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REVIEW

Cystic Fibrosis

A Review of Associated Phenotypes, Use of Molecular Diagnostic Approaches, Genetic Characteristics, Progress, and Dilemmas

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Cystic fibrosis (CF) is an autosomal recessive disease with significant associated morbidity and mortality. It is now appreciated that the broad phenotypic CF spectrum is not explained by obvious genotype-phenotype correlations, suggesting that CF transmembrane conductance regulator (*CFTR*)—related disease may occur because of multiple additive effects. These contributing effects include complex *CFTR* alleles, modifier genes, mutations in alternative genes that produce CF-like phenotypes, epigenetic factors, and environmental influences. Most patients in the United States are now diagnosed through newborn screening and use of molecular testing methods. We review the molecular testing approaches and laboratory guidelines for carrier screening, prenatal testing, newborn screening, and clinical diagnostic testing, as well as recent developments in CF treatment, and reasons for the lack of a molecular diagnosis in some patients. *(J Mol Diagn 2016, 18: 3—14; http://dx.doi.org/10.1016/j.jmoldx.2015.06.010)*

Although some genetic conditions already highlight the potential of precision medicine, much is yet to be learned. In this review, we discuss the current understanding and complexity of cystic fibrosis (CF) genetics. CF is a relatively common, autosomal recessive, and frequently lethal condition caused by mutations in the CF transmembrane conductance regulator gene (*CFTR*). *CFTR* consists of 27 exons, spanning approximately 250 kb on 7q31.2.[1] *CFTR* is a member of the ATP-binding cassette transporter family and encodes an anion transporter protein in the epithelium with five domains. Two membrane-spanning domains form a chloride channel pore that plays a role in chlorine and bicarbonate transport and have secondary effects on sodium transport. CFTR protein dysfunction leads to increased salt concentration in sweat and thickened secretions in various organ systems. Numerous genetic mutations have been identified; their characterization and contribution to disease pathogenesis are discussed below. The clinical presentation ranges from multiorgan symptoms, such as chronic respiratory tract infections, failure to thrive, and pancreatic insufficiency starting in infancy, to single-organ manifestations, such as male infertility or chronic sinusitis in adulthood.[1] The broad phenotypic spectrum is not fully explained by genotype-phenotype

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correlations. *CFTR*-related disease may arise because of multiple combining effects, such as complex alleles, modifier genes, mutations in genes that can mimic CF phenotypes, and additional effects, such as those influenced by epigenetic and environmental factors. Birth prevalence of CF approximates 1:2300 for non-Hispanic whites, 1:13,500 for Hispanic whites, 1:2270 for Ashkenazi Jews, 1:15,100 for African Americans, and 1:35,100 for Asian Americans.[2]

CF Phenotype

The consequences of CFTR dysfunction often commence before birth. Effects of CFTR dysfunction include incomplete embryologic formation of the Wolffian structures, causing congenital bilateral absence of the vas deferens (CBAVD), which causes infertility in virtually all males with CF. Females do not have structural abnormalities, but may face fertility issues as a result of thickened cervical secretions. Fetal ultrasonographic findings of hyperechogenic bowel with or without meconium peritonitis, bowel dilation, or an undetectable gallbladder are concerning for CF. Meconium ileus occurs in up to 20% of CF-affected newborns and is strongly correlated with CF (90% of such cases occur in CF patients).[1] The analogous condition in children and adults with thickened intestinal secretions is distal intestinal obstructive syndrome (10% to 47% of patients). Pancreatic insufficiency is a manifestation in 85% of patients, and fat malabsorption can be measured in 90% of affected infants by 1 year of age. Pancreatic dysfunction contributes to generalized malnutrition, failure to thrive, and suboptimal bone mineral content. CF-related diabetes (25% by the age of 20 years; 50% in adulthood) and pancreatitis are other manifestations.[3]

As the infant grows, additional symptoms present. Some, such as the CF hallmark of failure to thrive, are non-specific. High temperatures risk electrolyte abnormalities because of excess losses in sweat. Respiratory tract symptoms are highly variable and can look non-specific but are the most recognized complication. Most patients develop sinus opacification, and up to 30% will have nasal polyps. Impaired pulmonary function is an early finding in some.[4] Bronchiectasis, mucus plugging, and air trapping have been documented by 6 to 12 months. The CF respiratory phenotype progresses because of static mucus and chronic bacterial colonization, infection, and inflammation, with progressively deteriorating lung function. Over the years, significant improvements have been made in diagnosis, delivery of care, and treatment modalities, such that the median life expectancy is now 36.8 years.[5] With the increasing life span, however, hepatobiliary dysfunction is becoming increasingly prevalent.[3]

Diagnostic Criteria

The diagnosis of CF is on the basis of characteristic symptoms in addition to evidence of CFTR dysfunction (Table 1).[6]

Table 1 Diagnostic Criteria for CF

Criteria are met in the presence of (at least one):
Organ system symptoms consistent with CF, such as the following
Chronic sinopulmonary disease
Characteristic gastrointestinal and nutritional abnormalities
Salt loss syndromes
Obstructive azoospermia
Sibling with CF
Positive newborn screening result
Criteria are met in combination with (at least one)
CFTR dysfunction indicated by elevated sweat chloride levels (≥60 mmol/L, performed in accord with practice guidelines and adjusted for age) on two tests
Nasal potential difference consistent with CF
Presence of two pathogenic *CFTR* mutations on different alleles

CF, cystic fibrosis; CFTR, CF transmembrane conductance regulator.

Historically, it was on the basis of presenting clinical symptoms with sweat test verification. Over time, however, increasingly the diagnosis is solidified by molecular testing that identifies both symptomatic and presymptomatic patients. In this transition toward more frequent identification through screening and molecular analysis, several observations have emerged.

First, within the CF spectrum, a variety of symptoms and sweat chloride levels can be seen. Symptoms range from single-system (eg, CBAVD) to multiple-system involvement. As evidenced in approximately 2% of patients who meet diagnostic criteria, even in individuals with clinical CF, sweat chloride values can be normal (≤29 mmol/L) or indeterminate (30 to 59 mmol/L).[7] Such values only become a diagnostic conundrum when patients who are clinically suspected to have CF do not meet diagnostic criteria. These cases have long puzzled clinicians and have been variably designated as atypical, non-classic, non-traditional, or mild variant CF.[8]

Second, CFTR dysfunction encompasses the spectrum of CF, *CFTR*-related diseases, and CFTR-related metabolic syndrome. Individuals with *CFTR*-related disease (including chronic rhinosinusitis, idiopathic bronchiectasis, allergic bronchopulmonary aspergillosis, and chronic idiopathic pancreatitis) and CFTR-related metabolic syndrome have come to medical attention for clinical signs or screening results but have indeterminate sweat chloride or nasal potential difference values and do not meet diagnostic criteria. CFTR-related metabolic syndrome is a designation given with an initial positive CF newborn screen (CFNBS) but no symptoms on follow-up and either normal sweat chloride results and two *CFTR* mutations, with at least one being a variant of uncertain clinical relevance,[7] or an intermediate sweat result and one or zero *CFTR* mutations.[7,8] On longitudinal assessment, most of these children will not develop symptoms. In the past, children with CFTR-related metabolic syndrome who developed CF symptoms might have fallen into the atypical or mild variant CF