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Chapter 1

Introduction

1.1 Structure and diversity of the human genome

- The human genome is almost three billion **base pairs (bps)** in length, containing 20000-25000 protein-coding genes^{1,2} that span 1-3% of its length, with the remainder being non-coding. Each diploid human cell contains two copies of the genome; 46 chromosomes comprised of 23 maternal-parental pairs: 22 pairs of homologous autosomes and one pair of sex chromosomes.
- Variation in the genome between individuals in a population exists in the form of **single nucleotide polymorphisms (SNPs)**, short indels, and structural variants—the vast majority of common variants (**MAF** > 1 – 5%) are **SNPs** and short indels (> 99.9%)². On average, a pair of human genomes differs by one **SNP** per 1000-2000 **bp**³. Each version of a variant is called an allele; an individual has a maternal and parental allele at each variant.
- The many variants in a population are inherited in a smaller number of haplotypes: contiguous stretches of the genome passed through generations via meiotic segregation. The fundamental sources of genetic diversity are mutation and meiotic recombination, generating new alleles and breaking apart haplotypes into shorter ones over time. Variants at locations on a chromosome (loci) that are physically close are less likely to flank a recombination event, hence more likely to cosegregate on the same haplotype, referred to as genetic linkage.

consider moving awkward
defs to margin notes, in
the style of nature re-
views

LD decay just takes a
really really long time,
but there are evo forces
at work too that maintain
LD

1.2. GENETIC ASSOCIATION STUDIES AND FROM PRACTITIONERS

Genetic linkage is one source of **linkage disequilibrium (LD)**: the non-random association of alleles at two loci, differing from expectation based on their frequencies and the law of independent assortment⁴. LD is often quantified within a population by r^2 , the squared correlation coefficient between alleles⁴.

Recombination events are not distributed uniformly throughout the genome. The genome is a mosaic of blocks delimited by recombination hotspots, characterised by strong LD within blocks, and little LD between blocks^{5,6} (Fig. 1.1). The structure of correlated haplotypes reflects a population's unique evolutionary history, and can be used to trace the demography of human populations back through time⁷.

Heard it's good for the reader's attention span to have figures in intro. Unless it's ok to use figures from papers, I only want to spend the time making the min that are necessary though.

1.2 Genetic association studies for complex traits

1.2.1 Principles of genetic association

- Variation in human traits arises from an interplay between genetics and environment. Traits for which genetic variation explains a non-zero fraction of phenotypic variation are heritable. Many measurable human traits are heritable and twin studies provide upper bounds on this heritability <https://www.nature.com/articles/ng.3285>. Discovering the specific genetic variants that contribute to heritability, through association of variants and phenotypes measured from the same individual, is a mainstay of the field of human genetics. Barring somatic mutation, an individual's genome is fixed at conception, providing a causally upstream anchor. Genetic association studies have intrinsic resistance to many backdoor path effects that permeate observational studies of the causes of human phenotypes.
- Under the central dogma, information flows from gene to RNA to protein to phenotype via transcription and translation, thus it is assumed that genetic variants at loci in the genome affect phenotype by impacting on the function or regulation of target genes. How genetic variation contributes to any heritable trait defines its genetic architecture: the number of genes affecting that trait; along with the allele frequencies, effect sizes, and interactions of trait-associated variants⁸. The

add something sweeping about utility here or elsewhere: e.g. insights into trait biology and clinical translational potential for disease traits, genetically support drug target identification

