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Identification of a pleiotropic effect locus associated with a composite CVD risk trait in the genetic isolate of Norfolk Island

Rationale:

• Many CVD risk traits tend to be correlated suggesting the presence of underlying genetic variants that effect multiple phenotypes ie. pleiotropic effects.
• GWAS analysis aimed at multivariate (composite) CVD phenotypes may reveal such genetic loci which could remain latent using univariate (single) phenotype methods.
• Analysis of large pedigrees offers the added advantage of assessing heritability of such composite traits which can help prioritise genetically influenced phenotypes for GWAS analysis.
• A recent *population-based* GWAS of >25,000 Americans revealed that loci within APOC1, BRAP and PLCG1 genes may confer pleiotropic effects on composite traits associated with CVD. *(Avery et al, 2011 PLoS Genetics)*
• The aim of our study was to perform a multivariate 'phenome' scan of CVD risk traits to identify pleiotropic effect loci in a large pedigree from Norfolk Island.

Study design and methodology:

• Analysed phenotype/genotype data from 330 individuals from NI core pedigree.
• Performed PCA on 37 quantitative CVD risk traits using R.
• Analysed SNP data from Illumina 610K quad arrays.
• Performed heritability analysis using GenAbel (polygenetic function for mixed model variance components).
• Performed pedigree checking and structure analysis using PREST and KING.
• Perform GWAS using GenAbel (mmscore function for pedigree-based association).
• Performed replication in an unrelated NI outgroup (n=250).
• Genome-wide expression analysis of lymphocytes using Illumina HT-12 Bead array.

The Norfolk Isolate:

• Higher rates of CVD risk factor traits in NI population compared to general mainland Australia
• Partly attributed to Polynesian founders of NI
• The NI Pedigree has been reconstructed (Figure 1) and used to statistically measure influence of genetics on complex traits *(Bellis et al., 2006)*

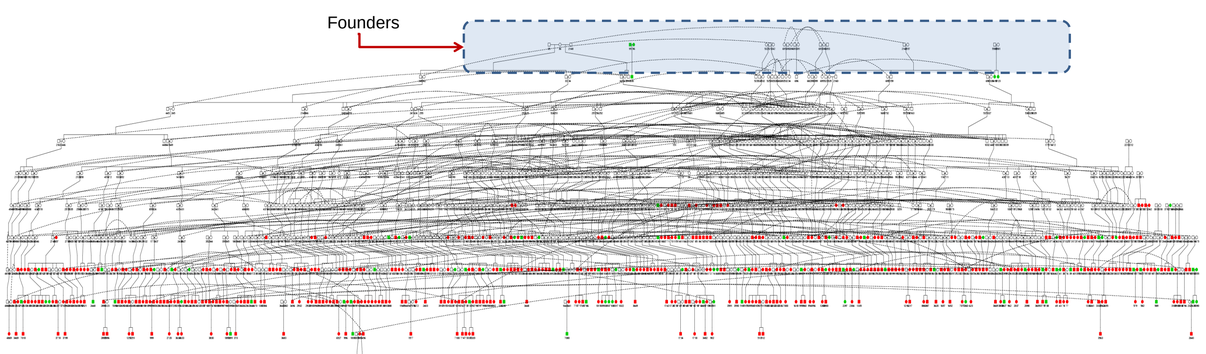
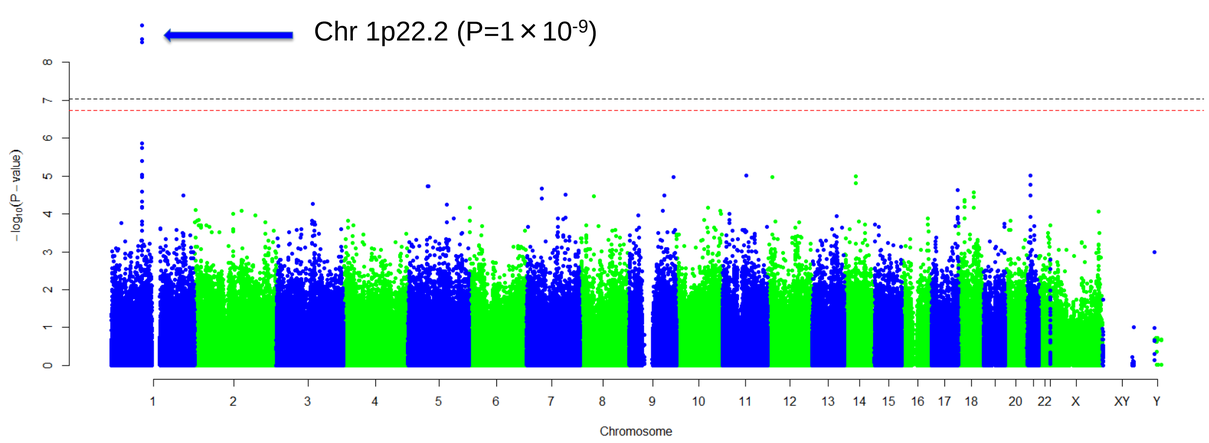


