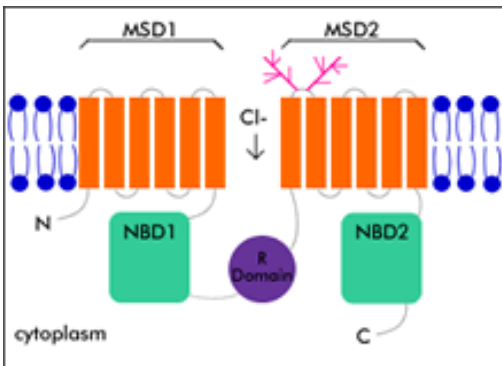


Cystic fibrosis

Cystic fibrosis is a hereditary disease that causes certain glands to produce abnormal secretions, resulting in tissue and organ damage, especially in the lungs and the digestive tract. It is the most common inherited disease leading to a shortened life span among white people in the United States. It occurs in about 1 of 3,300 white infants and in 1 of 15,300 black infants. It is rare in Asians. It is equally common in boys and girls.

Cystic fibrosis results when a person inherits two defective copies of the CFTR (*Cystic Fibrosis Transmembrane Conductance Regulator*)-encoding gene. CFTR is a member of the *ABC Transporter Family* (for ATP Binding Cassette Transporters; called this because they all bind and hydrolyze ATP). CFTR appear to function mainly as chloride ion channel and/or regulator of other ion channels, thereby regulating the transport of chloride and sodium (indirectly, through its effect on ENaC, epithelium sodium channel) across cell membranes.



Courtesy of US DOE Human Genome Project.
Source: CFTR: The Gene Associated with Cystic Fibrosis
(http://www.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/cftr.shtml),
September 12, 2003. After Sheppard, 1999.

As shown in the above figure, CFTR has 5 predicted domains: 2 transmembrane domains with 6 transmembrane helices each, 2 NBDs (nucleotide binding domains), and one R domain. NBDs serve multiple roles including opening and closing the CFTR channel as well as perhaps binding and regulating proteins in the cell by altering the gating of other ion

channels. The R-domain has more than one function. In addition to its inhibitory role in channel gating (when unphosphorylated) the R-domain seems to enable the NBDs to bind and hydrolyze ATP more efficiently (when the R-domain is phosphorylated). It also appears to use its C-terminus and N-terminus for targeting and regulation, respectively. There is increasing evidence that CFTR is able to use its intracellular loops to help in gating, providing a mainly stimulatory effect in pore opening overall.

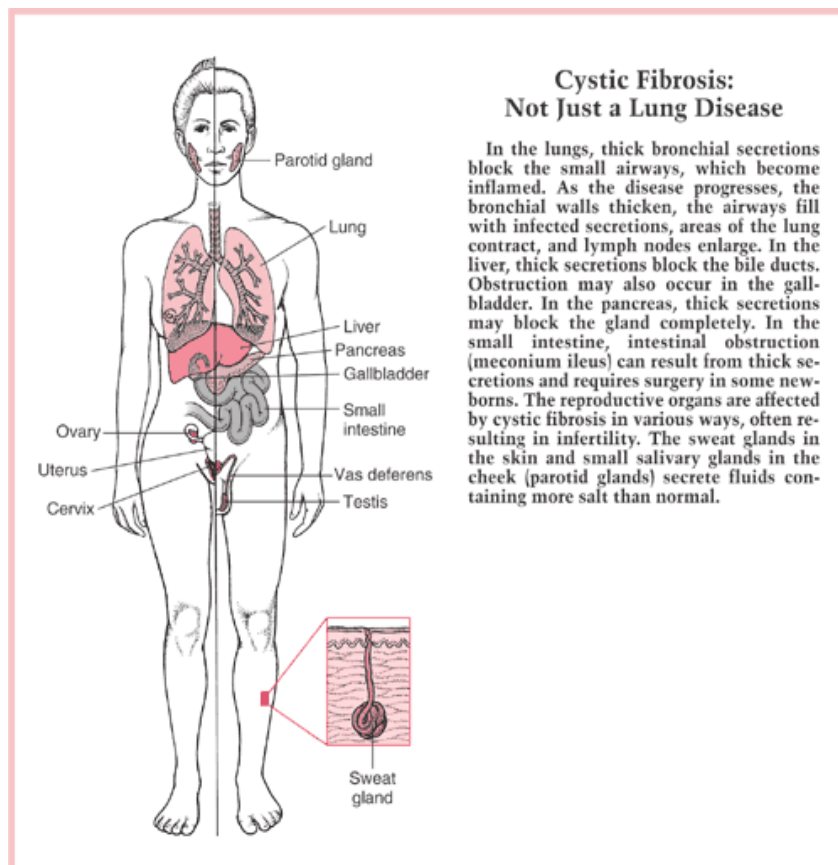
Consequences of the molecular variants in CF range from mutations leading to premature termination of mRNA translation, and thus essentially no protein production (class 1), to those leading to marginally reduced activity (classes 4 and 5). In class 2 mutations, which include the most common CF mutation, Phe-508, the CFTR protein fails to mature properly in the biosynthetic pathway, with degradation of translated protein before it can progress past the endoplasmic reticulum.

