A pedigree-based GWAS identifies UDP-glucuronosyltransferase variants associated with serum bilirubin concentration and risk of Type-2 Diabetes in the Norfolk Island genetic isolate

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QUT ihbi Institute of Health and Biomedical Innovation

Rationale

- The Norfolk Island Health Study
- Why are we doing this study?
- Increased risk of complex metabolic disorders within the NI population.
- Aim:

  Investigate the well established genetic isolate of Norfolk Island (NI) and leverage its unique genomic structure to increase the ability to detect related genetic markers
- This study revolves around the complex structure of the NI pedigree, but before we get there...

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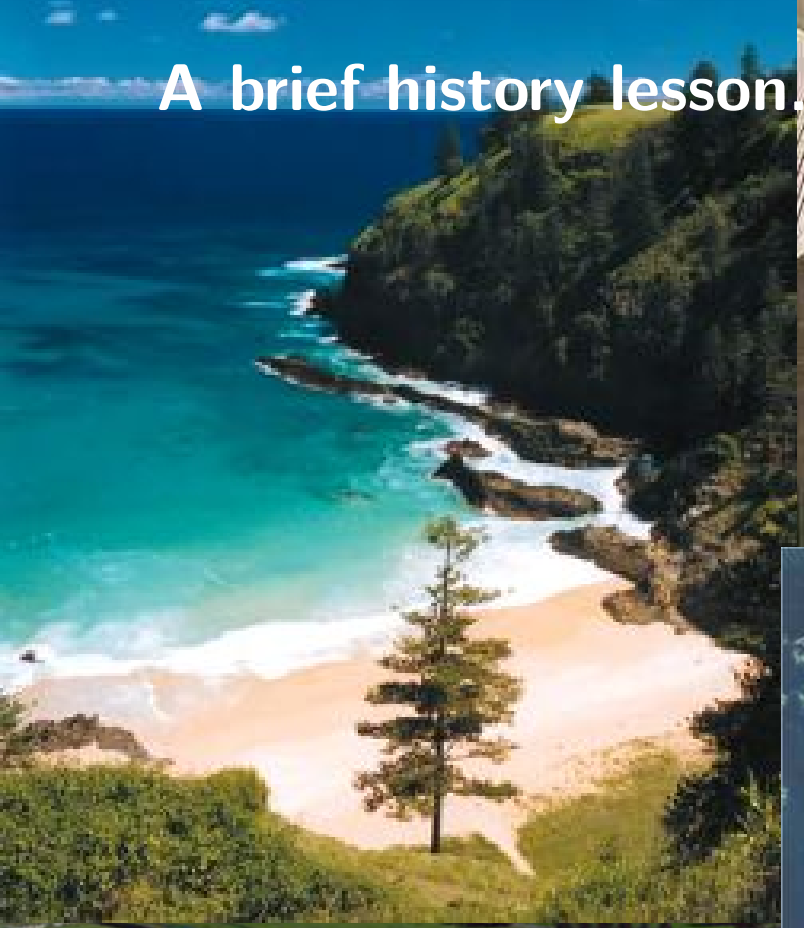
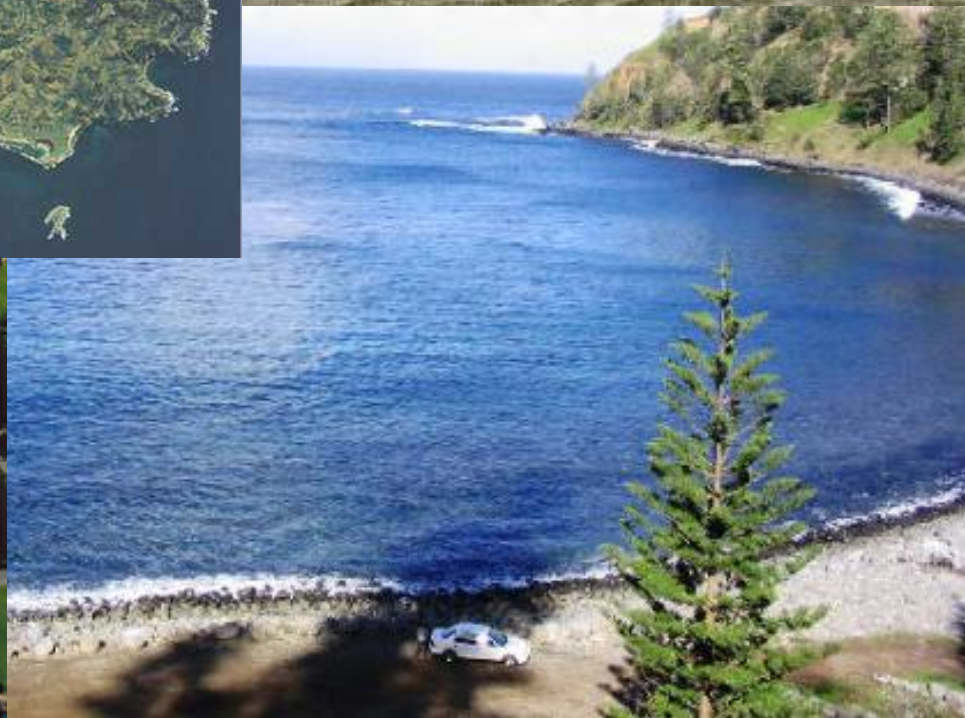
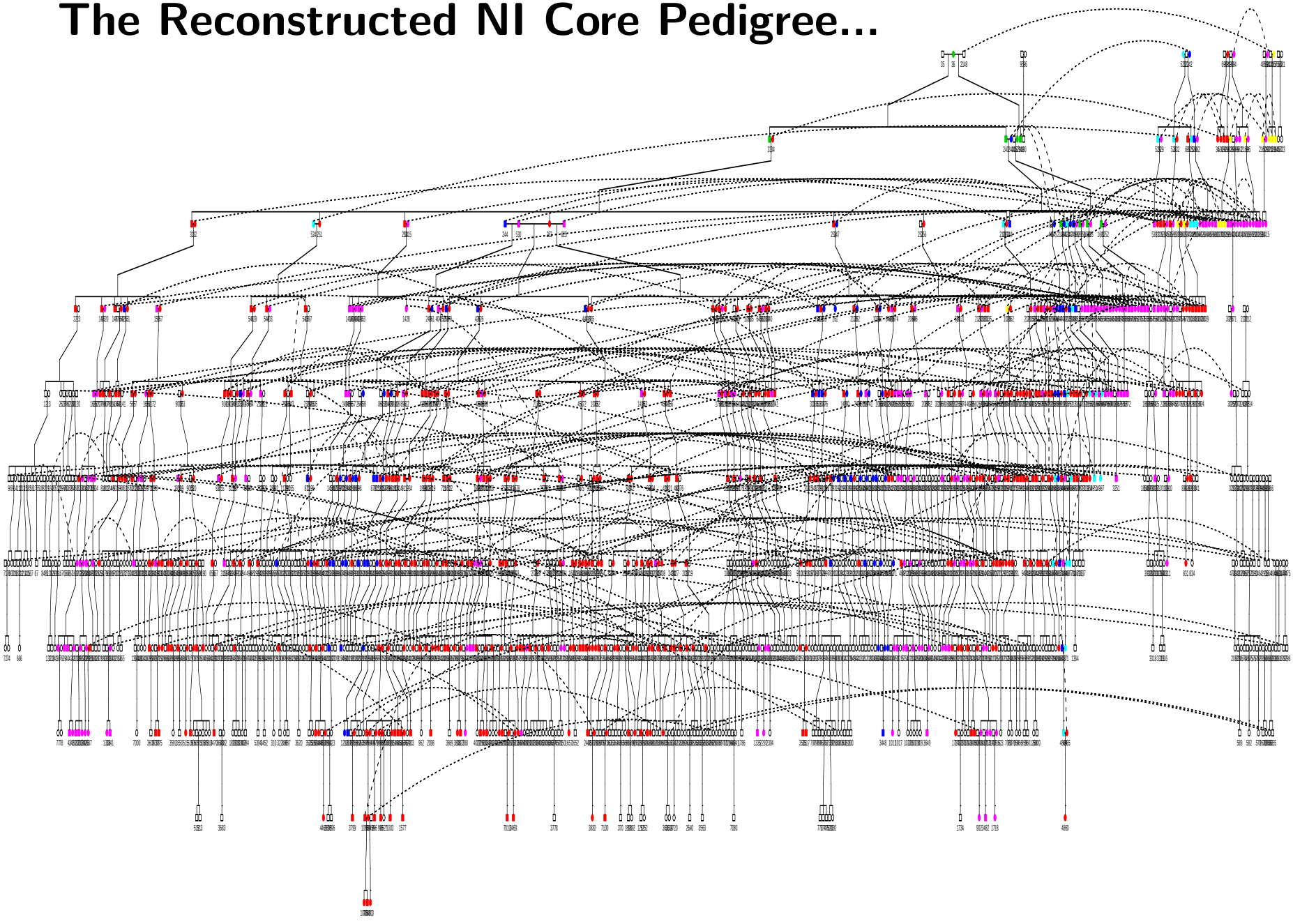




The Reconstructed NI Core Pedigree...



