Tuberous Sclerosis Complex

Genetics

-Genes: TSC1 (Hamartin, 9q34; 26% of cases), TSC2 (Tuberin; 16p13; 69% of cases)

-AD (2/3 de novo)

Clinical findings/Dysmorphic features

-Skin: hypomelanotic macules, confetti skin lesions, facial angiofibromas, shagreen patches (rough, elevated), fibrous cephalic plaques, ungual fibromas (under toenails)

-Brain: cortical tubers, subependymal nodules, cortical dysplasias, subependymal giant cell astrocytomas, seizures, ID/DD, psychiatric illness

-Kidney: angiomyolipomas, cysts, renal cell carcinomas

-Heart: rhabdomyomas, arrhythmias

-Lungs: lymphangioleiomyomatosis, multifocal micronodular pneumonocyte hyperplasia

-CNS tumors: leading cause of morbidity/mortality; renal disease: 2nd

Etiology

-Incidence may be as high as 1:5,800 live births

Pathogenesis

-Hamartin and tuberin form heterodimers --> regulate cell growth and proliferation; key regulators of AKT/mTOR signaling pathway; participate in several other signaling pathways (MAPK, AMPK, b-catenin, calmodulin, CDK, autophagy, cell cycle pathways)

-Most pathogenic variants are LoF --> uncontrolled cell growth and cell proliferation --> formation of hamartomas

Genetic testing/diagnosis

-Sequence analysis and gene-targeted del/dup of TSC1 and TSC2

-TSC1 sequencing (10% familial, 15% sporadic) and TSC2 sequencing (14% familial and 53% sporadic); InDel: ~1%

-Somatic mosaicism for pathogenic variant should be considered

Others

-TSC2/PCKD contiguous gene deletion syndrome with features of TSC and PKD --> renal cysts!