HEREDITARY HEMOCHROMATOSIS (HH)

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SBS11QHG02 PERIOD 6
5 JUNE 2013

CAUSED BY A MUTATION IN THE HFE (HIGH IRON FE) GENE

PHYSIOLOGY

- HH is a genetic disease characterized by an overload of iron in the human body.
- Males are more likely to inherit the disease than females
- Caucasians are more likely to inherit the disease than other races
- HH is an autosomal recessive disease
- Individuals with the genetic mutations that cause HH may remain asymptomatic due to incomplete penetrance of the symptoms.
- Symptoms:
  - Early Symptoms:
    - Lethargy, arthralgia, decreased libido, abdominal pain
  - Later Symptoms:
    - Hyperpigmentation, liver cirrhosis, hepatocellular carcinoma, diabetes mellitus, arthritis, cardiomyopathy
- Onset differs between genders
  - Males: Between the ages of 40 and 60
  - Females: After menopause

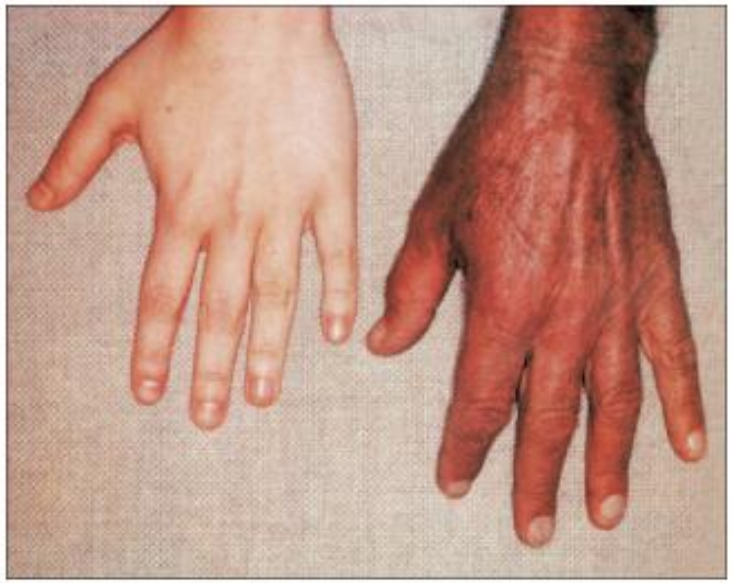


Figure 1(above): A hand of a normal human compared to a hand an individual affected with HH.
Note the discoloration of the latter's hand due to hyperpigmentation of the skin (skin bronzing).

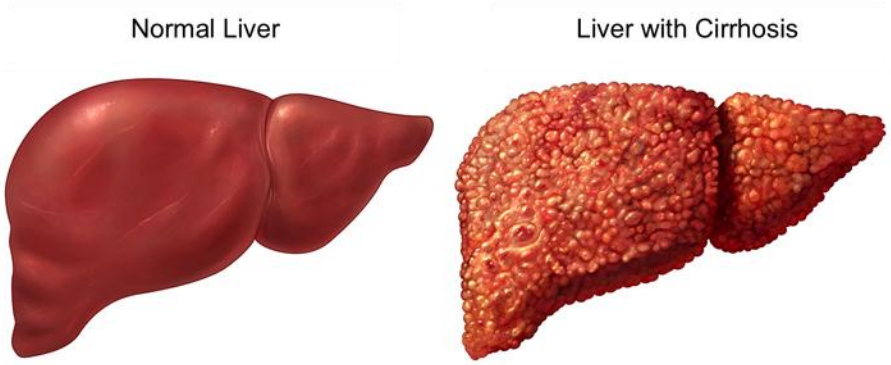
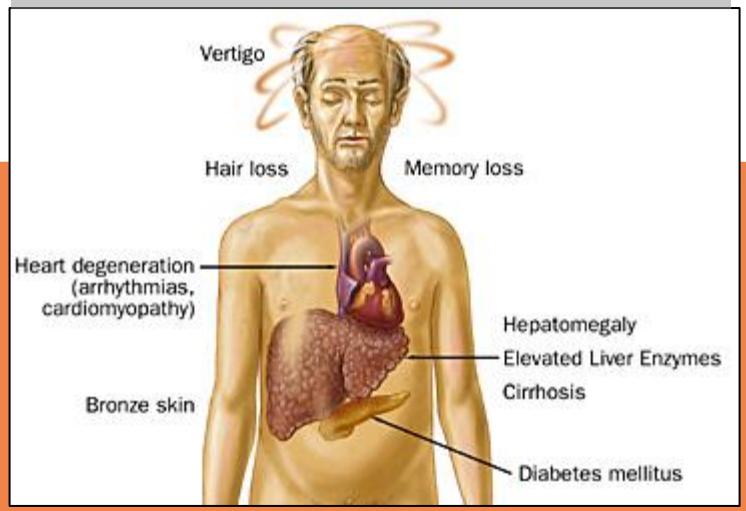


