Doctors in Training Grant

PRELIMINARY REPORT

Victor Chang Cardiac Research Institute

Dr Annabelle Enriquez

Master of Medicine
(Developmental Biology)

University of New South Wales
Sydney, New South Wales, Australia

In 2015 I enrolled in a Master of Medicine degree through the University of New South Wales, with the aim of studying genetic defects that may affect the development of the spine and the heart.

In clinical genetics, a significant proportion of the patients we see have birth defects affecting one or more body parts, resulting from genetic and/or environmental factors. Congenital malformations occur in 3-6% of human births, and are the leading cause of infant death. Despite the high prevalence and devastating impact of these defects, the underlying genetic causes of most malformations are unknown. This lack of a genetic diagnosis is incredibly frustrating for both families and the healthcare teams responsible for their care. Without a genetic diagnosis, we cannot predict prognosis, identify the best treatment, test other family members nor help plan future pregnancies.

To try to address some of these deficits in knowledge, I chose to begin a Master of Medicine, focusing on identifying the genes responsible for some of these malformations.

Specifically, I wanted to learn how to utilise the latest advances in gene technology, in the hopes of finding answers for the families I see day to day.

Additionally, I wanted to understand how the environment of the developing fetus can influence gene function, and lead to disease. Currently, I am recruiting patients and analysing their genomic data to try and identify the genetic causes of their congenital malformations. My aim is to identify gene mutations that cause congenital vertebral and heart defects using high-throughput DNA sequencing (next generation sequencing), specifically employing whole exome sequencing or whole genome sequencing. My research allows me to offer families a chance to find a diagnosis, when previously there were no further genetic tests we could pursue.

My research is based in the laboratory of Professor Sally Dunwoodie, part of the Developmental and Stem Cell Biology Division at the Victor Chang Cardiac Research Institute. Prof Dunwoodie is one of the most successful developmental biologists in the country, having published paradigm-shifting papers on the development of the embryo. The Dunwoodie laboratory is a world leader in identifying the genetic and environmental causes of congenital vertebral malformations.

This training provides me with the opportunity to use cutting-edge technology to tackle the genetic causes of developmental malformations. We now have the ability to look at the entire sequence of the human genome, an almost impossible challenge just twenty years ago. Our major challenge now is learning how to read and understand this enormous amount of genetic information. We know that not all variations in the genetic code lead to disease. Out of three billion base pairs, finding one specific mutation that causes a congenital malformation is akin to finding a needle in a huge haystack. At the Victor Chang Cardiac Research Institute, I have the opportunity to learn how to analyse and manipulate genetic data with some of the best developmental biologists and bioinformaticians in Australia. The MIGA Grant has enabled me to purchase computing equipment that is powerful enough to interrogate the astronomical amounts of genomic data generated from sequencing our patients' DNA. This will hopefully enable me to identify some of the genes that are essential for the development of the heart and the vertebral column in the embryo.

Given that we have entered the post-genome era, it is important to be able to deal with and interpret the vast swathes of genomic data that can be generated more easily and cheaply than ever. The problem lies not so much in generating the data but making sense of it for clinical benefit.

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The institute was established in memory of the late Dr Victor Chang with the vision of reducing the incidence, severity and impact of heart diseases

I am using bioinformatics to sift through genomic data to identify potential gene candidates. Once a candidate gene has been identified, confirming its involvement in developmental malformations is critical as it allows us to better translate the genetic findings into clinical practice.

By being part of the Dunwoodie laboratory, I am learning how animal models are used to confirm and validate the role of gene mutations in causing malformations. Furthermore, working at the Victor Chang Cardiac Research Institute has allowed me to hear about other groundbreaking research by local and international scientists.

This training will arm me with the skills to make a real difference in a clinical setting and furthermore, the knowledge gained from these studies has the power to reveal the identity of genetic defects that afflict a large number of patients. The aim of a genetics service is to help individuals and their families live and reproduce as normally as possible.

The findings of my research will have an immediate and profound benefit for the families involved. An accurate genetic diagnosis provides a cause for the congenital malformation. Identifying a genetic cause removes the uncertainties and exonerates the parents, particularly the mothers, of the burden of guilt that they may have somehow caused the birth defect.

It makes it possible for us to determine prognosis. Additionally, it allows the family to move on and make informed reproductive choices. A confirmed genetic mutation enables us to give an accurate recurrence risk and may be used for prenatal testing and pregnancy planning. Antenatal genetic diagnosis of an affected baby can then facilitate earlier intervention if necessary. We can also offer testing to relevant family members to see if they are also carrying the genetic change and are at risk of having an affected child. Hence it has benefits for current family members and for future generations.

For my research, I have been identifying and enrolling suitable families from my local hospitals and across Australia. Finding causative genes will allow us to offer diagnostic testing to other families presenting to a genetics service, both locally and globally. As a direct result of previous research on congenital vertebral malformations in the Dunwoodie laboratory, there are now genetic tests available worldwide for these malformations. I expect a similar progression to occur from my research results.

Moreover, finding a genetic cause will allow researchers to search for rationally designed, targeted treatment. My research is working towards the ultimate goal of disease prevention. It will also underpin further efforts to unravel the complex interplay between genetic and environmental factors that causes birth defects, making an important contribution towards shaping guidelines regarding pre-conception and antenatal care both in Australia and abroad, as well as increasing therapeutic options to reduce its incidence and severity.

I'm very grateful to MIGA for supporting my research training, which will allow me to be involved in most of the aspects of the bench to bedside cycle in caring for patients and their families.

Each year MIGA's Doctors in Training Grants Program offers four Grants of $5,000 to assist doctors in training whilst pursing advanced training opportunities in Australia and abroad. Many different training types are eligible - visit our website to find out more and to apply.

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