Inherited Genetic Single-gene Disease
Cystic Fibrosis (CF)

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INTRODUCTION

- Most common fatal genetic disease in the US

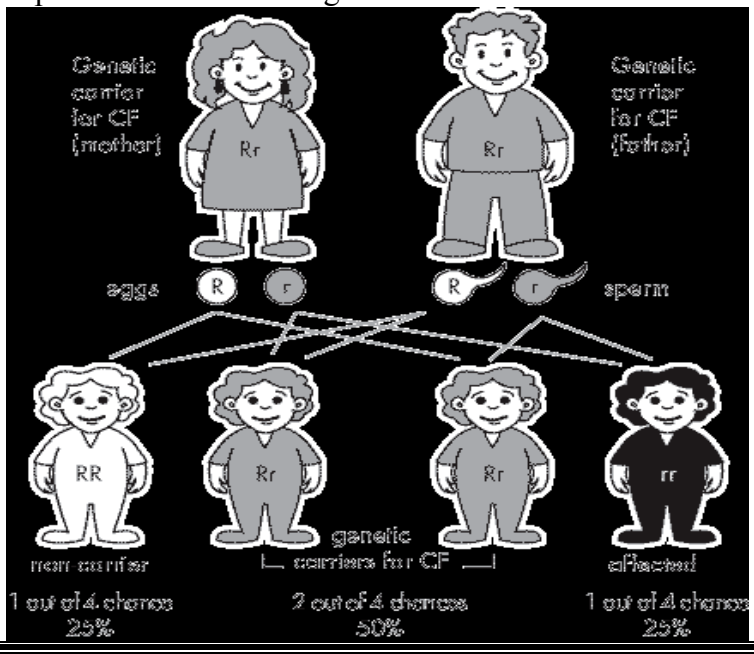
- Produces thick, sticky mucus that clogs the lungs resulting in infection and that blocks the pancreas, disabling the body from digesting food.

- Discovered in 1989, Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene located on chromosome 7.

- CFTR functions as a chloride channel and controls the regulation of various transport pathways in the body.

- Autosomal recessive gene.

- 25 percent chance of being affected; 50 percent change of being asymptomatic (carrier); 25 percent chance of being unaffected and not carriers.



- The average person with CF lives up to 36.5 years.

- Several hundred mutations have been found in the CFTR gene.

- How critical the disease is depends on the effects of the mutations affecting the CFTR gene that the patient has inherited.

How was the disease recognized (diagnosed) *classically*?

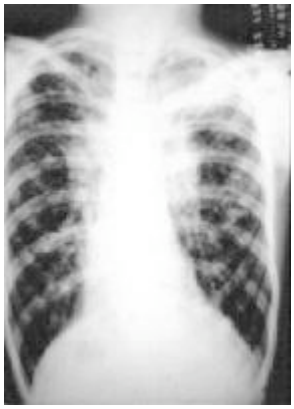
- Cystic Fibrosis was diagnosed based on phenotypic features.

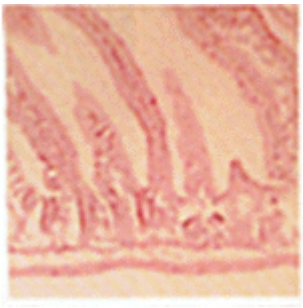
  (1) Chronic Sinopulmonary Disease – constant coughing and sputum, wheezing and air trapping, obstructive lung disease on lung function tests, etc.

  (2) Nutritional Abnormalities – mal-absorption, pancreatic insufficiency, fat-soluble deficiency, problems in production and transportation of bile, etc.

  (3) Obstructive Azoospermia – males not having any measurable level of sperm (infertile)

  (4) Salt-less Symptoms – acute salt depletion, hypocholremic dehydration (reduction in amount of blood chlorides, etc.)





- Sweat chloride values (>60mEq/L) – a chloride-sweat weight of more than 60 mEq/L is diagnostic

- Transepithelial nasal potential difference (NPD)

How was the disease treated *classically*?

- Treatments depended on the symptoms displayed by the CF-diagnosed patient.
  (1) Respiratory problems = antibiotics, anti-inflammatory agents
  (2) Gastrointestinal complications = nutritional therapy, fat-soluble vitamins

- Physical activity, regular exercise program
- Immunizations: vaccines for measles, varicella, influenza, etc.
- Scheduled visits to CF care providers to monitor for small changes in physical examinations
- Pancreatic enzymes to replace those that are missing
- Inhaled medicine to help open airways in lungs
- Pain relievers

Has knowledge of the causative disease gene resulted in new diagnosis (genetic or otherwise)?

- Three molecular genetic test methods for mutations in CFTR

  (1) **Targeted Mutation Analysis:** CFTR mutations detected using the 23-25 mutation panel.

  (2) **Deletion Analysis:** CFTR exonic and gene deletions

  (3) **Sequence Analysis:** check for CFTR sequence variants

  a. Poly T tract located on intron 8 of CFTR gene is associated with cystic fibrosis.

  b. 3 common penetrant variants of the poly T tract include 5T, 7T, and 9T.

- Sweat Chloride testing is still the primary test for CF.
- Molecular genetic testing is only used in prenatal testing for high-risk fetus, newborn screening, or possibly-affected babies who are too young to produce sufficient volumes of sweat.

Have any new treatments resulted from knowing the nature of the disease?

- Knowledge of CFTR gene has paved the way for possible gene therapy.
- Gene therapy is currently only in the research phase.

- Research includes the following:

  (1) CFTR “bypass” therapy = chloride channels

  (2) CFTR “protein assist” treatment

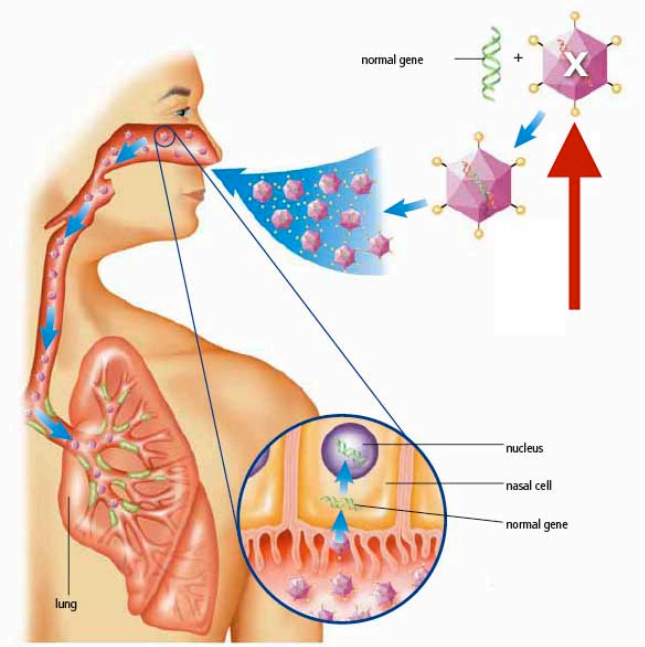
  (3) Use of small molecular modulators of CFTR

  (4) New anti-inflammatory agents

  (5) New IV and inhaled antibiotics

  (6) Possible Replacement therapy

      a. Goal = to replace the defective CFTR gene with a normal gene in affected area or slow the speed of the disease
      b. Process: therapy administered through a spray that is inhaled to deliver normal DNA to the lungs.
      c. Shuttle vectors transport a functional copy of the defective gene to cells throughout the body.



- Genetic clinics are a source of information concerning the history, treatment, manner of inheritance, and genetic risks of CF for families.

References
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