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PROGRESS REPORT

Project / Program Title		Bringing genomics of inherited tubulointerstitial and cystic kidney diseases into clinical practice in Australia
Name		A/Prof Andrew J Mallett
Award Received		2018 RACP Foundation Jacquot Research Establishment Fellowship
Report Date		9 June 2018
Chief Investigator / Supervisor		A/Prof Andrew J Mallett
Administering Institution		The University of Queensland
Funding Period	Start Date:	1 January 2018
	Finish Date:	31 December 2018

PROJECT SUMMARY

Kidney disease affects one in eight Australian adults, with one in ten of those having a genetic or inheritable form. Up to half of all Australian children with diagnosed kidney disease have a genetic or inheritable form. As yet there are no targeted or curative therapies and many patients travel a seemingly unstoppable pathway towards needing dialysis or kidney transplantation. This is associated with significant personal symptom burden, patient and family suffering, premature death and healthcare costs. Urgent change is needed.

One strategy is to improve fundamental understanding of kidney disorders, in this instance inheritable forms. Targeted therapies will rely upon this; “you have little hope of treating what you don’t understand”. New enabling tools are emerging, including advanced genomics, stem cell technologies and registry programs. Here I am applying these to the spectrum of inherited tubulointerstitial and cystic kidney diseases, which are inherited in different ways, affect children and adults, and can include non-kidney features, despite having renal changes at a microscopic level that are in common. Using these differences and commonalities with new tools, there is opportunity to acquire new knowledge of potential shared underpinning disease mechanisms. This understanding is critical for improving clinical outcomes and the lives of Australian patients affected by kidney disease.

PROJECT AIMS / OBJECTIVES

1. Identify, deep-phenotype and enrol into the ARRK registry an Australian cohort of patients with inherited tubulointerstitial and cystic kidney diseases

- The ARRK registry dataset for NPHP and ADTK have now been finalised, its updated ethics completed, the data custodians/housing identified and website finalised for imminent launch. Further, we are joining with international

registry efforts in these specific conditions to generate globally significant datasets for analysis. First patient recruitment is anticipated in Q3-Q4 of 2018.

2. Review and audit diagnostic genomic findings in known genes within this cohort.
   - Audit of the diagnostic genomic findings in this cohort via the current diagnostic services is underway and will transition to the ARRK dataset as enrolment continues.
3. Discover novel genetic causes using whole-genome sequencing in families for whom a variant/s in known genes is not identified
   - >10 families (trios/extended pedigrees) have been recruited with sequencing now underway to identify novel genetic causes. Initial results are planned for Q4 2018.
4. Determine evidence for oligogenic or disease modifier genotypes
   - Significant work has been undertaken in this space. Re-analysis of WGS data has identify unappreciated copy number variants (CNV) which appear to refute oligogenicity as a significant cause for disease. Analysis for disease modifier genotypes is now underway in a small number of families with appropriate family structures (multiple affected siblings in ARecessive disease; 3+ generations in ADominant disease), however this analysis is much more challenging than the former.
5. Collaboratively model and validate genetic changes to validate novel findings and unveil disease pathobiology
   - This project has continued and had a research outcome in 2018 in the form of an AJHG publication (https://www.ncbi.nlm.nih.gov/pubmed/29706353). We continue to identify potential families to proceed to disease modelling with an increased and renewed focus upon potential therapeutic targets.

SIGNIFICANCE AND OUTCOMES

This project has had significant progress thus far and is significant both within nephrology as well as medicine more broadly. The ability to treat a condition is reliant fundamentally upon the ability to (a) identify it, (b) understand its causes and (c) understand the pathological processes hence resulting in human disease. This project is making significant progress in the field of inherited tubulointerstitial and cystic kidney disease from the perspectives of registries, diagnostic genetics research genomics, and disease modelling. Importantly this is building a sustainable national translational infrastructure targeting this spectrum of kidney disorders within the emerging national nephrogenetics initiative. Together, this is highlighting a group of kidney diseases which are not as rare as previously thought and providing opportunities to expedite changes to clinical management for a group of patients experiencing significant excess morbidity and mortality.

Where to from here? 2018 is an important establishment phase for each of these sub-projects with 2019-2020 a core time for them to achieve major outcomes. Thus I am proposing to continue them through that period and additionally add a 6th sub-project to undertake proband-only WGS in a cohort of Australian patients with unexplained kidney disease. Within this, I propose to specifically target a sub-cohort with biopsy proven tubulointerstitial disease in order to identify if a significant proportion of such cases have an identifiable underlying genetic aetiology.

PUBLICATIONS / PRESENTATIONS

MANUSCRIPTS

- Published Jan 2018 to present (June 2018)

1. Antenatally Diagnosed Autosomal Dominant Polycystic Kidney Disease

a. Aldridge M, Patel C, Mallett A, Trnka P. In Press, accepted 7th May 2018, Kidney International Reports.

2. CFHR5 nephropathy in a Greek-Cypriot Australian family: ancestry-informed precision medicine.

a. Ng M, Mcclymont K, McCallum N, Dua R, Holman K, Bennetts B, Ho G, Patel C, Mallett A. In Press, accepted 17th April 2018, Kidney International Reports.

3. Patient iPSC-derived kidney organoids show functional validation of a ciliopathic renal phenotype and reveal underlying pathogenetic mechanisms.

a. Forbes TA, Howden S, Lawlor K, Phipson B, Maksimovic J, Hale L, Wilson S, Quinlan C, Ho G, Holman K, Bennetts B, Crawford J, Trnka P, Oschlack A, Patel C, Mallett A, Simons C, Little M. American Journal of Human Genetics (2018) 102(5):816-831.

4. Meeting Report of the 2017 KidGen Renal Genetics Symposium.

a. Jayasinghe K, Quinlan C, Stark Z, Patel C, Sampson MG, Saleem M, Mallett AJ. Human Genomics, Jan 2018, 12:5

- 2 additional manuscripts under revision (both revisions)

- 8 additional manuscripts under preparation for submission Q3-Q4 2018

ABSTRACTS

- 21 submitted to 2018 ANZSN ASM

- 12 submitted to 2018 ASN Kidney Week

- 4 submitted to 2018 HGSA ASM