

NCBI Advanced Case Study Workflow-based Answer



Based on Symptoms

- elevated liver enzymes
- excess ascites fluid
- enlarged spleen (splenomegaly)

Jeff is diagnosed with Hereditary Hemochromatosis

Clinical information

Lab & Gene Test Results

Jeff – his extremely high Serum Ferritin and very high Serum Transferrin Saturation suggests fairly advanced Hemochromatosis disease.

A specific heritable homozygous pathogenic variant (p.C282Y) was identified in Jeff's HFE gene which causes the loss of a Cysteine (C) at position 282 with the substitution of a Tyrosine (Y) in its place in both copies.

Gene information

HFE is a critical protective gene product in iron transport in all mammals. It is a membrane protein and associates with beta2-Microglobulin at the membrane to regulate the interaction of the Transferrin Receptor with Iron/Transferrin complex. Defects in this gene have been known to cause hereditary hemochromatosis, an iron storage disorder.

Protein information

Jeff's p.C282Y variants cause the removal of a critical residue participating in a disulfide-bridge stabilization of both copies of the HFE protein. The 3D Structure of the protein confirms this.

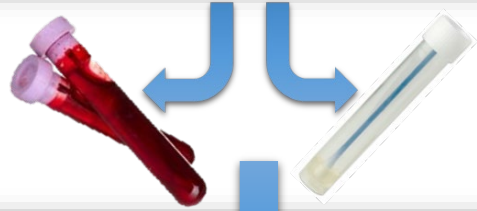
The unfolded protein has been shown to activate the newly discovered "unfolded protein stress response" in the endoplasmic reticulum which destroys the mutant protein, preventing its activity.

Physiological Pathway information

Due to the affect of the genetic variation on the stability of the HFE protein, it is degraded and can no longer regulate binding of the Iron/Transferrin complex to the Transferrin receptor. Thus, Iron ions are continually being dumped into the cell – causing a build-up of the potential for proliferation of damaging free radicals.

Hereditary hemochromatosis, an autosomal recessive disorder, is an iron "overload" disease.

- **Fe³⁺** High intracellular iron levels causes free-radical damage to intracellular proteins, lipids, and nucleic acids.
- **Fe³⁺** **Medical complications of Hemochromatosis:** hypermelanotic pigmentation of the skin, arthritis, cirrhosis of the liver, diabetes, heart failure and primary hepatocellular carcinoma
- **Fe³⁺** Iron is an essential nutrient required for the synthesis of hemoglobin, cytochromes, and many other proteins
- **Fe³⁺** Iron is transported around the body by Transferrin which binds to the extracellular Transferrin Receptor, causing internalization and cellular uptake of the complex.
- **Fe³⁺** HFE protein regulates cellular uptake of iron, thus preventing intracellular damage.



HFE hemochromatosis [Homo sapiens (human)]
Gene ID: 3077, updated on 10-Sep-2016

Summary

Official Symbol: HFE provided by HGNC
Official Full Name: hemochromatosis provided by HGNC
Primary source: HGNC:HGNC:4886
See related: Ensembl:ENSG0000010704 HPRD:01993; MIM:613609; Vega:OTTHUMG0000016348
Gene type: protein coding
RefSeq status: REVIEWED
Organism: Homo sapiens
Lineage: Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
Also known as: HH; HFE1; HLA-H; MVCD7; TFQTL2
Summary: The protein encoded by this gene is a membrane protein that is similar to MHC class I-type proteins and associates with beta2-microglobulin (beta2M). It is thought that this protein functions to regulate iron absorption by regulating the interaction of the transferrin receptor with transferrin. The iron storage disorder, hereditary haemochromatosis, is a recessive genetic disorder that results from defects in this gene. At least nine alternatively spliced variants have been described for this gene. Additional variants have been found but their full-length nature has not been determined. [provided by RefSeq, Jul 2008]
Orthologs: mouse all

Genomic context
Location: 6p21.3 See HFE in [Genome Data Viewer](#) [Map Viewer](#)

Conserved domains on [gi:4504377:refNP_000401:HFE:g.10633G>A, p.C282Y]

hereditary hemochromatosis protein isoform 1 precursor [Homo sapiens]

Graphical summary show options

Query seq. heterodimer interface MHC binding domain interface

Specific hits
Superfamilies MHC_I superfamily Ig

[Superfamily] c11960, Immunoglobulin domain: Ig immunoglobulin (Ig) domain found in the Ig superfamily. The Ig superfamily is a heterogeneous group of proteins, built on a common fold composed of a sandwich of two beta sheets. Members of this group are components of immunoglobulin, neuroglobin, cell surface glycoproteins, such as

..... A predominant feature of most Ig domains is a disulfide bridge connecting the two beta-sheets

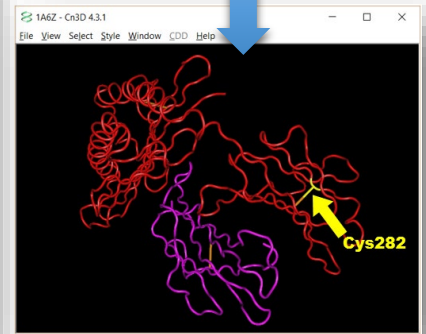
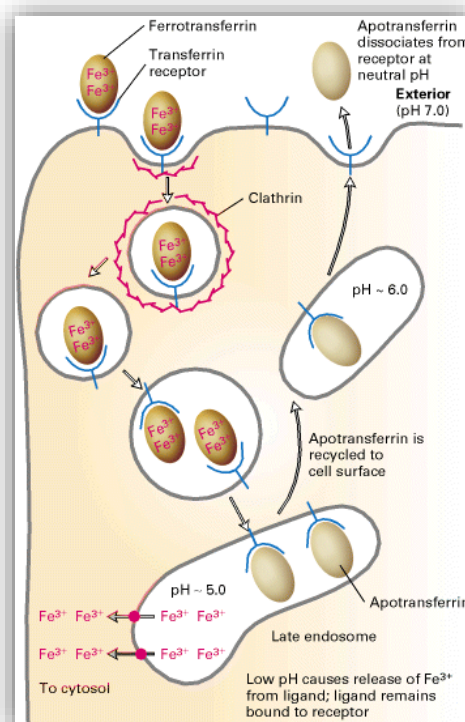


Figure 17-48. The transferrin cycle. Molecular Biology of the Cell by Lodish, et al.