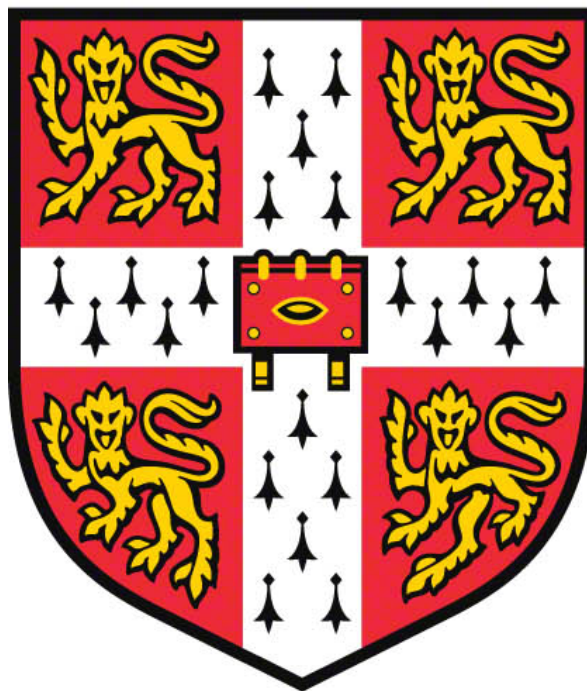


**Using genetic and genomic approaches to
understand haematopoietic cellular biology and
dysregulation in disease**

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Using genetic and genomic approaches to understand haematopoietic cellular biology and dysregulation in disease

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Summary

Genetic and genomic approaches have revolutionised the way we address disease aetiology, potential treatment and methods to understand fundamental biology. Many different approaches can be applied to attempt to resolve the mechanisms through which sequence variation disrupts downstream biological processes, which I discuss and apply in this thesis. Specifically, I use tractable haematopoietic cellular systems focusing mainly on neutrophils but also extending these analyses to monocytes and naïve CD4⁺ cells. First, I introduce the fundamental principles of human genetic variation and associated challenges in resolving functional mechanisms. I then discuss how immune functions are dysregulated in classical autoimmune diseases and emerging evidence for the role of these cells in complex disorders not previously considered immune-mediated. I then integrate molecular phenotypes from resting monocytes, neutrophils and CD4⁺ T cells with disease-risk loci. Molecular data have the advantage of enabling measurement in larger cohorts and have therefore been used in quantitative trait loci studies to identify variants influencing processes such as gene expression, histone modification or splicing. Using these data, I map molecular mechanisms acting at risk loci associated with a range of complex disorders.

Following this, I highlight recent efforts in applying systematic genome-wide association approaches to cellular and functional traits, many of which can represent intermediate processes disrupted by complex disease. I then apply such approaches to novel neutrophil functional phenotypes to ascertain whether such population-based approaches can be used to gain insight into neutrophil biology. Finally, I discuss studies of haematological blood cell count traits and immunophenotyping and apply a targeted recall-by-genotype study to dissect the relationship between these traits, specifically neutrophil count and surface receptor expression.

In summary, I demonstrate how describing biological mechanisms of genetic variants requires the integration of multiple and complementary datasets and offers insight into fundamental biology, disease risk and therapeutic utility.

Declaration

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text. It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text

It does not exceed the prescribed word limit for the Biology Degree Committee.

