**New method to map disease genes reveals a novel iron metabolism gene**

Scientists from the Marshfield Clinic Research Institute have developed a new statistical genetics method that has been applied to the iron overload disease, hemochromatosis. The approach specifically identifies genes harboring genetic variants that disrupt the function of both copies of a gene on a pair of chromosomes. This new way of mapping disease genes was termed an exome-wide, gene-based recessive diplotype scan and was applied to samples from the Marshfield Clinic Personalized Medicine Research Project (PMRP). PMRP subjects are from the homogeneous Central Wisconsin population and have been effectively used in numerous human genetics studies. This work has led to the identification of a new hemochromatosis gene and has revealed a novel mechanism involved in iron metabolism. Importantly, detailed functional studies using molecular and cell experiments conducted by scientists at Fudan University confirmed the discovery. The research team reported their findings in the leading hematology journal, *Blood*.

Frequently, disease gene mapping experiments rely on genome-wide association studies (GWAS). While GWAS 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 a novel iron overload gene, the fibroblast growth factor 6 (*FGF6*) gene. 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. GWAS 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 *FGF6*, 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.

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

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Full paper: “A Gene-Based Recessive Diplotype Exome Scan Discovers FGF6, a Novel Hepcidin-Regulating Iron Metabolism Gene” Authors of the study are Shicheng Guo#, Shuai Jiang#, Narendranath Epperla, Yanyun Ma, Mehdi Maadooliat, Zhan Ye, Brent Olson, Minghua Wang, Terrie Kitchner, Jeffrey Joyce, Robert Strenn, Joseph J. Mazza, Jennifer K. Meece, Wenyu Wu, Li Jin, Judith A. Smith, Jiucun Wang\*, Steven J. Schrodi\*

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