6q24-related transient neonatal diabetes mellitus

Genetics

-Genetic aberrations of the imprinted locus at 6q24

Clinical findings/Dysmorphic features

-Severe intrauterine growth retardation; shortage of the hormone insulin; hyperglycemia in the neonatal period in a term infant, resolves by age 18 months; dehydration; absence of ketoacidosis; macroglossia and umbilical hernia may be present

-Hypotonia, congenital heart disease, deafness, neurologic features (epilepsy), renal malformations

Etiology

-1:400,000

Pathogenesis

-Overexpression of imprinted, paternally expressed genes PLAGL1 and HYMAI

-Three different genetic mechanisms --> twice the normal dosage of PLAGL1 and HYMAI:

(1) paternal uniparental disomy of chromosome 6

(2) duplication of 6q24 on the paternal allele

(3) hypomethylation of the maternal PLAGL1 TSS

Genetic testing/diagnosis

-6q24-TNDM is caused by overexpression of the imprinted genes at 6q24 (PLAGL1 and HYMAI)

-DMR (i.e., PLAGL1 TSS alt-DMR) is present within the shared promoter of these genes

-Normally: expression of PLAGL1 and HYMAI is silenced on maternal allele and only paternal alleles of PLAGL1 and HYMAI are expressed

Others

-Biallelic ZFP57 pathogenic variants account 50% of TNDM associated with a multilocus imprinting disturbance (MLID)

-ZFP57 variants result in inactivation of ZFP57 --> important in maintaining genomic imprinting at the DMR of PLAGL1 and HYMAI