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

AUTHORS: Dong-Anh Khuong-Quang, MD, a Jeremy Schwartzentruber, MSc, b Mark Westerman, PhD, c Pierre Lepage, PhD, b Karin E. Finberg, MD, PhD, d Jacek Majewski, PhD, a, b and Nada Jabado, MD, PhD e

Department of a Human Genetics, and a Pediatrics, McGill University, Montreal, Canada; b McGill University and Genome Quebec Innovation Centre, Montreal, Canada; c Intrinsic LifeSciences LLC, La Jolla, California; and d Department of Pathology, Duke University School of Medicine, Durham, North Carolina

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
doi:10.1542/peds.2012-1303
Accepted for publication Oct 1, 2012
Address Correspondence to Nada Jabado, MD, PhD, Department of Pediatrics, McGill University/McGill University Health Center, 4060 Ste Catherine West, PT-239, Montreal, QC H3Z 2Z3 Canada. E-mail: nada.jabado@mcgill.ca

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2013 by the American Academy of Pediatrics

(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 TMPRRSS6, 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 macrophage 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 TMPRRSS6 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...
The proband administration.

transfusion or intravenous iron ad-

patient never required erythrocyte

12 months. All resulted in increased

therapy were attempted in both sib-

compliant with her iron therapy. Nota-

she has a normal Hb level when she is

week, also in response to a rising fer-

elimination of symptoms; the oral iron

hypoferremia, and high ferritin levels

years and also had microcytic anemia,

presentation of microcytic anemia,

cessive transmission, and the clinical

The pedigree suggested autosomal re-

levels, leading us to resume oral iron

The clinical presentation differed from

in serum ferritin did not suggest any

iron-de
ciency anemia. In congenital

deficiency anemia (Tables 1 and 2).

has had a normal growth curve, nor-

Hb levels. On the basis of the increase in

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 pre-

with similar symptoms at age 2

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 fer-

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. Nota-

several trials to stop oral iron therapy were attempted in both sib-

months. All resulted in increased

fatigue hampering normal daily activi-

ties and significant drops in the Hb

therapy.

The pedigree suggested autosomal re-

cessive transmission, and the clinical

presentation of microcytic anemia, hypoferremia, and hyperferritinemia, which responded to oral iron supple-

mentation with a concomitant increase

in serum ferritin did not suggest any

iron-deficiency anemia. In congenital

hypotransferrinemia, serum transferrin is low. Patients with mutated

SLC11A2 or glutaredoxin 5 deficiency exhibit hyperferrremia. Patients with IRIDA show no hematologic cor-

rection after oral iron. We thus per-

formed WES on genomic DNA from both siblings, a strategy proven by us and others to identify novel genes as-

associated with rare disorders. We

identified compound heterozygous mu-

tations in TMPRSS6 in both patients, caus-
ing p.G442R and p.E522K. To see if

the unusual clinical presentation could be associated with a coding poly-

morphism, we searched the exome data for rare variants (allele frequency <1%) in genes known to be involved in iron metabolism (Supplemental Table 4). However, we found no uncommon polymorphisms in the probands for 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 paren-
teral iron. 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 trans-

