Condition: Hemochromatosis

Inheritance:

Autosomal recessive.

Genetic etiology:

Most common form due to mutation in *HFE* gene, which encode a protein involved in the regulation of iron absorption. The most common mutations are C282Y and H63D. Homozygosity for C282Y or compound heterozygosity for C282Y/H63D are the most common genotypes associated with hemochromatosis. Penetrance is incomplete.

Frequency:

The allele frequency of HFE mutations in individuals of Celtic ancestry is 1/10, though the frequency of clinical disease is lower than the predicted 1/400 due to nonpenetrance. Penetrance is higher in males than females.

Clinical features:

Excessive dietary iron absorption leads to deposition of iron in tissues and consequent toxicity. Most commonly this leads to cirrhosis of the liver, cardiomyopathy, diabetes mellitus, bronze discoloration of the skin, and arthropathy. There is a wide range of variable expression and incomplete penetrance.

Management:

Phlebotomy to reduce iron stores, with monitoring of iron; supportive care for irreversible damage due to iron deposition.

Genetic counseling:

Based on autosomal recessive inheritance, with high carrier frequency leading to examples of pseudodominant transmission. Initial diagnosis usually based on determination of increased iron stores (for example by measurement of transferring saturation). Genetic testing for the common *HFE* alleles is available, but does not predict disease due to nonpenetrance.

Human Genetics and Genomics, Fourth Edition. Bruce R. Korf and Mira B. Irons.