Study Design

- Participants - 500 NIHS individuals
  1. Samples - Blood (circulating lymphocytes)
- Platforms:
  1. SNPs: Illumina 610quad

$\sim$ 590000 SNPs for 500 participants
37 CVD and T2D-related traits

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Analysis: Pedigree-Based GWAS

- Heritability analysis (batched using GenABEL/R: Polygenic Model)
- mmscore function - pedigree structure analysis
  1. study-wide significance for NI pop $= 1.84x10^{-7}$
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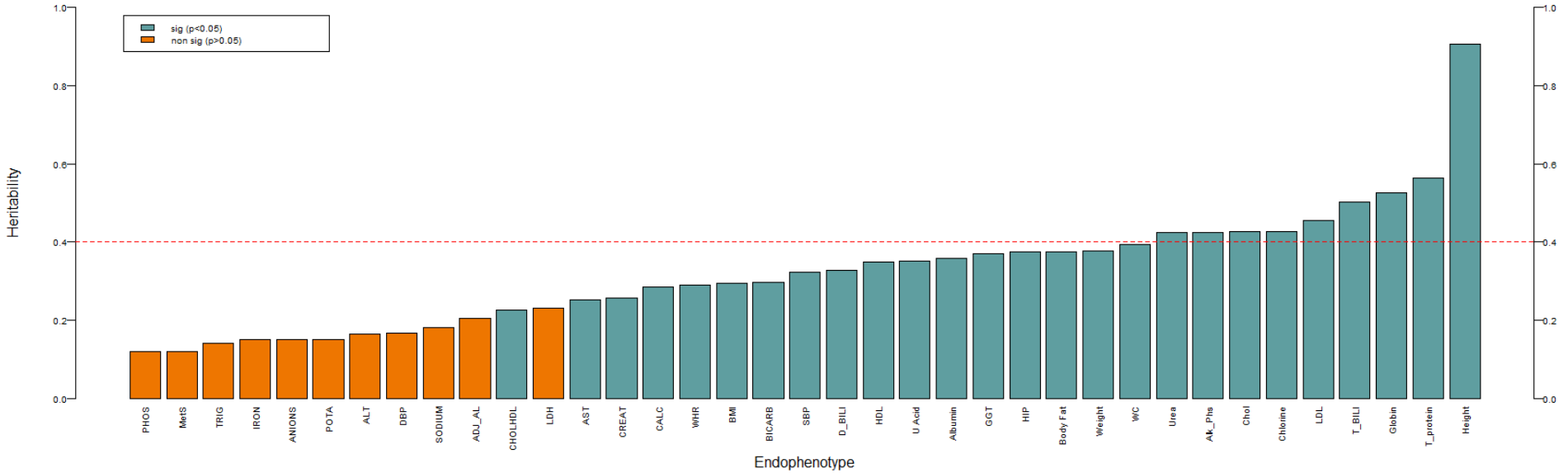
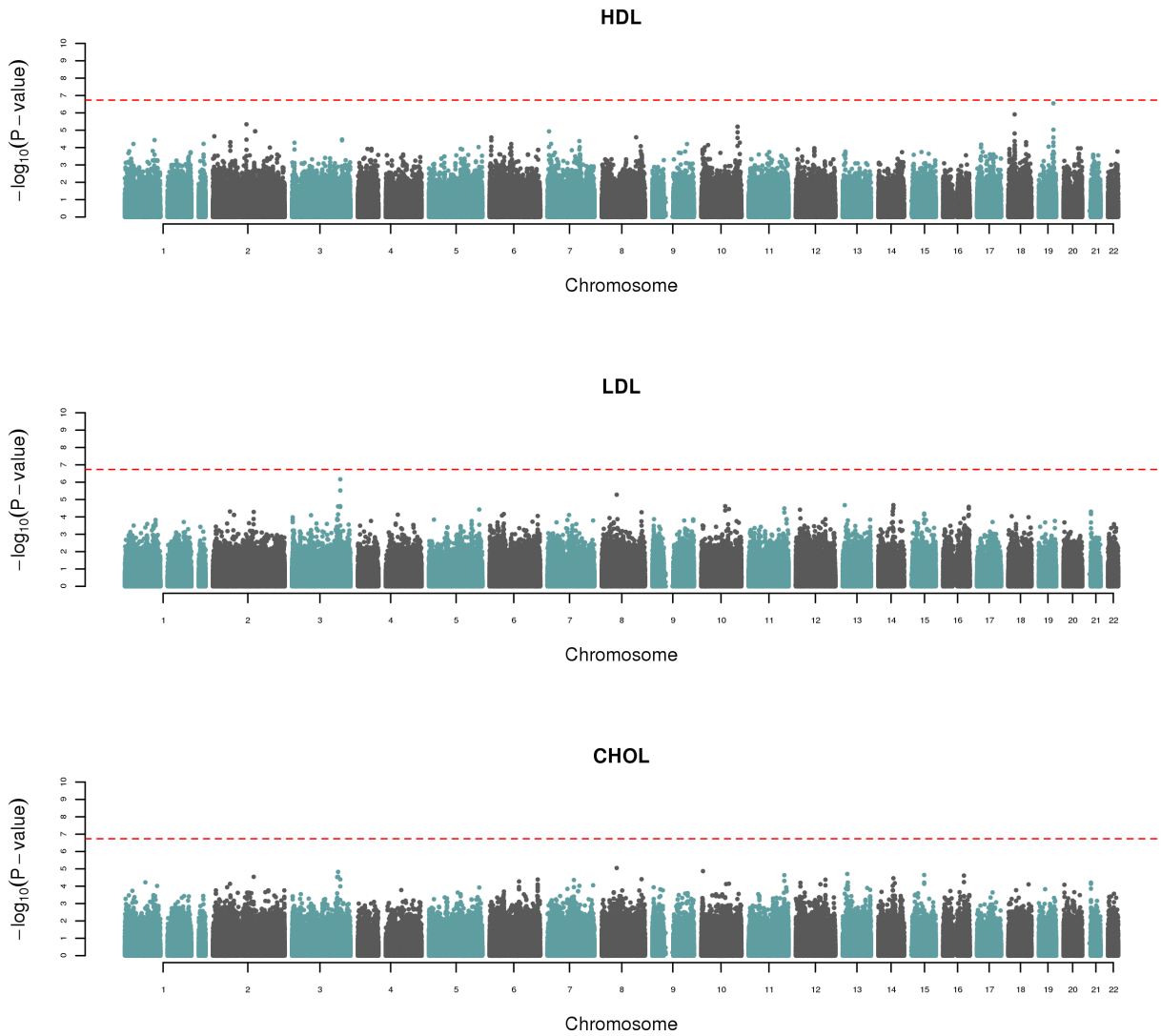
Trait Heritabilities