membrane 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,

**TABLE 3 Literature Review of Previously Reported Cases of IRIDA**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Mutation 1</th>
<th>Mutation 2</th>
<th>Ethnic origin</th>
<th>Age, (y)</th>
<th>Route of iron admin and additional therapies</th>
<th>Hb, (\mu g/L)</th>
<th>Ferritin, (\mu g/L)</th>
<th>Ferritin under Tx, (\mu g/L)</th>
<th>Follow-up, (y/) age at Dx, (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Our study</td>
<td>2012</td>
<td>p.G442R</td>
<td>p.E522K</td>
<td>French Canadian</td>
<td>3</td>
<td>PO</td>
<td>75</td>
<td>348</td>
<td>654</td>
<td>FUP 13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.K636fs</td>
<td>p.K636fs</td>
<td>Turkish</td>
<td>6</td>
<td>IV</td>
<td>88</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.A605fs</td>
<td>p.E522fs</td>
<td>Northern European</td>
<td>1.1</td>
<td>IV</td>
<td>92</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.G713fs</td>
<td>unknown</td>
<td>Nigerian</td>
<td>1.4</td>
<td>IV</td>
<td>70</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.G442R</td>
<td>p.D521N</td>
<td>Northern European</td>
<td>11</td>
<td>IV</td>
<td>82</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.R774C</td>
<td>unknown</td>
<td>African American</td>
<td>7</td>
<td>IV</td>
<td>75</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.Y335X</td>
<td>p.E461fs</td>
<td>African American</td>
<td>1.3</td>
<td>IV</td>
<td>79</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Guillemin et al(^2)</td>
<td>2008</td>
<td>p.Y398X</td>
<td>p.R598X</td>
<td>English</td>
<td>1.5</td>
<td>IV</td>
<td>60</td>
<td>11</td>
<td>109</td>
<td>FUP 12</td>
</tr>
<tr>
<td>Melis et al(^7)</td>
<td>2008</td>
<td>IVS6+1 G(\rightarrow)C</td>
<td>IVS6+1 G(\rightarrow)C</td>
<td>Sardinian</td>
<td>0.7–1</td>
<td>IV</td>
<td>100(^a)</td>
<td>NA</td>
<td>53</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IVS6+1 G(\rightarrow)C</td>
<td>Sardinian</td>
<td>14</td>
<td>IV</td>
<td>91(^b)</td>
<td>119(^b)</td>
<td>415</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Ramsay et al(^8)</td>
<td>2009</td>
<td>p.A1180</td>
<td>p.P686fs</td>
<td>Spanish</td>
<td>15</td>
<td>IV + EPO</td>
<td>98(^a)</td>
<td>123(^a)</td>
<td>365</td>
<td>Dx at 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.A1180</td>
<td>p.P686fs</td>
<td>Spanish</td>
<td>15</td>
<td>IV + EPO</td>
<td>1219(^a)</td>
<td>388(^a)</td>
<td>588</td>
<td>Dx at 1</td>
</tr>
<tr>
<td>Silvestri et al(^9)</td>
<td>2009</td>
<td>p.D521N</td>
<td>p.E522K</td>
<td>French</td>
<td>0.8</td>
<td>PO (failure) then IV</td>
<td>10</td>
<td>4</td>
<td>180</td>
<td>FUP 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.A605fs</td>
<td>p.E522fs</td>
<td>Sardinian</td>
<td>NA</td>
<td>IV</td>
<td>100(^a)</td>
<td>NA</td>
<td>129</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.G713fs</td>
<td>p.D521N</td>
<td>Sardinian</td>
<td>NA</td>
<td>IV + PO</td>
<td>128(^a)</td>
<td>NA</td>
<td>184</td>
<td>NA</td>
</tr>
<tr>
<td>Resmay et al(^10)</td>
<td>2009</td>
<td>p.A1180</td>
<td>p.P686fs</td>
<td>Sardinian</td>
<td>0.7–1</td>
<td>IV</td>
<td>139(^a)</td>
<td>NA</td>
<td>468</td>
<td>NA</td>
</tr>
<tr>
<td>Techou et al(^11)</td>
<td>2009</td>
<td>p.S304L</td>
<td>p.K478(_{K508del})</td>
<td>Swiss</td>
<td>3</td>
<td>IV + fresh-frozen plasma</td>
<td>77(^a)</td>
<td>46(^a)</td>
<td>310</td>
<td>Dx at 0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.I212T</td>
<td>p.R271Q</td>
<td>Italian</td>
<td>53</td>
<td>PO (failure)</td>
<td>114(^a)</td>
<td>68(^a)</td>
<td>NA</td>
<td>Dx at birth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.S304L</td>
<td>p.S304L</td>
<td>Belgian</td>
<td>8</td>
<td>PO</td>
<td>90</td>
<td>20</td>
<td>70</td>
<td>FUP 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.L166X+36</td>
<td>p.L166X+36</td>
<td>Dutch</td>
<td>6</td>
<td>IM</td>
<td>62.8</td>
<td>16</td>
<td>323</td>
<td>FUP 11</td>
</tr>
<tr>
<td>Altamuro et al(^12)</td>
<td>2010</td>
<td>p.Y141C</td>
<td>p.Y141C</td>
<td>Lebanese</td>
<td>10</td>
<td>PO (failure)</td>
<td>79(^a)</td>
<td>86(^a)</td>
<td>NA</td>
<td>Dx at 2</td>
</tr>
<tr>
<td>De Falco et al(^13)</td>
<td>2010</td>
<td>p.Y141C</td>
<td>p.Y141C</td>
<td>Indian</td>
<td>8</td>
<td>IV</td>
<td>91</td>
<td>26(^a)</td>
<td>25</td>
<td>Dx at 1.3 y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.L166X+36</td>
<td>p.L166X+36</td>
<td>Arabian</td>
<td>4</td>
<td>IV</td>
<td>80</td>
<td>50(^a)</td>
<td>113</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.W247fs</td>
<td>p.W247fs</td>
<td>Greek</td>
<td>2</td>
<td>IV</td>
<td>54</td>
<td>19(^a)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.W247fs</td>
<td>p.W247fs</td>
<td>Greek</td>
<td>2</td>
<td>IV</td>
<td>54</td>
<td>19(^a)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.S561X</td>
<td>p.S561X</td>
<td>Arabian</td>
<td>5</td>
<td>IV</td>
<td>88</td>
<td>101(^a)</td>
<td>NA</td>
<td>Dx at 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p.S561X</td>
<td>p.S561X</td>
<td>Arabian</td>
<td>2</td>
<td>IV</td>
<td>79</td>
<td>38</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cau et al(^14)</td>
<td>2011</td>
<td>IVS6+1 G(\rightarrow)C</td>
<td>IVS6+1 G(\rightarrow)C</td>
<td>Sardinian</td>
<td>0.4</td>
<td>PO (failure), then IV, then PO with ascorbic acid</td>
<td>75</td>
<td>102</td>
<td>450 (IV)</td>
<td>FUP 2</td>
</tr>
<tr>
<td>Choi et al(^16)</td>
<td>2011</td>
<td>p.G806R</td>
<td>IVS6+1 G(\rightarrow)T</td>
<td>Korean</td>
<td>2</td>
<td>PO (failure)</td>
<td>70</td>
<td>42(^a)</td>
<td>106 (IV)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Mutations are described at the protein level, except for the ones affecting splicing sites. Dx, diagnosis; EPO, erythropoietin; FUP, follow-up; IM, intramuscular; IV, intravenous; NA, not available; PO, per os; Tx, treatment.

