Genetic Testing in Liver Disease

What to Order, in Whom, and When

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KEYWORDS

- Genetic testing • Hemochromatosis • Wilson disease
- Progressive familial intrahepatic cholestasis
- Benign recurrent intrahepatic cholestasis • Lysosomal acid lipase deficiency
- Gilbert syndrome • Alpha-1 antitrypsin deficiency

KEY POINTS

- The most common cause of hereditary hemochromatosis is a C282Y mutation in the HFE gene with a penetrance of 10% to 52%.
- Gilbert syndrome is a common and benign cause of indirect hyperbilirubinemia with no signs of hemolysis and no associated liver injury.
- Progressive familial intrahepatic cholestasis is a rare cause of chronic cholestasis in children and young adults. Benign recurrent intrahepatic cholestasis is a benign cause of recurrent cholestasis seen in both adults and children.
- Alpha-1 antitrypsin deficiency causes both lung and liver disease. It is the most common genetic cause of liver disease in children.
- Wilson disease can cause neurologic disease and liver disease. Patients between the ages of 3 and 55 years with any acute or unexplained chronic liver disease should be tested for Wilson disease.

INTRODUCTION

When evaluating a patient with abnormal liver function tests, investigating genetic causes of liver disease is an important part of the work-up. The initial evaluation of a patient with abnormal liver function tests includes a history and physical examination. Family history plays a critical role because it can help determine which patients to consider for genetic testing. The age of onset of abnormal liver function tests and the pattern of abnormal liver function tests, hepatocellular or cholestatic, play a role

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in what testing is performed. This article evaluates common genetic causes of liver disease, when and in whom to test for them, and what tests to order.

HEREDITARY HEMOCHROMATOSIS

Hemochromatosis occurs from the unregulated transfer of iron from the intestine into the blood leading to toxic levels depositing in various organs and is usually caused by an underlying genetic disorder.[1] Most (80%–90%) cases of hereditary hemochromatosis are caused by an autosomal recessive mutation in the *HFE* gene, C282Y.[2–8] Two less common mutations are H63D and S65C, which usually only cause signs and symptoms of iron overload when present as compound heterozygotes with C282Y.[2,4,9] In patients with liver disease, 3% to 5.3% are homozygous for C282Y and therefore testing for hemochromatosis should be performed in the work-up of liver disease of unknown cause or in patients with iron overload on laboratory testing or imaging.[5,9] It is especially important to test those patients who have a first-degree relative with hereditary hemochromatosis as well as those patients with imaging studies that show iron overload.[2,5,8] At diagnosis, about 4.4% to 11.8% of C282Y homozygous male patients have cirrhosis and 0% to 2.7% of C282Y female patients have cirrhosis.[1,7,10] Therefore early diagnosis is important because initiation of phlebotomy before the development of cirrhosis can reduce or stop the progression of hereditary hemochromatosis.[2,10]

Hereditary hemochromatosis is most commonly seen in Caucasian of Northern European descent.[2,6,9] About 6% to 10% of Caucasian have 1 allele for C282Y and 1 in 250 to 300 Caucasian have 2 alleles.[1,4,5] Although the HFE gene mutations are fairly common, only 10% to 52% of patients homozygous for C282Y develop clinical signs of iron overload.[1,2,5–8,11] Manifestations of hereditary hemochromatosis are more prevalent in men and present earlier in men, likely in part because of menstruation and therefore iron loss in women.[2,5,6,8,10] Patients with hereditary hemochromatosis can show other symptoms of iron overload that may prompt testing, such as chondrocalcinosis, diabetes mellitus type 1, heart failure, or porphyria cutanea tarda[1,2,5,6] Up to 19% of patients with porphyria cutanea tarda are homozygous for C282Y.[5,8,12]

The initial screening tests for hereditary hemochromatosis include blood tests for ferritin and transferrin saturation, which is calculated from iron/total iron binding capacity.[2,5] Transferrin saturation greater than 45% should prompt genetic testing for the most common causes of hereditary hemochromatosis.[1,2,4–6,9] An increased ferritin level is also expected in hereditary hemochromatosis, but is not highly specific, thus an increased ferritin level with a normal transferrin saturation is not common in hereditary hemochromatosis and should lead to investigation into alternative causes of liver disease.[1,13] In hereditary hemochromatosis, a ferritin level is still useful because of its high sensitivity and because a level greater than 1000 μg/L can help predict patients who have advanced fibrosis.[2,10] Testing for advanced fibrosis or cirrhosis should be performed in patients who are homozygous for C282Y or compound heterozygotes for C282Y who have a ferritin greater than 1000 μg/L, hepatomegaly, age more than 40 years, or abnormal liver tests.[2,5,6,10,14] A liver biopsy is not always necessary because MRI can evaluate for cirrhotic morphology and can quantify the amount of iron in the liver, and transient elastography can also be used to evaluate for advanced fibrosis.[5,15,16]

In patients with laboratory testing consistent with iron overload, but who are not C282Y homozygotes, other causes of liver disease should be considered.[1,2,15] Iron