UTHealth
The University of Texas Health Science Center at Houston
School of Biomedical Informatics

CPH Seminar in Precision Medicine

"Computationally efficient hybrid rare variant association test for complex study samples"

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With the advance of sequencing technologies, a large number of rare genetic variants have been identified in whole genome sequencing (WGS) studies. Statistical methods commonly used for testing the genetic association with rare variants include burden tests, which aggregate rare variants into a single burden score and test the association with the burden score, and kernel machine-based variance component tests for rare variant genetic effects. Burden tests are more powerful when most rare mutations in a test region are deleterious, while variance component tests outperform burden tests when both beneficial and deleterious variants, or a large number of neutral variants are present. However, the genetic architecture is usually unknown in a specific test region for complex traits. On the other hand, large-scale WGS projects often involve complex study samples with population structure, admixture and relatedness. Here we present a generalized linear mixed model framework for rare variant association tests for these complex study samples and a hybrid test which combines burden tests and kernel machine-based variance component tests. Our hybrid test is applicable in single-cohort studies as well as meta-analysis using summary statistics from individual cohorts, and it does not require more computational resource than burden or variance component tests. We illustrate our method in simulation studies and a real data example.

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