HFE Hemochromatosis

Genetics

-Gene HFE (Hereditary hemochromatosis protein; 6p21.3)

-AR (low penetrance, many homozygotes never develop symptoms)

Clinical findings/Dysmorphic features

-High iron absorption by GI mucosa --> excessive iron storage in liver, skin, pancreas, heart, joints, testes

-Early symptoms: abdominal pain, weakness, lethargy, weight loss

-Clinical signs of advanced iron overload: diabetes mellitus, progressive increase in skin pigmentation, hepatomegaly, hepatic cirrhosis, arthropathy (metacarpophalangeal joints), primary liver cancer, cardiomyopathy, hypogonadism

Etiology

-Northern European: prevalence of ind. homozygous for p.Cys282Tyr is 2:1,000 to 5:1,000

-Non-Hispanic whites in US: prevalence of p.Cys282Tyr homozygotes is 1:200 to 1:400

-Less common in Asians and Hispanics

Pathogenesis

-HFE protein binds transferrin receptor 1 and inhibit cellular iron uptake --> LOF mutations lead to increased iron uptake

Genetic testing/diagnosis

-Increased fasting transferrin-iron saturation on at least 2 occasions

-Targeted mutation testing (60-90% C282Y/C282Y; 3-8% C282Y/H63D)

Others

-Treatment --> Clinical HFE hemochromatosis: induction treatment by phlebotomy to achieve serum ferritin concentration ≤50 ng/mL

-Clinical HFE hemochromatosis is more common in men than women (monthly period)