**Re: An alternative explanation for apparent epistasis**

Wood et al claim that the interaction effects that we detected and replicated in Northern Europeans could be removed by the inclusion of a single fine-mapped cis-acting variant in a relatively underpowered sample of 450 individuals of Italian origin. This paints an overly simplistic interpretation of the genetic architecture for the transcription levels that we reported, and we argue that neither the InChianti data, nor the BSGS data support this conclusion. We will discuss the cis-cis effects and cis-trans effects separately as the same genetic mechanisms do not operate on both.

**Cis-trans effects**

In order to detect most genetic interactions, sample size must be sufficiently large to have adequate representation in each genotype class. For almost all cases in the InChianti data, this criterion was not met for cis-trans effects. As such the original interactions were not replicated, and strong conclusions about these effects cannot be made from the InChianti data alone.

Of the three that did replicate in InChianti (p < 0.05), one remained significant (at the same p-value) even after adjusting for the InChianti variant, and the other two explained almost all the same variance through interaction terms as they did prior to adjusting for the InChianti variant.

In BSGS, 4 of the 11 cis-trans effects remained significant after fitting the InChianti variant (p < 0.05). Fine mapping across all 11 cis-trans regions identified epistatic interactions at imputed SNPs that were significant even after adjusting for the InChianti variant.

An obvious explanation for cis-trans interaction effects being captured by a second cis-acting variant is not forthcoming, but the haplotype model described by Wood et al neither captures all the epistatic variance, nor offers a plausible mechanism by which cis-trans interaction terms might manifest due to a single cis-acting locus. In addition, a single additive variant model is not consistent with our observation that those gene expression probes that were influenced by multiple interactions exhibited non-additive genetic variance as estimated in family studies (table 1).

**Cis-cis effects**

Haplotype effects, like those postulated by Wood et al, are known to be confounding factors in cis-cis interactions and we stated this in the original manuscript. It is not surprising that a single variant can tag two interacting variants, and this observation is uninformative as to the true underlying model. Convincing evidence for cis-cis interactions does exist where the experimental design is appropriate (Lappalainen 2011), and abundant evidence exists for multiple cis-acting variants at a single locus, including for those gene expression levels in these data.

- As reported in Westra et al, and as replicated in BSGS and InChianti, conditional analysis demonstrates that there are multiple additive effects working in cis in addition to the InChianti variants, so although a single cis-InChianti variant is a simple explanation, it is not consistent with the empirically deduced genetic architecture.

- Epistatic interactions between cis-cis effects remain in BSGS for 7 of the 15 original interactions even after adjusting for the InChianti variant (p < 0.05)

- Epistatic interactions between the InChianti SNP and the second SNP remain for 6 of the 15 original interactions after (p < 0.05)

- Fine mapping of genetic variants with imputed data in BSGS identifies significant interactions (p < 0.05) in 12 of the 15 cases even after adjusting for the InChianti variant.

Finally, we make an important final remark that Wood et al misrepresented the original manuscript, stating that our claim was that epistasis is widespread in humans. We must emphasise that no such claim was made. On the contrary we inferred that additive variance was substantially more abundant than non-additive variance. Our initial claim was that instances of epistasis could be robustly detected, and following further analysis it is evident that the data supports this conclusion.

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| **ILMN\_GENE** | **PROBE\_ID** | **PP** | **PO** | **DZ** | **SIB** | **MZ** | **h2** | **d2** |
| ADK | ILMN\_2358626 | 0.095 | 0.143 | 0.123 | 0.093 | 0.376 | 0.41 | 0.12 |
| ATP13A1 | ILMN\_2134224 | -0.02 | 0.162 | 0.138 | 0.202 | 0.606 | 0.67 | 0.16 |
| C21ORF57 | ILMN\_1795836 | -0.023 | 0.153 | 0.169 | 0.231 | 0.47 | 0.51 | 0.08 |
| CSTB | ILMN\_1761797 | -0.064 | 0.156 | 0.15 | 0.171 | 0.299 | 0.25 | 0.04 |
| CTSC | ILMN\_2242463 | 0.122 | 0.142 | 0.202 | 0.161 | 0.374 | 0.27 | 0.08 |
| FN3KRP | ILMN\_1652333 | -0.071 | 0.166 | 0.138 | 0.212 | 0.434 | 0.31 | 0.11 |
| GAA | ILMN\_2410783 | -0.047 | 0.163 | 0.143 | 0.13 | 0.387 | 0.39 | 0.06 |
| HNRPH1 | ILMN\_2101920 | 0.015 | 0.152 | 0.122 | 0.129 | 0.237 | 0.17 | 0.05 |
| LAX1 | ILMN\_1769782 | -0.065 | 0.142 | 0.175 | 0.19 | 0.356 | 0.27 | 0.04 |
| MBNL1 | ILMN\_2313158 | 0.022 | 0.179 | 0.158 | 0.184 | 0.239 | 0.18 | 0.11 |
| NAPRT1 | ILMN\_1710752 | -0.062 | 0.186 | 0.208 | 0.283 | 0.506 | 0.37 | 0.14 |
| NCL | ILMN\_2121437 | -0.019 | 0.141 | 0.178 | 0.145 | 0.399 | 0.31 | 0.08 |
| PRMT2 | ILMN\_1675038 | -0.045 | 0.199 | 0.193 | 0.183 | 0.402 | 0.34 | 0.06 |
| SNORD14A | ILMN\_1799381 | 0.028 | 0.17 | 0.146 | 0.13 | 0.525 | 0.43 | 0.14 |
| TMEM149 | ILMN\_1786426 | 0.065 | 0.267 | 0.233 | 0.173 | 0.489 | 0.41 | 0.09 |
| VASP | ILMN\_1743646 | -0.003 | 0.144 | 0.271 | 0.179 | 0.52 | 0.38 | 0.13 |

Table 1 | correlation coefficients between relative pairs in BSGS and estimates of additive (h2) and non-additive (d2) variance components.