Genotype-phenotype discord in Cystic Fibrosis

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What is Cystic Fibrosis (CF)?

- Cystic Fibrosis is a genetic disease caused by mutation(s) in the cystic fibrosis transmembrane regulator (CFTR) gene.

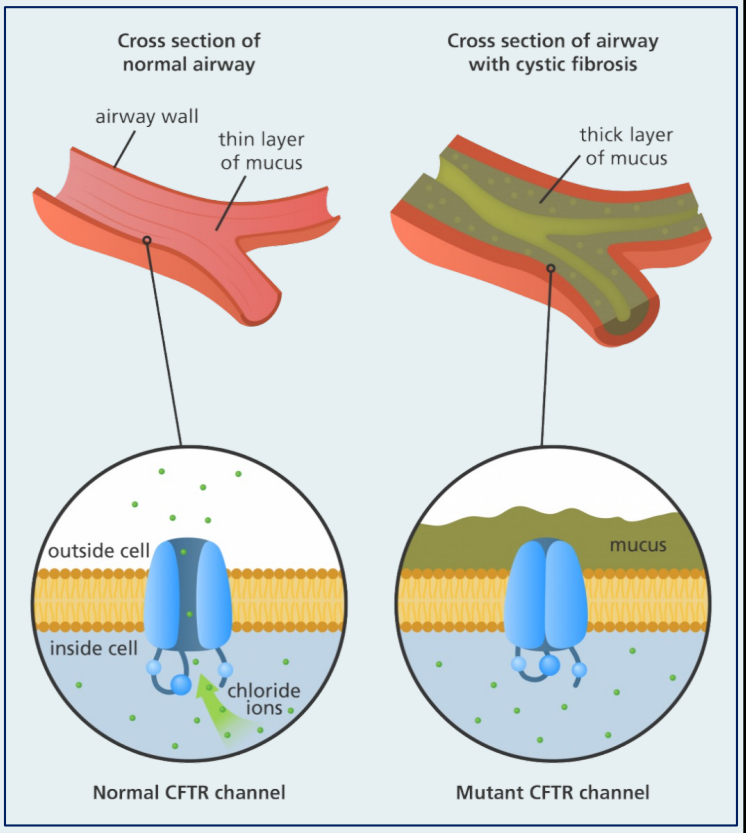
- The CFTR gene contains the blueprint for creating the CFTR protein. When there is a mutation in the CFTR gene, the blueprint is altered and so is the CFTR protein thus resulting in a change in its function.

- The CFTR protein is found in the cells of many important organs including the lungs, pancreas, and sweat glands

- There are over 1000 gene mutations associated with cystic fibrosis.

Cystic Fibrosis Transmembrane Conductance Regulator Protein (CFTR)

- CFTR protein acts as a channel on cell surfaces to move chloride (salt) in and out of the cell. When the CFTR gene is mutated, CFTR protein is not present or unable to move chloride.
- Dysfunction of the CFTR protein results in defective chloride secretion and defective mucus clearance.
- Chloride is required to draw in water, without it a thick and sticky mucus builds up in the lungs, pancreas, liver, and intestines

