Use of HFE Mutation Analysis for Hereditary Hemochromatosis: The Need for Physician Education in the Translation of Basic Science to Clinical Practice

MANISH KOHLI, MB, ChB, STEVEN A. SCHICHMAN, MD, PhD, LOUIS FINK, MD, and CLIVE S. ZENT, MB, BCh, Little Rock, Ark

ABSTRACT

Background. Hereditary hemochromatosis (HH) is a common hereditary disorder of iron metabolism causing iron overload, organ failure, and malignancy. Preclinical diagnosis using HFE gene analysis followed by prophylactic phlebotomy can completely prevent the disease.

Methods. We conducted a mail survey of all registered primary care physicians, gastroenterologists, and hematologists in Arkansas (n = 860) to determine utilization of HFE mutation analysis in clinical medicine a year after the new molecular test first became available.

Results. Of 346 responding physicians (40%), 71 (21%) were aware of the test, 36 (10%) knew that the test was available in Arkansas, and 10 (3%) had used the test. One physician had used the test to screen first-degree relatives of a homozygous HH proband.

Conclusions. Because of poor utilization of the test, the discovery of the role of HFE mutations in HH has had minimal impact on clinical care in Arkansas.

HEREDITARY HEMOCHROMATOSIS (HH) is a common autosomal recessive disorder of iron metabolism with a gene carrier frequency of 7% to 8% among Americans of European ancestry.[1] The disease is caused by a gradual accumulation of tissue iron, which results in chronic liver disease, arthritis, impotence, diabetes, cardiomyopathy, and death. In untreated patients, life-threatening events due to cirrhosis, diabetes, congestive cardiac failure, or cardiac arrhythmias occur at a median age of 54 years (range, 20 to 74 years) in men and 63 years (range, 28 to 82 years) in women. Patients with HH have a substantial increase in incidence of hepatocellular carcinoma, with a lifetime risk of 5% among those with a noncirrhotic liver and 19% in those with a cirrhotic liver.[2]

Preclinical diagnosis of HH is potentially life saving; iron overload and clinical disease in homozygous HH individuals is completely preventable with regular phlebotomy. The recent discovery of the mutation responsible for most cases of HH may have an important role in preclinical diagnosis.

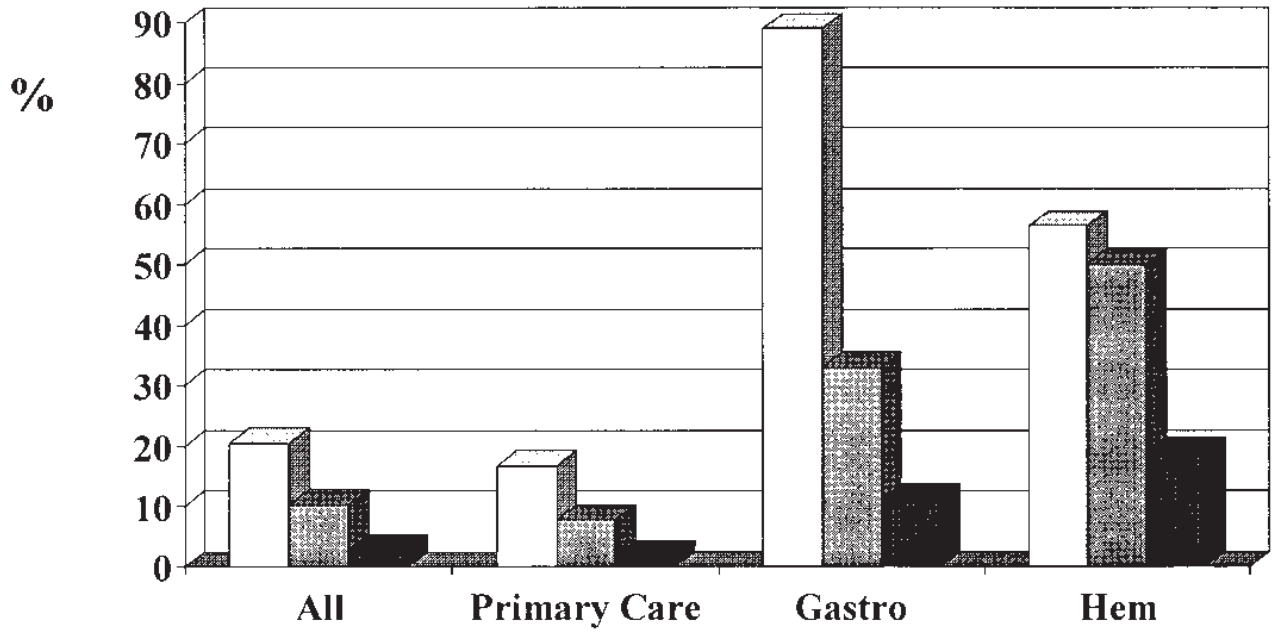
From the Department of Internal Medicine, Division of Hematology/Oncology and the Department of Pathology, John L. McClellan Memorial Veteran's Hospital and University of Arkansas for Medical Sciences, Little Rock.

Reprint requests to Clive S. Zent MB, BCh, University of Arkansas for Medical Sciences, Division of Hematology/Oncology, Slot 508, 4301 W Markham St, Little Rock, AR 72205.

