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Hemochromatosis: Niche Construction and the Genetic Domino Effect in the European Neolithic

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Hemochromatosis: Niche Construction and the Genetic Domino Effect in the European Neolithic

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Abstract

Hereditary hemochromatosis (HH) is caused by a potentially lethal recessive gene (*HFE,* C282Y allele) that increases iron absorption and reaches polymorphic levels in Northern European populations. Because persons carrying the allele absorb iron more readily than non-carriers, it has often been suggested *HFE* is an adaptation to anemia. We hypothesize

positive selection for *HFE* began during or after the European Neolithic with the

adoption of an iron-deficient high grain and dairying diet and consequent anemia, a

finding confirmed in Neolithic and later European skeletons. *HFE* frequency compared

with rate of lactase persistence in Eurasia yields a positive linear correlation coefficient

of 0.86. We suggest this is just one of many mutations that became common after the

adoption of agriculture.

Contrary to received wisdom (Gould 2000), the human genome is undergoing rapid

evolutionary change (Hawks et al 2007; Hughes et al 2008; Perry et al 2007; Bryk et al

2008), especially loci related to the major shift in diet during food domestication and later

(McCracken 1971; Perry et al 2007; Cochran and Harpending 2009). We suggest the

hemochromatosis mutation is another polymorphic artifact of the Neolithic Revolution.

Hereditary hemochromatosis (HH) is a potentially lethal disorder of iron

metabolism based on a partially recessive gene (*HFE*; OMIM 235200. 6p22.2; 6p21.3)

reaching polymorphic levels throughout western Eurasia, especially northwest Europe

(Barton et al 2010; Enattah et al 2007; Merryweather-Clarke et al 2000; Cummings

2000). The disorder is characterized by increased levels of iron absorption and a gradual

accumulation of excess iron stores in the liver and kidneys occasionally approaching

lethal levels in homozygotes (Britton 2000). Heterozygotes have also slightly elevated

levels of iron (Bulaj et al 1996: Edwards et al 2000, inter alia) but penetrance for clinical

symptoms of HH is low in either zygosity (Waalen et al 2002).

The two most prevalent mutant alleles associated with hemochromatosis are the

C282Y and H63D variants (Merryweather-Clarke et al 2000). The former allele is related

to development of HH when inherited in the homozygous state but double heterozygotes

of the two mutants may also produce increased iron levels (Cartwright et al 1979). Males

are more often affected than females (Loreal et al 1992; Bulaj et al 1996). Clinical

hemochromatosis may also develop from high levels of alcohol intake with or without

presence of the *HFE* allele (Adams and Agnew 1996; Scotet et al 2003).

While excess iron poses an occasional threat to health, anemia is a more common

and serious worldwide health problem (Greer and Arber 2014), characterized by lethargy,

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fatigue, weakness, poor concentration and dyspnea. Anemia affects the health of over 2 billion humans (Zimmermann and Hurrell 2007), costing up to a 4% loss in world GDP (Horton and Ross 2003) and continues to be extremely common in developing countries (DeMaeyer and Adiels-Tegman 1985; Kohlmeier et al 1998). It is still observed in developed countries, such as the United Kingdom (Heath and Fairweather-Tait 2002), France (Hereberg et al 2001), Russia (Kohlmeier et al 1998) and the United States (Scholl 2005).

Mothers suffering anemia may be at risk for poor maternal outcomes or higher mortality (Brabin et al 2001a; Khan et al 2006). Babies born of anemic mothers are often underweight (World Health Organization 2008) and at risk for health problems (Stuart-Macadam 1989; Brabin et al 2001b). In a meta-analysis of 92 studies it was shown iron supplementation resulted in increased newborn weight (Haider et al 2013). Low birth weight infants in Europe had a lower frequency of the C282Y allele than expected (Maier et al 1999). A counter-argument is that iron deficiency may serve as an adaptation to some infectious diseases such as malaria, plague and tuberculosis (Denic and Agarwal 2007).

Toomajian and Kreitman (2002) discovered that the C282Y allele was a young mutation at high frequency; his team later suggested it was due to rapid positive selection in an iron-deficient dietary environment (Toomajian et al 2003). Williamson et al (2007) disagreed, noting that the *HFE* allele is located in the area of chromosome 6 where the genes defining histones important in DNA synthesis are situated; Hartfield and Otto (2011) agreed with their interpretation and noted the importance of finding a lethal gene caught by linkage in a sweep for a beneficial gene, namely histones. Although not

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mentioned in either critical study, *HFE* is also closely linked with numerous HLA and other loci that must be the objects of selection (Apanius et al 1997).

Motulsky (1979) first suggested that the *HFE* mutation might be an adaptation to iron deficiency, and others have made similar suggestions (Rotter and Diamond 1987; Salter-Cid et al 1998; Fairbanks 2000; Toomajian et al 2003; Raddatz et al 2003). Denic and Agarwal (1999) first proposed the Neolithic Revolution as the historical event responsible for the presence of *HFE*. Naugler (2008) later hypothesized that the specific cause of anemia was adoption of a high grain diet. Phytates present on the surface of whole cereal grains and other seeds chelate dietary iron and several other minerals, making them physiologically unavailable (Committee on Food Protection, Food and Nutrition Board, National Research Council 1973; Hurrell 2003), thus increasing the risk of anemia.

