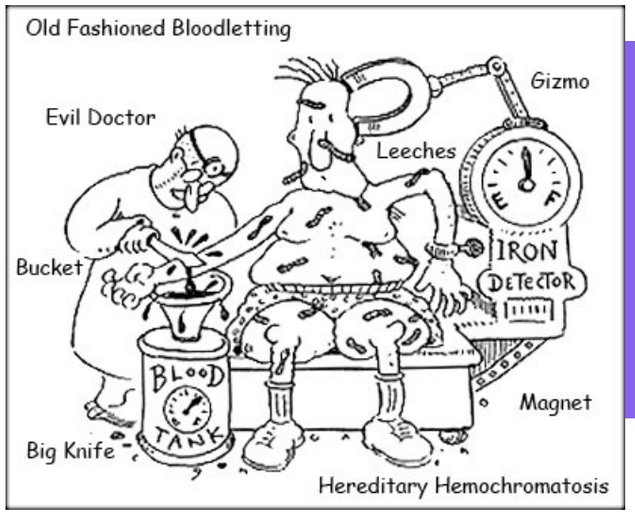
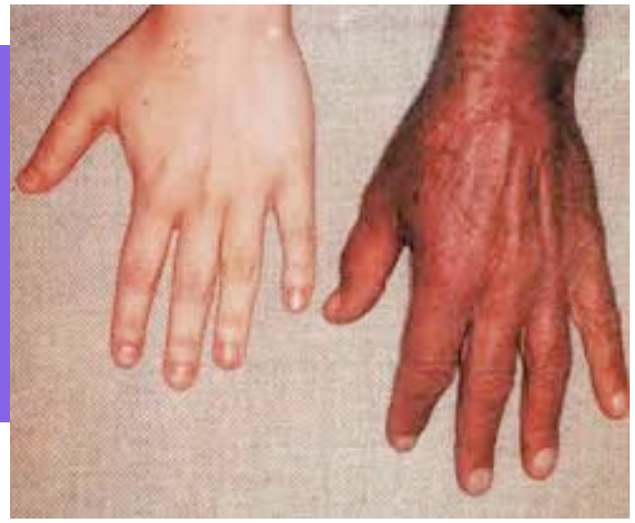
Hereditary Hemochromatosis

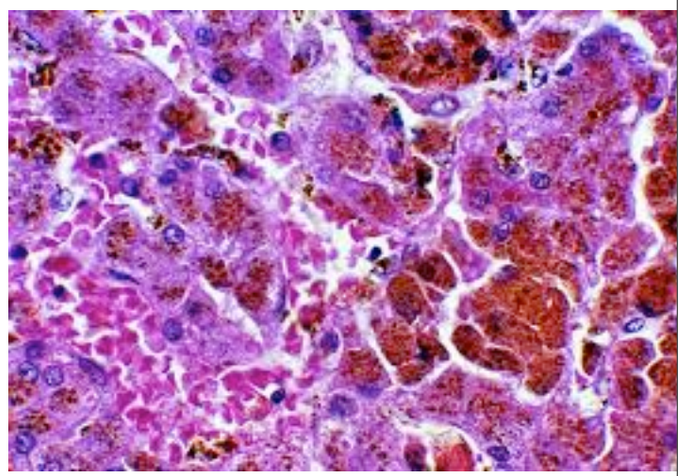
Aleksandra Stanisavljevic
Stuyvesant High School
June 5, 2013



Physiology

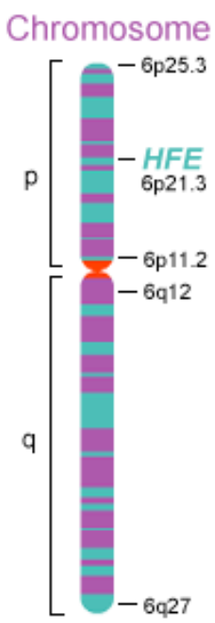


Hereditary Hemochromatosis is a disease that causes the body to stop regulating the absorption and storage of iron by the body's cells.
> It causes an over absorption of iron, which is stored in major organs (i.e. liver, heart) and in tissues and joints.



> This disease can cause heart problems (i.e cardiomyopathy), liver failure, and could lead to diabetes.
> In extreme cases the disease results in damage/ destruction of organs.
> The only visible symptom of the disease is bronzing of the skin. Other symptoms include: fatigue, impotence, muscle aches (arthritis), depression, disorientation, loss of body hair, premature menopause, loss of sex drive, abdominal pains.
> Hereditary Hemochromatosis has a late onset (manifests between 40 and 60 years of age) > It is "5 times more common in men than in women" - This is thought to be because women loose iron during menstruation and men do not menstruate.

