Retinoblastoma

Genetics

-Genes: RB1 (Retinoblastoma-associated protein; 13q14.2); MYCN

Clinical findings/Dysmorphic features

-AD susceptibility for retinoblastoma; from cells with cancer-predisposing mut in 2 RB1 copies

-Malignant tumor of developing retina in children < 5y; may be unifocal or multifocal;

-~60%: unilateral RB (age of diagnosis 24 mths); ~ 40%: bilateral RB (age of diagnosis 15 mths)

-Individuals are also at increased risk of developing non-ocular tumors; sarcomas

Etiology

-Incidence between 1:15,000 and 1:20,000 live births

Pathogenesis

-RB1 encodes ubiquitously expressed nuclear protein involved in cell cycle regulation (G1 to S transition) --> RB is phosphorylated by members of the cyclin-dependent kinase system prior to the entry into S-phase --> binding activity of pocket domain is lost --> release of cellular proteins

-Pathogenic variants in RB1 --> loss of cell cycle-regulating function

-Partial active proteins associated with low-penetrance retinoblastoma

Genetic testing/diagnosis

-Eye exam using indirect ophthalmoscopy; imaging studies: support diagnosis and stage tumor

-Diagnosis: proband with retinoblastoma AND family history of retinoblastoma OR identification of het germline variant in RB1

-Seq and In/Del analysis of RB1 are performed on peripheral blood DNA

-If tumor tissue available: Seq and In/Del analysis of RB1 on tumor DNA

--> if pathogenic variants found --> blood is tested for presence of these variants

--> if no pathogenic variants found: methylation analysis of RB1 promoter CpG island --> if no hypermethylation --> amplification of MYCN is tested (cause of retinoblastoma in absence of RB1 variants in ~ 1.5% of individuals with isolated unilateral retinoblastoma)

Others

-Eye examination under anesthesia every 3-4 weeks until 6mths, then less frequently until 3y

-15% of unilateral retinoblastoma patients carry a germline mutation --> 1% recurrence risk for unilateral (it is 5-7% for bilateral, due germline mosaicism, mainly in father)