To the Editor:

We read with interest the editorial “H63D genotyping for hemochromatosis: Helper or hindrance?” by Adams (1) and the article “Iron overload is rare in patients homozygous for the H63D mutation” by Kelley et al (2) in the April 2014 issue of the Journal. The author questions whether H63D mutation testing may actually be harmful to patients and whether H63D homozygosity leads to iron overload. While H63D is considered to be a minor mutation, other non-HFE gene mutations may also be responsible for hyperferritinemia and hepatic siderosis. These mutations are less common and are, therefore, less frequently tested for. There is also a significant geographical variation in the incidence of gene mutations in different populations.

Malta is a small island located in Southern Europe. We analyzed all genetic tests performed for the three common HFE hemochromatosis genes (C282Y, H63D and S65C) in the Maltese islands. Ninety-five individuals underwent genetic testing for hemochromatosis, with two being H63D homozygotes (mean serum ferritin level 570 ng/mL). A liver biopsy from one of these patients confirmed moderately abundant iron stores in hepatocytes with Perl staining. Thirty-four patients were H63D heterozygotes, with a mean serum ferritin level of 729 ng/mL (range 207 ng/mL to 1625 ng/mL). Seven of these patients underwent a liver biopsy, with two having moderate cirrhosis with extensive fatty changes but negative Perl staining, and five having moderately increased iron stores on Perl staining but with different degrees of steatohepatitis.

There were also two patients with persistently elevated serum ferritin levels (mean 4780 ng/mL [range 3091 ng/mL to 6469 ng/mL]) and no detectable HFE mutations who underwent a liver biopsy. Histology revealed moderate steatohepatitis and grade 1 siderosis in one patient and liver cirrhosis consistent with hemochromatosis (as indicated by a large amount of Perl-staining pigment in hepatocytes) in another patient. These results suggest that:

- Compound heterozygotes, H63D homozygotes and H63D heterozygotes frequently have other comorbidities that contribute to hyperferritinemia (particularly steatohepatitis) (3).
- The liver biopsy in one patient with the H63D homozygous mutation was indicative of hemochromatosis, suggesting either a role for H63D homozygosity in leading to increased iron stores or the presence of other undetected gene mutations that may lead to hemochromatosis. Other genes that are not routinely checked for (including non-HFE genes such as ferroportin 1, IREG1 and transferrin receptor 2 [Tfr2]) may be responsible for several cases of histologically confirmed hemochromatosis with no detected HFE mutations or with H63D mutations (4). These uncommon genes tend to be more prevalent in particular geographical areas.
- While liver biopsy is no longer considered to be the gold standard for the diagnosis of hemochromatosis (homozygosity to C282Y and increased transferrin saturations are sufficient to make a diagnosis), liver biopsy remains necessary in patients with hyperferritinemia with confounding factors in whom no genetic mutations are identified, and to confirm underlying liver fibrosis (3).

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REFERENCES