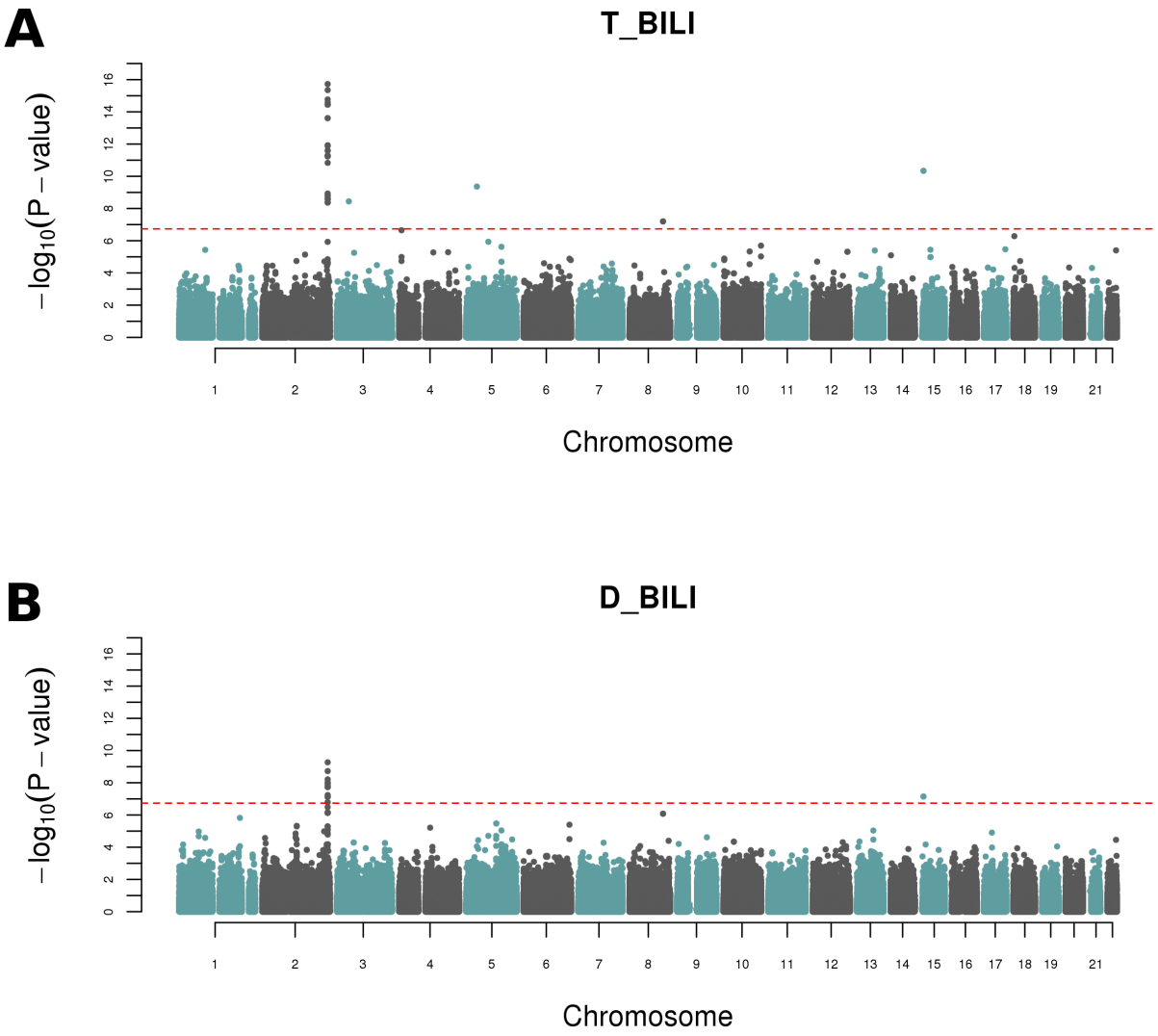


A range of metabolic-related traits show 