HFE Gene

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Homeostatic iron regulator

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1. Introduction

The *HFE* gene provides instructions for producing a protein that is located on the surface of cells, primarily liver and intestinal cells. The HFE protein is also found on some immune system cells.

The HFE protein interacts with other proteins on the cell surface to detect the amount of iron in the body. When the HFE protein is attached (bound) to a protein called transferrin receptor 1, the receptor cannot bind to a protein called transferrin. When transferrin receptor 1 is bound to transferrin, iron enters liver cells. So, it is likely that the HFE protein regulates iron levels in liver cells by preventing transferrin from binding to transferrin receptor 1.

The HFE protein regulates the production of a protein called hepcidin. Hepcidin is produced by the liver, and it determines how much iron is absorbed from the diet and released from storage sites in the body. When the HFE protein is not bound to transferrin receptor 1, it binds to a group of other proteins that includes hepcidin. The formation of this protein complex triggers the production of hepcidin. So when the HFE protein is bound to transferrin receptor 1, hepcidin production is turned off and when the HFE protein is not bound to transferrin receptor 1, hepcidin production is turned on.

When the proteins involved in iron sensing and absorption are functioning properly, iron absorption is tightly regulated. On average, the body absorbs about 10 percent of the iron obtained from the diet.

2. Health Conditions Related to Genetic Changes

2.1. Porphyria

Mutations in the *HFE* gene can increase the risk of developing a condition called porphyria. Porphyria is a group of disorders caused by abnormalities in the chemical steps that lead to heme production. Heme is a vital molecule for all of the body's organs, although it is most abundant in the blood, bone marrow, and liver. Heme is a component of several iron-containing proteins called hemoproteins, including hemoglobin (the protein that carries oxygen in the blood). *HFE* gene mutations are found more frequently in people with the most common form of porphyria, known as porphyria cutanea tarda, than in unaffected people.

Researchers suspect that *HFE* gene mutations may trigger this type of porphyria by increasing the absorption of iron. A buildup of excess iron, in combination with other genetic and nongenetic factors, interferes with the production of a molecule called heme. Heme is a component of iron-containing proteins called hemoproteins, including hemoglobin (the protein that carries oxygen in the blood). A blockage in heme production allows other compounds called porphyrins to build up to toxic levels in the liver and other organs. These compounds are formed during the normal process of heme production, but excess iron and other factors allow them to accumulate to toxic levels. The abnormal buildup of porphyrins leads to the characteristic features of porphyria cutanea tarda.

2.2. Hereditary Hemochromatosis

Researchers have identified more than 100 mutations in the *HFE* gene that cause type 1 hemochromatosis, a form of hereditary hemochromatosis that begins during adulthood. Hereditary hemochromatosis is a disorder that causes the body to absorb too much iron from the diet. The excess iron accumulates in, and eventually damages, the body's tissues and organs.

Two particular mutations are responsible for most cases of type 1 hemochromatosis. Each of these mutations changes one of the protein building blocks (amino acids) in the HFE protein. One mutation replaces the amino acid cysteine with the amino acid tyrosine at position 282 in the protein's chain of amino acids (written as Cys282Tyr or C282Y). The other mutation replaces the amino acid histidine with the amino acid aspartic acid at position 63 (written as His63Asp or H63D).

The Cys282Tyr mutation prevents the altered HFE protein from reaching the cell surface. The His63Asp mutation likely alters the three-dimensional shape of the protein. These mutations prevent the HFE protein from interacting with transferrin receptor 1 and other proteins. As a result, iron regulation is disrupted, and too much iron is absorbed from the diet. This increase in the absorption of dietary iron leads to the iron overload characteristic of type 1 hemochromatosis.

2.3. X-linked Sideroblastic Anemia

The Cys282Tyr mutation, which is a common cause of type 1 hereditary hemochromatosis (described above), may also increase the severity of the iron overload in X-linked sideroblastic anemia when it is inherited along with a mutation in the *ALAS2* gene. The combination of *HFE* and *ALAS2* gene mutations leads to more severe signs and symptoms of X-linked sideroblastic anemia by further increasing the absorption of dietary iron, leading to an even greater iron overload.

3. Other Names for This Gene

- hemochromatosis
- hemochromatosis, genetic; GH
- Hemochromatosis, Hereditary; HH
- Hereditary hemochromatosis protein
- HFE_HUMAN
- HLA-H antigen

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