

## Hereditary Hemochromatosis-Special Reference to Indian Scenario

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**ABSTRACT** Hereditary haemochromatosis (HH) manifested as iron overload in different organs due to homozygosity of a single autosomal mutation. If untreated it leads to conditions such as liver cirrhosis, type 1 diabetes mellitus, hypogonadotropic hypogonadism, cardiomyopathy, arthritis, and bronze coloring of the skin. Two different mutations C282Y and H63D in the HFE gene have been shown to be associated with over 93 per cent of HH cases. The disease is seen in Northern European population but in India the reports of genetic study is rare. Large population based studies are required to investigate the prevalence of this disease and association with other diseases in Indian subcontinent.

### INTRODUCTION

Hereditary haemochromatosis (HH) is an autosomal recessive disorder with iron overload in different organs, especially in the liver (Sheldon 1935; Dooley 1997; Bothwell and Mac Phail 1998; Franchini and Veneri 2005). The monoallelic genetic disease was first described by Trousseau (1889) as a triad of glycosuria, cirrhosis and hyperpigmentation of skin. The term 'hemochromatosis' was first used by von Recklinghausen (1889). In spite of increasing store of body iron, the inappropriately low iron status of the hereditary hemochromatosis, enterocyte continues to drive the hyper-absorption of dietary iron leading to iron overload (Poddar and Talukder 2002; Wood 2002). The close association between HH and the histocompatibility antigen HLA-A3 on the short arm of Chromosome6 was first described by Simon et al. (1977). Approximately 64-100% of patients with primary haemochromatosis are homozygous for a missense mutation that alters a major histocompatibility complex class I-like protein designated HFE involving a substitution of Cysteine to tyrosine at amino acid residue 282 (Cys282Tyr) (Beutler 2005). A second mutation His63Asp(H63A) in the HFE gene is enriched in primary haemochromatosis patients, concomitantly heterozygous for the Cys282Tyr-mutation. Iron builds up over time in various organs such as the liver, heart and brain. If untreated it leads to conditions such as cirrhosis of the liver, cardiomyopathy and diabetes. Early diagnosis and treatment however prevents these problems

developing. Molecular genetic data exclude a primary role for transferrin, transferrin receptor and ferritin since they are not expressed from chromosome6 (Dooley 1997). Homozygosity for the Cys282Tyr mutation with biochemical and clinical evidence of iron overload renders the diagnosis of HFE related primary haemochromatosis. Liver biopsy remains the gold standard for diagnosis in other cases. First degree relatives of index patients should be screened for the disease (Swinkels and Jacobs 2003).

### PREVALANCE OF THE DISEASE

More than 80% of HH patients in populations of European origin are homozygotes for a single mutation C282Y, or compound heterozygotes for C282Y and H63D mutations in the HFE gene. However, in the majority of Asian, Indian subcontinent, African, Australasian, and Amerindian populations, frequencies of C282Y are close to zero (Hanson et al. 2001). In Russian population, homozygosity for C282Y is found only in a small proportion (5%) of patients with biochemical and clinical signs of HH (Potekhina et al. 2005).

Very few cases of idiopathic hemochromatosis have been reported in India (Seshadri et al. 1982; Bothwell et al. 1983; Mithal et al. 1988; Shankaran et al. 1994).

Bezuda et al. (1976) has studied the pattern of food iron absorption in iron-deficient white and Indian subjects and in venesectioned hemochromatotic patients. They found that malabsorption of non-haem iron from a meal

containing bread, presumably due to a defect at the luminal level and found that it is prevalent among Indian women living in Durban.

Bhansali et al. (1992) reported a case of primary hemochromatosis with hypogonadotropic hypogonadism and decreased Leydig cell reserve.

The first cell line from a patient with hemochromatosis was done by Sing et al. (1994). They found multiple chromosomal aberrations, with deletion in the long arm and deletions/rearrangements in the short arm of chromosome 1.

Sood and Jain (2000) have reported a case of hemochromatosis in a female patient, associated with porphyrins in urine and an unusual finding on compound tomography of kidney. This is the first report of a female patient from India.

