A Novel Ferroportin Disease in a Japanese Patient

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Hereditary hemochromatosis (HH) is an iron accumulating disorder in the liver with a raised serum transferrin saturation and ferritin concentration; it is common in Northern European descendants (1). To date, four types of HH have been identified (Online Mendelian Inheritance in Man (OMIM), reference 606069): type 1, the common form, is autosomal recessive with a mutation in the HFE gene on chromosome 6 (p21.3): type 2 (juvenile hemochromatosis) is autosomal recessive with a causative mutation identified in the HFE2 gene (hemojuvelin) on chromosome 1 (q21) or the HAMP gene (hepcidin) on chromosome 19 (q13): type 3 is also autosomal recessive with mutation in the transferrin receptor 2 (TfR2) gene on chromosome 3 (7q22): type 4 is autosomal dominant with a heterozygous mutation in the ferroportin 1 gene. However, few cases of Japanese HH have mutations of HFE and the genetic cause of HH in Asians remains to be elucidated.

Ferroportin 1/MTP1/IREG1, the product of SLC40A1, formerly called SLC11A3, is a transmembrane protein involved in the export of iron from duodenal enterocytes and likely from macrophages and hepatocytes (2). Circulating hepcidin can bind to ferroportin 1, cause its internalization and trap iron in hepatocytes, macrophages and absorptive enterocytes. Most HH are thought to be characterized by hepcidin deficiency (3–6) or less frequently, by autosomal dominant mutation of ferroportin 1 (7–9). Unlike classical HH (HFE-related), HH patients of Asian descendants have genetic abnormalities of the ferroportin 1 gene (10, 11). In April issue, Liu et al report a case with a new mutation of non-coding region of ferroportin 1 gene (12). This 43-year-old Japanese woman has suffered from liver function disturbance of unknown origin when she was 27 years old. Laboratory data represents high serum ferritin, high serum transferrin saturation, and impaired glucose tolerance in addition to the abnormal density on liver CT scan. The biopsied specimen showed chronic hepatitis with massive hepatocellular siderosis as well as iron deposition in the bile duct cells and macrophages. The deposition profile of iron is not compatible to the classical HH, but type 4 HH is most likely due to the mutation of ferroportin 1 gene. Her father had died already from hepatocellular carcinoma.

The patient’s two children, a son and a daughter, have normal serum ferritin levels, indicating that there is no iron overload at their age. Accordingly, the type of inheritance is not clear yet, but an interesting issue of this case is that there is a mutation in the ferroportin 1 gene; 117 adenine (A) was changed to guanine (G) in the heterozygous pattern. This mutation was not found in the patient’s children and not in 50 healthy individuals. Further studies are necessary to clarify whether or not this mutation is autosomal dominant.

Most ferroportin disease or type 4 HH is characteristic for reticuloendothelial iron accumulation rather than parenchymal iron deposition, but exceptional cases have been reported. All of the mutations of ferroportin gene are located in the coding region and they seem to be functional. Actually, transfection experiments with ferroportin siRNAs resulted in a marked reduction in ferroportin mRNA levels and an increase of iron staining (13). It is necessary to clarify whether the mutation of this non-coding region is functional or not.

Concerning the phenotype of the genetic abnormalities of ferroportin disease, it is noteworthy that some patients have a predominant reticuloendothelial iron loading and normal transferrin saturation, whereas others have predominant parenchymal iron loading and elevated transferrin saturation as shown in the present case. The reasons for this variability remain to be determined, reinforcing the importance of functional analysis of ferroportin protein and its transcriptional regulation.

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References