Figure 1: Reconstructed large multigenerational NI pedigree (**n=1389**). Pedigree spans 11 generations/200 years. Currently genotyped individuals indicated in red.

Results: GWAS - Component 3 – body fat, blood pressure, kidney/liver function



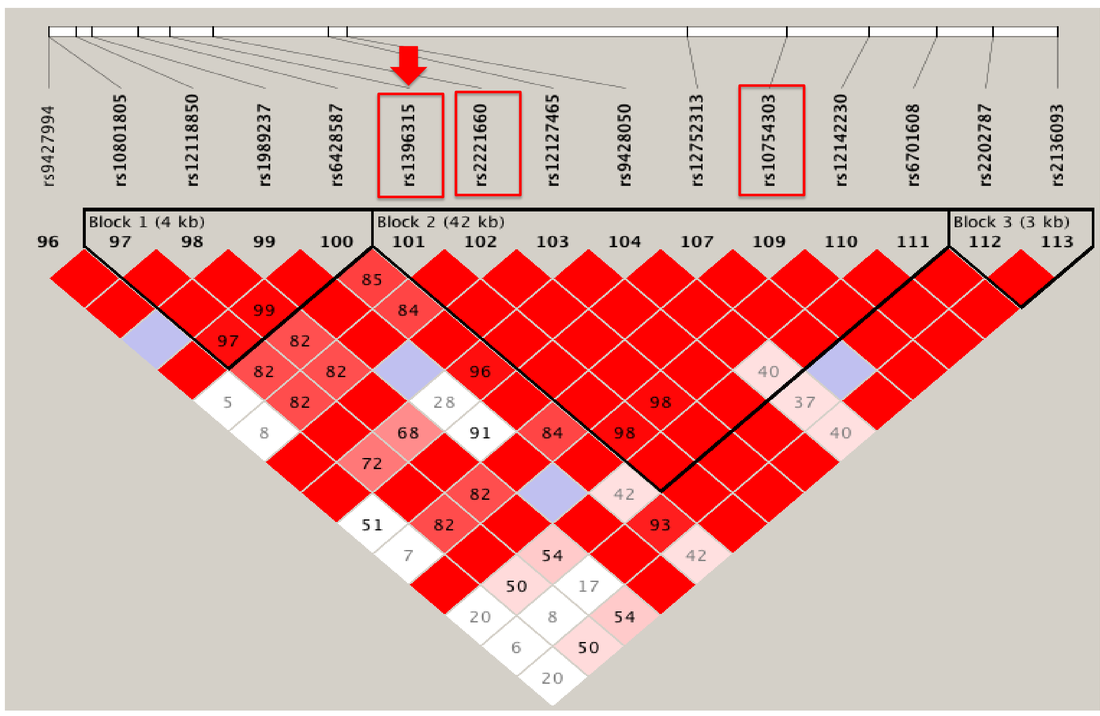
- Identified a potential pleiotropic effect locus for multiple CVD-related traits.
- Results adjusted for age, sex and structure.