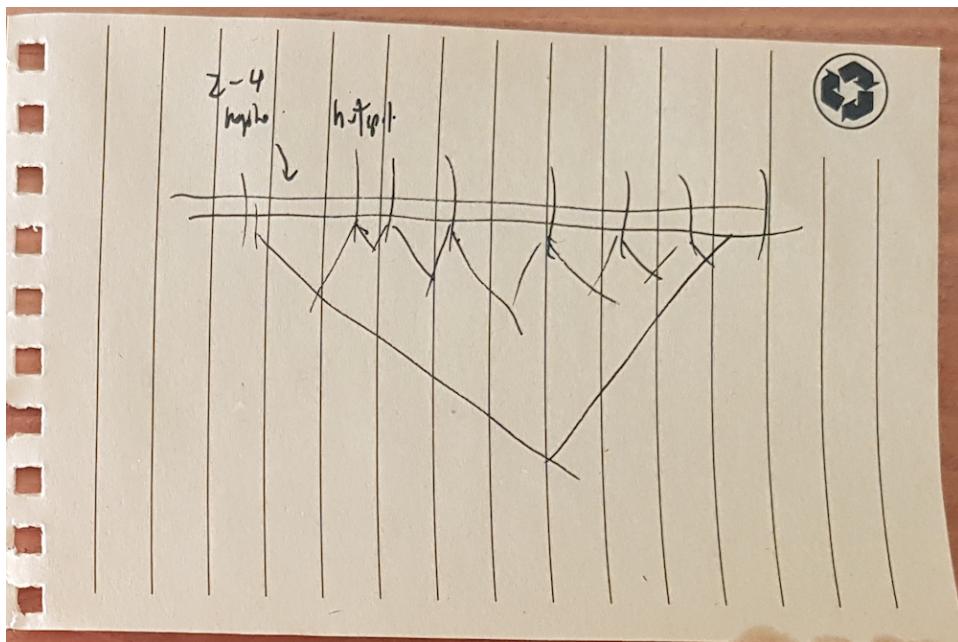


Figure 1.1: The genomic mosaic: block-like LD structure of the genome

number of genes defines a spectrum of traits from monogenic (where inheritance follow simple Mendelian patterns) to polygenic (where inheritance is complex). Many architectures have been proposed for complex traits; all have in common that the number of genes that affect a complex trait is large (ranging from dozens to many thousands), thus the average effect of each trait-associated loci is small^{9,10} <https://www.pnas.org/content/106/23/9362>.

1.2.2 Lessons from 15 years of genome-wide association

- For decades, linkage analysis had been successfully applied to map loci affecting Mendelian traits by tracing their cosegregation with the trait through pedigrees¹¹. Small-scale genetic association studies were also performed, focusing on variants in or near candidate genes selected on the basis of prior biological knowledge¹². These approaches were not successful for complex traits, as small effect sizes lead to low penetrance in pedigrees¹¹ and poor power at the sample sizes typically used in early candidate gene studies¹³.
- Genome-wide association studies (GWAS) systematically test common

1.2. GENETIC ASSOCIATION STUDIES AND FROM PLEIOTROPY TO COMPLEXITY

variants selected in a hypothesis-free manner across the genome for association with a trait (Fig. 1.2). Using large sample sizes to overcome small effects and large multiple testing burden, thousands of associations have been discovered for complex traits and disease, many robustly replicated across populations^{11,14}. Most genetic variance is explained by additive effects, the contribution of epistatic interactions is small⁸, and pleiotropy is widespread¹¹. Sample sizes in the millions are increasingly commonplace, and discovery of new associations with increasing sample size shows no sign of plateauing¹⁵. It is now appreciated that most heritable phenotypes are complex, and have remarkable polygenicity.

1.2.3 From complex trait to locus

GWAS rely on the tendency of common variants on the same haplotype to be in strong LD. As the number of haplotypes is comparatively few, it is possible to select a subset of tag variants such that all other known common variants are within a certain LD threshold of that subset. In practice, there is enough redundancy that the number of variants measured on a modern genotyping array (in the order of 10^5 to 10^6) is sufficient to tag almost all common variants^{16,17}. Associations with unmeasured variants are indirectly detected through their strong correlation with a tag variant. Furthermore, as unrelated individuals still share short ancestral haplotypes, study samples can be assigned haplotypes from a panel of haplotypes derived from reference samples by matching on the directly genotyped variants. This process of genotype imputation allows ascertainment of many more variants not directly genotyped¹⁸, but helps to recover rarer variants that are poorly-tagged¹⁴. Modern imputation panels enable cost-effective GWAS including tens of millions of variants down to frequencies of ~0.01% <https://www.biorxiv.org/content/10.1101/563866v1>.

