Alpha thalassemia

Genetics

-HBA1 (Hemoglobin subunit alpha 1); HBA2 (Hemoglobin subunit alpha 2); 16p13.3

-AR

Clinical findings/Dysmorphic features

-Alpha thalassemia results from deletions involving HBA1 and HBA2 --> both of these genes provide instructions for making a protein called alpha-globin (subunit of hemoglobin A)

1) Hemoglobin Bart hydrops fetalis (Hb Bart) syndrome: deletion of all four α-globin genes; hydrops fetalis, severe hypochromic anemia, death in neonatal period

2) Hemoglobin H (HbH) disease: deletion of three α-globin genes; splenomegaly, mild jaundice, sometimes thalassemia-like bone changes

-α-thalassemia trait --> loss of 2 α-globin genes either in cis (--/αα, α0 carrier) or in trans (-α/-α)

-α-thalassemia silent carrier --> Loss of 1 α-globin gene (-α/αα, α+ carrier)

Etiology

-Mediterranean: alpha-thalassemia trait -α3.7/-α3.7 is common (highest AF in Sardinia (0.18))

-Southeast Asia: alpha0-thalassemia alleles (--/αα) and α+-thalassemia alleles (-α/ αα) common

--> incidence of Hb Bart expected: 0.5 - 5 per 1000 births

--> incidence of HbH disease 4 and 20 per 1000 births

Pathogenesis

-Inability to form normal Hb A (normally composed of two alpha and two beta chains)

Genetic testing/diagnosis

-Hb Bart: characteristic radiographic and laboratory features

-HbH: characteristic laboratory and clinical features

-Targeted deletion analysis for common deletions of HBA1and HBA2 can be performed first:

1) Common 2 α-globin gene deletions (α0): Southeast Asian, Filipino, Mediterranean; common single α-globin gene deletions (α+): 3.7-kb deletion, 4.2-kb deletion --> 85%

2) Sequence analysis of HBA1 and HBA2 if no common deletion was identified --> 15%

3) Deletion analysis of HBA1, HBA2 and HS-40 (regulatory region located 40 kb upstream from the α-globin cluster) can then be performed --> 5%

Others

-One parent has α-thal trait in cis (--/αα) and other parent is α-thal silent carrier (-α/αα):

--> 25% chance of having HbH disease (-α/--); --> 25% chance of having α-thalassemia trait (--/αα); --> 25% chance of being an α-thalassemia silent carrier (-α/αα); --> 25% chance of being unaffected and not a carrier (αα/αα)