MetS and T2D risk in NI:

• Clinical MetS calculated using "harmonised" criteria
  - **MetS prevalence in NI – 26.3% of the population**
  - 20% higher than mainland Australia (relative risk = 1.2)

• Type 2 Diabetes risk was calculated with AUSDRISK tool
  - **~43% of NI population estimated high risk of developing T2D in next 5 years**
  - 31% of mainland Australia are estimated as high risk
  - NI has a relative risk of 1.4 (i.e. 40% higher than mainland)

Results: LD analysis of Chr 1p22.2 SNPs



A Phenome Scan for Heritable CVD Risk Traits:

Principle Component Factor Analysis (PCFA)
Data reduction technique – making multivariate data easier to understand while searching for hidden 'structures' within a dataset (natural clusters = components)

- Analysis of all possible CVD related variables (n = 37)
- 13 components, explains 75% of total variability, 9 found to be heritable
- Component 3 had highest H^2 (55%)

Loaded with:
- Blood Pressure
- Waist/Hip
- Body Fat
- Creatine
- Uric Acid
- Urea

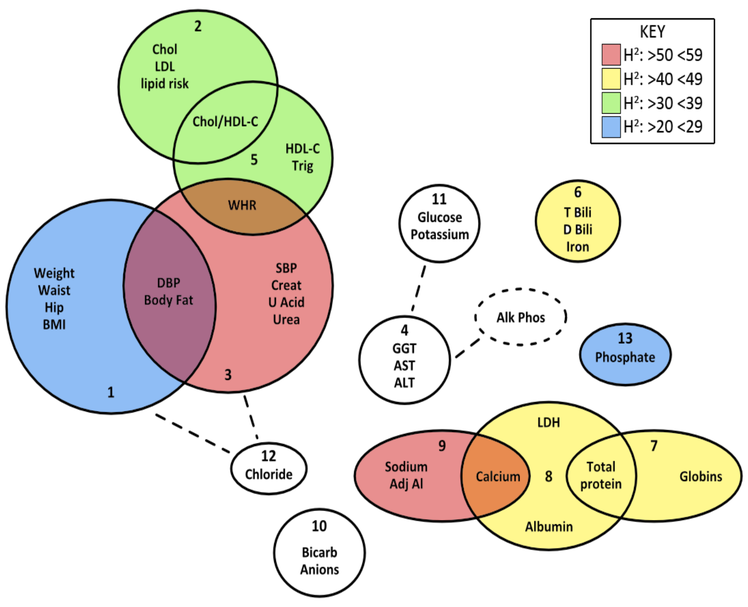


Figure 2: Venn diagram showing PCFA components and H^2 estimates

Summary of Findings:

• We have used a phenomics approach to identify a potential pleiotropic effect locus for a composite CVD trait on chromosome 1p22.2
• This composite trait is comprised of 7 phenotypic measures relating to body fat, blood pressure, creatine, uric acid and urea
• A GWAS of this composite phenotype implicated 3 SNPs on 1p22 that form a 42kb haplotype block and account for 11% of the genetic variance of the phenotype
• This locus may influence expression of gene(s) located on ch2q (i.e. trans-acting eQTL)
• Other GWAS studies hitting Ch 1p22.2
  - Metabolic syndrome including body fat in 2554 Indian Men
  - Liver enzymes in 133,653 European and Asians
  - Coronary Artery Disease in 984 Whites
• Future Directions
  - Replicate in large generational populations with same phenotype data
  - Further interrogate functional relevance of trans eQTL on gene expression and CVD risk-

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