Iron Refractory Iron Deficiency Anemia: Presentation With Hyperferritinemia and Response to Oral Iron Therapy

abstract

Iron-refractory iron-deficiency anemia (IRIDA) is an autosomal recessive disorder caused by mutations in TMPRSS6. Patients have hypochromic microcytic anemia refractory to oral iron and are only partially responsive to parenteral iron administration. We report a French-Canadian kindred in which 2 siblings presented in early childhood with severe microcytic anemia, hypoferremia, and hyperferritinemia. Both children have been successfully treated solely with low-dose oral iron since diagnosis. Clinical and biological presentation did not fit any previously described genetic iron-deficiency anemia. Whole exome sequencing identified in both patients compound heterozygous mutations of TMPRSS6 leading to p.G442R and p.E522K, 2 mutations previously reported to cause classic IRIDA, and no additional mutations in known iron-regulatory genes. Thus, the phenotype associated with the unique combination of mutations uncovered in both patients expands the spectrum of disease associated with TMPRSS6 mutations to include iron deficiency anemia that is accompanied by hyperferritinemia at initial presentation and is responsive to continued oral iron therapy. Our results have implications for genetic testing in early childhood iron deficiency anemia. Importantly, they emphasize that whole exome sequencing can be used as a diagnostic tool and greatly facilitate the elucidation of the genetic basis of unusual clinical presentations, including hypomorphic mutations or compound heterozygosity leading to different phenotypes in known Mendelian diseases. Pediatrics 2013;131:e620–e625

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KEY WORDS
iron, TMPRSS6, hypomorphic mutations, hepcidin, whole exome sequencing, anemia

ABBREVIATIONS
Hb—hemoglobin
IRIDA—iron refractory iron deficiency anemia
MCV—mean corpuscular volume
WES—whole exome sequencing

Drs Khuong-Quang, Schwartzentruber, and Jabado designed the study, analyzed data, and wrote the manuscript; Dr Jabado diagnosed the patients; Drs Schwartzentruber, Lepage, and Majewski designed and performed sequencing experiments and analyzed data; Dr Westerman measured plasma hepcidin and reviewed data; Dr Finberg reviewed data and the manuscript; and all authors read and approved the final manuscript. www.pediatrics.org/cgi/doi/10.1542/peds.2012-1303
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(Continued on last page)
The main causes of iron-deficiency anemia are blood loss or an inadequate dietary iron intake. However, several genetic defects can lead to ineffective iron intestinal absorption or impaired iron recycling by macrophages, the 2 main processes that fulfill iron needs in mammals. Iron-refractory iron deficiency anemia (IRIDA; Online Mendelian Inheritance in Man database #206200) is an autosomal recessive disorder caused by loss-of-function mutations in TMPRSS6, first described in 1981. Patients exhibit severe, congenital hypochromic, microcytic anemia with low serum iron and transferrin saturation that occurs in infancy and is refractory to oral iron treatment and partially recovered after parenteral iron administration. They also show an inappropriate elevation of hepcidin, a circulating hormone that inhibits iron duodenal absorption and macroporphage iron recycling. To date, >30 TMPRSS6 mutations have been identified in patients without any common ethnic or geographic distribution, suggesting that TMPRSS6 mutations might be underestimated in patients with iron-deficiency anemia. Here, we report a family in which whole exome sequencing (WES) identified compound heterozygous TMPRSS6 mutations in 2 siblings with iron deficiency anemia that differed clinically and biologically from classic IRIDA.

**PATIENT PRESENTATION**

Written informed consent and assents were obtained from the patients and their guardians for whole exome sequencing and publication of this case report.