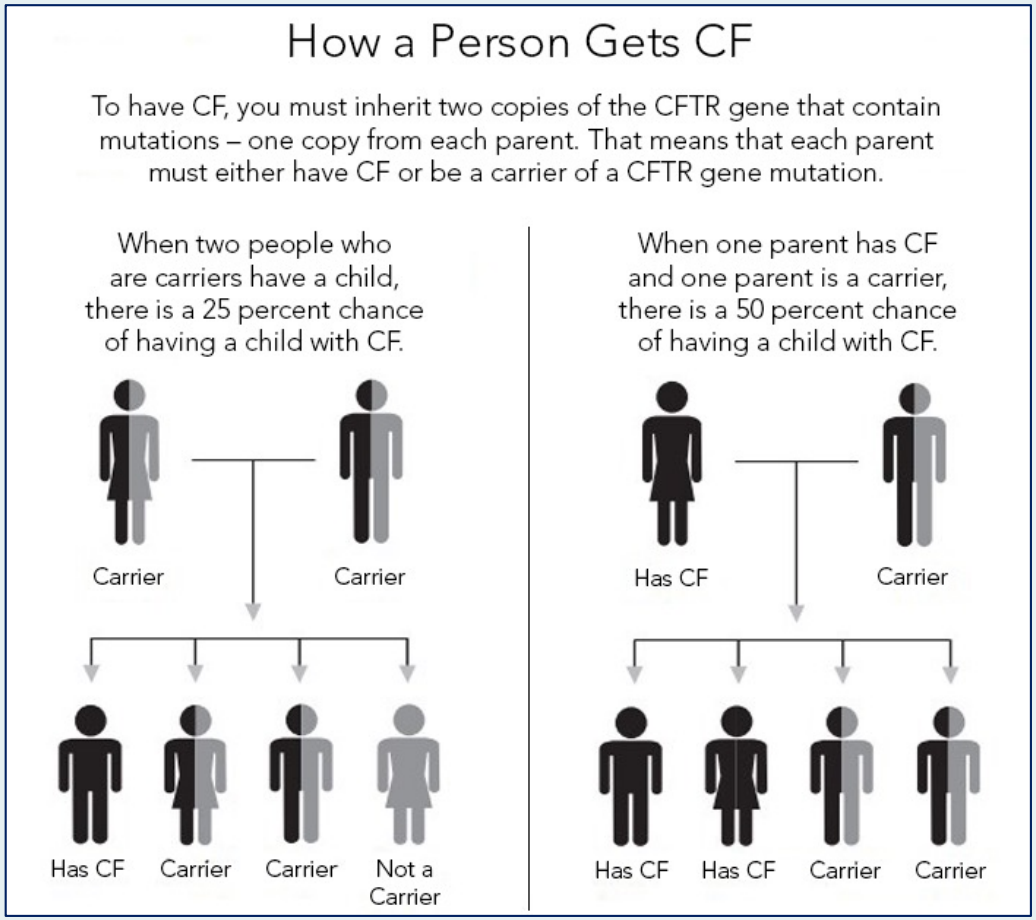


Source: https://www.yourgenome.org/facts/what-is-cystic-fibrosis

How is CF inherited?

- CF is an autosomal recessive genetic disease (see figure to the right)

- The frequency of CF occurrence in the United States is about 1 in 3,500 live births of European (Caucasian) descent; the frequency is much lower in other ethnic groups



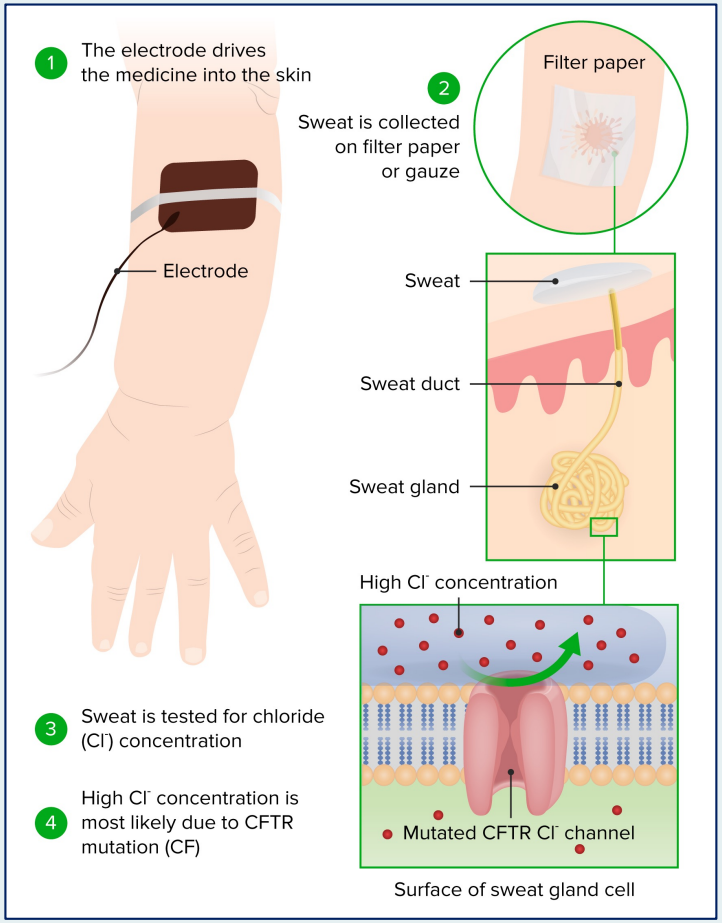
Source: https://www.cff.org/intro-cf/cf-genetics-basics

How is CF diagnosed?

