

# Hemochromatosis

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## Abstract

*Hemochromatosis is a genetic disease of iron overload due to intestinal hyperabsorption of iron. It is one of the most prevalent autosomal recessive diseases in Caucasian populations. Hemochromatosis causes severe visceral and metabolic complications at adulthood, which include cirrhosis, diabetes, arthropathy and cardiac failure. A major breakthrough has been the discovery, in 1996, of the HFE gene which is strongly associated with the phenotypic expression of the disease. This discovery has, very quickly, provided a powerful genetic blood test which permits, in most cases, to establish the diagnosis in a non invasive way (i.e. without a liver biopsy). Hemochromatosis can be cured by repeated venesections provided that the diagnosis has been made sufficiently early. Moreover, an efficient preventive strategy can be applied to family members and should now be proposed to the general population. The identification of the HFE gene joined to the discovery of key proteins involved in cellular iron transport and body iron regulation have not only lead to the individualization of new iron overload syndromes but paved the way for novel therapeutic approaches of the disease.*

## Key-words

Hemochromatosis, Iron overload, HFE gene, C282Y mutation, H63D mutation, Serum iron, Transferrin saturation, Ferritin, Liver biopsy, Phlebotomy, Venesection

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## Disease name and synonyms

- Hemochromatosis
- Hemochromatosis HFE-1
- Genetic hemochromatosis
- Hereditary hemochromatosis

## Definition/Diagnostic criteria

Hemochromatosis is a genetic disease of iron overload due to intestinal hyperabsorption of iron.

The diagnostic strategy rests upon the following three successive steps.

**First step: to evoke the diagnosis from miscellaneous clinical presentations**

Diagnosis is immediately suspected on the basis of the classical triad of «bronzed cirrhosis with diabetes» in a middle-age patient. This triad consists of: **i)** diffuse melanoderma, more often metallic grey than brown; **ii)** hepatomegaly. The liver is markedly enlarged, firm and sharp to palpation, and despite its cirrhotic features this hepatomegaly is accompanied neither by signs of hepatocellular insufficiency (no palmar erythema, no spider nevi, no bruises, normal prothrombin time) nor by signs of portal hypertension; **iii)** diabetes mellitus, often requiring insulin. There may be also signs of cardiomyopathy. However, this clinical picture corresponds to a stage of irreversible complications, which compromise vital prognosis, so that establishing the diagnosis at this stage is far too late and must be considered as a diagnostic failure.

Therefore, it is essential to pay attention to other features of hemochromatosis to establish an earlier diagnosis. Three types of features, which can be summarized as the «rule of three A's» correspond usually to earlier signs: **i)** asthenia. Unexplained chronic fatigue, often with a sexual component in males, can be the only feature of the disease and, paradoxically, iron overload is sometimes discovered while iron deficiency was initially expected; **ii)** arthralgia. Arthropathy is an often misdiagnosed presenting feature of hemochromatosis, the diagnostic delay being estimated between 4 and 10 years. The most characteristic manifestation is chronic arthritis of the second and third metacarpophalangeal joints, resulting in a «painful handshake», a symptom which should be highly suggestive of the disease. Other joints can also be affected, especially wrists and knees. Patients can also suffer from attacks of pseudo-gout (by pyrophosphate arthropathy). Radiologically, the most common changes are subchondral arthropathy and chondrocalcinosis. Arthropathy greatly affects quality of life in hemochromatosis; **iii)** aminotransferase (transaminase) increase. Any hypertransaminasemia, less than three times the upper normal limit, which is not related to alcohol, non alcoholic steato-hepatitis (NASH), virus, auto-immunity or drugs may reflect hepatic iron overload.

Other possible, although non specific, features of hemochromatosis include ichthyosis and nail abnormalities, especially on the first three digits, such as platonychia or true koilonychia, the latter sign being rather paradoxical since it is also manifested in the chronic iron deficiency syndrome.

**Second step: to ascertain biochemical abnormalities of iron metabolism**

Increased transferrin saturation (TS) reflects the basic metabolic abnormality of hemochromatosis and is acknowledged as the most sensitive single test for phenotypic identification of the disease. TS is higher than 45%, and usually above 60% in men and 50% in women.

