

Autosomal Recessive Inheritance Cystic Fibrosis: A Literature Review

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Abstract: -Cystic fibrosis is a disorder caused by mutation in the Cystic Fibrosis Transmembrane Conductance Regulatory gene known as CFTR. This mutation occurs on chromosome 7. This disease is an autosomal recessive disorder which means that the disease is inherited when a child inherits a defective copy of the gene from both parents who are carriers of the gene. A carrier is an individual who has a defective copy and a normal copy of a gene and is unaffected themselves. The CFTR gene codes for the CFTR protein which is an important chloride channel. The purpose of the channels is to pump ions in and out of the cell. The symptoms and associated complications of cystic fibrosis are caused by the dysfunctional CFTR protein channel which is found throughout the gastrointestinal tract. Affected individuals have elevated sweat electrolyte levels, pancreatic insufficiency and lung infections. These signs are observed in most patients but not all. Since severity of the disease can range widely amongst individuals.

Keyword: - Cystic fibrosis; autosomal recessive; CFTR; phenylalanine

Introduction:

Cystic fibrosis or CF is a genetic disorder that affects the lungs. (1) In fact the name cystic fibrosis, refers to the disease's effect on the pancreas, where it can lead to cysts, which are fluid filled sacs wrapped in a membrane and fibrosis excess deposition of connective tissue that can replace or infiltrate normal tissue in an organ. (1) CF is an autosomal recessive disorder involving the CFTR gene which stands for "Cystic Fibrosis Transmembrane Conductance Regulator" and this gene codes for CFTR protein. CF develops when there's a mutation in the CFTR gene, but because it's autosomal recessive, you need to inherit two mutated CFTR genes, one from mom and one from dad. Now if mom and dad both have one copy of the mutated gene and one normal gene, they're considered carriers and they don't have the disease. (2) And inheriting CF is much more common in people of European descent. Now the CFTR protein is a channel protein that pumps chloride ions into various secretions, those chloride ions help draw water into the secretions, which ends

up thinning them out. The most common mutation is with CFTR is the delta f508 mutation. 'Delta' means a deletion and the 'F' (which can also be written as "phe") is short for phenylalanine, and the 508 is the 5 hundred and 8th amino acid in the CFTR protein. So, the delta f508 mutation is where the 508th amino acid of 1480 phenylalanine, is deleted or missing. (2) The CFTR protein with the delta f508 mutation gets misfolded and can't migrate from the endoplasmic reticulum to the cell membrane, meaning there's a lack of CFTR protein on the epithelial surface, and this means that it can't pump chloride ions out, which means water doesn't get drawn in, and the secretions are left overly thick. (3,4) In a newborn, thick secretions can affect a baby's meconium or first stool, or which can get so thick and sticky that it might get stuck in the baby's intestines and not come out, and this is called a meconium ileus and is a surgical emergency. (5) In early childhood, pancreatic insufficiency is the most prominent effect of CF. and this happens because thick secretions jam up the pancreatic ducts, not

allowing digestive enzymes to make it to the small intestine. Without those pancreatic enzymes, protein and fat aren't absorbed and overtime this can lead to poor weight gain and failure to thrive. Fat malabsorption can lead to steatorrhea or fat containing stools. Eventually the pancreas gets damaged, because backed up digestive enzymes the cells that lining the pancreatic duct, causing local inflammation. And this can lead to acute pancreatitis and with repeated episodes chronic pancreatitis, with the development of cysts and fibrosis like we talked about, giving the disease its name. Finally, the destruction of pancreatic tissue can also compromise of the endocrine function of the pancreas, causing insulin-dependent diabetes.(6) Its usually not until later in childhood that lung problems start to crop up. Normally the cilia hair-like projections lining the Airways do a pretty good job of keeping them clean by moving mucus, which catches like debris and bacteria, toward the pharynx, called mucociliary action. With thick mucus, though it gets a lot harder to clear and then mucociliary action becomes defective, which means bacteria is allowed to chronically colonize the lungs. If the bacterial load suddenly increases, the cause's symptoms like a cough and a fever, a decrease in lung function, and sometimes changes on a chest x-ray and this is called CF exacerbation and usually prompts a round of antibiotics. Examples of problematic bacteria include gram staphylococcus aureus which is gram positive and pseudomonas aeruginosa which is gram-negative, both of which can be hard to treat if they are resistance to typical antibiotics. In addition, to bacteria usually form of biofilm where individual bacterial cells are fixed in a matrix of slime which protects them from the immune system as well as antibiotics.(7) Chronic bacterial infection and inflammation can lead to bronchiectasis, which is airway wall damage causing permanent dilation of the bronchi.(8) Occasionally, if the inflammation erodes into a blood vessel, there can even be hemoptysis or coughing up of blood. overtime the repeated CF exacerbations can ultimately lead to respiratory failure, the leading cause of death with CF. other CF related issues include infertility in men who commonly lack the vas deferens which of

