

Iron absorption in carriers of the C282Y hemochromatosis mutation^{1–3}

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Hereditary hemochromatosis is a disorder of iron homeostasis in which the body iron content may be greatly increased. Most patients with hereditary hemochromatosis are homozygous for the C282Y mutation of the *HFE* gene. Because the iron content of the body is regulated by modulation of iron absorption, the increased body iron of those who are homozygous for the C282Y mutation must be due to enhanced iron absorption, and many studies have documented that such increased iron absorption occurs in homozygotes (1–3).

The gene frequency of the C282Y mutation in Northern European populations is extremely high. For example, in Ireland, a gene frequency of 0.123 has been documented, such that >20% of the population is heterozygous (4). The frequency of the genotypically weaker H63D mutation is even higher. Molecular studies show that this is a mutation of relatively recent origin, estimated at some 100–140 generations ago (5, 6). The mutations of the *HFE* gene have all of the hallmarks of a balanced polymorphism. A balanced polymorphism is one in which the beneficial effect of the heterozygous state balances the deleterious effect of the homozygous state. A typical example is the hemoglobin S mutation. During the time that the frequency of the sickle gene was increasing in Africa, homozygotes with sickle cell disease rarely lived for more than a few years, but heterozygotes were protected against malaria, the great killer of children. Thus, the gene frequency for the sickle mutation rose to a point at which the degree of protection afforded the heterozygotes balanced the loss of sickle genes with the early death of homozygotes.

In this issue of the Journal, Hunt and Zeng (7) report the results of an elegant investigation of iron absorption in heterozygotes for the C282Y mutation. Although, as they point out, increased serum transferrin saturation and serum ferritin concentrations have been inconsistently associated with the heterozygous state, the effect is evident and highly significant in all of the very large studies with more than 1000 heterozygotes but not demonstrable in smaller cohorts of patients. The difference in serum transferrin saturation and ferritin concentrations is that small. Consistent with those findings, Hunt and Zeng now show that the effect of this mutation on absorption, if it exists at all, is so small that it could not be shown for either heme or nonheme iron.

What can be the selective advantage of the heterozygous state for *HFE* mutations? It has been conventional wisdom that inheritance of the C282Y mutation increases iron absorption, which prevents iron deficiency anemia. But, although some small studies seemed to show such an effect (8), we have not been able to

show a decrease in the prevalence of frank iron deficiency anemia in a much larger cohort of patients (9). Could it be that the selection of heterozygotes for *HFE* has a basis other than the prevention of iron deficiency? Rochette et al (6) reasoned that, given the low mortality that is associated with the homozygous state, preventing iron deficiency anemia would be such a potent selective force that the mutation would have achieved fixation in some populations if this were its advantage. They suggested that *Hfe* might serve as a receptor for microorganisms and that the mutation would protect against infection. Hemochromatosis is characterized not only by an excess of iron in the body, but also by an abnormal distribution. Macrophages contain less iron than expected. If this type of distribution occurred in heterozygotes, the lack of iron in macrophages might protect against intracellular infectious agents, such as *Chlamydia*, *Coxiella*, *Francisella*, *Legionella*, *Mycobacterium*, *Salmonella*, and *Yersinia* (10). Finally, one should not forget that the *HFE* gene is imbedded in the immune response region of the genome on chromosome 6. Perhaps the mutation is just a hitchhiker, being carried along with a group of immune response genes that are favorable for survival.

Recently, it was shown that the penetrance of the C282Y-homozygous state is extremely low (11). Most of the clinically affected persons are >40 y old—quite old from the point of view of their role in perpetuating the species. A large majority of the affected persons are male, but the loss of a few men is not important in ensuring the biologic success of a species. They are readily replaced. It follows that even a very small selective advantage for heterozygotes can result in a high gene frequency. Such small advantages can be very difficult to detect. For the present, we can only speculate as to how C282Y carriers benefit from their genotype. 

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REFERENCES

1. Lynch SR, Skikne BS, Cook JD. Food iron absorption in idiopathic hemochromatosis. *Blood* 1989;74:2187–93.
2. McLaren GD, Nathanson MH, Jacobs A, Trevett D, Thomson W. Regulation of intestinal iron absorption and mucosal iron kinetics in hereditary hemochromatosis. *J Lab Clin Med* 1991;117:390–401.

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3. Williams R, Manenti F, Williams HS, Pitcher CS. Iron absorption in idiopathic haemochromatosis before, during, and after venesection therapy. *BMJ* 1966;2:78–81.
4. Byrnes V, Ryan E, Barrett S, Kenny P, Mayne P, Crowe J. Genetic hemochromatosis, a Celtic disease: is it now time for population screening? *Genet Testing* 2001;5:127–30.
5. Toomajian C, Ajioka RS, Jorde LB, Kushner JP, Kreitman M. A method for detecting recent selection in the human genome from allele age estimates. *Genetics* 2003;165:287–97.
6. Rochette J, Pointon JJ, Fisher CA, et al. Multicentric origin of hemochromatosis gene (HFE) mutations. *Am J Hum Genet* 1999;64:1056–62.
7. Hunt JR, Zeng H. Iron absorption by heterozygous carriers of the HFE C282Y mutation associated with hemochromatosis. *Am J Clin Nutr* 2004;80:924–31.
8. Datz C, Haas T, Rinner H, Sandhofer F, Patsch W, Paulweber B. Heterozygosity for the C282Y mutation in the hemochromatosis gene is associated with increased serum iron, transferrin saturation, and hemoglobin in young women: a protective role against iron deficiency? *Clin Chem* 1998;44:2429–32.
9. Beutler E, Felitti V, Gelbart T, Waalen J. Haematological effects of the C282Y HFE mutation in homozygous and heterozygous states among subjects of northern and southern European ancestry. *Br J Haematol* 2003;120:887–93.
10. Moalem S, Weinberg ED, Percy ME. Hemochromatosis and the enigma of misplaced iron: implications for infectious disease and survival. *Bio-metals* 2004;17:135–9.
11. Beutler E. The *HFE* Cys282Tyr mutation as a necessary but not sufficient cause of hereditary hemochromatosis. *Blood* 2003;101:3347–50.