Next Generation Sequencing to identify mutations causing Maturity-Onset Diabetes of the Young (MODY)

Maturity-Onset Diabetes of the Young (MODY) is a form of monogenic diabetes mellitus, characterised by young age of onset (usually before the age of 25 years), negative islet cell antibody testing, autosomal dominant inheritance and pancreatic β-cell dysfunction with impaired insulin secretion but minimal or no defects in insulin action. The exact prevalence of MODY is not known; however it is estimated to be responsible for 2-5% of cases of diabetes mellitus in Australia. There are currently 13 genes known to be associated with MODY.

Genetic testing to confirm a clinical diagnosis of MODY has important implications for both the patient and their family. Confirmation of a MODY mutation results in commencement of appropriate treatment, targeted screening for associated complications, and more certainty with regard to prognosis. For family members it offers an accurate diagnosis in symptomatic individuals and the ability to carry out predictive screening in those who are non-symptomatic.

In the recent past, genetic testing for monogenic diabetes relied on the patient's phenotype to determine which of the MODY genes should be tested (and the order in which they should be tested). This was necessary due to the relatively low throughput and high cost of 'traditional' Sanger sequencing. This meant that MODY testing could be an expensive and time consuming process, often ending without a genetic diagnosis.

The introduction of Next Generation Sequencing (NGS) has seen a major transformation in the way genetic testing is conducted, enabling multiple samples to be tested in parallel for mutations in multiple genes. In 2011, Mater Pathology's Molecular Genetics department designed a Next Generation Sequencing custom panel approach to detect mutations in the 13 genes known to be associated with MODY. This expanded on the 5 core genes that the laboratory had previously tested for using a Sanger sequencing approach.

A pilot translational research project was carried out, partly supported by the RCPA Technical Assistance Grant. In this pilot study, we tested 59 patients referred to the laboratory over a 6 month period. Mutations were detected in 24 patients, in 9 different genes (*ABCC8*, *GCK*, *HNF1A*, *HNF1B*, *HNF4A*, *INS*, *INSR*, *KCNJ11* and *PAX4*). In approximately 46% of positive cases, a mutation would not have been detected using our previous testing approach. This was due to either a mutation in a gene that had not been requested for testing, or a mutation in one of the genes that was not previously tested by our laboratory.

NGS has proven to be a rapid, cost-effective approach for MODY testing. It has significantly increased the diagnostic yield of testing by nearly 50% with limited impact on the cost of testing. The MODY panel is now available as a NATA accredited clinical test through Mater Pathology's Molecular Genetics Department.

The Mater Pathology Molecular Genetics department would like to thank the RCPA Foundation, for helping us to make this test available to Australasian patients.