# Nature Genetics 25 September 2018

Editorial Office

One New York Plaza, Suite 4500

New York, NY 1004-1562, USA

T: +1 212 726 9314

Email: [genetics@us.nature.com](mailto:genetics@us.nature.com)

Dear Editor,

I am submitting the Letter entitled “A Gene-Based Recessive Diplotype Exome Scan Discovers *FGF6* as a Novel Iron Metabolism Gene” on behalf of all authors for consideration of publication in *Nature Genetics*. In this original manuscript, we conduct an exome-wide, gene-based scan for single site recessive effects and compound heterozygous effects underlying iron overload susceptibility. We have identified *FGF6*, encoding for the fibroblast growth factor 6, as being experiment-wide significant in our study and demonstrate that FGF-6 induces transcriptional regulation of hepcidin—a central hormone central in the maintenance of iron homeostasis and decreases ferrous absorption in hepatocytes. Moreover, specific *FGF6* variants identified in our study are shown to carry functional effects, reducing FGF-6 activity compared to wildtype alleles. These findings reveal a novel iron metabolism mechanism and will motivate subsequent studies in this field. Additionally, our approach uses exome genotype data to interrogate a mode of inheritance—recessive diplotypes—that standard GWAS statistical methods are poorly powered to uncover. Hence, not only does our study discover a novel protein involved in iron metabolism, but we foresee our genetic approach enjoying wide applicability across all complex diseases using existing genetic datasets. It is for these reasons that we believe the readers of *Nature Genetics* will find this manuscript highly interesting.

This manuscript has not been submitted elsewhere. Thank you for your consideration.

Sincerely,

cid:image002.jpg@01D0512D.1C082B60

Steven J. Schrodi, Ph.D.

Principal Investigator

Laboratory of Immunopathology Genomics and Theoretical Genetics

Center for Human Genetics

Marshfield Clinic Research Institute

1000 North Oak Avenue -- MLR

Marshfield, WI  54449

Tel: (715) 221-6443

Email: [schrodi.steven@mcrf.mfldclin.edu](mailto:schrodi.steven@mcrf.mfldclin.edu)

Faculty, Computation and Informatics in Biology and Medicine

University of Wisconsin-Madison

Email: [schrodi@wisc.edu](mailto:schrodi@wisc.edu)