Russell-Silver Syndrome

Genetics

-Abnormalities at imprinted domain on chromosome 11p15.5

Clinical findings/Dysmorphic features

-IUGR; postnatal growth deficiency; proportionately short stature, normal head circumference, fifth-finger clinodactyly, typical facial features with triangular facies characterized by broad forehead and narrow chin, limb-length asymmetry (hemihypotrophy)

-Significant risk for developmental delay (both motor and cognitive) and learning disabilities

Etiology

-1 in 100,000

Pathogenesis

-IC1 hypomethylation on paternal allele --> CTCF binds --> blocks transcriptional signals from cis enhancer sequences --> IGF2 is off/biallelic expression of H19

-H19 is an imprinted, maternally expressed non-coding RNA; IGF2 is an imprinted, paternally expressed transcript: insulin-like growth factor II

-Maternal uniparental disomy of chromosome 7 can also cause RSS (loci unknown)

Genetic testing/diagnosis

1) Chromosome 11p15.5-related RSS:

-Loss of IC1 methylation of paternal 11p15.5 (35-50% of cases) --> methylation analysis

-Duplication of maternal 11p15.5 (maternal UPD) --> In/Del analysis

2) Chromosome 7-related RSS:

-Maternal UPD (7-10%) --> SNP/marker analysis, methylation specific MLPA

-Deletion/Duplication --> cytogenetic or In/Del analysis

Others

-RSS caused by epigenetic alterations at IC 1, while BWS is caused by alterations at IC1 and IC2