A Phenome Scan for Metabolic Syndrome in the Norfolk Island Isolate

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Metabolic Syndrome

A clustering of risk factors for cardiovascular disease (CVD) and type-2 diabetes (T2D), which occur together more often than by chance alone (*Figure 1*)

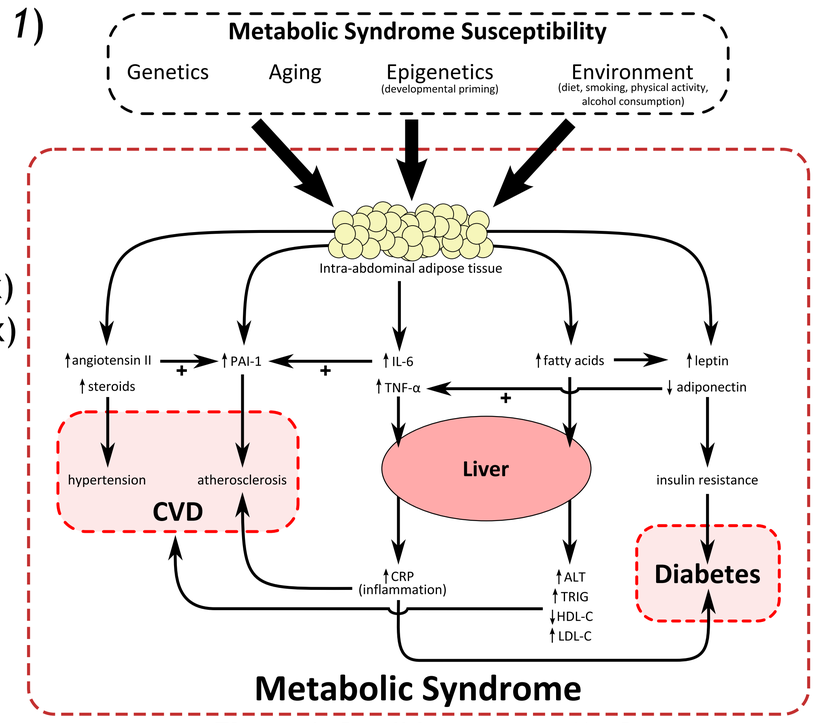


Figure 1: Possible routes to MetS

Presence of MetS:
- elevated risk of T2D (5x)
- elevated risk of CVD (2x)

Prevalence:
~20-30% of Australians
(Cameron *et al.*, 2007)

~35-40% of US adults
(Alberti *et al.*, 2009)

Therefore MetS is a major public health concern!

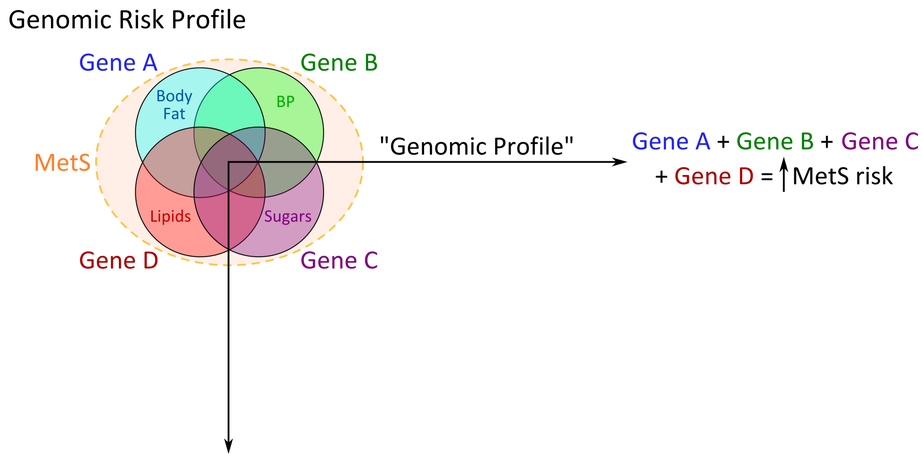


***Figure 2:** A hypothetical genetic model for MetS*

Clinical Risk Factors:
Raised bp, dyslipidemia (raised triglycerides and lowered HDL-C), raised fasting glucose, and central obesity

Environmental Risk Factors:
Decreased physical activity, high fat diet, smoking, alcohol consumption

