

# Europe's most common genetic disease is a liver disorder

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Much less widely known than the dangerous consequences of iron deficiencies is the fact that too much iron can also cause problems. The exact origin of the genetic iron overload disorder hereditary hemochromatosis (HH) has remained elusive. In a joint effort, researchers from the European Molecular Biology Laboratory (EMBL) and the University of Heidelberg, Germany, have now discovered that HH is a liver disease. They report in the current issue of *Cell Metabolism* that the disorder develops when a crucial gene is lacking in liver cells.

Iron is essential for our body, because it is a central component of red blood cells. Too little iron can lead to dangerous anemias, but also too much iron can be detrimental as it promotes the formation of toxic radicals that lead to tissue damage. Hereditary hemochromatosis is an iron overload disorder that, affecting about one in 300 people, is probably the most common genetic disorder in Europe. Scientists have identified a gene, called HFE, that when mutated causes hemochromatosis in mice and humans. But as yet it is unknown in which tissue or organ the gene is acting to prevent iron overload.

A group of researchers around Matthias Hentze at EMBL and Martina Muckenthaler and Wolfgang Stremmel at the University of Heidelberg have now found that mice that are genetically engineered to lack HFE only in liver cells show all central features of the disease.

“For a long time scientists thought of HH as a disease of the intestine, because this is where iron uptake actually takes place,” says Matthias Hentze, Associate Director of EMBL. “Our research now reveals the crucial point is actually the liver and explains why HH patients suffer from increased iron absorption.”

HFE encodes a protein that is likely involved in transmitting signals about the current iron contents

of the body to liver cells. In response to these signals, the liver cells make a special iron hormone, hepcidin that is released into the blood stream and reduces iron uptake in the intestine.

“HFE influences hepcidin expression through a series of intermediate molecules, but when the HFE gene is mutated the result is that less hepcidin is produced. This in turn means iron uptake in the intestine cannot be limited as effectively and an overload develops,” says Martina Muckenthaler, professor at the University of Heidelberg.

The research is a landmark for the joint Molecular Medicine Partnership Unit of EMBL and the University of Heidelberg. The Unit is dedicated to elucidating the molecular mechanisms of a range of different diseases, among which disorders of iron metabolism constitute a central focus.

Source: European Molecular Biology Laboratory

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