Human Gene Tied to Rare Iron-Deficiency Disorder

Points Toward Mechanism that Blocks Iron Transport

A ter 12 years of clinical and laboratory research, a team of physicians and scientists has identified the genetic defect that causes a rare iron-deficiency disorder they have termed iron-refractory iron-deficiency anemia. The journey started in 1994, when a child was referred to Nancy Andrews, then a pediatric hematologist at Children’s Hospital Boston, because of her expertise in iron metabolism. The patient had severe iron deficiency anemia that on iron supplements did not correct. Even intravenous iron did not fully correct the anemia. Because of the early presentation, Andrews suspected the anemia was congenital. A subsequent sibling showed a similar clinical picture, strengthening her hunch. One pair of siblings, however, simply was not enough to go on. So Andrews, now dean of Duke University School of Medicine, and co-author senior researcher Mark Fleming, then in the Andrews lab at CHB, is now at Duke, and co-author Dean Capecchi, lead research technologist in the Fleming lab, had begun to sequence this subset of genes in the stored DNA of their IRDA patients, the investigators got another lucky break.

“We had just started sequencing them when the Boelter group released their abstract for the American Society of Hematology meeting,” said Fleming. “This abstract, submitted by Ernest Boulet from the Scripps Research Institute, described a mouse model with a defect in the murine homolog of a gene called Tmprss6 within the 22q11.2-13 region. In terms of IRDA, said Fleming, “this mouse looked very similar to our patients.” She and Capecchi immediately sequenced that gene and saw a variety of mutations. “We realized wild hit the jackpot.” Their results appeared online in the April 13 Nature Genetics.

Slow and Steady “The real hero in this whole thing was the mouse they and the slow genetic process of testing it.” Fleming said. Fleming and Capecchi set out to investigate the gene, which they had inappropriately elevated levels of hepcidin, a hormone produced by the liver that regulates iron absorption, to find that the IRDA patients’ “in some form of iron overload in which there is little hepcidin. This work will help determine if pharmacological modulation of ‘J Kemp could dampen the iron overload of hemochromatosis.”

Meanwhile, in the clinic, Heeney and Fleming will explore the possibility that this gene could also be involved in less severe forms of iron deficiency. “To investigate this hypothesis, we will continue their clinical protocol of collecting and analyzing data from patients. “Every experienced hematologist will tell you about a patient. ‘Oh, yes, old Mrs. Williams. She had iron deficiency, and we just couldn’t make it better,’” said Heeney. “It would be great to be able to identify those with a genetic risk for this and, also, it would be even better to be able to do something about it.”

If this broad influence pans out, this discovery could trigger a change in thinking about iron deficiency. The same way clinicians now know that diabetes has a genetic component, there may also be a genetic susceptibility to iron deficiency.” There might be estimating reas whether you want to do more than the conventional therapy of supplemental oral iron, said Heeney. “We’re trying to break down the notion that nutritional deficiencies are purely nutritional deficiencies.”

—Elizabeth Dougarty

Iron Deficiency (from page 3)

paperwork and legwork, most of which has become more burdensome over time. According to Fleming, the original 1998 protocol and consent were right and one page long, respectively. They stuck to 40 and eight pages today. Though the regulatory changes driving this increase are in the best interest of research subjects, Fleming said, they also increase the energy required to do clinical research.

In this case, the extra effort paid off. Those with IRDA were found to have severe Tmprss6 mutations that likely cause loss of function in the encoded protein. Family members who have at least one normal copy of the Tmprss6 gene do not have IRDA. Moreover, mutations found in families with IRDA were not detected in chromosomes from a large group of control individuals.

Though the team has not yet identified a molecular mechanism by which the Tmprss6 mutation impairs iron absorption, they hypothesized that a loss of function would result in inappropriate high levels of hepcidin, a hormone produced by the liver that regulates iron absorption (see figure, page 1) and, normally, iron deficiency anemia results even though the house is warmer.” In the Andrews lab at Duke, Fleming is working to understand the exact molecular mechanism by which loss of normal function leads to elevated hepcidin levels and IRDA in human and mouse models. Fleming also plans to cross-tip transfusor-deficient mice with mouse models of hemochromatosis, a