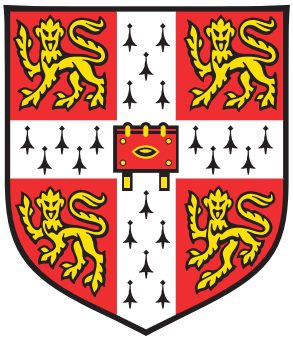
The Genetics of Cellular Phenotypes



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To my grandmother, my parents and my wife

Declaration

I hereby declare that except where specific reference is made to the work of others, the contents of this dissertation are original. This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration, except where specifically indicated in the text. This thesis does not exceed the length limit of 60,000 words specified by the Biology Degree Committee.

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Abstract

Waves of genome wide association studies (GWAS) have identified a large number of loci associated with disease predisposition and natural traits in the past decade. A number of identified variants have revealed potential causal mechanisms for the associated diseases. However, despite the early success, much of the phenotypic variation is not explained by the GWAS variants and the effect sizes tend to be very small. The real challenge in advancing our understanding, and subsequently making it relevant for clinical application, is deciphering the biological functions of these loci, which remain largely uncertain. Compared to the whole organism phenotypes that are distal to the genetic variants, cellular phenotypes are closer to genetic regulation, thus not only tend to offer effect size, as shown in expression QTL studies, but also are likely to mediate between genotypes and whole organism phenotypes, supporting biological functions.

In chapter 2, I describe a genetic association study on binding of a primary transcription factor CCCTC binding factor (CTCF) in human populations. We search for quantitative trait loci (QTL) for tens of thousands of CTCF binding sites in a group of 51 individuals, making this the first well powered QTL study on a major transcription factor in humans. We discovered a large number of QTLs and revealed a strong genetic component that contributes to binding variation. We found the associated variants are often located near to predicted binding sites, some perturbing the binding motif directly, and others affecting indirectly. We observed allele specific effect (intra-individual) consistent with QTL signals (inter-individuals), supporting a strong genetic component in CTCF binding variation.

In chapter 3, I address the problem of low power in associations between gene

expression levels and phenotypes. This is largely driven by the high degree of stochasticity in the measured gene expression levels. We showed that by applying factor analysis both to remove global confounding effects and to create summarizing factors for biological pathways, the heritability and association strength can be substantially elevated as a result. We applied this idea to a cohort with skin expression data with ageing phenotypes, and discovered heritable ageing pathways.

It is also of great interest to develop new methods for obtaining measurements of cellular phenotypes. In chapter 4 I describe a novel computational method to estimate telomere length from whole genome or exome sequencing data. Using data from the TwinsUK cohort that has both DNA sequencing data and experimental telomere length measurements available, I show that our method can effectively extract telomere length information. The method has been applied to a few cancer studies in collaboration and achieved early success in confirming experimental findings.

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