Authors: Jacob Meyjes-Brown, Heidi Sutherland, Kim Ngan Tran, Miles Benton, Rod Lea, Lyn Griffiths

Title: Using founder effect and *in-silico* analysis to discover functional metabolic syndrome genes in the Norfolk Island genetic isolate.

Background: The Norfolk Island Health Study has worked with the Norfolk Island community since 2000, yielding genetic insights into multiple health conditions and illuminating the genomic consequences of the Island's fascinating history. Approximately half of the study participants are descended from the Pitcairn Island founder population of 12 Tahitian women and 7 British men—the *Bounty* mutineers of 1789. The genomic features of isolated populations offer complementary strengths to large-cohort methods like GWAS for mapping genes related to health and disease.

Metabolic Syndrome (MetS) is a set of five highly correlated metabolic risk traits which predisposes people to type 2 diabetes, cardiovascular disease, and chronic kidney disease. It is a serious and increasingly common global health issue, with well understood environmental contributing factors. However, each person's individual susceptibility to these influences is mediated by their genetics. The full syndrome is between 10% and 30% heritable, with the individual component traits having greater than 50% heritability. The Norfolk Islanders have an elevated incidence of MetS compared to mainland Australia, which may be due to their genetics.

Methods: Using whole genome sequence data from a sub-sample of our cohort, we have identified candidate variants that appear to have a higher allele frequency than global references. We then used a suite of five bioinformatic analytic tools to identify variants with predicted functional consequences for targeted genotyping in the full cohort.

We then genotyped and analysed these variants for association with MetS and component traits in the Norfolk founder population. The associations observed In NIHS then formed the basis for investigating these specific variants, and others in the implicated genes, in the UK Biobank and All of Us whole genome sequence data.

Results: Multiple functional founder effect variants were identified in the NIHS with significant associations with MetS component traits. There were notable differences in allele frequency across ancestry groups in the biobank cohorts. Several associations were replicated but not all.

Conclusion: The complementary strengths of isolated founder population analysis combined with biobank-scale cohorts allow us to identify biologically and clinically relevant variants that either approach alone might not be sensitive enough to recognise. The variants and genes identified through this approach will need further analysis and functional studies to determine causal status. Nevertheless, the associations we observe can be incorporated into the body of evidence untangling the genetic basis of MetS and its component traits.