

Introduction

Hemochromatosis (iron storage disease) is often misdiagnosed since not all patients develop the complete clinical picture of the disease and unclear clinical symptoms may complicate its differential diagnosis. The isolation of the alleles C282Y and H63D of the hemochromatosis gene Hfe located in the vicinity of the HLA loci in the year 1996 elucidated the cause of the development of hemochromatosis in most clinical cases. Nowadays molecular genetic analysis can be used to screen patients and family members affected. Early diagnosis of the disorder enables the doctor to initiate an adequate therapy when progression of the disease can still be prevented. Furthermore genetic testing allows to distinguish between primary and secondary forms of hemochromatosis (primary form = hereditary; secondary form = acquired, e.g. hepatic cirrhosis).

Epidemiology and clinical picture

Hereditary hemochromatosis is a congenital metabolism defect characterized by an increased up-take of iron in the intestine. Due to the prevalence of 1:400 to 1:200 of homozygotes amongst Caucasians hereditary hemochromatosis is one of the most common autosomal recessive hereditary diseases. 200,000 to 400,000 individuals are supposed to be carriers of these mutations in Germany. Females are 10 times less affected than males because of pregnancy, menstruation and breast feeding. Clinical symptoms of the disorder usually appear in males at an age between 20 and 40 years whereas females get affected after the onset of the menopause.

The abnormal resorption of iron in the intestine causes accumulation of iron in the skin, numerous organs like the liver as well as joints and endocrine glands. The combination of hyperpigmentation of the skin and failure of the endocrine pancreas for instance is referred to as bronze diabetes seen in up to 70 % of hemochromatosis patients.

Mutation	Total population	Haemochromatosis patients
HZ for C282Y	4-9%	1%
HZ for H63D	17%	nk
MU for C282Y	0,2%	80-90%
MU for H63D	nk	nk
HZ for C282Y & H63D	2%	4-5%

Table 1: Overview about the prevalence of the Hfe mutation in the total population and in patients suffering from hemochromatosis (HZ = HeteroZygous MU = homozygous Mutation nk = not known)

Diagnosis

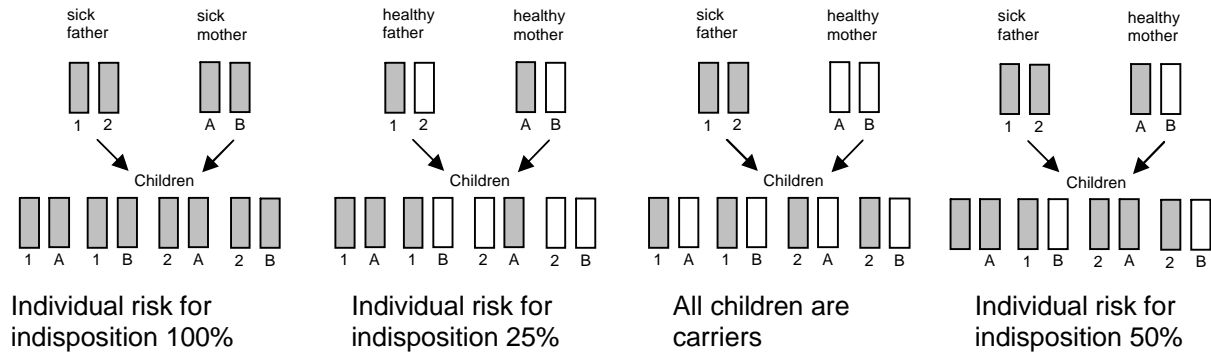
The discovery of the Hfe gene and its mutations C282Y and H63D is the hallmark for an early diagnosis and prognosis of patients suffering from hemochromatosis. These two mutations cause conformational changes of the Hfe protein leading for example to an inhibition of the transferrin receptor.

Homozygous carriers of the C282Y mutation are of clinical importance because up to 70 % of male and 40 % of female homozygotes develop a haemochromatosis. Heterozygous carriers of C282Y are not likely to show clinical signs of the disorder. However, an increased fibrosis of the liver has been

HEMOCHROMATOSIS

observed in heterozygous carriers suffering from liver disorders such as viral hepatitis or toxic liver cirrhosis due to a moderate accumulation of iron in the organ.

Hereditary scheme of hemochromatosis



Genotyping

Genotyping of the patient samples is done by comparing the band pattern of the samples with controls (see fig. 1)

Genotypes:

WT = homozygous WildType
 HZ = HeteroZygous
 MU = homozygous MUtation

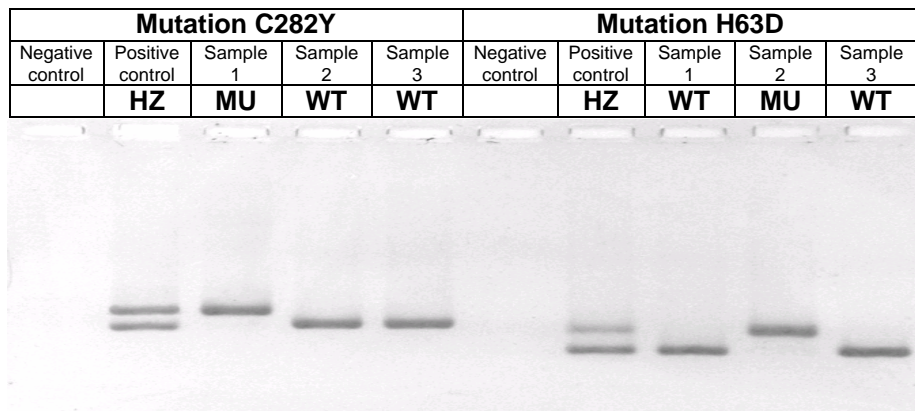


Fig. 1: Typical picture of quicktype-amplified samples, DNA separated in a 3 % agarose gel

Products:

Code	Product	Detection of:
1019	attomol[®] Hemochromatosis-QT 2 x 20 Determinations	Mutation C282Y Mutation H63D
1031	attomol[®] Hemochromatosis S65C-QT 20 Determinations	Mutation S65C