Molecular Cause



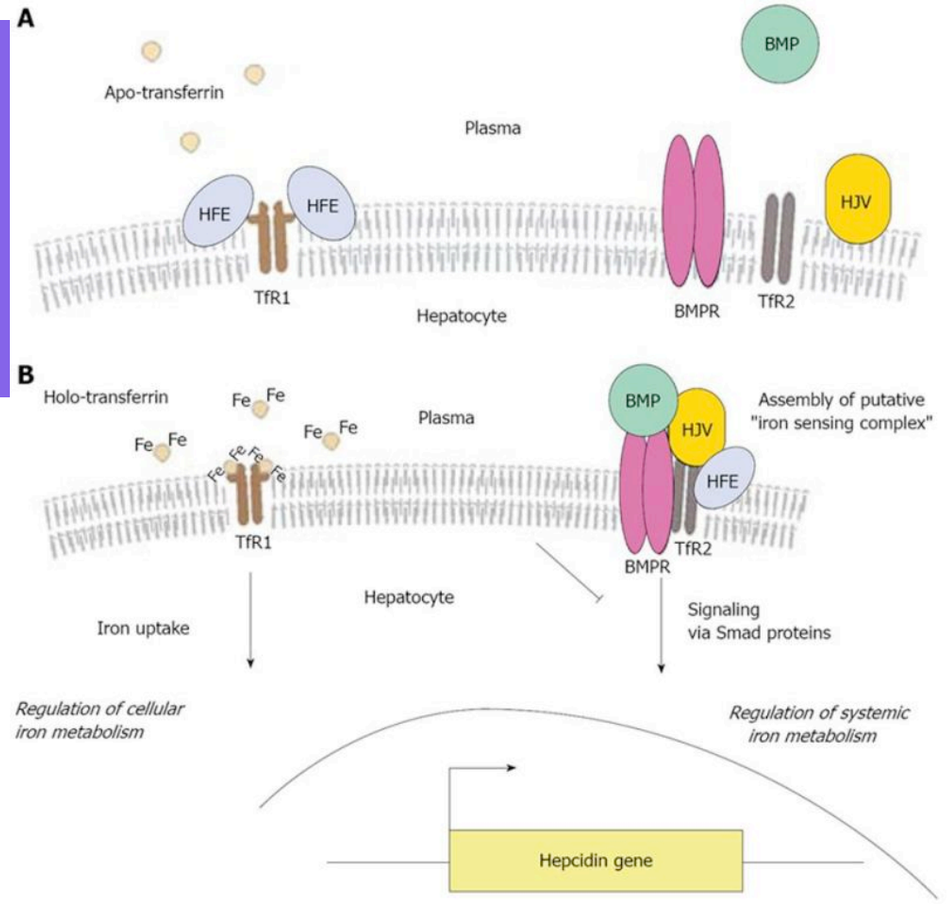
> Autosomal Recessive > Point Mutation > Mutates HFE gene, which is located on Chromosome 6. This mutation changes the structure of the HFE Protein. > Normally the HFE protein regulates iron by first binding with ß-2 microglobulin, and then communicating with transferrin receptors on the surface of the cell.

>>C282T mutation<< This is the most common mutation

> It is the "more severe phenotype" > change of amino acid at position 282 on the HFE protein > change from (amino acids) tyrosine to cysteine causes hemochromatosis. > caused by change from G to A at nucleotide 845 on HFE gene > this specific mutation causes: - protein can't bind to ß-2 microglobulin and can't be expressed on the cell surface - thus can't interact with transferrin receptor - result is over absorption of iron by the cells

>>H63D<<

> change of amino acid at position 63 on the HFE protein: change from (amino acids) histidine to aspartate causes hemochromatosis



> caused by change from C to G at nucleotide 187 on HFE gene > this specific mutation causes: - thought to affect "pH- dependent intramolecular salt bridge" causing miscommunications between HFE protein and transferrin - prevents proper function of protein to be carried out, thus iron absorption by the body cannot properly be regulated

>>S65C<<

> change of amino acid position 65 on the HFE protein > change from (amino acids) serine to cysteine causes hemochromatosis. > caused by change from A to T at nucleotide 193 on HFE gene > how the mutation causes hemochromatosis is currently unknown.