seems like there is some connection to be made between the tagability of common variation and the feasibility of imputation both being enabled by the relatively small number of common haplotypes compared to variants

Testing such large numbers of variants incurs a massive multiple testing burden, but acknowledging the correlation between variants due to LD, there are only the equivalent of $\sim 10^6$ independent tests in the European genome, regardless of the number of tests actually performed¹⁹. The field has thus converged on a fixed discovery threshold of $0.05/10^6 =$

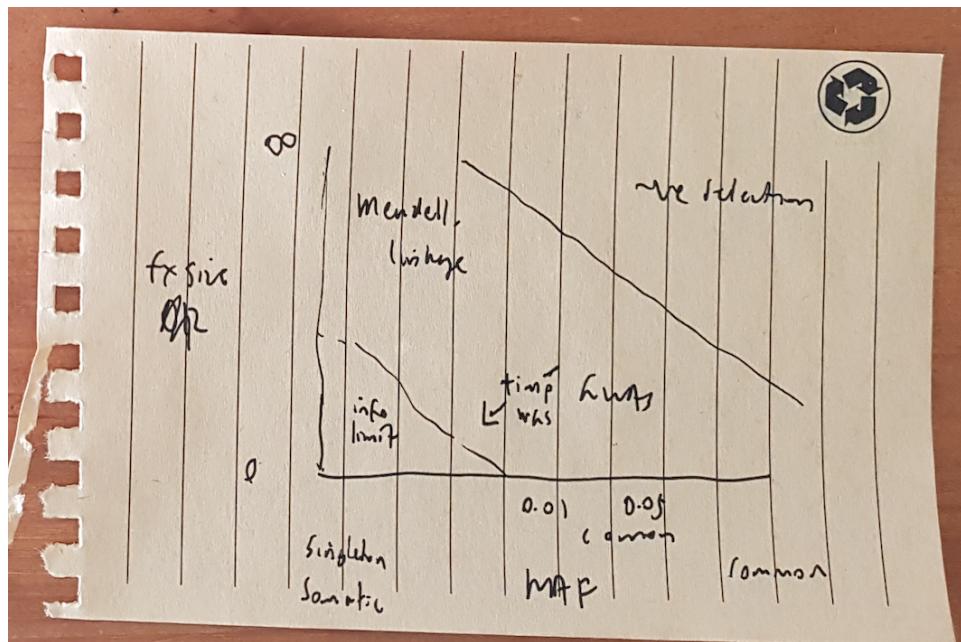


Figure 1.2: The reach of GWAS. OR vs MAF ala tam2019BenefitsLimitationsGenomewide, extended by imputation, sample size, WGS based genotypes, but may be indistinguishable from noise at the limits

5×10^{-8} for genome-wide significance in European populations²⁰, akin* to controlling the family-wise type I error rate at using the Bonferroni correction.

1.2.4 From locus to causal variant

- By design, a significantly-associated variant from a **GWAS** needs not be a variant that causally affects the trait, and may only tag a causal variant.
 - Fine-mapping is the process of determining which of the many correlated variants at a **GWAS** locus are causal.
 - The power to separate causal and tag variants depends on **LD** and sample size¹⁴.

*The Bonferroni procedure makes no assumptions about the dependence structure of the p -values, and is conservative (i.e. controls the **family-wise error rate (FWER)** at a stricter level than the chosen α) even for independent tests. In fact it is always conservative unless the p -values have strong negative correlations²¹.

1.2. GENETIC ASSOCIATION STUDIES AND FROM PINT TO NDITION

- State-of-the-art methods (e.g. CAVIAR, PAINTOR, FINEMAP, SuSiE) provide Bayesian posterior probabilities that associated variants are causal, and some methods can consider the presence of multiple causal variants at the same locus²².
- Naturally, these methods assign probabilities assuming the causal variant is in the set of variants observed.
- The causal variant must either be genotyped or imputed. Denser genotyping e.g. by WGS, and larger imputation panels will help.

