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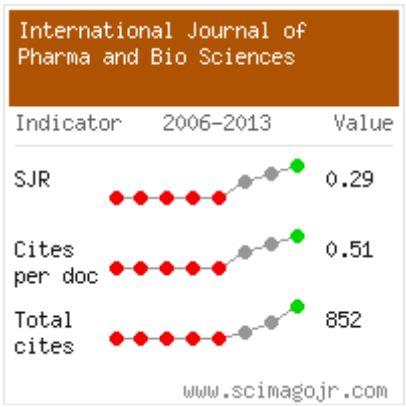

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Review Article **Biochemistry**

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MUTATION IN ΔF508 : A MAJOR CAUSE OF CYSTIC FIBROSIS

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ABSTRACT

Cystic fibrosis is the most common serious inherited disorder or autosomal recessive disorder. This disorder is appearing when the CFTR [cystic fibrosis transmembrane conductance regulator] gene mutation is takes place. The CFTR gene is responsible for the formation of CFTR protein which is normally required for the regulation of sweat, mucus and some other body fluids, CFTR protein act as a channel which is helping to transport chloride from inner membrane space to outer membrane space, it also help to transport some other material like bicarbonate ions. The CFTR protein is present in apical membrane. When this protein is not synthesized properly because of mutation in CFTR gene, the regulation of sweat, mucus and some other body fluids is imbalanced; this condition is known as cystic fibrosis. The most common mutation is deletion of phenylalanine amino acid at position 508.Deletion of amino acid is done by delta F508 mutation, 70% of cystic fibrosis is caused due to this mutation. Sign and symptoms are cough with thick mucus, lung infections. Lungs are the most prone area for infection. Cystic fibrosis have no cure permanently but the symptoms can be reduced by therapies and medications.

KEY WORDS: CFTR gene, sweat glands, pathophysiology, delta 508 mutation and blockage.

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INTRODUCTION

Cystic fibrosis is a genetic disorder inherited in autosomal recessive pattern. Out of 2500 lives birth only 1 person is affected. The disorder was first enlisted in 1930 [1]. The endorsement of this disorder includes less amount of pancreatic enzyme due to secretory duct obstruction, pulmonary blockage and lessens fertility in males [2]. The thick sticky mucus impediment the mucus glands throughout the body (mucovisicodosis) as the mucus gland run all over the body they are affected hence the disorder is also known as generalized exocrinopathy (effecting exocrine glands) [3]. The patients suffering from cystic fibrosis show increase amount of sodium and chloride in their sweat [4]. The CF gene identification was substantiated using cells obtained from sweat glands. This gene encrypts cAMP regulated chloride channels and CFTR. CFTR that is asserted in various pancreatic ducts biliary tree, vas deferens and sweat glands which can ascent to elevated sweat chloride concentration, biliary cirrhosis. Bronchiectasis and congenital mutual absence of vas deferens recurrently in combination [5-7] . CFTR gene is located on the long arm of human chromosome number 7 that spans 25000 base pairs and encrypts for a protein of 1480 amino acids. This protein subsists of to anchoring domains (realms) 2 nucleotide binding realms and a part termed R-realm [8]. Although CFTR have some other functions like regulates the bicarbonates ions passage terminated epithelial cells membrane and for other proteins . It also act as a channel but the main function of the CFTR gene is to act as chloride channel in apical membrane for transportation of chloride from intracellular space to extracellular space. [9-13]. Due to mutation in this gene the cystic fibrosis eventualize. There are more than 1500 mutations of CFTR gene, the most common mutation is the deletion of 3 base pairs or phenylalanine amino acids at position 508(DF508). 70% of cystic fibrosis is caused due to this mutation. DF508 mutation caused the misfolding of the CFTR proteins which is required for the balance of normal concentration mucus, sweat and other fluids. Due to misfolding of CFTR proteins it will never reached to membrane (e.g. apical membrane). This can result in thick sticky mucus, high salt in sweat etc. [14-17].

