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Summary of research

Key words: blood, hematology, genetics, heart diseases, stroke

1a: The proliferation and differentiation of hematopoietic progenitor cells into mature blood cells is a tightly regulated process. Red blood cell (RBC), white blood cell (WBC) and platelet counts are used in medicine as biomarkers to monitor general health status, to diagnose diseases, and as prognostic indicators of various clinical disorders. The goals of our study are: (1) to identify novel genetic variants associated with blood-cell trait variation in the UK Biobank participants and (2) test if these genetic variants also associate with cardiovascular diseases, including stroke.

1b: Variation in blood-cell traits is observed in various human diseases (e.g. cancer) and is used as predictive marker for heart diseases and stroke. Our project will explore the genetic contribution to inter-individual blood-cell variation, and test whether these genetic factors also influence our risk of heart diseases and stroke.

1c: The number and features of the main blood cells (red blood cells, white blood cells, and platelets) have been measured in all UK Biobank participants. Similarly, the DNA of all UK Biobank participants will be

genotyped on the UK Biobank Affymetrix array. We propose to test the correlation between genotypes and inter-individual variation in blood-cell traits using standard genetic association methodologies. When appropriate, we will control blood-cell variables with potential confounders (such as sex, age, cancer status, infectious disease status, kidney or liver disease, etc.).

1d: Full cohort.

Project Extension Detail:
In our original application, we proposed to use the UK Biobank dataset for two aims:

1. To identify genetic variation associated with blood-cell traits (routinely measured during complete blood count (CBC)).

2. To further dissect, using genetic and phenotypic data, the link between blood-cell parameters and cardiovascular diseases (CVD).

In Aim #2, we originally proposed to explore how variants associated with bloodcell traits can (alone or within a genetic risk score) help in discriminating between CVD cases and controls (using standard biostatistic methods such as Cox regression). In this aim, we are proposing two changes:

a. We plan on extending disease status prediction to more sophisticated methodologies, including machine-learning-based methods (e.g. deep learning).
b. Because our interest resides in the predictive value of blood-cell traits (and variants associated with these phenotypes), we would also like to explore how genetic variants (across the genome and not necessarily associated with blood-cell traits) can predict CVD. These analyses would let us know whether predictions are possible. They would also help in describing a baseline model, to which we could then compare performance of models where "weights" are higher for variants associated with blood-cell traits.

These two minor changes do not require additional data and do not impact our original proposal. These analyses will be performed in my lab by members that are already approved by the UK Biobank Project.

Project extension:

"Using ICD10 codes, we provide below the list of additional human diseases and phenotypes that we would like to include to this project. These include CVD, cancers, and immune/inflammatory, which all have a strong hematological component, as well as other diseases which are indirectly affected by blood-cell phenotypes.

Infectious and parasitic diseases A00-B99 (many of these infectious agents affect blood cells)
Neoplasms C00-D48 (including blood cancers)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism D50-D89
Mental and behavioural disorders F00-F99 (although unexpected, there appears to be a strong immune cell component to diseases like schizophrenia).
Diseases of the nervous system G00-G99 (many of these diseases have strong immune or inflammatory components)
Diseases of the eyes and ears H00-H95 (many of these diseases have strong immune or inflammatory components)
Diseases of the circulatory system I00-I99 (already approved)
Diseases of the respiratory system J00-J99 (all main blood cells may play a role)
Diseases of the digestive system K00-K93 (many of these diseases have strong immune or inflammatory components)
Diseases of the skin and subcutaneous tissue L00-L99 (many of these diseases have strong immune or inflammatory components)
Diseases of the musculoskeletal system and connective tissue M00-M99 (many of these diseases have strong inflammatory components, e.g. arthritis)
Diseases of the genitourinary system N00-N99 (kidney diseases are influenced by erythropoiesis and erythrocytes)

Phenome-wide association studies (PheWAS) have become a powerful strategy to identify the role of biomarkers (in our case, blood-cell traits) in human disease aetiology. Because these PheWAS analyses are hypothesis-free, they allow for the discoveries of unanticipated links between biomarkers and human diseases. My laboratory is familiar with the PheWAS methodology, including methods to properly control for multiple testing."