

Relationship between Cystic Fibrosis with CFTR and a Common Mutation DelF508 with Its Treatment

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ABSTRACT

Chronic obstructive pulmonary illness, decreased pancreatic exocrine function, and excessively increased sweat electrolytes are all symptoms of cystic fibrosis, a hereditary exocrine gland disease. The cystic fibrosis gene has a number of mutations. G542X, G551D, Gly542X, Asn1303Lys, and others, for example. The most prevalent cystic fibrosis gene mutation, deltaF508 or F508del, is discussed in this research, as well as how it impacts the cystic fibrosis conductance regulator (CFTR). It will also have an impact on associated treatments like genetic therapy, inhaled antibiotics, dose type, and so on. This paper finds how cystic fibrosis occurs, how delF508 impact human and corresponding treatment (inhaled antibiotics, mucilagins, and genetic therapies like CRISPER) may help cure the cystic fibrosis.

Keywords: CFTR, cystic fibrosis, deltaF508, therapy

1. INTRODUCTION

Cystic fibrosis is a lung illness marked by fibroblast proliferation and extracellular matrix buildup, as well as inflammation and tissue structure degradation. Human respiratory function is severely impacted by cystic fibrosis, which manifests as a dry cough and dyspnea. The patient's respiratory performance continues to decline as the disease and lung injuries worsen. The most frequent hereditary mutation in CFTR is the Delta F508 mutation. This mutation causes a mutation in the protein's 508 amino acids by deleting three nucleotides. Mucus production is aberrant due to the mutant protein. It is important to discover the therapy for cystic fibrosis because there is no cure for cystic fibrosis, but millions of people suffer from it. The disease impacts patients' daily activity negatively and bring economic loss.

2. WHAT IS CFTR AND HOW DELTAF508 AFFECT THE LUNG?

CFTR stands for cystic fibrosis transmembrane conductance regulator. It has 1480 amino acids and is a transmembrane protein. The ATP binding cassette (ABC) transporter superfamily includes CFTR. ABC transporters are involved in the absorption of nutrients, the excretion of toxins, and the mediating of eukaryotes. The fundamental function of ABC transporters is to assist

in the transit of chloride ions both inside and outside the membrane. In normal cells, chloride ions are transferred via active transport using the CFTR protein: ions flow from a low concentration to a high concentration side, which takes energy. The CFTR gene produces a protein that functions as a channel in cell membranes, allowing body fluids like saliva and tears to be produced. This channel transfers chloride ions, which helps the body maintain a proper level of bodily fluid. Cystic fibrosis is an autosomal recessive genetic illness caused by a mutation in the CF gene on the seventh chromosome. Both of his parents are heterozygous, while the patient is homozygous. The recessive gene may be present in half of a patient's siblings, with one-quarter developing the condition. Even if the parents are in good health, their children may have cystic fibrosis. According to the World Health Organization, heterozygotes with recessive genes affect 2% to 5% of neonates and 1 in 2000 to 2500 babies in 2016. Furthermore, Europe has the world's largest patient population.

Increased sodium chloride in perspiration and saltier sweat are symptoms of cystic fibrosis. Because so much salt is lost through sweating, it disturbs the body's delicate mineral balance. Because the pancreatic duct is clogged and trypsin is insufficient, the gut cannot effectively digest food. Due to a lack of food absorption, patients with cystic fibrosis may not grow adequately. Dyspepsia may occur as a result, leading to oily stools

and frequent defecation, as well as developmental delay and low weight in the child. The CFTR protein shuts down when the CF gene is altered, causing water molecules to flow more slowly out of the membrane. Mucus rheology was also altered as the acid glycoprotein concentration of mucus gland discharge increased. As a result, the mucus that coats the surface of the lung cells is unable to be diluted and builds up over time. Some bacteria (such as staphylococcus aureus, pseudomonas aeruginosa, and others) are able to thrive and replicate in the bronchial mucus, leading in recurring lung and bronchus infection. Coughing, viscous sputum that is difficult to cough out, shortness of breath, and asthma impede the patient's functioning. The condition progressed to cystic pulmonary fibrosis, bronchiectasis, and severe lung function impairment, eventually leading to right ventricular hypertrophy and heart failure.

In the United Kingdom, DeltaF508 is the most frequent cystic fibrosis gene mutation, accounting for 68 percent of cases. Delta denotes a deletion, F denotes phenylalanine, and 508 denotes the amino acid's position in the CFTR polypeptide. As a result, delF508 refers to the deletion of three nucleotides from the CFTR polypeptide chain, as well as a phenylalanine (508th amino acid) codon. The reading frame is intact even if three nucleotides are deleted. The removal of nucleotide CUU causes the last U in phenylalanine to become the last nucleotide of isoleucine (see Figure 1). Despite the fact that the code for isoleucine AUU has been changed to AU"U," the codon for phenylalanine has been removed. As a result, the original CFTR gene codon should be "...Ile Ile Phe Gly Val...", while the delF508 one should be "...Ile Ile Gly Val..."