We accept Naugler's phytate hypothesis but believe the total dietary shift of the Neolithic Revolution provides a broader bio-cultural context in which the incidence of anemia is expected to rise. While the increased ingestion of phytates decreases the physiological availability of ingested dietary iron, the partial substitution of iron-poor milk products for heme iron-rich meat as a major protein source further diminished iron ingestion.

The Northern European hunter-gatherer diet with traditional iron-rich high dependence on mammals and/or shellfish shifted to heavy dependence on grains and milk products in the Neolithic (Straus 1977; Cordain et al 2000; 2002). Red meat and many species of shellfish provide a rich source of highly digestible heme iron (U.S. Department of Agriculture, Agricultural Research Service. 2012). Conversely, bovid milk is virtually

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devoid of iron (Fox 1955; Pennington et al 1987), and calcium present in bovid milk inhibits iron ingestion (Baynes and Bothwell 1990).

The combination of reduced iron intake from the partial substitution of milk products for meat, in combination with the negative effects of phytates on mineral absorption, later compounded by the effect of increased parasitism associated with higher agricultural population densities (Gonçalves et al 2003) must have reduced effective iron ingestion among European agriculturalists which is first seen commonly in Neolithic skeletal material (e.g., Wittwer-Bachofen and Tomo 2008). We suggest this confluence of events resulted in a new set of diet-based pressures that created an environment ripe for anemia to develop among the early farmers, thereby making advantageous a mutation increasing iron absorption.

Thus, we hypothesize a strong statistical association between the geographic distributions of the allele frequencies of the C282Y allele of hemochromatosis (*HFE*) and phenotypic lactase persistence (LP) as a measure evolutionarily derived of historic milk dependence and population-wide adoption of European style agriculture in general.

Materials and Methods

To test this hypothesis we compared the frequency of the major mutant allele associated with HH (C282Y), and the prevalence of phenotypic lactase persistence (LP). Our hypothesis is restricted to populations traditionally living in Eurasia and surrounding geographical zones. This would include Europe, proper, and nearby North Africa and Western and Southwestern Asia; four East Asian populations for which we have both

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HFE and LP data were also included for the sake of completeness but have little influence on the statistical outcome.

  HFE data for this study were taken from two major databases that include genetic data from European populations in Distante et al (2004) and Merryweather-Clarke et al (2000), as well as other sources published subsequently; a complete listing is found in Table 1.

  Lactose tolerance data were taken from the University College, London, Global Lactase Persistence Association Database in May of 2013. (http//:www.ucl.as.uk/macelab/resources/glad/LP_phenotype and http//:www.ucl.as.uk/macelab/resources/glad/LP_genotype).

  The *HFE* and LP geographic locations were linked as closely as possible. When *HFE* studies specified the study site, that location was used for comparison with the closest within-country location in the LP dataset. Our analysis relates specifically to populations most likely affected by or tested for the C/T (-13910*T) "European" allele of the LP gene. Much is known concerning the distribution of African and Arabian LP variants that have been well described in the literature, but there are too few available data regarding these variants from Europe to conduct a reliable analysis of their prevalence. Separate ethnic groups within countries such as the Saami, Basques and Roma (Gypsies) were considered independent of the national population.

  In some cases there was only one datum for either the *HFE* or the LP frequencies. Where there were multiple studies done in a similar location we transformed the corresponding data to a single sample-weighted mean. For instance, for Northern Italians we had a single value for LP but numerous results for the *HFE* allele; these latter were

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merged into a single sample-weighted value to compare with the sole LP value. In the

case of Turks both the *HFE* and LP data were merged to present a single datum point for

each (Table 2). Accumulating many small samples into a single value also had the

advantage of reducing variability due to the random fluctuations inherent in small

samples.

Results

There is a high positive linear relationship (r = 0.86; adjusted r^2 = 0.68; t = 9.23; F =

85.19, d.f. = 41, p < 0.0001) between the frequency of the C282Y allele of *HFE* and the

prevalence of lactase persistence (Figure 1). The resulting regression equation is "*HFE*

(%) = -1.2838+0.0812 (LP%)". The alternative mutation involved in hemochromatosis,

H63D, is unrelated to LP (r^2 = 0.030; p=0.93). In an attempt to relate grain consumption

to C282Y frequencies we compared these to wheat per capita consumption rates in

Europe (FAO 2007); the results demonstrated the lack of relationship between these rates

and the *HFE* allele (r = 0.014) and also LP (r = 0.040).

Because we are comparing two genetic-based traits in the same species our results

are obviously autocorrelated. To account for this statistical violation we followed the

suggestion by Legendre (1993) and generated a series of partial correlation coefficients

using 19 loci for which there are adequate national sample sizes for controls

(Roychoudhury and Nei 1988). Despite many attempts at statistical correction the

relationship between the C282Y allele and LP remained strongly positive and significant

(Table 3).

Discussion

Niche Construction Theory posits that populations are adapted to stable surroundings, but should a change occur in the selection environment, the initial response to stress will likely be cultural or behavioral. If the cultural response is inadequate the next level of response is genetic (Laland and Brown 2002; 2006:95). Lactase persistence is one of the most obvious and widely cited cases of niche construction (e.g., Gerbault et al 2011). Here we propose that for agricultural Europeans the failure to provide a strong behavioral response to anemia led to a genetic adaptation that eventually allowed for more successful milk and grain utilization.