The status of HFE mutations has not been explored among Indians, particularly in patients with thalassaemia major. A cohort of 59 unrelated, healthy individuals from North India, 57 from South India and 75 thalassaemia major patients from North India for HFE mutations (C282Y and H63D) in cis/trans by the PCR sequence-specific primer method shows C282Y and H63D mutations in the HFE gene were rare among Indians. Although the HFE mutations were increased among patients of Thalassaemia (Kaur et al. 2003a).

Primary iron overload disorders and HFE mutations appear to be rare and cases have not been well characterised in India (Kaur et al. 2003b).

Thakur et al. (2004) studied the prevalence of C282Y mutation in chronic liver disease (CLD) patients and healthy subjects in a tertiary care referral center in India found almost 10% of nonalcoholic CLD patients have iron overload, but this is independent of C282Y mutation of the HFE gene.

Garewal et al. (2005) determined the allele frequency in the North Indian population of the two mutations C282Y and H63D, and correlated these mutations with the iron status in beta thalassemia traits. They found that H63D prevalent and C282Y rare in North Indians and the presence of 63D mutation did not increase body iron in coexistent beta thalassemia traits. Haplotype of H63D gene mutation was of an European haplotype, suggesting a possible common origin.

Wallace et al. (2005) identified a patient from the Indian subcontinent with features typical of

ferroportin disease. This is the first report to identify V162del or indeed any ferroportin 1 mutation in an individual from the Indian subcontinent. V162del mutation of ferroportin 1 causing non HFE haemochromatosis.

### Mechanisms for Iron Excess

The mechanisms accounting for iron excess are not only digestive hyperabsorption of iron but also excessive recycling of macrophagic iron coming from erythrophagocytosis and secreted into the blood. Both mechanisms are linked to an HFE-related hepatic failure in producing hepcidin, a key hormone of body iron regulation (Brissot et al. 2005).

**Symptoms:** Symptoms in the early years except for a healthy skin colouring that resembles a suntan. However early symptoms may include weakness, weight loss, apathy, loss of sexual drive (*libido*), and pain in the arms and legs. Muscle tenderness and cramps in the legs may also develop. Symptoms may occur earlier in men than in women because women lose blood during menstruation and childbirth. Edwards et al. (1994) showed the ratio of male:female showing clinical manifestation was 4:1. When blood is lost, iron levels in the body are reduced. a person with haemochromatosis already has extensive liver damage, they have a shortened life expectancy and a high risk of developing cancer of the liver. C282Y homozygotes found to have high serum ferritin levels, with or without increased transferrin saturation, should have regular therapeutic venesection. Those with normal iron studies should be monitored expectantly, but do not require venesection unless they develop persistent abnormalities in serum ferritin levels. Supplements of iron and vitamin C are to be avoided. The detailed diagnostic tests and treatment is depicted in table 1.

Pathological mutations have been discovered in 5 genes: HFE (encoding HFE), TFR2 (encoding transferrin receptor-2), SLC40A1 (encoding ferroportin), HAMP (encoding hepcidin) and HJV (encoding hemojuvelin) (Feder et al. 1996; Camaschella 2000; Montosi et al. 2001; Njajou et al. 2001; Roetto et al. 2003; Papanikolaou et al. 2004). The autosomal recessive diseases associated with mutations in HFE, TFR2, HAMP and HJV have similar clinical presentations. All are characterized by systemic iron overload with deposition of excess iron in parenchymal cells of

the liver, heart, pancreas and other endocrine tissues. Hemochromatosis disorders due to HFE and TFR2 mutations tend to be less severe, with later clinical onset, than those caused by HAMP and HJV mutations, the later are characterized by accelerated iron loading which if untreated may be lethal before fourth decade of life (Huang et al. 2005).