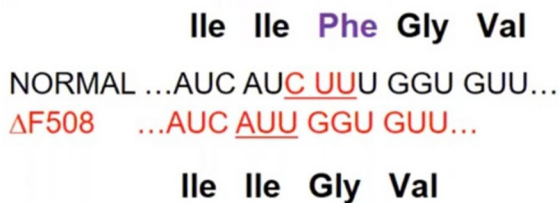


Figure 1: When comparing the normal CFTR amino sequence to the delF508 CFTR amino sequence, the mutation deletes "CUU," resulting in the loss of the amino acid Phenylalanine.

Although only one amino acid is removed, it is critical and affects the structure of the CFTR protein. Although CFTR protein is still produced, most proteins are unable to reach the cell surface in the absence of phenylalanine. They are unable to function because they have remained in the endoplasmic reticulum. Normal CFTR protein in the human body is properly folded and has a three-dimensional shape. The mutated CFTR protein, on the other hand, is misfolded and recognised by the endoplasmic reticulum's ubiquitin complex. The ubiquitin complex prevents the CFTR protein from

occupying its normal position in the cell membrane and degrades it. As a result, there is less CFTR protein on the cell surface, indicating that the cells are storing more water. Mucus thickens in the epithelium of the damaged organ; mucus thickening obstructs the narrow respiratory tract. Bacterial growth produces thick, nutrient-rich mucus, which increases the risk of respiratory infections; pancreatic insufficiency due to mucus clogging the pancreatic duct; bacterial growth produces thick, nutrient-rich mucus, which raises the risk of respiratory infections.

CFTR channel gating is disabled by the delF508 mutation. The action of normal channel gating occurs on a regular and quick basis. Despite this, the gating activity of the delF508 CFTR channel is lengthy and erratic. Figure 2 reveals that wild-type CFTR had more gating actions than mutant CFTR throughout the same 20-second timeframe.

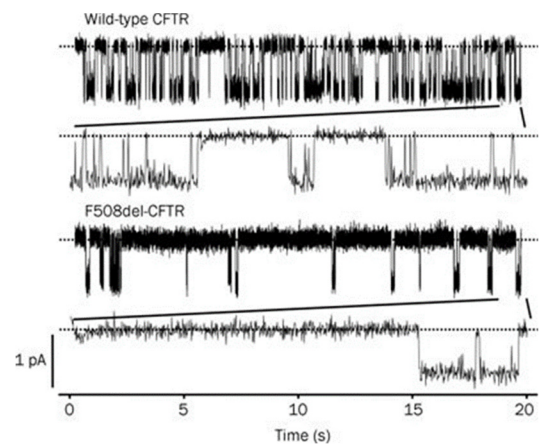


Figure 2: Channel gating activities of wild-type CFTR and delF508 CFTR in 20 seconds. The amplitude of wild-type CFTR is greater than that of F508del-CFTR.

The channel gating activity of wild type CFTR is three times that of mutant CFTR, according to Dalemans et al's findings. Furthermore, the time cost of open-close gate activity for delF508 CFTR is five times lower than for wild type CFTR, showing that delF508 cuts the time necessary to close the channel gate in half. Because fewer chloride ions can pass through the CFTR protein, a faster time for closing the channel gate is not helpful to the human organism. Due to a lack of energy, the mutant CFTR channel's nucleotide-binding region has lower ATP appetency than the normal CFTR channel, resulting in a reduced gate open rate. Furthermore, because the structure of the aromatic cluster alters and the loss of the F508 side chain influences channel opening significantly, delF508 disturbed the link between the N-terminal transmembrane and the nucleotide-binding domain, making channel gating more unstable and irregular.

CFTR is transported to the plasma membrane by the Golgi complex. After the ER's quality control system identifies it as abnormally misfolded, the proteasome

degrades it. Apart from producing misfolded proteins, domain assembly has problems as well. "F508 interacts with ICL4 in TMD2, and its absence leaves a cavity and disturbs the NBD1–TMD2 interface, which is crucial for folding and function," Mijnders et colleagues. write. It shows that delF508 causes the NBD1–TMD2 interaction to be disrupted, which is essential for folding. CFTR proteins must also be glycosylated in order to develop. However, glycosylation in delF508 is incomplete, leading the protein to rapidly breakdown.

3. TREATMENT FOR DELF508

To cure delF508, more mutant CFTR proteins must be delivered to the apical membrane. Because of delF508, the protein structure of CFTR is changed, and some mutants can reach the apical membrane. More mutant proteins will be able to reach the cell membrane if doctors can optimise the transportation pathway and reduce CFTR breakdown in the endoplasmic reticulum. Chemical molecular chaperones such as 42phenylbutyrate (42PBA) compounds, for example, can minimise mutant retention in the endoplasmic reticulum, boosting CFTR transit and raising CFTR density at the top membrane of cells. Alternatively, lumacaftor, a medication combination, can help the nonfunctional delF508 CFTR protein fold into a more typical 3-D form. Although this drug combination is not ideal, it can assist the CFTR mutant protein in moving some of the chlorides. Because more chloride ions can reach the cell membrane, cystic fibrosis may be less severe. Chest physical therapy, in which patients repeatedly pat mucus on the chest, is another common treatment. Alternatively, they will inhale antibiotics to kill bacteria that cause lung infections. Bronchodilators are also used to keep airways open, and trypsin replacement therapy is used to ensure proper food digestion. Finally, gene therapy for delF508 is currently being tested in clinical trials. The idea is to insert a healthy CFTR gene into the lung cells of a delF508 patient to compensate for the defective gene. Although cystic fibrosis cannot be completely cured, medical treatments can help patients reduce pain and live longer lives.