The Agricultural Revolution of 11,000 years ago initiated the most dramatic change in the human diet since the adoption of a high meat regimen some two million years earlier (Cordain et al 2002). At the time of the Neolithic Revolution a sudden dietary shift occurred, from the Paleolithic and Mesolithic hunter-gatherer foods with high independence on meat and/or shellfish (Stiner et al 2000; Cordain et al 2000; 2002; Eaton and Eaton 2000) that provide rich sources of iron (U.S. Department of Agriculture, Agricultural Research Service. 2012) to primary dependence on grain and milk products. The bio-archaeological record clearly demonstrates that human populations, European in particular, were highly dependent on meat or and seafood resources during the Late Paleolithic and were only slightly less so during for the Mesolithic (Price 2000; Richards et al 2005). These diets would have provided ample sources of iron and few sources of phytates so that iron-deficiency anemia would be expected to have been less common.

The switch to farming resulted in a shift in the diet from one higher in iron-rich foods to one higher in carbohydrates but poorer in iron. Bovid milk is virtually devoid of

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iron (Fox 1955; Pennington et al 1987). Additionally, calcium present in milk inhibits iron intake and iron ingestion from bovid milk, but lactoferritins present in human milk adequately supply the child with iron at a level two and a half times higher than from cow's milk (Hallberg et al 1992).

Fresh milk ingestion early in the Neolithic must have been difficult for adults but gradual increase of the lactase persistence (LP) allele, primarily the -13910 C>T mutation allowing production of lactase beyond childhood, would have facilitated ingestion. Early on when the LP allele was in low frequencies reduction of lactose content could be accomplished by transformation of milk to yogurts, cheeses, butter and alcoholic beverages (Kolars et al 1984).

Once adopted, the transition to agriculture was extremely rapid and complete in Britain (Legge 1981, 2008; Brown 2007; Schulting and Richards 2002) and elsewhere in Northern Europe (Whittle 1996; Price 2000; Richards et al 2003; Bogaard and Jones 2007; Rowley-Conway 2011). Dates for the first evidence of dairying coincide with the first evidence of grain utilization in Britain. Both appear to have arrived around or slightly before approximately 4000 BC and increased in prominence for the next thousand years (Brown 2007). Analysis of lipid residues in ceramic shards show evidence of fats derived from milk or milk products from the earliest Neolithic horizons (Copley et al 2003; Soberl and Evershed 2009). Later sites of Stanwick (Iron Age to Roman) and West Cotton (late Saxon to Medieval) show a substantial continuation of the dairying tradition (Dudd and Evershed 1998).

The archaeology of Central Europe paints a similar dietary history (Schibler 2006). The Arbon 3 site in Switzerland, dated to the Late Neolithic (3384-3370 BC) also

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shows signs of milk lipid residues on pottery (Spangenberg et al 2006). Other archaeological evidence for early milk processing in Central Europe has been found in ceramic sieves of the LBK Culture dating earlier than 4500 BC that are similar to historic period strainers used to separate curd lumps from lactose-rich liquid whey (Bogucki 1984; Sherrat 1981) and may be an indicator of milk processing to a lower lactose product. Earliest dates for milk processing comes from Northwest Anatolia and southeastern Europe dated at 6000 to 6500 BC (Evershed et al 2008). The hooks of *Galium aparine* (Goosegrass), a plant commonly found in LBK Neolithic sites (Colledge et al 2005), was used by ancient Greek shepherds and modern Swedes as sieves to filter milk (Grieve 1971:207),

Plant sources of ascorbic acid may ameliorate negative effects of iron depletion by phytates. However, as farming spread from Southwest Asia into Central and Northwestern Europe, an increasingly impoverished version of the original Neolithic Crop Package is carried out of the Fertile Crescent. Only two of the five original grains, three of the original five pulses and about a third of the non-crop/weed taxa are found in LBK sites. Colledge et al (2005) ascribe this depletion to a combination of inhospitable northern climate and cultural preference. Because of the difficulty in sampling biases, they also only use a present/absent datum for plants at each site.

Colledge et al (2005) also note the difficulty in ascribing dietary roles to other plant remains that they cautiously call "other plants or weeds." Surely other plants were used either as foods or as medicines or ceremonially. Leafy plants must have been used in warmer seasons, but oxalates or other chelating compounds are commonly present in plants such as rhubarb or seeds such as acorns and may have been used sparingly.

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Conversely, many plant parts contain ascorbic acid that would have facilitated absorption of iron (Grieve 1971; Hopping and Ruliffson 1966).

Both the LP and *HFE* mutations appear at or after the adoption of milk-based agriculture in the Middle East or Europe, though estimates vary widely. The European lactose persistence gene (-13910 C>T) is dated from 8000 or 10,000 years BP (Holden and Mace 1997) to about approximately 4310-6730 years BP (Itah et al 2009) and the *HFE* C282Y mutation at from 1000 to 4000 years ago (Thomas et al 1998; Rochette et al 1999; Pietrangelo 2004; Ajioka et al 1997; Toomajian et al 2003) to over 6000 years ago (Distante et al 2004). Earlier, Raha-Chowdhury and Gruen (2000:87) found 23 mutations in 730 meioses, suggesting an age for the original C282Y mutation of approximately 200-250 generations earlier, or roughly 6000+ years ago, assuming 30 years per generation. If *HFE* has been the subject of strong selection the more recent dates for mutation may be overly conservative (Maruyama 1974).

