


Cointheritance of Alleles Associated With Hemochromatosis and Hereditary Hyperferritinemia-Cataract Syndrome

To the Editor:

A 52-year-old white woman was referred for additional evaluation because she was intolerant of phlebotomy therapy of her presumed hemochromatosis and iron overload, and her serum ferritin concentration had not changed significantly. Her diagnosis was based on serum iron 122 µg/dL, transferrin saturation 28%, serum ferritin 1,188 ng/mL, normal complete blood count and serum concentrations of hepatic enzymes, and heterozygosity for a hemochromatosis-associated mutation. Evidence of presumed iron overload included persistent hyperferritinemia and dual-energy computed tomography (CT) scanning densitometry and volumetry estimates of hepatic iron concentration (4.3 mg Fe/cL liver; normal ~0.8 mg/g; “typical” range for hemochromatosis patients 5 to 15 mg/g) and total hepatic iron content (4,400 mg). After 5.5 units of phlebotomy (~1,100 mg Fe), she developed severe weakness, hematoctrit 23%, and mean corpuscular volume 66 Fl. Her serum ferritin concentration remained in the range of 836 to 1,200 ng/mL (mean, 1,064 ng/mL; n = 5). She reported no blood loss (other than therapeutic phlebotomy), and had no history of receiving blood transfusions, donating blood, or using medicinal iron. She and her brother had bilateral congenital cataracts. Her father, from Alsace-Lorraine, had apparently good health but died due to a motor vehicle accident during her infancy; her mother, of German-Swiss ancestry, did not have cataracts. There was no other family history of iron-associated disorders. We found that our patient did not have the “major” 845G → A (C282Y) mutation, but was compound heterozygote for the 187C → G (H63D) mutation of the hemochromatosis-associated HFE gene on 6p1 and the A → G mutation of the CAGUGU motif of the iron-responsive element (IRE) loop of the ferritin L-chain gene on 19q13.1 associated with hereditary hyperferritinemia-cataract syndrome.2 Restoration of her iron stores relieved her weakness and corrected her microcytic anemia, but did not change her serum ferritin concentration.

The clinical findings and coincidental inheritance of mutations of the HFE and L ferritin genes in our patient show several important principles. The transferrin saturation values of persons with hemochromatosis, particularly those with iron overload, are usually elevated; normal or subnormal values suggest that patients have other complications or disorders.3,4 Regardless of the L ferritin gene mutation that causes hereditary hyperferritinemia-cataract syndrome, affected patients do not have iron overload.3,5 This emphasizes that the demonstration of hyperferritinemia does not necessarily verify that iron overload is present, and well-intended therapeutic phlebotomy of patients with hereditary hyperferritinemia-cataract syndrome does not alter their serum ferritin concentrations significantly.5,6 CT scanning suggested that far more iron was stored in our patient’s liver than could be mobilized by phlebotomy, indicating that this noninvasive technique lacks sufficient sensitivity for the measurement of normal or near-normal quantities of hepatic iron.3 Iron stores and responses of serum iron concentration, transferrin saturation, and erythropoiesis to iron depletion and subsequent repletion were normal in our patient, like most persons with hereditary hyperferritinemia-cataract syndrome.6,7 Our patient, like ~25% of normal whites of western European descent, is heterozygous for the H63D mutation9,10; therefore, cointheritance of the H63D mutation and mutations on other chromosomes should occur relatively frequently. However, persons who inherit a single hemochromatosis allele infrequently have a hemochromatosis clinical phenotype.1,3,8 Taken together, these observations suggest that there was no interaction between these two iron-associated mutations or their gene products in our patient that significantly affected routine clinical parameters of iron metabolism.

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REFERENCES


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