Initial observations on the genetic landscape of human healthspan

Aging populations face diminishing quality of life due to increased disease and morbidity. These challenges call for research focusing on understanding the pathways controlling healthspan. We aimed to understand determinants of human healthspan using genetics and genomics. We used the data from the UK Biobank mega-cohort and observed that the risks of major chronic diseases increased exponentially and double every eight years, at a rate compatible with the Gompertz mortality law. Assuming that aging drives the morbidity rates acceleration, we built a risk model to predict the age corresponding to the end of healthspan depending on their age, gender, and the genetic background. Using a large database including tens of billions of genetic associations, we performed functional genomic investigation into molecular pathways underlying healthspan, and explored which (modifiable) risk factors are likely to be causatively related to the healthspan.

Twelve genome-wide significant healthspan loci were identified, with several acting in sex-specific manner. Phenome-wide association scan demonstrated that action of majority of loci was restricted to specific disease domain (e.g. cancer, dementia, cardio-metabolic). The strongest genetic correlations were observed between healthspan and all-cause mortality (as derived from parental survival, with genetic correlation equal to -0.76). Other strongly (absolute genetic correlation > 0.3) genetically correlated traits included life-history (metrics of obesity, age at first birth), and lifestyle traits (e.g. smoking behaviour).

We conclude that healthspan is a very complex trait integrating genetic predisposition to major ageing diseases and responses to environmental exposures. Although genetic correlation between health- and life-span is high, the overlap between loci that are genome-wide significantly associated to these traits is limited, underlining their differences.