1.2.5 From causal variant to target gene via expression

- Unlike for Mendelian traits where most causal variants are coding <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4573249/>, over 90% of **GWAS** loci fall in non-coding regions of the genome²³, and often too far from the nearest gene to be in LD <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5291268/>. Thus even if the causal variant at a locus is fine-mapped, it may not be obvious how to find the target genes through which that variant affects the trait.
- Rather than directly impacting the coding sequence of a gene, many non-coding GWAS loci are thought to affect traits by affecting the regulation of target genes²³. **GWAS** loci are enriched in regulatory elements annotated by functional genomics studies, such as regions of open chromatin, DNase I hypersensitive sites, splice sites, UTRs, histone binding sites, **transcription factor (TF)** binding motifs, and enhancers^{23,24} <https://genome.cshlp.org/content/22/9/1748.full>. For complex diseases, enrichment is observed in disease-relevant tissues¹⁴. As these regulatory elements not only have *cis*, but also *trans* regulatory effects on gene expression, these enrichments put forth expression as an important molecular phenotype linking non-coding **GWAS** variants to their associated traits (Fig. 1.3).
- Studies of the genetic architecture of quantitative molecular phenotypes have further reinforced this hypothesis.
 - Molecular phenotypes like expression are heritable complex traits²⁵

- The variants associated with expression are called **expression quantitative trait loci (eQTLs)**.
- eQTLs can also be *cis*- or *trans*- to their target gene²⁶.
- Their effect size declines with distance to the TSS, so most eQTLs detected are *cis*, and within 1Mb²⁷
- GWAS variants are enriched for eQTLs <https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1000888>
 - So GWAS loci that are also eQTL naturally prioritise target genes.
 - Is it a narrow view to assume that the effect of GWAS loci on complex traits not only act through a target gene, but are specifically mediated by eQTL effects?
 - Over many complex traits, a median of 11% heritability could be explained by mediation of GWAS loci by common (MAF > 0.01) *cis*-eQTL, and this proportion does not include *trans* or post-transcriptional effects.
- With increasing sample size, most genes (60-80%) have a detectable eQTL²⁷. Assuming that a locus on the genome is associated with both a complex trait and an **eQTL**, how can we separate the scenario where one variant affects both trait and expression (pleiotropy), from coincidental overlap between distinct causal variants that may possibly in **LD**? Bayesian probabilistic colocalisation methods (e.g. eCAVIAR, Sherlock, coloc²⁸) address this by estimating the posterior probability that the same causal variant is associated with both phenotypes. distinguishing pleiotropy from linkage, but not vertical pleiotropy (mediation) from horizontal pleiotropy (independent effects on trait and expression)²⁹. As colocalisation of a **GWAS** loci with **eQTLs** is necessary but not sufficient for mediation, it should be supported by complementary lines of evidence from other methods that integrate intermediate phenotypes (TWAS, MR, mediation analysis etc.)²⁹ to help untangle the multiplex of possible causal pathways from variant to trait.

