

# Should the children of patients with hemochromatosis be screened for the disease?

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**ABSTRACT:** Idiopathic hemochromatosis is an underdiagnosed treatable condition inherited in an autosomal recessive pattern. Since early treatment is of demonstrated value, screening of high risk groups of individuals is a valuable exercise in preventive medicine. Although examination of siblings is always recommended, the frequency of the hemochromatosis gene makes the screening of children of patients with hemochromatosis an important undertaking, as illustrated by the families described in this report. *Can J Gastroenterol* 1988;2(4):143-6

**Key Words:** Gene frequency, Genetic screening, Hemochromatosis, Recessive genes

VENESECTION EARLY IN THE COURSE of idiopathic primary hemochromatosis can prevent the iron overload which results in life threatening complications in this underdiagnosed disorder (1). Inheritance of hemochromatosis is autosomal recessive; it has been estimated that approximately 10% of the population in North America and Europe are heterozygous for the hemochromatosis gene, formally designated HFE (2,3). These two observations have important implications, in terms of screening relatives of patients to determine whether they are homozygous for HFE and, therefore, have the hemochromatosis genotype.

Screening itself is inexpensive and simple; measurement of transferrin saturation will accurately identify at least 90% of persons homozygous for HFE (4-6). The autosomal recessive inheritance of the condition implies that siblings of patients are at 25% risk of being homozygotes themselves and should be screened. However, because of the high frequency of the HFE gene in the general population, offspring of affected individuals are also at a considerably elevated risk of homozygosity and clinical disease. Two Newfoundland families which illustrate the value of screening offspring, as well as siblings, of hemochromatosis patients are presented.

## PATIENTS AND METHODS

**Diagnosis:** A provisional diagnosis of hemochromatosis was made with a transferrin saturation (serum iron/total iron binding capacity  $\times$  100) greater than 55% and a serum ferritin level greater than the 90th percentile (6). Percutaneous liver biopsies were performed on these individuals and histological demonstration of parenchymal iron deposition was taken as confirming the diagnosis of hemochromatosis. HLA typing of affected and unaffected family members allowed the cotransmission of the HFE gene and particular HLA haplotypes to be followed in families (3,7).

**Patients:** The index case of family 1 (Figure 1) was a man of 55 years who presented with dark skin pigmentation and had a history of arthritis involving hands and shoulders; he had no children. In his sibship of five, one sister had hemochromatosis; she was asymptomatic. Of her six children, three were found to be affected. Of note, two of her affected sons were attending a rheumatology clinic on account of arthritis but had not previously been diagnosed as having hemochromatosis.

The index case in family 2 (Figure 2) presented at age 73 with abnormal skin pigmentation. He had one son, unaf-

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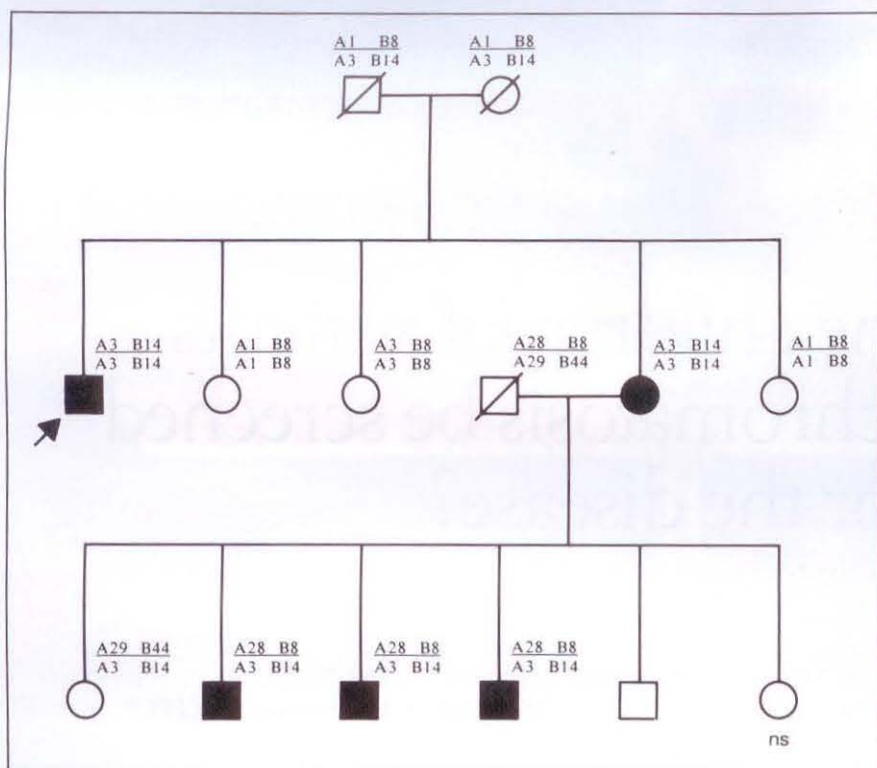


Figure 1) Family 1. □ Male; ○ Female; ■ Affected; ○ Unaffected; ↗ Proband; ∅ Deceased; ns Not studied

ected. In his sibship of eight, one brother was affected and of this brother's offspring, seven were tested and three were found to have hemochromatosis.

