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***.

(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 are assumed to be independent and additive, but there has been a long standing debate that encompasses evolutionary theory and complex trait genetics about whether 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 its existence and importance, but due to computational and statistical hurdles epistasis is almost never searched for directly.

Using a study design that maximizes statistical power, and cutting edge computational hardware and software, we report for the first time the detection of hundreds of epistatic interactions that influence gene expression in humans. Crucially, we demonstrate that these patterns of epistasis replicate in two independent populations

This study presents perhaps the largest statistical analysis ever performed in the field of genetics (over 1 quadrillion statistical tests), and provides the first empirical evidence for a long standing question: does epistasis exist in