The earlier estimated mutation dates for *HFE* would coincide with the arrival of agriculture in Britain or its earlier existence appearance on the continent (James 1997; Cunliffe 2003; Thomas 2003) and the Middle East. Klitz, et al (1992) estimated the ages of the HLA-A and HLA-B complexes which are closely-linked with *HFE* and concluded that their spread corresponds chronologically with the spread of agriculture from the Middle East, approximately 10,000 years ago (Sokal et al 1991). The extremely low frequencies of the C282Y allele in the Mediterranean and Near East argue against an early farming origin in these regions. The H63D mutation is more widespread within the populations described, but exhibits a less structured distribution; it appears to be much older, having arisen several thousand years earlier (Rochette et al 1999; Candore et al

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2002). If the H63D geographical distribution resulted from positive selection, its spread would be relatable to an event independent of and earlier than dairying.

Two major bioarchaeological skeletal indicators of iron deficiency increase dramatically in the Early Neolithic relative to earlier periods (Stuart-Macadam 1998). Both porotic hyperostosis and cribra orbitalia appear to have been almost completely absent in the central European Mesolithic, but are common in the early Neolithic (Wittwer-Backofen and Tomo 2008). A similar pattern is observed in the Eastern Mediterranean (Angel 1984), Iraq and Iran (Rathbun 1984), Estonia (Jankauskas and Palubeckaité 2006) and the Ukraine, even before evidence of dense settlements that would be have been associated with increased parasitization (Zvelebil and Lillie 2000:81). Central European communities remained small for long periods and did not enlarge to the level of permanent towns until the Late Bronze Age, about 800-600 BC (Wells 1984:38). Urbanization did not arrive in the British Isles until the founding of Londinium by the Romans (Wells 2008:88-120).

These two bioarchaeological markers may indicate dietary deficiencies of either vitamin C (ascorbic acid) or iron. However, functionally the two nutrients are linked because vitamin C is important in iron ingestion and metabolism, and a decrease in vitamin C would leads to a reduction in the physiological bioavailability of iron (Prom-U-Thai 2006). Addition of vitamin C to the diet reduces the chelating effect of phytates on iron metabolism (Macfarlane et al 1988).

Another trend in skeletal morphology from Upper Paleolithic to Neolithic in Europe is a steady decrease in stature (Meiklejohn and Babb 2011) and has also been reported as a general trend elsewhere (Ruff 2002), but because a number of competing

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environmental stresses may result in a generalized decrease in stature, by itself this cannot be considered a definitive indicator of nutritional inadequacy (Brues 1959; Frayer 1981). However, in New World populations the most significant skeletal factor associated with stature suppression is anemia (Steckel et al 2002). The role of iron in stature diminution is not known. Because iron is found in bone collagen rather than in the mineral portion of bone (Klepinger 1984; Ezzo 1994), it is likely to be involved in the growth process. Recently Cippa and Krayenbuehl (2013) found that Swiss male and female C282Y homozygotes on average were 4.3 and 3.3 cm taller, respectively, than age- and sex-matched controls suggesting an important role of hemochromatosis, and by implication, iron in growth. Iron is water-soluble and is rapidly leached from or absorbed into bone after death making paleo-osteological analysis of bone for iron content dubious (Klepinger 1984).

Parasites form a significant risk for iron loss and anemia in modern, densely settled populations (Kent 1986; Awasthi and Bundy 2007). Early to Middle Neolithic settlements in Central Europe seem to have consisted primarily of isolated households or small groups of houses, but by Late Neolithic some settlements appear to have experienced a rapid growth in size and density (Bogaard 2004:11,13, 16-17). The incidence of parasitism as an aggravating factor would be expected to intensify through the Neolithic as population densities rose and settlements were inhabited for longer periods of time, resulting in an additional factor contributing to dietary stress (Holland and O'Brien 1997; Gonçalves et al 2003). The extent of this effect is difficult to measure, but should not be forgotten. However, paleopathological signs of anemia appear in the European Neolithic context well before settlement size and density could be considered

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to have been major factors affecting the frequency of the skeletal indicators of dietary stress discussed above. (Zvelebil and Lillie 2000:81).

Iron may leach from cooking vessels and provide an indirect dietary source. While the Early Iron Age began in Central Europe at 600 BC, bronze and ceramic remained the primary materials for cooking vessels until after 400 BC when iron became readily available (Wells 1984:119, 135). Despite the widening use of iron vessels, indicators of anemia continued to be present in archaeological and European historical populations through the 19th century, as in continental Roman (Miritoiu 1992), British Roman and Medieval (Stuart-Macadam 1991; Wells 1982; Lewis 2002; Roberts and Cox 2003; Hart and Holbrook 2011) and industrial (Molleson and Cox 1993; Lewis 2002) skeletal series with some pre-adult series showing cribra orbitalia frequencies between 50 and 60% in children (Lewis 2002).

In the Middle East and Eastern Mediterranean cribra orbitalia values vary from 0% in the Iranian Paleolithic to 100% in the Levant Neolithic; no post-Paleolithic sample had a value less than 8% and most were in the 20-40% range (Papathanassiou 2005). Greek Neolithic series have the cribra orbitalia and porotic hyperostosis lesions reaching prevalences of 40% to 50% (Papathanasiou 2003). A small Polish skeletal series yielded cribra orbitalia frequencies of 59% for the Neolithic and 44% for the Early Bronze samples (Glén-Haduch et al 1997).