In both families, liver biopsies of those individuals provisionally diagnosed using iron metabolism studies revealed moderate to heavy parenchymal iron deposition in every case. In no case was any alteration of liver architecture found, nor was any excess fibrous tissue deposition found.

The sharing of HLA haplotypes by affected and unaffected family members is consistent with the cotransmission of HFE with HLA in these families, haplotypes 'marking' the HFE genes contributed by homozygous and heterozygous parents.

All affected members of each family are undergoing or have recently completed a course of venesection. Therefore, each has excellent prospects of escaping long term liver injury and the

other clinical consequences of iron overload, and every expectation of a normal life span (1).

DISCUSSION

Estimates of the frequency of HFE range around 0.05, making it the most common deleterious autosomal recessive gene as yet described in the white populations of northern Europe, North America and Australia (8). Consequently, about 10% of persons are expected to be heterozygous for the gene and two to three persons per 1000 are homozygotes and at risk of clinical hemochromatosis by late middle age if not before.

Because 10% of the spouses of hemochromatosis patients will be HFE heterozygotes, simply by chance, it is not surprising that families, such as those reported here, are observed in which hemochromatosis occurs in the offspring of patients. In a mating between an affected (homozygous) and a carrier (heterozygous) individual, all offspring will necessarily receive the HFE gene from the affected (homozygous) parent and each has a 50% chance of receiving the HFE gene from the unaffected, heterozygous parent. On average, one-half of the offspring of such matings are expected to be homozygous for HFE, likely to develop clinical hemochromatosis eventually. This is illustrated by the families reported here: three of six children in family 1 and three of seven children in family 2 are affected.

As indicated, 10% of matings of patients are expected to be of this type; families showing vertical transmission of hemochromatosis are probably not observed more frequently simply because the onset of hemochromatosis is relatively late in life. Such pseudodominant transmission of the clinical disease confused early attempts to elucidate its mode of inheritance. Clear appreciation of recessive inheritance required the discovery that the HFE locus is closely linked to the HLA A locus on chromosome 6 and the use of measurements of iron load to identify family members with pre-symptomatic disease (9-11). Families such as those reported here would have escaped notice because some family members with hemochromatosis are asymptomatic and because affected younger

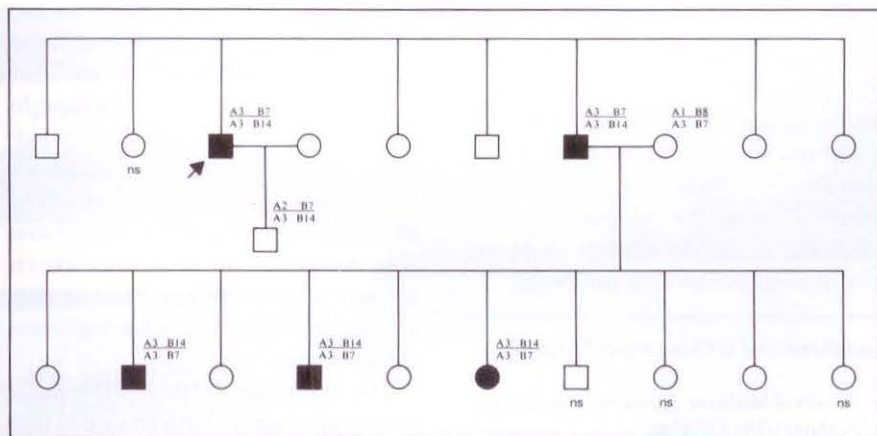


Figure 2) Family 2. See Figure 1 for key to symbols

members showed minimal clinical signs of hemochromatosis. These two families highlight the significance of arthropathy as an early manifestation of this disease and as a useful clue in differential diagnosis (1,12).

If approximately 10% of spouses of hemochromatosis patients are expected to be HFE heterozygotes and one-half of the offspring of such matings are expected to be homozygous, overall, about 5% of offspring of all patients taken together will be HFE homozygotes. Clearly, there is a strong case for investigating, screening and following-up patients' offspring, as well as patients' siblings.

Thought should be given to the most economical method of investigating persons at risk. Serum transferrin saturation is an efficient screening test and will identify persons at risk of iron overload. Transferrin saturation screening of patients' families should, therefore, identify most relatives who are also HFE homozygotes. If transferrin saturation is elevated, a repeat fasting test should be done; if this is elevated, serum ferritin concentration should be measured; if ferritin is elevated, liver biopsy studies are indicated (13).