Figure 2 (above): Comparison of a normal liver and a liver with cirrhosis (severe liver scaring) which is a later symptom of HH.

Figure 3 (below): General appearance of an individual affected with HH.



MOLECULAR CAUSE

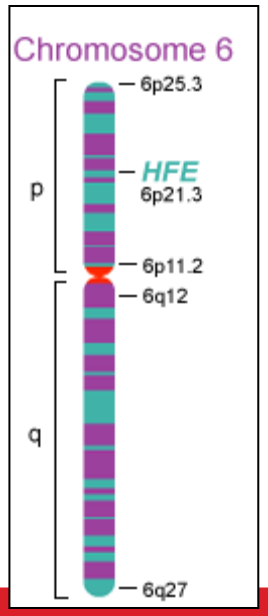


Figure 4 (above): Affected chromosome and locus shown

- HH is caused by two point mutations each one on one of the two homologues of chromosome 6 at the HFE gene (locus 6p21.33)
- The mutations have to change the normal expressed amino acids such that either a Cys282Tyr/ Cys282Tyr genotype or a Cys282Tyr/His63Asp genotype is present
- The former of the two genotypes occurs in 90-95% of HH cases while the latter occurs in 5-10% of HH cases.
- Both variants of HH have a chance to manifest as asymptomatic due to the incomplete penetrance of the disease's symptoms
- In the Cys282Tyr/ Cys282Tyr variant of HH a disulfide bond cannot form in the alpha 3 region of the expressed protein (the HFE protein).
- It should be noted that the HFE protein is
- The lack of the disulfide bond prevents the HFE protein from binding to TfR1 and TFR2 (transferrin receptors 1 and 2) which are responsible for bonding to transferrin (an iron transporter) and producing hepcidin (signals for the internalization and destruction of ferroportin) respectively.
- TfR1 can only do its job when not in a complex with the HFE protein while TfR2 is the opposite and needs to be in a complex with the HFE protein to produce hepcidin.
- Thus in HH, the HFE gene codes for a misfolded protein that can no longer form complexes withTfR1 to inhibit iron internalization and complexes with TfR2 to promote hepcidin production which destroys ferroportin in order to prevent iron exportation from duodenum villus enterocytes and macrophages.

