WHOLE GENOME ANALYSIS OF ABORIGINAL AUSTRALIANS REVEALS VARIANTS ASSOCIATED WITH KIDNEY DISEASE

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Background

- Indigenous Australians in remote areas are up to 20 times more likely to develop end stage renal disease
- Genetic factors are thought to affect 36-75% of kidney function and chronic kidney disease (CKD) progression
- Population genomic studies have established that the frequencies of specific disease-associated vary substantially between populations
- Identifying these alleles can offer insights useful for preventing, diagnosing, and treating these diseases in a population-specific manner
- The Tiwi people (Northern Territory) have participated in a 25 year longitudinal study of chronic disease incidence, progression, treatments, and outcomes, offering a wealth of biochemical and physical phenotyping data

We conducted a whole genome sequencing (WGS) analysis of 120 individuals from the Tiwi islands and identified several genetic loci associated with traits linked to kidney disease, including serum creatinine, EGFR, and uric acid levels

Pharmacogenomics

- Pharmacogenomics is the study of how genes affect a person’s response to drugs
- The Tiwi genomes have a significant number of known pharmacogenomic variants for drugs used in treatment of chronic ailments

Prevalence of pharmacogenomic variants in Tiwi population

We sequenced the whole genomes at 30x coverage

Study participants were categorized as cases (n=60) or controls (n=60) for kidney disease, based on albumin/creatinine ratio and estimated glomerular filtration rate

We sequenced the whole genomes at 30x coverage and filtered down to 11 novel significant kidney associated variants

All variants were also mapped to known pharmacogenomic variants in related diseases

Remarkably high frequency (3-fold) in alleles associated with Alport syndrome in cases relative to controls

Conclusion

- Population-specific CKD risk alleles exist in the Tiwi people that were not detected by previous lower coverage population genomics studies
- These novel variants offer a potential means of screening individuals in this population to identify those at risk of kidney disease
- The combination of this genomic data with the available 25 years of compiled longitudinal clinical data represents an invaluable resource that can be harnessed to improve health among all Indigenous Australian populations
- Existence of known pharmocogenomic variants and their effect on Tiwi health also need to be explored

References


Acknowledgement

This work has been ongoing, despite many obstacles and interruptions, since 1992. We sincerely thank the Tiwi people and the Tiwi Land Council for expressing their strong desire to understand their genetic makeup and for their participation in, and support for, this project for so many years. We admire their desire to contribute to understanding of genetics on the world stage, and thank them for their patience and understanding through the many delays.

Funding Sources

- 1995–99: NHMRC Australia Project Grant and Senior Research Fellowship.

Figure 1 Chromosomal Phenogram of statistically significant (p-value < 1e-6) genomic imbalances detected in cases associated with chronic kidney disease (CKD). The colored circle represent the genomic deletions (blue) and insertion/duplication (green). In 60 cases, we identified 194 different genetic lesions

Figure 2 Drugs consumed by number of Tiwi patients out of 120 vs. number of known pharmacogenomic variants associated in their genomes. Atorvastatin is consumed by 42 patients, and have 38 known pharmacogenomic variants present in the Tiwi genomes

Figure 3 Atorvastatin pharmacogenomic variant distribution across Tiwi islander genomes with 5 variants occurring only in one genome and 5 in all 120 genomes