# Questions on Liu et al (2014) *Nature Genetics* 46:200-204

Meta-Analysis of Gene Level Tests for Rare Variant Association.

1. Why are studies of rare coding variants attractive?

2. Why are studies of rare coding variants challenging? What sort of recent advances have enabled these studies?

3. What are some of the different strategies and choices for grouping rare variants in a gene? What are the ideal scenarios for each of these strategies?

4. How does the adaptive Monte-Carlo method for estimating p-values work?

5. Fisher's method for combining p-values is often used as a baseline for comparisons of meta-analytic strategies. How does the approach work? What are some of its strengths and weaknesses?

6. The authors mention that their methods can be applied to discrete traits, but with some caveats. What are the caveats? Why?

7. Based on the results presented, do you think rare variants will advance our knowledge of complex trait genetics? Do you think rare variants will explain a large fraction of complex trait heritability? Why?

8. Given a vector of score statistics (where each entry represents statistics for one marker), write out the definition of: (a) a simple burden test, (b) a variable threshold burden test, (c) a SKAT test. How is knowledge of the variance-covariance matrix between these statistics important?

9. What are some remaining open questions about the analysis of rare variants?