In summary, when clinical data suggest hemochromatosis, a normal serum TS value excludes the diagnosis, provided that there is no co-existing inflammatory syndrome (normal CRP), whereas an increased TS is highly indicative of the disease.

**Third step: to prove hereditary hemochromatosis**

This genetic diagnosis is based on a single blood analysis for the HFE mutation C282Y. Three situations may occur :

*The patient is C282Y/C282Y (he/she is homozygous for this mutation)*

HFE-1 hemochromatosis is ascertained and no further investigations are needed to confirm the diagnosis. At this stage, a work-up is required to evaluate the degree of iron overload and the possible visceral and/or metabolic consequences of the disease. Iron excess, is evaluated by measuring the concentration of serum ferritin which, in hemochromatosis, closely correlates with the total iron burden. However serum ferritin values must be interpreted cautiously as iron overload may be overestimated by some confounding factors such as inflammation, cytotoxicity, alcoholism or dysmetabolic syndrome, or on the contrary, this overload may be underestimated when the data are only interpreted on the basis of the upper normal limits of this parameter. Indeed, there is a wide range of normal values (usually 10-300 µg/l) and the pitfall is for instance to consider a level of 200 µg/l in a young adult woman as normal, whereas the normal expected value approximates 30 µg/l. A multicenter American study reported that the median serum ferritin concentration increased from 23 µg/l for ages 12-16 years and reached a plateau of 120-130 µg/l after 32 years. In women, values were in the range of 30 µg/l until menopause after which values rose to approximately 80 µg/l. Iron excess can also be quantified using non invasively hepatic magnetic resonance imaging (MRI), provided that it is accessible and adequately calibrated for this purpose. This technique enables determination of a reliable "MRI hepatic iron concentration".

Visceral and/or metabolic consequences are evaluated with a general work-up, which includes serum transaminases, glucose studies and, depending on the clinical context, electro-

echocardiogram, joint and bone x-rays, hormonal tests. In fact, one of the major difficulties for the clinician is to decide whether a liver biopsy should or not be performed in order to appreciate the possible development of severe fibrosis. Liver biopsy remains an invasive procedure which should not be performed if the probability for fibrosis is only minimal. On the other hand, marked hepatic fibrosis (grade 3 - bridging fibrosis- or grade 4 -cirrhosis) must not be missed due to its high risk for subsequent hepatocellular carcinoma development. The absence of hepatomegaly and normal serum aspartate aminotransferase and serum ferritin < 1000 µg/l are the three criteria, which, taken all together, indicate in a C282Y/C282Y patient that there is no risk for hepatic fibrosis and therefore no need for liver biopsy.

In summary, diagnosis of hemochromatosis is established in a given patient with increased transferrin saturation, on the basis of the identification of HFE mutation C282Y/C282Y. A liver biopsy is then only performed in case of suspicion of fibrosis and has only a pronostic value.

*The patient is C282Y/WT (WT=Wild Type)(he/she is heterozygous for the mutation C282Y).*

The most likely genetic status is compound heterozygosity and the commonest expected genotypic profile is C282Y/H63D compound heterozygosity (the patient is heterozygous for both C282Y and H63D). In this setting, iron overload remains however generally mild so that possible associated co-factors of iron overload must always be searched for (such as alcoholism, dysmetabolic hepatosiderosis or porphyria cutanea tarda). Exceptionally, other profiles of compound heterozygosity (i.e. not involving H63D), which are mostly not yet identified, may be involved.

In practice, when iron overload is associated with heterozygosity for the C282Y mutation, H63D mutation should be searched for. Even if compound heterozygosity is found, co-factors of iron overload should also be searched for. Simplex heterozygosity for C282Y cannot explain by itself the development of iron excess in the large majority of cases and other factors must be found.

*The patient, despite a phenotypic picture of hemochromatosis, is C282Y WT/WT.*

The following situations are then possible: **i)** juvenile hemochromatosis. Named also HFE-2 hemochromatosis, this exceptional disease should be evoked in subjects less than 30 years of age, with massive iron overload, cirrhosis, heart failure and/or endocrine disorders (hypogonadotropic hypogonadism); **ii)** HFE-3

and HFE-4 hemochromatosis. They are rare diseases due to mutations in transferrin receptor 2 and ferroportin, respectively (see below).