Therefore, in people with cystic fibrosis, chloride and sodium transport is disrupted and dehydration and increased stickiness of secretions occur. Cystic fibrosis affects many organs throughout the body and nearly all the glands that secrete fluids into a duct (exocrine glands). The secretions are abnormal in different ways, and they affect gland function differently. In some glands, such as the pancreas, the secretions are thick or solid and may block the gland completely. Eventually, the pancreas can become scarred. The mucus-producing glands in the airways of the lungs produce abnormal secretions that clog the airways and allow bacteria to multiply. The sweat glands and small salivary glands in the cheek (parotid glands) secrete fluids containing more salt than normal.

An example of how a defect in CFTR causes CF is what happens in the respiratory system: Let's imagine that an irritant makes its way into the lungs from the outside (anything from a harmless speck of dust or a pollen grain to a potentially lethal virus or bacteria). The immune system operates under

the assumption that an over-reaction to a foreign invader is better than no reaction at all (which is also the reason why many of us suffer from allergies). These specialized immune cells in the lungs recognize the invader as foreign and dutifully send out a chemical signal into the blood stream telling the rest of the body that the bad guys have made their way into the lungs and the body had better do something about it, and fast. Sneezing would be nice. So would an increase in mucus in the lungs as well as faster swaying cilia hairs which would all help to push irritants out of the lungs. However, if the body is going to increase the amount of mucus in the lung, it had better also increase the amount of water which keeps the mucus moist and free-flowing, otherwise this strategy could backfire and the lung could end up becoming a trap for bacteria. Hydration (water content) of the mucus in the lung is acquired in the submucosal glands in the lower airway of the lungs. This is also the place where the large glycoprotein, mucin, is made and secreted into the mucus. Proper hydration of mucus is therefore necessary for

its timely removal by the tiny hairs (cilia) on the outside of the airway cells, otherwise, the mucus will become too sticky trapping bacteria as well as the body's immune system cells (which can add to the inflammation) in the lungs. When CFTR is not working properly, chloride (and therefore water) will not flow from the bloodstream into the mucus at the submucosal glands of the lower lung. This means that in CF, the mucus deep down in the lungs is already starting out on its journey to the throat as being too sticky. In addition to this, paradoxically, in the upper airway, where the mucus normally has *some* of its water removed back to the bloodstream, CFTR is needed to keep the sodium ion channel, ENaC, from working. When there's no CFTR in the upper airway, as in CF, too much sodium travels back from the mucus into the cells of the upper airway, meaning that the water will also travel from the mucus back to the bloodstream. This makes the mucus lose even more of what little water it already has, and as a result becomes even more sticky and viscous than it otherwise would be.



