determined as platelet diameters on peripheral blood smears in genetically confirmed Bernard-Soulier syndrome and MYH9 disorders were 5.3 (± 1.1) μm (n = 14) and 4.9 (± 1.1) μm (n = 81), respectively. These data are comparable with that of the patient in our study. Because routine automated blood cell counting systems differentiate blood cells by their size and therefore do not recognize giant platelets as platelets, mean platelet volume (MPV) does not reflect actual platelet size. As is quite often the case, an automated counter did not generate MPV in the patient or the mother. We believe that the determination of platelet diameter on peripheral smear is a more reliable way to detect macrothrombocytopenia.

We admit that it is premature to make definite conclusions about how W318 β1-tubulin affects the normal platelet production and results in macrothrombocytopenia. This is mainly because the causative relationship between the mutation and giant platelets was not convincingly investigated in our work. To clarify this, we are planning to establish knockin cell models that equally express wild-type and mutant β1-tubulins identified in human and canine macrothrombocytopenia.

Shinji Kunishima
National Hospital Organization Nagoya Medical Center
Nagoya, Japan

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Shinji Kunishima, PhD, Department of Advanced Diagnosis, Clinical Research Center, National Hospital Organization Nagoya Medical Center, 4-1-1 Sannomaru, Naka-ku, Nagoya 4600001, Japan; e-mail: kunishis@nhn.hosp.go.jp.

References


Table 1. Clinical and laboratory parameters of 3 generations of family members carrying C326S ferroportin mutation

<table>
<thead>
<tr>
<th>Patient</th>
<th>IA</th>
<th>IIA</th>
<th>IIB</th>
<th>IIC</th>
<th>IIA</th>
<th>IIB</th>
<th>IIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis/sex</td>
<td>35/M</td>
<td>16/F</td>
<td>16/M</td>
<td>16/M</td>
<td>8/F</td>
<td>10/F</td>
<td>10/F</td>
</tr>
<tr>
<td>Transferrin sat, initial</td>
<td>79%*</td>
<td>89%*</td>
<td>70%*</td>
<td>89%*</td>
<td>93%*</td>
<td>91%*</td>
<td>51%*</td>
</tr>
<tr>
<td>Transferrin sat, current</td>
<td>69</td>
<td>99</td>
<td>81</td>
<td>394*</td>
<td>114</td>
<td>21</td>
<td>111</td>
</tr>
<tr>
<td>S-ferritin current, ng/mL</td>
<td>278*</td>
<td>198</td>
<td>297*</td>
<td>459*</td>
<td>453*</td>
<td>396*</td>
<td>131</td>
</tr>
<tr>
<td>S-hepcidin, ng/mL</td>
<td>1308</td>
<td>2743*</td>
<td>2270*</td>
<td>3183*</td>
<td>3463*</td>
<td>3036*</td>
<td>72</td>
</tr>
<tr>
<td>U-hepcidin, ng/mg creat</td>
<td>Cirrhosis</td>
<td>↑ hepatocyte iron</td>
<td>↑ hepatocyte iron</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>Arthritis, hip replacement</td>
<td>mild arthritis</td>
<td>mild arthritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td>mild LFT changes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Normal serum hepcidin median (5%-95% range) was 112 ng/mL (29-254 ng/mL) for men, and 65 ng/mL (17-286 ng/mL) for women. Normal urine hepcidin median (full range) was 502 ng/mg creatinine (71-1762 ng/mg creatinine). M indicates male; F, female; sat, saturation; and creat, creatinine.

*Above-normal values.
†Below-normal values.
One of the patients (IIIC) has become iron-deficient due to phlebotomy combined with menstrual blood loss. Except for patient IIIC, all affected family members had serum and urinary hepcidin concentrations in the upper limit of the normal range or above (Table 1). These relatively high hepcidin levels are probably a consequence of patients’ elevated transferrin saturation. Only IIIC patient had lower hepcidin, likely reflecting the appropriate response of hepcidin to iron deficiency.

The high levels of hepcidin in patients with C326S despite relatively depleted iron stores are in contrast to the low or undetectable hepcidin levels observed in treated patients with HFE, transferrin receptor 2, or hemojuvelin hemochromatosis.9-11 Thus, our study provides the first direct evidence that hereditary hemochromatosis can be caused by the resistance of ferroportin to hepcidin. The absence of hepcidin binding to mutant ferroportin in C326S patients leads to excessive ferroportin activity in duodenal enterocytes and unrestrained dietary iron absorption, which would account for the early-onset systemic iron overload similar to that seen in juvenile hemochromatosis. Our findings support the concept that hereditary hemochromatosis with parenchymal iron-loading phenotype can be caused by either hepcidin deficiency or resistance to the effect of hepcidin.

References
Hereditary hemochromatosis due to resistance to hepcidin: high hepcidin concentrations in a family with C326S ferroportin mutation

Ronald L. Sham, Pradyumna D. Phatak, Elizabeta Nemeth and Tomas Ganz