1.3. GENETIC EFFECTS ON EXPRESSION AND ENVIRONMENT

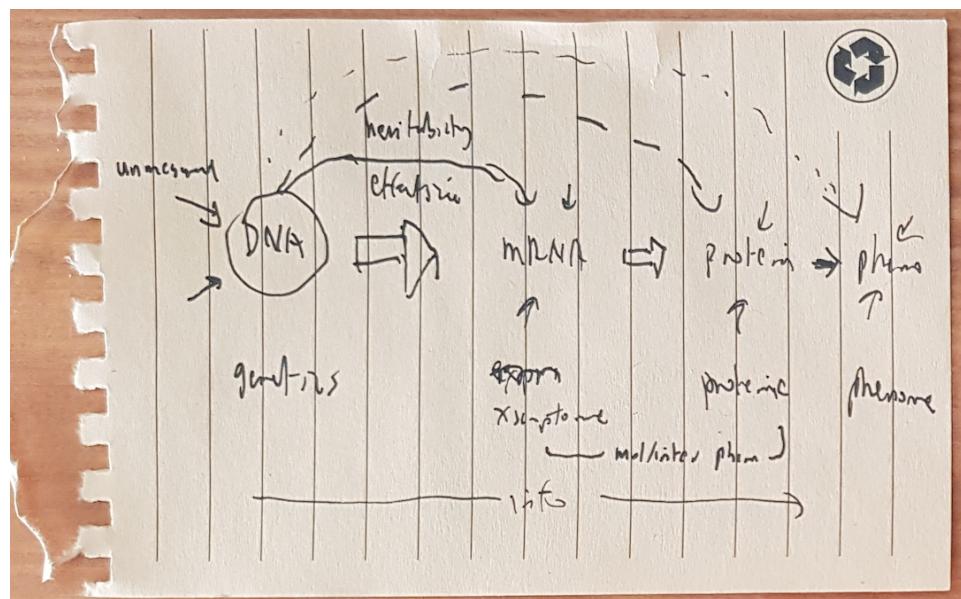


Figure 1.3: Mediation of genetic effect to phenotype, through the biological system

1.3 Genetic effects on expression: environment is key

- The effects of **eQTLs** (and molecular quantitative trait loci (QTLs) in general) are incredibly context-dependent^{26,27}.
 - This represents genotype-environment interactions at those eQTL.
 - A non-exhaustive list of environments that **eQTLs** have been found to interact with:
 - * sex, age <https://academic.oup.com/hmg/article/23/7/1947/655184>
 - * ancestry^{30–32}
 - * tissue^{33,34}
 - * cell type composition in bulk samples^{35–38}
 - * individual cell type^{30,38–41}
 - * disease status⁴⁰,
 - * and experimental stimulation (see subsection 1.3.1).
- Given the effect of an eQTL can be starkly different between environments, it is difficult to determine the appropriate **eQTL** dataset to use

for target gene prioritisation at GWAS loci.

- It has already been shown that use of cell-type specific eQTLs increases coloc rates with GWAS hits³⁸
- Successful colocalisation of GWAS loci with coloc may prioritise not only the target gene, but the specific environments most relevant to a trait.
- What molecular mechanisms might facilitate genotype-environment interactions at eQTLs?
 - ⁴²: defines static, conditional, dynamic eQTLs
 - ⁴³: proposes TF-based mechanisms for cis-eQTL (here, define mag, damp, flip) (Fig. 1.4)
 - ^{25,44}: suggests info on more regulatory layers will help break down transcriptional and post-transcriptional

1.3.1 Immune response expression quantitative trait loci

- A important subclass of context-dependent eQTL are **response expression quantitative trait locus (reQTL)**, where the interacting environment is experimental stimulation^{27,45}. Most reQTL studies to date have been conducted on immune cells *in vitro*, not only because the immune system is specialised for responding to environmental exposures, but due to the abundance of immune cells easily accessible in peripheral blood, and amenable to separation (e.g. FACS) and stimulation.
 - *In vitro*, potential interacting variables such as cell type, and the nature, length, and intensity of stimulation can be precisely controlled.
- A seminal early study was conducted by⁴⁶, where eQTLs were mapped separately in monocyte-derived dendritic cells before and after 18h infection with *Mycobacterium tuberculosis*.
 - reQTLs were detected for 198 genes, 102 specific to the uninfected state, and 96 specific to the infected state.

