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RACP Foundation Research Awards

FINAL REPORT

Project / Program Title		Next generation sequencing approaches to identify digenic and multigenic models of disease in genetic endocrinopathies
Name		Dr Sunita De Sousa
Award Received		2019 Servier Staff 'Barry Young' Research Establishment Fellowship
Report Date		May 2021
Chief Investigator / Supervisor		Prof David Torpy
Administering Institution		Royal Adelaide Hospital
Funding Period	Start Date:	1 July 2019
	Finish Date:	31 December 2019

PROJECT SUMMARY

Endocrinology is the study of hormones and glands. Hormones are chemical signals produced by glands. These signals travel in the bloodstream to trigger essential changes in our body. Endocrine tumours are abnormal growths in these glands that disrupt our normal hormonal signals.

Some endocrine conditions run in families. Such conditions are due to genetic (DNA) variations that are passed from parents to children. Routinely available genetic testing can often diagnose the responsible genetic variant, helping to guide management of the individual and to clarify the risk of the condition in relatives. However, in our local practice, we have found almost 50% of patients receive uninformative genetic testing results and over 10% of patients cannot be offered genetic testing as the genes responsible for a given condition are unknown.

With the generous support of the Servier Staff 'Barry Young' Research Establishment Fellowship, my research has looked at novel genetic causes of endocrine conditions using state-of-the-art DNA sequencing and analysis techniques. This will hopefully expand the genetic testing options available to patients in routine clinical practice. Findings from this research include:

- Discovery of abnormal gene processing as a cause of a type of endocrine tumour called 'paraganglioma' that frequently runs in families;
- Identification of a possible role for genes involved in our sleep-wake cycle in a condition known as 'cyclical Cushing's syndrome', where individuals experience fluctuations in their steroid hormone levels resulting in serious complications including diabetes, high blood pressure and brittle bones;
- Discovery of abnormal patterns of chromosomes (packages of DNA) in in another endocrine tumour called 'pituitary adenoma'; and
- Characterisation of a novel change in the molecule that is responsible for transporting steroid hormones around the body, resulting in a type of inherited steroid hormone deficiency.

PROJECT AIMS / OBJECTIVES

Aims:

To use genomic and ancillary molecular testing to determine novel contributions to genetic endocrinopathies, including di/multigenic models and aberrant splicing.

Hypothesis:

That genomic (i.e. whole exome/genome) testing will reveal novel genetic causes of endocrinopathies that would otherwise be missed by the single/staged-gene and panel tests employed in current clinical practice.

SIGNIFICANCE AND OUTCOMES

This research has demonstrated the utility of genomic testing and ancillary molecular testing in patients with unsolved genetic endocrinopathies in terms of achieving aetiological diagnoses and guiding prognostication and management. It has also highlighted putative roles for aberrant splicing in succinate dehydrogenase-related tumorigenesis, clock genes in cyclical Cushing's disease, and copy number variation in pituitary adenomas.

This translational research has developed synergistically with establishment of the SA Endocrine Genetics Clinic which serves as a quarternary referral endocrine genetic service, including the opportunity for clinically relevant second-line testing guided by recent genetic discoveries.

Drawing upon the research undertaken during my fellowship and my work in the SA Endocrine Genetics Clinic, I am now establishing a study looking at a streamlined approach to screening for and diagnosing monogenic diabetes. Using a clinical probability calculator and exome sequencing, this study will evaluate the detection rate of monogenic diabetes in the Australian clinic setting and investigate candidate genes in families with especially high clinical suspicion of monogenic diabetes and negative results on standard testing.

I am also a member of national groups looking at hereditary pancreatitis

(HEPATA: Hereditary Pancreatitis and Autolslet Transplant Trials in Australia), and the role of aberrant splicing across all genetic disorders

(SpliceACORD: The Australasian Consortium for RNA Diagnostics).

ACKNOWLEDGEMENTS

My award was acknowledged in the key paper of this fellowship i.e.: De Sousa SMC, Toubia J, Hardy TSE. Aberrant splicing of SDHC in families with unexplained succinate dehydrogenase-deficient paragangliomas. J Endocrinol Soc 2020; 4(12):bvaa071.
It will also be acknowledged in my upcoming publications on TSHomas and CBG Montevideo, and the ANZ Hyperparathyroidism Guidelines.