The CF gene

Cystic fibrosis gene origin took place by positional cloning in 1989 by the 3 research groups, those of Lap-Chee Tsui and Jack Riordan at the Hospital for Sick children in Toronto, and Francis Collins at the University of Michigan [18-19]. CFTR gene is located on the long arm of human chromosome number 7 at position q31.2 and encoded for protein of 1480 amino acids. It belongs to a family of ABC transporter gene super family in both eukaryotic and prokaryotic proteins [20-21]. CFTR gene have some other functions like regulates the bicarbonates ions passage terminated epithelial cells membrane but the main function of the CFTR gene is act as chloride channel in apical membrane for transportation of chloride[9-12]. CFTR gene helps to transport chloride from inner membrane space to extracellular membrane space.

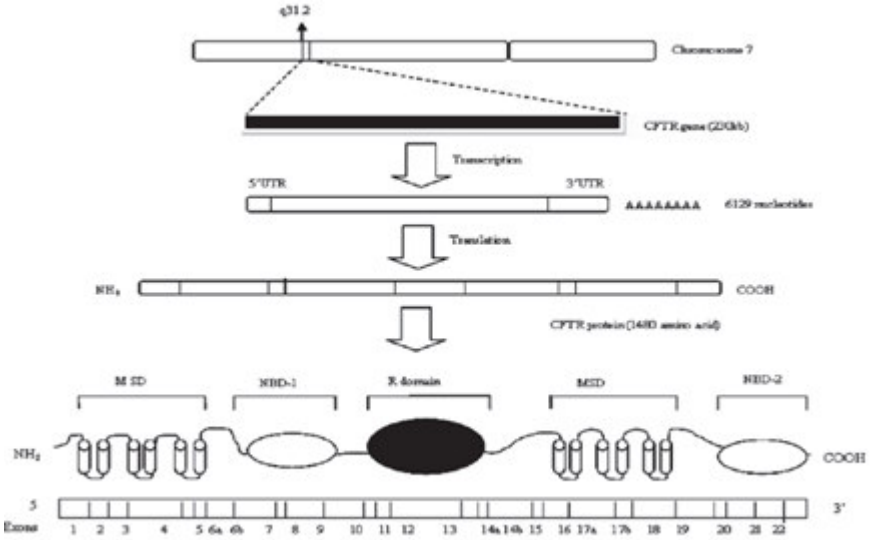

Figure 1

Diagram showing CFTR gene and resulting protein[CFTR cystic fibrosis transmembrane conductance regulator, MSD; membrane spanning domain, NBD; nucleotide binding domain, R domain; regulatory domain].

CFTR is made up of five domains:two membrane spanning domains[MSD1 and MSD2] that formsthe chloride ion channel, two nucleotide binding domains [NBD1 and NBD2] that binds and hydrolyze ATP, and a regulatory domain. [22].

Mutation of CFTR gene

There are more than 1500 mutations in CFTR gene, but most common mutation is deletion of 3-bp (phenylalanine amino acid at position 508) in the CFTR polypeptide [23].

∆F508 most common mutation

∆F508 is the major mutation in CFTR gene; it will lead to deletion of 3bp or one amino acid phenylalanine at position 508. 70% of the CF is caused by this mutation as shown in figure. 2[23]. Due to this mutation, the CFTR protein is misfolded and improperly synthesized. CFTR protein fails to reach cell membrane or recognised as abnormal protein [24-25]. Because of this the CFTR protein does not work properly and cause problems. CFTR protein has many different functions in different body parts like this protein allows chloride to move out from the cell and also allows to transport bicarbonate ions from the cell [26]

