Principal Investigator

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Summary of research

genetics, aging, heritability, early-life, reproduction

Application Lay Summary:

1a: Differences among individuals in distinct changes in their physiology as they age lead to differences in their susceptibility to negative later-life outcomes, and ultimately to differences in lifespan. This proposal aims to test whether genetic differences among individuals influence changes in cognition and physiological function in later life, to identify the genomic regions and biochemical pathways associated with these changes, and to test for genetic associations between early-life reproduction and later-life outcomes. This is crucial to understanding and predicting transitions across different human life stages.

1b: Understanding the genetic basis of relationships between early-life phenotypes, reproductive events, and later-life outcomes is of considerable research and public health interest. This proposal will identify new genetic relationships among physiological and cognitive functions, identify genomic regions of age-specific effect, estimate genetic relationships among life stages, and test the effects of genetic homozygosity in the genome in humans across life. It will lead to a better understanding of the genetic factors and biochemical pathways underlying cognitive and physiological decline in people as they age.

1c: Establishing robust genetic links between early and later-life health outcomes is challenging as (i) it usually requires studying people across their lives, and, when using families, (ii) relationships are confounded by other factors, such as shared environment between relatives. A novel design for studying the genetics of ageing will be used, so that even when different traits are measured on different individuals, the genetic basis of changes across life can be studied unbiased of shared environment. This enables an assessment of the genomic basis of multiple later-life phenotypes across different ages, testing theories for the genetics of ageing.

1d: For sufficient power to accurately estimate genetic relationships between characters, we require access to the full cohort. Even though individuals in the UKBiobank sample are measured across different ages, we can utilize the estimated genetic relationships among them to ask whether the genetic basis of characters is consistent across later life. We can then assess whether variation in genetic effects across life alters genetic relationships among characters throughout life (i.e., do the impacts of early-life on cognitive or physiological function only become apparent in individuals over 65). This requires data on all individuals recorded across all ages.

Project extension details:

The extension aims to summarise the brain imaging data and calculate correlations between derived brain phenotypes and traits such as cognition, depression, and other traits. From such an analysis, we can infer the contribution of genes and the environment to variation in traits that are important in health and disease. Our approach is to extract vertex-wise measures of the cortex (surface, thickness, volume), and of subcortical structures (shape) using FreeSurfer 6.0. In addition, we will extract voxel-wise measurement of resting-state fMRI (functional connectivities, regional homogeneity, amplitude of low frequency fluctuation) using SPM12. For DTI images, we will extract voxel-wise measurements of fractional anisotropy, radial diffusivity, mean diffusivity axial diffusivity, using FSL. Our image processing will follow the ENIGMA processing pipelines (available online, http://enigma.ini.usc.edu/protocols/) and use the processing pipelines developed at University of Queensland Centre for Advanced Imaging (https://caisr.github.io/pages/imaging_tools.html) . When available, we will use the pre-processed images provided by the UKB. The aim of this study is to quantify the contribution of these measurements to the inter-personal differences in the UKB population.

Project Extension text:

As part of our proposed investigations on inbreeding we have discovered the existence of individuals in the UK Biobank who have a very high estimated inbreeding coefficient. This cohort comprises approximately 200 individuals. These individuals are likely the progeny of parents who are first or second degree relatives. We seek permission to study this unique group of individuals for association with complex traits and environmental exposures, to better understand the cause and consequence of high levels of homozygosity in the genome. In particular, we will assess the association between extreme inbreeding and anthropometric, developmental, fertility and brain related traits. Use of this cohort with high levels of inbreeding will not seek to identify individuals or family groups within the expanded UK Biobank cohort. Phenotypes used in these analyses will be to infer cause and consequence of inbreeding and not be used to distinguish or discriminate participants. In addition to the phenotypes linked to this project we request traits from hearing tests and from impedance measures. We would also like to complement the list of anthropometric traits we have been granted access to include sitting height.