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Detection of the Secrets of Cystic Fibrosis

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ABSTRACT

Cystic fibrosis affects the cells that produce mucus, sweat and digestive juices are affected by Cystic fibrosis. Indians may have a higher prevalence of cystic fibrosis. The tubes, ducts and air passageways are plugged by thick, sticky mucus. Cough, repeated lung infections, fatty stools are the main symptoms of cystic fibrosis It is a life-limiting, genetic disease of the Caucasians, and Indians. Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that encodes a cAMP-regulated anion channel. Although CF is a multi-organ system disease, most people with CF die of progressive lung disease that begins early in childhood and is characterized by chronic bacterial infection and inflammation. Cystic fibrosis (CF), a monogenic disease caused by mutations in the CFTR gene on chromosome 7, is complex and greatly variable in clinical expression. Airways, pancreas, male genital system, intestine, liver, bone, and kidney are involved.

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INTRODUCTION

The history of cystic fibrosis (CF), the severest autosomal recessive disease in caucasians, can be considered a paradigm of the successful outcomes achievable by collaborative international efforts in basic and clinical research. (1)

It was almost always considered lethal in the early childhood. (2,3)

In several countries, the majority of patients are represented by adults and this preponderance is expected to amplify in the next years. (4)

Long-term issues include difficulty breathing and coughing up mucus as a result of frequent lung infections.(5)

In epithelial cell CFTR, an ABC protein exhibits the properties of a chloride and anionic channel involved in a variety of physiological processes. (6)

In lower and upper airways, the intestine, pancreatic, and liver ducts, lack of functional CFTR is the major factor in determining the degree of disease expression, and eventually mortality. (7)

Although cystic fibrosis is a monogenic disease, its phenotypic variability is substantial — as shown by the broad range of disease severity observed in patients with the same genotype. (8)

CFTR mutations have also been described in patients with cystic fibrosis-like organ manifestations including pancreatitis, sinusitis or ‘idiopathic’ bronchiectasis. (9)

The introduction of prenatal genetic screening in western countries seems to correlate with decreasing incidence in some countries. (10)

In the United States (58%) of the people with cystic fibrosis were diagnosed by new-born screening. (11,12)

The risk for the development of cystic fibrosis-related diabetes has recently been shown to be influenced by modifier genes that include variants at SLC26A9 and at four susceptibility loci for type 2 diabetes mellitus. (13)

Cystic fibrosis (CF) is a rare genetic disorder that affects mostly the lungs, but also the pancreas, liver, kidneys, and intestine. (14,15)

Since this discovery, aggressive early interventions have been established to improve the quality of life of people with CF, however progressive lung disease remains difficult to manage and is the leading cause of morbidity and mortality. (16,17)

A one-time treatment administered early in life for people with CF might prevent the onset of lung disease. (18,19)

It is an autosomal recessive disorder that requires mutations in the CF gene in both genetic alleles. (20)

History

In the 19th century, Carl von Rokitansky described a case of fetal death with meconium peritonitis, a complication of meconium ileus associated with CF. Meconium ileus was first described in 1905 by Karl Landsteiner. (21)

In 1936, Guido Fanconi described a connection between celiac disease, cystic fibrosis of the pancreas, and bronchiectasis. (22)

She also first hypothesized that CF was a recessive disease and first used pancreatic enzyme replacement to treat affected children. In 1952, Paul di Sant' Agnese discovered abnormalities in sweat electrolytes; a sweat test was developed and improved over the next decade. (23)

Because mutations in the *CFTR* gene are typically small, classical genetics techniques had been unable to accurately pinpoint the mutated gene. (24)

Using protein markers, gene-linkage studies were able to map the mutation to chromosome 7. Chromosome walking and chromosome jumping techniques were then used to identify and sequence the gene. (25)