Whenever there is a strong clinical suspicion of pronounced iron overload and the patient is not C282Y/C282Y, a liver biopsy must be carried out accordingly to the "pre-HFE" diagnostic strategy. Indeed, in this type of situation, hepatic histology is essential in many diagnostic aspects: **i)** it confirms iron overload; **ii)** it identifies its predominantly periportal and hepatocytic distribution; **iii)** it provides a semi-quantitative evaluation of iron excess using a special grading system; **iv)** it enables determination of hepatic iron concentration (HIC), which is closely correlated with the level of iron stores. Furthermore, when related to the age of the patient, it is possible to determine the hepatic iron index (ratio HIC/age) which, prior to the HFE era, was highly suggestive of homozygous hemochromatosis when  $\geq 2$ , provided that other kinds of iron overload (especially of hematological origin) had been excluded. **v)** finally, liver biopsy detects associated lesions (steatosis for instance).

#### **Differential diagnosis**

It consists of hereditary and/or acquired types of iron overload.

#### **Hereditary iron overload**

##### *Neonatal (or perinatal) "hemochromatosis"*

This is a generally fatal disease characterized by severe liver failure of intrauterine onset and by massive hepatocytic iron deposition with cirrhosis. Iron overload is present, to a lesser extent, in parenchymal cells of endocrine organs, the heart, and kidneys. Small amount of iron is found in the mononuclear phagocytic system. The overall pattern of iron excess recalls that of hemochromatosis. Neonatal "hemochromatosis" is probably not a single entity: a genetic (non-HFE related) factor may be involved, as well as environmental or immune components.

##### *Cerebrohepatorenal syndrome (Zellweger's syndrome)*

This is a fatal autosomal recessive disorder clinically characterized by hypotonia, abnormal facies and polycystic kidneys. In some cases, increased parenchymal iron is found in the liver (with fibrosis), spleen, kidneys, and lungs.

##### *Hereditary tyrosinaemia*

Hepatic iron overload is inconstant and moderate in this disease, which is associated with a peculiar fishy odour, cirrhosis and renal abnormalities.

##### *Congenital atransferrinaemia*

Due to the absence of transferrin (the plasma iron transport protein), this exceptional disorder is characterized by microcytic hypochromic anaemia, which contrasts with iron overload in the liver (within the hepatocytes), heart, kidneys, thyroid and pancreas. Anemia is improved by transferrin infusion.

#### *Aceruloplasminemia*

It is due to mutations in the *ceruloplasmin* gene. Like hemochromatosis, it is a family disease responsible for massive hepatocytic iron overload and diabetes mellitus. It differs from hemochromatosis by the association of neurological (extrapyramidal and cerebellous) and ocular symptoms, due to iron deposition in the central nervous system. No serum ceruloplasmin is detectable. This disease does not present copper accumulation.

#### **Acquired iron overload**

##### *Iron-loading anemias*

They include congenital (thalassemia major, and to a lesser degree, thalassemia intermedia, sickle-cell disease, red cell dysplasia, and congenital sideroblastic anemia) or acquired disorders (acquired refractory sideroblastic anemia, and hypoplastic or myelodysplastic disorders). In these conditions, iron accumulation is related mainly to transfusions (e.g. aplastic anemias), to increased iron absorption due to increased erythroid activity (e.g. thalassemia intermedia), or to both mechanisms (e.g. thalassemia major or sideroblastic anemias). The excess absorbed iron is mainly deposited in parenchymal sites (i.e. in hepatocytes but also in the pancreas and heart) in a similar fashion to hemochromatosis. Transfused iron is initially deposited within macrophages in the mononuclear phagocytic system but iron redistribution occurs subsequently, leading to parenchymal deposition and damage, so that finally the pattern of organ involvement resembles that encountered in hemochromatosis. The clinical picture of thalassemia major, which represents the most frequent cause of major iron excess within this group of iron loading anemias, is schematically as follows: hepatomegaly (with fibrosis) occurs during the first decade of life. The second decade is marked by lack of sexual development and by the appearance of cardiac dysfunction, which is a major cause of death. Serum parameters (iron, transferrin saturation, ferritin) are markedly increased. Liver biopsy is important to assess iron overload and especially to evaluate liver damage (fibrosis).

