Multi-phenotype GWAS of Chronic Kidney Disease in the Norfolk Island isolate

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Background

- **Chronic kidney disease (CKD)** is defined as the persistent impairment in kidney function.
- The most severe form is end-stage renal disease where kidney transplant or dialysis is vital.
- Around 1.7 million Australians (1 in 10) aged 18 years and over have clinical evidence of chronic kidney disease.
- GWAS have identified more than a thousand of loci in relation to CKD, eGFR or complementary biomarkers, e.g. serum creatinine and blood urea.
- However, **the complete genetic basis of CKD is not yet clear.**

Rationale

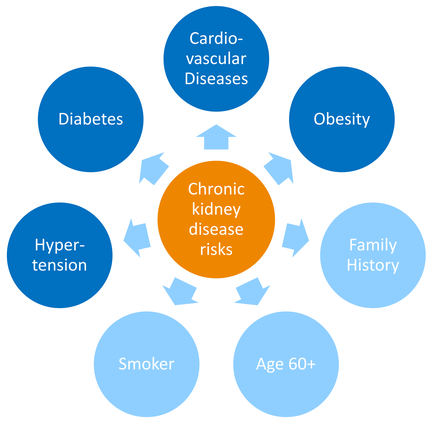

Figure 1. *Chronic kidney disease risk factors*

- Other chronic disorders such as diabetes, high blood pressure, and obesity exhibit co-morbidity with CKD.
- Pleiotropic loci may play a role in the genetic basis of CKD but can go undetected when using single phenotype GWAS

➔ **Multi-phenotype GWAS might identify pleiotropic loci associated with CKD**

Research Cohort

- **Use of genetically isolated cohorts can offer additional advantages for gene mapping**
- **Norfolk Island (NI)** is a small and remote island located in the Pacific Ocean and is about 1,400 kilometers away from mainland Australia.
- NI population exhibits founder effect, admixture and increased homozygosity

Methods

- In total, we included 380 related individuals of NI isolate with 29 continuous phenotypic measurements and 4.7 million genotyped and imputed SNPs.
- We performed factor analysis to extract phenotypic components representative for multiple traits, examined their narrow-sense heritability and finally used significantly heritable components as dependent variables in the downstream linear mixed association models.

Results

Single phenotype analysis

Table 1. *Heritability estimates for CKD-primary traits in the study.*

Trait	Heritability	P-value
Serum creatinine	0.30	$5.76x10^{-3}$
eGFR	0.27	$8.77x10^{-3}$
Serum urea	0.30	$8.62\ x10^{-4}$

- GWAS of these individual traits showed no loci passed the genome-wide significance p-value threshold of $1.84x10^{-7}$.

Principle components of the 3 CKD-primary traits

- CGU-PC1 captured the most information of the underlying kidney function status in the samples.

Table 2. *Statistics of principal components extracted from eGFR, creatinine, and urea (CGU).*

PC	% Variance	Correlation Coefficient*			Heritability	
		eGFR	Creatinine	Urea	h^2	P
CGU-PC1	66	-0.84	0.85	0.73	0.33	$7.75x10^{-4}$
CGU-PC2	21.1	0.32	-0.26	0.68	0.26	$6.66x10^{-3}$
CGU-PC3	12.9	0.43	0.45	-	0.12	$1.35x10^{-1}$

(*) all correlations are statistically significant P<0.05
(-) not available

- GWAS of CGU-PC1 identified a peak mapped to *KCNIP4* gene on chromosome 4 to be significantly associated ($p_{min}=1.67x10^{-7}$)

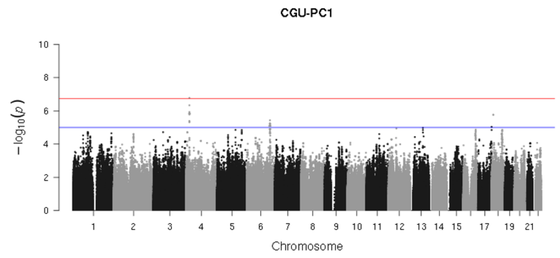

Figure 2. *Manhattan plots for PC1 extracted from the 3 CKD primary traits. CGU – creatinine, eGFR, and urea.*

Combinations of the 3 CKD traits and other measurements

- We expanded the combined analysis to include other CKD secondary phenotypes.
- **The inclusion of the 3 CKD traits with cholesterol HDL-C ratio, HDL-cholesterol, triglyceride, and waist hip ratio again identified the *KCNIP4* locus with greater statistical significance** ($p_{min}=1.59x10^{-9}$).

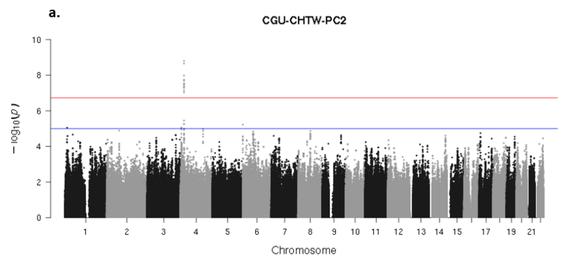

Figure 2. *Manhattan plots for CGU-CHTW-PC2 showing KCNIP4 peak with high statistical power. CGU: creatinine, eGFR, and urea; CHTW: cholesterol HDL-C ratio, HDL-cholesterol, triglyceride, and waist hip ratio.*

KCNIP4 rare variant analysis

- Further examination of rare variants located on *KCNIP4* identified 2 SNPs highly associated with the mentioned component.

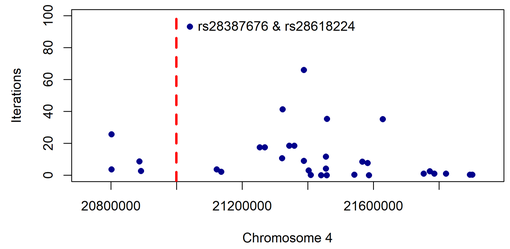

Figure 4. *Association analysis of 38 potentially deleterious rare variants on KCNIP4 against CGU-PC1. The red vertical line indicates the position of the lead variant rs12640604 in above GWASs*

Conclusion

- This study implicated *KCNIP4* as a novel pleiotropic gene underlying CKD.
- Further studies are underway to assess functional relevance of this locus.