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

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

Fe+3 **High intracellular iron levels causes free-radical damage to intracellular proteins, lipids, and nucleic acids.**

Fe+3 ***Medical complications of Hemochromatosis:*** **hypermelanotic pigmentation of the skin, arthritis, cirrhosis of the liver, diabetes, heart failure and primary hepatocellular carcinoma**

Fe+3 **Iron is an essential nutrient required for the synthesis of hemoglobin, cytochromes, and many other proteins**

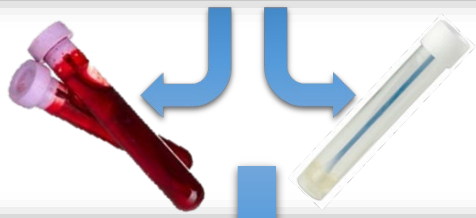
Fe+3 **Iron is transported around the body by Transferrin which binds to the extracellular Transferrin Receptor, causing internalization and cellular uptake of the complex.**

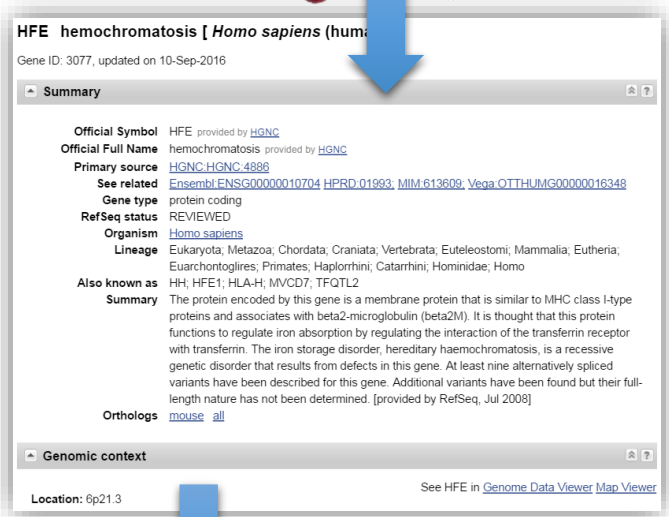
Fe+3 **HFE protein regulates cellular uptake of iron, thus preventing intracellular damage.**

Clinical information

Lab & Gene Test Results

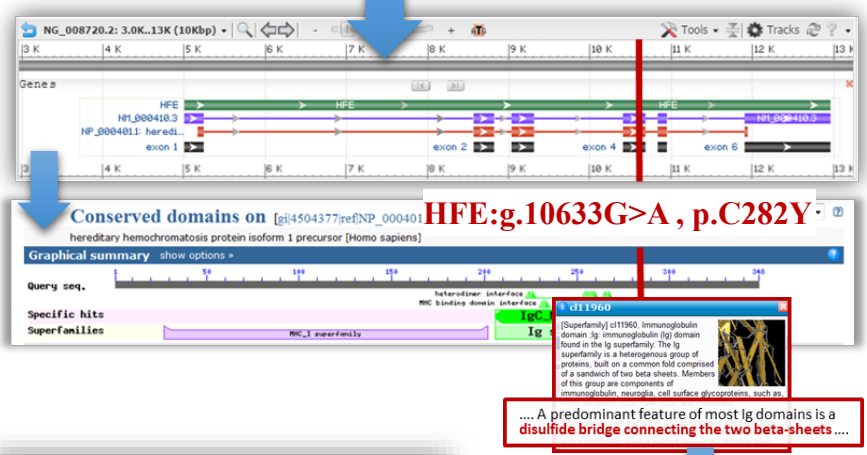
Jeff – his extremely high Serum Ferritin and very high Serum Transferrin Saturation suggests fairly advanced Hemochromatosis disease.
A specific hereditable homozygous pathogenic variant (p.C282Y) was identified in Jeff's HFE gene which causes the loss of a Cysteine (C) at position 282 with the substitution of a Tyrosine (Y) in its place in both copies.





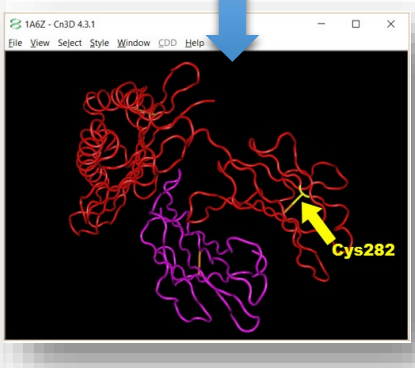
Gene information

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.

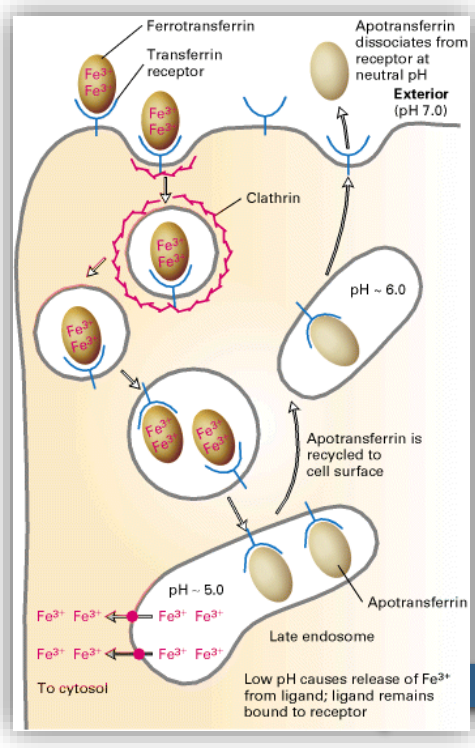


Figure 17-48. The transferrin cycle. Molecular Biology of the Cell by Lodish, et al.