Genetic Risk Factors:
Not fully understood (see *Figure 2*) but recent studies show promising associations:
- CNVs and SNPs adjacent to insulin gene enhancer protein associated with MetS (Kristiansson *et al.*, 2010)
- Haplotype of 3 SNPs found upstream of ATK1 to be a predictor of MetS (Devaney **et al.**, 2011)

The Norfolk Island Isolate

- Higher rates of CVD risk factor traits in NI population compared to general mainland Australia - Partly attributed to by Polynesian founders of NI

- The NI Pedigree has been reconstructed (*Figure 3*) and used to statistically measure influence of genetics on complex traits: (Bellis *et al.*, 2006)

- Sampled ~70% adult pop. Numerous baseline traits that underlie complex disorders such as MetS have been assessed and shown to have significant genetic heritabilities

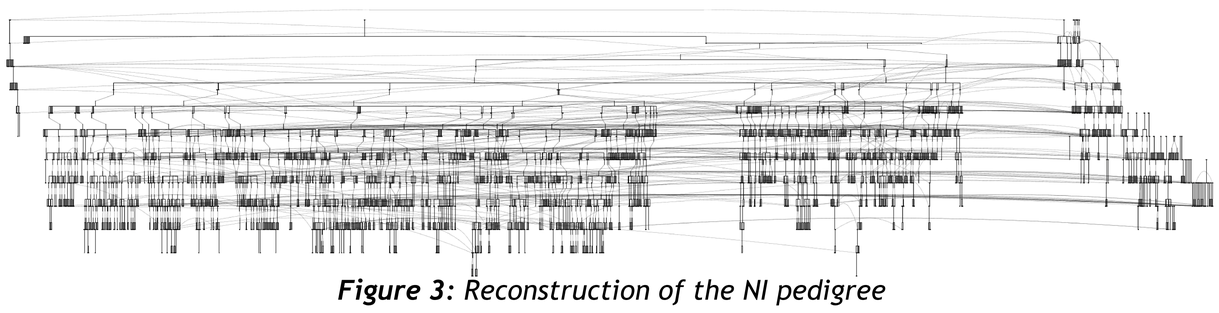
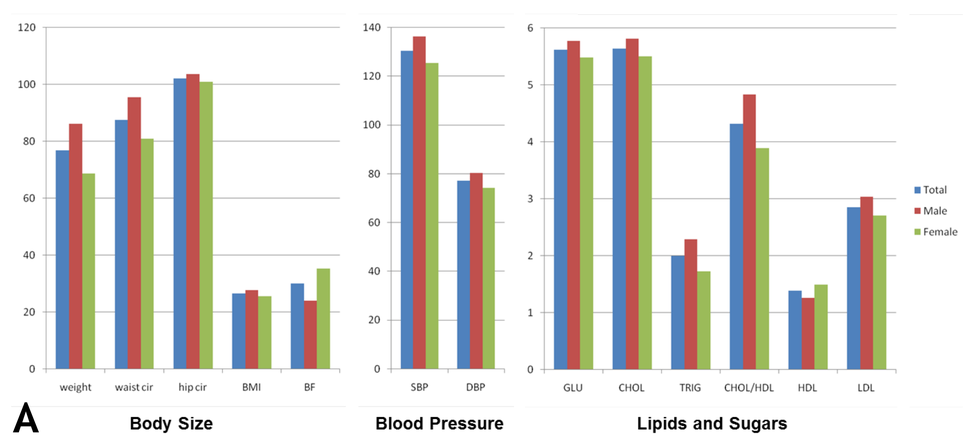