the tubes that transport the sperm from the testes to the urethra in the penis.(9) men and women can also have digital clubbing where the fingernails begin a spoon around the fingertips, nasal polyps which are tissue growths in the nose, and Allergic BronchoPulmonary Aspergillosis (or ABPA), which is a hypersensitivity reaction to the fungus aspergillus fumigates which can live in a sinus or a lung cavity.(10,11)

History:

cystic fibrosis was rediscovered in the modern era by this doctor dr. Dorothy H. Anderson and, she was a pathologist hired by Columbia Presbyterian hospital in new York city and in the 1930's when she was the pathologist for the children's hospital there the babies hospital there are a series of children who were admitted with something call celiac syndrome these children were all noticed to be very slender they had tend to be malnourished and they tend to die very early. Dr Anderson performed the autopsies on these babies on these young children and what she discovered was that all of them had something wrong with a particular organ specifically in Organ called the pancreas now the pancreas is an organ which makes among other things pancreatic enzymes which passed from the pancreas into the intestines absorb fat what she noticed in these children with this syndrome was that their pancreas were full of scar tissue and small cyst are like bubbles and so she termed this condition fibrocystic disease of the pancreas also known as cystic fibrosis.(12) So she got a collection of these patients together or reports together and published it in 1938 and a result of that publication several other physicians said similar to my patients and started gathering a collection of patient's children who had the same findings.(12) Based upon their findings they all had problems with severe malnutrition. They tend to have low serum chloride and their blood and dehydration and by looking at the patient's history and family histories. they are able to work out that this was a genetic condition in the 1940s than the words they figured out it was inherited disease and sadly in the 40s, 50s and early 60s the life expectancy of these children after diagnosis was only about <1 year of age.(12)

Discussion:

Cystic fibrosis is well first of all it's an inherited or genetic disease that means you're born with it affects the lungs and digestive systems of about 30,000 patients in the United States and around 70,000 people worldwide. Each year in the United States there are approximately 1000 new cases that are discovered the majority of which are in the state of California.(13) The majority of patients 70% are diagnosed before the age of two years. In the United States newborn screening bounces in treatment and identification more than 50% of CF patients in the United States. The mean survival age now is 38 years.(14) but cystic fibrosis is actually an ancient disease it's believed to have been first described in the dark ages as evidenced by the old German folk saying "woe the child who taste salty from a kiss on the brow, for he is hexed, and soon must die", in a nutshell that kind of describes cystic fibrosis in the era patients were born with it they tended to taste salty because the problems with the salts and water going in and out of the cells and sadly they tended to die very early from severe malnutrition because at that time they didn't have any of the medications or treatments that would have prolonged their lives.(12) Cystic fibrosis well first of all they are born with it. They get a copy of the abnormal CF gene from each parent now appear at themselves may not have cystic fibrosis they usually don't. but they are carrying 1 copies remember you need two copies of the CF gene before you can have cystic fibrosis so they have to get it so CF patient has to get a copy of the abnormal CF gene from each

parent. Unfortunately, CF if never goes away your born with it you don't grow out of it. Cystic fibrosis patients tend to have more called intestinal malabsorption that means they can't absorb fat and so therefore they have a lot of those greasy stools and that results in they don't gain weight if poor weight gain. And they also have problems with lower respiratory tract infections they get a lot of problems with bronchitis and pneumonia. In the 1980s they figured out that CF was primarily due to a problem in something called the CF epithelial cells. In other words the cells in our body that makes the secretions that line the cavities of our bodies and tubes and it had to do with abnormal ion transport those are charged particles and specifically the ion called chloride. The chloride ion particle itself was normal but the way I could get in inside the cell to the outside of the cell the way could move from inside the cell to outside so it was not normal being blocked (exit blocked) or hadn't formed. They also noted to make electrolyte problem worse that's sodium reabsorption back into the cell was accelerated. So finally in 1980s the investigators were finally able to locate where the CF gene rulest was and it was in humans it's on the long arm of chromosome 7.(2) CF gene is like acts like a blueprint for how to create a particular protein that regulates membrane transport that protein is called cystic fibrosis transmembrane conductance regulator (CFTR). CFTR protein creates the main epithelial cell chloride channel. It's the way fluoride that particle goes from inside the cell to outside the cell.