- **Immunoreactive Trypsinogen (IRT) enzyme test**
  - A blood test for IRT, an enzyme that may have increased levels as a result of pancreatic blockage due to mucus accumulation

- **Sweat chloride level test**
  - Using a sweat-inducing topical medication and light electrical stimulation, sweat is tested for high chloride levels

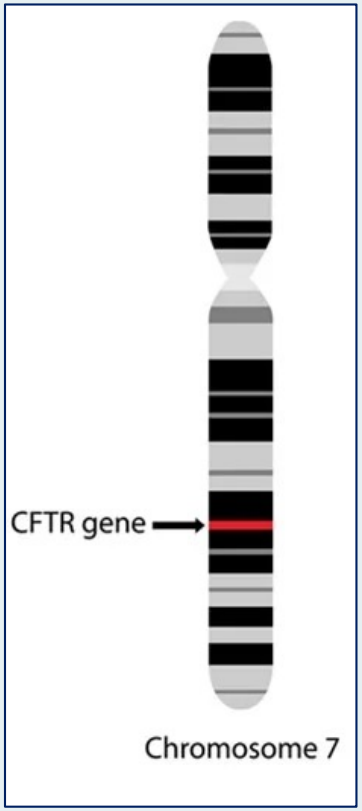
- **Genetic testing**
  - DNA is analyzed for known CFTR gene mutations using polymerase chain reaction (PCR), a technique used to amplify sections of DNA for various types of analysis



Source: https://www.lecturio.com/concepts/cystic-fibrosis/

Genetic testing

- Deletion of the amino acid phenylalanine at position 508 on chromosome 7 is the most common mutation causing CF; there are many other mutations each carrying differing risks
- Genetic testing can provide insight into what type of mutation an individual has and if they are at higher risk for certain symptoms
- Therapy differs significantly for each class of mutation, and CF treatment can be tailored toward the individual for better outcomes

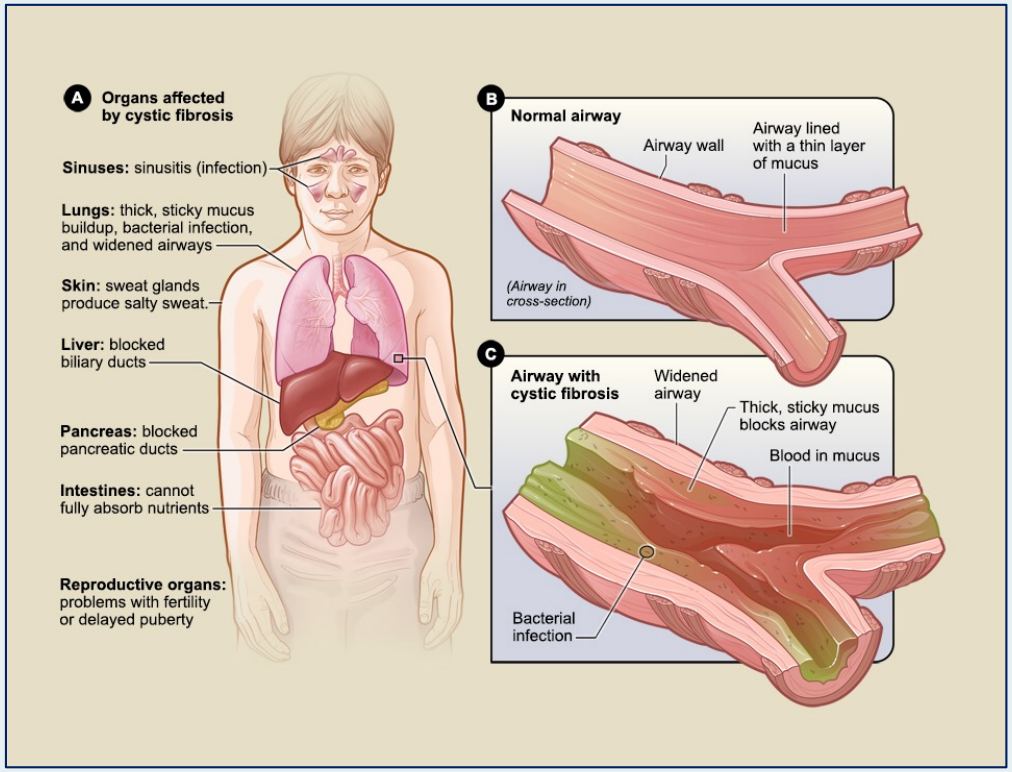


Source: https://www.news-medical.net/health/Tests-for-Cystic-Fibrosis-During-Pregnancy.aspx

