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Short communication

Case report of a patient with non-alcoholic fatty liver disease, moderate iron overload who is homozygous for the S65C mutation in the *HFE1* gene

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Hereditary hemochromatosis (HH) is a genetically heterogeneous disease [6]. The most common form of disorder called, hereditary hemochromatosis type I (OMIM 235200) is inherited in an autosomal recessive pattern and, since its description in 1996, is associated with two *HFE1* gene mutations: the change of aminoacid 282 from cysteine to tyrosine (C282Y) and the substitution of aminoacid 63 from histidine to aspartic acid (H63D) [12]. Homozygosity for C282Y has now clearly been shown to be associated with HH in 60–100% of patients [8,10,12,19]. H63D is considered as a mild mutation and compound heterozygotes for both mutations (C282Y/H63D) have a significant risk of developing HH [5,8,10,12,19]. Other putative mutations have been described, especially the substitution of aminoacid 65 from serine to cysteine (S65C) close to the H63D mutation. The involvement of the S65C substitution in hemochromatosis was extensively studied in 711 hemochromatosis French probands [20]. The authors found that the substitution was significantly enriched

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in probands with at least one chromosome without an assigned mutation. The S65C mutation accounted for 7.8% of HH chromosomes that were neither C282Y nor H63D, whereas only 2.49% of similar control chromosomes carried the S65C substitution ($P = 0.0078$) [20]. A large screening of 9179 patients using parametric data analysis showed a higher mean transferrin saturation in heterozygotes for S65C mutation [7] and confirmed that this variant may contribute to iron overload in mildly affected hemochromatosis subjects. However, in a retrospective study, Wallace et al. [23] found that some C282Y/S65C compound heterozygotes (7/12) have no evidence of iron overload. Hollström et al. [14] have also shown that compound heterozygosity with S65C and C282Y or H63D did not significantly increase the risk of iron overload in a retrospective study in patients with suspected iron overload and healthy controls. In this study, screening of relatives revealed one S65C homozygote who had no sign of iron overload. In the mean time, Arya et al. [2] analysed the occurrence of S65C mutation in a group of blood donors with transferrin saturation over 45%: they found that the group with high transferrin saturation was significantly enriched with the H63D but not the S65C mutation compared to the group with low transferrin saturation. Robust data about the effect of S65C mutation have been difficult to obtain because of its low frequency in the population. Moreover, other genetic and environmental factors may influence the expression of iron loading. Recently, two genes involved in iron homeostasis have been proposed as modifier genes in hereditary hemochromatosis: *HAMP* and *HJV*, encoding hepcidin and hemojuvelin, respectively. Data from Ferec et al. reveal that mutations of these genes increase iron burden in *HFE1* C282Y homozygotes [15,16].

In routine analyses, in patients with iron overload, the two mild mutations (H63D and S65C) are commonly tested, in association with the major C282Y mutation. Other uncommon mutations or polymorphisms have been described extensively (reviewed in [21]).

We report here, to our knowledge, the first observation of a patient with non-alcoholic fatty liver disease (NAFLD) and moderate iron overload, who is homozygous for the S65C mutation. A 56 year-old man was referred in 1994 in our hospital for the evaluation of a moderate elevation of serum alanine aminotransferase activity ranging between 1 and 2 times the upper limit of normal values on repeated tests. He was an asymptomatic overweight patient (BMI: 28.3 kg/m^2, normal range< 25) with no alcoholic, viral, auto-immune or drug-induced liver disease. The γ-glutamyl transpeptidase level was normal. Total cholesterol (TC) and triglyceride (TG) concentrations were normal: TC 4.64 mmol/l (normal range = 3.85–7.0), TG 0.8 mmol/l (normal range = 0.45–2.05) but a moderate elevation of fasting plasma glucose level was confirmed on repeated tests. Ultrasonography showed a diffuse hyperechoic structure. Liver biopsy was performed and revealed a massive macrovesicular steatosis (70%) with mild portal and lobular necro-inflammatory activity and a limited portal fibrosis leading to the diagnosis of NAFLD. Weight reduction was recommended. Seven years later (2002) the patient was again referred to our hospital with the same abnormal liver functions: no diet was followed since the last evaluation. BMI was 29.3 kg/m^2. A fasting plasma glucose level ranging between 7 and 8.5 mmol/l was noticed on repeated tests. Both obesity and diabetes were associated with peripheral insulin resistance with hyperinsulinemia (basal insulin level: 40 μU/ml; normal range between 2.5 and 25 μU/ml). Lipid tests remained normal (TC 4.39 mmol/l, TG 1.8 mmol/l). A new liver biopsy was performed to evaluate a possible progression of steatohepatitis and revealed a massive macrovesicular steatosis (80%) with moderate necro-inflammatory activity and some portal septa. As

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