Reviewer’s report

Title: Characterizing Human Genomic Coevolution in Locus-Gene Regulatory Interactions

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Reviewer: Roberto Lozano

Reviewer’s report:

Savel and Koyutürk studied the coevolution between eQTL - target gene. They showed that the conservation status between an eQTL locus is predictive of the conservation status of the target gene. They also claim that measures of coevolution can be useful to predict new interactions. The paper is well written and even includes a theoretical framework on protein coevolution and eQTL interactions. Here some comments:

. In the last paragraph of the introduction: "relationship between SNPs and proteins" should be relationship between SNPs and genes. eQTL interactions do not involve proteins.

. The authors are only exploring cis-eQTL interactions. Most of the cis-eQTL interaction are between markers in the promoter of the gene they are affecting. Can't the coevolution observed between these eQTL-gene pair be confounded by the fact that most eQTLS-SNPs will be really close to its target gene? Can the authors please comment on that? A histogram of the distance from SNP-eQTL to genes would be informative.

. On the same line as the last comment. Why the authors didn't include trans-eQTLS in the study.

. How do PhyloP scores compares to other evolutionary conservation metrics like GERP?

. More work on the methods would be appreciated. Clearly stating the SNP dataset used, the eQTL studies with links, and if possible a code summary on an online repository (github, bitbucket) to allow reproducibility.

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