##### *Chronic alcoholic liver disease*

Iron overload is found in about 30% of chronic alcoholics and is usually mild to moderate. The

mechanism(s) of this slight increase is (are) unclear. The systematic involvement of hemochromatotic heterozygosity has been ruled out. A direct favoring effect of alcohol on iron absorption has not been conclusively shown, but indirect effects of alcohol are possible through: i) the iron content of alcoholic beverages, particularly red wines; ii) folic acid deficiency which may increase iron absorption; iii) transferrin desialylation which could account for an increase in parenchymal cell iron. Clinically, the picture may involve some degree of skin pigmentation associated with hypogonadism, glucose intolerance, marked increase in serum iron load parameters especially ferritin, so that the diagnosis of 'hemochromatosis' can be evoked. Direct iron-load parameters, especially liver biopsy (if necessary via the transjugular route) must then be used to visualize and quantify hepatic iron. In the case of alcoholic siderosis, iron deposition is mild and found primarily within Kupffer cells rather than hepatocytes. Furthermore, the ratio of liver iron concentration to age is below 2, which helps to differentiate alcoholic siderosis from iron overload in young alcoholic hemochromatosis homozygous. However, cirrhosis *per se* can be responsible for heterogeneous iron deposition in the liver, which may fortuitously provide a biochemical hepatic iron index over 2, especially in end-stage cirrhosis. On the other hand, when major hepatic iron excess is certified in an alcoholic patient, the diagnosis of homozygous haemochromatosis associated with alcoholism is highly likely; this event is relatively frequent since alcoholism aggravates the hepatic expression of hemochromatosis.

##### *Porphyria cutanea tarda*

This is a chronic hepatic porphyria due to deficient activity of uroporphyrinogen decarboxylase. Two main forms of the disease are described: in the sporadic form, uroporphyrinogen decarboxylase deficiency is restricted to the liver (erythrocyte activity is normal), whereas the genetic deficiency (ascribed to mutations at the urodecarboxylase locus on chromosome 1) is found in all tissues (particularly the red cells) and is transmitted as an autosomal dominant trait in the familial form. The excessive amount of porphyrins in blood and skin accounts for the characteristic cutaneous photosensitivity (with skin fragility and bullae). Clinical expression of both forms of the disease usually requires exogenous factors such as alcohol, estrogen intake, liver disease and iron. Iron overload is frequently observed in porphyria cutanea tarda but remains of moderate intensity (it does not exceed four times the normal values); its origin is controversial but its effect on disease expression is certain. Oral or

parenteral iron administration is followed by relapse of porphyria cutanea tarda, whereas phlebotomies lead to clinical and biochemical remission of the disease with a return to normal of hepatic uroporphyrinogen decarboxylase activity. Phlebotomy is efficient even in the absence of iron overload, indicating that iron removal may not be the sole factor in the beneficial effect of venesections.

*Dysmetabolic hyperferritinemia (also called insulin resistance-associated hepatic iron overload or dysmetabolic hepatosiderosis)*

Despite normal (or only moderately elevated) transferrin saturation, hyperferritinemia is marked and most often associated with mild hepatic iron excess (less than 2 to 3 times the upper normal limit of hepatic iron concentration). It is observed in patients presenting a special polymetabolic profile, such as increased body weight, increased blood pressure, hyperlipidemia, non insulin-dependent diabetes, or hyperuricemia. HFE mutations (simple or composite heterozygosity) are frequently present.

*Chronic viral C hepatitis and iron overload*

Moderate iron excess is frequent in chronic viral C hepatitis. Hyperferritinemia is recognized as a factor of lesser response to interferon. The decrease in iron load by venesections causes a decrease in serum transaminase activity. Ribavirin increases hepatic iron load, whereas interferon decreases hepatic iron. In contrast with those admitted data, the following ones are still under debate: the mechanism of hepatic iron excess in this disease; the influence of hepatic iron concentration on the response to interferon; the effect of decreasing iron load by venesections on the response to antiviral therapy.

