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LETTER TO THE EDITOR

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The evolutionary adaptation of hemochromatosis associated mutations during the neolithic

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In a recent paper (Heath, Axton, McCullough, & Harris, 2016), the spread of the C282Y allele in Europe was considered as a genetic adaptation to the chilly and damp environments of Neolithic Europe, where adequate iron was required for thermoregulation. The C282Y allele frequency has an inverse linear relationship with mean daily temperatures, an inverse linear relationship with the mean maximum temperatures, and a linear relationship with mean wet days per year.

Many genetic polymorphisms in Europe are characterized by a North–South gradient, such as pigmentation of hair and eyes (Cavalli-Sforza, Menozzi, & Piazza, 1994). Correlations do not always offer an explanation for the observed findings. There are some facts which plead against the C282Y climate hypothesis.

A similar mutation occurred in Sub-Saharan Africa, where a ferroportin *Q248H* mutation, which has a strikingly similar biological effect, causes hemochromatosis type IV, which was spread all over Western, Central, and Southern Africa during the Bantu Trek (2000 BC–AD 1000) (Gordeuk et al., 2003). Here, the average temperature is much higher; a lowering environmental temperature cannot have been a driver since the *Q248H* mutation initially moved toward the equator. In the cold climates of Central Asia, hemochromatosis-like conditions causing iron overload are very rare (Lok et al., 2009).

Heath et al. use rather artificial national averages based on present-day European states. In this way, contributions of Celtic minorities are diluted into pooled national data and are underrepresented in the final statistics. The sunny North Portugal, with a C282Y allele frequency of 5.8% (Cardoso et al., 2001), which has a mild Mediterranean climate, has a higher allele frequency than many North European countries like Denmark or the Orkney Islands. Similarly, the sunny Jersey Island has the double C282Y allele frequency than the cold and rainy Orkneys (Heath et al., 2016). These findings plead against a climate driven spread of C282Y in Europe.

In HFE hemochromatosis, the clinical penetrance of symptoms of iron-loading disease is relatively low and highly variable. Large studies of newly diagnosed C282Y homozygotes have obtained data showing that penetrance occurs in 24–43% of males and 1–14% of females (Rossi, Olynyk, & Jeffrey, 2008). Current evidence suggests a limited role for digenic inheritance of mutations in iron homeostasis genes in modifying the penetrance of HFE hemochromatosis.

In case of hemochromatosis, iron overload does not spread uniformly over the human body. It is remarkably that *HFE*-linked hemochromatosis patients display a widespread tissue iron overload, but rather limited iron storage in macrophages and enterocytes until later stages of the disease (Valberg, Simon, Manley, Corbett, & Ludwig, 1975). In this respect, the HFE mutation could be regarded as a protection mechanism against siderophilic infections (Lettinga et al., 2002).

The role of iron conservation as a driver in human evolution is further highlighted by the transient gene equilibrium of other iron conserving mutations like the haptoglobin-2 allele (Langlois & Delanghe, 1996).

Apart from providing iron storages (which may help to recover from blood loss and anemia), HFE may play an important role in immune defence. Next to climatological explanations, biological factors may play a causative role in the spread of C282Y in Northwestern Europe.

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