HOMO - Journal of Comparative Human Biology 68 (2017) 38–41

Contents lists available at ScienceDirect

HOMO - Journal of Comparative Human Biology

journal homepage: www.elsevier.com/locate/jchb

C282Y/H63D hemochromatosis mutations and microevolution: Speculations concerning the Basque population

F. Bauduer[a,b,*]

[a] UMR 5199 PACEA, University of Bordeaux, Pessac, France
[b] Department of Hematology, Centre Hospitalier de la Côte Basque, Bayonne, France

ARTICLE INFO

Article history:
Received 10 August 2016
Accepted 8 December 2016

Keywords:
Basques
Hereditary hemochromatosis
Microevolution
Population genetics

ABSTRACT

The Basques live at the Western extremity of the Pyrenees. According to linguistic and genetic data they could be considered as one of the most ancient European populations. Numerous studies have evidenced particular patterns in the frequency of several genetic polymorphisms in this relatively unmixed human group. We discuss herein the puzzling distribution of the two major hemochromatosis *HFE* mutations associated with hereditary hemochromatosis. Thus, one can observe a low frequency of C282Y and, in contrast, one of the highest European frequencies of H63D. Genetic drift (enhanced by the long history and the small size of this population), long persistence of Paleolithic iron-rich diet, lower exposure to major infectious threats and limited mixing with both Celts and Vikings (who demonstrate the highest prevalence of C282Y) could be the underlying factors explaining these particular genetic features. Historical and environmental data represent key elements for understanding the role of the different evolutionary forces which shape the genetic profile of human populations.

Background

Hereditary hemochromatosis (HH)

HH is an autosomal recessive disorder caused by mutations in the *HFE* gene which induce a progressive iron accumulation in a series of tissues resulting ultimately in severe organ damage. Two missense mutations, C282Y and H63D, account for most cases of HH (Bomford, 2002). C282Y homozygosity (C282Y/C282Y) is found in the vast majority of HH cases, C282Y/H63D and H63/H63D rarely causing symptomatic iron overload (Bomford, 2002). The distribution of C282Y is similar to that of HH but elevated H63D frequencies may be found among populations demonstrating a low prevalence of HH (Merryweather-Clarke et al., 1997).

* Correspondence to: F. Bauduer, Department of Hematology, Centre Hospitalier de la Côte Basque, 13 Avenue J. Loeb, 64100 Bayonne, France.
E-mail address: frederic.bauduer@u-bordeaux.fr

http://dx.doi.org/10.1016/j.jchb.2016.12.004
0018-442X/

C282Y and H63D mutations

The C282Y mutation seems contemporary to the Neolithic agricultural revolution (Distante et al., 2004). There is a negative gradient of distribution of this mutation from Northern toward Southern part of Europe (Lucotte, 2001). It is at its highest frequency in the Irish population (about 10%) (Merryweather-Clarke et al., 1997) but is also prevalent in other populations of Celtic origin from French Brittany and United Kingdom or in individuals of Viking descent (Lucotte, 2001). Thus, there were speculations about its "Celtic" versus "Viking" origin (Lucotte and Dieterlen, 2003). According to Whittington (2006), this Irish-origin polymorphism could have been transmitted to Vikings explaining its high frequency in today Celtic populations and Scandinavians. For Milman and Pederen (2003) it originated from Southern Scandinavia and was disseminated with Viking migrations.

H63D seems considerably older than C282Y and demonstrates a worldwide distribution due to a multicentric origin (Rochette et al., 1999). It is highly prevalent in Europe (10–30%) especially in Mediterranean countries, but is also present in North Africa, the Middle East and some regions of Asia (Merryweather-Clarke et al., 1997; Rochette et al., 1999). Its highest frequency is observed among Spaniards and Basques (Aguilar-Martinez et al., 1999). The H63D mutation may have occurred at least twice: once in the Mediterranean area and once in some part of Asia (Rochette et al., 1999).

The Basques

The Basques who live at the Western end of the Pyrenees in France and Spain have been considered as European 'outliers' by population geneticists (Cavalli-Sforza et al., 1994). They demonstrate a series of genetic particularities (i.e., a genetic fingerprint) which are attributed to their pre-Neolithic local settlement and limited genetic mixing especially with the Near East Neolithic immigrants (Bauduer et al., 2005a; Cavalli-Sforza et al., 1994; Wilson et al., 2001). In the Western Pyrenees, farming may have spread more through cultural transmission than through migration (Wilson et al., 2001). Thus, the extant Basques express the lowest frequency of chromosome Y-associated Neolithic haplotypes (Alonso et al., 2005; Semino et al., 2000). On the other hand, a recent study performed on eight skeletons of early farmers from Atapuerca using genome-wide sequencing suggests that Basques may rather relate to Neolithic groups (Günther et al., 2015). In addition, a relative genetic isolation was maintained throughout the subsequent historical periods (Adams et al., 2008; Bauduer et al., 2005a; Botigué et al., 2013; Cavalli-Sforza et al., 1994; Chikhi et al., 2002; Günther et al., 2015; Martinez-Cruz et al., 2012).

The Basques have one of the lowest frequencies of the C282Y allele in Europe (around 1.6%) (Mercier et al., 1998) and, on the other hand, the highest frequency of H63D at about 30% (de Juan et al., 2001; Merryweather-Clarke et al., 1997). Hereditary hemochromatosis (HH) is rarely encountered in the Basques (Bauduer et al., 2001) and the prevalence of C282Y in HH Basque patients is significantly inferior to that seen on average in European patients (Bauduer et al., 2005b).

Hypothesis

The evolution of genetic structure in human populations depends, besides mutations, on three evolutionary forces: random genetic drift, natural selection and gene flow (Cavalli-Sforza et al., 1994). We will speculate on the respective role of these three factors in order to explain the particular distribution of *HFE* mutations in the Basques.

Discussion

Extreme frequencies of C282Y and H63D as indicators of genetic drift

The effect of drift is significant after a long period of time among small and isolated populations. This phenomenon reduces the intra-population genetic diversity (and in contrast increases inter-population distances); ultimately it tends to fix some alleles (frequency near 100%) or to eliminate other ones.

The genetic Basque profile has been shaped by a marked effect of drift (Bauduer et al., 2005a; Cavalli-Sforza et al., 1994; Chikhi et al., 2002). Drift has been also implicated for explaining the similar *HFE* profile of *Chuetas* (Majorcans of Sephardic origin) who demonstrate a high H63D frequency (about 26%) and an absence of C282Y (Matas et al., 2006). In addition, when studying the distribution of *HFE* mutations in Slovenia, Cukjati et al. (2007) found a significantly higher frequency of H63D in the isolated mountainous region of Koroska characterized by a low genetic admixture (21.3% versus average 12.8%, $p = 0.005$).

C282Y and natural selection

The relative high frequency of C282Y seen in Europe could have been favored by (recent) positive selection (Rochette et al., 1999) presumably via an indirect mechanism (Williamson et al., 2007). Heath et al. (2016) focused on the role of adaptation to culture and climate during the Neolithic period for explaining the spread of this allele. Interestingly, iron is implicated in two major functions in the human body: the production of red blood cells and the host defense against microbes (Ganz, 2013). Iron is a key element within the hemoglobin molecule. This element comes from diet, especially meat, and its absorption may be disturbed by some vegetal components. The major way of iron depletion is blood loss (menses, intestinal bleeding