A. L. Mann
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This thesis is dedicated to my husband,
Timothy Mann

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Abbreviations

| | |
|-----------------|--|
| AAT | Anti-inflammatory alpha-1-antitrypsin |
| AAV | Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis |
| ABCA1 | ATP-binding cassette transporter |
| AID | Autoimmune disease |
| AMD | Age-related macular degeneration |
| AML | Acute myeloid leukaemia |
| ANCA | Antineutrophil cytoplasmic antibodies |
| APC | Allophycocyanin |
| APOE | Apolipoprotein E |
| APP | Amyloid precursor protein |
| <i>ARHGEF26</i> | Rho guanine nucleotide exchange factor 26 |
| ATAC-seq | Assay for transposase-accessible chromatin using sequencing |
| ATP | Adenosine triphosphate |
| ATRA | All trans-retinoic acid |
| A β | Amyloid β |
| BAFF | B cell activating factor |
| BBB | Blood-brain barrier |
| BM | Bruch's membrane |
| BPI | Bactericidal/permeability-increasing protein |
| BRE | TFIIB recognition element |
| C/EBP | CCAAT/enhancer binding protein |
| CAD | Coronary artery disease |
| CANTOS | Canakinumab Antiinflammatory Thrombosis Outcome Study |
| CBR | Cambridge BioResource |
| CD | Crohn's disease |
| CDCV | Common disease-common variant |
| CEL | Celiac disease |
| CETP | Cholesterylester transfer protein |
| CFH | Complement factor H |
| CFI | Complement factor I |
| CHD | Coronary heart disease |
| ChIA-PET | Chromatin interaction analysis by paired-end tag sequencing |
| ChIP-seq | Chromatin immunoprecipitation with next-generation sequencing |
| CLP | Common lymphoid progenitor |
| CMP | Common myeloid progenitor |
| CNV | Choroidal neovascular membranes |

| | |
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| COPD | Chronic obstructive pulmonary disorder |
| CR1 | Complement factor 1 |
| CRC | Colorectal cancer |
| CRISPR | Clustered Regularly Interspaced Short Palindromic Repeats |
| CRP | C-reactive protein |
| CTCF | Transcriptional repressor CTCF |
| CVD | Cardiovascular disease |
| CytoB | Cytochalasin B |
| DC | Dendritic cell |
| DG | Diacylglycerol |
| DHS | Dnase I hypersensitive site |
| DMSO | Dimethyl sulfoxide |
| DNMT | DNA methyltransferase |
| DPE | Downstream promoter element |
| DTT | Dithiothreitol |
| EA | Effect allele |
| EAE | Experimental autoimmune encephalomyelitis |
| EAF | Effect allele frequency |
| eQTL | QTL for gene expression |
| ERK | Extracellular signal-related kinase |
| FACs | Fluorescence-activated cell sorting |
| FBC | Full blood count |
| FEV1 | Forced expiratory volume |
| FITC | Fluorescein isothiocyanate |
| fMLP | N-formylmethionine-leucyl-phenylalanine |
| FPKM | Fragments per kilobase of transcript per million fragments sequenced |
| FS | Forward scatter |
| FVC | Forced vital capacity |
| GARFIELD | GWAS Analysis of Regulatory or Functional Information Enrichment with LD correction |
| GCSFR | Granulocyte colony-stimulating factor receptor |
| GM-CSF | Granulocyte-macrophage colony-stimulating factor |
| GMP | Granulocyte/macrophage progenitor |
| GPCR | G-protein-coupled receptors |
| GPI | Glycosyl phosphatidylinositol anchor |
| GTFs | General transcription factors |
| GWAS | Genome-wide association studies |
| HAT | Histone acetyltransferase |

| | |
|--------|--|
| HDAC | Histone deacetylase |
| HDM | Histone demethylase |
| Hep3B | Human hepatocellular carcinoma cells |
| HFGP | Human Functional genomics project |
| HLA | Human Leukocyte antigen |
| hQTL | QTL for histone modification |
| HRP | Horseradish peroxidase |
| HSC | Haematopoietic stem cells |
| IBD | Inflammatory bowel disease |
| ICAM | Intercellular-adhesion molecules |
| IFN | Interferon |
| IGAP | International Genomics of Alzheimer's Project |
| IL | Interleukin |
| Inr | Initiator element |
| iPSC | Induced pluripotent stem cell |
| LBP | Lipopolysaccharide binding protein |
| LCL | Lymphoblastoid cell lines |
| lcrRNA | Long non-coding RNA |
| LD | Linkage disequilibrium |
| LDL | Low-density lipoprotein |
| LDL-C | Low-density lipoprotein cholesterol |
| LFA-1 | Lymphocyte function-associated antigen 1 |
| LIPC | Lipase C |
| LOAD | Late-onset Alzheimer's disease |
| LPS | Lipopolysaccharides |
| MAC | Membrane attack complex |
| MAC-1 | Macrophage-1 antigen |
| MAF | Minor allele frequency |
| MAPK | Mitogen-activated protein kinase |
| MD | Maximum difference (effect size estimate for isotype QTLs) |
| MDP | Muramyl dipeptide |
| MEP | Megakaryocyte/erythroid progenitor |
| MFI | Median fluorescence intensity |
| MHC | Major histocompatibility complex |
| miRNA | micro RNA |
| MPO | Myeloperoxidase |
| MR | Mendelian randomization |
| MS | Multiple sclerosis |

