GENETIC DISEASE ANALYSIS: CYSTIC FIBROSIS

GENE TESTED

Cystic fibrosis transmembrane conductance regulator (CFTR) - OMIM 602421

DISEASE

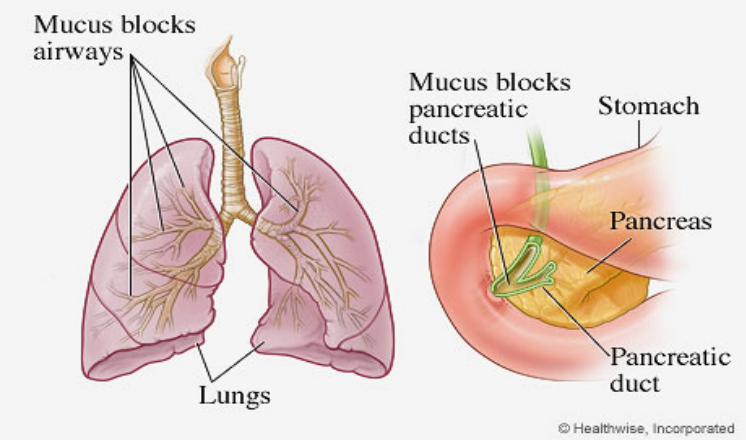
Cystic fibrosis - OMIM 219700
Congenital bilateral absence of vas deferens - OMIM 277180
Pancreatitis, idiopathic - OMIM 167800
Bronchiectasis with or without elevated sweat chloride 1, modifier of - OMIM 211400
Sweat chloride elevation without CF
Hypertrypsinemia, neonatal

BACKGROUND

Cystic fibrosis (CF) is a chronic genetic condition involving multiple organ systems. Two defective CF alleles cause the body to produce abnormally thick, sticky mucus that clogs the lungs and leads to life-threatening infections. Classical CF primarily involves the respiratory and digestive systems, and may have a range of clinical severity. Pulmonary symptoms often include lower airway inflammation, chronic cough, sinusitis, and recurrent infections. People with CF have a variety of other symptoms including high sweat chloride levels, persistent coughing, wheezing or shortness of breath, and excessive appetite but poor weight gain. Thick secretions also obstruct the pancreas and prevent digestive enzymes from reaching the intestines to help break down and absorb food. Digestive symptoms often include meconium ileus, pancreatic insufficiency resulting in malabsorption and/or failure to thrive, and hepatobiliary disease. CF mutations may also lead to congenital bilateral absence of the vas deferens (CBAVD) and infertility. Sweat chloride testing has a clinical sensitivity of 90 percent in classic CF and is considered the gold standard for diagnosis. Individuals with nonclassic CF may have clinical findings limited to a single organ system, such as idiopathic pancreatitis, bilateral absence of the vas deferens, nasal polyposis, or bronchiectasis. Nonclassic CF often presents in adulthood and may not decrease life expectancy. Sweat chloride values in individuals with nonclassic CF are often border-line but may also be elevated or in the normal range.

GENETICS

CF is inherited as an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance



regulator (CFTR) gene. Classic CF occurs in one in 3,000 Caucasians and Ashkenazi Jewish individuals, one in 8,000 Hispanics, one in 15,000 African-Americans, and one in 32,000 Asians. The incidence of nonclassic CF is unknown. CFTR mutations that result in a dysfunctional or deficient protein are classified as severe, while those that produce a partially functional protein are moderate or mild. Penetrance is high for severe mutations and variable for mild mutations. Classic CF is caused by two severe pathogenic CFTR mutations on opposite chromosomes. Nonclassic CF may be caused by one severe and one mild CFTR mutation or two moderate/mild mutations on opposite chromosomes.The severity of symptoms varies greatly between individuals diagnosed with CF due, in part, to the more than 1,600 different CF mutations described to date.

TESTING

Genetic testing is performed using the polymerase chain reaction (PCR) followed by bidirectional sequencing of the amplified targets.

RESULTS

Over 1,600 mutations are known; most are point mutations or small deletions detectable by gene sequencing. DeltaF508 accounts for over 60% of all mutations in northern Europeans. Large deletions/duplications would not be detected by these tests.

