Cystic Fibrosis

Cystic Fibrosis is an autosomal recessive disorder, usually horizontal transmission. Affected Individual must inherit the defective alleles from both parents. Parents almost always heterozygote for this condition.

Cystic Fibrosis Overview

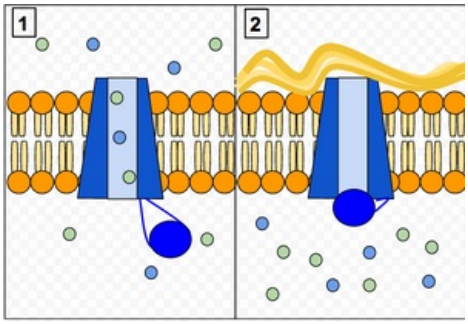
A form of balanced polymorphism. **Mutation in CFTR gene** (cystic fibrosis transmembrane regulator gene). Commonly found in white populations (especially children). Affects 1 in every 2000 children. The *frequency of (mutant allele) heterozygote is greater than frequency (mutant allele) homozygous*. Therefore determining carrier frequency is essential for genetic counselling.

CFTR Gene

CFTR Gene relates to chromosome 7. The coding region comprises 27 exons and encodes for the large integral membrane protein. Over half of the mutations are missense mutations and the remaining relate to other point mutations.

CFTR Protein

Main structural unit, chloride channel composed of five domains which also regulates other ion channels. This type of channel is found in the lungs, pancreas, digestive tract, liver etc. It belongs to the family of proteins called ABC transport proteins which utilise ATP, which serves to increase the conductibility of certain anions, such as chloride ions.

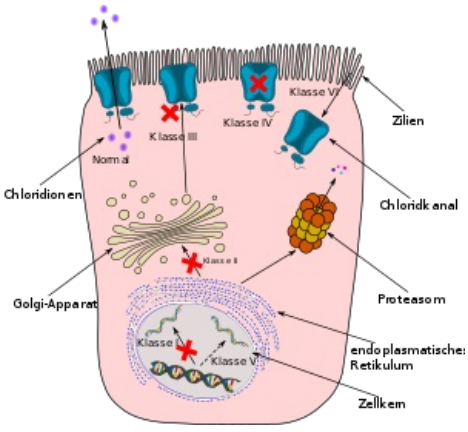


The CFTR protein is a channel protein that controls the flow of H2O and Cl- ions in and out of cells inside the lungs. When the CFTR protein is working correctly, as shown in Panel 1, ions freely flow in and out of the cells. However, when the CFTR protein is malfunctioning as in Panel 2, these ions cannot flow out of the cell due to a blocked channel. This causes Cystic Fibrosis, characterized by the buildup of thick mucus in the lungs.

Causes of Cystic Fibrosis

There are many possible mutations in the CFTR gene which have varying degrees of effect on the domains that make up this integral membrane protein, thus impairing its functionality. Largest single group of mutations is caused by missense substitution.

- **Class 1 mutation**: Causes defect in protein synthesis as a result of reduction in number of RNA transcript, due to generation of unstable RNAs.
- **Class 2 mutation**: is the most common cause and affects the first ATP binding domain. Defective protein processing due to initial incorrect folding of protein caused by loss of 3 nucleotides at 508th position on the protein.
- **Class 3 mutation** which have led to alterations in the regulatory domain which may affect phosphorlyation sites.
- **Class 4 mutation** are localized in membrane spanning domains which causes a significant decline in cholride conductivity.
- **Class 6 mutation** which causes a change in the stability at cell surface.



CFTR mutation classes

Physiology/Pathophysiology of Cystic Fibrosis

Physiology in epithelial cells of the pulmonary system.

CFTR protein is located in the membrane of epithelial cells such as those lining the airways, which establishes a chloride electrochemical gradient, which in turn causes a net movement of chloride ions to the extracelluar space. This then leads to a separation of charges which causes a net movement of sodium ions in the direction of the chloride ions. Therefore this increases the salt concentration in the extracelluar space and in turn causes a net flow of fluid by osmosis in the same direction, resulting in an increase in the fluidity of the mucus overlaying the epithelia cells.

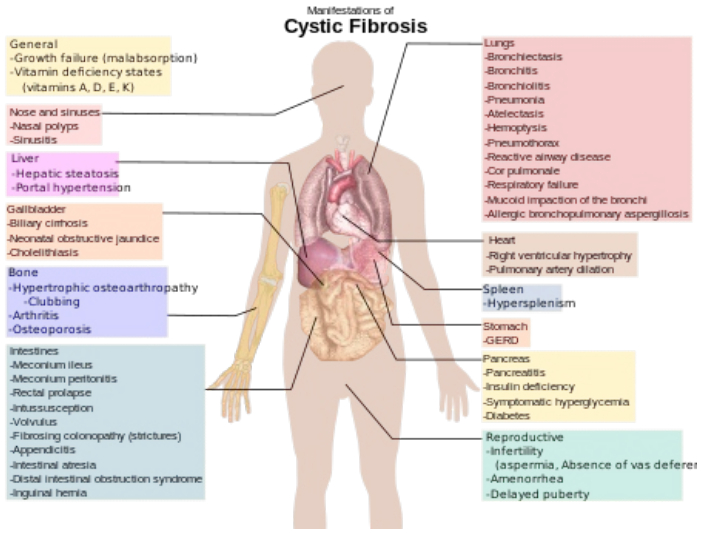
Pathophysiology in epithelial cells of the pulmonary system.

The defective CFTR protein causes an imbalance in the transport of various ions across the membrane, this results in low chloride ion secretions and hyper absorption of sodium ions. Thus the intracellular electrolyte levels increase and this reduces the surface liquid of airways and in turn creates abnormally thick surface mucus layer. This mucus inhibits the activity of cilia and prevents expectoration, so creating an environment favourable for bacterial growth.

Additional Information

Sweat glands is a preliminary diagnostic tool, particularly noticeably in children.

Dysfunction of the transport mechanism in the epithelial cells lining the ducts of the sweat gland results in reduction in reabsorption of chloride ions and this affects the electrochemical gradient that would then drive sodium ions into the cell, which results in high concentration of sodium and chloride ions in sweat.



Manifestation of Cystic fibrosis

Phenotypes in Cystic Fibrosis

Pancreatic insufficiency is maldigestion due to a reduction in secretions of pancreatic enzymes; however to a certain degree this can be managed via pancreatic enzyme supplements.

Pancreatic sufficiency is maldigestion prevented due to functionality of the exocrine part of the pancreas.

Pulmonary disease is a chronic obstructive lung disease which is a result of recurrent infections. Management of this disease is possible however death will result due to eventual pulmonary failure, survival age perhaps to mid 30’s.

Other effects include postnatal lower intestinal tract obstruction (meconium ileus). Effect on the genital tract of both sexes. In women reduced fertility and in males complete loss due to lack of vas deferens.

Genotype/Phenotype Correlation

CFTR genotype is considered a good indicator of exocrine pancreatic function. In individuals with mutation caused by deletion of amino acid phenylalanine, they usually suffer pancreatic insufficiency while those individuals which acquire mutant alleles of CFTR gene caused by another form of mutation may have a partly functional CFTR protein and this can lead to pancreatic sufficiency.

CFTR poor indicator of the severity of pulmonary disease. In individuals relating to the mutation caused by the deletion of phenylalanine, the magnitude of pulmonary diseases varies.

Links

References

- Wikipedia Encyclopedia
- Genetics in Medicine - Thompson & Thompson (7th Edition)
- Medical Genetics at a Glance – Pritchard & Korf (2nd Edition)