Dear Editor,

We are delighted to submit the manuscript “Detection and replication of epistasis influencing transcription in humans” for publication as a Letter in ***Nature***. To our knowledge it provides the first empirical evidence for a central question in human complex trait genetics and evolutionary theory that will be of interest to a wide audience. Our study contradicts the prevailing view that performing exhaustive epistatic genome scans are both computationally impossible and experimentally lack power.

(i) Why is this study important?

***Nature*** published the first major genome wide association study (GWAS) (the WTCCC paper, ***Nature*** 2007), and since then thousands of single nucleotide polymorphisms (SNPs) have been found to affect complex traits in human populations, including common diseases. Typically the effects of the SNPs have been assumed to act independently and additively. But there has been a long-standing debate about how much the effect of a SNP on a trait depends on the genotypes of other SNPs elsewhere in the genome (epistasis) (for example see: Cordell, ***Nature Reviews Genetics*** 2011; Bloom *et al*. ***Nature*** 2013; Breen *et al*. ***Nature*** 2012). Though epistasis has been revealed in some model organisms and domesticated species, very few convincing examples have been demonstrated in humans.

One of the next frontiers in human genetics is extending GWAS to identify genetic interactions. Here we present results from the first full scale analysis of epistasis across the genome for the expression levels of thousands of genes in humans. We believe this study is the first to identify and replicate the existence of epistasis in humans.

(ii) What did we find?

Using a study design that maximizes statistical power, and using cutting-edge computational hardware and software, we report for the first time the detection of hundreds of pairs of common, natural polymorphisms in humans that exhibit epistasis. Crucially, we demonstrate that these patterns of epistasis replicate in two completely independent populations. Complex networks of epistatic effects involving numerous SNPs are replicable, and a sizeable fraction of gene expression levels are influenced by epistasis. We present results from functional analysis of epistatic pairs and suggest novel putative mechanisms that might lead to epistasis.

(iii) Why is this study interesting to a wide audience?

This is the first empirical evidence that the phenomenon of epistasis may arise from common, natural polymorphisms in humans. This has implications in

* Complex trait genetics – for disease prediction and gene mapping, and understanding the genetic architecture of complex traits
* Computational biology – this study presents perhaps the largest statistical analysis ever performed in the field of genetics (over 1 quadrillion statistical tests)
* Evolutionary genetics – epistasis is a necessary mechanism for the maintenance of phenotypic variation in human populations
* Molecular biology – the mechanisms underlying phenotypic variation can be better explored when it is known how different genes interact with one another.

We suggest the following expert reviewers;

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All authors have approved of submission.

Yours sincerely,

Gibran Hemani, on behalf of all authors