3 Year PhD Studentship available for September 2019

Department:  Leicester Precision medicine Institute / Leicester Biomedical Research Centre / Cardiovascular Sciences

Supervisors:  Dr Christopher P Nelson  cn46@le.ac.uk  
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Eligibility:  UK/EU applicants only

Project Title:  The genetic contribution of biological age differences in disease risk

Project Description:
Telomere length (TL) is reflective of cellular age, shortens over time and is proposed as a marker of biological age. Here in Leicester we are measuring mean Leucocyte Telomere Length (LTL) in all 500,000 individuals participating in UK Biobank, these exciting data will be used for this project.

This PhD will examine if TL, interacts with genetically determined disease risk and influences disease risk and the age of disease onset, including investigations of gene environment interactions on single diseases and multimorbidity clusters. It will examine the interactions of biological age with genetic data in disease risk or with a polygenic risk score (PRS). A polygenic hazard score (PHS) for telomere associated diseases will also be considered. PHS has the potential to be a stronger predictor of early disease onset than PRS. TL interaction with PHS will determine if genetic determinants of early disease onset are dependent on the biological age of the individual. This PhD provides an excellent foundation for a career in medical statistics or statistical genetics.

Background
Telomere length (TL) is reflective of cellular age, shortens over time and is proposed as a marker of biological age. Mean leucocyte TL (LTL) shows considerable inter-individual variability, is highly heritable and has been causally associated with increased risk of several age-associated diseases, including coronary artery disease (CAD) and some cancers\textsuperscript{1,2}. However, the extent to which an individual’s biological age contributes to age-related disease risk or onset remains unclear.

Proposed study
The contribution of genetics to disease risk is well established and yet the role of other factors on the genetically determined elements of disease risk is less well known. Here we will look at the role of TL,
as a marker of biological age, in disease risk. This will investigate gene environment interactions using telomere length as the environmental factor in single diseases and previously defined multimorbidity clusters.

The project will then investigate the interaction of telomere length with a polygenic risk score (PRS) for disease to determine the genetic extent to which TL associates with the time of disease onset using polygenic hazard scores (PHS).

We will investigate high profile diseases, including cardiovascular disease and type-2 diabetes, where a higher PRS for disease may also have shorter telomeres that would infer an underlying disease mechanism.

**Hypothesis**

Telomere length, a marker of biological age, interacts with genetically determined disease risk and influences disease risk and the age of onset.

**Experimental Methods and Research Plan**

Genome-wide association studies now allow a polygenic approach to differences in risk that can be attributed to TL. The PRS gives a tool for quantifying the polygenic contribution to risk and is the sum of risk alleles carried by an individual, weighted by their effect sizes.

The student will have access to relevant MSc Medical Statistics and MSc Bioinformatics modules, including modules on genetic epidemiology in addition to postgraduate training courses offered by the university. They will have access to UK Biobank and unique access to TL data within this cohort including support from the Telomere team responsible for these measurements.

In Year 1-2, accessing the whole of UK Biobank, the student will perform genome wide gene-environment interaction analyses for telomere associated diseases, starting with CAD. They will then collate and investigate PRS data measuring the degree to which genetic risk differences are altered due to an individual’s telomere length via an interaction analysis.

In Year 2 the student will then use selected, previously defined, multimorbidity clusters to investigate the genetics associated with multiple diseases and their relationship with TL.

In Years 2-3 the student will consider age as the time scale and calculate a PHS for telomere associated diseases. The PHS is a tool for quantifying the polygenic contribution to the age of disease onset, which has the potential to be a stronger predictor of early disease onset than PRS and will indicate if there is an interaction with TL to determine if genetic determinants of disease onset.
References:


Funding details:
This project is in competition for a LPMI/BRC College of Life Sciences (CLS) PhD Studentship. The Studentships are for three years, starting September 2019, and offer tuition fees at UK/EU rates and a Stipend at UK Research Council rates.

Entry requirements:
Applicants are required to hold/or expect to obtain a UK Bachelor Degree 2:1 or better in a relevant subject. The University of Leicester English language requirements apply where applicable.

How to apply:
You should submit your application using our online application system.

Apply for a PhD in Cardiovascular sciences

In the funding section of the application please indicate you wish to be considered for a LPMI/BRC studentship

In the proposal section please provide the name of the supervisor and project you want to be considered for.

You do not need to submit a proposal but please include a personal statement detailing your interest in this project

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Closing date for applications  27th January 2019