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Generalized Correlation Coefficient in Genome-Wide Association Analysis of Cognitive Ability in Twins

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Abstract : Cognitive impairment in the elderly is a key issue affecting the quality of life. Despite a strong genetic background in cognition, only a limited number of single nucleotide polymorphisms (SNPs) have been found. These explain a small proportion of the genetic component of cognitive function, thus leaving a large proportion unaccounted for. We hypothesize that one reason for this missing heritability is the misspecified modeling in data analysis concerning phenotype distribution as well as the relationship between SNP dosage and the phenotype of interest. In an attempt to overcome these issues, we introduced a model-free method based on the generalized correlation coefficient (GCC) in a genome-wide association study (GWAS) of cognitive function in twin samples and compared its performance with two popular linear regression models. The GCC-based GWAS identified two genome-wide significant (P-value < 5e-8) SNPs; rs2904650 near ZDHHC2 on chromosome 8 and rs111256489 near CD6 on chromosome 11. The kinship model also detected two genome-wide significant SNPs, rs112169253 on chromosome 4 and rs17417920 on chromosome 7, whereas no genome-wide significant SNPs were found by the linear mixed model (LME). Compared to the linear models, more meaningful biological pathways like GABA receptor activation, ion channel transport, neuroactive ligand-receptor interaction, and the renin-angiotensin system were found to be enriched by SNPs from GCC. The GCC model outperformed the linear regression models by identifying more genome-wide significant genetic variants and more meaningful biological pathways related to cognitive function. Moreover, GCC-based GWAS was robust in handling genetically related twin samples, which is an important feature in handling genetic confounding in association studies.

Keywords : cognition, generalized correlation coefficient, GWAS, twins
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