'high' h^2 in NI

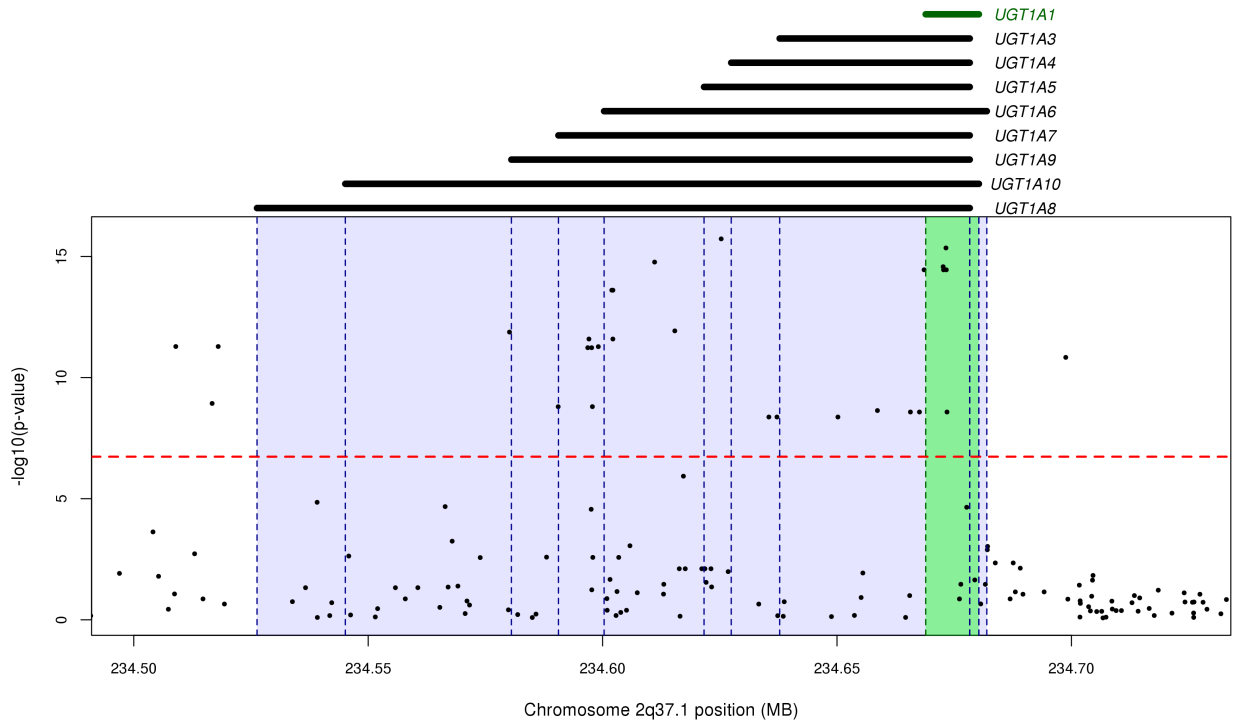
Lack of association?



