BCL 2023

Edition IV

Bratati Kahali

Associate Professor,
Centre for Brain Research,
IISc, India

10 Jan | 16:30 - 17:00

Genetic architecture of human cognition inferred from whole genome sequencing studies

Abstract: Genetic architecture of human cognition inferred from whole genome sequencing studies Cognitive function is heritable, with metabolic risk factors known to accelerate age- associated cognitive decline. Identifying genetic underpinnings of cognition is thus crucial. Analyzing whole-exome sequencing data from >155,000 individuals for neurocognitive phenotypes at single-variant and gene level, we uncover the genetic architecture of human cognition. We found 18 independent novel loci associated with five cognitive domains while controlling for APOE isoform-carrier status and metabolic risk factors. Our novel variants are mostly in genes which could also impact cognition via their functions on synaptic plasticity and connectivity, oxidative stress, neuroinflammation. Variants in or near these identified loci show genetic links to cognitive functioning in association with APOE, Alzheimer's disease and related dementia phenotypes and brain morphology phenotypes. These exome-wide significant variants can also substantially regulate expression of their corresponding genes in various regions of the brain. We further identify four novel pairwise interactions between exome-wide significant loci and APOE variants influencing episodic memory, and simple processing speed while accounting for serum lipid and serum glycemic traits. We obtain both main and interaction effects for APOC1 and LRP1 upon complex processing speed and visual attention. Variants in APOC1 and LRP1 are also observed to regulate their expression in basal ganglia and cerebellar hemispheres, crucial to visual attention. We also uncover variants showing evidence of pleiotropy and mediation effects through serum glucose/HDL levels affecting cognition. Our research highlights a novel set of loci that augments our understanding of the genetic underpinnings of cognition during ageing, considering co- occurring metabolic conditions that can confer genetic risk to cognitive decline in addition to APOE, which can aid in finding causal determinants of cognitive decline.

Brief Bio: *Bratati is a computational biologist focusing on human genetics and genomics. Her research examines the role of genetic variants in shaping our predisposition to complex diseases, especially, neurodegeneration, particularly in the Indian population, with special emphasis on whole genome and whole exome sequencing analyses. Her group's research is aimed to better understand the shared genetic architecture and causal relationship between cardiometabolic disorders and of psychiatric and neurodegenerative disorders, including genetic overlap between different disorders, and genetic and phenotypic heterogeneity within disorders in Indian population. She also leads the identification of genetic variants in the Indian population, from CBR, particularly in the Genome India consortium .*