| | |
|------------|--|
| NE-FSC | Neutrophil forward scatter parameter |
| NE-SFL | Neutrophil side fluorescence |
| NET | Neutrophil extracellular traps |
| NK cells | Natural killer cells |
| NOD2 | Nucleotide-binding oligomerization domain-containing protein 2 |
| nvAMD | Neovascular AMD |
| OA | Other allele |
| OR | Odds ratio |
| P-TEFb | Positive transcription elongation factor b |
| PAF | Platelet-activating factor |
| PBMC | Peripheral blood mononuclear cells |
| PBPC | Peripheral blood progenitor cells |
| PBPCT | Peripheral blood progenitor cells transplantation |
| PBS | Phosphate-buffered saline |
| PChIC | Promoter-capture HiC |
| PD | Parkinson's disease |
| PDAC | Pancreatic ductal adenocarcinoma |
| PE | Phycoerythrin |
| PI3K | Phosphoinositide 3-kinase |
| PKC | Protein kinase C |
| PLAUR/uPAR | Urokinase receptor |
| PLC | Phospholipase C |
| PMA | Phorbol myristate acetate |
| PMNs | Polymorphonuclear leukocytes |
| Pol II | RNA polymerase II |
| PP | Posterior probability |
| PR3 | Proteinase 3 |
| PRCS | Peripheral retinal pigment epithelium/choroid/sclera |
| PSGL-1 | P-selectin glycoprotein ligand-1 |
| QTL | Quantitative trait locus |
| RA | Rheumatoid arthritis |
| RbG | Recall-by-genotype |
| RCT | Randomised clinical trial |
| RDW | Red cell distribution width |
| RFU | Relative fluorescence unit |
| RISC | RNA-induced silencing complex |
| RNAP | RNA polymerase |
| ROS | Reactive oxygen species |

| | |
|------------------|---|
| RPE | Retinal pigment epithelium |
| SCN | Severe congenital neutropenia |
| SD | Standard deviation |
| SE | Standard error |
| siRNA | Small interfering RNA |
| SJIA | Systemic juvenile idiopathic arthritis |
| SLE | Systemic lupus erythematosus |
| SNP | Single nucleotide polymorphism |
| SS | Side scatter |
| STZ | Serum-treated zymosan |
| T1D | Type 1 Diabetes |
| T2D | Type 2 diabetes |
| TAD | Topologically-associated domain |
| TF | Transcription factor |
| TLR | Toll-like receptor |
| TM | Transmembrane domain |
| TNF | Tumour necrosis factor |
| TNFRSF10A | Tumour necrosis factor receptor superfamily 10A |
| TRAIL | Tumour necrosis factor-related apoptosis-inducing ligand |
| TRAILR | Tumour necrosis factor-related apoptosis-inducing ligand receptor |
| T _{REG} | Regulatory T cells |
| TSS | Transcription start site |
| UTR | Untranslated region |
| VCM | Variable chromatin modules |
| VEGFA | Vascular endothelial growth factor A |
| VLDL | Very-low density lipoprotein |
| WGS | Whole-genome sequencing |
| YRI | Yoruba in Ibadan |