Polycystic Kidney Disease (AD and AR)

Genetics

-Gene: PKD1/PKD2 (Polycystin-1; 16p13.1/Polycystin-2; 4q21); PKHD1 (Fibrocystin; 6p21.1-p12)

-AD (PKD1, PKD2) and AR (PKHD1)

Clinical findings/Dysmorphic features

1) ADPKD:

-Generally late-onset multisystem disorder with bilateral renal cysts, liver cysts, increased risk of intracranial aneurysms (5x increased); ~50% with ESRD by age 60 years

-Others: cysts in pancreas; seminal vesicles; arachnoid membrane; dilatation of aortic root and dissection of thoracic aorta; mitral valve prolapses; abdominal wall hernias

2) ARPKD:

-Congenital hepatorenal fibrocystic syndrome; renal/liver-related morbidity/mortality in kids

-Majority presents in neonatal period with enlarged echogenic kidneys: renal disease with nephromegaly, hypertension, varying degrees of renal dysfunction (>50% ESRD in 1st decade)

-Pulmonary hypoplasia due to oligohydramnios in a number of affected infants (~30% of these infants die in the neonatal period or within the first year of life from respiratory insufficiency)

-Others: subset with hepatosplenomegaly; histologic hepatic fibrosis present at birth

Etiology

-ADPKD: most common potentially lethal single-gene disorder; prevalence at birth is ~ 1:1,000; it affects ~300,000 persons in the US

-ARPKD: incidence is estimated at 1:10,000 to 1:40,000

Pathogenesis

-PKD-related proteins are involved with function of the primary cilia (located on apical surface of most epithelial cells including kidney tubule and biliary cells)

-Fibrocystin, polycystin-1 and polycystin-2 interact at molecular level in addition to direct interactions of the protein products --> these cystoproteins exist as multimeric protein complexes at multiple sites including primary cilia

Genetic testing/diagnosis

-ADPKD: PKD1 (78% of cases; 97%/3%); PKD2 (12% of cases; 97%/3%); GANAB (0.3% of cases); DNAJB11 (0.1% of cases); unknown (7% of cases)

-ARPKD: PKHD1 (73% of cases/1-2%); DZIP1L (<1%/?)

Others

-PKD2 mutations show later onset and slower rate of progression. ESRD age 60 yrs

-TSC2/PKD1 contiguous gene syndrome