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

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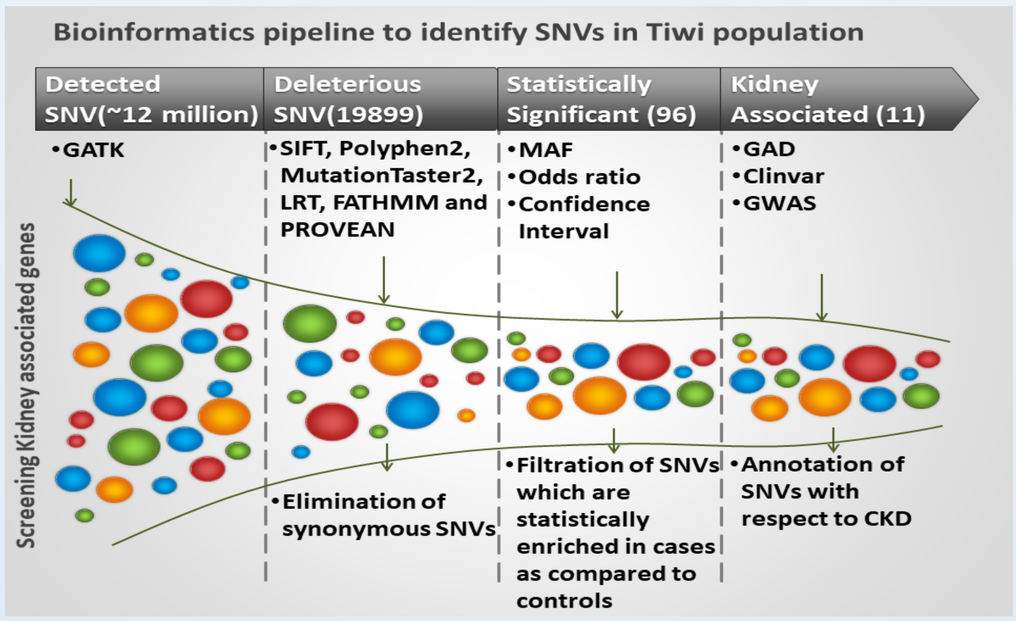
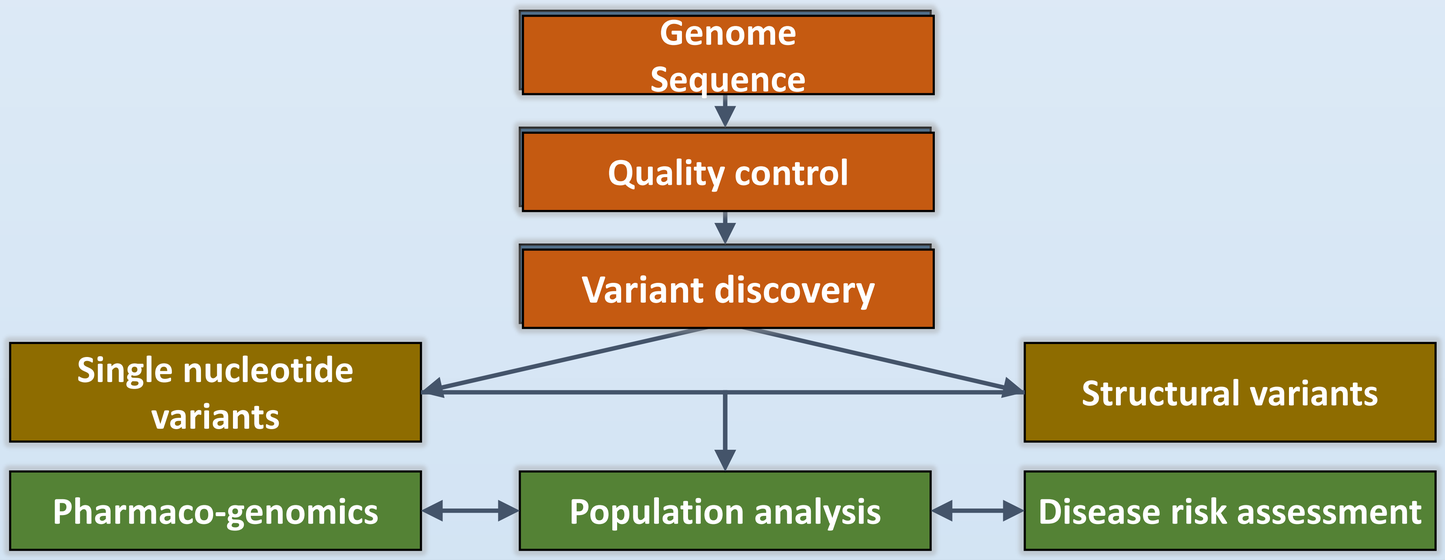
Background