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AVAILABLE TESTS

Test# 2001.
The most prevalent mutation (deltaF508) is analyzed by amplifying and sequencing exon 11.

Test# 2002.
33 common mutations in exons 3, 4, 6, 8, 10-12, 14, 16, 18, 20, 22-24 are analysed: I507del, 1717-1G>A, 1898+1G>A, 2184delA, 2789+5G>A, 3120+1G>A, 3659delC, 3849+10kbC>T, 3876delA, 394delTT, 621+1G>T, 711+1G>T, A455E, F508del, G542X, G551D, G85E, N1303K, Q493X, R1162X, R117H, R334W, R347P, R553X, R560T, S549N, W1282X, 2055del9>A, 406?1G>A, E60X, R1066C, S492F,2105-2117del13insAGAAA.

Test# 2003.
95 common mutations in exons 3-14,16-25 and 3849+10kbC>T in intron 22 are analysed: 1078delT (c.948delT), 1154insTC (c.1022_1023insTC), 1248+1G>A (c.1116+1G>A), 1288insTA (c.1153_1154insAT), 1471delA (c.1340delA), 1717-1G>A (c.1585-1G>A), 1898+1 G>A (c.1766+1G>A), 1898+3A>G (c.1766+3A>G), 1949del84 (c.1817_1900del84), 2055del9>A (c.1923_1931del9insA), 2143delT (c.2012delT), 2183AA>G (c.2051_2052delAAinsG), 2184delA (c.2052delA), 2184insA (c.2052insA), 2307insA (c.2175_2176insA), 2347delG (c.2215delG), 2585delT (c.2453delT), 2622+1G>A (c.2490+1G>A), 2789+2insA (c.2657+2_2657+3insA), 2789+5G>A (c.2657+5G>A), 3120+1G>A (c.2988+1G>A), 3120G>A (c.2988G>A), 3199del6 (c.3067_3072delATAGTG), 3272-26A>G (c.3140-26A>G), 3600G>A (c.3468G>A), 3659delC (c.3528delC), 3849+10kbC>T (c.3717+12191C>T), 3876delA (c.3744delA), 3905insT (c.3773_3774insT), 394delTT (c.262_263delTT), 4005+2T>C (c.3873+2T>C), 405+1G>A (c.273+1G>A), 406-1G>A (c.274-1G>A), 4209TGTT>AA (c.4077_4080delTGTTinsAA), 621+1G>T (c.489+1G>T), 663delT (c.531delT), 711+1G>T (c.579+1G>T), 935delA (c.803delA), p.A455E (c.1364C>A), p.D1152H (c.3454G>C), p.E116K (c.346G>A), p.E1371X (c.4111G>T), p.E384X (c.1150G>T), p.E585X (c.1753G>T), p.E60X (c.178G>T), p.E92X (c.274G>T), p.G1061R (c.3181G>C), p.G1244E (c.3731G>A), p.G178R (c.532G>A), p.G330X (c.988G>T), p.G480C (c.1438G>T), p.G542X (c.1624G>T), p.G551D (c.1652G>A), p.G551S (c.1651G>A), p.G85E (c.254G>A), EX2del, EX2_3del, deltaF508 (c.1521_1523delCTT), deltaI507 (c.1519_1521delATC), p.L1077P (c.3230T>C), p.L467P (c.1400T>C), p.M1101K (c.3302T>A), p.N1303K (c.3909C>G), p.P67L (c.200C>T), p.Q1042X (c.3124C>T), p.Q220X (c.658C>T), p.Q414X (c.1240C>T), p.Q493X (c.1477C>T), p.Q552X (c.1654C>T), p.Q98R (c.293A>G), p.Q98X (c.292C>T), p.R1066C (c.3196C>T), p.R1066H (c.3197G>A), p.R1070W (c.3208C>T), p.R1158X (c.3472C>T), p.R1162X (c.3484C>T), p.R117C (c.349C>T), p.R117H (c.350G>A), p.R334Q (c.1001G>A), p.R334W

Test# 2004.
Full CFTR gene sequencing. All 27 exons, 20 bp of intronic DNA flanking each exon, 982 bp in the 5' untranslated promoter region, as well as portions of introns 12 and 22 are sequenced and analyzed.

REQUIRED FORMS

Sample requisition form (includes payment options and consent form).

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