Hereditary Hemochromatosis for Clinicians

SYNOPSIS AND RELEVANCE

While the term *hemochromatosis* was used previously to refer broadly to iron overload, it has more recently been applied specifically to a genetic disorder in which pathogenic mutations lead to a clinicopathologic condition featuring iron overload and elevated transferrin saturation.[1] Mutations in at least five genes can contribute to hemochromatosis, but most cases are encountered in individuals of European ancestry and result from homozygosity for the p.C282Y variant in *HFE*.[2] *HFE*-related hemochromatosis is a common autosomal recessive disorder of iron metabolism with low penetrance that, if left untreated, can lead to severe complications from iron overload, including hepatic failure, diabetes, and malignancy.[3] Other *HFE* genotypes (eg, compound heterozygosity for p.C282Y and p.H63D) have much lower penetrance and account for only rare cases of hemochromatosis.

Unexplained elevation in serum transferrin saturation that is greater than (>) 45%, especially if reproducible on repeat testing, is an indication for *HFE* genetic testing.[4] A family history of hereditary hemochromatosis is another indication for *HFE* genetic testing. Selection of appropriate criteria for HFE genetic testing and accurate interpretation of test results to inform treatment and management are important considerations to optimize care.

INSIGHTS

1. *HFE* gene testing for p.C282Y is indicated for patients with unexplained elevated transferrin saturation (≥ 45%) levels and/or with clinical findings suggestive of iron overload, and also for first-degree relatives of people with homozygous p.C282Y hemochromatosis.
2. The value of testing for p.H63D is controversial, as the risk of severe iron overload is low in patients with compound heterozygosity for p.C282Y/p.H63D or homozygosity for p.H63D.[5]
3. *HFE* testing for hereditary hemochromatosis is generally not indicated for screening or in patients with normal iron studies unless there is a family history.
4. Hyperferritinemia alone without elevated transferrin saturation should not be used as an indication for *HFE* gene testing.[6]
5. *HFE* genetic testing should only be performed once unless there is some concern about reliability of prior test results.

BACKGROUND

Serum ferritin, iron, iron binding capacity, and transferrin saturation are common laboratory studies used to evaluate iron status. Transferrin saturation normally ranges between 15-30%. Approximately 2% of the adult US population have highly elevated transferrin saturation levels (> 45%) which is associated with higher risk for all-cause mortality.[4]

High transferrin saturation is most often associated with secondary causes such as chronic blood transfusions, hemolytic disease, poisoning, or chronic liver disease (eg, viral hepatitis, alcohol use, porphyria). Less often, elevated transferrin saturation is a sign of hereditary hemochromatosis, an autosomal recessive disorder of iron metabolism. This is one of the most common hereditary disorders, affecting about 1 in 200 individuals of northern European descent.

While serum ferritin is also elevated in patients with hemochromatosis, this is usually due to secondary causes such as inflammation or tissue injury and does not accurately reflect iron status, especially if transferrin saturation is not likewise elevated.[7] Furthermore, abnormal transferrin saturation levels typically appear sooner than elevated serum ferritin in patients with early, asymptomatic hemochromatosis. Therefore, *HFE* gene testing is indicated when transferrin saturation is elevated, even when serum ferritin is normal. Transferrin saturation (≥ 45%) is preferred over hyperferritinemia as an indicator for genetic testing.[6,8]

The most important pathogenic *HFE* variant is p.C282Y (c.845G>A), with homozygosity for this variant accounting for most cases of clinical hemochromatosis. While compound heterozygosity for p.C282Y and p.H63D (c.187C>G) may contribute to hemochromatosis, this is typically the case only in the presence of a pathogenic mutation of another hemochromatosis-related gene and/or the presence of another predisposing environmental factor (eg, HCV infection, alcohol use disorder, metabolic-associated fatty liver disease). While more than 20 other pathogenic variants in the *HFE* gene have been identified, the vast majority of clinical hemochromatosis cases are associated with homozygous p.C282Y, while most of the remaining are associated with compound heterozygosity for, p.C282Y/p.H63D or rarely p.C282Y/p.S65C (c.193A>T). These genotypes (especially homozygous p.C282Y) may be associated with toxic injury to the liver and other organs that can be prevented by removing iron by regular therapeutic phlebotomies.[9,10] Other genotypes, such as heterozygous p.C282Y or homozygous p.H63D, are not associated with complications and do not require treatment despite elevated transferrin saturation levels.

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