In 1999, a 3-year-old boy was referred to our clinic at the Montreal Children’s Hospital for investigation of a microcytic hypochromic anemia diagnosed after symptoms of fatigue and abdominal pain. His growth and development were normal, and no anterior hemoglobin (Hb) measurement was available. He was of French Canadian descent with no known parental consanguinity. His parents and older sister had normal complete blood counts, reticulocyte counts, and ferritin levels. Laboratory values, described in Table 1, showed a severe microcytic, hypochromic anemia (Hb of 75 g/L, mean corpuscular volume [MCV] of 64 fL), low serum iron, low fractional transferrin saturation, and normal transferrin levels. Unexpectedly, the serum ferritin level was elevated at 348 μg/L, well above the normal range of 6 to 110 μg/L. Hb electrophoresis did not detect a hemoglobinopathy, there was no clinical or biological evidence of chronic inflammatory state, and gastroenterological investigations provided no evidence for occult blood loss or malabsorption. His diet was well diversified. During a course of oral iron supplementation (6–10 mg/kg/day of elemental iron) for 1 year, the proband’s symptoms disappeared, and he experienced a slow rise of Hb up to 119 g/L with normalization of the MCV. The transferrin saturation remained low (0.07), as did the circulating iron level at 4 μmol/L. However, ferritin rose up to 654 μg/L. The time course of hematologic and iron parameters under treatment is summarized in Table 2. After 9 years of follow-up, the patient.

### TABLE 1  TMPRSS6 Genotype and Hematologic and Biochemical Parameters in Patients, Their Parents, and Their Unaffected Sister

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>5.5–15.5 10^9/L</td>
<td>8.6</td>
<td>10.2</td>
<td>6.39</td>
<td>8.05</td>
<td>7.3</td>
</tr>
<tr>
<td>RBC</td>
<td>3.90–5.30 10^12/L</td>
<td>4.31</td>
<td>5</td>
<td>4.81</td>
<td>3.91</td>
<td>4.43</td>
</tr>
<tr>
<td>Hb</td>
<td>115–153 g/L</td>
<td>75</td>
<td>76</td>
<td>145</td>
<td>121</td>
<td>131</td>
</tr>
<tr>
<td>Hct</td>
<td>0.340–0.400</td>
<td>0.276</td>
<td>0.249</td>
<td>0.413</td>
<td>0.352</td>
<td>0.386</td>
</tr>
<tr>
<td>MCV</td>
<td>75.0–87.0 fl</td>
<td>64.1</td>
<td>49.7</td>
<td>85.9</td>
<td>90</td>
<td>87</td>
</tr>
<tr>
<td>MCH</td>
<td>24.0–30.0 pg/cell</td>
<td>17.4</td>
<td>15.1</td>
<td>30.2</td>
<td>30.9</td>
<td>29.6</td>
</tr>
<tr>
<td>MCHC</td>
<td>310–370 g/L</td>
<td>271</td>
<td>304</td>
<td>351</td>
<td>343</td>
<td>341</td>
</tr>
<tr>
<td>RDW</td>
<td>11.4% to 14.6%</td>
<td>16.9</td>
<td>22.4</td>
<td>13.2</td>
<td>13.4</td>
<td>14.1</td>
</tr>
<tr>
<td>Platelet</td>
<td>140–450 10^12/L</td>
<td>292</td>
<td>616</td>
<td>223</td>
<td>250</td>
<td>271</td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>10–99/μL</td>
<td>0.024</td>
<td>0.045</td>
<td>0.046</td>
<td>0.025</td>
<td>0.046</td>
</tr>
<tr>
<td>Sedimentation rate</td>
<td>3–13 mm/h</td>
<td>8</td>
<td>8</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Iron</td>
<td>4–25 μmol/L</td>
<td>&lt;1</td>
<td>1.6</td>
<td>12.3</td>
<td>15.5</td>
<td>19.6</td>
</tr>
<tr>
<td>Transferrin</td>
<td>2.00–3.70 g/L</td>
<td>2</td>
<td>2.14</td>
<td>2.34</td>
<td>2.93</td>
<td>3.17</td>
</tr>
<tr>
<td>Fractional Transferrin saturation</td>
<td>0.20–0.55</td>
<td>0.02</td>
<td>0.07</td>
<td>0.21</td>
<td>0.21</td>
<td>0.24</td>
</tr>
<tr>
<td>Ferritin</td>
<td>6–110 μg/L</td>
<td>348</td>
<td>195</td>
<td>112</td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td>Hepcidin</td>
<td>17–260 ng/mL</td>
<td>142.4</td>
<td>198.6</td>
<td>116.1</td>
<td>58.4</td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td></td>
<td>115</td>
<td>94</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td></td>
<td>2.6</td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Parameters at diagnosis are shown in the upper panel. Mutations are described at the protein level. Plasma hepcidin was measured in 2011 while patients were receiving oral iron supplementation (0.5 mg/kg/wk). Results are shown in the lower panel along with Hb and serum iron. Hct, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; NA, not available; RBC, red blood count; RDW, red cell distribution width; WBC, white blood count; WT, wild type.