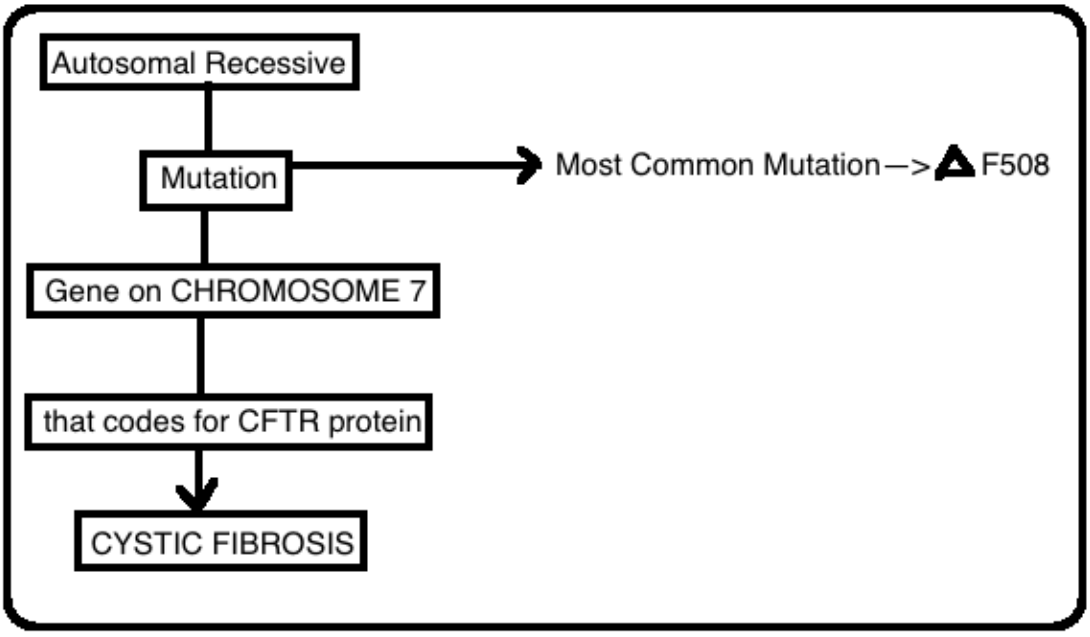
CF Pathophysiology

CFTR protein will not be synthesized because of the absence of the CF gene.

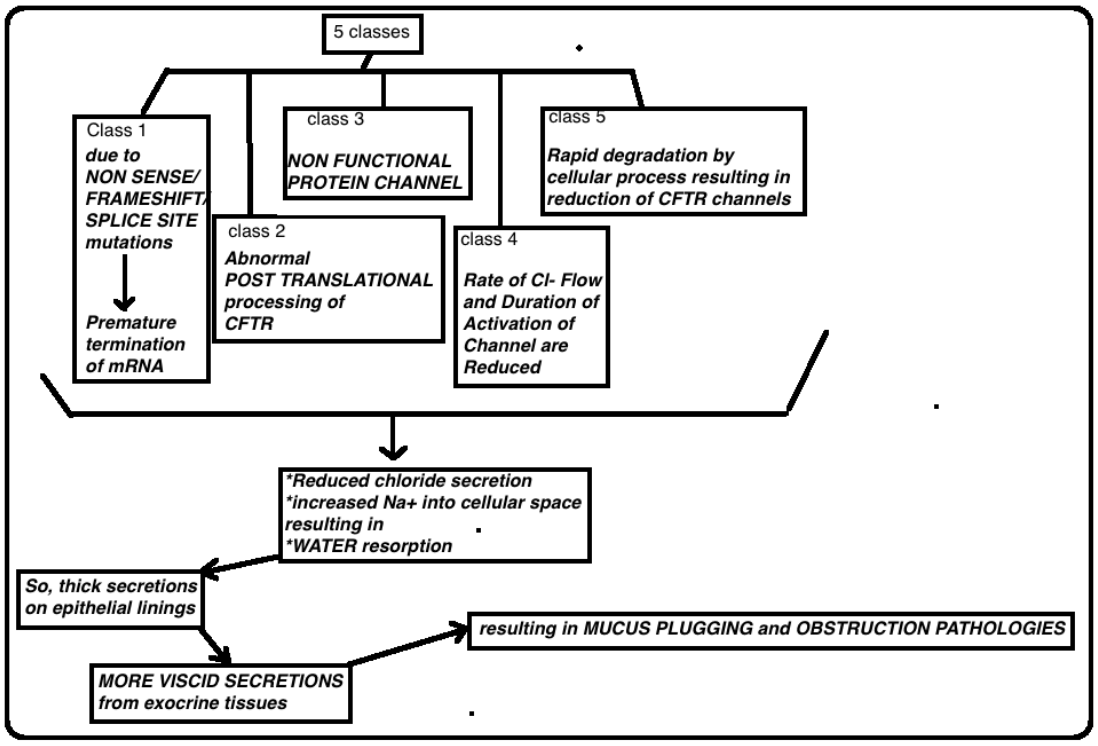
Abnormal chloride conductance on the apical membrane of the epithelial cell results.

