Functional genomics in disease gene discovery and diagnosis of Mendelian disorders

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The uptake of next generation sequencing in research and diagnostic laboratories around the world has revolutionised the ability to identify novel human Mendelian disease genes and diagnose patients. The NATA-accredited PathWest Diagnostic Genomics Facility, the premier facility for molecular diagnosis of neurogenetic diseases in Australasia now has the capacity to sequence ~500 disease genes in up to 40 patients per week. However, our ability to accurately call variants as disease-causing or benign has not kept pace and many rare variants are classified as “variants of unknown significance” which is confusing for patients and clinicians alike and not clinically useful. There is thus a need for relatively high-throughput, low-cost functional genomics to assay VUS, such that these can be reclassified as benign or pathogenic. This is one aim of Australian Genomics.

Our research group has been involved in the identification of novel human disease genes since 1988 and as such has become a node of a worldwide network for gene discovery in Mendelian disorders. Since 2013, the Laing Group has led or contributed to the identification of seven novel published neuromuscular disease genes, with a further six unpublished. Each of these discoveries has required the interaction nationally and internationally with clinical teams, bioinformaticians, fundamental biologists and groups working on model organisms.

In addition to novel gene discoveries, the phenotypic expansion associated with mutations in known neurogenetic disease genes has been equally important, including the identification of recessive SCN4A, TOR1A and TTN disease.

Each new gene discovery or phenotypic expansion is of immediate clinical utility for the affected families and patients that are subsequently screened for these genes.

The same next generation sequencing technologies that have revolutionised disease gene discovery and molecular diagnosis, also provide tools that could be used to screen couples for hundreds of recessive diseases in preconception carrier screening programs.