Module I: Introduction to the disease

• Give a brief introduction to the disease, considering the following: the symptoms that define the syndrome, the range of phenotypes exhibited by individuals with the disorder, whether environment plays a role in the severity of the disease, the physiological and psychological effects of having the disorder, and the prognosis and quality of life.

• What is the epidemiology of the disease? That is, how often does the disease occur, in how many births? Is there higher incidence in certain populations or geographical areas? If so, what explanations have been proposed?

• Briefly discuss the history of the disease. Who discovered it and when? How has understanding of the disease changed over time? What issues concern advocacy groups for the disorder (e.g., legal, ethical, social, financial)?

• What is the inheritance pattern (e.g., autosomal, sex-linked, dominant, recessive, etc.)?

• Define the genetic cause of the disease. What gene(s) are affected? What is the locus on the human genome? Briefly describe the wild-type function of the gene product. What types of mutations most commonly lead to the disease? How do these mutations arise?

Sixty-Five Roses
Cystic Fibrosis: Summary

Give a brief introduction to the disease, considering the following: the symptoms that define the syndrome, the range of phenotypes exhibited by individuals with the disorder, whether environment plays a role in the severity of the disease, the physiological and psychological effects of having the disorder, and the prognosis and quality of life.

- Body produces thick mucus due to a malfunction in the Na and chloride channels
- Symptoms:
  - Salty skin
  - Coughing
  - Pneumonia
  - Excessive Appetite
  - “Failure to Thrive”

Cystic Fibrosis: Range

Give a brief introduction to the disease, considering the following: the symptoms that define the syndrome, the range of phenotypes exhibited by individuals with the disorder, whether environment plays a role in the severity of the disease, the physiological and psychological effects of having the disorder, and the prognosis and quality of life.

- Symptoms can vary in severity, though all patients progressively worsen
- 15-20% of CF newborns have an obstructed intestine and need surgery
- Clubbing of the fingers and toes can result from low blood O_2 levels
- Males are generally infertile (90%), while females can sometimes conceive
- Environment has little affect on severity
Cystic Fibrosis: Effects

Give a brief summary of the disease, considering the following: the symptoms that define the syndrome, the range of phenotypes exhibited by individuals with the disorder, the physiological and psychological effects of having the disorder, and the prognosis and quality of life for individuals with the disorder.

- Afflicted individuals cannot maintain physical activity
- Therapies are difficult and time-consuming, and most treat only symptoms
- Secondary lung infection is common
- Diets must be enriched to compensate for nutrient malabsorption

Back drumming to loosen mucus is a common CF therapy

Source -- Cystic Fibrosis Foundation: www.cff.org/facts.htm

Cystic Fibrosis: Prognosis

Give a brief summary of the disease, considering the following: the symptoms that define the syndrome, the range of phenotypes exhibited by individuals with the disorder, the physiological and psychological effects of having the disorder, and the prognosis and quality of life for individuals with the disorder.

- There is no cure
- Quality of life deteriorates with time
- Modern treatment has increased survival, but only 1/2 of CF patients will live beyond 30 years

Figure 1: Prior to 1940, children with cystic fibrosis rarely survived to their first birthday, by 1995, increasingly effective treatment of infection and other secondary manifestations had raised median survival to 30 years or more. (Adapted from Cystic Fibrosis Patient Registry. National Cystic Fibrosis Foundation, Bethesda, MD, 1997)
Cystic Fibrosis: History

Briefly discuss the history of the disease. **Who discovered it and when? How has understanding of the disease changed over time?** What issues concern advocacy groups for the disorder (e.g., legal, ethical, social, financial)?

1955: Cystic Fibrosis Foundation

1990: Gene therapy in vitro

1938: Dorothy Anderson

1989: CF gene discovered

• Better understanding has led to more effective treatment of symptoms
  • Newborns may be treated with surgery to clear an obstructed intestine.
  • Enriched diet compensates for nutrient malabsorption.
  • Antibiotics treat lung infections.

• Median life expectancy was less than a year in 1940, and is now over 30 years.

Sources: www.cff.org/facts.htm Cystic Fibrosis Foundation

Cystic Fibrosis: Epidemiology

What is the epidemiology of the disease? **That is, how often does the disease occur, in how many births? Is there higher incidence in certain populations or geographical areas?** If so, what explanations have been proposed?