- 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





Prevalence of pharmacogenomic variants in Tiwi population

- 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

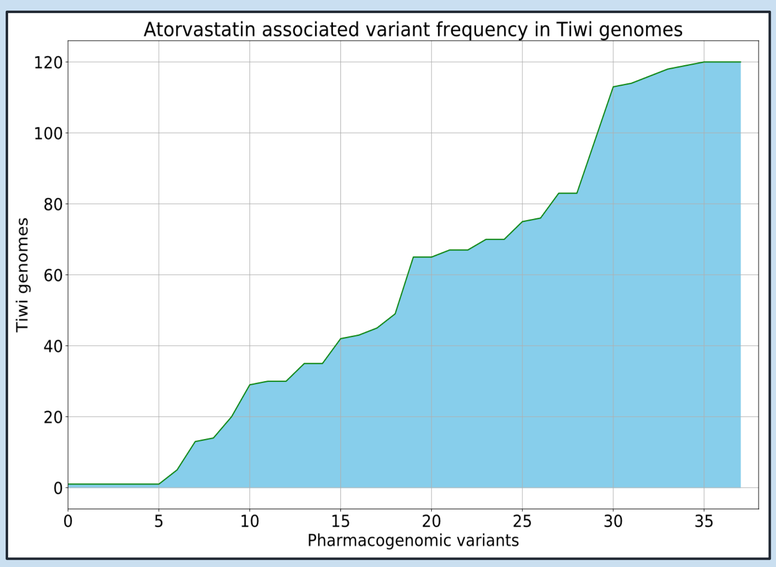


Figure 3 Atorvastatin pharmacogenomic variant distribution across Tiwi islander genomes with 5 variants occurring only in one genome and 3 in all 120 genomes