### Relation with Other Diseases

Hepatic iron overload may be associated with decreased survival after liver transplantation, even in patients without HH. Early diagnosis of hepatic iron overload using HFE gene testing and iron depletion prior to liver transplantation may improve post transplantation survival, particularly among patients with HH (Kowdley et al. 2005). The future challenge will be to identify the few C282Y homozygotes other genetic and environmental factors that regulate iron absorption and thus may modulate the phenotype of C282Y homozygotes need to be identified (Andersen et al. 2004).

Shet and Desai (2001) had not found any association of hemochromatosis with pigment accumulation within epidermal cysts which occurs after cyst rupture in Indian patients.

Ristic et al. (2005) found that HFE polymorphisms do not contribute to the susceptibility to multiple sclerosis (MS) but MS patients carrying the mutant C282Y allele exhibited earlier onset of disease symptom relative to other genotypes.

The hemochromatosis gene (HFE) produces a protein that interacts with Transferrin receptor (TfR) and Muller et al. (2005) hypothesized that malignant cells would selectively mutate HFE to improve their iron-uptake and thus provide themselves a growth advantage over non-tumor cells. High frequency of heterozygosity for the C282Y mutation in patients with alcoholic cirrhosis plus hepatocellular carcinoma suggests the presence of this mutation could be associated with an increased risk of developing hepatocellular carcinoma (Lauret et al. 2002). HH patients with HCV present with advanced fibrosis/cirrhosis at a younger age and at a lower hepatic iron concentration compared to HH patients without HCV (Diwakaran et al. 2002). The association between hepatocellular carcinoma and HFE homozygosity is well documented, but recently HFE hetero- and homozygosity has also

been linked to non-hepatocellular malignancies, including female breast cancer. Syrjakoski et al. 2005 showed that C282Y and H63D mutations could contribute to male breast cancer (MBC) and prostate cancer (PC) susceptibility but carriers of both BRCA2 9346(-2)→G and an HFE mutation is at an increased risk at the population level in Finland. According to Abraham et al. (2005) variants of the hemochromatosis-transferrin receptor system have no direct effect on the incidence of breast cancer in Germany.

Chan et al. (2005) showed that HFE gene mutations were not associated with risk of colorectal adenoma in women. Individuals with a single HFE mutation, C282Y or H63D, are unlikely predisposed to develop colorectal cancer (Robinson et al. 2005).

Pietrangelo (2003) suggests HFE gene modifies course of hepatitis C viral infection. Association between C282Y mutation and HBV infection in male patients with HCC, a careful evaluation and follow-up should be considered in the C282Y-positive subjects with hepatitis B virus related liver disease. The interaction between the H63D mutation and HCV, observed only in women, may reflect a higher sensitivity to H63D-induced iron metabolism abnormalities and a reduced antioxidant capability in the presence of an even minor increase of iron which may occur as a consequence of the coexistence of hepatitis C infection and heterozygosity for HH (Fracanzani et al. 2005).

Diabetes mellitus in patients with thalassaemia major is caused by secondary haemochromatosis due to transfusional iron overload. Insulin resistance is of central importance for the development of diabetes (Cario et al. 2003). North and Central European patients with gestational diabetes mellitus (GDM), the C282Y allele frequency is higher than in healthy pregnant women, suggesting a genetic susceptibility to the development of GDM (Cauza et al. 2005). Blood donation is simultaneously associated with increased insulin sensitivity and decreased iron stores. Stored iron seems to impact negatively on insulin action even in healthy people, and not just in classic pathologic conditions associated with iron overload (hemochromatosis and hemosiderosis) (Fernandez-Real 2005). Early diagnosis and treatment by phlebotomy can improve blood glucose control in the early stages of the disease. If diagnosis occurs later, when the patient already

needs insulin therapy, diabetes will not be improved by phlebotomy (Thielen et al. 2005).

Iron homeostasis is altered in Parkinson's disease (PD) hereditary haemochromatosis possession of the 282Tyr allele may offer some protection against the development of PD (Buchanan et al. 2002). Candore et al. (2003) reported negative association between the HFE mutations and ageing in Alzheimer disease patients from North Italy. While Pulliam et al. (2003) reported strong association of HFE mutation with neurodegeneration and oxidative stress in Alzheimer disease and correlation with APOE.

