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***. We believe that this is a long awaited study that many thought was computationally impossible. To our knowledge it provides the first empirical evidence for a central question in complex trait genetics and evolutionary theory that will be of interest to a wide audience.

(i) Why is this study important?

***Nature*** published the first major genome wide association study (the WTCCC paper, ***Nature*** 447, 661-678 (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). Numerous recent and not so recent reviews have argued for and against the existence and importance of epistasis, but due to computational and statistical hurdles epistasis is almost never searched for directly in human traits, so empirical evidence has been conspicuously absent.

(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 independent populations. Complex networks of epistatic effects involving up to 19 SNPs are common and replicable, and a sizeable fraction of gene expression levels are influenced by 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
* Molecular biology – the mechanisms underlying phenotypic variation can be better explored when it is known how different genes interact statistically