Cystic Fibrosis and Congenital Absence of the Vas Deferens

Genetics

-Gene: CFTR (cystic fibrosis transmembrane conductance regulator; 7q31.2)

-AR

Clinical findings/Dysmorphic features

-CF: multisystem disease affecting epithelia: respiratory tract, exocrine pancreas, intestine, hepatobiliary system, exocrine sweat glands

-Progressive obstructive lung disease with bronchiectasis; pulmonary disease (Staphylococcus aureus and Pseudomonas aeruginosa)

-Pancreatic insufficiency and malnutrition

-Recurrent sinusitis and bronchitis

-Male infertility: Congenital Absence of the Vas Deferens (CAVD); > 95% of males are infertile

-Pulmonary disease is major cause of morbidity and mortality

-Meconium ileus occurs at birth in 15%-20% of newborns with CF

Etiology

-Most common life-limiting AR disorder in individuals of northern European background; incidence of CF is 1:3,200 live births in this population; ~30,000 affected persons live in the US

-Carrier frequencies: AJ 1:29; NE background 1:28; African American 1:61; Asian American 1:118

Pathogenesis

-CFTR is cell membrane chloride channel --> 4 mutation classes: I. reduced/absent synthesis, II. block in protein processing, III. block in regulation of chloride channel, IV. altered conductance of chloride channel

Genetic testing/diagnosis

-Diagnosis of CF established in

1) Proband with ≥ characteristic phenotypic features + evidence of defective CFTR function (2 elevated sweat chloride values/biallelic CFTR variants/transepithelial nasal potential difference)

2) Infant with elevated trypsinogen on NBS + biallelic CFTR variants or elevated sweat chloride

3) CAVD in male with azoospermia + absence of vas deferens on palpation or biallelic CAVD-causing CFTR variants

-Targeted analysis can be performed first: panel of 23 pathogenic variants

--> Detection rates: 97% in Ashkenazi Jewish, 88.3% in non-Hispanic whites, 69% in African Americans, 57% in Hispanic Americans

-Sequencing and del/dup of CFTR if only one or no pathogenic variant is found

Others

-Poly T tract in intron 8 is associated CFTR-related disorders --> 7T/9T are polymorphic variants; 5T (5% of people) is variable penetrant variant --> 90% lacks exon 9

-Poly T testing as reflux if R117H is detected (not primary test, indication is CF and not CAVD)

-TG tract lies just 5' of the poly T--> longer TG tract (12 or 13) in conjunction with 5T has strongest adverse effect on proper splicing

-Kalydeco (Ivacavftor): approved by FDA in 2012 for G551D for kids >6 years; 37 mutations approved July 2017; now approved for patients >2 years --> helps defective CFTR to function (potentiator, opens channel; Phe508del2 not enough CFTR at membrane for Kalydeco to work)

-Symdeko (Ivacavftor/Tezacaftor or Lumacaftor): FDA approved for patients > 12 years; also for p.Phe508del2 (Tezacaftor helps to get CFTR to membrane; Ivacaftor opens the channel)