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March 10, 2018

Dear Editors,

We’re pleased to submit the attached manuscript entitled “Bayesian model comparison for rare variant association studies of multiple phenotypes” for consideration as a Research Article in PLOS Genetics. In this manuscript, we present a statistical method for rare variant association analysis across multiple phenotypes from exome and genome sequencing studies using individual and summary level data. Furthermore, we present results from its application to two diseases, asthma and glaucoma, in the UK Biobank study. The manuscript contains several major components that contribute substantially to the current body of knowledge available for both statistical genetics methods and genetic analysis in population biobanks.

1. We first present a Bayesian model comparison method for summary and individual level data as input from common and rare variant association studies. We present approximations that allows users to compute p-values from Bayes Factors.
2. We then seek to compare the method to commonly used frequentist statistical tests including the Sequence Kernel Association Test and Burden test.
3. Second, we apply a model that prioritizes protective modifiers of disease risk and jointly analyze multiple phenotypes and variants from the UK Biobank data to identify promising gene associations.
   1. We find strong evidence of association between asthma, eosinophil counts, and forced vital capacity and forced expiratory volume in 1-second (FEV1) with rare variants in *IL33* previously reported by Smith et al. PLOS Genetics 2017, and moderate evidence of association with rare coding variants in *CCR3*.
   2. We find strong evidence of association between glaucoma, intra-ocular pressure and corneal resistance factor with rare variants in *ANGPTL7*. The effects are consistent with protection to glaucoma, illustrating the power of the approach at prioritizing potential targets.

Since this paper introduces a novel statistical approach for identifying genetic associations using multiple phenotypes, variants, and studies, we would like to include the Methods section after the Introduction section so readers can read about the details of the approach and how we applied it to data from the UK Biobank. We think that this will aid in interpreting the Results and Discussion sections and more accurately convey the utility of this work.

Given the strong interest in the field of human genetics to identify rare variant associations, and the emergence of population-scale datasets from UK Biobank and Million Veterans Program we think this method and manuscript are timely and will be of great interest to the PLOS Genetics readership.

Sincerely,

Dr. Manuel A. Rivas