1.3. GENETIC EFFECTS ON EXPRESSION VARIATION IN THE ENVIRONMENT

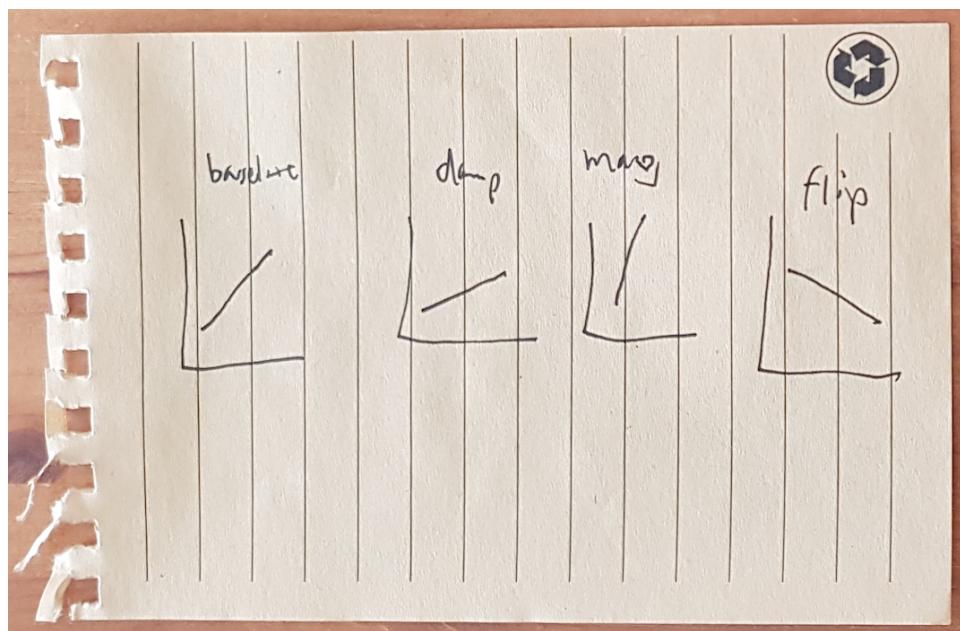


Figure 1.4: eqtl mech models: magnify, dampen, flip

list a few from⁴⁷ until⁴⁸

- Since then, *in vitro* immune reQTL studies have been conducted for a variety of cell types (e.g. primary CD14+ monocytes⁴⁷) and stimulations (IFN γ and LPS⁴⁷).
 - A complementary approach is *in vivo* reQTL mapping
 - There are numerous pros to *in vivo* stimulation.
 - * the innumerable interactions in the immune system that are absent *in vitro*
 - * ability to get whole organism phenotypes
 - * ability to get repeated measures: can reason about change in expression over time
 - Major disadvantages: the choice of stimulation must be ethical *in vivo*, and many environmental factors (e.g. diet, lifestyle, immune exposures) cannot be controlled, leading to greater experimental noise (?), and more complex interpretations.
 - There are few published *in vivo* reQTL studies.
 - * ⁴⁹: seasonal trivalent inactivated influenza vaccine (TIV), whole blood, antigen processing and intracellular trafficking genes, attempted mediation for Ab titres, but underpowered

- * ⁵⁰: fold-change expression after inactivated vaccinia vaccine, focus was on pairwise epistatic interactions, apoptosis pathways
- * ⁵¹: whole blood, IFN status and anti-IL6 drug exposure, reQTL driven by ISRE and IRF4 motifs
- <why care about immune reQTLs>
 - Exposes differences in regulatory architecture between conditions, but does not automatically reveal the mechanisms behind those differences
 - Immune *in vitro* reQTL have been shown to be enriched more so than non-reQTL among GWAS loci for immune-related phenotypes such as susceptibility to infectious^{46,52} and immune-mediated diseases^{52,53}.
 - Not yet clear whether *in vivo* reQTL have any utility on top of *in vitro* reQTL for interpreting GWAS loci: note that many studies, and complex interpretations.
 - Nevertheless, as the number of cell types systems and stimulations both *in vitro* and *in vivo* increases, the number of known reQTLs continues to grow.

1.4 Immunity is a complex trait

- Heritability of immune phenotypes is not only restricted to the expression phenotypes discussed above.
 - Studies of interindividual variation in the healthy immune system shows many aspects of the immune system are heritable and complex.
 - Immune parameters are influenced by age, sex, and chronic infection^{54–58}, but most individuals have a healthy baseline immune state that is individual-specific, and relatively stable over time^{55,56,59}.
 - Overall estimates of the heritability of many immune parameters, such as cell composition and serum protein levels, lies between 20-40%^{55–58}

a little out of order, but since most reQTL studies are immune, I went context-specific -> reQTL -> immune rather than context-specific -> immune -> reQTL