\(^a\) At evaluation.

\(^b\) Highest level reported.

\(^c\) In the kindreds reported by Finberg et al\(^1\), ferritin levels were reported to be low-normal, although specific ferritin values were not included.

\(^d\) Hb and/or ferritin levels were measured under iron therapy. Age of patients at the time of diagnosis is included in the comments.
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 report a 5-month-old Sardinian female with IRIDA and homozygous 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 TMPRSS6 mutation did not respond to oral iron. Beutler et al described a Belgian family in which the proband with compound 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 hypoferrremia 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, our patients’ presenting hyperferritinemia could reflect greater hepcidin sensitivity in macrophages versus enterocytes, in keeping with previous studies.

Recently, a single nucleotide polymorphism encoding V736A in the TMPRSS6 catalytic domain was found in several genome-wide association studies to correlate with decreased Hb and serum iron in healthy populations. Our study suggests that 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. Accordingly, our results suggest that genetic testing for TMPRSS6 mutation have clinical utility in cases of hypochromic, microcytic anemia with hypoferrremia that do not exhibit the classic IRIDA phenotype. We suggest that 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). 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 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. 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.

REFERENCES


\textbf{FINANCIAL DISCLOSURE:} Mark Westerman is cofounder and CEO of Intrinsic LifeSciences, developer of hepcidin C-ELISA, and holds patents on the methods and compositions for hepcidin measurement. He has received honoraria from Centocor-Ortho Research and Development, Inc. The other authors have indicated they have no financial relationships relevant to this article to disclose.

\textbf{FUNDING:} This work was selected for study by the FORGE Canada Consortium and funded by the Government of Canada through Genome Canada, the Canadian Institutes of Health Research and the Ontario Genomics Institute (OGI-049). Additional funding was provided by Genome Quebec, Genome British Columbia, the McLaughlin Centre, the Canadian Gene Cure Foundation, and the Cole Foundation. Dr Jabado is the recipient of salary support from the Fonds de la Recherche en Sante au Quebec, and Dr Khong-Quang is the recipient of a studentship from the Foundation of Stars. Dr Finberg is a recipient of a Burroughs Welcome Fund Career Award for Medical Scientists and National Institutes of Health grant K08 DK084204.
Iron Refractory Iron Deficiency Anemia: Presentation With Hyperferritinemia and Response to Oral Iron Therapy

Dong-Anh Khuong-Quang, Jeremy Schwartzentruber, Mark Westerman, Pierre Lepage, Karin E. Finberg, Jacek Majewski and Nada Jabado

Pediatrics 2013;131;e620; originally published online January 14, 2013;
DOI: 10.1542/peds.2012-1303

Updated Information & Services
including high resolution figures, can be found at:
/content/131/2/e620.full.html

Supplementary Material
Supplementary material can be found at:
/content/suppl/2013/01/09/peds.2012-1303.DCSupplemental.html

References
This article cites 23 articles, 12 of which can be accessed free at:
/content/131/2/e620.full.html#ref-list-1

Citations
This article has been cited by 2 HighWire-hosted articles:
/content/131/2/e620.full.html#related-urls

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Hematology/Oncology
/cgi/collection/hematology:oncology_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml
Iron Refractory Iron Deficiency Anemia: Presentation With Hyperferritinemia and Response to Oral Iron Therapy
Dong-Anh Khuong-Quang, Jeremy Schwartzentruber, Mark Westerman, Pierre Lepage, Karin E. Finberg, Jacek Majewski and Nada Jabado
Pediatrics 2013;131;e620; originally published online January 14, 2013;
DOI: 10.1542/peds.2012-1303

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/131/2/e620.full.html