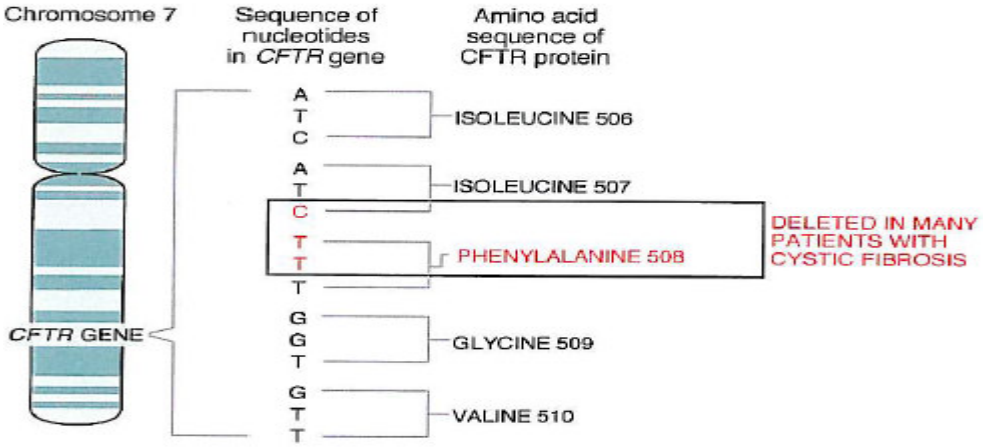

Figure 2

Diagram showing the deltaF508 mutation and deletion of phenylealaninine amino acid[27]

Sign and symptoms of cystic fibrosis

As cystic fibrosis is a genetic disorder,so the sign and symptoms do not appear at early stage. Due to appearance of delayed symptoms the cystic fibrosis sometime is not diagnosed at first or early stage [28-29]. Most common sign and symptoms are following:-

1. Salty tasting skin
2. High concentration of salt in sweat
3. Cough with thick mucus
4. Lung infections repeatly
5. Pneumonia
6. Weight loss
7. Growth retardation
8. Puffy abdomen
9. Digestive problems like constipation
10. Broadening of the fingertips and toes.

Pathophysiology or pathogenesis

Many types of complications or pathophysiology can be seen in cystic fibrosis affected patients depending upon the different types of mutation. Also some patients have no pathological changes in all the system usually affected by the cystic fibrosis [30].

- ***Respiratory system***

The most common affected area of cystic fibrosis is lungs. Most commonly the people affected with cystic fibrosis experience with acute respiratory failure due to pneumonia or acute haemoptysis. In the cystic fibrosis patients who have pneumonia include Staphylococcus aureus, Haemophilus influenza and Pseudomonas aeruginosa [31]. Respiratory or lung infections are the leading cause of the morbidity and motility in patients with cystic fibrosis [32]. Regular infections and the inflammatory response result in ongoing irreversible lung damage. Bronchial mucous stuff due to solid mucus makes easy colonization by microorganisms. Continuous infection leads to bronchiolitis and Bronchiectasis. Other respiratory infections are also there like bronchial squamous metaplasia [33]. Disrupting of the pulmonary parenchyma leads to enhance pulmonary arterial pressure that causes right heart failure [34].

- ***Endocrine system***

Exocrine pancreas insufficiency is present in the greater number of patients with cystic fibrosis. The main clinical features or symptoms are failure to thrive and fatty bulky stools due to loss of pancreatic enzymes [35]. Patients who have cystic fibrosis they have deficiency of normal acinar development. Elevated secretion of the thick mucus in the pancreas duct result in the degradation of pancreatic acini. Due to this the blockage and pathologic change of the pancreas is appear [36, 37]. The most common or major function of the pancreas is secretion of insulin from beta cells. But in the cystic fibrosis disorder the destruction of the beta cells is there, due to this the cystic fibrosis related diabetes is appear or caused. [38]. Glucose level is altered by many factors specific to CF, such as severe dehydration, malabsorption, poor nutrition and liver dysfunction [39].

- ***Hepatobiliary system***

Hepatobiliary system is also affected by cystic fibrosis. It is directly related to the CFTR gene expression. Males are more affected than the females [40]. In the epithelial cells of biliary tract the CFTR gene is expressed. So if the mutation is appear in the CFTR gene the all biliary trees are affected and variety of liver disease occurs [41-42] along with fatty infiltration common bile duct tightness, Sclerosing cholangitis [43- 44] and gallbladder disorder [45-46]. Due to liver disorder the death rate of cystic fibrosis patients are also increased [47].

- ***Sweat glands***

CFTR protein is normally required to regulate the normal level of salt in sweat. But due to the low level or absence of the CFTR protein, the salt level is more in cystic fibrosis patients. Some patients suffer from dehydration, weakness, lethargy and loss of appetite [30].

