To the editor:

Homzygous deletion of HFE: the Sardinian hemochromatosis?

Type 1 hemochromatosis is generally due to homzygous p.C282Y mutation in HFE.1,2 We report the case of a young woman with a classical hemochromatosis phenotype due to a homzygous deletion in the 6p chromosome region containing HFE.

The proband is a 29-year-old woman of Sardinian (Italian) origin. At the age of 27, serum iron was 33.2 μmol/L (186 μg/dL), serum ferritin 3146 pmol/L (1400 μg/L), and serum alanine aminotransferase (s-ALT) 70 U/L. Diagnosis of hemochromatosis was confirmed at subsequent analyses including magnetic resonance. A test for HFE mutations (NLM, Settala, Italy) gave no signal. There were no indications of secondary iron overload. She began phlebotomies every 2 weeks and after 3.5 g of iron removal serum ferritin decreased to 422 pmol/L (188 μg/L), s-ALT normalized (23 U/L), whereas serum iron did not change (36 μmol/L [201 μg/dL]), indicating she was not iron-depleted. Nevertheless, therapy was stopped, and after 3 months serum ferritin raised to 1229 pmol/L (547 μg/L). She came to our attention in June 2008. She denied family consanguinity up to the fifth generation. Her grandparents originated from different regions of Sardinia.

After obtaining informed consent, we analyzed her DNA sample for pC282Y and pH63D by real-time polymerase chain reaction (PCR; Celbio, Milano, Italy), confirming the absence of signal and suggesting a deletion in HFE-containing region. By analyzing several polymorphic markers centromeric and telomeric to HFE, we roughly define the upstream and downstream limits at 26 181 749 and 26 225 235, respectively. Meanwhile, Le Gac et al3 reported a very similar rearrangement in a different woman from Sardinia. By using their primers (gap-F and gap-R) and those for HFE exon 5,4 we confirmed that the proband was homzygous and her parents heterozygous for a gross deletion (Figure 1). To better mark deletion boundaries, we designed an internal forward primer and confirmed, by sequencing, that the proband and her parents had the same deletion [Chr6 g.(26 175 442)_g.(26 208 186)del] reported by Le Gac et al.3

The patient we describe in the present report showed a more marked iron overload than that described by the French group, as indicated by the higher serum ferritin and iron removed despite her younger age, supporting the role of modifier factors in modulating phenotype expression in HFE-related hemochromatosis.5 The absence of close consanguinity within the present family and, as far as we could assess, with the case reported by LeGac et al,3 suggest that this deletion is present at the population level in Sardinia and may derive from a common ancestor. Sardinian population is an ancient genetic isolate, and the few data available indicate that p.C282Y mutation is very rare or even absent.6 Thus, it is possible that the deletion might be the most common cause of hemochromatosis in this geographic area. However, considering the mechanism of deletion, it cannot be excluded it can result from multiple mutational events and explain other hemochromatosis cases.

References

5. Milet J, Dehais V, Bourgain C, et al. Common variants in the BMP2, BMP4, and HVJ genes of the hepcidin regulation pathway modulate HFE hemochromato-