Title: **Researchers use novel gene mapping approach to find new iron metabolism gene**

Researchers from the Center for Precision Medicine Research at Marshfield Clinic Research Institute (MCRI) recently discovered fibroblast growth factor 6 (FGF-6), a gene that helps regulate iron, using a new approach to mapping disease genes.

The researchers believe treatments targeting this gene could help those with conditions such as hemochromatosis, anemia, sclerosis and cancers. These findings were recently reported in the leading hematology journal, *Blood*.

The new approach finds genes with genetic variants that disrupt the function of both copies of a gene on a pair of chromosomes and could find additional genes for other conditions.

“This method provides a new angle to identify disease genes which cannot be identified by conventional statistic method. We are working to use this novel method to discover genes for other traits and diseases such as obesity, type 2 diabetes and rheumatoid arthritis” said Shicheng Guo, Ph.D., one of the primary authors of the study and postdoctoral fellow for Marshfield Clinic Research Institute.

The new approach, termed an exome-wide, gene-based recessive diplotype scan, was first used to study hemochromatosis by analyzing DNA samples from the Personalized Medicine Research Project at the Research Institute. Hemochromatosis is a genetic disorder characterized by excessive iron accumulation that results in tissue damage. Common symptoms include skin bronzing, liver disease, diabetes mellitus, arthorapathy, amenorrhea and impotence.

Upon further testing, the team found that the FGF-6 gene interacts with the iron metabolism subnetwork and could be used to regulate iron for patients. FGF-6 decreases iron uptake in liver cells and increases hepcidin (encoded by *HAMP*) expression. Hepcidin regulates the entry of iron into our circulation. FGF-6 may be able to be used to increase iron or inhibited to reduce iron.

**More about the study**

Frequently, disease gene mapping experiments rely on genome-wide association studies (GWAS). While these studies are effective at identifying additive disease-susceptibility effects at single nucleotide polymorphisms (SNPs), this approach ignores more complex effects.

By specifically looking at disruptive variants on both copies of a gene, the researchers were able to discover FGF-6. The authors speculate that the large number of very rare genetic variants found in humans may produce these effects across a wide array of diseases as individuals without one copy of a normally functioning gene may be predisposed to pathologies.

Genome-wide association studies have difficulty finding these genes, but the new recessive diplotype scan is a powerful method to discover these disease genes. Once these disease genes are found, they can serve as targets for new treatments.

In the study, the authors not only show that the FGF-6 protein regulates a key hormone in iron metabolism, hepcidin, but that the loss-of-function variants in *FGF-6*, strongly attenuate the signaling in this important iron pathway.

The researchers also show that FGF-6 changes the uptake of iron into cells. Further, they demonstrate the involvement of FGF-6 in the iron overload condition observed in cancers and systemic sclerosis.

The authors provide evidence that the disruption of iron metabolism by the *FGF6* variants are driven by dysfunctional binding to heparin and the FGF receptor. As such, the study provides a new understanding of the mechanisms underlying iron homeostasis and may aid the development of therapeutic interventions for patients with hemochromatosis and possibly anemia.

Detailed functional studies using molecular and cell experiments conducted by scientists at Fudan University confirmed the discovery.

This study was completed through a collaboration between the Marshfield Clinic Research Institute, University of Wisconsin-Madison, Fudan University, The Ohio State University, Soochow University, Marquette University and the Fudan Huashan Hospital.

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This study was supported by the Clinical and Translational Science Award (CTSA) program (1UL1RR025011), the National Center for Advancing Translational Sciences (NCATS) grant (9U54TR000021), NCATS grant UL1TR000427 and Marshfield Clinic Research Institute grant SCH10218 and generous donors to the Marshfield Clinic Health System.

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