A Japanese Family with Ferroportin Disease Caused by a Novel Mutation of SLC40A1 Gene: Hyperferritinemia Associated with a Relatively Low Transferrin Saturation of Iron

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Abstract

Ferroportin disease, autosomal-dominant reticuloendothelial iron overload, may be more prevalent than hemochromatosis in Japan. Hyperferritinemia of 822 ng/ml with 24.8% transferrin saturation of iron was incidentally noted in a 43-year-old man. His iron overload was selective in Kupffer cells of the liver. Subsequently, his father was found to have asymptomatic hyperferritinemia of 2,283 ng/ml with 62.1% saturation. These affected subjects were heterozygous for 1467A>C (R489S) in SLC40A1, and without other mutations of the hemochromatosis genes. Here, we report a Japanese family with ferroportin disease, characterized by hyperferritinemia with relatively low transferrin saturations of iron. (Internal Medicine 44: 990–993, 2005)

Key words: hemochromatosis, reticuloendothelial

Introduction

It has been clarified that hemochromatosis is genetically heterogeneous (1, 2). A major mutation C282Y in the HFE gene accounts for about 80% of cases in Caucasians (3), and the genetic background responsible for non-HFE hemochromatosis includes hemojuelin (4) and hepcidin (5) for the juvenile type, transferrin receptor 2 (TfR2) (6) for the classic type of middle age-onset and SLC40A1 for ferroportin disease (7, 8). Genetic differences among Caucasians and Japanese with hemochromatosis are also apparent (9–11). An almost complete lack of HFE mutations in the population accounts for the low prevalence of hemochromatosis in Japan. Previously, we reported 3 patients from a family homozygous for mutations of TfR2 in whom iron overload predominantly involved parenchymal cells of the liver (12). Recent studies indicated that iron overload in reticuloendothelial cells was one of the characteristics of ferroportin1 dysfunction caused by heterozygous SLC40A1 mutation (13, 14). This autosomal-dominant ferroportin disease has been identified in different ethnic groups worldwide, probably being a more common iron overload disorder in affected subjects than autosomal-recessive HFE hemochromatosis (15, 16).

Case Report

A 43-year-old male co-medical officer was accidentally found to have hyperferritinemia of 822 ng/ml with 24.8% transferrin saturation of iron (Table 1). Liver function test results were almost within normal limits. Liver biopsy showed selective iron deposition in the Kupffer cells with a histological hepatic iron score of 9/60 (Fig. 1) (17). The staging of the hepatic lesion was F0 and the disease activity was A0 (18). He had no diabetic symptoms, skin pigmentation or arthropathy. His parents were asymptomatic. His 79-year-old father had hyperferritinemia of 2,283 ng/ml with 62.1% transferrin saturation of iron, while his mother was within normal limits of iron parameters. The proband and his father were negative for hepatitis B and C virus markers, and
denied any history of heavy drinking, blood transfusions or iron supplement therapy.

Genomic DNA was isolated from peripheral blood leukocytes after obtaining informed consent from family members and 50 healthy volunteers according to the guidelines for Human Research of Asanogawa General Hospital. Concerning gene analysis of the proband and his father, all of the coding regions and splicing sites of the HFE, hemojuvelin, hepcidin, TfR2 and SLC40A1 genes were sequenced. Table 2 shows the primer sets used for the SLC40A1 gene. In the mother and 50 healthy volunteers, the mutant gene identified in the proband was examined by direct sequencing.

A novel missense mutation 1467A>C (Fig. 2) was heterozygous in exon 8 of the SLC40A1 gene of the proband and his father. The mutation causes the substitution of the basic amino acid arginine with a neutral serine in the 4th cytoplasmic loop of the transmembrane iron transporter ferroportin1 (R489S). This mutation was not found in the mother and 50 healthy volunteers studied. Neither the proband nor his father were homozygous or compound heterozygous for any mutation in other hemochromatosis genes.

**Discussion**

The SLC40A1 gene encodes a major iron export protein ferroportin1 that plays an essential role in releasing iron from cells, particularly enterocytes and reticuloendothelial cells (19–21). The mutation products of the gene are responsible for the reticuloendothelial iron overload of autosomal dominant inheritance, namely ferroportin disease (15, 16). To date, at least 10 mutations of the gene have been reported (Table 3) (7, 8, 13, 22–26), including the amino acid change G490D in an Asian family, that is close to the mutation R489S first identified in our patient. The proband and his father exhibiting hyperferritinemia had no known causes for the secondary hemochromatosis. Involvement of other hemochromatosis genes in their iron overload was excluded by the direct sequencing. In addition, clinical features of the affected members were different from the classical form of hemochromatosis with iron overload with a high transferrin saturation of iron, and compatible with ferroportin disease reported from other institutes (7, 8, 13). Their transferrin saturations of iron were relatively low compared to the serum ferritin levels. The liver histology of the proband showed selective iron overload in the Kupffer cells. His father showed no signs of liver dysfunction at the age of 79.

Table 2. Primers Sets for PCR and Sequencing of the SLC40A1 Gene

<table>
<thead>
<tr>
<th>Exon</th>
<th>Forward</th>
<th>Reverse</th>
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<tbody>
<tr>
<td>1</td>
<td>5’TGCTTTTCCAACCTCAGCTA-3’</td>
<td>5’TTCACCACATGCTTTCGG-3’</td>
</tr>
<tr>
<td>2</td>
<td>5’CAATTAAGTGACTACCACCTC-3’</td>
<td>5’CTAACTCACTGGGAAAGA-3’</td>
</tr>
<tr>
<td>3</td>
<td>5’TATGTAGCCAGGAAATGCGCC-3’</td>
<td>5’AGGTAAGCTCAGGCATTTGTC-3’</td>
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<td>4</td>
<td>5’ATTGAGAGTAGTTGGACAG-3’</td>
<td>5’CATTCTTACCTGCACGAG-3’</td>
</tr>
<tr>
<td>5</td>
<td>5’GGACATTATGGCCATTGACT-3’</td>
<td>5’GCCTCATTGATCACACCAG-3’</td>
</tr>
<tr>
<td>6</td>
<td>5’TGTGTAAATGGGCAGTCTC-3’</td>
<td>5’TATTTACCTACTGCGGCCC-3’</td>
</tr>
<tr>
<td>7-1</td>
<td>5’GGAGGGAATAGAAGGA-3’</td>
<td>5’CATTTTCGACTGCTAGCAAGT-3’</td>
</tr>
<tr>
<td>7-2</td>
<td>5’GTGGTCCATCTCCTCATT-3’</td>
<td>5’AAATGGATTCCTGCAACCTAC-3’</td>
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<tr>
<td>8-1</td>
<td>5’CTTAAAGGCAAGGCCTATG-3’</td>
<td>5’AAACAGAGCACCAACACCC-3’</td>
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</table>

*Parameters are presented as serum levels except for age. **The tests were performed 3 years after those of the proband. TIBC: total iron binding capacity, Tf-S: transferrin saturation of iron.
years, and biopsy was not permitted ethically. However, the serum ferritin level of 2,283 ng/ml determined under a stress-free state suggested the same iron overload condition as found in his son with the same genetic background. Therefore, it is possible that a novel mutation 1467A>C (R489S) in the SLC40A1 caused their mild iron overload. In conclusion, we described here the clinical characteristics of ferroportin disease observed in a Japanese family.

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References


