

Gene Section

Review

HFE (hemochromatosis)

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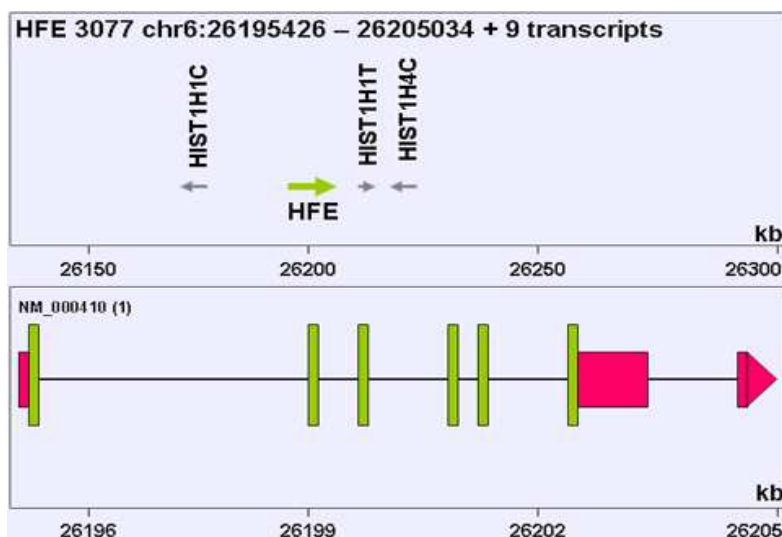
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Identity

Other names: HFE1; HH; HLA-H; MGC103790; dJ221C16.10.1

HGNC (Hugo): HFE

Location: 6p22.1



DNA/RNA

Note

History and Nomenclature: The HFE gene was discovered in 1996 by Feder et al after a long search in the vicinity of the HLA-A locus. It is around 5 Mb telomeric to HLA-A in physical distance but genetic distance is less than 1 cM. Unfortunately, it was originally named HLA-H as the HLA class I-like hemochromatosis gene but there was already a gene called HLA-H. Thus, the hemochromatosis gene should not be called HLA-H. According to nomenclature conventions, the gene is called HFE and the protein

product is HFE. There is no pseudogene derived from HFE.

Description

HFE encompasses 9,609 bp of DNA on chromosome 6 (6p22.1) between 26,195,426 - 26,205,034 bp from pter within the extended HLA class I region. Histone genes populate either side of the HFE gene. It is an HLA class-I-like molecule but is not involved in antigen presentation or immune response.

Transcription

HFE has at least nine alternatively spliced forms.

The full-length transcript contains six exons, however, the number of exons can be as few as three (see Figure).

Protein

Description

HFE is a beta2-microglobulin-associated membrane protein similar to HLA class I molecules. It consists of an a-chain encoded by HFE and beta2-microglobulin as the b-chain.

Expression

Expressed in a wide range of cell types and tissues including lymphocytes and placenta.

Localisation

HFE is a cell surface membrane protein.

Function

HFE is primarily involved in iron homeostasis. Initially it was thought that it directly regulated intestinal iron absorption. It is now believed that functional HFE is required for normal regulation of hepcidin synthesis, which is the main regulator of iron metabolism. Mutations of HFE result in iron overload.

Mutations

Note

Two missense mutations C282Y (rs1800562) and H63D (rs1799945) are relatively common. C282Y is most common in Northern European populations and H63D has a global distribution. Whereas the prevalence of these mutations is high, the clinical penetrance of the disease they cause is low.

There is no nonsense mutation described in HFE.

Missense mutations are involved in pathogenesis of iron overload.

HFE is not involved in any known translocations.

Hfe knockout mice are viable and develop iron overload.

Implicated in

Iron Overload

Disease

Mutations in HFE increase body iron levels and homozygosity or compound heterozygosity may cause iron overload. The penetrance is low. Dietary iron intake, alcohol consumption and blood loss are environmental modifiers. The importance of iron overload is that it increases the risk for cancer development presumably due to its potential to cause oxidative DNA damage.

Hereditary Hemochromatosis

Disease

Hereditary hemochromatosis (HH; OMIM 235200) is a recessive iron storage disorder resulting from defects in

HFE. HH (type 1) is the most common autosomal recessive disease in Caucasians adults. Most patients (about 90%) are homozygous for the C282Y mutation and another 4% are compound heterozygotes (C282Y, H63D). Different forms of non-HFE hemochromatosis are caused by other iron-related genes: type 2 (mutations in HFE2), type 3 (mutations in TFR2) and type 4 (mutations in SLC40A1 'ferroportin'). HH is characterized by abnormal intestinal iron absorption and elevated total body iron levels. Iron overload results in clinical complications including cirrhosis, cardio-pathy, endocrine dysfunctions including diabetes, arthropathy and susceptibility to liver cancer. The penetrance is higher in males due to regular blood loss in premenopausal women. Disease complications can be prevented by regular phlebotomy. The effect of HFE on disease phenotype can be modified by other iron-related genes including hepcidin (HAMP), transferrin (TF), transferrin receptor (TFRC), haptoglobin (HP) and ceruloplasmin (CP).

Porphyria variegata

Disease

Defects in HFE also cause porphyria variegata (OMIM 176200). Porphyrias are inherited defects in the biosynthesis of heme, resulting in the accumulation and increased excretion of porphyrins or porphyrin precursors. Porphyria variegata is the prevalent form in South Africa. It is characterized by skin hyperpigmentation and hypertrichosis, abdominal pain, tachycardia, hypertension and neuromuscular disturbances. Iron overload is the hallmark of the disease.

Leukemias

Disease

HFE mutations do not cause cancer and HFE mutations are not detected preferentially in cancer cells as somatic mutations. Both C282Y and H63D mutations, however, have been implicated in susceptibility to leukemias and other cancers. In South Wales (U.K.), C282Y mutation is associated with increased risk to childhood acute lymphoblastic leukemia in boys only. This association has not been noted in other studies in Finland, Spain and Mexico. In Italy, adult leukemia shows an association with H63D mutation.

Breast Cancer

Disease

Studies in USA, Russia and Turkey have found risk associations with HFE mutations C282Y and/or H63D with breast cancer. A Swedish study found a risk association only in women homozygous for the TFRC variant S142G.

Other cancers

Disease

In Sweden, combination of HFE mutation C282Y and/or H63D and homozygosity for the TFRC variant

S142G increase susceptibility to multiple myeloma, hepatocellular carcinoma and colon cancer (besides breast cancer). An interaction of HFE mutations with dietary intake of excessive iron also increases the risk for colorectal cancer. Various studies have reported increased frequency of HFE mutations in hepatocellular carcinoma secondary to hepatic iron overload but not in HCV-induced hepatocellular carcinoma. There appears to be an interaction between HFE and alcohol in the induction of iron overload, cirrhosis and subsequent hepatocellular carcinoma. For each genetic association report between HFE and any cancer, there is also one or more negative association report. It appears that only large and comprehensive studies taking into account gene x gene and gene x environment interactions may conclude this issue.

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