

Review of: "Accounting for *cis*-regulatory constraint prioritizes genes likely to affect species-specific traits"

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This is a nice paper describing a new method to incorporate population level gene expression data to prioritize candidate genes under divergent selection between humans and chimpanzees, as identified from allele specific expression differences in a hybrid. This research was possible with the development of allotetraploid organoids that contain the genomes of both these species. The idea is to prioritize genes that are highly constraint in expression WITHIN species, but divergent in expression BETWEEN species for further studies. This concept (i.e. contrasting within to between species variation) is not new but so far has not been applied to human-chimpanzee hybrid allele specific gene expression divergence. It is indeed quite fascination that this is now possible with the development of organoids.

I have only a few very minor criticisms with this paper.

Line 126: "divergence within species" should be replaced by "variation within species"

Line 311: Why did the authors use such a high FDR cutoff here?