As a result of it, liquid depletion occurs on the airway surface of the lung.

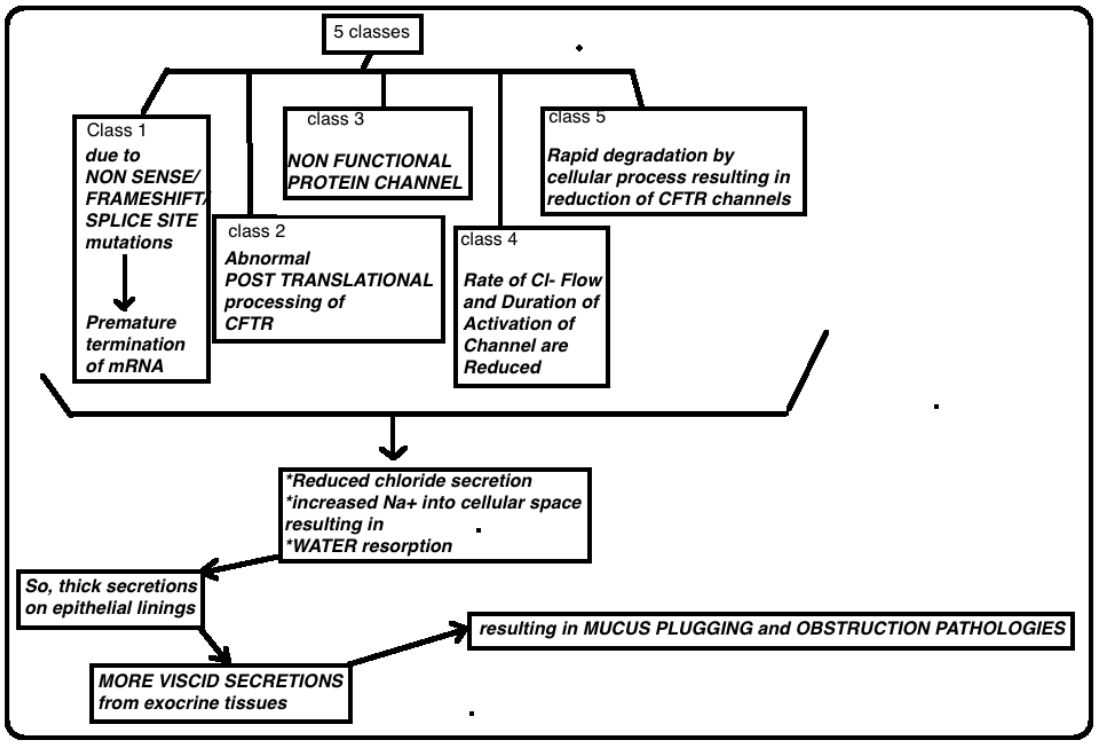
Airway surface liquid is essential to support ciliary stability and functioning, ciliary collapse and decreased mucociliary transport.