Common symptoms

- **Decreased pulmonary function**
  - Mucus in the lungs blocks airways and traps bacteria, leading to infections
- **Pancreatic insufficiency**
  - The pancreas absorbs chloride and secretes bicarbonate via the CFTR channel, maintaining the proper pH of digestive fluids and other pancreatic secretions.
  - Altered functions of CFTR causes improper pancreatic secretions, resulting in mucus which blocks the release of digestive enzymes and thereby improper nutrition and growth
  - Many CF patients regain pancreatic sufficiency in adulthood with proper treatment
- **Male infertility**

  97% of men who have CF are infertile. They produce sperm but are missing the sperm canal.



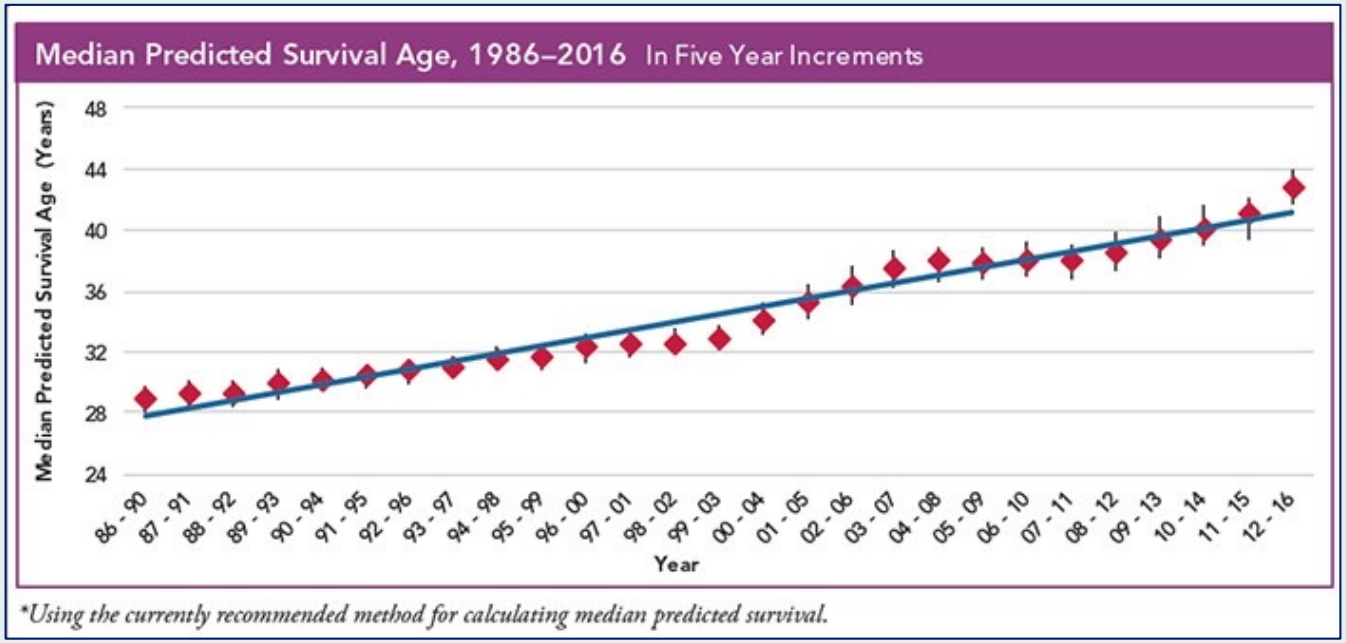
Source: https://www.nhlbi.nih.gov/health/cystic-fibrosis/symptoms

Other common symptoms and complications

- **Chronic constipation and digestive issues**
  - Possibility for newborns to have meconium ileus, a blockage of stool from leaving the small intestine.
  - May cause chronic constipation in adulthood
- **Liver disease**
  - Mucus can block the bile duct, a tube that releases a fluid to help digestion, and lead to liver disease
- **Reduced uptake of nutrients**
  - Mucus buildup in the pancreas and intestines cause low uptake of proteins, vitamins, and minerals essential for proper nutrition
  - Teens especially require more caloric intake than others their same age, around 1½ to 2 times the energy intake compared to others
  - Dietary supplements may be required to ensure proper nutrition
  - A dietician who specializes in CF can develop plans to assist in creating a diet plan

