

Dear Editor,

The purpose of this email is to ask whether *Nature Protocols* would be interested in receiving the submission of a manuscript on the methods and framework required for genome-wide epistasis analysis.

We have recently had our manuscript "Detection and replication of epistasis influencing transcription in humans" accepted for publication in *Nature*. This paper reports 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. This paper builds on our previous work on software (Hemani et al. 2011 *Bioinformatics*), theory (Hemani et al., 2013 *PLoS Genetics*), data (Powell et al., 2012 *PLoS One*; Powell et al. 2012 *Genome Research*) and analysis of the genetics of the transcriptome (Powell et al. 2013 *PLoS Genetics*, Westra et al. 2013 *Nature Genetics*).

A fundamental component of this research reported in the *Nature* manuscript was the use of cutting-edge computational hardware and software, as well as a series of specific and robust statistical analyses. Whilst this research focused on gene expression, our analysis framework can be applied to any complex trait or common disease. Our proposal *Nature Protocols* manuscript would include;

1. Expansion of the methods to provide a fuller and more in-depth description of the scientific reasons behind the statistical models.
2. Provide a step-by-step description of the series of analyses required for other researchers to follow. In particular this would focus on required data QC, correct initiation and configuration of software, steps required to avoid false-positives.
3. Include some novel work demonstrating;
 1. The effects of incorrect data normalization on false positives.
 2. Relationship between linkage disequilibrium cutoffs and haplotype effects.
 3. Description of the statistical power to detect epistasis.

I've attached a proof of the current *Nature* manuscript. We look forward to hearing back from you.

Kind regards,

Joseph Powell and Gibran Hemani