Five classes of CFTR



Mucous plugging and obstruction Pathogenesis



Pathophysiology underlying CF lung disease

Following the debilitated CFTR protein in the airway epithelium, chloride secretion and epithelial sodium channel regulations are damaged.

As a result, reduction in anion secretion combined with increased sodium and water reabsorption from the ASL through the apical cellular membrane occurs. (26)

The first line of defence in the respiratory system against pathogens is blocked.

Concomitantly, insufficient HCO_3 -secretion lowers ASL pH. Acidic conditions have been shown to alter bacterial killing by reducing the activity of ASL antimicrobial. (27)

Overall, impaired lung innate immunity predisposes to pathogen colonization, which subsequently triggers neutrophil recruitment and proinflammatory cytokine secretion. (28)

Tissue destruction ensues and results clinically in chronic respiratory infection, lung function decline, and ultimately, respiratory failure. (29)

ORGANS AFFECTED BY C F

Sinuses

Lungs: Thick, sticky, mucus build up, bacterial infection, widened airways

Skin: Sweat glands produce salty sweat

Liver: Blocked biliary ducts

Pancreas: Blocked pancreatic ducts

Intestines: Unable to fully absorb nutrients

Reproductive organs: Male/female complications

Pathogenesis of cystic fibrosis lung disease

This life-threatening genetic disorder causes a build-up of thick, viscous mucus secretions in various organ systems, most commonly the gastrointestinal, pulmonary, and genitourinary systems. (30)

A major emphasis is placed on the active transport systems that regulate the airway surface liquid (ASL) volume and, particularly, regulate the volume of the periciliary liquid (PCL) layer. A sequence is developed for CF whereby there is a depletion of the PCL that reflects the combined dysfunctions of accelerated Na(+)-dependent volume absorption and failure to secrete Cl(-) (31).

A combination of decreased mucociliary clearance and an altered ion transport allow for bacterial colonization of the respiratory tract, most commonly *Pseudomonas*, *Haemophilus influenzae*, and *Staphylococcus aureus*. These pathogens cause an overwhelming inflammatory response. (32)

Inheritance

CF is inherited in an **autosomal recessive pattern**. In this, the parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

The Role of CFTR in Pancreatic Disease Pathogenesis

Cystic fibrosis is the most common autosomal recessive genetic disease characterized by multiorgan pathology and significantly decreased life expectancy caused by the impaired function or expression of CFTR. (33)

Pancreas-Congenital anomalies-Cystic fibrosis

The pancreas is one of the earliest- and most commonly- affected organs in patients with cystic fibrosis (CF).

- Autosomal recessive disorder affecting most critically the lungs; also pancreas, liver, intestines; characterized by abnormal transport of chloride and sodium across an epithelium, leading to thick, viscous secretions.

- Mutations cause reduced chloride ion in secretions, thicker respiratory secretions, upper respiratory infections.

- Complications: pancreatic insufficiency late in disease course in 90%, diabetes, malabsorption, pancreatitis.

- Mutations also cause defective cilia and infertility; may cause meconium ileus (5 - 10%), intussusceptions. (34)

Pathogenesis of cystic fibrosis intestinal disease

In cystic fibrosis patients, the sticky mucus interferes with the proper digestion of food and causes blockages in the intestines.

The gastrointestinal (GI) system is among the earliest parts of the body affected in CF, with a significant proportion of neonates showing damage. (35,36)

The lack of this major acid neutralizing power, the lack of fluid for hydration of the intestinal contents, and reduced enzymatic capacity to digest ingested food contributes in a multifactorial way to GI symptoms and signs. (37)

Clinically significant CF liver disease rarely develops de novo in patients over age 18. However, in CF mice faecal loss of bile salts does not appear to affect fat absorption. (38)

What causes salty skin in cystic fibrosis?