The HFE gene (initially named HLA-H), first reported in 1966 by Feder et al,[3] was discovered using a positional cloning technique in families with HH. Although the exact physiologic role of HFE is not yet fully determined, mouse knockout studies have shown that HFE is essential for normal control of iron absorption. Mice homozygous for HFE gene disruption have the same biochemical and histologic features of iron overload as patients with HH.[4]

The most common HFE gene mutation in patients with HH is single base mutation (G to A transition at nucleotide 845 of the open reading frame), which results in a cysteine to tyrosine substitution at amino acid 282 (C282Y).[3] A second mutation of uncertain clinical significance is a C to G change resulting in a histidine to aspartic acid substitution at position 63, which disrupts the formation of a salt bridge with an aspartic acid residue at position 73.[3,5,6]

Although the exact clinical role of HFE mutational analysis is not yet defined, the assay can provide novel and helpful information. HFE mutation analysis is most useful in screening first-degree relatives of a patient who has HH and is homozygous for the HFE C282Y mutation. Children of the patient can be screened to determine whether they are carriers or homozygous for the mutation. The patient's siblings without the mutation are not at increased risk of HH, and heterozygotes can be educated about



Knowledge about use of HFE mutation analysis in diagnosis of hereditary hemochromatosis (column 1, no shading), availability of assay to physicians in Arkansas (column 2, gray shading), and number of physicians who had used HFE mutation analysis (column 3, black shading) are expressed as percentages of responding physicians for all physicians surveyed (All), primary care physicians (Primary Care), gastroenterologists (Gastro), and hematologists (Hem). Total number of responders was 346 (321 primary care physicians, 9 gastroenterologists, and 16 hematologists).

the increased risk of HH in their children. Homozygous individuals require careful evaluation and appropriate management. HFE mutation analysis can replace diagnostic liver biopsies in a small select group of young (less than age 30), asymptomatic patients with normal liver function tests who are suspected of having HH because of increased transferrin saturation (>40%).[7,8] In older or symptomatic patients and those with high iron load (ferritin level >500 ng/mL), liver biopsy is still necessary to evaluate hepatic damage.

Mutational analysis is also of value in determining the cause of iron overload in patients with hepatic disease of uncertain cause, especially in patients with a history of alcohol abuse in whom distinction between primary and secondary iron overload may be difficult. Patients with cirrhosis of uncertain cause, who are candidates for liver transplantation should be tested by HFE mutation analysis for occult HH, which is associated with a higher risk of posttransplant cardiac complications and increased risk of recurrent liver failure if iron overload is not treated.[2,9]

Hereditary hemochromatosis is a potentially fatal inherited disease of insidious onset that can be safely and effectively prevented by phlebotomy. These characteristics make it a model genetic disease for the future development of a population screening program. The role of HFE mutation analysis as a population screening test for HH is currently the subject of intense research. Use is still limited by uncertainty about the sensitivity and specificity of analysis for the C282Y mutation in the general population. Although the initial study in patients of European descent in the United States reported an 85% rate of homozygous C282Y mutation,[3] subsequent studies from Europe and Australia have shown rates as low as 64%.[7,10] In addition, the penetrance of the genetic defect in HFE C282Y homozygous subjects is as yet not well defined and is likely to depend in part on dietary iron load and extent of chronic blood loss. Current data suggest that about 50% of males and 25% of females homozygous for HH are likely to have potentially life-threatening complications of the disease in countries with high dietary intake of iron.[8]

Discovery of the HFE gene and the role of HFE mutations in HH can be translated into improved health care only if physicians are aware of the discovery, availability, and utility of HFE mutation analysis. To evaluate the impact of this fundamental development in molecular genetics on patient care, we conducted a survey of all physicians likely to use the assay in the state of Arkansas 1 year after it became available as a routine clinical test.

METHODS

We surveyed all primary care physicians, gas-

troenterologists, and hematologists registered with the Arkansas State Medical Board, using a simple anonymous mail questionnaire. Physicians were asked (1) if they were aware of the HFE (HLA-H) assay for the diagnosis of HH, (2) if they were aware that the assay was available in Arkansas, and (3) if they had ever used the assay. If physicians had used the assay, they were asked if the assay was used to diagnose a new case of HH or to confirm a previous diagnosis, and whether the results of the assay had affected patient management or been used to screen or counsel family members.

RESULTS

We mailed 860 surveys between July and October 1998 and received 346 replies (40%) by the end of 1998. Seventy-one respondents (21%) were aware of the HFE mutation analysis assay, 36 (10%) knew that the assay was available to physicians in Arkansas, and 10 (3%) (6 primary care physicians, 3 hematologists, and 1 gastroenterologist) had used the test (Figure). Knowledge of the HFE assay was significantly higher among responding specialists (gastroenterologists, 89%; hematologists, 56%) than among responding primary care physicians (17%) ($P < .001$, chi-square test). Utilization of the HFE mutation analysis was also significantly higher among specialists (gastroenterologists, 11%; hematologists, 19%) than primary care physicians (2%) ($P = .004$, chi-square test). There were no significant differences in knowledge or utilization between gastroenterologists and hematologists. Only one physician reported using the test to screen first-degree relatives of a homozygous C282Y HH proband.

DISCUSSION

One year after HFE mutation analysis became available for routine clinical use, only 21% of responding physicians were aware of the development of this valuable diagnostic tool, only 10% knew that the assay was routinely available to them, and less than 3% of respondents had ever used the test. Of the 10 physicians who had used the assay, only 1 had used the test for preclinical screening of first-degree relatives of a C282Y homozygous proband, which is currently the most important indication for use. The discovery of the HFE gene, which defined the disease in most patients at a molecular level, followed shortly by the routine availability of mutation analysis, has had minimal effect on the practice of medicine and health care in Arkansas.

Clinical application of new findings in medicine require evaluation of their utility for the purpose of improving patient care. Furthermore, new knowledge needs to be taught to physicians and their patients. HFE mutation analysis has a role in the care of individual patients and for specific genetic screening, but this knowledge has not yet reached the relevant target population of health care providers. We propose that this deficiency should be addressed by the medical press and continued medical education programs.

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