General Retrospective Mega-Analysis Framework for Rare Variant Association Tests

Li -Chu Chien

Center for Fundamental Science, Kaohsiung Medical University

Abstract

Here, we describe a retrospective mega-analysis framework for gene-or region-based multimarker rare variant association tests. Our proposed mega-analysis association tests allow investigators to combine longitudinal and cross-sectional family-and/or population-based studies. This framework can be applied to a continuous, categorical or survival trait. In addition to autosomal variants, the tests can be applied to conduct mega-analyses on X-chromosome variants. Tests were built on study-specific region- or gene-level quasi-score statistics and, therefore, do not require estimates of effects of individual rare variants. We used the generalized estimating equation approach to account for complex multiple correlation structures between family members, repeated measurements, and genetic markers. While accounting for multilevel correlations and heterogeneity across studies, the test statistics were computationally efficient and feasible for large-scale sequencing studies. The retrospective aspect of association tests helps alleviate bias due to phenotype-related sampling and type I errors due to misspecification of phenotypic distribution. We evaluated our developed mega-analysis methods through comprehensive simulations with varying sample sizes, covariates, population stratification structures, and study designs across multiple studies. To illustrate application of the proposed framework, we conducted a mega-association analysis combining a longitudinal family study and a cross-sectional case-control study from Genetic Analysis Workshop 19.

This is a joint work with Dr. Chiu, Yen-Feng