Genetics of Cystic Fibrosis
Clinical Implications

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KEYWORDS

• Cystic fibrosis transmembrane conductance regulator protein mutation • Potentiator • Corrector • Read through agent • Genetic modifier

KEY POINTS

- Understanding the consequence of cystic fibrosis transmembrane conductance regulator protein (CFTR) mutations is essential for prescribing appropriate drugs and providing optimal patient care.
- It is important to know the class of CFTR mutation an individual patient carries; newly approved drugs target specific gene alterations, and additional therapies are being developed.
- Pulmonary phenotype is greatly influenced by modifier genes that are distinct from CFTR.
- Some individuals with mutations of both CFTR genes may not be identified until adulthood. Cystic fibrosis should be considered when patients present with pancreatitis, sinusitis, diffuse bronchiectasis, or male infertility.

INTRODUCTION

Cystic fibrosis (CF) is a common life-shortening autosomal recessive genetic disorder that is characterized by eccrine (sweat) gland dysfunction, chronic obstructive lung disease, and exocrine pancreatic dysfunction. Mutations in the gene that encodes for the CF transmembrane conductance regulator protein (CFTR), which is located on chromosome 7, underlie this multisystem disorder.[1] CFTR is a large glycoprotein and a member of the adenosine triphosphate (ATP)-binding cassette superfamily of proteins. CFTR is expressed in many cell types, with phenotypic alterations primarily identified in epithelial cells of airways, sinuses, the gastrointestinal tract (including the pancreas and biliary system), the sweat glands, and the genitourinary system. Dysfunction of CFTR leads to a wide and variable array of presenting manifestations and complications.[1]

CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR PROTEIN MUTATIONS AND THE DISEASE SPECTRUM

CF occurs most frequently in persons of European descent. The prevalence in the Caucasian populations of Europe, North America, Australia, and New Zealand varies, but approximates 1 out of every 2800 to 1 out of every 3500 live births.[1] Although less common, the disorder exists in many other populations including African, Hispanic, Middle Eastern, South Asian, and eastern Asian populations.[1,2]

Many CFTR variants have been identified, and they have been grouped into 5 or 6 mutation classes. The clinical consequence of all variants has not been determined. In fact, only a few of these mutations account for 85% of the disease burden.[1,2] These mutations are often used in diagnostic screening panels.[1,2] In addition to disease-causing mutations, there is increased complexity, because some alterations in the gene are thought to be of little or no clinical consequence.[1,2]

Although more likely to be diagnosed during infancy, some individuals with mutations of both CFTR genes may not be identified until adulthood. Often their clinical course appears to be relatively mild (compared with individuals diagnosed in infancy), and their clinical symptoms are often attributed to other disease states. Ultimately the diagnosis of CF is considered when individuals present with pancreatitis, sinusitis, diffuse

Disclosure: None.
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Clin Chest Med 37 (2016) 9–16
http://dx.doi.org/10.1016/j.ccm.2015.11.002
0272-5231/16/$ – see front matter

bronchiectasis, or male infertility. Clearly, the relationship between CFTR genotype and clinical phenotype is highly complex, and is not predictable for individual patients.[1,2] However, as a general rule, mutations categorized as severe are associated almost uniformly with high sweat chloride values, pancreatic insufficiency, and generally with more rapid progression of lung disease. There are exceptions to that rule, such as patients who carry 3849 + 10kbC→T, as they often have borderline sweat chloride concentrations and pancreatic sufficiency. However, these individuals do develop chronic lung disease and are colonized with *Pseudomonas aeruginosa* as frequently as patients who carry F508del.[1,2]

The most common CFTR mutation is the deletion of a single phenylalanine residue at amino acid 508 (F508del, Phe508del). This mutation is responsible for the high incidence of CF in European populations. Approximately 80% of individuals with CF of northern European descent carry at least 1 copy of the F508del mutation, and nearly half of patients are homozygous for this mutation.[1,2] Although F508del is present in other populations, its prevalence is much lower. It should be noted that in certain populations the prevalence of mutations other than F508del could be quite high.[1]

CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR PROTEIN MUTATIONS DIVIDED INTO FUNCTIONAL CLASSES

To date, almost 2000 CFTR mutations have been identified. These mutations affect the CFTR protein either by reducing the amount of protein that reaches the cell membrane surface, or by reducing the function of CFTR as a chloride channel.[2] CFTR mutations are grouped into 5 to 6 classes based on their functional effects (**Fig. 1**).[3–7] Class I, II, III, and VI mutations result in essentially no functional CFTR at the cell surface. Class IV and V mutations allow some CFTR to reach the surface, and are often associated with residual function.[7]

Each mutation class will be discussed separately.

Class I mutations are nonsense mutations, which introduce premature stop codons that prevent the translation machinery from producing full-length CFTR. These mutations appear in 10% of CF patients.[3,6,7]

Class II mutations lead to misfolded, or improperly processed CFTR protein. Most of this protein is degraded by cellular quality control mechanisms.[5,6,8] F508del or Phe508del (a deletion of phenylalanine at position 508), the most common CFTR mutation, is a class II mutation.[5,6,9] F508del leads to misfolded CFTR protein, the majority of which is degraded by cellular quality control mechanisms.[5,6,8] Of note, the F508del mutation has additional consequences that affect other aspects of channel function, demonstrating that some mutations may actually fit into more than one mutational class.

Class III gating mutations result in a full-length CFTR protein that has difficulties with activating/gating. These mutations are present in a minority of individuals with CF (4%). The G551D mutation is part of this class.[3,8]

Class IV mutations affect chloride conductance, which is the movement of chloride through the pore of the channel.[3] These mutations are also quite rare. One of the most common class IV

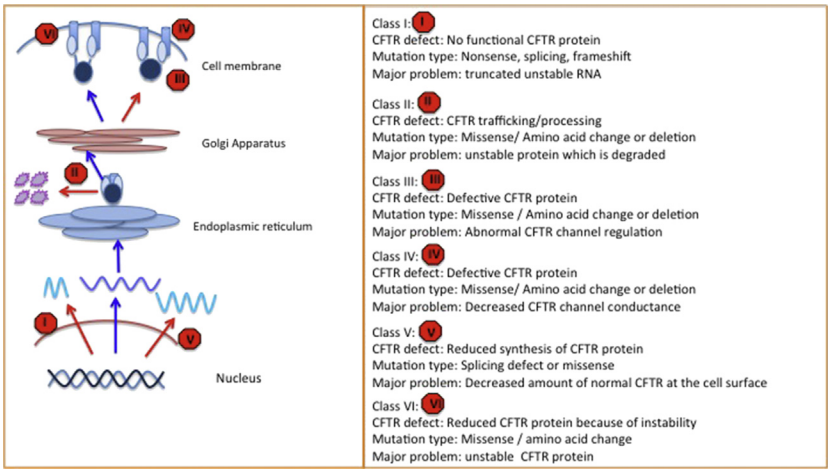

Fig. 1. Mutational classes I. Class I mutations Gly542X, Trp1282X II. Class II mutations Phe508del, Asn1303Lys III. Class III Gly551Asp, Gly551Ser IV. Class IV mutations ArgR117His, Arg347Pro, V. Class V mutations 3849 + 10kbC→T, 5T VI. Class VI mutations Gln1412X, 4279insA.