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Hemochromatosis: A Neolithic adaptation to cereal grain diets

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Summary The Neolithic period in Europe marked the transition from a hunter-gatherer diet rich in red meat to an iron-reduced cereal grain diet. This dietary shift likely resulted in an increased incidence of iron deficiency anemia, especially in women of reproductive age. I propose that hereditary hemochromatosis and in particular the common *HFE C282Y* mutation may represent an adaptation to decreased dietary iron in cereal grain-based Neolithic diets. Both homozygous and heterozygous carriers of the *HFE C282Y* mutation have increased iron stores and therefore possessed an adaptive advantage under Neolithic conditions. An allele age estimate places the origin of the *HFE C282Y* mutation in the early Neolithic period in Northern Europe and is thus consistent with this hypothesis. The lower incidence of this mutation in other agrarian regions (the Mediterranean and Near East) may be due to higher dietary intakes of the iron uptake cofactor vitamin C in those regions. The *HFE C282Y* mutation likely only became maladaptive in the past several centuries as dietary sources of iron and vitamin C improved in Northern Europe.

Introduction

Evolutionary medicine attempts to apply the principles of natural selection to answer questions about the ultimate causation of human diseases. Such explanations often involve a genetic adaptation to an ancient (e.g. Paleolithic hunter-gatherer) environment, which has become maladaptive in modern environments [1]. The previous adaptive advantage of these alleles explains their high incidence in modern populations despite their associated disease states. For instance, this nature/nurture mismatch has been invoked to explain the modern epidemics of hypertension, obesity and coronary artery diseases [2]. The presence of striking geographic variation in the frequencies of disease-associated alleles can also be seen as suggestive of prior selection pressure [3].

Hereditary hemochromatosis is one such disease that shows strong geographic differences in allele frequencies, with the highest incidence in Northern Europe (up to 10% allele frequency) and in populations originating in Northern Europe [4]. Hereditary hemochromatosis is also of interest in evolutionary medicine as the age of the common *HFE C282Y* allele mutation in hemochromatosis has been estimated to be 138 generations [5] (about 3450 years), allowing correlation with archeological and environmental factors. In Northern Europe,

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this places the origin of the *HFE C282Y* allele mutation in the Neolithic period, approximately 1500 years after the latest start of agriculture in that region [6]. The Neolithic period in Europe marked the transition from a Paleolithic hunter-gatherer diet high in red meat to an agricultural diet high in cereal grains [7]. Indeed, phytochemical, vitamin and mineral intakes all appear to have decreased with the switch from a red meat to a cereal grain diet [8].

Hypothesis

I propose that hereditary hemochromatosis and in particular the common *HFE C282Y* allele mutation may represent an adaptation to decreased dietary iron in cereal grain-based Neolithic diets.

Evaluation and consequences

Iron deficiency anemia was likely a significant problem for Neolithic peoples [8], especially women of reproductive age, and thus a gene mutation that increased iron stores would have conferred a definite selective advantage. For the *HFE C282Y* allele mutation, both heterozygotes and homozygotes display increased iron stores [4] with homozygotes showing variable penetrance for the clinical disease of hemochromatosis.

If the *HFE C282Y* allele mutation presented a selective advantage to Neolithic Northern Europeans, why did the allele not spread south and east to other agrarian populations? It may be that other dietary factors such more readily available vitamin C (an important cofactor in iron uptake) from citrus fruits ameliorated the decrease in dietary iron among human populations in the Mediterranean and Near East regions. In Northern Europe the *HFE C282Y* allele mutation has likely only become maladaptive during the past few centuries, as dietary sources of iron and vitamin C have improved.

The high prevalence of the *HFE C282Y* allele mutation in Canada, the United States, Australia, New Zealand and Caucasian South Africa may be explained as a founder effect in immigrants from affected areas of Northern Europe.

The significance of this hypothesis is twofold. First, it provides a plausible explanation for the evolutionary origin of the most common inherited metabolic disease in the Western World. Second, it points to the potential importance of Neolithic rather than Paleolithic adaptations as a source of disease-associated alleles.

References

[1] Harris EE, Malyango AA. Evolutionary explanations in medical and health profession courses: are you answering your students' ''why'' questions? BMC Med Educ 2005;5:16.
[2] Nesse RM, Williams GC. Why we get sick: the new science of Darwinian medicine. New York: Times Books; 1994.
[3] Bradbury J. Ancient footsteps in our genes: evolution and human disease. Lancet 2004;363:952—3.
[4] Adams P et al. Hemochromatosis and iron-overload screening in a racially diverse population. New Eng J Med 2005;352:1769—78.
[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] Ammerman AJ, Cavalli-Sforza LL. Measuring the rate of spread of early farming in Europe. Man 1971;6:674—88 [New Series].
[7] Eaton SB, Eaton III SB. Paleolithic vs. modern diets — selected pathophysiological implications. Eur J Nutr 2000;39:67—70.
[8] Cordain L, Miller J, Mann N. Scant evidence of periodic starvation among hunter-gatherers. Diabetologia. 1999;42(3):383—4.