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FINAL REPORT

Project / Program Title		Bringing genomics of inherited tubulointerstitial and cystic kidney diseases into clinical practice in Australia
Name		Prof Andrew Mallett
Award Received		2018 RACP Foundation Jacquot Research Establishment Fellowship
Report Date		17 February 2022
Administering Institution		University of Queensland
Funding Period	Start Date:	1/01/2018
	Finish Date:	31/12/2018

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

. 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.

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.

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 completed and reanalysis continuing to identify novel genetic causes.

4. Determine evidence for oligogenic or disease modifier genotypes

- Significant work has been undertaken in this space. Re-analysis of WGS data has identified 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 was an important establishment phase for each of these sub-projects.

- The gene lists curated subsequently established the kidney gene panels in PanelApp Australia and formed the basis for establishing the ClinGen Kidney Clinical Domain Working Group

- The HIDDEN project has subsequently concluded recruitment having met the full target (Dec 2020) with results now being analysed for dissemination in 2022.

PUBLICATIONS / PRESENTATIONS

MANUSCRIPTS:

1. Renal Genetics in Australia: Kidney Medicine in the Genomic Age.

Jayasinghe K, Quinlan C, Stark Z, Patel C, Mallawaarachchi A, Wardrop L, Kerr PG, Trnka P, Mallett AJ; KidGen Collaborative. Nephrology. 2019 Mar;24(3):279-286.

2. Antenatally Diagnosed Autosomal Dominant Polycystic Kidney Disease

Aldridge M, Patel C, Mallett A, Trnka P. Kidney Int Rep. 2018 May 15;3(5):1214-1217

3. CFHR5 nephropathy in a Greek-Cypriot Australian family: ancestry-informed precision medicine. Ng M, Mcclymont K, McCallum N, Dua R, Holman K, Bennetts B, Ho G, Patel C, Mallett A. Kidney Int Rep. 2018 Apr 22;3(5):1222-1228

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

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

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

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

6. Genome-wide association study of medication-use and associated disease in the UK Biobank Wu Y, Byrne EM, Zheng Z, Kemper KE, Yengo L, Mallett AJ, Yang J, Visscher PM, Wray NR. Nat Commun. 2019 Apr 23; 10(1): 1891.

7. Adult-diagnosed non-syndromic nephronophthisis in Australian families causes by biallelic NPHP4 variants

Hudson R, Patel C, Hawley C, O'Shea S, Snelling P, Ho G, Holman K, Bennetts B, Crawford J, Francis L, Simons C, Mallett A. AJKD (accepted 31 August 2019).

8. Precision Medicine Diagnostics for Rare Kidney Disease: Twitter as a tool in Clinical Genomic Translation

Mallett AJ, Quinlan C, Patel C, Fowles L, Crawford J, Gattas M, Baer R, Bennetts B, Ho G, Holman, K, Simons C. Kidney Medicine, 2019 (published online 14 August 2019).

9. Proposed minimum information guideline for kidney disease: research and clinical data reporting - A Cross Sectional Study

Kumuthini J, van Woerden C, Mallett A Zass L, Chaouch M, Thompson M, Johnston K, Mbiyavanga M, Baichoo S, Mungloo-Dilmohamud Z, Patel C, Mulder N. BMJ Open, 2019,

9:e029539.

ABSTRACTS:

- 21 submitted to 2018 ANZSN ASM
- 12 submitted to 2018 ASN Kidney Week
- 4 submitted to 2018 HGSA ASM

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