Multi-SNP mediation intersection-union test

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Abstract: Tens of thousands of reproducibly identified GWAS (Genome-Wide Association Studies) variants, with the vast majority falling in non-coding regions resulting in no eventual protein products, call urgently for mechanistic interpretations. Although numerous methods exist, there are few, if any methods, for simultaneously testing the mediation effects of multiple correlated SNPs via some mediator (e.g. the expression of a gene or a cytokine in the neighborhood) on phenotypic outcome (including microbiome). We propose multi-SNP mediation intersection-union test (SMUT) to fill in this methodological gap. Our extensive simulations demonstrate the validity of SMUT as well as substantial, up to 92%, power gains over alternative methods. In addition, SMUT confirmed known mediators in a real dataset of Finns for plasma adiponectin level, which were missed by many alternative methods. We believe SMUT will become a useful tool to generate mechanistic hypotheses underlying GWAS variants, facilitating functional follow-up.