Hemochromatosis is not found among East African herders who do utilize milk and, have a different LP lactase persistence mutation, thus possibly indicating an independent milking and dairying history. The frequency of anemia in these populations is not expected to be present at the levels observed in European and Europe-adjacent

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populations, due at least in part, to the practice of mixing bovine blood with milk before ingestion (Little and Leslie 1999), thus fortifying iron-poor milk with a supply of iron-rich blood. Here a cultural adaptation has eliminated the necessity for a genetic resolution, as predicted by Laland and Brown (2006:95; 2012). It appears that Africans were able to directly solve the anemia problem culturally while Europeans may not have done so.

While over three quarters of hemochromatosis patients are homozygotes for the C282Y allele, among Europeans the vast majority of alleles are carried by C282Y/wt heterozygotes, a ratio of approximately 23.5:1 (9.2/0.4). If double heterozygotes (C282Y/H63D) are included the ratio increases to 27.5:1 (9.2 + 1.8/.4) (Hanson et al 2001). Thus, selection will have the most likely opportunity to act on the heterozygote phenotype.

HFE induces higher absorption of iron into the body than the wild-type ("wt") allele. This is so in the homozygous state (282/282), double heterozygous state (282/63) and, to a lesser so extent, also in the heterozygous state (282/wt) (Cartwright et al 1979; Raddatz et al 2003).

Iron dietary absorption is similar in wt or heterozygote C282Y carriers, although the studies have included only very small sample sizes. Roe et al (2005) found no significant differences in most absorption measures but heterozygotes had consistently higher pre-test values (initial serum iron 11%, serum ferritin 13% and transferrin saturation13% higher) and increased post-test intake of Fe-57 (12%) and Fe-54 (8%); they noted that increasing sample size from their 30 subjects to 332 would yield statistically significant results. Heterozygotes also had a significantly increased ability to

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absorb non-heme iron but not heme iron. In a meat-deficient diet non-heme iron would be the significant or major source of iron (Roe et al 2005).

Heterozygotes have serum iron concentrations 17 µg/dL higher and mean transferrin saturation 9% higher than wt/wt homozygotes. In both measures there is a progressive increase in values from wt/wt, H63D/wt, C282Y/wt, H63D/H63D, C282Y/H63D and C282Y/C282Y genotypes; the increase is especially noticeable in the last two genotypes (Bulaj et al 1997; Edwards et al 2000; Adams et al 2005).

Blood iron levels are highest in homozygotes but are also elevated in heterozygotes. Mean ferritin levels are the best estimate of body iron stores, (McDonnell and Witte 1997), and are closely associated with clinical manifestations (Bradley, Hadlow and Palomaki 1996). The proportion of ferritin levels are significantly elevated in heterozygous males 31 to 60 years old and females 31 to 90 years old. In other 30-year groups there are no significant differences between heterozygotes and wt homozygotes. Serum iron and transferrin saturation are both higher in heterozygotes for all age categories from 1 to 90 in both sexes (Cartwright et al 1979; Bulaj et al 1996).

Proportion of individuals with anemia (sub-normal serum ferritin concentrations of < 12µg/L) is lower in female heterozygotes than wt/wt normals (21% vs. 32%, respectively; p = 0.02). In males 2% of heterozygotes have low serum ferritin concentrations compared with 4% of normal, a result not statistically significant (p = 0.44) (Edwards et al 2000; Bulaj et al 1996). Iron deficiency is less common in heterozygous women in screening tests conducted in California and Australia; (Rossi et al 2000; Rossi et al 2001; Beutler et al 2000).

Heterozygotes almost never present clinically but there are two possible effects that may be triggered by environmental factors, especially high levels of alcohol consumption. One is direct damage by an elevated iron concentration and the other is ailments associated with hemochromatosis homozygotes (hepatic fibrosis, steatohepatitis, diabetes, and arthritic pain and associated arthritic symptoms) (Barton et al 1994).

To summarize, heterozygotes have slightly but significantly elevated values of iron storage and circulation but little evidence of pathological sequelae. Fewer heterozygous women are anemic but men show no difference.

While increased iron intake uptake is almost universal in C282Y heterozygotes and homozygotes, today few die from symptoms related to hemochromatosis. During adulthood, especially after age 40, the excess iron accumulation in the tissues of the body can produce the serious or potentially lethal sequelae of classic hemochromatosis: including general fatigue, cirrhosis, liver fibrosis and cancer, cardiac disease, changes in pigmentation, orthopedic complications, and, in men, reduced libido and impotence (Adams et al 1997; Buettler et al 2002; Kelly et al 1984). Manifestation of these clinical symptoms is extremely variable presenting clinically in 1.2% of homozygotes or less (McCune et al 2002; Anderson et al 2004). Indeed, while increased iron intake is almost universal for all carriers, they rarely present clinically in either the homozygous (Beutler et al 2002) or heterozygous (Bulaj et al 1996) states. Thus, there is high penetrance for increased iron absorption, but low penetrance for manifestation of clinical symptoms (Adams and Barton 2007).

Severity of symptoms depends upon whether the mutation is found on an ancestral haplotype (Barton et al 1996; Piperno et al 1996), the presence of other

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modifying genetic factors (e.g., Merryweather-Clarke et al 2003; Pelucchi et al 2012; Livesey et al 2004) and environmental influences such as alcoholism (Adams and Agnew 1996; Adams and Barton 2007).