- Genetic regulation is more important for the innate immune system than the adaptive immune system⁵⁷.
- A central goal of systems immunology is to establish causal relationships between the many parts and levels of the immune system
 - Natural genetic variation represents small scale perturbation that is causally anchored^{60,61}
 - But as discussed in the context section above, specific effects may not be apparent in the baseline state, stimulation is required
 - Studies of natural infection are complicated by e.g. determining exposure.
 - As in the immune in vivo reQTL studies, vaccines and drugs used as controlled immune perturbations to study the activated immune system
 - reQTL may have utility for interpretation of these immune-related complex traits too, not just IMIDs/infectious disease discussed in reQTL section above

1.4.1 Immune response to vaccination is a complex trait

- Vaccination has enormous impact on global health⁶²
 - <quick vaccine bio>
 - * Vaccines stimulate the immune system with pathogen-derived antigens to induce effector responses (primarily antigen-specific antibodies) and immunological memory against the pathogen itself.
 - * These effector responses are then be rapidly reactivated in cases of future exposure to the pathogen, mediating long-term protection.
 - * <...>
 - A vaccine that is highly efficacious in one human population may have significantly lower efficacy in other populations. Particularly

CHAPTER 1. INTRODUCTION. IMMUNITY IS A COMPLEX TRAIT

challenging populations for vaccination include the infants and elderly, pregnant, immuno compromised patients, ethnically-diverse populations, and developing countries.

- * <1 example statistic on vaccine efficacy differences e.g. rotavirus>
- Traditional vaccine dev is empirical (classical "isolate, inactivate, inject" paradigm), often successful vaccine dev does not offer insights into the mechanisms of efficacy
- The immunological mechanisms that underpin a specific vaccine's success or failure in a given individual are often poorly understood.
- A sub-discipline of systems immunology is systems vaccinology.
 - Systems vaccinology is the application of -omics technologies to provide a systems-level characterisation of the human immune system after vaccine-perturbation.
 - Systems vaccinology has been successfully applied to a variety of licensed vaccines [yellow fever, influenza], and also to vaccine candidates against [HIV, malaria], resulting in the identification of early transcriptomic signatures that predict vaccine-induced antibody responses. define what a signature is
 - * <add more to list of what vaccines have been studied, pull out of sysvacc_review_docx>
 - Sysvacc informs more mechanism-based and cost-effective design (rational paradigm), and the move towards personalised vaccinology.
 - Sysvacc has revealed many influences on vaccine response (age, sex, dose, adjuvants, expression signatures, microbiome, strain etc.)
 - Studies of impact of host genetics is underrepresented⁶³
- Like for other complex traits, from twin studies it's known that vaccine Ab responses are heritable.
 - Moving out of the candidate gene era (e.g. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3570049/>) into GWAS.

- Many loci have been implicated by GWAS e.g. HLA^{63–68}
- Overall, systems vacc studies that include genetics are nowhere near as mature compared to the trait to gene pipeline described in above e.g. for immune-mediated disease

find best GWAS
ref, probably
mooney2013SystemsIm
then prune and reassig
these citations

1.4.2 Immune response to (biologic therapies for immune-mediated diseases) is a complex trait

WIP, need to do more reading up on PANTS background.

Not yet sure if I need to go as wide as X=biologics for IMIDs, or only as narrow as anti-TNFs for CD

- There is variation in response success to X for immune-mediated disease
- Many subphenotypes may be complex: immunogenicity, primary response, loss of response, remission rate, adverse fx
- Existing work on expression response to X
- Existing work on genetic factors for X

1.5 Thesis overview

- <By chapter context-content-conclusion overview.>
 - <ch 2: systems vaccinology study of Pandemrix>
 - * meta analysis
 - <ch 3: in vivo reQTL study of Pandemrix>
 - * Gap: relatively few studies have assessed the impact of human genetic variation on responses.
 - <ch 4: systems immunology and reQTL study of response to anti-TNF treatment in CD>
 - <discussion: limitations, future outlook>

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List of Abbreviations

bp base pair

eQTL expression quantitative trait locus

FWER family-wise error rate

GWAS genome-wide association study

LD linkage disequilibrium

MAF minor allele frequency

QTL quantitative trait locus

reQTL response expression quantitative trait locus

SNP single nucleotide polymorphism

TF transcription factor

TIV trivalent inactivated influenza vaccine