Current state of treatment

- Median life expectancy has increased tremendously over the past few decades
- Changes in diet, development of new drugs, and antibiotics are contributing factors



https://www.cff.org/community-posts/2017-11/survival-trending-upward-what-does-really-mean

Current state of treatment

- Disciplined regimen including taking prescribed medication, daily exercise, physical therapy, enzyme supplementation, and proper diet

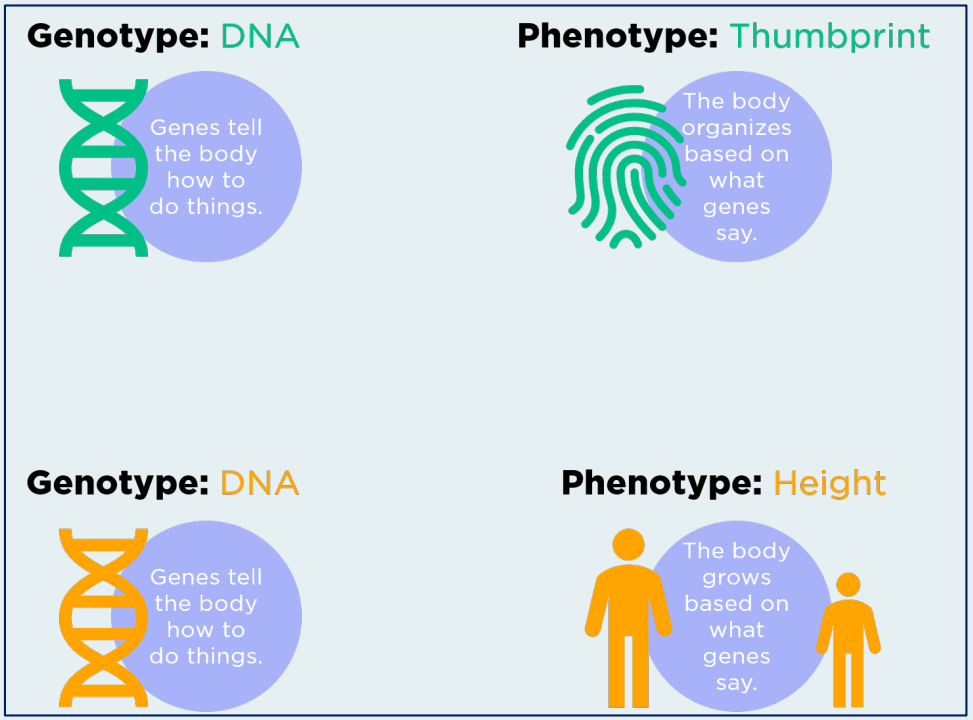
- Cystic fibrosis remains difficult to manage and can cause overwhelming stress for patients and parents. The mental health challenges cannot be ignored and should be monitored in both children and adults.

- An increasing number of patients can live productive, happy lives. Studying at college, marrying, and starting families can be within reach of most CF patients.

Source: https://www.medindia.net/patients/patientinfo/cystic-fibrosis.htm

What is genotype-phenotype discord?

- A person's genotype is their collection of genes that were inherited from their parents
- A person's phenotype is the set of observable traits that arise from inherited genes and their interaction with the environment
- In some cases, a person's observed phenotype does not coincide with what is expected based on their genotype
- Understanding what causes the discord between genotype and phenotype allows for better treatment of genetic disease