* Results for both parents and their healthy sister were within the normal range.
TABLE 2 Time Course of Hematologic and Biochemical Parameters in Probands Under Oral Iron Supplementation

<table>
<thead>
<tr>
<th>Date</th>
<th>Tx duration, mo</th>
<th>Patient age, y</th>
<th>OEI suppl</th>
<th>Hb, g/L</th>
<th>MCV, fL</th>
<th>RDW, %</th>
<th>Retic, 10^9/L</th>
<th>Iron, μmol/L</th>
<th>Ferritin, μg/L</th>
<th>Transf, g/L</th>
<th>Transf saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/16/1999</td>
<td>—</td>
<td>3</td>
<td>6 mg/kg/d</td>
<td>75</td>
<td>64.1</td>
<td>16.9</td>
<td>0.024</td>
<td>&lt;1</td>
<td>548</td>
<td>2.00</td>
<td>0.02</td>
</tr>
<tr>
<td>1/19/2000</td>
<td>4</td>
<td>3</td>
<td>↑ to 10 mg/kg/d</td>
<td>100</td>
<td>64</td>
<td>16.4</td>
<td>0.050</td>
<td>3.0</td>
<td>217</td>
<td>2.24</td>
<td>0.05</td>
</tr>
<tr>
<td>10/14/2000</td>
<td>12</td>
<td>4</td>
<td>Stop Tx</td>
<td>112</td>
<td>71.9</td>
<td>14.8</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>11/22/2000</td>
<td>—</td>
<td>3</td>
<td>—</td>
<td>104</td>
<td>72.8</td>
<td>14.6</td>
<td>ND</td>
<td>ND</td>
<td>325</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>1/19/2000</td>
<td>4</td>
<td>3</td>
<td>↑</td>
<td>104</td>
<td>72.8</td>
<td>14.6</td>
<td>ND</td>
<td>ND</td>
<td>325</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>5/3/2002</td>
<td>—</td>
<td>5</td>
<td>Restart at 10 mg/kg/d</td>
<td>101</td>
<td>73.4</td>
<td>13.6</td>
<td>2.0</td>
<td>291</td>
<td>1.73</td>
<td>0.05</td>
<td>ND</td>
</tr>
<tr>
<td>6/12/2002</td>
<td>1</td>
<td>6</td>
<td>↓ down to 6 mg/kg/d</td>
<td>107</td>
<td>73.3</td>
<td>15.1</td>
<td>0.068</td>
<td>3.0</td>
<td>379</td>
<td>2.16</td>
<td>0.05</td>
</tr>
<tr>
<td>9/8/2002</td>
<td>6</td>
<td>6</td>
<td>Stop Tx</td>
<td>113</td>
<td>75.5</td>
<td>13.8</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>5/28/2003</td>
<td>—</td>
<td>6</td>
<td>Restart at 9 mg/kg/d</td>
<td>102</td>
<td>69.5</td>
<td>16.4</td>
<td>ND</td>
<td>4.0</td>
<td>376</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>11/3/2003</td>
<td>7</td>
<td>7</td>
<td>Stop Tx</td>
<td>114</td>
<td>75.7</td>
<td>14.6</td>
<td>0.066</td>
<td>4.0</td>
<td>654</td>
<td>2.12</td>
<td>0.07</td>
</tr>
<tr>
<td>5/11/2004</td>
<td>—</td>
<td>7</td>
<td>No Tx</td>
<td>109</td>
<td>81.6</td>
<td>14.5</td>
<td>2.0</td>
<td>467</td>
<td>2.14</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>10/18/2004</td>
<td>—</td>
<td>8</td>
<td>Restart at 4 mg/kg/d</td>
<td>106</td>
<td>73.6</td>
<td>15.3</td>
<td>2.0</td>
<td>391</td>
<td>2.06</td>
<td>0.04</td>
<td>ND</td>
</tr>
<tr>
<td>3/17/2006</td>
<td>16</td>
<td>9</td>
<td>Stop Tx</td>
<td>119</td>
<td>78</td>
<td>14.3</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3/17/2006</td>
<td>10</td>
<td>10</td>
<td>Restart at 6 mg/kg/d</td>
<td>103</td>
<td>74.9</td>
<td>15.5</td>
<td>3.1</td>
<td>439</td>
<td>2.07</td>
<td>0.06</td>
<td>ND</td>
</tr>
<tr>
<td>10/26/2007</td>
<td>14</td>
<td>11</td>
<td>↓ down to 1.2 mg/kg/d</td>
<td>119</td>
<td>76.1</td>
<td>14.6</td>
<td>5.0</td>
<td>598</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>5/23/2008</td>
<td>21</td>
<td>12</td>
<td>↓ down to 1 mg/kg/d</td>
<td>113</td>
<td>73.1</td>
<td>15.6</td>
<td>4.1</td>
<td>390</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>11/20/2009</td>
<td>39</td>
<td>13</td>
<td>↓ down to 0.7 mg/kg/d</td>
<td>119</td>
<td>72.2</td>
<td>17.2</td>
<td>ND</td>
<td>512</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>12/17/2010</td>
<td>51</td>
<td>14</td>
<td>↓ down to 0.5 mg/kg/d</td>
<td>109</td>
<td>67.2</td>
<td>18.9</td>
<td>3.2</td>
<td>168</td>
<td>2.24</td>
<td>0.08</td>
<td>ND</td>
</tr>
<tr>
<td>12/20/2011</td>
<td>64</td>
<td>15</td>
<td>0.5 mg/kg/d</td>
<td>115</td>
<td>66.8</td>
<td>19.1</td>
<td>2.6</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND, not determined; OEI suppl, oral elemental iron supplementation; RDW, red cell distribution width; Retic, reticulocytes; Transf, transferrin; Tx, treatment; ↑, increase; ↓, decrease.