Health-affecting symptoms seldom manifest before age 40, so that reproductive capacity is not negatively affected in the most productive years (Edwards et al 2000). The beneficial effects of carrying some variety of the *HFE* mutation are probably manifested in the early and reproductive years. Although survival even beyond the childbearing years can have a positive effect on evolutionary success (Hawkes 2003, 2004; Kaptijn et al 2010) selection preferentially favors attributes that directly influence generative capacity during reproductive years. These chronic conditions associated with hemochromatosis may have a negative influence late in life, but not until after the majority of the childbearing years have passed. Thus, a balance between the positive effects of increased iron early in life and negative effects of clinical manifestations in middle to late adulthood may be struck.

Despite the increasing risk of clinical sequelae with age, there may be no additional risk of death. Studies in France (Coppin et al 2003), Holland (Van Aken et al 2002), Germany (Niederau et al 1996; Niederau et al 1985), Italy (Fargion et al 1992) and Canada (Adams et al 1991) found no change in proportion of *HFE* carriers in the population with advancing age and thus weak selection against them.

A problem with our analysis is the absence of LP data from major European countries. While we have *HFE* data for Norway, Iceland, Holland, Switzerland, Spain and Portugal, we have no LP information for comparison. We may guess the appropriate values, but having the actual data would be extremely useful as a retest of our hypothesis.

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Conclusions

Both the C282Y *HFE* allele and LP phenotype are more common in Northwestern Europe where bovid dairying practices are ancient and widespread (Beja-Pereira et al 2003) and reduced in southern Europe where fresh milk products are have historically been more difficult to preserve and less commonly consumed (Kindstedt 2012:12).

Dairying became a major food source in the European Neolithic. Before mutation of the LP locus, maximum utilization of unprocessed milk was not possible, but with the mutation of the LP locus it became so (Gerbault et al 2011). Unless artificially fortified, non-human sources of milk are deficient in iron. As soon as there is evidence of early dairying in Europe there is strong evidence of iron deficiency in skeletons of the same period, in the form of porotic hyperostosis and/or cribra orbitalia. As iron-deficiency anemia is a potentially life-threatening condition, we suggest that the C282Y mutation of the *HFE* gene, which induces higher absorption of iron into the body than the wild-type ("wt") allele, was an advantageous change in the genome in the dietary context arising in the Neolithic and that this fact explains why *HFE* is so common in areas in which milk ingestion has been historically common.

In conclusion, despite ethnic-based hypotheses regarding the origin and spread of the *HFE* C282Y variant (Whittington 2006, Milman and Pedersen 2003, inter alia) we suggest the high prevalence of hemochromatosis is directly related to the adoption of dairying and phytate-heavy grains in the northern Europe diet, where genes increasing iron absorption were favored after foraging was abandoned for the lure of high carbohydrate production and the more productive utilization of milk. In addition, this

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adaptation is potentially a balanced polymorphism, trading the advantage of anemia

avoidance in youth and early adulthood with potentially lethal pathology late in life for a

small proportion of affected individuals.

The genes associated with hemochromatosis and lactase persistence are only two

of a number of loci that have been seriously affected by the adoption of agriculture. Other

notable examples are the increased number of amylase repeats (Perry et al 2007) and milk

proteins in cattle (Beja-Pereira et al 2003). It seems clear that there are many other falling

ancestral dominos to be discovered in this evolutionary cascade precipitated by

agriculture in Northern Europe and elsewhere (Cochran and Harpending 2009; Voight et

al 2006; Wang et al, 2006; Weinberg 1999).

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Table 1. List of samples along with sample sizes, allele frequencies (%) and references for the HFE (C282Y) allele used in the analysis.

Population	Sample Size	C282Y Allele Frequency	Reference
England, Northeast	117	7.7	Grove et al 1998
England, Birmingham	368	6	Merryweather-Clark et al 1997
England, East Anglia, Norwich	200	8.5	Willis et al 1997
England, Oxford	330	10	Mullighan et al 1998
Northeast Scotland, Aberdeen	188	1.4	Merryweather-Clarke etal 2000 Miedzybrodzka et al 1999
Northern Ireland	404	9.9	Murphy et al 1998
Orkney Islands	103	4.9	Merryweather-Clarke et al 2000
Ireland	45	10	Merryweather-Clarke et al 1997
Ireland	150	6	Merryweather-Clarke et al 1997
Ireland	800	11.4	Merryweather-Clarke et al 2000
Ireland	1119	10.1	Merryweather-Clarke et al 2000
Ireland, Dublin	109	14	Ryan et al 1998
Ireland, Dublin	411	10.9	Byrnes et al 1999, in Byrnes 2001
Ireland, Dublin	100	10.4	Byrnes et al 2001

