

# Genes-4U

## **Hemochromatosis HFE-1 : C282Y, H63D and S65C**

Hereditary hemochromatosis (HHC) is a common autosomal recessive disorder of iron metabolism which in its homozygous form occurs in Caucasian populations with a prevalence of 0.2 - 0.5 % (1). Characteristic of the disease is the excessive accumulation of dietary iron and a progressive rise in iron stores. This may lead to serious clinical consequences including cirrhosis, cardiac failure, diabetes, arthritis and hepatocellular carcinoma. Treatment involves removal of the iron burden by regular venesection and leads to a normal life expectancy if implemented before the development of cirrhosis.

**Key Mutations.** Identification of a **hemochromatosis gene HFE-1** (initially termed HLA-H) by Feder et al. in 1996 allows early genetic diagnosis and greatly simplifies the screening of a family once affected individuals have been identified (2, 3). The HFE gene protein product is structurally similar to MHC class I - type molecules and interacts with b2-microglobulin and the transferrin receptor to limit iron absorption. Three disease-associated mutations have been detected in the HFE gene. **Most individuals with hemochromatosis (80-100% depending on the population studied) are homozygous for the mutation C282Y.** In addition, a small number of compound heterozygotes for C282Y and the second mutation, H63D, may develop clinical iron overload. Recently, the third mutation, S65C, was found to be enriched in hereditary hemochromatosis patients with a mild form of the disease without other HFE mutations. While mutations in the HFE gene thus account for most cases of hereditary hemochromatosis, it is clinically important that a minority of hereditary iron overload syndromes are not associated with mutations in the HFE gene. Absence of mutations may not be interpreted to mean that the patient in question does not have hereditary iron overload. Other rare mutations in the HFE-1 gene have been reported, and hereditary hemochromatosis not caused by HFE-1 mutations has been mapped to the loci HFE-2 (1q) and HFE-3 (7q22).

**Modifier Genes.** Severe iron overload usually develops in patients with HHC, but variability in the phenotypic expression of the disease has been reported. **Recently, genetic variants of the inflammatory cytokine TNF have come into focus.** In a recent Italian study (4), the prevalence of the 308 TNF-alpha polymorphism was similar in patients and controls, whereas the prevalence of the 238 polymorphic allele was significantly lower in patients (3% versus 16%;  $P = .002$ ). Interestingly, a trend to lower prevalence of cirrhosis was observed in patients with TNF-alpha polymorphism than in those without it (27% versus 57%;  $P = .07$ ). In nonhomozygotes for the C282Y mutation, severe liver siderosis was less prevalent in patients with the 308 polymorphism than in those without it ( $P = .05$ ). Alanine aminotransferase (ALT) values were significantly lower in patients with TNF-alpha polymorphism ( $P = .006$ ), even when patients with other hepatotoxic factors were excluded. Multivariate analysis showed that TNF-alpha polymorphism was independently associated with ALT values and siderosis. Thus, TNF-alpha appears to play a role in HHC by modulating the severity of liver damage, and determination of these TNF alpha polymorphisms may become useful in the management of hereditary hemochromatosis.

## **References**

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- (3) Hemochromatosis-a clinical update. Burt MJ et al. *Med J Aust* 1996;164:348-51.
- (4) Tumor necrosis factor alpha promoter polymorphisms influence the phenotypic expression of hereditary hemochromatosis. Fargion S et al. *Blood* 2001 Jun 15;97(12):3707-12 (PMID: 11389006)