

Study designs for the analysis of complex traits and testing for rare variants associations: application to the analysis of sequence data.

Suzanne M. Leal¹

Abstract

There is strong evidence that rare variants play an important role in complex disease etiology. Although studies of rare variants have been limited to a handful of phenotypes and candidate genes, several association studies have successfully implicated rare variants in the etiology of complex traits. The advancement of sequencing technologies is leading to the wide-spread use of rare variant association studies of candidate genes, exomes and entire genomes to elucidate the genetic etiology of complex traits. Although genome wide association studies have been successful in identifying common variants involved in complex trait etiology, for the vast majority of complex traits < 10% of genetic variance is explained by common variants. Genetic variance may also be explained by gene interactions, structural variation and in particular there is strong evidence that rare variants play an important role. These variants although individually rare are collectively frequent and even though their effect sizes are greater than those observed for common variants they are not large enough to produce familial aggregation.

Rare variant identification should have a great impact on risk assessment, disease prevention and treatment. The analysis of rare variants is challenging since methods used for the analysis of common variants are underpowered due to the extreme allelic heterogeneity of rare variants. Additionally, misclassification of rare variants, i.e. inclusion of non-causal variants and exclusion of causal variants in the analysis, can greatly reduce the power of detecting associations. This presentation will compare and contrast methods as well as study designs to analyze rare variant association data for complex qualitative and quantitative traits. Additionally it will address some of the many challenges of rare variant association analysis.

¹Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas 77025
sleal@bcm.edu