



Editorial

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Hemochromatosis: clinical implications of genetic testing

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Hemochromatosis is one of the most common genetic diseases affecting Canadians of European ancestry. However, too often this disease is diagnosed in people who do not have it and is missed in those who do. By the time a diagnosis is made on the basis of symptoms, irreversible organ damage has often occurred. A missense mutation (the C282Y cysteine-to-tyrosine substitution) on chromosome 6 of the HFE gene (previously known as HLA-H) is present in 95% of Canadian patients with hemochromatosis¹ and can be readily detected by a simple blood test based on a polymerase chain reaction (PCR).

Since the description of a candidate gene for hemochromatosis in August 1996 by Mercator Genetics,² studies have suggested that the population prevalence of the homozygous C282Y mutation is as high as 1 per 100 in Ireland and 1 per 150 in Australia.³ The discrepancy between such estimates of genetic prevalence and the clinical impression that hemochromatosis is an uncommon condition has 2 explanations, which are not mutually exclusive. First, the disease goes undetected in some cases because of its nonspecific symptoms, such as arthritis, diabetes, fatigue, impotence and minor liver dysfunction. Second, because of the incomplete penetrance of the hemochromatosis mutation, iron overload does not always develop. Within families affected by hemochromatosis, some individuals have been found with a homozygous C282Y mutation but no demonstrable iron overload; investigations for occult blood loss in such patients have been unrevealing.^{1,4} Canadian population screening studies have also identified asymptomatic young adults who are homozygous for the mutation without iron overload.⁵ The value of detecting such cases is controversial. On the one hand, these people may be predisposed to develop iron overload later in life and may therefore benefit from surveillance. Family studies may lead to the discovery of relatives who are homozygous for the mutation and *do* have iron overload.⁵ On the other hand, indiscriminate testing can cause unnecessary anxiety and could lead to discrimination with regard to health or life insurance.

Population screening studies using genotyping have suggested that the C282Y mutation is more prevalent than the clinical symptoms associated with iron overload.⁵ For example, in the first patient identified in our population screening study as homozygous for the mutation, the disease was not expressed (i.e., serum transferrin saturation and serum ferritin concentration were normal). Her sister had been under investigation for 2 years at another centre for an undiagnosed liver disorder. After the proband notified her sister about her genetic status, the sister underwent liver biopsy; a diagnosis of hemochromatosis with significant iron overload was confirmed.

Another common problem is the misdiagnosis of hemochromatosis in some patients with abnormally high serum transferrin saturation or serum ferritin concentration or both. It is now recognized that end-stage liver disease from any cause can result in high serum transferrin saturation or ferritin levels and minor iron overload, and many patients previously classified by liver biopsy as having hemochromatosis have now been shown by genetic testing not to have the C282Y mutation. This is particularly relevant to patients with alcoholic liver disease and chronic viral hepatitis.^{6,7}