- ***Reproductive system***

Cystic fibrosis disorder affected to male reproductive system because they have no vas deferens or it is malformed. In females the mucus clogs in the ovarian duct and thicker cervical mucus the decrease sperm movement have been detected [48].

Diagnosis of cystic fibrosis

Cystic fibrosis is a genetic disorder and it may have present with various symptoms [49, 50]. Diagnosis is done on the basis of which organ is affected. The most common or standard test

The most common or standard test is sweat test. In sweat test determination of sodium and chloride is check.[51,52]

1. *Sweat test*: - Sweat test is done in cystic fibrosis. This is the most commonly used for the diagnosis of cystic fibrosis, in this test chloride values is estimated.[53-54]

2. *Prenatal diagnosis*: This test is done in the early stages of pregnancy. In this the both mother and father testing is done for cystic fibrosis mutation. If the both parents are carrier then the parental diagnose of foetus is done by the chorionic villus biopsy.[55]

3. *Neonatal screening:-* In this test the most commonly done the detection of the enhanced value of immunoreactions trypsin in blood. This test is done by only experienced person which is known about the false results.[56]

4. Fecal and Duodenal Trypsin:- This is the improved neonatal screening test in which L-benzoylarginine-p-nitroanilide is used as synthetic substrate for the enzyme. Initially there may be false result come which is decresed by second fecal test.

5. Serum amylase isoenzyme and Lipase:- The serum amylase isoenzymes and lipase activity is greatly decreased or absent in cystic fibrosis children [57].

Treatment of cystic fibrosis

There is no cure for cystic fibrosis but the treatment is done by reduced symptoms of cystic fibrosis. The treatment is done on the basis of sign and symptoms.

1. *Lung transplantation*: Lung transplantation is done in the severe cases of cystic fibrosis because the very most prone area of infection is lungs. The first lung transplantation is done in 1983; 100 patients are received new lungs per year. Lung transplantation is only done when the therapeutic treatment is failed and the life expectancy is only bases on lung transplantation.[58]

2. *Anti-inflammatory therapy:* - In this the anti-inflammatory drugs given because the inflammation of lungs, digestive tract is there.[59]

3. Nutritional repletion:- More than 85% of the total patients with cystic fibrosis is suffering from the pancreas insufficiency and pancreas enzyme deficiency. Due to this the digestion is improper. The enzymes of pancreas are important to maintain the pH alkaline, when their occurs pancreatic enzyme deficiency then some enzymes do not work because some enzymes only works on alkaline pH. So the nutrition repletion is done in CF patients, deficient enzymes and vitamins are given.[60-61]

4. Physical exercise:- Physical activity and excercise is very helpful in cystic fibrosis for mucus clearance with the intention to prevent recurrent lung infections.

5. *Replacement of defective gene :-* CFTR gene replacement is helpful to increased the life expectancy of the CF affected patients if the correct copy of CFTR gene is transfer to the lungs.

CONCLUSION

The cystic fibrosis is an autosomal recessive genetic disorder. This is 2nd life threatening disorder in United States after sickle cell anaemia. Cystic fibrosis occurs when the mutation takes place on the CFTR gene that is present on human chromosome no.7 long arm at position q31.2-31.3. There are more than 1500 mutations of the CFTR gene but the most common mutation is delta F508 mutation. In this the phenylalanine amino acid is delete which is required for the proper folding of the CFTR protein. The CFTR protein is normally required for the regulation of mucus, sweat and some fluids. When the mutation is takes place then the protein do not done their work properly and the concentration of chloride is increased in sweat and other fluids. Common signs and symptoms of Cystic fibrosis is cough with thick mucus, constipation, lung infections, and high salt concentration in sweat or salty tasting skin. Diagnosis is done by the sweat test, prenatal test, and neonatal test. There is no permanent cure of cystic fibrosis but the symptoms can be reduced by medications like anti-inflammatory medicines, nutrition repletion is done, gene therapy is done, replacement of the affected gene with normal gene.

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