A genetic cause for iron deficiency

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The discovery of a gene for a rare form of inherited iron deficiency may provide clues to iron deficiency in the general population – particularly iron deficiency that doesn't respond to iron supplements - and suggests a new treatment approach. The finding was published online by the journal *Nature Genetics* on April 13.

Iron deficiency is the most common nutritional deficiency and the leading cause of anemia in the United States. Most cases are easily reversed with oral iron supplements, but over the years, Mark Fleming, MD, DPhil, interim Pathologist-in-Chief at Children's Hospital Boston, and pediatric hematologist Nancy Andrews, MD, PhD, formerly of Children's and now Dean of Duke University School of Medicine, had been referred a number of children with iron deficiency anemia who didn't respond to oral supplements, and only poorly to intravenous iron.

The cause of their condition – termed iron-refractory iron-deficiency anemia (IRIDA) –was a mystery. The children all had good diets, and none had any condition that might interfere with iron absorption or cause chronic blood loss, the most common causes of iron deficiency. All had evidence of anemia from a very early age, and many also had siblings with iron deficiency anemia. Seeing reports of several similarly afflicted families in the medical literature, Fleming and Andrews were convinced that genetics was a factor.

"After nearly 15 years, we finally had enough families that we could begin to think about positionally cloning the gene for the disorder," says Fleming.

Fleming and Andrews, experts in iron metabolism, and their colleagues Karin Finberg, MD, PhD, and Matthew Heeney, MD, studied five extended families with more than one chronically iron-deficient member. They found a variety of mutations in a gene called TMPRSS6 (the acronym stands for transmembrane serine protease S6) in all of these families, as well as several patients without a family history of the disorder.

Although IRIDA is quite rare, the authors believe it might be the extreme end of a broad continuum of disease, since TMPRSS6 mutations varied widely in the five families and caused different degrees of iron deficiency and anemia.

“Our observations suggest that more common forms of iron deficiency anemia may have a genetic component,” says Andrews.

All patients in the study apparently had recessive mutations, since their parents did not have iron deficiency anemia. The investigators now want to determine whether people with just a single abnormal copy of TMPRSS6 have subtler alterations in iron absorption that might not otherwise have come to the attention of a hematologist.

Although the mechanism is still unknown, deficiency of the TMPRSS6 protein causes the body to produce too much hepcidin, a hormone that inhibits iron absorption by the intestine. Normally, hepcidin is produced to protect the body against iron overload – but patients with IRIDA make large amounts of hepcidin even though they are iron deficient. “People with this disorder make too much hepcidin, putting the brakes on iron absorption inappropriately,” Fleming says.

In addition, patients with TMPRSS6 mutations cannot make new red blood cells efficiently because the iron needed to make them comes from macrophages, and hepcidin causes macrophages to hold on to iron.

This explains the patients' poor response to intravenous iron – the iron is trapped in macrophages and cannot be used for red blood cell production.

The fact that TMPRSS6 regulates hepcidin may open up new avenues for therapy, the researchers say. For example, blocking TMPRSS6 may help patients with iron overload disorders make more hepcidin in order to limit intestinal iron absorption. Conversely, stimulating TMPRSS6 may have therapeutic benefit in certain patients with anemia, particularly those in which hepcidin is overproduced.

Source: Children's Hospital Boston