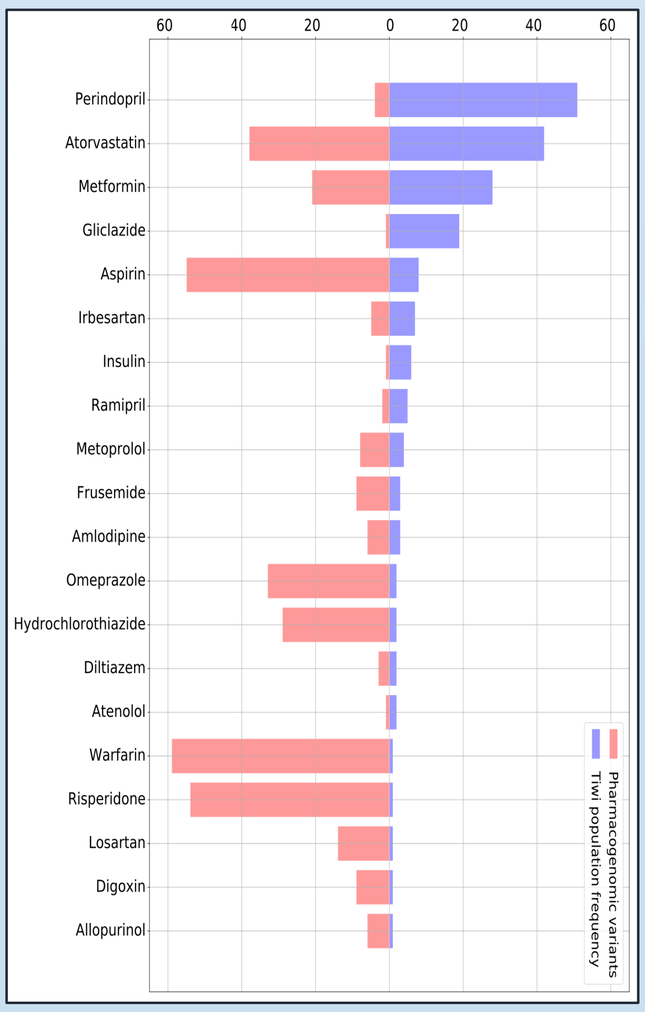


Figure 2 Drugs consumed by number of Tiwi patients out of 120 vs. number of known pharmacogenomic variants associated in their genomes. Atorvastatin is consumed by 42 patients, and have 38 known pharmacogenomic variants present in the Tiwi genomes

- 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

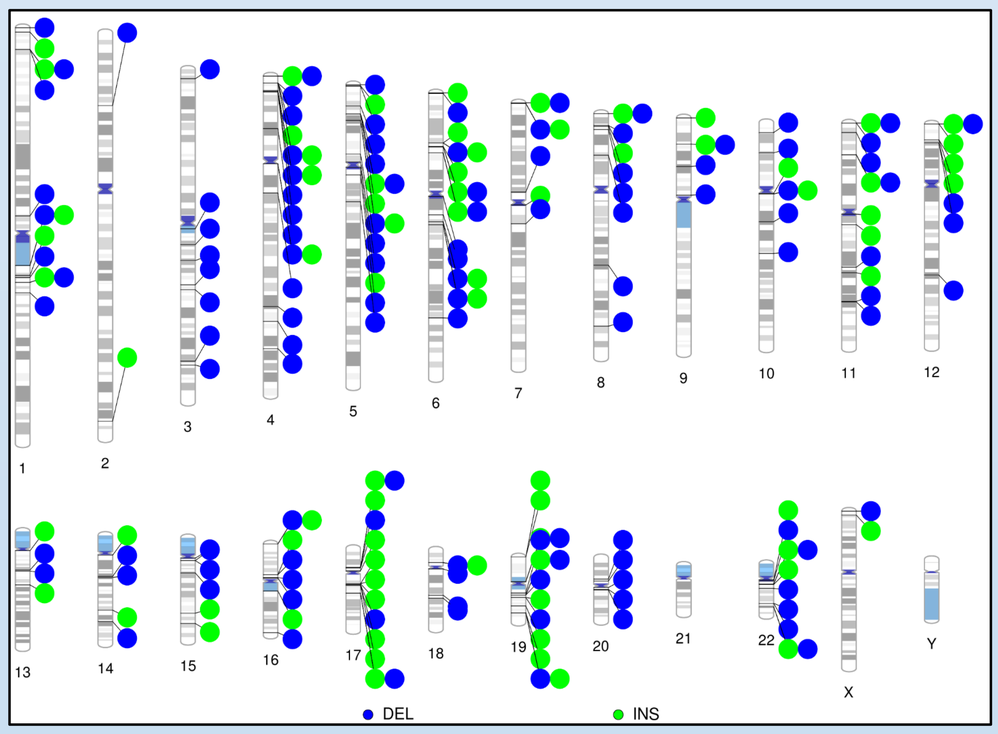


Figure 1 Chromosomal Phenogram of statistically significant (p-value < 1e-6) genomic imbalances detected in cases associated with chronic kidney disease (CKD). The colored circle represent the genomic deletions (blue) and insertion/duplication (green). In 60 cases, we identified 194 different genetic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

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

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