Factor V Leiden Thrombophilia

Genetics

-Gene F5 (Coagulation factor V; 1q23)

-AD (moderately increased risk for venous thromboembolism), AR (significantly increased risk)

Clinical findings/Dysmorphic features

-Poor anticoagulant response to activated protein C (APC) --> increased risk for VT

-Most commonly deep venous thrombosis (DVT)

-Heterozygous: 2-3x increased recurrence risk of pregnancy loss

-FVL and oral contraceptive use: HETs with 35-50x risk for VT (risk is 1 in 20,000 FVL HETs vs. 1 in 140,000 in wt); HOM with >100x risk

Etiology

-Heterozygosity: 3%-8% of the US and European populations; high prevalence in Sweden (10%-15%); extremely rare in Asian, African, and indigenous Australian populations

-Frequency of homozygosity for the Leiden variant is approximately 1:5,000

Pathogenesis

-G>A substitution affects an APC cleavage site --> FVL inactivation 10x more slowly and persists longer in circulation --> increased thrombin generation

Genetic testing/diagnosis

-Suspected in individuals with:

--> History of 1st/recurrent VTE manifest as DVT or pulmonary embolism, especially in women with history of VTE during pregnancy or in association with estrogen-containing contraceptives

--> A family history of recurrent thrombosis

-APC resistance assay: sensitivity and specificity for factor V Leiden approaches 100%

-Identification of a heterozygous or homozygous c.1691G>A variant (100%)

Others

-Factor II/Prothrombin: common variant in 3’ UTR (G20210A; AF478696.1: g.21538G>A; c.\*97G>A) --> changes polyA signal --> stabilizes mRNA --> more prothrombin produced

-Incidence: ~2% in Caucasians; heterozygotes with 3-fold increased risk

-Oral contraceptives --> 149-fold increased risk for cerebral vein thrombosis; 16.3-fold increased risk for DVT