Dear Magdalena,

Regarding: Nature manuscript 2013-07-08948 (“Detection and replication of epistasis influencing human transcription”)

Thank you for sending comments from the two reviewers of our manuscript. We were obviously disappointed with the decision. Reviewer 1 was very positive and recognized the novelty and scientific advance. Reviewer 2 misunderstood and misrepresented the key components of our study. We note the very strong contrast between the two sets of comments. A number of comments from Reviewer 2 are clearly based upon an opinion and not qualified or quantified by evidence. In particular, Reviewer 2 speculates that the results are analysis artifacts without suggestion how or why these could have occurred, and despite our strong empirical evidence of replication in 2 independent datasets.

In any case, all of the comments made by the reviewers are easy to address in a robust manner. In addition, we can address the two concerns stated in your email.

1. Advances made by this study

This study uses advanced computational methodology to answer the previously unresolved question of whether epistasis arises in human complex traits. As Reviewer 1 points out, the topic of epistasis is of considerable significance to the field of complex traits, primarily because it has important implications for disease prediction and evolutionary theory. Despite numerous highly cited reviews debating its importance over the past decade, statistical and computational limitations have made it impossible to search for epistasis empirically. Reviewer 2 correctly states that epistasis has already been shown (as do we in the manuscript!), but the crucial difference is that when epistasis has been previously reported it has been in model organisms (e.g. yeast, chickens, mice) where genetic variation is generated artificially (e.g. through gene knockout studies or extreme selective breeding). This is largely irrelevant to the topic of our study, and the presentation of credible empirical evidence for epistasis influencing human complex traits is conspicuously absent from the literature.

2. Statistical robustness

We were surprised that Reviewer 2 raised concerns about the statistical robustness of our analysis without specifying where any errors may have arisen. We believe that statistical robustness is of the utmost importance, particularly when dealing with such a difficult problem, hence the emphasis of the manuscript was placed on the epistatic interactions that showed replication in two independent datasets, and this is the gold-standard for any statistical inference. The high degree of replication and concordance between discovery and replication populations reflects the robustness and highly conservative nature of the statistical methods we have used.

Since receiving the reviewer comments we have performed three further extensive analyses to demonstrate the statistical robustness of these results. First, we calculated the type 1 error rate of the discovery stage. Second, we quantified the similarity of patterns of epistasis between independent datasets. Third, we performed simulations that demonstrate that replication of epistasis in independent datasets is statistically disadvantaged compared to replication of additive effects. All three of these additional analyses provide further strong support for our results, and we believe that our study has been strengthened further through their inclusion. In addition we have sought to clarify sections of the manuscript that may have led to any confusion regarding the methods used or the statistical inferences drawn. In doing so, large sections have been completely rewritten.

Attached is a fully revised version of the manuscript and a detailed point-by-point response to the reviewers’ comments. We would be grateful if you would consider sending these to the reviewers (and/or to other reviewers) for further consideration.

Kind regards,

Peter Visscher and Gibran Hemani, on behalf of all authors