*African iron overload*

It is found in sub-Saharan Africa and is likely to result from the combination of two factors: **i)** excess dietary iron related to a traditional maize beverage, fermented in iron pots at a low pH which enhances intestinal iron absorption; **ii)** a (not yet identified) non-HFE related gene. Iron deposition is found in the mononuclear phagocytic system throughout the body as well as in parenchymal cells. African iron overload may present clinical manifestations similar to hemochromatosis, but differs in its good correlation between bone marrow iron stores and total body iron.

### Prevalence

HFE-1 Hemochromatosis is one of the most prevalent autosomal recessive diseases in the Caucasian populations, affecting approximately

1/300 persons of Northern European descent. The prevalence of C282Y homozygosity in subjects presenting a phenotype compatible with genetic hemochromatosis is above 90% in northern Europe (96% in Brittany) and lower in southern Europe (72% in the South of France and 64% in Italy). The prevalence of C282Y homozygosity among European populations has been evaluated between 3 and 8/1000, with also a North-South gradient, the highest prevalence being found in Ireland and the lowest in Italy.

### Therapeutic management

Beside the symptomatic treatment of visceral and metabolic complications for the disease, which will not be reviewed here due to their lack of specificity, the major curative challenge is to eliminate iron excess.

### Admitted data

- Low iron diet is generally considered as useless since a one year diet is equivalent to only two or three venesections. However, supplemental iron and supplemental vitamin C (which increases intestinal absorption of iron) are contra-indicated. Tea (which decreases iron absorption) may be beneficial.
- Chelation therapy is reserved for the rare contraindications to venesection such as anemia, hepatocellular insufficiency, or associated general disease (e.g. arteriosclerosis). It is then based on prolonged subcutaneous desferrioxamine infusion. The putative place of oral chelators such as hydroxypyridinones remains to be defined. Erythrocytapheresis may be an interesting method in those cases contraindicating venesections.
- Venesection therapy represents, by far, the best means to eliminate iron overload, according to a two-phase protocol; **i)** the initial phase consists of one 400 to 500 ml venesection per week (corresponding to the removal of 200 to 250 mg of iron); follow-up is based on hemoglobin values for tolerance, and on serum ferritin levels for efficacy. The duration of this phase depends on the degree of iron overload. The initial schedule is stopped as soon as the various serum iron load parameters reach the appropriate levels (< 50 µg/l for ferritin and ≤ 20% for transferrin saturation, provided that hemoglobin levels do not drop below 110 g/l). For heavily iron-loaded patients, a period of 2 years of weekly venesections may be necessary, but more and more, due to moderately iron overloaded forms, several weeks or a few months are sufficient; **ii)** Maintenance therapy consists of 400 to 500 ml venesection every 1 to 3 months. Its goal is to keep serum iron parameters within the normal range (in practice, serum ferritin ≤ 50 µg/l and transferrin saturation

≤ 45%). With venesections survival rate returns to normal, provided that neither cirrhosis nor diabetes were present at the time of the diagnosis. However, even in case of cirrhosis, the prognosis is far better than for other types of cirrhosis, especially of alcoholic origin. With regard to the various syndromes of the disease, the efficacy of phlebotomies is variable: **i)** good for asthenia, skin pigmentation, and hypertransaminasemia; **ii)** inconstant for arthralgia, which may even worsen during (and sometimes after) the depletive treatment, for glucose abnormalities and non cirrhotic fibrosis (which can be steady or decrease); **iii)** the results are poor for impotence. The treatment is inefficient for two types of lesions: a) cirrhosis, which is an irreversible process whatever the etiology, and b) hepatocellular carcinoma which may develop in cirrhotic patients, despite adequate iron elimination by phlebotomies.

### Special Issues

- Cases of mild iron overload. A 400-500 ml weekly regimen may be unnecessary and/or imperfectly tolerated. A pragmatic attitude is to test the tolerance of phlebotomies while starting for instance with 200-300 ml per week and to progressively increase the volume possibly up to the "standard" schedule.
- Clinically asymptomatic and young individuals. It seems reasonable to propose venesection therapy after 18 years of age, considering that iron needs are important during infancy and adolescence, and that the youngest subjects were 18 and 19 years old in two large series of asymptomatic patients.

