A powerful association test of rare variants using a random-effects model

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Abstract

There is an emerging interest in sequencing-based association studies of multiple rare variants. Most association tests suggested in the literature involve collapsing rare variants with or without weighting. Recently, a variance-component score test, SKAT, was proposed to address the limitations of collapsing method. Although SKAT was shown to outperform most of the alternative tests, its applications and power might be restricted and influenced by missing genotypes. In this paper, we suggest a new method based on testing whether the fraction of causal variants in a region is zero. The new association test, T_{REM}, is derived from a random-effects model, allows for missing genotypes and the choice of weighting function is not required when common and rare variants are analyzed simultaneously. We performed simulations to study the type I error rates and power of four competing tests under various conditions on the sample size, genotype missing rate, variant frequency, effect directionality, and the number of non-causal rare variant and/or causal common variant. The simulation results showed that T_{REM} was a valid test and less sensitive to the inclusion of non-causal rare variants and/or low effect common variants, or to the presence of missing genotypes. When the effects were more consistent in the same direction, T_{REM} also had better power performance. Finally, an application to the Shanghai breast cancer study showed that rare causal variants at the FGFR2 gene were detected by T_{REM} and SKAT, but T_{REM} produced more consistent results for different sets of rare and common variants.