Dear Editors –

We write in regard to your request for voluntary retraction of our study, Hemani *et al.* “Detection and replication of epistasis influencing transcription in humans” published in *Nature* on 10 April, 2014 (volume 508, pp 249-253). After consultation among ourselves and with colleagues, we are unanimous in the position that the reasons that you provided do not fairly reflect the issues surrounding this paper, and we believe that retraction on those grounds would be in opposition to the normal scientific process.

**Background**

In the two weeks after publication, we received correspondence from Wood *et al*. proposing an alternate interpretation of the data, which led us to conduct extensive follow-up investigation. Wood *et al*. suggested that many of the epistatic signals, which were detected using a firmly established statistical method, could be abrogated when accounting for haplotype effects. Magdalena Skipper, the handling editor at the time, agreed to publish a Brief Communication Arising (BCA) from Wood *et al.* along with our response. During the time period in which we had to submit our reply to the BCA we were unable to fully resolve the reason for the observation offered by Wood *et al*. We concluded that there was a possibility that their explanation could hold for *cis-cis* interactions, but disputed the explanation for *cis-trans* effects.

To resolve this discrepancy we voluntarily performed substantial further work and identified that in some instances the distribution underlying test statistic deviates from the expected null distribution leading to an increase in the false positive rate. To communicate this to the scientific field we subsequently, in October 2015, submitted an Addendum. Critically, the statistical issue that we have identified is not the explanation offered by Wood *et al*. Also, our addendum shows no inflation of the test statistic for many of our original epistatic signals. Through discussion with the handling editor we were informed that an Addendum would be an appropriate way to communicate our new findings with the scientific community, and that a decision would be made to either publish or not publish the addendum. It has taken numerous emails and phone calls over a period of more than 18 months during which we were enquiring about the decision of whether or not to publish the Addendum.

The external reviewers of the Addendum show a range of opinions, and appear to have been asked to express their thoughts on whether retraction is warranted. During our discussions with the handling editor it was never mentioned to us that reviewers of the addendum would be specially asked if a retraction was appropriate. We would welcome the opportunity to shed light on this issue through publication of the attached Addendum, because it does illuminate a potential issue with the statistical method that has been used extensively throughout the field. However, though we understand that you deal with these issues on a case-by-case basis we strongly believe that retraction of this paper is not in line with the scientific process.

You state in your letter of June 8, 2017, that you have decided that “the conclusions of the paper are no longer supported by the data”. We argue that a) There are several important conclusions in the paper, and issue identified in our Addendum only effects some of them, and importantly only some of the epistatic signals; and b) Every retraction that we can find has arisen because of ‘invalid results’ and though some of our conclusions may have alternative explanations to those that we provided, our results are certainly valid. We expand on these points below.

**Validity of conclusions**

This study was an extra-ordinary computational accomplishment which remains unmatched three years later. It is critical to note that arguably the major claim of the paper is that replicated epistasis is exceedingly rare and where it exists it only explains a minor fraction of the variance in gene expression. This is not in doubt. Retraction would remove from the literature this important observation. There has been extensive debate on the issue, with major reviews (e.g. Carlborg et al 2004; Phillips 2008; Cordell 2009) calling for investigation of the prevalence of epistasis and proportion of phenotypic variance that it explains. Many authors continue to argue for its prevalence, whereas Hemani *et al*. is the strongest comprehensive empirical study establishing its limited role. We note that negative results regarding other aspects of the underlying genetic architecture of complex traits have been published previously also (e.g. Hunt et al 2013 regarding the role of rare variants). A slight change in wording of the title of the paper would have emphasized this conclusion and there would likely be no debate.

The conclusions in dispute are in regard to the few epistatic signals that we detected and replicated in independent samples. We would argue that it remains far from clear that the initial claim of replicated epistasis has been fully refuted.  Our initial response included re-analyses which agreed that there was an alternative interpretation that could explain some of the cases but that their explanation couldn’t be the complete story. The Addendum further establishes this reasoning, and we would point out that of the three external referees, one fully agrees with us, one acknowledges that there is legitimate debate, and only the first categorically suggests retraction without addressing the scientific issues.