### Etiology

#### HFE1 hemochromatosis

The *HFE1* gene, identified in 1996, is located on the short arm of chromosome 6, 4.5 Mb apart from *HLA-A* gene. It encodes an HLA-A like protein, called HFE1 protein, which contains 343 amino-acids. Different point mutations may arise in *HFE1* gene: **i)** the major C282Y mutation, which leads to the substitution, at position 282, of one cysteine by one tyrosine in HFE1 protein; **ii)** the "minor" mutation H63D, which leads to the substitution of one histidine by one aspartic acid at position 63. These two mutations are mutually exclusive on a same chromosome: therefore, an individual who is homozygous for the mutation C282Y (= C282Y/C282Y) is "obligatorily" devoided of the H63D mutation (= H63D wild type/wild type i.e. WT/WT) and reciprocally. **iii)** Other mutations have been reported. They are usually present at the heterozygous state in association with the major mutation C282Y, defining new profiles of compound heterozygosity (beside C282Y/WT and H63D/WT).

As to the genotype-phenotype correlation: **i)** homozygosity for C282Y (= C282Y/C282Y) is very strongly associated with the classical phenotypic expression of hemochromatosis, since this genetic status is present in more than 90% of patients defined on strict phenotypic criteria. However there is increasing evidence that the penetrance of C282Y homozygosity is incomplete; **ii)** classical compound heterozygosity (C282Y/H63D) is associated to phenotypic hemochromatosis in 1.3 to 8.2% of the series, but corresponds usually to moderate iron overload and mild clinical expression; **iii)** the other types of compound heterozygosities, except S65C which corresponds to a moderate iron excess phenotype, correspond to typical hemochromatotic pictures but have only been reported in a few patients so far; **iv)** simplex heterozygosity (C282Y/WT or H63D/WT) does not expose to the risk of iron excess, but may act as a cofactor of iron overload in situations such as chronic alcoholism or the polymetabolic syndrome.

The basal mechanism, whereby the *HFE1* mutation generates iron overload, is increased intestinal absorption of iron at the duodenal level. An increased expression of membrane iron carriers, such as DMT-1 and ferroportin-1, which are located at the luminal and basolateral membranes of the villus enterocytes, respectively, plays a major role in the development of iron body excess iron. The key role of hepcidin in the regulation of intestinal iron absorption has been recently emphasized and a number of data indicate that, in HFE1-hemochromatosis, there is a decreased hepcidin production by the liver which accounts for the abnormally enhanced iron absorption.

#### HFE2 hemochromatosis

Two entities, corresponding to the clinical picture of juvenile hemochromatosis, are now individualized: **i)** "HFE2-A" hemochromatosis, due to a recently identified gene located on chromosome 1; **ii)** "HFE2-B" hemochromatosis due to mutations in the *hepcidin* gene located on chromosome 19.

#### HFE3 hemochromatosis

This gene maps to chromosome 7 and encodes the Transferrin receptor-2 (TFR2). A mutation within this gene leads to the development of a hemochromatosis-like picture in adults.

#### HFE4 hemochromatosis

This gene encodes the protein ferroportin and locates to chromosome 2. The main features caused by mutations in ferroportin are: **i)** the dominant mode of inheritance; **ii)** the contrast between very high serum ferritin levels and normal (or low) transferrin saturation values; **iii)**

the dominant iron deposition within macrophages; **iv)** the poor tolerance to venesection therapy.

### **Genetic counseling (HFE-1 hemochromatosis)**

Once the diagnosis of hemochromatosis has been established, it is essential to initiate family screening.

The preventive strategy has been considerably modified and simplified by HFE1 testing. With a C282Y proband, it is now possible to evaluate "immediately" the hemochromatosis risk among the family members.

Schematically: **i)** C282Y/C282Y subjects are homozygous for the *HFE* gene and either already express the disease or are at high risk of developing it; **ii)** C282Y/WT individuals are heterozygous for the *HFE* gene. They will not develop the disease but can transmit the gene to their offsprings; **iii)** WT/WT subjects do not carry the causative mutation and can be totally reassured.