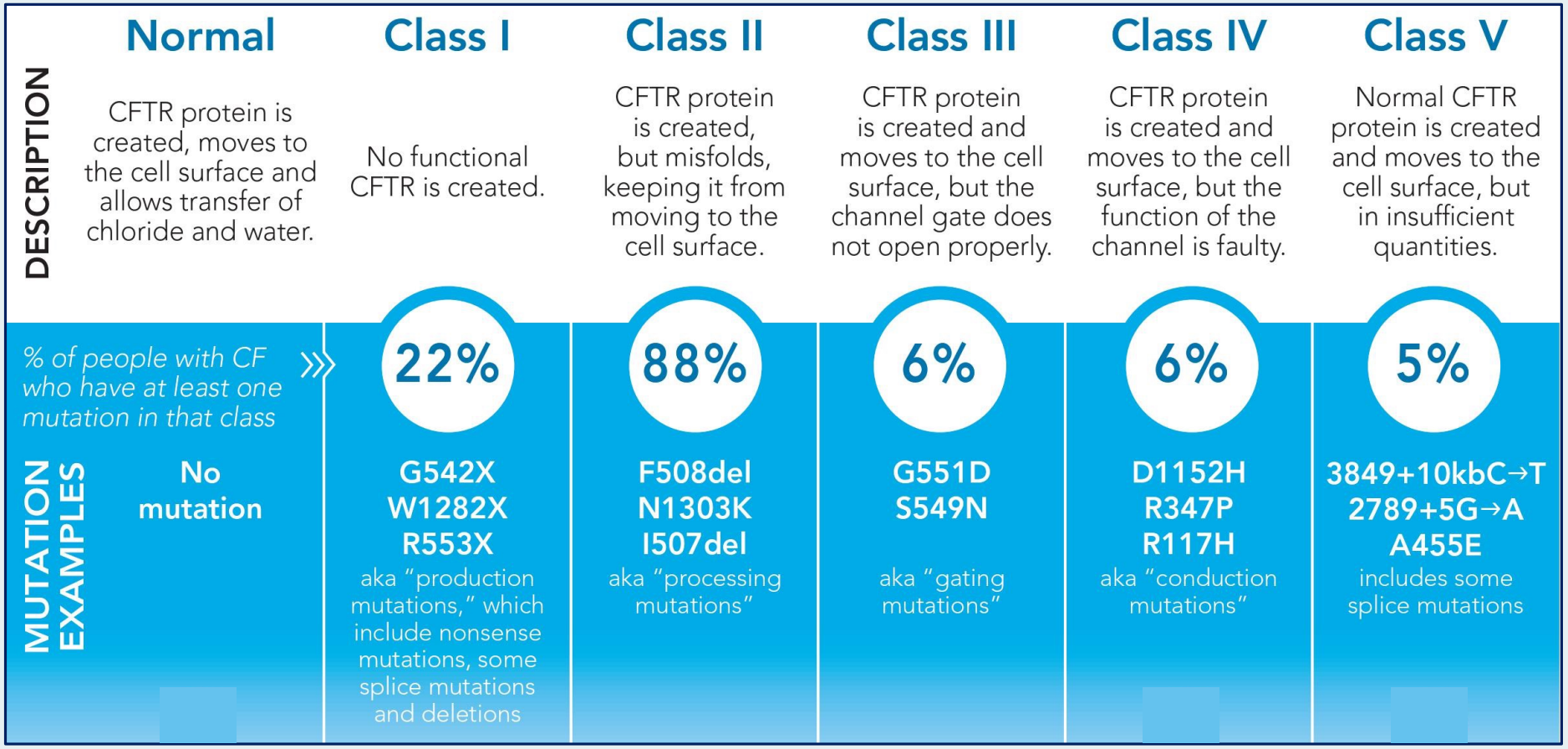
Source: https://www.expii.com/t/phenotype-definition-overview-10228

What affects the expression of CF Symptoms?

- Proper treatment including medication, diet, and exercise has a positive effect on the severity of symptoms
- There are 5 classes of mutations that correlate to the severity of some symptoms
- Modifier genes are genes that are not associated with CFTR but change phenotypic expression and severity of symptoms
- Still many unknowns, but progress is constantly being made in understanding CF and developing new treatment.