The issue that the reviewers and Wood *et al*. raised – namely that moderate levels of LD between each of the two SNPs in an epistatic pair and a single causal allele caused false associations – is not the cause of the issue raised in the Addendum. Instead, it is caused by differences between the actual and theoretical distribution of the *F*-statistic in the presence of additive eQTLs. This is a technical but important point of distinction, and it appears that the reviewers of the addendum may have confused these issues. Importantly, despite this statistical issue that we have identified, we note that many of the putative epistatic associations do not appear to be liable to the problem - as evidenced by figure 1 in the addendum showing no or very little inflation of the test statistic for many of the original pairs.

**Validity of results**

Where it has been argued that this paper should be retracted, the justification cited has been due to ‘invalid conclusions’. We hope it is clear that we do not agree that the conclusions of the study are categorically invalid. But we also feel that it is critical to point out that the *Nature* policy (<http://www.nature.com/authors/policies/corrections.html>) states that retractions arise due to ‘invalid results’.  We performed our analysis using a well-established statistical method that has been used and described extensively in the literature (for examples of high profile cases see Strange *et al.* 2010, Ripke *et al.* 2014; but the method is used extensively - for high profile reviews describing many more instances see Carlborg *et al.* 2004, Cordell 2009, Wei *et al.* 2014).

The novelty in our approach was being able to implement the method at a much larger computational scale than had been achieved previously. This had no bearing on the issues that we described previously. Our results were entirely valid, and while we replicated them in two independent datasets they have subsequently been replicated in two additional independent datasets (including by Wood et al). There was no inappropriate scientific conduct. We followed established scientific practices in adopting extremely stringent evidence thresholds and demanding replication in independent datasets, and published findings that either surprised most in the community for the rarity of the phenomenon, or contradicted long-held assumptions (including those of several of us) of additivity. There was no attempt to push an unfounded or controversial conclusion, there is no claim that the data itself is compromised, and neither the reviewers nor Wood *et al*. question our implementation of the established methods.  Rather, subsequent analysis revealed the alternate interpretation of the test statistic under certain circumstances, which we have taken very considerable efforts to confirm while also investigating further to improve the scientific understanding of the method. All of this is acknowledged in two of your three external opinions and addressed in our proposed Addendum, and establishes without doubt that there was neither fraudulent scientific practice, nor was there a procedural error that would give rise to invalid results.

We have studied examples of retractions in Nature and other journals, including a recent example highlighted to us by Orli (Gao *et al.* 2016, Nature Biotechnology), to understand the circumstances that give rise to retraction. Every retraction that we have seen has arisen due to either mistakes in the implementation or scientific fraud. We fully understand that each case is considered separately, but we need to make it clear that the issues in our paper are fundamentally different to that of fraud or mistakes in implementation. For example, the Gao *et al.* (2016) retracted paper proposed a method that was impossible to replicate by different laboratories following the same protocol. Consequently their results were deemed invalid, presumably due to a technical error in their original experiments. Retraction was appropriate in this case because invalid results contribute nothing but confusion to the scientific record. In contrast, the results in Hemani *et al.* (2014) are entirely replicable when using our protocols in independent datasets. Through the scientific process we now have a clearer understanding of the pitfalls of a method that was previously well established within the community. We fully acknowledge, and have voluntarily taken steps to make the community aware, that this established method is liable to alternative interpretations.

As you will be well aware, there are papers where subsequent research over a three-year period has shone light called into question the initial conclusions. This is the way science does and should work. In the most recent major review on epistasis (Wei *et al.* 2014), a central conclusion is that the vast majority of reported epistatic signals in the literature, arising from a range of different methods, can be attributed to alternative statistical explanations. To our knowledge, this has not resulted in any of the studies being retracted. Such practice would strongly discourage authors to self-correct their published work.

We cannot envisage retraction of this paper being interpreted differently from any other retraction: arising due to fraud or error in implementation; and we believe that it will strike an important body of work from the scientific record. Having read your policy on refutations, corrections, and retractions we see no reason why this debate does not fall within the ordinary category of scientific correspondence with correction. The statement acknowledges that scientific debate is often inconclusive and provides for “Corrigendum or Author Correction where notification of an important error made by the author(s) that affects the publication record or the scientific integrity of the paper, or the reputation of the authors or the journal” occurs, as here.  For these reasons, we respectfully request that you reconsider your decision.

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