Genetic study of the causes of excess liver iron may lead to better treatment

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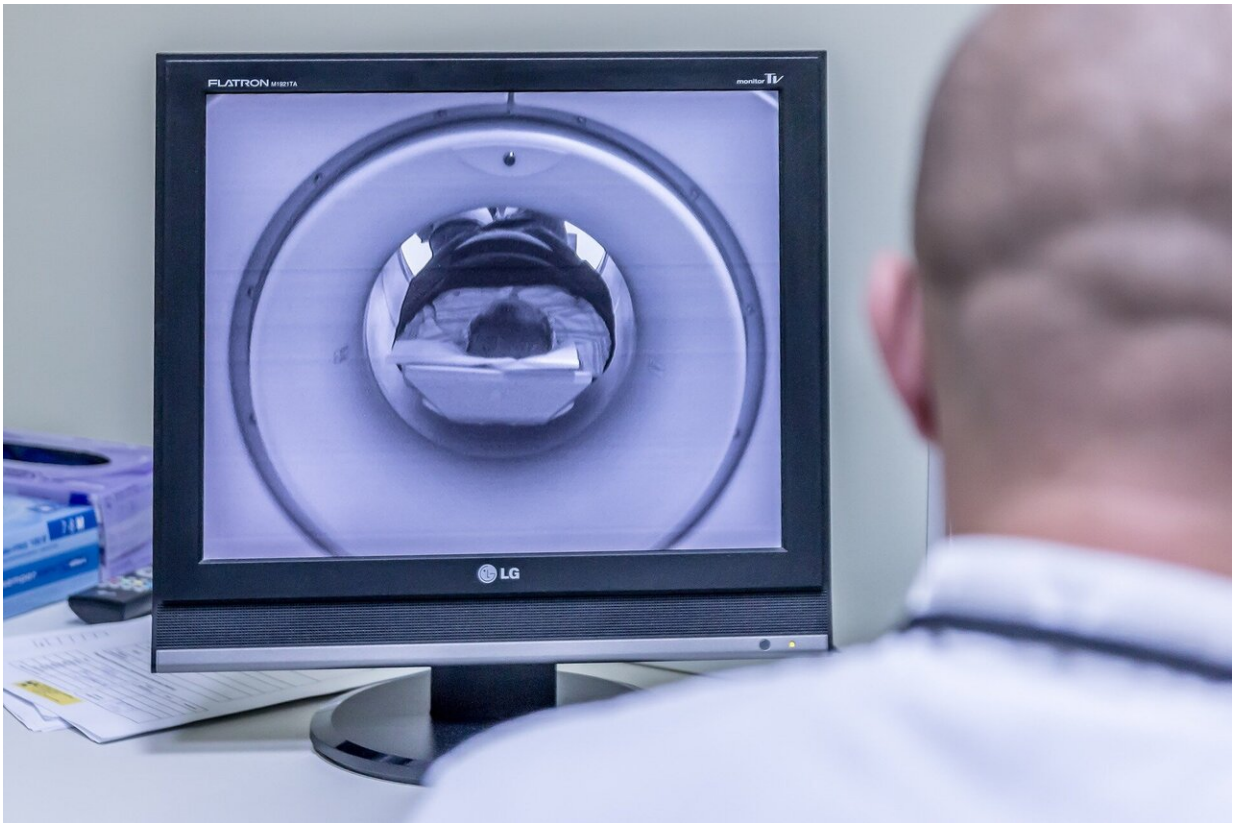

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High levels of iron in the liver are linked to a number of serious health conditions including cancer, diabetes, high blood pressure and cardiovascular as well as liver disease. But measuring liver iron is

difficult and until recently could only be done through an invasive biopsy.

Now researchers from University of Exeter, U.K., together with colleagues from the University of Westminster,London, UK, Lund University, Sweden and Perspectum Diagnostics, Owford, UK, have shown that genes regulating iron metabolism in the body are responsible for excess liver iron. These genes are the driving cause of high levels of iron in the liver in populations of European, especially Celtic, ancestry, and suggest that this is most likely a systemic and not organ-related problem. This finding can point the way to simple strategies for reducing the excess. The research is presented at the annual conference of the European Society of Human Genetics today (Monday).

Dr. Hanieh Yaghootkar and colleagues carried out genome-wide association studies on liver iron content, measured via magnetic resonance imaging (MRI), in 8200 volunteers who had provided biological samples to the U.K. Biobank. Genome-wide association studies work by scanning markers across the complete sets of DNA of large numbers of people in order to find genetic variants associated with a particular condition.

They found three independent genetic variants associated with higher liver iron and involved in the production of hepcidin, a protein that regulates the entry of iron into the blood. The results were validated in 1500 individuals whose data had been collected in the pan-European Diabetes Research on Patient Stratification (DIRECT) Consortium. "This is the first time such a study has been carried out in an unselected, large population," says Dr. Yaghootkar.

The investigators used a genetic approach to explore the causal link between higher waist-to-hip ratio and elevated liver iron content. This provided genetic evidence that higher central (abdominal) obesity was

associated with increased liver iron levels. "There are animal studies that indicate that fat cells trigger macrophages, a type of white blood cell, to cause inflammation, and that this in turn leads to defective iron handling in the liver. We need to research this association further, but it is a plausible explanation of the phenomenon," says Dr. Yaghootkar.

The fact that the mechanisms causing elevated liver iron were generalized and not organ-specific means that high iron levels probably occur in other organs too, including the brain. The researchers found an association between excess iron and many other disorders, including neuropsychiatric conditions. Because the clinical manifestations of elevated iron levels are so diverse, a multi-specialty approach will be needed to assess and evaluate new therapies, including treating patients with hepcidin to reduce iron accumulation.

MRI is continuing for 100,000 individuals in the Biobank study. "This will allow us to find many more genetic factors associated with this trait. We are also interested in performing such studies in other ethnicities, since our current results are only valid for people of European ancestry," Dr. Yaghootar will conclude.

Chair of the ESHG conference, Professor Joris Veltman, Director of the Institute of Genetic Medicine at Newcastle University, Newcastle upon Tyne, U.K., said: "Iron overload is bad for the body and needs to be tightly regulated. The genetic study presented at the ESHG today reveals a key role for genes regulating iron metabolism, and also revealed a link between certain types of obesity and iron overload."

More information: Abstract no: C. 21.5 Genome-wide association study of MRI liver iron content in 9,800 individuals yields new insights into its link with hepatic and extrahepatic diseases

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