Five classes of CFTR mutations

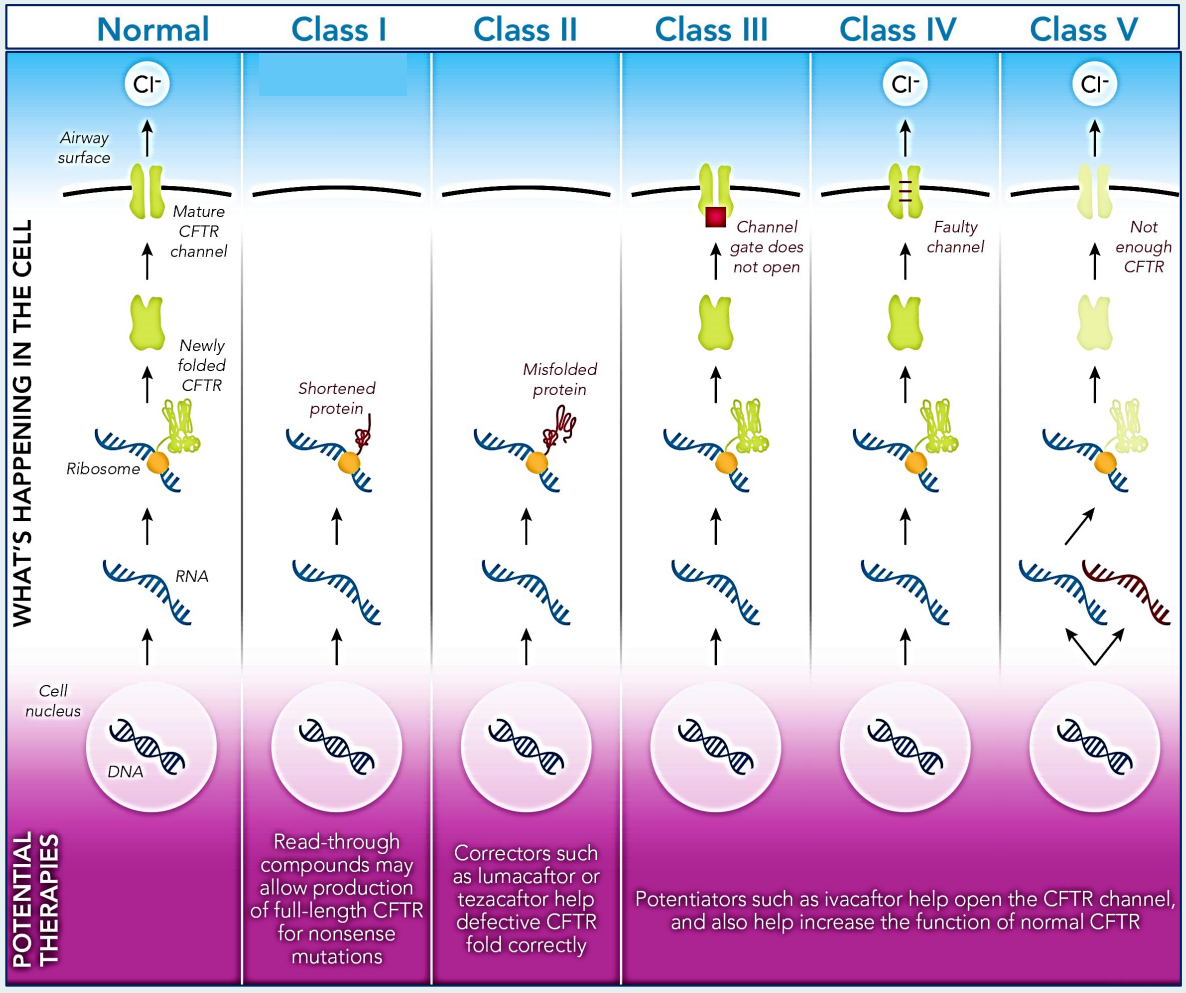
Phenotypic severity is generally highest with a class 1 mutation and lowest with a class 5 mutation



Source: https://www.cff.org/sites/default/files/2021-12/Know-Your-CFTR-Mutations-Infographic.pdf

Five classes of CFTR mutations

- Mutation class may be determined through genetic testing
- Certain medications may only be used depending on a patient's mutation class
- While mutation class may influence the severity of symptoms, there are many other factors that effect phenotypic expression



Source: https://www.cff.org/sites/default/files/2021-12/Know-Your-CFTR-Mutations-Infographic.pdf