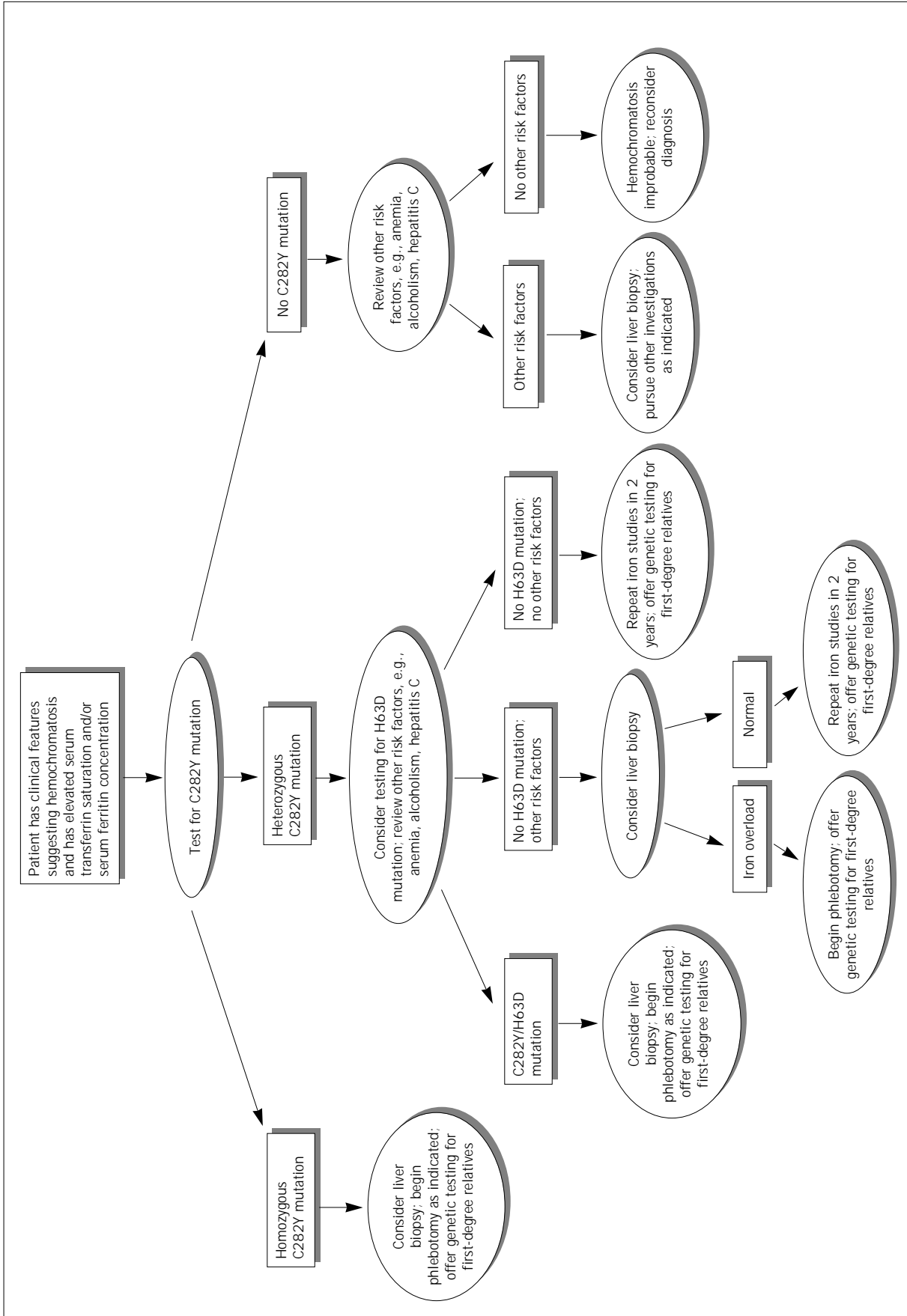


Fig. 1: One approach to the investigation of patients with suspected hemochromatosis. At each stage in the investigation the physician should be guided by factors such as the severity of symptoms, abnormal laboratory findings, family history and ethnic background. The potential for familial iron overload to exist without the C282Y mutation should also be taken into account. Genetic testing for hemochromatosis will evolve as new mutations come to light. Liver biopsy should be considered in patients with suspected liver disease.



Clinical use of genetic testing

The genetic test for hemochromatosis is a PCR-based test performed on a blood sample collected in a tube containing EDTA (ethylenediamine tetra-acetic acid). The test is available at many laboratories across Canada. Most provinces have established a reference laboratory in which molecular genetic tests for a variety of diseases are performed. In view of the prevalence of the disease, the test for hemochromatosis is likely to become the most common diagnostic genetic test in these facilities. The cost of the test is likely to be under \$100, including royalties. A list of provincial laboratories is available from the Canadian Hemochromatosis Society (home.iSTAR.ca/~chcts/). A home diagnosis kit based on genetic testing of a buccal smear is already being promoted in the US.

Genetic testing should be offered to any patient suspected of having hemochromatosis on the basis of clinical symptoms, abnormal serum transferrin saturation or ferritin concentration, or family history. Once a patient is found to be homozygous for the C282Y mutation, disclosure of the result to family members should be discussed with the patient so that testing can be offered to first-degree relatives. Testing of the spouse can be a cost-efficient strategy for directing investigations in children, since a normal test result in the spouse would mean that any children are not homozygous for the mutation.⁸

The ideal strategy for screening the general population is under study. It appears that at least 5% of patients with hemochromatosis have clinical manifestations without the C282Y mutation. This problem has been reported most frequently in Italian populations.⁹ A second mutation (H63D) has been described in some of these cases, and it is likely that other mutations will be described in the future. One approach to the investigation of patients who present with symptoms of hemochromatosis is shown in Fig. 1. In this strategy, clinical suspicion together with the presence of high serum iron levels provides a starting-point; genetic testing is used to confirm whether the cause of these initial findings is in fact hemochromatosis. The merits of proceeding with liver biopsy to assess iron load is a matter of some controversy and should be guided by the physician's assessment of benefits and risks. At each stage in the investigation the physician should be guided by his or her clinical judgement in light of the severity of symptoms, abnormal laboratory findings, family history and ethnic background. The use of genetic testing for hemochromatosis will of course evolve as other genetic mutations that give rise to the disease are discovered.⁹ It is likely that the application of liver biopsy will shift from diagnosis to prognosis.

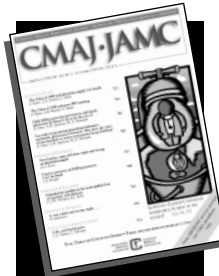
The new genetic test for hereditary hemochromatosis is a powerful tool to confirm a diagnosis in suspected cases.

Because early intervention with phlebotomy in patients with iron overload can lead to normal long-term survival,¹⁰ the use of genetic testing to expedite diagnosis can improve the outlook for patients with hemochromatosis.

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