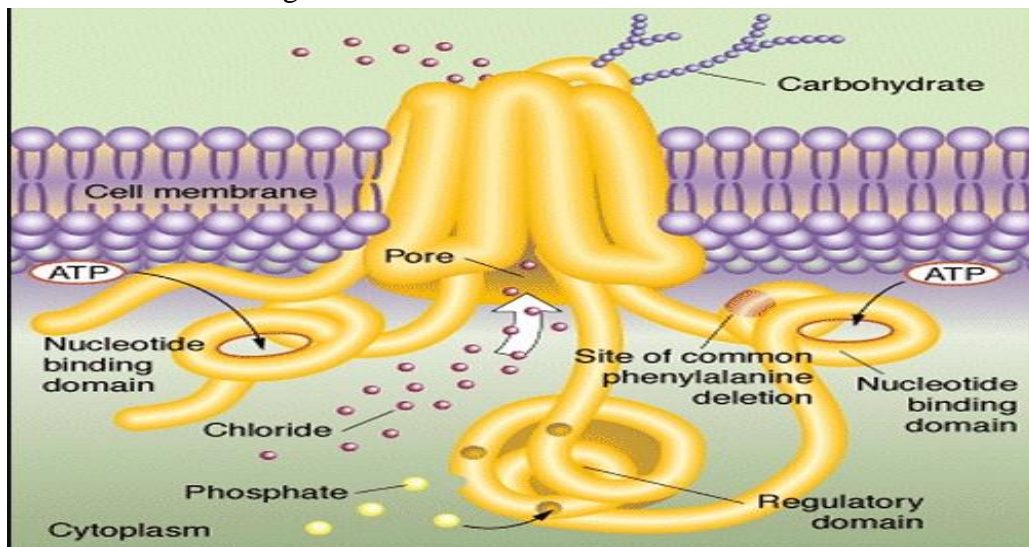


Figure 1: CFTR protein.

This yellow or gummies have a figure is the CFTR protein which is folded to form this passage where channel and permits of chloride particles which of these little purple dots to go from inside the cell pass through the cell membrane in the cell membrane is the outside coating of all the cells as tends to be flexible it permits these chloride particles to go from the inside of the cell to the outside of the cell now there are three important areas of the CFTR protein seems to control how the protein functions and how it's folded these are include the nucleotide binding domain type 1 and the imaginatively named nucleotide binding domain 2 and the regulatory domain these are the three sites that CF researchers are investigating to correct or cure cystic fibrosis.(figure 1)

Classification:

There are six classifications of CF mutations (table 1)

Class I is when there's no CFTR protein made that means there is no Proteins at all doesn't get up to the membrane now these patients with class **I** mutations tend to have the more severe mutations or diseases.(13) **Class II** is was defective protein processing now this in this also includes some of the more common CF mutation such as delta f508

Table 1: classifications of CF mutations

CF Mutation classes
Class I – no CFTR protein made
Class II – defective protein processing
Class III – gating defect
Class IV – conductance defect
Class V– not enough CFTR protein
Class VI – CFTR protein destroyed fast

But basically we can categorize CF mutations there's six different classes to CF mutation but we can categorize them in only two different categories .first category is CFTR they have reduced CFTR function. In the second category is they have reduced CFTR quantity or amount. In the reduced CFTR functions category or mutation classes III, IV and VI. In the CFTR mutations that have reduce quantity or amount of CFTR protein those include class I, II and V. (13, 15)

and while the protein is made it does it doesn't get incorporated or its damaged before it actually reaches the membrane.(13) **Class III** is a gating defect CFTR protein is made it up to the membrane but it doesn't work now at this time we do have a medication which seems to be effective in treating a certain number like up to seven or eight of these gating mutations on that is now available .(13) **Class IV** are those patients who have we called conductance defect the CFTR protein is made it gets up into the membrane but the channel or the pore the opening is defective its either warped or shut it doesn't function.(13) **Class V** is where CFTR protein is made but it's not normal for should say it's normal but there's not enough of it so therefore while to CFTR protein is normal because there's not enough of it have manifestation or clinical signs and symptoms of CF and these patients tend to have more mild disease.(13) **Class VI** these are patient in which the CFTR protein is destroyed very rapidly so in other words the CFTR protein is made it folds correctly it gets up to the cell membrane is incorporated and it works but the problem is it doesn't work for very long and before the whole protein is destroyed and they have to make more so again these patients tend to have more mild CF disease.(13)

Signs and Symptoms:

Cystic fibrosis will have very common signs and symptoms they tend to have a chronic productive cough that doesn't make a lot of sputum and phlegm, they have frequent bowel movements and these bowel movements are stools can be very greasy and very strong smelling they often because of the problem with malabsorption will have poor weight gain they tend to be skinny these are the kind of people who can eat everything and not gain

weight unfortunately then they have a lot of bowel movements also these patients tend to get chronic lung infections pneumonia particular with types of bacteria such as pseudomonas now CF pt can also have lung infection with other common bacteria like staphylococcus but also with burkholderia.(16) So they tend to get chronic infections with these bacteria and despite very powerful antibiotics they're never clear and finally the males tend to be infertile or unable to have children without intervention surgical treatment.(9) Even with newborn screen stuff like that we do know that there are certain symptoms which are very more common in children and adults with cystic fibrosis. so for example, the most common finding inside CF patients or patients we suspect CF are acute or recurrent or chronic respiratory symptoms such as recruit bronchitis or pneumonia patients will tend to have problems with fetus thrive or malnutrition they'll be skinny they'll have steatorrhea or also known as greasy stools for abnormal stools . they will tend to have a family history of cystic fibrosis maybe not so much a cystic fibrosis but if children who died early from pneumonia or malnutrition . Cystic fibrosis can be typical or atypical presentation. the typical CF patients will have chronic sinusitis all of their sinuses will be filled up with mucus an infection ,they will have an abnormal sweat chloride High sweat chloride findings, they tend to get recurrent chronic lung infections, they will also tend to have get liver disease, their pancreas the one that makes pancreatic enzymes well they also tend to have problems with creating or passing sufficient pancreatic enzymes into the intestines to absorb fats and other nutritional, patients will have CF will have tendency to get meconium ileus or plugging at birth and the males 98% of them will have something we call obstructive azoospermia in other words they tend to be infertile without some kind of procedures. However, the atypical CF patients those atypical presentations they will also have chronic sinusitis and they will also have obstructive

azoospermia their males will tend to be infertile. However they will have normal or borderline abnormal sweat chlorides they may or may not have recurrent lung infections and they may or may not have problems with their liver. However most of the patients were atypical CF patients presentation will be pancreatic sufficient that means they will still be able to make enough pancreatic enzymes from the pancreas will pass into the intestines so they don't need to take additional pancreatic supplements.

Diagnosis:

Sweat chloride testing, Blood test for cystic fibrosis genes (may need different panel, depending on race and ethnicity). It is possible to screen for CF in newborns, something that's done in some countries where CF is coming and the helps treatment get started earlier. The newborn screen detects a pancreatic enzyme called IRT or immunoreactive trypsinogen, which is released into the fetal blood to when there is pancreatic damage from CF. and then if a sweat test then detects high levels of chloride in the sweat CF is confirmed. unlike in the lungs and pancreas where chloride can't get out, when CFTR's not working in the sweat glands , chloride can't come in, or be reabsorbed so there's actually high chloride in the sweat. In fact, of children with CF sometimes noticed that when they're kissing their baby the baby taste salty. Chlorides blood testing there is really no single test that is 100% accurate. cystic fibrosis is like a menu one from column A and at least one from column B. so in order to establish if a patient has cystic fibrosis they have to have at least one of these findings one or more typical clinical features of cystic fibrosis, a brother or sister with cystic fibrosis or they have a positive newborn screening ,so they have to at least one of these findings, Plus one of these and elevated sweat chloride on at least two separate occasions two identified CFTR mutations which are known to cause CF disease and an abnormal nasal potential difference . (Table 2)

Table 2: diagnosis of Cystic Fibrosis can be established if a patient has.

Column A - One of these :	Column B - PLUS one of these:
≥ 1 typical clinical features of CF	Elevated sweat chloride on 2 occasions
Brother/Sister with CF	2 identified CFTR mutations
Positive newborn screening test	Abnormal nasal potential difference

Common indication:

Acute or recurrent respiratory symptoms, they have recurrent pneumonia or bronchitis, if they tend to have poor weight or be malnourished ,if they have fatty or abnormal stools, if they have a history of meconium ileus or they have small bowel obstruction ,if there's a family history of cystic fibrosis or history of children dying very young from pneumonia or malnutrition ,if the patients are admitted with hyponatremic dehydration, there was a of low serum sodium the face of dehydration and if the patients have rectal prolapse without evidence of a parasitic infection. However like all his other tests an abnormal or elevated sweat chloride is not unique or old does not only occur with cystic fibrosis it can occur with other conditions for example and patients its can be atopic dermatitis or skin conditions it can occur in patients who have hypogammaglobulinemia which means they have an inherited immunodeficiency it can also occur in patients with severe malnutrition such as occurs with anorexia nervosa or protein calorie malnutrition and it can occur in patients with untreated adrenal insufficiency or untreated hypothyroidism, byler’s disease (familial cholestasis),klinefelter syndrome, nephrogenic diabetes insipidus, nephrosis . It is very important to treat or reverse these conditions before do a sweat chloride. CF dna currently there >2,000 known CF mutations identified (and counting) if a patient CF patient or patient is Caucasian and then and is of northern European descent delta f508 mutation accounts for the majority of those CF genes and only 15 to 20% other CF genes will take up another like account for another 2 to 15%. however so in other words if your patient is Caucasian, northern European descent you only need like 15 to 20 CF mutation panel to get a 90% sensitivity or accuracy in diagnosing CF that population. However if your patient Hispanic if your patient are not Caucasian then you will need this sensitivity drops down to

below 50% . So you will need other special panels to be able to look at more CF Mutations in order to detect at 90% of mutations. So for example Hispanic you need a minimum of like 80 to 150 CF mutations before you can get 90% accuracy of being able to check CF mutations and the problem is that there is no commercially available CF panel that tests for all CF mutation. In CF mutations therefore is very important before you do this expensive test ask for the patient's ethnic background race and family history.

Treatment:

A number of treatments have been proposed with intent of these treatments being to prevent and control instructions and lungs by removing mucus and to prevent blockages in the intestines .a number of treatments for this disease are available including antibiotics for infections of the airways, chest physical therapy and other specific medication. Antibiotics are generally the primary treatment for people with cystic fibrosis, as they most likely will have a lung infection based on the type of bacteria and the severity of the patient’s condition. There are different types of antibiotics that are available.(17) Some of which include oral inhaled or intravenous antibiotics, a second type of treatment is chest physical therapy, which serves us a way to loosen and remove mucus from the lungs. This should be done three to four times a day and it involves repeatedly pounding one's chest and back in order to dislodge the mucus.(17) (Figure 2) As it might be physically demanding for some people their devices such as mechanical percussor or a positive expiratory pump mask (Figure 3 & 4) which both serve the purpose of clearing mucus from the air. Cystic fibrosis can also be treated by medications most notably a group called bronchodilators which help to open the airways relaxing the surrounding muscles.



Figure 2: chest physiotherapy.



Figure 3 and 4: Device used in chest physical therapy.

A major goal around are nutrition and healthy weight gain. Fortunately, fat soluble vitamins (A, D, E and K) extra calories, and replacement of pancreatic enzymes, can all be supplemented to help boost nutrition and help the patient absorb nutrients.(17) In terms of pulmonary treatment there's chest physiotherapy, which loosens the mucous by literally banging on the chest as well as inhalers. There are some medications like N-acetylcysteine which cleaves disulfide bonds in the mucus glycoprotein and dornase Alfa which is a nucleus that cuts up nucleic acids in the mucus to thin it out. CF lung disease is obstructed (like asthma and COPD) so pulmonary function tests are regularly used to monitor the disease. Finally because of chronic infections and loss of pulmonary function overtime, a lung transplant is sometimes needed. A new hope for patients with CF has been the development of personalized treatments that Target specific CFTR mutation types. For example, lumacaftor is a chaperone that can bring the mutated Delta f508 CFTR to the cell membrane and is given

in combination with ivacaftor, which helps the protein work well when it gets there. Even though this isn't cure, these drugs are a good example of a potential of personalized medicine.(13,18) In addition there are new genetic technologies on the horizon aimed at correcting specific gene mutations.

Conclusion:

Cystic fibrosis is an autosomal recessive disorder involving the CFTR gene, which most notably causes issues with the lungs and the pancreas, but can affect other organs liver, intestine and sinuses. cystic fibrosis is really advanced because of the improved treatments antibiotics and nutrition compared to the 1960s the mean survival age now is 38 years that means half of the CF patients in the United States are over the age of 38 compare that to only about one year in the 50s and 60s. Digestion of food becomes difficult and eventually malnutrition becomes a cause of the disease. Prevention and malnutrition has become a greater focal point in recent years. It could help the patient fight

persisting lung infection. Oral pancreatic enzymes are provided to help digest fats and proteins and supplements of vitamin A, D, E and K are provided to replenish the fat soluble vitamins of intestine can no longer up absorb .by implementing these techniques we can hope to continue lessening the incidence of this disease.

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Conflicts of interest:

The authors declare no conflicts of interest.

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