People with CF have a defective cystic fibrosis transmembrane conductance regulator (CFTR) gene, and this mutation prevents the CFTR protein from working properly. (39,40)

With cystic fibrosis, salt cannot move as it normally does through the cells that line the sweat duct. Since sodium and chloride travel together as one molecule, the sodium/salt ends up excreted in the sweat.

This makes for very salty sweat, though it is not thick and sticky like other CF secretions. (41)

What is the impact of Covid-19 on children with cystic fibrosis?

Cystic fibrosis is an inherited disease caused by a faulty gene. This gene controls the movement of salt and water in and out of cells, so the lungs and digestive system become clogged with mucus, making it hard to breathe and digest food. The first global research, published in the *Journal of Cystic Fibrosis*, assessed the outcomes of 105 children across 13 countries, ranging from infants through to teenagers. (42)

'Cystic fibrosis spreading wings, sweat test a must'

For, paediatricians in the premier tertiary care institute, PGIMER, say that once known to be a rare genetic disorder, Cystic Fibrosis (CF) has gradually spread its wings among the children and there are increasing instances of the disorder, with a significantly higher prevalence rate especially among the north Indian children.

Says Dr Meenu Singh, of the Advanced Paediatrics Centre, who is one of the few experts in the country who are doing extensive research work on the disorder, "There is no precise data as of now on the disorder in India but there are cases which are being reported in various tertiary care hospitals in the country. In PGI, in our special clinics, we see 4-5 children every week suffering from the disorder which also includes follow up cases".

Interestingly, as per the statistics of the PGIMER, the cases of CF are usually diagnosed at a later stage and in 80 per cent cases the patients end up getting treatment for Tuberculosis instead of CF. "One of the reasons for this is that many general physicians are not aware of the disorder," said Dr Meenu Singh. (43)

Fatal Cystic Fibrosis eludes diagnosis, experts push for awareness

Expressing helplessness, doctors claim that this rare genetic disease affects mostly children, and shows up symptoms like diarrhoea, breathing problems, severe lung infections and failure to gain weight, and goes under diagnosed as these are also symptoms of other common infection-related diseases. Dr Naveen Benkappa of Indira Gandhi Institute of Child Health in Bengaluru, told TNIE, "We see two or three patients a month with this disease. However, compared to countries like United Kingdom, it is very rare in India." Meanwhile, Dr Srihari, a paediatrician, said, "We have no other measure but to look for symptoms which are chronic in nature, and do a screening test to confirm if it is CF. Though there is no cure yet, we have been able to diagnose it through genetic screenings," he explained.(44)

Diagnosis

- **Immunoreactive trypsinogen (IRT) test.** The IRT test is a standard newborn screening test that checks the blood for abnormal levels of the protein called IRT. A high level of IRT may be a sign of CF.

- **Sweat chloride test**. The sweat chloride test is the most commonly used test for diagnosing CF. It checks for increased levels of salt in the sweat. The test is performed by using a chemical that makes the skin sweat when triggered by a weak electric current. Sweat is collected on a pad or paper and then analyzed. A diagnosis of CF is made if the sweat is saltier than normal.

- **Sputum test.** During a sputum test, the doctor takes a sample of mucus. The sample can confirm the presence of a lung infection. It can also show the types of germs that are present and determine which antibiotics work best to treat them.

- **Chest X-ray.** A chest X-ray is useful for revealing swelling in the lungs due to blockages in the respiratory passageways.

- **CT scan.** A CT scan creates detailed images of the body using a combination of X-rays taken from different directions. These images allow your doctor to view internal structures, such as the liver and pancreas, making it easier to assess the extent of organ damage caused by CF.

- **Pulmonary function tests (PFTs).** PFTs determine whether your lungs are working properly. The tests can help measure how much air can be inhaled or exhaled and how well the lungs transport oxygen to the rest of the body. Any abnormalities in these functions may indicate CF.

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are chronic in nature, and do a screening test to confirm if it is CF. Though there is no cure yet, we have been able to diagnose it through genetic screenings," he explained.(45)

Treatment

There's no cure for cystic fibrosis (CF). But many treatments can reduce your symptoms and improve your quality of life.