However, these genetic data must be interpreted in light of: **i)** the penetrance of C282Y homozygosity. It is increasingly acknowledged that a significant proportion of these homozygous individuals will never develop problematical iron overload throughout their life; **ii)** the putative risk of heterozygosity since the risk for developing iron excess seems absent or limited to compound heterozygosity (confined, in clinical practice, to the profile C282Y / H63D) and/or to the presence of co-factors such as alcoholism or dysmetabolic features. Whether heterozygosity for the *HFE* gene confers upon HFE individuals an increased risk to develop cancer or cardiovascular disease requires further evaluation. Homozygosity may occur in the offspring of an heterozygous individual, despite the fact that hemochromatosis is a recessive disease. Indeed, due to the high prevalence of the *HFE* gene in the general population, the probability for an heterozygote to marry another heterozygote is approximately 10 %; **iii)** the young age of the patient. As no treatment has been yet indicated during infancy and adolescence, specific screening has not justification. A phenotypic evaluation (including clinical examination, serum transferrin saturation and ferritin) may be proposed at 15 years of age and genetic testing can be postponed to 18. It is however sometimes difficult to resist to the parental pressure to "know" about their children's status. An indirect way to cope with this demand is to perform the genetic test in the spouse. If the spouse does not carry the C282Y mutation (and provided that there is no problem of "biological" paternity), it can be deduced that the maximal genetic risk for the offsprings is only heterozygosity for the *HFE* gene.

### **Unresolved questions and general comments *This disease suffers from a general lack of recognition***

Although hemochromatosis is one of the most prevalent genetic diseases, it remains too often ignored. The reasons are multiple: **i)** the common view that iron can only be beneficial for body health; **ii)** the misappreciation of the disease by a number of practitioners who have probably been insufficiently taught in this domain and tend to think that hemochromatosis is a rare disease, seen only in males, within limited geographical areas (such as Brittany in France) and due to chronic alcoholism. It remains frequent that an increased serum iron is neglected, leading to an important (and damaging) delay in the diagnosis; **iii)** the nature of the symptomatic treatment (venesections) does not attract pharmaceutical companies.

### ***The molecular mechanisms underlying iron accumulation remain to be fully understood***

As seen above, a number of new proteins involved in transmembrane iron transport and in the regulation of cellular iron homeostasis have been recently identified and have largely improved our understanding of the disease. However, it is not yet possible to propose a totally rational explanation, probably due to the fact that other molecular factors remain to be found and integrated in the overall sequence of events linking *HFE* mutation and iron overload. Moreover, it is increasingly suggested that a variety of gene interactions are responsible for the final phenotypic expression.

### ***The penetrance of the disease***

If the high frequency of C282Y homozygosity among Caucasian populations is unanimously accepted, the real degree of penetrance of this genotypic profile is still debated. Large screening studies have recently pointed out that clinical expressivity of C282Y homozygosity was much lower than previously thought. In fact, the interpretation of the various data reported in this field is delicate, as the notion of penetrance is often not clearly defined. If a distinction is established between clinical and biochemical expression, it appears that globally 30 to 50% of the C282Y/C282Y individuals (with a higher ratio for men) may fulfil the criteria for phlebotomies.

### ***Therapeutic perspectives***

With a better understanding of the disease, new therapeutic tools, such as compounds susceptible to compensate hepcidin deficiency, will probably emerge in the future.

### ***The issue of population screening***

General screening in Caucasian populations is supported by several arguments: **i)** the

frequency of the disease (despite incomplete penetrance of the C282Y/C282Y profile) remains high; **ii**) it is a potentially severe disease, both in terms of morbidity and mortality; **iii**) the diagnosis can be established on the sole basis of non invasive investigations clinical data and blood studies); **iv**) the treatment is both simple and efficient, not only improving the quality of life but restoring normal life expectancy, provided that the diagnosis is made sufficiently early in the course of the disease.

The screening strategy should be based on the assessment of serum transferrin saturation in adults aged 25 or more. Then, genetic testing for C282Y would be confined to individuals with significant increased transferrin saturation. This strategy would avoid the ethical, logistic, and financial problems raised by systematic genetic testing, as well as the impact of discovering a genetic mutation in asymptomatic persons which would never expressed the disease. A series of multicenter studies are in progress, throughout the world, in order to improve the knowledge of the prevalence and penetrance of *HFE* mutations in the concerned areas, and will help to define for each country the best cost/benefit screening approach. In any case, it is essential that major changes occur in the psychological perception of unexpressed or slightly expressed *HFE* homozygosity, especially by insurers and health care administrators, in order to avoid any adverse genetic discrimination.

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