HLA studies will almost always identify those relatives homozygous for HFE, and may be of use in interpreting borderline results of iron loading tests or results complicated by other considerations. For instance, for a young female relative of a patient, HLA studies of the family could show whether a marginally elevated transferrin saturation was in fact associated with HFE homozygosity. HLA studies might also prove informative in disentangling the effects of the HFE gene and alcohol abuse in families. HLA studies are, however, considerably more expensive than measurements of iron loading and because transferrin (and, if indicated, ferritin) studies should be done on all relatives of patients, HLA studies do not seem strictly necessary in most families. In family 2, for instance, the authors chose not to obtain HLA genotypes for a number of relatives whose transferrin saturations did not indicate a provisional diagnosis of hemochromatosis.

In evaluating relatives of patients and following the transmission of HFE genes

in families, it should be remembered that occasional HFE heterozygotes may suffer from iron overload, either by virtue of metabolic abnormality or the coexistence of heterozygote status and environmental factors such as alcohol abuse.

The authors believe family screening with the aim of presymptomatic identification and treatment of persons homozygous for the HFE gene is a fundamental aspect of appropriate clinical management of hemochromatosis. Edwards and colleagues (12) have demonstrated marked variability of liver iron stores in hemochromatosis patients of similar ages and at present it does not seem possible to predict the progression of the disease in homozygotes. It seems reasonable to treat all homozygotes prophylactically once evidence of iron overload is found; venesection is harmless, effective treatment which can be adjusted to achieve a quantifiable clinical response (13). Niederau and co-workers (1) demonstrated a significant reduction of life expectancy in patients whose hemochromatosis had resulted in cirrhosis or diabetes and that patients treated prior to the onset of cirrhosis had an expectation of survival indistinguishable to that of the general population. Of particular note, hepatocellular carcinoma, a recognized complication of hemochromatosis, has never been reported in noncirrhotic patients with hemochromatosis (1).

The pattern of association of the HFE gene with certain HLA haplotypes suggests that a small number of mutations, or perhaps a single mutation event, is responsible for this gene (14). This raises the possibility that tests using oligonucleotide DNA probes could be developed, which would allow homozygotes and heterozygotes to be identified accurately, simply and cheaply. Developing such probes would not be easy; this

would require that the HFE gene actually be found and sequenced. At present, although the linkage of HFE to HLA on chromosome 6 is certain, its actual position, within at least a million base pairs, is not known and the gene would have to be found before it could be sequenced.

The frequency of the HFE gene would make developing oligonucleotide probes worthwhile. However, even assuming the clinical impact of the HFE gene becomes better appreciated, as it should, the treatability of hemochromatosis may place its molecular genetics at a lower priority than that of numerous disorders less susceptible to clinical management. Also, population screening for iron overload rather than the HFE allele has the additional benefit of identifying persons with iron overload due to other causes, who also require diagnosis and therapy.

The authors conclude that members of the families of hemochromatosis patients should be screened for iron overload, that this screening should include the children as well as the siblings of affected individuals and that screening should be early, with the aim of preventing iron overload and its well documented complications.

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The Canadian Hemochromatosis Society was established in 1982 and maintains a central registry of hemochromatosis patients and their families. The society provides information about hemochromatosis for patients and physicians and operates a referral service to put patients in touch with physicians in their area with an interest in hemochromatosis. The Canadian Hemochromatosis Society, Box 94303, Richmond, BC V6Y 2A6.

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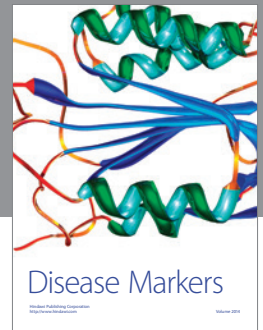
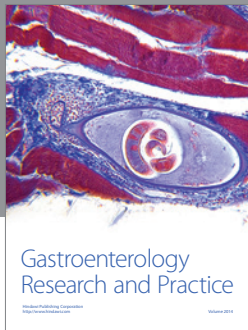
### **Les enfants des patients atteints d'hémochromatose : Devraient-ils être soumis à un examen de dépistage ?**

L'hémochromatose est une condition curable sous diagnostiquée qui se transmet sur le mode autosomique récessif. L'importance de traiter le sujet atteint le plus tôt possible étant certaine, le dépistage des groupes à haut risque est une mesure de médecine préventive impérative. Bien que l'examen des frères et sœurs soit toujours recommandé, la fréquence du gène porteur de l'hémochromatose accentue la nécessité de dépister les enfants des patients atteints d'hémochromatose, ainsi que le démontre les familles dont fait état ce rapport.

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