**New method could help mapping disease genes with exome genotyping data**

Scientists from the Marshfield Clinic Research Institute have developed a new statistic method that could identify novel disease genes with exome-wide array/sequencing data.

The study provided a way to map disease genes with a novel method named: gene-based recessive diplotype exome scanning approach and applied the method they identified a new hemochromatosis gene with exome-array data derived from Marshfield Clinic Personalized Medicine Research Project (PMRP). Researchers published their findings Feb 25th 2019 in Blood.

Genome-wide Association Studies (GWAS) are well-designed to detect additive effects of modest effect sizes. However, recessive single site effects and compound heterozygosit may reveal additional genes underlying complex diseases which may be ignored by conventional GWAS study. Furthermore, Deep sequencing studies have conclusively shown a vast reservoir of rare variants segregating in human populations. Rare variants in functional categories (e.g., missense, regulatory motifs) may generate pathogenic effects through recessively-acting diplotypes, and such effects are apt to remain concealed from standard GWAS analyses.

In the study, the authors applied the novel gene-based recessive diplotypes approach in the hemochromatosis samples with exome-array data derived from Marshfield Clinic Personalized Medicine Research Project (PMRP) and *HFE* (Hereditary Hemochromatosis Protein) and *FGF6*, a fibroblast growth factor-encoding gene, was identified to be a potential hemochromatosis associated genes. Genetic variations of FGF6 within and nearby heprin-binding sites (HBS) and FGF receptor binding domains (FGFR) might affect the bindings among them. Both heprin and FGFR signals have been shown to be associated with another important iron homeostasis protein: Hepcidin (encoded by *HAMP*). With the collaboration from Fudan University, FGF6 was up-regulated and down-regulated in multiple cell experiments and regulation to *HAPM* expression was confirmed. The authors also found FGF6 might be involved with the iron over-load in cancers and systemic sclerosis. The study provided new understanding to the mechanisms of iron metabolism dysfunction and can aid the development of therapeutic interventions for patients with hemochromatosis and possibly anemia.

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The Central Wisconsin population is largely stationary and primarily derived from Bavarian migrants in the late 1800s. The population carries high utility for disease gene mapping through reduction in confounding by population stratification and lower expected levels of allelic and locus heterogeneity. In addition, environmental exposures are thought to be relatively uniform across this population. For these reasons, the PMRP has been effectively used in numerous human genetics studies.

This study completed by the collaboration from Marshfield Clinic Research Institute (MCRI), University of Wisconsin-Madison, Madison (UW-Madison), Fudan University, The Ohio State University, Marquette University and 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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