Ellervik et al. (2005) showed that hereditary hemochromatosis C282Y/C282Y, C282Y/H63D, and C282Y/wild-type genotypes were not associated with ischemic heart disease (IHD) or myocardial infarction (MI); however, they could not exclude the possibility that C282Y/C282Y and C282Y/H63D individuals have a modestly increased risk of IHD or MI. Polymorphism of the HFE gene is not a risk factor for restenosis after coronary stent implantation (Ferrari et al. 2001).

Primary Chronic venous disease (CVD) progressing in approximately 10% of cases toward chronic venous leg ulceration and the C282Y mutation consistently increases the risk of developing venous leg ulceration (Zamboni et al. 2005). Hruskovicova et al. (2005) studied two variants C282Y and H63D in HFE gene and investigated their association with atherothrombotic cerebral infarction in a case control study design in Slovenia and failed to show an association with the disease. Saleheen et al. (2005) suggests further study before concluding a negative link of HFE gene.

Rovetta et al. (2002) had compared the frequency of C282Y in patients with rheumatoid arthritis with different form of spondylarthritis and correlates these findings with iron metabolism parameters. They found 8.34% patients positive for C282Y mutation in case of heterozygosis compared with 12.5% of patients with spondylarthritis. Half of the patients with HH have arthritis and hip arthropathy remains a frequent but unknown event in genetic hemochromatosis (12.5%) and it involves the functional prognosis (Lecoules et al. 2002).

Haba-Rubio et al. (2005) suggests that local brain iron deficiency may occur in patients with haemochromatosis this shows a role for brain

iron metabolism in the pathophysiology of restless legs syndrome (RLS).

Occult celiac disease (CD) may compensate for increased divalent metal ion transporter 1 (DMT1) expression in a specific subset of individuals with homozygous C282Y mutations in the HFE gene, thus contributing to the low penetrance of HH (Geier et al. 2005).

Iron plays a major role in the pathogenesis of *V. vulnificus* strains isolated from different sources of Cuddalore coastal waters, India infections of *V. vulnificus* have been correlated with pre-existing liver disease and hemochromatosis (Jayalakshmi and Venugopalan 1992).

Wallen and Beutler (2005) suggested that studies involving a large number of comparisons have a high likelihood of finding statistically significant associations by chance alone (Type 1 error). Genetic association studies should be scrutinized for the possibility of Type 1 error.

## Future Opening

The Human Genome Project has made a great step forward in mapping tens of thousands of genes, but it may be decades before we can predict which individuals are most likely to develop serious disease. Even for a condition as apparently straightforward as hereditary haemochromatosis, the path to general population genetic screening has proven more complicated than initially expected (Gertig et al. 2003). But population genetic screening to

**Table 1: Diagnostic tests for haemochromatosis and treatment (modified after Dooley 1997)**

### Investigations:

Serum iron and transferring saturation (best for Screening)  
 Serum ferritin (reflects degree of overload)  
 Liver biopsy for architecture (normal/fibrosis/cirrhosis) and grading of excess iron (Perl stain)  
 Liver iron concentration  
 Hepatic iron index: mmol/g dry weight of liver divided by age in years at time of biopsy (>1.9 in homozygous genetic haemochromatosis)  
 MRI (upto 30mg/g dry tissue) of liver and succceptibility measurement: to evaluate iron overload (Carnerio et al. 2004)  
 Multicolour multiplex HFE assay – classify all possible genotypes for HFE (C282Y and H63D) mutations (Ugozzoli et al. 2002)

### Treatment:

Venesection once or twice weekly (500mL) until serum ferritin and percentage saturation low normal.  
 Maintenance venesection 3-6 monthly (according to level of ferritin and transferring saturation)



prevent HFE-associated hereditary haemochromatosis can be practicable and acceptable (Delatycki et al. 2005). Although the reports of this disease is mere more studies are required to investigate the prevalence of this disease and association with other diseases among the Indian population as well as the Asian.

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