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Nature Genetics
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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,

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