Finns, Jyvaskyla	38	0	Merryweather-Clarke et al 1997
Finland, Kuopio	1361	3.4	Tuomainen et al. 1999
Finland, North	173	5.2	Beckman et al. 1997
Finland, Oulu	128	5.1	Parkkila et al 2001
Denmark	876	5.6	Pedersen et al 2008
Denmark, Aalborg	200	6.8	Steffensen et al 1998
Denmark, Aalborg	219	8.2	Merryweather-Clark et al 1999
Denmark, København	37	9.5	Merryweather-Clark et al 1997
Denmark, København	420	6.2	Simonsen et al 1999
Denmark, København	9174	5.6	Ellervik et al 2001
Denmark, København	1889	5.7	Milman et al 2005
Sweden	358	5.2	Merryweather-Clarke et al 2000
Sweden, Stockholm	117	3.8	Cardoso et al 1998
Sweden, Umea	206	7.5	Beckman et al 1997
Swedish Saami	151	2	Beckmann et al 2001
Germany, Bremen	53	1.9	Merryweather-Clark et al 1997
Germany, Hsmburg	157	4.8	Nielsen et al 1998
Germany, Frankfurt	153	2.6	Gottschalk et al 1998
Germany, Frankfurt	251	3.6	Gottschalk et al 2000

Germany, Cologne	250	3.2	Höhler et al 2000
Germany, Göttingen	500	4.6	Raddatz et al 2003
Germany, Central	126	2.4	Hellerbrand et al 2001
Germany, East	425	3.8	Merryweather-Clarke et al 2000
Germany, East	115	4	Merryweather-Clarke et al 1997
Germany, Bavaria	62	5.6	Merryweather-Clarke et al 1997
Germany, Regensburg	180	7.2	Braun et al 1998
Austria, Salzburg	271	4.1	Datz et al 1997
Austria	487	4.8	Kazemi-Shirazi et al 1999
Czech Republic	139	5	Zdarsky et al 1999
Czech Republic	100	4.5	Hrachovinova et al 1999
Czech Republic, Prague	254	3.9	Cimburova et al 2002
Hungary	277	5.6	Tordai et al 1998
Hungary, East	304	2.6	Raszeja-Szakony et al 1999
Hungary, Budapest	994	3.4	Andrikovics et al 1999
Poland, North	117	4.7	Wyszomirska et al 2008
Poland, Central	871	3.1	Moczulski et al 2001
Roma, Slovakia	367	4.9	Gabriková et al 2012
Roma, Hungary	140	1.1	Szakony et al 1999
Russia, Moscow	850	3.5	Potekhina et al 2005

Russia, Novosibirsk	150	3.7	Mikhailova et al 2003
Russia, Obninsk	260	3.3	Khondrashova et al 2006
Russia, Udmurts	46	0	Merryweather-Clark et al 1997
Russia, Mansis	43	0	Mikhailova et al 2003
Russia, Khantys	53	0	Mikhailova et al 2003
Ashkenazim	381	1.4	Reish et al 2010
Tunisia, Tunis & Nabeul	97	0.5	Zorai et al 2003
Tunisia, Tunis	570	0.1	Sassi et al 2004
Iran, Hormozgan	294	0	Karimi et al 2004
Iran Fars (Shiraz)	506	0	Karimi et al 2004
Iran, Tehran	104	9	Jazayeri et al 2003
France, Paris	126	4	Mercier et al 1998b
France, Amiens	991	5	Merryweather-Clarke et al 2000
France, Toulouse	95	4.2	Borot et al 1997
France, South	60	3.3	Aguilar Martinez et al 1997
France, Catalans	166	2.1	Mercier et al 1998a
France, Brittany	62	5.6	Mercier et al 1998a
France, Brittany	410	7.7	Mura et al 1999
France, Brittany	139	2.9	Moirand et al 1999
France, Brest	7000	7.8	Merryweather-Clarke et al 2000
France, Rennes	1000	6.5	Jouanolle et al 1998

France, West	254	9.4	Jézéquel et al 1998
Italy, Naples	91	0.5	Merryweather-Clark et al 1997
Italy, Rome	139	1.1	Piperno et al 1998
Italy, South	458	1.7	Restagno et al 2000
Italy, South	100	0	Campo et al 2001
Sardinia	61	0.5	Candore et al 2002
Sicily	106	0	Candore et al 2002
Italy	1331	2.1	Restagno et al 2000
Italy, Brescia	114	1.8	Costarelli et al 2007
Italy, Piemonte	104	4.8	Candore et al 2002
Italy, Piemonte	189	1.1	Longo et al 1999
Italy, North	50	1	Carella et al 1997
Italy, Torino	310	2.7	Restagno et al 2000
Italy, Northeast	131	2.3	Borgna-Pignatti et al 1998
Italy, Friuli	100	6	Candore et al 2002
Italy, Emilia Romagna	207	1.7	Candore et al 2002
Italy, Cimbri (Verona)	149	4.8	Pozzato et al 2001
Italy, Genoa	130	4.2	Racchi et al 1999
Italy, Milan	128	0.8	Sampietro et al 1998
Italy, Milan	139	1.1	Piperno et al 1998

Italy, Modena	2100	1.6	Cassanelli et al 2001
Italy, Modena	149	3.4	Pozzato et al 2001
Italy, Monza	606	4.7	Salvioni et al 2003
Greece	139	1.4	Merryweather-Clark et al 1997
Greece	158	0.3	Papanikolaou et al 2000
Greece	196	0.9	Papanikolaou et al 2000
Greece, Alexandropoli	264	0	Papazoglou et al 2003
Greece, Cyprus	57	0	Merryweather-Clark et al 1997
Turkey	31	0	Merryweather-Clark et al 1997
Turkey, Istanbul	158	0	Barut et al 2003
Turkey, Istanbul	138	0.7	Yönal et al 2007
Turkey, Cyprus	39	0	Merryweather-Clark et al 1997
Estonia, West	158	5.1	Mikelsaar et al 1999
Estonia, Southeast	92	4.3	Mikelsaar et al 1999; Pärlist et al
Estonia, Saaremaa	96	2.1	Mikelsaar et al 1999; Pärlist et al
Estonia, Hiiumaa	96	1.6	Mikelsaar et al 1999; Pärlist et al
Estonia, Hiiumaa	442	3.5	Mikelsaar et al 1999
Basques, France, Biarritz	92	1.6	Mercier et al 1998a
Basque, Spain	28	3.6	Merryweather-Clark et al 1997
Basque, Spain	51	2	Baiget et al 1998