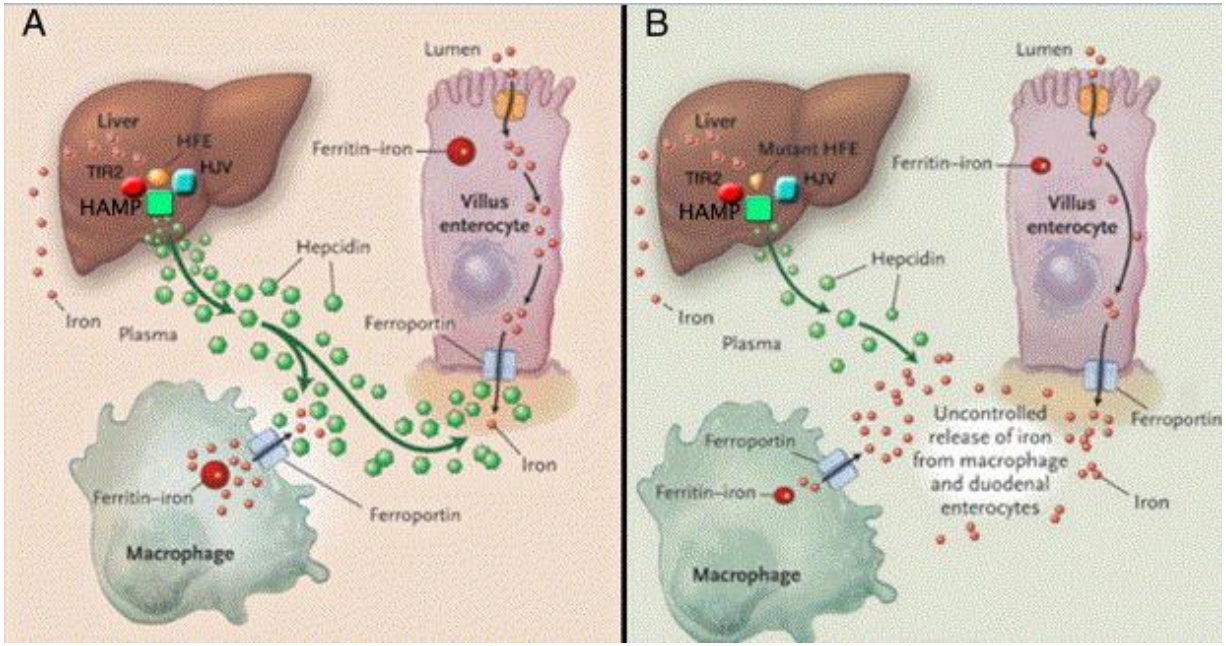


Figure 5 (left): The normal and mutated molecular pathway/interaction of the HFE protein with TFR2

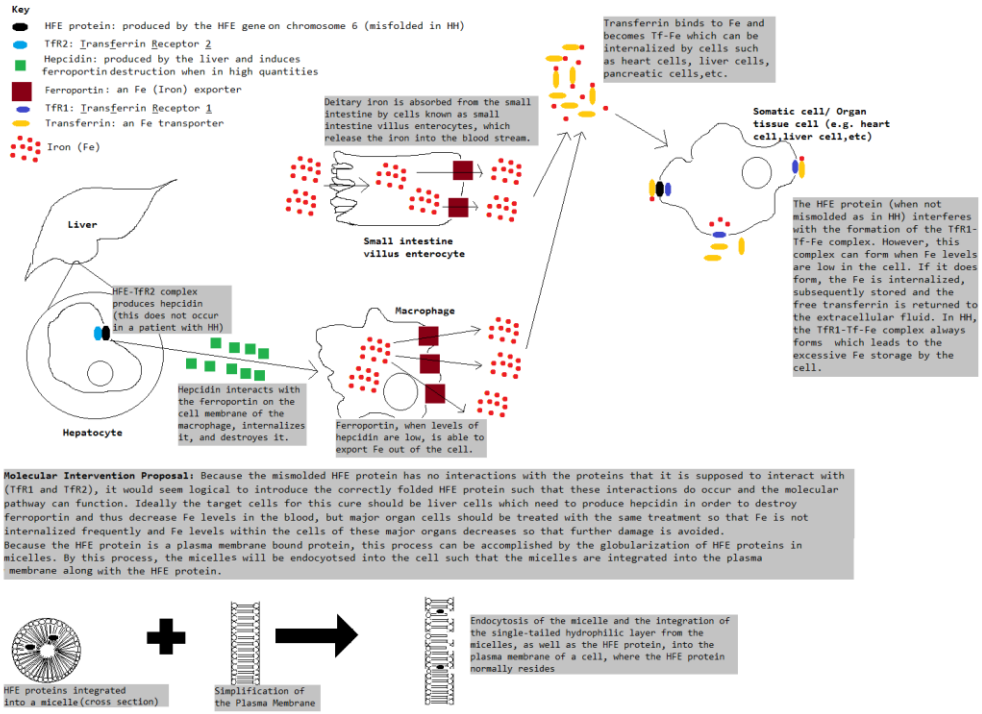


Figure 6 (right): The general molecular pathway of HFE interactions with TfR1 and TfR2.