has had a normal growth curve, normal physical activities, and improved Hb levels. On the basis of the increase in ferritin levels after oral iron therapy, oral iron supplementation has been continued with the dose tapered to 3.5 mg/kg per week, which has maintained ferritin levels similar to those seen at diagnosis and the Hb >110 g/L. The patient never required erythrocyte transfusion or intravenous iron administration.

The proband’s youngest sister presented with similar symptoms at age 2 years and also had microcytic anemia, hypoferremia, and high ferritin levels (Table 1). She was initially treated with 6 mg/kg per week of oral iron with elimination of symptoms; the oral iron dose was tapered to 3.5 mg/kg per week, also in response to a rising ferritin level during iron therapy. She is now aged 12 years and, like her brother, has a normal growth curve; she has a normal Hb level when she is compliant with her iron therapy. Notably, several trials to stop oral iron therapy were attempted in both siblings during periods ranging from 2 to 12 months. All resulted in increased fatigue hampering normal daily activities and significant drops in the Hb levels, leading us to resume oral iron therapy.

The pedigree suggested autosomal recessive transmission, and the clinical presentation of microcytic anemia, hypoferremia, and hyperferritinemia, which responded to oral iron supplementation with a concomitant increase in serum ferritin did not suggest any of these genes. Other family members each carried 1 mutation.

### DISCUSSION

We describe here a family in which WES identified compound heterozygous TMPRSS6 mutations in the 2 siblings affected with iron deficiency anemia. The clinical presentation differed from classic IRIDA in that ferritin levels were high at diagnosis and the anemia in both children has been responsive to low-dose oral iron with >9 years of follow-up.

These 2 missense mutations have been previously reported in patients with the IRIDA phenotype who required parenteral iron.6 To our knowledge, this specific compound heterozygosity is described here for the first time, in association with this atypical clinical and biological presentation of iron-deficiency anemia (Tables 1 and 2). TMPRSS6 encodes the hepatic transmembrane serine protease matriptase-2.