Bilirubin associations

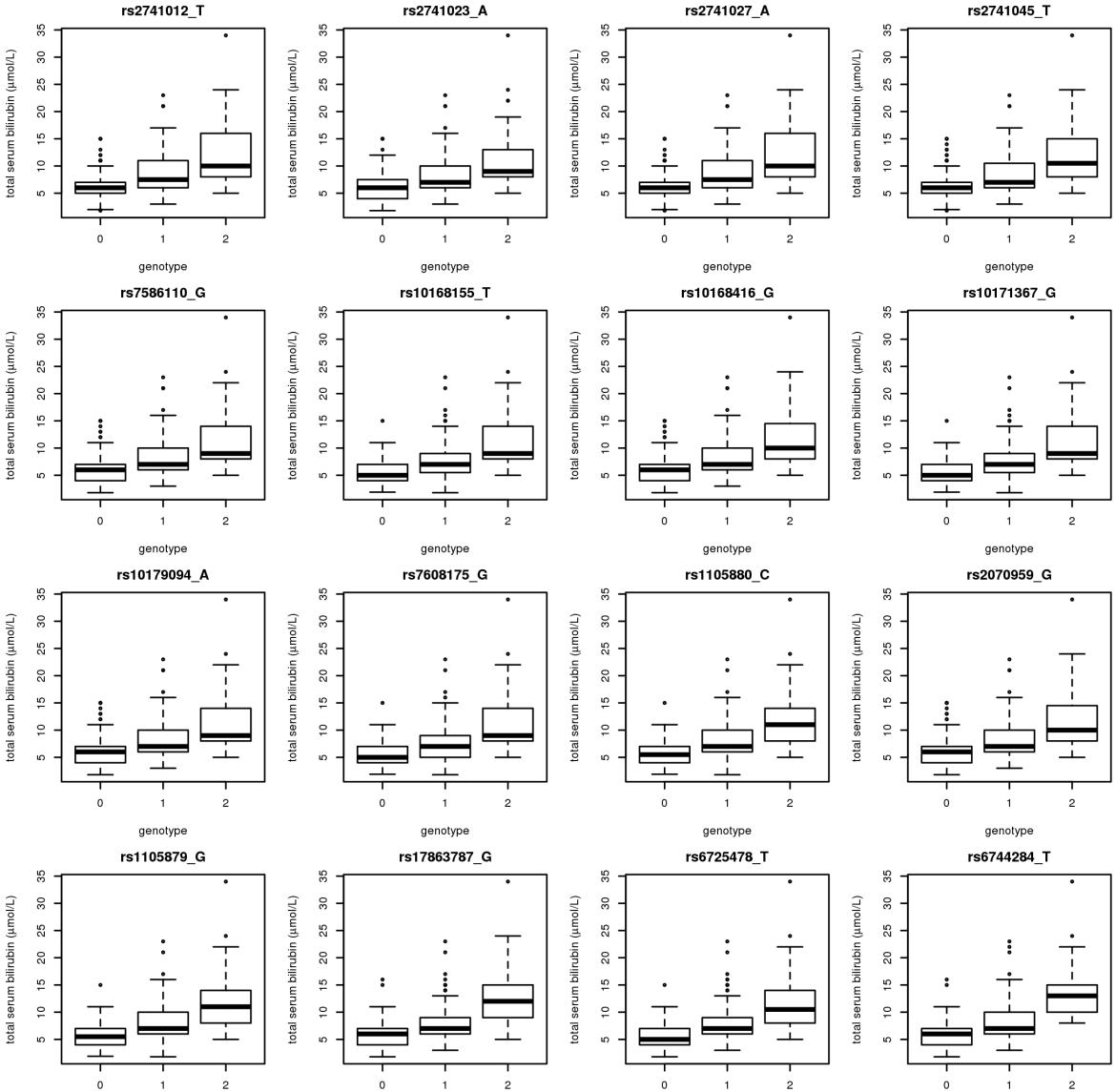


What's in a region?