CURRENT TREATMENTS

- **Detection:**
  - Measure the levels of ferritin (an iron storage protein) in the blood
  - Liver biopsy to look for liver scaring (really only effective if the disease has gone unnoticed for a long time)
  - Genetic analysis
- **Palliative Treatments (for relieving pain felt from symptoms):**
  - Liver transplant to “remove” damage from liver cirrhosis (Fig. 2).
- **Interventive Treatments (to treat the symptoms):**
  - Weekly or biweekly phlebotomy (consists of the removal of 450-500 mL of blood to normalize the levels of ferritin (an iron storage protein) in the blood
  - Use of chelating chemicals such as desferroxamine which is used to remove iron from the body
  - Prevent the ingestion of iron to prevent later absorption by the duodenum villus enterocytes
  - Limit Vitamin C intake to prevent the development of heart arrhythmia (a later complication of HH)
- **Limits of Current Treatments:**
  - Iron and ferritin levels in the blood will constantly need to be monitored
  - No foods which high concentrations of iron can be consumed because any further iron ingestion leads to irreversible damage.
- **Therapies Under Treatment:**
  - None

PROPOSED CURES

- **The integration of the correctly folded HFE protein in the cell membrane**
  - Note that the HFE protein is a plasma membrane protein and thus partially insoluble and cannot pass through the phospholipid bilayer of the plasma membrane.
  - In individuals with HH it cannot form complexes with TfR1 and TfR2 because the protein is misfolded.
  - Thus this "cure" involves the globularization of correctly folded HFE proteins in micelles such that by globularizing them, the HFE protein can pass into the cell membrane when the micelle is endocytosed by the cell (see Fig. 6).
- **Ingestion of Calcium Supplements (to be taken with the "cure" described above) in order to lower iron levels in the body**
  - In normal individuals ingesting 300-600 mg of calcium has prevented the absorption of iron by duodenal villus enterocytes by either lowering the possibility that iron will bind to iron receptors on those cells or by affecting the metabolism of iron within those enterocytes.
  - This has not been tested in HH individuals, but it seems plausible that it may have the desired effect.

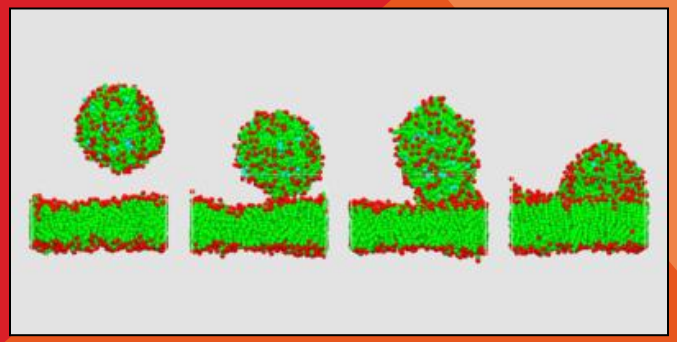


Figure 7 (left):
A micelle is being endocytosed and integrated into the cell (the mechanism and logic behind the cure involving the integration of the correctly folded HFE protein)

WORKS CITED

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Images

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- Figure 2: http://depts.washington.edu/hepstudy/definitions/?let=c
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Images

- Figure 4: http://www.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/hfe.shtml
- Figure 5: http://www.sciencedirect.com/science/article/pii/S0167488906001145
- Figure 6: Jorge Reyes (me)

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Proposal Slide

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Images

- Figure 7: http://scienomics.com/drug-release-through-micelles