Treatments, Risks, and Limits

Currently there is no cure for Hereditary Hemochromatosis, there are only treatments.

Phlebotomy:

- blood is drawn 1-2 times a week to lower blood iron levels
- 1 unit of blood is taken every phlebotomy session (250 mg of iron in each unit) - treatment can last up to 3 years. - when iron levels are finally normal, phlebotomy continues every 2-4 months for the rest of the patient's life

When detected, diet will be altered

- no iron supplement pills - no vitamin C supplements: Vitamin C increases absorption of iron in the cells - no alcohol: 2+ drinks a day can increase iron intake - no raw shellfish: very high in iron - coffees and teas help lower absorption of iron

Proposed Cure/ Limits

Synthetic HFE protein injections
- would work like synthetic insulin used to treat those with diabetes
- Genetic recombination would be used to create a synthetic HFE protein; it would be synthesized in a lab and would be pre- bound with ß-2 microglobulin. The protein would be delivered via syringe into the blood stream, and then carried to the cells via carrier protein. It could also be administered via cream, and diffuse through the skin. After entering the blood stream, and reaching the cells, the synthetic protein would properly communicate with the transferrin receptors. This would result in proper regulation of iron intake.

References

(1) "Genomics.energy.gov--genome Programs of the U.S. Department of Energy." *Genomics.energy.gov--genome Programs of the U.S. Department of Energy*. N.p., 3 Dec. 2002. Web. 21 Feb. 2013. <http://genomics.energy.gov/>.

(2) Gray, Steven G., John Crowe, and Matthew W. Lawless. "Hemochromatosis: As a Conformational Disorder." *ScienceDirect.com*. N.p., Nov. 2009. Web. 20 Mar. 2013. <http://www.sciencedirect.com/science/article/pii/S1357272509001265>.

(3) "Hemochromatosis." *Hemochromatosis*. American Association for Clinical Chemistry, 21 Oct. 2009. Web. 21 Feb. 2013. <http://labtestsonline.org/understanding/conditions/hemochrom/>.

(4) "HFE (W-24): Sc-133654." *Santa Cruz Biotechnology, Inc.* Santa Cruz Biotechnology, Inc., n.d. Web. 20 Mar. 2013. <http://www.scbt.com/>.

(5) "Iron Overload and Hemochromatosis." *Cdc.gov*. Centers for Disease Control and Prevention, Feb. 2002. Web. 6 May 2013. <http://www.cdc.gov/ncbddd/hemochromatosis/pdf/IronOverload.pdf>.

(6) "KidsHealth from Nemours." *KidsHealth*. Ed. Christopher N. Frantz, MD. Neumors Foundation, 2012. Web. 21 Feb. 2013. <http://kidshealth.org/>.

(7) Lee, Dennis, MD. "Hereditary Hemochromatosis (Iron Overload)." *MedicineNet - Health and Medical Information Produced by Doctors*. Ed. Jay W. Marks, MD. N.p., n.d. Web. 21 Feb. 2013. <http://www.medicinenet.com/script/main/hp.asp>.

(8) Limdi, J. K., and J. R. Crampton. "QJM: An International Journal of Medicine." *Hereditary Haemochromatosis*. QJ Med, 2004. Web. 23 Feb. 2013. <http://qjmed.oxfordjournals.org/content/97/6/315.2.full>.

(9) "NewYork-Presbyterian. The University Hospital of Columbia and Cornell." *Hemochromatosis*. New York Presbyterian, 30 Nov. 2008. Web. 21 Feb. 2013. <http://nyp.org/health/blood-hemachro.html>.

(10) "Role of Iron in the Human Body." *Role of Iron in the Body*. Pur Absorb Iron, n.d. Web. 21 Feb. 2013. <http://www.nelsonsnaturalworld.com/en-us/uk/our-brands/spatone/iron-essentials/role-of-iron-in-the-body/>.

(11) "What Is the HFE Gene?" *Hemochromatosis DNA*. Hemochromatosis DNA Test, n.d. Web. 20 Mar. 2013. <http://www.hemochromatosisdna.com/>.

(12) Zelman, Kathleen M., MPH,RD,LP. "Top 10 Iron-Rich Foods: Foods High in Iron." *WebMD*. WebMD, n.d. Web. 20 Mar. 2013. <http://www.webmd.com/diet/features/top-10-iron-rich-foods>.