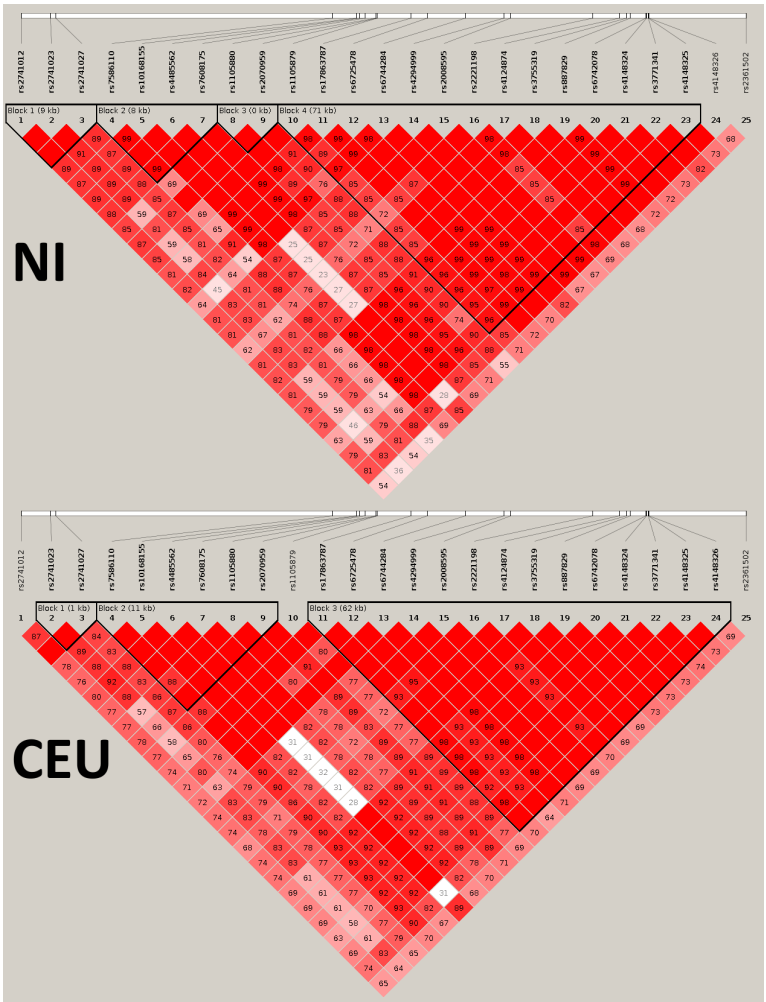


A striking association peak located at chromosome 2q37.1 was observed for both total bilirubin and direct bilirubin, with 29 SNPs passing multiple correction ($1.84x10^{-7}$). Strong linkage disequilibrium (LD) was observed across a 200 kb region spanning the UDP-glucuronosyltransferase (UDPGT) gene family, including *UGT1A1*, which codes an enzyme known to metabolise bilirubin.

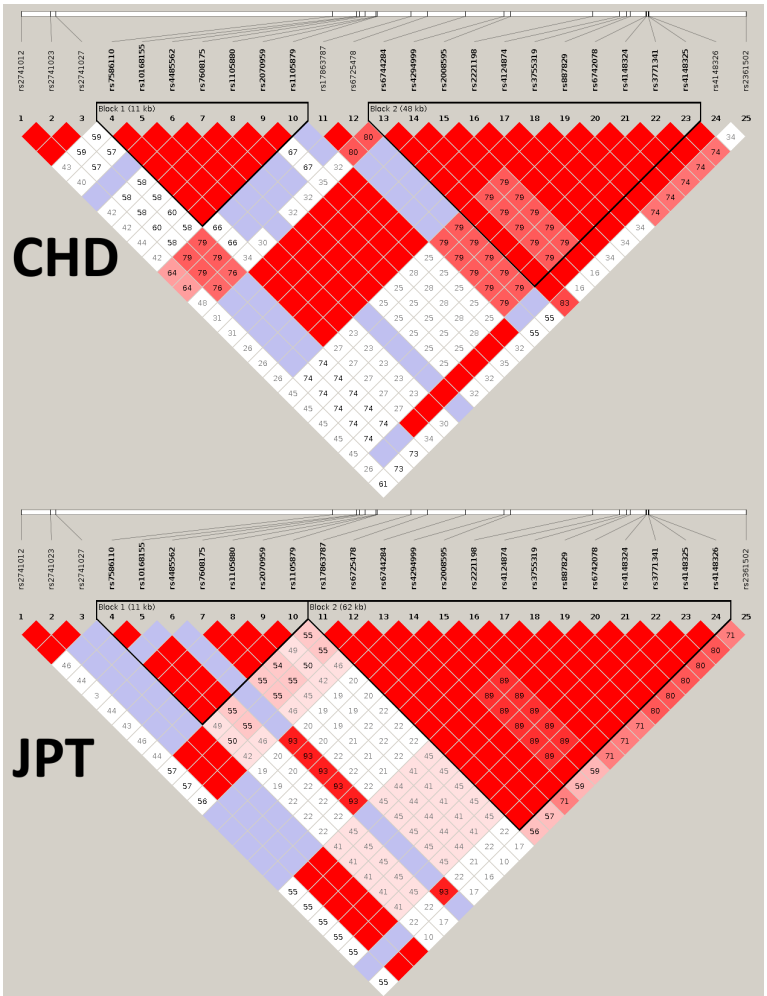
Genotype effect on bilirubin concentration



