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Common and rare variants in topologically associated domains for cognitive function in South Asians from the LASI-DAD Study

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Abstract

Background: Genome-wide association studies (GWAS) in European ancestry (EA) participants have identified many loci associated with cognitive function. However, the association between variants at these loci and cognition has not been evaluated in South Asians. Due to ancestral genetic heterogeneity, the functional SNPs/variants in South Asians may be different than those identified in EA GWAS, even if the same genes/genomic regions are associated. Topologically associated domains (TADs), a basic unit of chromosome foldin, reflect a high level of intradomain interaction. This study used a region-based approach to investigate whether the TAD regions tagged by SNPs identified in EA GWAS were associated with a general cognitive factor and the Hindi version of the Mini-Mental State Examination (HMSE) score in 932 South Asians from the Diagnostic Assessment of Dementia for the Longitudinal Aging Study of India (LASI-DAD).

Method: Participants were genotyped using the Illumina Global Screening Array and imputed to 1000G Phase 3v5. The sequence kernel association test (SKAT and SKAT-O) was used to assess the joint effects of multiple SNPs/variants in 146 TAD regions after controlling for age, gender, and population structure, with or without education. We used two weighting schemes: equal weight for all SNPs/variants (beta(1,1)), and upweighting of rare variants (beta(1,25)). Due to the large size of each TAD region, we used a moving window approach (window size: 300 variants).

Result: Three windows (in TAD region tagged by rs6819372) were significantly associated with the general cognitive factor using the equal SNP/variant weighting approach (FDR<0.1). Using the rare variant weighting approach, five windows (in TAD regions tagged by rs889956, rs7494275, and rs830386) were significantly associated with the general cognitive factor after adjusting for education. Those windows, however, often do not overlap with the SNPs identified from EA GWAS.

Conclusion: Given that the associated regions often do not contain the EA GWAS SNPs GWAS, there may be substantial genetic heterogeneity between EA and South Asians even when the same gene regions are associated with cognition. Future work is needed to identify the specific variants that influence cognitive function in South Asians.