Population				
North India	275		0	Gurjeewan et al 2005
Japan, Fukuoka	252		0	Sohda et al 1999
Taiwan, Taipei	596		0.3	Chang et al 1997
China, Linhai	395		0	Lin et al 2007

Table 2. Samples used in the regression analysis – The C282Y values and the

corresponding Lactase Persistence values. Statistical software used to analyze was

StatPlusMac 2009, Build 5.8.3.8.

Population	Number of Studies	Sample Number	C282Y Frequency (%)	Lactase Persistence (%)
England	4	1015	8	95
Scotland	2	1197	10.6	95
Northern Ireland	1	404	9.9	100
Ireland	7	3636	10.5	96
Orkney Islands	1	103	4.9	90
Finland	5	1700	3.6	84
Denmark	8	18835	5.7	96
Sweden	4	931	5.8	93
Saami	1	151	2	31
North Germany	3	919	4.7	91
Central Germany	5	1280	3.7	86
East Germany	2	540	3.8	78

Bavaria	2	242	6.8	86
Austria	2	758	4.5	81
Czech Republic	3	493	4.3	82
Hungary	3	1575	3.6	63
North Poland	1	117	4.7	71
Central Poland	1	871	3.1	63
Roma	2	507	3.9	44
Russia, Russians	3	1260	3.5	42
Russia, Udmurts	1	46	0	41
Russia, Mansis	1	43	0	28
Russia, Khantys	1	53	0	29
Ashkenazim	3	381	1.4	16
Tunisia	2	667	0.2	16
Iran	3	904	0	14
North France	2	1117	4.9	78
South France	3	321	2.9	43
France, Brittany	6	8865	7.6	78
South Italy	7	3112	1.5	52
Sardinia	1	61	0.5	14
Sicily	1	106	0	29
North Italy	17	8614	3.1	49
Greece	5	814	0.5	13

Turkey	4	366	0.3	31
Estonia	4	442	3.5	50
Basques	3	171	1.5	89
North India	1	275	0	55
Thailand	1	154	0	2
Japan	1	252	0	28
Taiwan	1	596	0.3	12
China	1	395	0	8

Table 3. Correlations of HFE allele C282Y and Lactase Persistence partialled by 19 other

loci for which there are at least 16 comparable samples. Chromosome loci from OMIM;

Table numbers from Roychoudhury and Nei (1988).

Type	Locus	Allele	Sample Number	Chromosome Locus	Rp Value	Significance	Table #
Enzyme	ACP1 (1)	a	22	2p25	.726	***	2
	ADA (2)	1	24	20q13.11	.832	***	6
	AK 1 (3)	1	24	9q34.13	.758	***	7
	C1 (4)	u	18	3q25.2	.84	***	20
	ESD (5)	1	22	13q14.2	.695	**	29
	GPT (6)	1	26	8q24.3	.921	***	42
	GLO1 (7)	1	19	6p21.3	.653	**	47
	PGD (8)	A	22	1p36.2	.744	***	64

Protein	PI (9)	M	20	14q32.1	.835	***	77,77.1
	Gc (10)	Gr2	28	4q12	.794	***	104,104.1
	HPA (11)	2	25	16q22.1	.649	***	105,105.1
	BF (12)	S	26	6p21.3	.902	***	127
	T (13)	C	26	6p22.2	.807	***	136
Blood Gp.	ABO (14)	O	25	9q34	.8	***	141
	LU (15)	Lu(a)	16	19p13	.686	**	154
	MNS (16)	MS	23	4q28	.773	***	156
	P (17)	P1	22	3q25	.636	**	158
	RH (18)	cde	23	1q36.2	.558	**	159
Misc	PTC (19)	T	20	7q24	.765	***	217

** = < .01

*** = < .001

(1) Acid Phosphotase (ACP1); (2) Adenosine Deaminase (ADA); (3) Adenylate Kinase 1; (4) Cholinesterase (serum) 1; (5) Esterase D (ESD); (6) Glutamic Pyruvate Transaminase (GPT); (7) Glycoxalase I (GLO1); (8) Phosphogluconate dehydrogenase (PGD); (9) Alpha-1 Antitrypsin (PI); (10) VDBG (Gc); (11) Haptoglobin, alpha (HPA); (12) Properdin Factor B (BF); (13) Transferrin; (14) Landsteiner ABO; (15) Lutheran (LU); (16) MNSs (MNS); (17) P System (P); (18) rhesus system (RH); (19) PTC Sensitivity.

Figure 1. Lactose Persistence Frequency by C282Y Allele Frequency. Linear Regression:

$r = .86$, $r^2 = .68$, $t = 9.23$; $F = 85.19$, d.f. $= 41$, $p < 0.0001$