Corresponding Author:

 Dr Andrew W. George

Data61, CSIRO

Ecosciences Precinct

41 Boggo Road, Qld 4102, Australia

Tel: +61 7 3833 5543

Email: andrew.george@csiro.au

23/10/18

Dear Editors,

Thank you for this opportunity to describe our work for consideration in *Nature Methods.*

**Novelty:** Our method is unlike any other association mapping method. It can find the “best” set of SNP in strongest association with a trait, while accounting for all SNP-trait associations simultaneously. We depart from the standard way of thinking about association mapping as a parameter estimation problem. Instead, we treat it as a model selection problem. In doing so, we have no troublesome significance thresholds or tuning parameters to worry about. Our method is also only a little more complicated than fitting a linear mixed model to the data.

**Significance:**  Currently, the methods-of-choice for analysing GWAS data are single-locus (or locus-by-locus) methods. Our goal is to fundamentally shift the community from single-locus to higher-powered multi-locus analysis. In doing so, we are equipping the genetics community to gain greater insights from their GWASs.

**Potential Audience**: Given the proliferation of GWAS being performed across multiple domains and the need to analyses these data better, we believe our paper will have broad appeal to audiences in the academic and industry spaces

**Practical Relevance**: To make the methods immediately accessible and of benefit to a wide audience, we have implemented the methods in a production level packaged. The package was written in R but with a GUI for users unfamiliar with R. We have also developed a website with supporting videos, tutorials, demos, and user guides.

**Validation**: To validate our method, we performed a large simulation study where we benchmark the performance of our method against seven other available single- and multi-locus approaches. We also analysed GWAS data collected on an outbred mouse population and found twice as many true findings than the single-locus method-of-choice.

**Application:** To make the methods immediately accessible and of benefit to a wide audience, we have implemented the methods in a production level easy-to-use package. The package was written in R but it comes with a web-based GUI making the package accessible to users less familiar with the R language. It is fully documented, along with a dedicated website with supporting videos, tutorials, demos, and user guides.

We are excited by the potential impact of this work on the animal, plant, and human genetic communities. We are looking to raise the analysis of GWAS data to a new level of sophistication.

On behalf of the authors,

Dr Andrew George

CSIRO