Galactosemia

Genetics

-Genes: GALT (galactose-1-phosphate uridylyltransferase; type I), GALK1 (galactokinase 1; type II) and GALE (UDP-galactose-4-epimerase; type III)

-AR

Clinical findings/Dysmorphic features

1) Classic galactosemia/type I/GALT: most common; most severe; if infants not treated promptly with a low-galactose diet --> life-threatening complications within few days after birth: feeding difficulties, lethargy, FTT, jaundice, liver damage, abnormal bleeding, bacterial infections (sepsis), shock, DD, clouding of lens (cataract), speech difficulties, ID

2) Galactokinase deficiency/type II/GALK1: fewer medical problems than the classic type; affected infants develop cataracts but otherwise experience few long-term complications

3) Galactose epimerase deficiency/type III/GALE: mild to severe: cataracts, delayed growth and development, ID, liver disease, kidney problems

4) Clinical variant galactosemia: 1%-10% residual GALT activity in erythrocytes and/or liver

5) Biochemical variant galactosemia: 15%-33% residual GALT enzyme activity in erythrocytes (includes D2 Duarte biochemical variant state)

Etiology

-NBS results: prevalence of classic galactosemia is 1:48,000

Pathogenesis

-Galactose in many foods; part of larger sugar lactose (in dairy products and baby formulas)

-Pathogenic variant p.Gln188Arg largely prevents formation of a GALT-UMP intermediate

-Duarte D2: deletion in E-box (carbohydrate response element --> reduced GALT expression)

Genetic testing/diagnosis

-Classic galactosemia + clinical variant galactosemia: elevated erythrocyte galactose-1-phosphate (> 10 mg/dL), reduced GALT activity, and/or biallelic variants in GALT

-Seq of GALT first (95%) --> del/dup analysis if only one or no variant is found (5.2-kb del in AJ)

-Targeted analysis for common variants can be done first in ind. of European or African ancestry

Others

-Almost all females with classic galactosemia with premature ovarian insufficiency

-100% of classic galactosemia or clinical variant galactosemia can be detected in NBS that include testing for galactosemia in their panel (clinical variant galactosemia may be missed if NBS only measures blood total galactose level and not erythrocyte GALT enzyme activity)

-Neonate with emesis, diarrhea, icterus and hepatomegaly