Editorial Board
*The American Journal of Human Genetics*

24th June, 2020

Dear Editorial Team,

We are writing to submit our manuscript titled "**A multi-omic integrative scheme characterizes tissues of action at loci associated with type 2 diabetes**" for your consideration at *The American Journal of Human Genetics*.

There is a considerable body of published research that focuses on elucidating regulatory mechanisms and causal genes at loci associated with complex diseases. These have attempted to determine which tissues - and regulatory features - are most relevant to the genetic architecture of a disease **overall**, and have resulted in multiple methods to address this problem (i.e. genome-wide enrichment methods, heritability partitioning).

However, there is an intimately related but distinct question concerning how to best resolve the most relevant tissues and cell types that mediate risk at **specific** disease-associated loci. This has been far less studied and systematic methods for this do not exist. This problem is most pronounced for syndromic diseases that involve dysfunction across multiple physiologically-relevant tissues, and is directly relevant to the design and interpretation of experimental studies that seek to define the mechanisms through which GWAS risk variants act.

To address this problem, we have developed a systematic and scalable approach to integrate various types of genetic and genomic information to infer relevant *tissues-of-action* at specific loci implicated through GWAS. Our results show that this integrative, and flexible, scheme can effectively inform relevant tissues at trait-associated loci and can enhance existing approaches to resolve regulatory mechanisms. As such, we believe that this manuscript will be of significant interest and benefit to your readers.

More specifically, we show that:

- This scheme can probabilistically assign genetic signals to effector tissues through the integration of genetic fine-mapping, gene expression, and epigenomic features.
- A simple classifier based on this framework results in tissue assignments that are supported by orthogonal data types that were not explicitly used to construct tissue scores.
- By applying this approach to a set of 380 fine-mapped loci associated with type 2 diabetes, we implicate genetic signals that act exclusively in individual tissues, as well as signals that involve multiple tissues involved in insulin signaling and secretion.
- A large share of secondary signals at loci with multiple conditionally-independent associations have disparate tissue profiles that implicate distinct effector tissues within the same region.
- Integrative tissue scores can be coupled with eQTL co-localisation analysis to advance the resolution of effector transcripts at specific loci by delineating eQTLs in prioritised tissues.

Our findings make clear that our framework provides a principled approach for data integration, an approach that will become all the more valuable as more refined regulatory annotations and epigenome maps become available across a wider array of cell and tissue types. To facilitate its adoption by the research community, we have implemented our method in an R package: Tissue of ACTion scores for Investigating Complex trait-Associated Loci (TACTICAL).

This manuscript has not been previously published and is not under consideration by any other journal, but it will be simultaneously submitted to the bioRxiv server as a preprint. This work does not require any additional permissions or entail any databank submissions. All genes are referenced according to approved HUGO

guidelines for human gene nomenclature. Please note that the first author for this work, Dr. Jason Torres, was a postdoctoral research fellow for the duration of this project and a current member of the American Society of Human Genetics. We hope you will find our work of sufficient interest to review.

On behalf of all the authors,

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