• Most common fatal hereditary disease in the US and much of Europe

• 30,000 people in the US have CF

• 1 of 25 Caucasians is a carrier, and 1/2400 individuals are affected

• Frequencies are lowest in Asian populations, with only 1/150 being carriers and 1/89,000

http://www3.nbnet.nb.ca/normap/CF.htm
Cystic Fibrosis: Advocacy

Briefly discuss the history of the disease. Who discovered it and when? How has understanding of the disease changed over time? **What issues concern advocacy groups for the disorder (e.g., legal, ethical, social, financial)?**

- Advocacy and research groups are common world-wide
- Groups provide education and support networks, sponsoring local community events
- Research funding aims to provide better treatments and create greater quality of living

Cystic Fibrosis: Inheritance

What is the inheritance pattern (e.g., autosomal, sex-linked, dominant, recessive, etc.)?

- Autosomal Recessive Trait
- Simple Mendelian Inheritance

Two Carrier Parents have a 25% chance of having a child with CF with each pregnancy
Cystic Fibrosis: Gene

Define the genetic cause of the disease. **What gene(s) are affected?** **What is the locus on the human genome?** Briefly describe the wild-type function of the gene product. What types of mutations most commonly lead to the disease? How do these mutations arise?

- CFTR is the Cystic Fibrosis Transmembrane Conductance Regulator
- Mutations in this gene cause CF
- Found in 1989
- Locus: 7q31.2 (long arm of chromosome 7, band 31, subband 2)

Source: OMIM, NCBI MapViewer, and Entrez Gene

Cystic Fibrosis: Gene Function

Define the genetic cause of the disease. **What gene(s) are affected?** **What is the locus on the human genome?** **Briefly describe the wild-type function of the gene product.** What types of mutations most commonly lead to the disease? How do these mutations arise?

- CFTR codes for a transmembrane protein that functions in transporting chloride ions in and out of cells
- Lack of CFTR causes excess mucus secretion

CFTR
Cystic Fibrosis: Mutations

Define the genetic cause of the disease. What gene(s) are affected? What is the locus on the human genome? Briefly describe the wild-type function of the gene product. **What types of mutations most commonly lead to the disease? How do these mutations arise?**

- Deletion of codon 508 (TTT-phenylalanine)
  - ΔF508
  - Accounts for 70% of mutations in CF patients
  - 700 reported mutations
  - 12 other mutations account for 15%
  - Remaining 15% much less frequent

- Because the disorder is recessive, most mutations are inherited.


CF: Heterozygous Advantage?

What is the epidemiology of the disease? That is, how often does the disease occur, in how many births? Is there higher incidence in certain populations or geographical areas? **If so, what explanations have been proposed?**

- Cystic fibrosis is surprisingly common in Caucasians (1/25 are carriers)
- The mutated CF gene may be advantageous to the heterozygote.
- *Salmonella typhi*, which causes typhoid fever, uses CFTR for entry into epithelial cells. Heterozygous delta-F508 Cftr mice internalized 86% fewer S. typhi than did wildtype mice.

CF: Heterozygote Advantage?

What is the epidemiology of the disease? That is, how often does the disease occur, in how many births? Is there higher incidence in certain populations or geographical areas? If so, what explanations have been proposed?

- *Cholera* and pathogens that cause chloride ion-secreting diarrheas also use CFTR as a gate into the cells.
- But diarrhea-causing pathogens are found all over the world--why were mutations only preserved in N. Europe?
- Mutant alleles lead to chronic excessive salt loss--a major disadvantage in hot climates?

Source: [http://www.people.virginia.edu/~rjh9u/cysfib.html](http://www.people.virginia.edu/~rjh9u/cysfib.html)

---

**CF: Take Home Message**

1. Cystic Fibrosis results in thick mucus buildup due to faulty salt transport, leading to respiratory and digestive problems

2. Many populations are affected but it is most common in Caucasians of European descent

3. CF is inherited in an autosomal recessive pattern

4. CF is caused by defects in the CFTR gene

5. Deletion of phenylalanine 508 accounts for 70% of mutations.

6. Heterozygotes may be more resistant to Typhoid fever, *Cholera*, and chloride ion-secreting diarrheas.