Antibiotics

Whenever pneumonia is suspected or decline in lung function is seen, antibiotics are necessarily used.

Inhaled therapy with antibiotics such as tobramycin, colistin, and aztreonam is often given for months at a time to improve lung function by impeding the growth of colonized bacteria. (46,47)

Lancovutide, was initially developed as an antibiotic but was also found to increase the intracellular calcium level and activate the alternative chloride channel. It does not bind to a receptor, but directly interacts with phospholipids in plasma and organelle membranes.

Denufosol. ATP plays a role in increasing airway surface liquid and is induced by movement and is functional in both healthy and CF epithelium. ATP and other purines bind to the P2Y receptor and induce intracellular calcium release.

In inhaled levofloxacin may be used to treat *Pseudomonas aeruginosa* in people with cystic fibrosis who are infected. (48)

The early management of *Pseudomonas aeruginosa* infection is easier and better, using nebulised antibiotics with or without oral antibiotics may sustain its eradication up to two years. (49)

When choosing antibiotics to treat CF patients with lung infections caused by *Pseudomonas aeruginosa* in people with cystic fibrosis, it is still unclear whether the choice of antibiotics should be based on the results of testing antibiotics separately (one at a time) or in combination with each other. (50)

Antibiotics by mouth such as ciprofloxacin or azithromycin are given to help prevent infection or to control ongoing infection. (51)

Dr. Reddy's unveils generic drug for cystic fibrosis

Dr. Reddy's Laboratories (DRL) said it had launched in the U.S. Tobramycin Inhalation Solution USP, a therapeutic equivalent generic version of Tobi (tobramycin) Inhalation Solution. Indicated for the management of cystic fibrosis.

Antibiotic resistance in *Pseudomonas aeruginosa*: mechanisms and alternative therapeutic strategies

Pseudomonas aeruginosa is an opportunistic pathogen that is a leading cause of morbidity and mortality in cystic fibrosis patients and immunocompromised individuals. Eradication of *P. aeruginosa* has become increasingly difficult due to its remarkable capacity to resist antibiotics. Strains of *Pseudomonas aeruginosa* are known to utilize their high levels of intrinsic and acquired resistance mechanisms to counter most antibiotics. (52)

The journey from scientific breakthrough to a life-changing cystic fibrosis drug

In August 1989, scientists made a blockbuster discovery: They pinpointed the faulty gene that causes cystic fibrosis, a cruel lung disease that killed many of its victims before they reached adulthood.

The human genome was uncharted territory, and the gene hunt had become an all-out international race, with laboratories in three countries searching for the root of the disease.

Science seemed on the cusp of a revolution — hope was spreading that researchers might soon be able to identify genes that caused diseases that had bedevilled humanity for centuries and use that knowledge to devise medicines that were true cures. (53)

Prevention

The disease can be prevented from being passed on to future generations by prenatal genetic screening. Interestingly, CF is also present in adults. Infertility is another symptom. 80%-90% of Cystic Fibrosis mutation in adult males causes 'Obstructive azoospermia' which is due to congenitally absent vas deferens. Lung transplantation is the only option to push life expectancy. Hence, gene-corrected airway stem cells are an alternative strategy. Cystic fibrosis tests may be recommended for older children and adults who weren't screened at birth.

CONCLUSION

Cystic fibrosis tends to get worse over time and can be fatal if it leads to a serious infection or the lungs stop working properly. But people with cystic fibrosis are now living for longer because of advancements in treatment. Exciting new treatments are being developed that have the potential to treat the causes, rather than just the symptoms, of CF lung disease. There is continuing progress on treating the downstream aspects of CF, such as sputum retention, airway infection, and inflammation, but our improving understanding of the underlying pathophysiology will help us target the early abnormalities in CF, and early results from studies of several compounds look promising. Treating the early and root causes of CF will improve outcomes and hopefully also reduce the substantial burdens of treatment.

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