Reported IRIDA cases show low or normal ferritin levels at diagnosis that increase after parenteral iron (Table 3). In our patients, however, ferritin was high at diagnosis and increased with oral iron treatment. Moreover,
whereas typical IRIDA patients are refractory to oral iron, both patients were effectively treated exclusively by oral supplementation. Review of the literature indicates that the clinical and biological presentations of the siblings we report herein are unique (Table 3). Cau et al\textsuperscript{12} report a 5-month-old Sardinian female with IRIDA and homozygous \textit{TMPRSS6} mutation who had normal ferritin at diagnosis. Unlike the patients in our study, this patient failed to respond to oral iron. Interestingly, after showing a partial response to intravenous iron, she responded to a combination of oral iron and ascorbic acid. Notably, other family members carrying the same homozygous \textit{TMPRSS6} mutation did not respond to oral iron. Beutler et al\textsuperscript{19} described a Belgian family in which the proband with compound \textit{TMPRSS6}/heterozygous mutations was diagnosed at age 8 years when the Hb was 90 g/L and the ferritin was 20 ng/mL. The proband and his affected sibling both showed a partial response to oral iron. However, in contrast to the patients in our study, neither developed hyperferritinemia with long-term oral iron therapy.

In these specific cases, iron absorption may be less impaired than reported IRIDA patients, perhaps because of the combined residual function of these particular mutant alleles. These phenotypic differences might also reflect modifier genes that promote iron uptake by enterocytes or reduce hepcidin release by hepatocytes. Plasma hepcidin was assessed during iron therapy when Hb was improved but hypoferremia persisted. Thus, even if seemingly within normal range for the patients, hepcidin appeared inappropriately elevated relative to serum iron level. Comparison of hepcidin deregulation in our patients to reported IRIDA cases is, however, complicated by likely differences in erythropoiesis and hepatic iron stores, stimuli known to modulate hepcidin transcription. Because macrophages are a major source of serum ferritin,\textsuperscript{19} our patients’ presenting hyperferritinemia could reflect greater hepcidin sensitivity in macrophages versus enterocytes, in keeping with previous studies.\textsuperscript{20}

Recently, a single nucleotide polymorphism encoding V736A in the \textit{TMPRSS6} catalytic domain was found in several genome-wide association studies\textsuperscript{21,22} to correlate with decreased Hb and serum iron in healthy populations. Our study suggests that \textit{TMPRSS6} sequence variants lead to a spectrum of matriptase-2 dysfunction, including severe loss-of-function mutations causing classic IRIDA, hypomorphic mutations as seen in our patients and potentially similar atypical ones, and the mild reduction in matriptase-2 activity associated with the common V736A SNP.\textsuperscript{23} Accordingly, our results suggest that genetic testing for \textit{TMPRSS6} mutation have clinical utility in cases of hypochromic, microcytic anemia with hypoferremia that do not exhibit the classic IRIDA phenotype. We suggest that \textit{TMPRSS6} sequencing should be considered in a subset of patients presenting with iron deficiency anemia of unknown cause in which blood loss, inadequate dietary intake, and chronic inflammatory conditions have been ruled out (see online Supplemental Fig 1 for a diagnostic algorithm). \textit{TMPRSS6} sequencing is available in several CLIA (clinically accredited) certified laboratories. Although hepcidin measurement is not yet widely available as clinical test, we note that the finding of a markedly reduced hepcidin level in the setting of iron deficiency anemia would indicate the anemia is unlikely to be attributed to \textit{TMPRSS6} mutation.

Our results further emphasize that next generation sequencing technologies, particularly WES, greatly facilitate the elucidation of the genetic basis of unusual clinical presentations exhibiting Mendelian inheritance, including hypomorphic mutations leading to different phenotypes. Clinical application of WES in undiagnosed clinical conditions has already been shown to be feasible, yielding an encouraging 50% rate of success in uncovering an underlying genetic defect in select clinical cases in which the probability of a genetic origin is high.\textsuperscript{24} There is growing interest in its introduction into the clinic to aid in the diagnosis of conditions for which no genetic cause can be found with targeted testing. Although the mutations identified currently require validation in a Clinical Laboratory Improvement Amendments–certified laboratory, this technology is becoming accessible to clinicians through academic consortia (Finding of Rare Disease Genes in Canada[FORGE Canada], Broad Institute, etc.) or private companies that offer the possibility of sequencing the exome and performing the analysis. The broader use of WES will expand the range of clinical phenotypes associated with mutations in known disease genes.

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