORMAL) FUNCTION OF CFTR IN EPITHELIUM

- CFTR protein: transmembrane (conductance) regulator
  - Only ABC that consumes ATP to function
  - Only ABC that is an ion channel (Cl^- = anion)
- Regulates general osmolarity (transport of Cl across membrane)
  - Pancreas/intestine: pumps Cl^- ions OUT of the cell, CFTR can regulate water secretion in some epithelial cells
  - Lung: pumps Cl^- ions INTO the cell, CFTR can regulate absorption of ions in excess of water, thereby creating hypotonic water outside the cell
- Epithelia containing CFTR protein exhibit array of normal functions:
  - Volume absorbing (airway, distal intestine)
  - Salt absorbing without volume (sweat ducts)
  - Volume secretory (proximal intestine, pancreas)

CFTR DYSFUNCTION: caused by mutations → different effects on patterns of electrolyte & water transport

MUCOSAL CHANGES:
1. Abnormal reabsorption of water
2. Thickened mucus
3. Inadequate mucociliary function/clearance

LUNGS	GI TRACT
• ASL hydration & mucociliary clearance • Cough	• Microvillus & luminal hydration • Peristalsis
• Antimicrobials from submucosal glands	

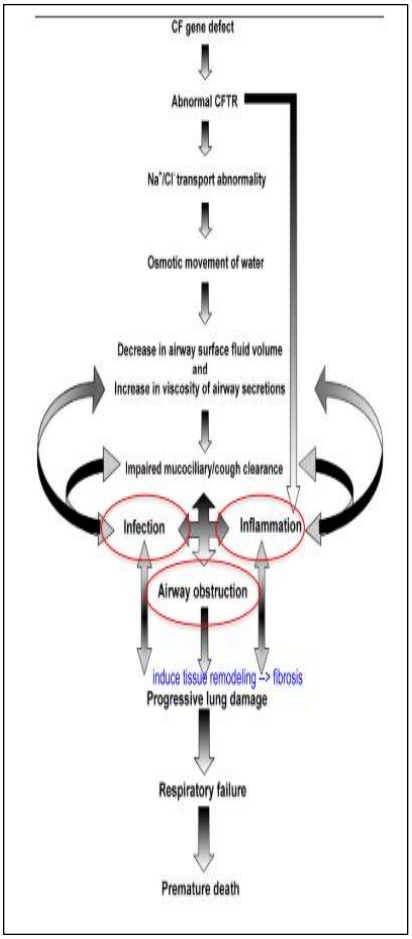
LUNGS:
1. High rate of sodium absorption & low rate of chloride secretion → reduced salt and water content in mucus → depletes peri-ciliary liquid
2. Mucus adheres to airway surface → decreased mucus clearing
3. Predisposition to Staph and Pseudomonas infections

PANCREAS:
1. Absence of CFTR limits function of chloride-bicarbonate exchanger to secrete bicarbonate
2. Leads to retention of enzymes in the pancreas → destruction of pancreatic tissue

INTESTINE:
1. Decrease in water secretion → thickened mucus & dessicated intraluminal contents
2. Obstruction of small and large intestines

BILIARY TREE: *don't memorize*
1. Retention of biliary secretion
2. Focal biliary cirrhosis
3. Bile duct proliferation
4. Chronic cholecystitis, cholelithasis

SWEAT:
1. Normal volume of sweat
2. Inability to reabsorb NaCl from sweat as it passes through sweat duct



MANIFESTATIONS

CLINICAL PRESENTATION:
CF PANCREAS
Chronic respiratory disease
Failure to thrive
Polyps
Alkalosis, metabolic
Neonatal intestinal obstruction
Clubbing of fingers
Rectal prolapse
Electrolyte in sweat
Aspermia/absent vas deferens
Sputum contains S. aureus/ P. aeruginosa

COMMON PRESENTATIONS:
- Chronic cough
- Recurrent pulmonary infiltrates
- Failure to thrive
- Meconium ileus

RESPIRATORY TRACT:
- Chronic sinusitis: nasal obstruction, rhinorrhea, nasal polyps
- Chronic cough: persistent; viscous, purulent, green sputum
  - > Exacerbations require aggressive therapy: postural drainage, antibiotics
  - > Become more frequent age → progressive loss of lung fxn
- Infection
  - > Initially: *H. influenza & S. aureus*
  - > Subsequently: *P. aerugonisa*
  - > Occassionally: *Xanthomonas xylosoxidans, Burkholderia gladioli, Proteus, E. coli, Klebsiella*
- Lung function: small airway disease is first functional lung abnormality
  - > Progress to reversible, as well as irreversible changes in FEV1
  - > CXR: hyperinflation, mucus impaction, bronchial cuffing, bronchiectasis

GASTROINTESTINAL:
- Exocrine pancreatic insufficiency
  - > Protein, fat, and Vit A, D, E, K malabsorption
  - > Frequent bulky, foul-smelling stools
  - > Sparing of pancreatic beta cell but beta cell function decreases with age
- Increased incidence of GI malignancy

GENITOURINARY:
- Late onset puberty
- > 95% males azoospermia → obliteration of vas deferens
- 20% females infertile
- 90% completed pregnancies → viable infants

DIAGNOSIS:

DIAGNOSTIC TESTS:

SWEAT TEST:

- Measures sodium or chloride in person's sweat
- Two samples to ensure false-positive does not occur
- Not reliable on newborns

GENETIC ANALYSIS:

- Newborn with signs and symptoms may confirm diagnosis with blood test
- Inherited disease → recommend checking family members and first cousins

DIAGNOSTIC CRITERIA:

- One of the following:
  - Presence of typical clinical features
  - History of CF in a sibling
  - Positive newborn screening test
- Plus lab evidence for CFTR dysfunction
  - 2 elevated sweat chloride concentrations on 2 separate days
  - Identification of two CF mutations (allelic dosage)
  - Abnormal nasal potential difference measurement

DIAGNOSTIC DEFINITIONS:

- DNA analysis ambiguous if not seen before = **V**ARIENT OF **U**NKNOWN **S**IGNIFICANT (VUS)
- Sweat chloride test > 70 mEq/L
- 1-2% of patients with clinical manifestations of CF have a normal sweat chloride test
  - > Nasal transepithelial potential difference