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PROGRESS REPORT

Project / Program Title		Molecular Pathogenesis of Inherited Kidney Disease
Name		Dr Amali Mallawaarachchi
Award Received		2017 RACP Jacquot Research Entry Scholarship in Nephrology
Report Date		13 July 2017
Chief Investigator / Supervisor		Prof John Shine
Administering Institution		Garvan Institute of Medical Research
Funding Period	Start Date:	31 March 2017
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PROJECT SUMMARY

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a common genetic condition that affects about 1 in 1000 Australians. The disease causes cysts to form in the kidney, that eventually take over the normal kidney tissue and lead to kidney failure. Patients with kidney failure then require dialysis or a kidney transplant to survive. Even though ADPKD is so common, genetic testing for the condition is challenging. This is because the genes that are involved in ADPKD are difficult to sequence by standard laboratory techniques. In the initial part of my project, we have successfully trialed a new genetic sequencing technique, Whole Genome Sequencing (WGS), to diagnose ADPKD. We have demonstrated that WGS is highly effective in diagnosing ADPKD. The test allows all mutation types to be detected at once and allows broader analysis for patients who don't have an immediate diagnosis found. These findings have been translated into a new genetic test for ADPKD that has been established in Australia for the first time.

Our project is now focusing on understanding the reason that cysts develop in the kidney. It is theorised that the cysts are caused when a person has two mistakes in their PKD1 or PKD2 gene in the kidney cell, one that they inherit and one mistake that is acquired in the kidney cell alone (called a somatic mutation). We are performing deep sequencing on kidney tissue of patients with ADPKD to demonstrate this theory. Understanding the cause of cysts developing is a key step in understanding how to treat and cure the disease.

Another arm of our project is to understand the genetic cause in the ten percent of patients that are undiagnosed by standard genetic testing. WGS sequences the entire genome and therefore allows an ideal opportunity to discover new genetic causes for ADPKD. In the long term, improved understanding of the genetics of ADPKD will help in improving our understanding of the underlying cause of ADPKD; this is an important step in curing the disease.

PROJECT AIMS / OBJECTIVES

- To validate WGS as a clinical test for ADPKD - this has been achieved by sequencing a set of blinded samples via collaboration with Mayo Clinic.
- To assess variant pathogenicity in ADPKD - this project is underway through analysis of population datasets.
- To demonstrate the two-hit hypothesis in ADPKD - tissue from affected ADPKD kidneys has been collected and a pilot of a deep sequencing method is underway.
- To investigate novel causes of ADPKD - a cohort of ADPKD patients that are undiagnosed after standard sequencing is being collected.

SIGNIFICANCE AND OUTCOMES

Accessible and reliable genetic testing is valuable for optimal management of patients with ADPKD as this information can be used for clarifying diagnosis, family planning, living donor selection and estimating prognosis. The initial findings of our project have translated into a new genetic test for ADPKD that has been accredited in Australia for the first time. This will improve access to genetic diagnosis for ADPKD families.

Our analysis of population and disease datasets is assisting in better understanding variant pathogenicity and penetrance in ADPKD. This information is crucial for making accurate genetic diagnosis and in understanding disease mechanism. The findings from this project will clarify the pathogenicity of many currently uncertain variants and challenge the current understanding of the penetrance of variants in PKD1 and PKD2. This data is currently being prepared for publication. Another aspect of our project is in investigating the two hit hypothesis of cyst formation. This project is underway and aims to improve the understanding of the underlying pathogenesis of ADPKD. Understanding the mechanism of disease is an essential step on the pathway to treatments and cure.

PUBLICATIONS / PRESENTATIONS

Mallawaarachchi A, et al, 'Whole genome sequencing overcomes pseudogene homology to diagnose Autosomal Dominant Polycystic Kidney Disease', Eur J Hum Genet. 24:1581-1590 (2016).

Mallawaarachchi A et al, 'Extended Analysis of an Australian cohort of Autosomal Dominant Polycystic Kidney Disease patients by WGS', Abstract, Nephrology 21, Suppl. 2:58-149 (2016).

Mallawaarachchi A et al, 'Validating WGS as a Diagnostic Technique in ADPKD', Abstract submitted, American Society of Nephrology 2017.

Presentation at Patient Education Seminar, for the PKD Foundation of Australia - Genetics of Polycystic Kidney Disease.

Invited Presentation for the Mayo Clinic PKD Group - Whole Genome Sequencing in ADPKD.

Invited Presentation at Australian Renal Genetics Symposium – Whole Genome Sequencing in ADPKD.