

https://dspace.org/

Genetic and environmental factors associated with cognition in an ageing South African population

Soo, Cassandra Claire

2021
https://hdl.handle.net/10539/33511

Downloaded from a DSpace repository. https://dspace.org/

Genetic and environmental factors associated with cognition in an ageing South African population

Cassandra Claire Soo

An integrated Thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of PhD in Human Genetics

Abstract

This research was the first to look at genetic associations with latent cognitive function using socially appropriate screening tools in a rural-dwelling African population. By leveraging on existing infrastructure and the added resources of the collaborative studies; The Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa (HAALSI) and the Africa Wits-INDEPTH Partnership for Genomic Studies (AWI-Gen), we were able to pioneer the first cross-sectional population study of genomics and cognitive function in a sub-Saharan African population.

Three separate studies, each with their own objectives, explored aspects of genetic associations with five cognitive traits namely, total cognition score, verbal episodic memory, executive function, language, and visuospatial cognition

Apolipoprotein E (*APOE*) and its effect on cognitive function in this cohort was examined due to documented associations of *APOE* ε4 with poorer cognitive performance in studies assessing cognitive function at the domain level. Marginal associations were found where *ε*2 homozygotes exhibited higher levels of executive function and *ε*3/*ε*4 heterozygotes had poorer visuospatial cognition.

Our genome-wide association study detected novel genome-wide significant signals for verbal episodic memory and language performance. Common and rare African variants had

modest effects on cognitive function, which showed the importance of using the Illumina Human Health and Heredity in Africa custom array with a population-specific reference panel for imputation.

Finally, an *in-silico* method for determining the length of a homopolymer (T) repeat in Translocase of Outer Mitochondrial Membrane 40 (*TOMM40)* was developed and validated. Allele frequency distributions and the co-segregation patterns of *TOMM4*0 and *APOE* in our cohort versus that of African and European 1000 Genomes populations revealed differences in linkage disequilibrium structure between populations. Regression models showed marginal significance for the association between individuals homozygous for the long allele of *TOMM40* and lower episodic memory scores.

This work has set the stage for future genetic studies of cognitive function in Africa. AWI-Gen Phase 2 presents an opportunity to increase sample size and replicate observed associations across the whole AWI-Gen cohort. Furthermore, longitudinal data from later HAALSI waves may enable assessment of the prevalence and genetic correlates influencing cognitive decline and dementia.