TFLF Research Grant recipient, PhD Student Sarah Beecroft – 1st Year Report

In line with the Liuzzi Foundation values, this project aims to improve genetic diagnosis for neuromuscular disease patients, and highlight future avenues for treatment development.

Using a combination of new and existing techniques, Sarah is giving genetic answers to patients that are beyond the scope of current best practice. This research will improve the diagnostic process for patients around the world, long into the future. Additionally, improved understanding of neuromuscular disease genetics is essential for developing new treatments in years to come. Key aspects include genetic data analysis, muscle pathology, and validation experiments in the laboratory.

There are 35 families recruited so far, spanning 19 diseases, one paper submitted for publication within 10 months of starting, and two conference presentations.

Patients are recruited through the Victorian Muscle Bank, under Professor Catriona McLean. Sarah is based at the Neurogenetic Diseases Laboratory at the Harry Perkins Institute of Medical Research and UWA (Perth). Her PhD supervisors are Professor Nigel Laing AO, Dr Gina Ravenscroft, Professor Catriona McLean and Dr Mark Davis.

Project Highlights:

Sarah's work on the *DYNC1H1* gene has led to the diagnosis of patients from Australia and Turkey. Previously, *DYNC1H1* was known to cause lower limb weakness, brain malformations and movement disorders. Sarah identified *DYNC1H1* mutations in three Australian and one Turkish family diagnosed with congenital myopathy, which has expanded the known disease spectrum for this gene. This will help future families with this condition, by providing a diagnosis. With the pathology skills from Catriona McLean, we were able to understand how these mutations cause disease. Catriona analysed the muscle changes from the same patient at 3 and 39 years of age, and found that specific motor neurons were being targeted for destruction. This paper has been submitted for peer-review in a leading neuromuscular journal, and the data was presented at the 21st World Muscle Society International Congress, Granada, Spain in 2016.

Structural myopathies are diseases caused by abnormal arrangement of normal muscle structures. Although these diseases are very rare, they are a significant burden on patients. Through the Victorian Muscle Bank, Sarah has access to many of these rare diseases, including tubular aggregate myopathy and cylindrical spiral myopathy. These diseases involve an abnormal build-up of proteins that form tubules or spirals and impair muscle function. The rarity of these cases means genetic research is difficult, and very few patients receive a diagnosis. Collaboration with Bradley Launikonis at UQ has yielded new insights into the mechanism of tubular aggregates, using cutting edge techniques on live (fresh) muscle biopsies from a patient. The patient flew to Brisbane to get the test, and a paper will be produced from this experiment. Sarah also has a candidate gene for cylindrical spiral myopathy, which would be a world first if proven.

The research team is combining new techniques to solve the very difficult patients, including RNA-sequencing of muscle. This is in collaboration with the MacArthur Lab at the Broad institute of Harvard and MIT (Boston). DNA and RNA sequencing together are powerful complementary techniques that have been shown improve diagnostic success, but also answer fundamental questions about difficult-to-interpret genetic variants.