Comparison of LD across populations

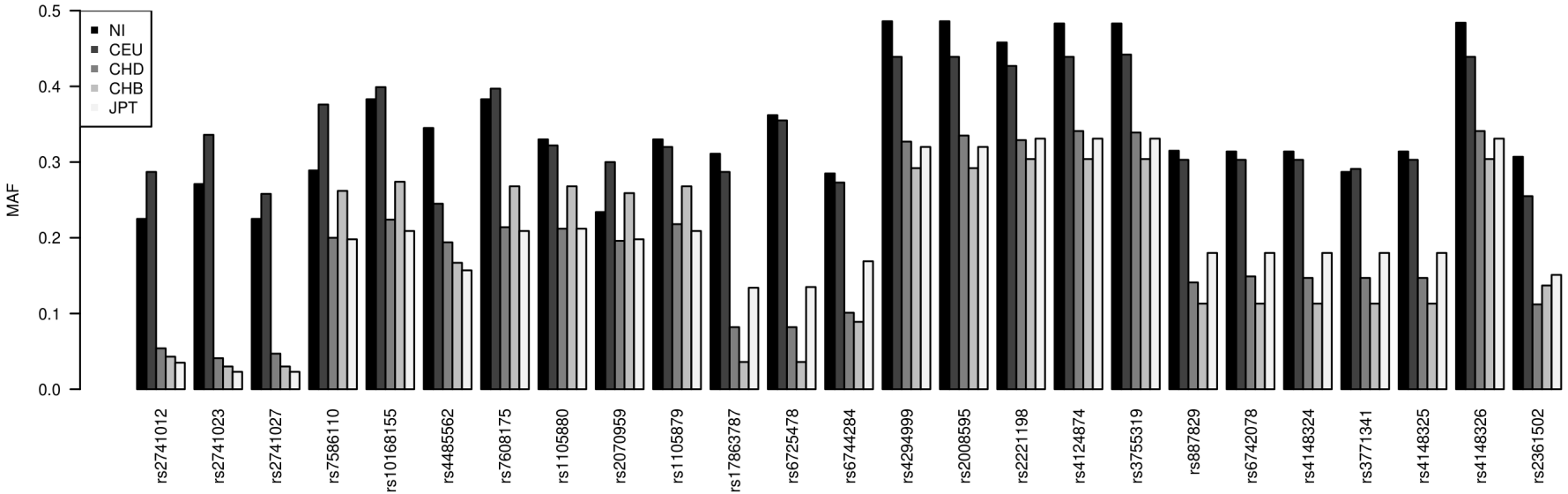


(a)



(b)

Minor Allele Freq Comparisons



Bilirubin: A protective role?

Bilirubin:

- component of haemoglobin
- formed during metabolic breakdown in liver
- direct form is soluble and secreted via blood or urine

Protective role:

- potent antioxidant
- vital role in protecting the body from reactive oxygen species

Clinical Associations:

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UDPGT region and associations

UDP-glucuronosyltransferase:

- family of enzymes
- large group of isoforms on Chr 2q37.1
- major importance in conjugation and elimination of potentially toxic xenobiotics and endogenous compounds
- UGT1A1 primarily metabolises bilirubin, UGT1A3 and UGT1A4 have also been shown to have some affinity

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Explored clinical associations in the NIHS cohort:

- logistic regression modelling
  - revealed a significant association between direct bilirubin concentration and T2D-risk[1]

In NIHS increased direct bilirubin was associated with a **28% reduction** in T2D risk

- (OR: 0.72, 95% CI: 0.57-0.91, p-value: 0.005).

When adjusted for genotype the overall model was validated:

- adjusted model predicting a **30% reduction** in T2D-risk with increasing direct bilirubin concentrations
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- Identified the UDPGT region (2q37.1) with bilirubin levels
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Identification of potential blood biomarkers to predict bilirubin levels

Further explore population differences (additional populations)

Starting to collaborate with other groups that have populations/cohorts with bilirubin measures (USA and NZ)

Potentially modifiable outcome (can change bilirubin levels)

UDPGT region (2q371.1) contains many different isoforms, act on thousands of different compounds
- potential to screen other compounds against UDPGT variants

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Co Supervisors: Dr Donia Macartney-Coxson, Dr Geoff Chambers

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The people of Norfolk Island

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