WAGR Syndrome (PAX6-Related Aniridia)

Genetics

-Isolated aniridia: PAX6 (Pair box protein; 11p13) --> AD; 30% de novo

-WAGR: PAX6 + WT1 (Pair box protein + Wilms Tumor 1; 11p13; ~700kb heterozygous deletion) --> AD; usually de novo (rarely, asymptomatic parent may be mosaic)

Clinical findings/Dysmorphic features

-WAGR= Wilms Tumor-Aniridia-Genital Anomalies-Retardation

-Aniridia: pan ocular disorder: cornea, iris, intraocular pressure (resulting in glaucoma), lens (cataract and subluxation), fovea (hypoplasia), optic nerve (optic nerve coloboma/hypoplasia)

-WAGR:

--> Risk for Wilms tumor is 42.5%-77% (of those: 90% by age four; 98% by age seven)

--> Genital anomalies (males: cryptorchidism, hypospadias, ambiguous genitalia, ureteric abnormalities, gonadoblastoma; females: normal external genitalia, may have uterine abnormalities and streak ovaries)

--> ID in 70%, behavioral abnormalities (ADHD, ASD, anxiety, depression, OCD)

Etiology

-Prevalence of aniridia 1:40,000 to 1:100,000; prevalence of WAGR is 1:500,000

Pathogenesis

-PAX6 important for ocular devel. during embryogenesis: proliferation, differentiation, migration, adhesion

-PAX6 expression continues in adult retina, lens, cornea (maintains ocular health) --> het mut disturb ocular morphogenesis --> aniridia and related ocular phenotypes; mild CNS defects; hom or comhet mut --> anophthalmia and CNS defects; often fatal (incomplete dominance)

-WAGR caused by cryptic or cytogenetically visible deletions (11p that include band 11p13) --> loss of WT1 --> genitourinary + renal abnormalities --> predisposes to Wilms tumor

Genetic testing/diagnosis

-Isolated aniridia: PAX6 --> Seq 85%, In/Del 15%; WAGR: PAX6 and WT1 --> CMA/FISH 100%

Others

-Het variant in PAX6 regulatory element (150kb from PAX6 in ELP4 gene) --> isolated aniridia

-Screen children with abdominal US every 3 month until age 8 years

-Wilms tumor (=Nephroblastoma) = childhood kidney cancer