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### Retraction Note

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# Retraction Note: Detection and replication of epistasis influencing transcription in humans

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**Gibran Hemani, Konstantin Shakhbazov, Harm-Jan Westra, Tonu Esko, Anjali K. Henders, Allan F. McRae, Jian Yang, Greg Gibson, Nicholas G. Martin, Andres Metspalu, Lude Franke, Grant W. Montgomery, Peter M. Visscher & Joseph E. Powell**

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In this Letter, we reported the detection and replication of epistatic interactions between common single nucleotide polymorphisms (SNPs) that influence gene expression in peripheral blood, including both *cis-cis* and *cis-trans* interactions. We applied a statistical method widely used to detect epistasis. Wood et al.<sup>1</sup> replicated these findings statistically in an additional whole-genome sequencing dataset but found that a large fraction of these epistatic effects could be explained by tagging sequence variants that were not genotyped in our study. They suggested that the interactions arose owing to haplotypes that tag single additive variants. In our response<sup>2</sup>, we argued that such a mechanism could not explain *cis-trans* interactions. We have since undertaken further analyses to try to understand the mechanism that gives rise to *cis-trans* associations<sup>3</sup>.

We find that in the presence of imperfectly tagged *cis*-expression quantitative trait loci with large additive effects, the *F*-test statistic used to detect interactions can result in an inflated false positive rate. As a result, we voice concern over whether our reported epistatic associations arose owing to biological mechanisms or from inflated test statistics caused by imperfectly tagged additive effects. All authors agree with the revised scientific interpretation of the original findings but opinions on whether to voluntarily retract the paper are mixed. Authors Gibran Hemani, Konstantin Shakhbazov, Harm-Jan Westra, Tonu Esko, Anjali K. Henders, Allan F. McRae, Jian Yang, Nicholas G. Martin, Andres Metspalu, Lude Franke, Grant W. Montgomery, Peter M. Visscher and Joseph E. Powell agree with the Retraction. Greg Gibson disagrees with the Retraction.

1. Wood, A. et al. Another explanation for apparent epistasis. *Nature* **514**, E3–E5 (2014).
2. Hemani, G. et al. Hemani et al. reply. *Nature* **514**, E5–E6 (2014).
3. Hemani, G. et al. Phantom epistasis between unlinked loci. *Nature* <https://doi.org/10.1038/s41586-021-3765-z> (2021).

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