Beckwith-Wiedemann Syndrome

Genetics

-Gene: IGF2 and H19 in domain 1; CDKN1C, KCNQ10T1, and KCNQ1 in domain 2

-AD in 15%

Clinical findings/Dysmorphic features

-Neonatal hypoglycemia, macrosomia (large baby, 90%), macroglossia (50%), ear creases/pits, hemihyperplasia, omphalocele (organs, including liver, outside abdomen with covering membrane vs. Gastroschisis has no sac and is likely caused by a rupture of a hernia of the cord)

-Embryonal tumors (e.g. Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma)

-Visceromegaly, adrenocortical cytomegaly

-Renal: medullary dysplasia, nephrocalcinosis, medullary sponge kidney, nephromegaly)

-Clinical spectrum (affected ind. may have many of these features or only one)

-Early death may occur from prematurity, hypoglycemia, cardiomyopathy, macroglossia, tumors

Etiology

-Prevalence of 1:10,000

Pathogenesis

-Domain 1: imprinted genes H19 and IGF2 (H19: ncRNA may function as tumor suppressor; IGF2: potent fetal growth factor):

--> IC1 unmethylated on mat allele --> CTCF binds DNA --> prevents enhancer to activate IGF2 --> IGF2 is not expressed/H19 is expressed

--> IC1 methylated on pat allele --> CTCF cannot bind --> IGF2 expressed/H19 not expressed

-Domain 2: imprinted genes CDKN1C, KCNQ1, and KCNQ1OT1; IC2 in promoter for KCNQ1OT1:

--> IC2 methylated on mat allele --> KCNQ1OT1 not expressed/CDKN1C and KCNQ1 are expressed

--> IC2 not methylated on pat allele --> KCNQ1OT1 expressed/CDKN1C and KCNQ1 are not expressed

-Loss of methylation at IC2 on the maternal chromosome --> biallelic expression of the normally paternally expressed KCNQ1OT1 and reduced CDKN1C and KCNQ1 expression

Genetic testing/diagnosis

-Cytogenetically detectable abnormalities on 11p15 only in < 1%

-Causes: 1) Hypomethylation on maternal IC2 (50%); 2) Paternal UPD for 11p15 (20%), 3) unknown (20%) 4) Hypermethylation on maternal IC1 (5%), 5) Maternal CDKN1C SNV in ~40% of familial cases and 5%-10% of cases with no family history

Others

-Screening for embryonal tumors: abdominal US every 3 months until 8y

-Serum AFP concentration is monitored in the first few years of life for hepatoblastoma

-pUPD of 11p15 and gain of met at IC1 --> highest risk for WT and hepatoblastoma