Inhaled and oral medicines, airway clearing, and optimal nutrition are all part of the established standard of care for cystic fibrosis (CF) treatment. Orally administered drugs are available in a variety of forms. The medication immediately enters the airways after inhalation and is absorbed into the circulation in modest concentrations. Many technologies directly deliver drugs to the lungs. Meter-dose inhalers (MDI), dry powder inhalers, nebulizers, and soft mist inhalers are now available for a variety of drugs. The primary goal of topical inhalation therapy is to relieve lung symptoms such as airway irritation and tightness by minimising and/or preventing them. Inhaled medications include corticosteroids, sympatholytic agents, muscarinic

antagonists, and antibiotics. Inhaling these medicines has substantial advantages over systemic delivery preparations. Importantly, by directly delivering medications to the target organ, the lungs, large pulmonary drug concentrations can be attained. As a result, a modest inhaled dose could be therapeutically equivalent to or better than a greater systemic dose. Inhalation results in a high lung concentration but a low systemic medication concentration, resulting in high lung efficacy and less adverse effects.

As a result, oral or intravenous doses that deliver equal lung efficacy to inhaled levels frequently have more systemic adverse effects. Inhalation can give a faster onset of action in the lungs than other modes of administration, in addition to a favourable pulmonary efficacy versus systemic safety ratio ("pharmacodynamic (PD) airway selectivity"). Opportunistic infections induce chronic lower respiratory tract infection in people with CF, which is a defining hallmark of the disease. *Pseudomonas aeruginosa* is the most frequent pathogen, and its acquisition and persistence are related with increased morbidity, decreased lung function, and higher death. Antibiotics are commonly considered as the primary treatment for CF lung illness, and their active usage, as well as the availability of efficient antibacterial medications, have become essential variables in today's CF patients' health and prognosis. Clinicians in the United Kingdom have been prescribing inhaled antibiotics for more than 30 years, dating back to the initial use of aerosolized carboxypenicillin and gentamicin. In the UK, 90 percent of patients with chronic *P. aeruginosa* infection (3000 patients) should be administered at least one aerosolized antibiotic, based on the types of inhaled medicines available and the view of drug delivery leading to efficacy progression. A wide range of antibiotics are used, according to UK national registry statistics, however polymyxin products are the most prevalent overall (Colomycin 39.6%; Promixin 29.8%), followed by aminoglycodybramycin (31.4%) and -lactam tronam (31.4%). (6.8 percent). Advances in the use of mucilages, as well as a large increase in the use of inhalation antibiotics, have helped clinical practise. The benefits of atomized chainase alpha (recombinant human deoxyribonuclease I (rhDNase)) for enhanced lung function and airway clearing are well known. The use of rhDNase and hypertonic saline has increased dramatically in the previous five years, according to statistics from the UK National Registry.

The most prevalent treatment for cystic fibrosis is inhaled medications. Dosage Form efficacy is insufficient, especially in the treatment process to supplement nutrition, such as vitamin K. Vitamin K is needed by the body to make particular proteins, and calcium ions employ vitamin K-related proteins to control blood clotting. In the lack of vitamin K, blood clotting is significantly hampered, and uncontrolled

bleeding can result. Vitamin K deficiency may weaken bones, cause osteoporosis, and accelerate calcification of arteries and other soft tissues, according to preliminary clinical investigations. Because cystic fibrosis can cause coagulation problems, fat-soluble vitamin supplementation is critical, particularly in younger individuals. Vitamins A, C, D, E, and K are among them.

4. CONCLUSION

Deletion of three nucleotides and a codon for phenylalanine, the 508th amino acid in the CFTR polypeptide chain, characterises delF508, the most frequent CFTR mutation. As a result of this type of mutation, most proteins get misfolded and are unable to reach the cell surface. The delF508 mutation causes CFTR channel gating to be inefficient, resulting in inconsistent channel gating activity and a reduced gate close time cost. The NBD1–TMD2 interaction, which is needed for protein folding, is similarly disrupted. DelF508 is a hereditary exocrine gland condition that causes cystic fibrosis. Indigestion, lung infection, thick mucus in the body, and other symptoms are all possible outcomes. On the other hand, treatments like 42phenylbutyrate or the medication combination lumacaftor can assist more mutant CFTR protein reach the cell membrane. Inhaled antibiotics, mucilaginants, and genetic therapies are also popular currently. Today, the options for curing cystic fibrosis are still restricted. The current medical treatments are unable to completely cure CF. Genetic treatment, like as CRISPER, may one day be used to repair and design the faulty gene, curing delF508 or CF.

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