Figure 3: Reconstruction of the NI pedigree

Baseline Traits in the NI population



Trait Heritability in NI pedigree

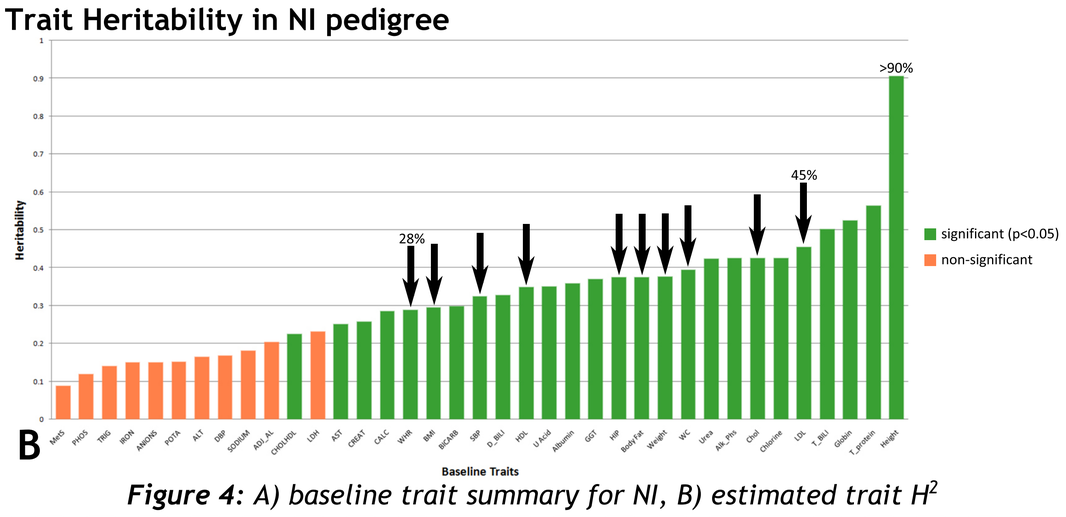


Figure 4: A) baseline trait summary for NI, B) estimated trait H^2

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)

A Phenome Scan for Heritable MetS 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)

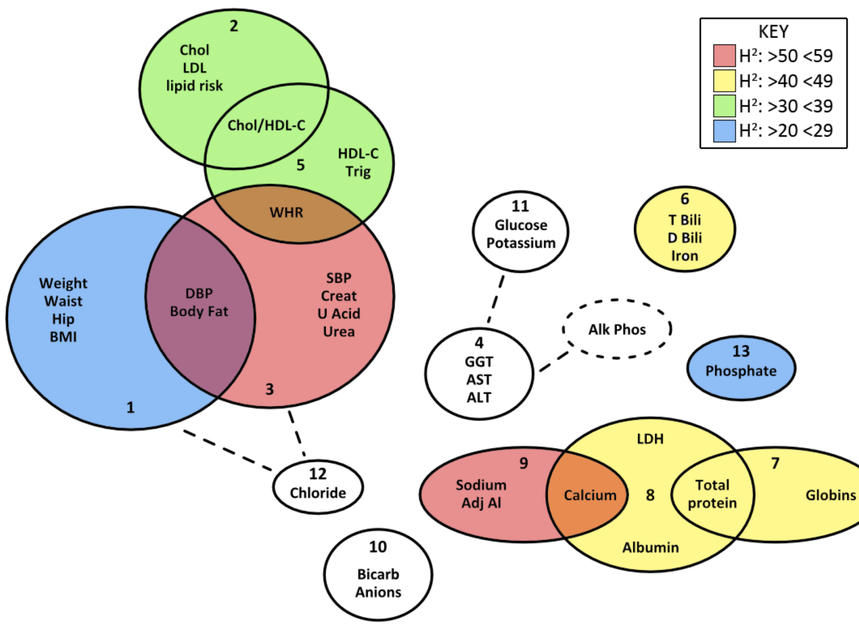


Figure 5: Venn diagram showing PCFA components and H^2 estimates

A Phenome Scan for heritable MetS traits:
- Analysis of all possible MetS related variables (n=37) – see what comes out
- 13 components, explains 75% of total variability - 9 found to be heritable (*Figure 5*)
- Component 3 had highest H^2 (55%)
  - loaded with: Blood Pressure, Waist/Hip, Creatine, Uric Acid and Urea

Findings and Outcomes

MetS Clinical Diagnosis:
- Higher prevalence of MetS in NI (26.4%) than mainland Australia (rr = 1.2)

T2D risk:
- NI shows higher risk of T2D (43%) than mainland Australia (rr = 1.4)

Phenome Scan Analysis:
- Unsupervised PCFA – let data speak for itself (natural clusters within data)
- 13 extracted components, 9 show heritability within the NI cohort
- Most heritable component (H^2 = 55%) - Possible indication towards genetic predisposition to kidney disorder

Where to next?

- Initially all single genomic factor associations of heritable MetS phenotypes will be assessed using statistical methods implemented by SOLAR program

- For multi factor profiling the genomic signature analysis (GSA) method will be employed (Lea *et al.*, 2010)

- Associations may also indicate new molecular pathways for MetS risk