Variation in phenotypic expression

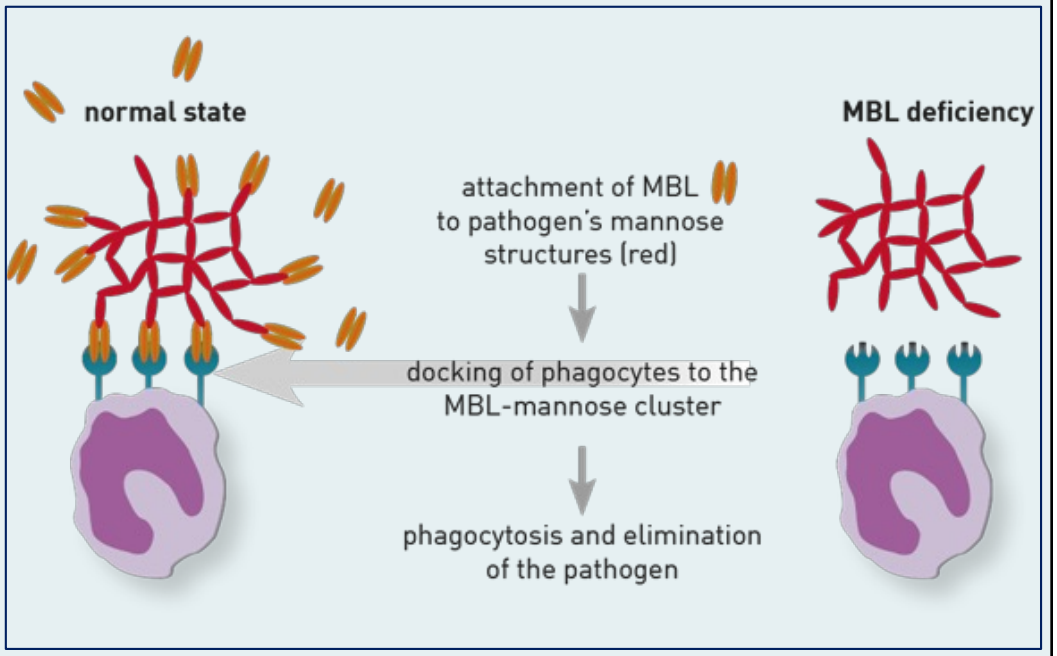
- **Some phenotypes seem to have no dependence on genotype**
  - This class includes liver disease which is only found to be correlated with a gene called GSTP1
  - Phenotypic expression of pulmonary symptoms has no correlation to any specific genotype nor class of mutation

- **Some genotypes are correlated with milder phenotypes**
  - Two genotypes known as “R117H” and “DelF508” contain a likelihood of milder symptoms including pancreatic sufficiency, lower sweat chloride levels, and older age at first diagnosis
  - Other genotypes known as “G551D” and “DelF508” carry a possible decreased risk of meconium ileus at birth

Other genotype-phenotype correlations

- Patients with pancreatic insufficiency (often associated with Class I-IV mutations) have worse pulmonary function than patients with pancreatic sufficiency

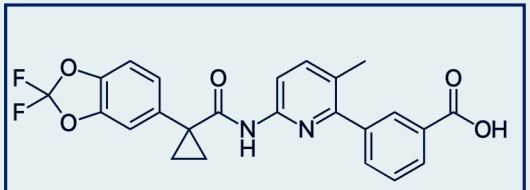
- Deficiencies in Mannose Binding Lectin (MBL), a protein that acts as the first line of defense of the immune system, increases likelihood of the severe pulmonary phenotype as bacterial infections become more common (see figure). The basis is unclear.



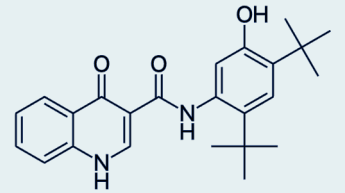
Source: https://www.imd-berlin.de/en/subject-information/diagnostics-information/deficiency-of-mannose-binding-lectin-mbl-as-a-cause-of-impaired-pathogen-defence.html

Lumacaftor, Tezacaftor, and Ivacaftor

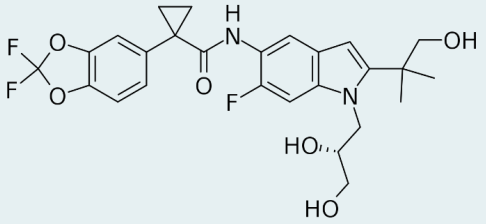
- Three new drugs that treat CF at a molecular level have recently been approved for treatment (2012, 2015, and 2018)
- Lumacaftor and tezacaftor stabilize the mutant CFTR protein and allowing it to reach the outer cell surface to perform its function
- Ivacaftor is the only drug that enhances CFTR channel activity allowing the movement of chloride across the membrane
- F508del homozygotes (class 2 mutation) are treated with a combination of ivacaftor and either lumacaftor or tezacaftor



Lumacaftor



ivacaftor



Tezacaftor

Available resources

Cystic Fibrosis Foundation

- Funds and allows access to CF research
- Provides care and support options for CF patients
- Provides financial assistance and help navigating insurance

CYSTIC FIBROSIS FOUNDATION

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