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Using External Reference Panel and Meta-Analysis Summary Statistics for Rare-Variant Aggregation Tests

Genome-wide association studies (GWAS) have identified thousands of associations between common genetic variants and a wide range of human diseases and traits. These studies are often underpowered to identify associations with rare genetic variants, which are thought to contribute to the heritability of many common diseases and traits. Aggregation tests pool the genetic signal across multiple variants in a region of the genome to test the cumulative effect of these variants on a disease or trait. These aggregation tests can increase the power to detect rare variant genetic association in these regions. To further increase power, meta-analysis is employed to pool information across studies via summary statistics such as effect sizes and p-values. To perform proper aggregation test meta-analysis, accurate estimates of the covariances for the single-variant test statistics are also needed. Covariance files are often too large to be shared and estimation requires access to individual level data for each of the participating studies. Unfortunately, individual-level genetic data is often unable to be shared due to privacy concerns. In this study, we apply a previously proposed method of estimating single-variant test statistic covariance from an external reference panel to perform aggregation tests on a variety of traits from the UK Biobank. We propose a two-stage approach by first filtering genes using a null covariance to perform aggregation tests and in stage two testing only those genes passing a p-value threshold. We find this to be an efficient strategy which can lead to significant computational improvements.