Response to: An alternative explanation for apparent epistasis

We thank Wood *et al*. for the interest in our work. Wood *et al*. do not replicate 19/30 of our reported replicated pairwise interactions (Table 1 of Hemani *et al*.) at a multiple testing corrected type-I error rate of 0.05/30 = 0.002, including none of our reported *cis-trans* interactions. For 5/19 pairs they don’t find evidence that these two SNPs together explain any variation, whether additively or non-additively. For those pairs that do replicate, Wood *et al*. report sequenced SNPs (IncSeq SNPs) in *cis* that explain a large proportion of phenotypic variation when fitted singly and additively, and that after a linear (additive) adjustment for the IncSeq SNPs in the InCHIANTI dataset (N = 450) there is no remaining statistically significant interaction variation explained by the original SNP pairs. Wood *et al*. conclude that additive effects of ungenotyped *cis*-eSNP created spurious interaction variation due to the confounding correlation between the pair of genotyped SNPs and the ungenotyped *cis*-eSNP, and claim that this alternative explanation implies that there remains ‘no compelling evidence for widespread epistasis in humans’.

For 11 of the *cis*-*cis* pairs that were replicated by Wood *et al*. there is strong evidence for additional genetic variation over and above the additive variation explained by the IncSeq SNPs, both from SNP association in *cis* (Table 1) and from pedigree analysis [[1](#_ENREF_1)] (Table 2). Hence the IncSeq SNPs are not the only (causal) variants in *cis* for these transcripts and therefore the additive effect of the IncSeq SNPs may contain additive effects of additional variants in *cis*.

Due to lower minor allele frequencies of the IncSeq SNPs many of the pairwise genotype classes are missing, meaning epistatic effects cannot be tested for between the IncSeq SNP and genotyped SNPs. However, for the genotype classes are missing For #/# well-imputed IncSeq SNPs in our BSGS discovery data, there is evidence for interaction variation between the imputed IncSeq SNP and the SNP from the original pair that was in least LD with it (4 df test, p-values #, #.... and #). For the remaining # pairs we cannot rule out a haplotype effect such as postulated by Wood et al. and this may indeed be a more parsimonious explanation for these # pairs.

From the non-replication of the majority of our reported results (likely due to lack of statistical power), no evidence presented for any of the cis-trans interactions, evidence of additional additive variation in cis and evidence of interaction variation for pairs of SNPs that include the IncSeq SNPs themselves, we do not believe that the conclusions drawn by Wood et al. are supported by the data presented. Finally, we did not report that epistasis was ‘widespread’ and in fact pointed out that for gene expression, additive genetic variation explains much more of the total genetic variation than non-additive variation [[1](#_ENREF_1),[2](#_ENREF_2)]. Fine-mapping of both additive and non-additive effects using (imputed) sequence data is an obvious next step in further dissecting genetic for gene expression.

1. Powell JE, Henders AK, McRae AF, Kim J, Hemani G, et al. (2013) Congruence of Additive and Non-Additive Effects on Gene Expression Estimated from Pedigree and SNP Data. PLoS Genet 9.

2. Hemani G, Shakhbazov K, Westra H, Esko T, Henders AK, et al. (2014) Detection and replication of epistasis influencing transcription in humans. Nature In Press.

3. Powell JE, Henders AK, McRae AF, Caracella A, Smith S, et al. (2012) The Brisbane Systems Genetics Study: genetical genomics meets complex trait genetics. PLoS One 7: e35430.

**Table 1 |** Details of additive SNP effects at the cis-locus for each probe. SNP effects are estimated using a conditional analysis, initially fitting the IncSeq SNP, followed by the additionally identified SNPs. For each probe the conditional analysis was run until no additional significant effects were identified.

**Table 2 |** Familial correlations [[3](#_ENREF_3)] and estimates of additive and non-additive variance components from pedigree analysis[[1](#_ENREF_1)].