Liddle's syndrome

The epithelial sodium channel (ENaC) is of fundamental importance in the control of sodium fluxes in epithelial cells. Modulation of sodium reabsorption through the distal nephron ENaC is an important component in the overall control of sodium balance, blood volume and thereby of blood pressure.

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See Figures 1 in Gormley, K., Dong, Y. and Sagnella, GA. 2003. Regulation of the epithelial sodium channel by accessory proteins. *Biochem. J.* 371; 1-14.

ENaC is composed of α -, β -, and γ -subunits that contains PY motifs recognized by WW domains in NEDD4, a member of the HECT E3 ubiquitin ligase family. Its steady state is therefore regulated by the ubiquitin-proteasome system (endocytosis and lysosomal degradation also play a role in controlling ENaC levels).

The adrenal hormone aldosterone is a major mechanism in the preservation of salt and water in response to sodium depletion. This hormone modulates ENaC expression of serum- and glucocorticoid-regulated kinase-1 (SGK1), which phosphorylates NEDD4 on serine residues, thereby abolishing its interaction with ENaC. Thus, defective regulation of ENaC expression by aldosterone and SGK1 may also disturb Na^+ homeostasis and contribute to hypertensive states.

Liddle's syndrome is an autosomal-dominant form of hypertension characterized by early onset of severe hypertension, hypokalemia

(serum potassium (K^+) concentration is below the normal range), metabolic alkalosis, salt sensitivity, and low values of serum aldosterone and rennin. Mutations in subunits of ENaC lead to increased numbers of membrane channels and sustained channel activity. In patients with Liddle's syndrome, mutations in the PY motifs result in channels that cannot be ubiquitinated and are therefore stabilized resulting in higher-than-normal levels of activity.

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See Figures 7 in Gormley, K., Dong, Y. and Sagnella, GA. 2003. Regulation of the epithelial sodium channel by accessory proteins. *Biochem. J.* 371; 1-14.

CFTR is needed to regulate ENaC activity so both of their functions are "knocked-down" in CF:

ENaC function depends critically on the state of CFTR in a purely salt-absorbing epithelium. Major pathophysiological symptoms of CF probably result from an inability of the mutant CFTR to inhibit ENaC, manifesting itself in an increased rate of sodium reabsorption in the airway, pancreatic and colonic epithelia of affected individuals. The impaired secretion of Cl^- from the serous cells of airway submucosal glands and the enhanced absorption of Na^+ and consequent hyperabsorption of electrolytes and water are crucial for the pathophysiology of the lung disease seen in CF. CF airways are unable to enhance their secretory transport and may even be hyperabsorbing due to enhanced activity of ENaC. This leads to a volume depletion of the airway surface liquid

layer in CF airways. Consequently, mucus impactions form, resulting in an impaired mucociliary clearance and subsequent predisposition towards bacterial infections.

By contrast, it has long been known that CF is associated with a reduction in sodium reabsorption within the sweat gland lumen. This accounts for the presence of 'salty sweat' in individuals with CF and provides a characteristic diagnostic feature for CF. To some extent this can be accounted for by the reduction in Cl^- conductance of the apical membrane of the epithelial cell. This is expected to decrease the electrochemical driving force for sodium to enter the cell and thereby leads to the secretion of fluid containing a much higher content of sodium. However, it has been suggested that failure to reabsorb sodium is due not only to the electrochemical effects arising from the primary loss of chloride conductance through the CFTR but also to a secondary inability to activate sodium-channel conductance.

It may therefore be possible that both the activation and inhibition of ENaC are governed by CFTR under different circumstances.

..As you may imagine, in these diseases a global electrolyte imbalance occurs since the homeostasis of other electrolytes also depend in that of Na^+ and Cl^- , therefore resulting affected as well.