GENOMICS OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE IN THE MALTESE POPULATION

Maria Cini Masini

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common hereditary kidney disease, characterized by enlarged kidneys, bilateral formation and progressive expansion of renal cysts, leading to end stage renal disease (ESRD) where the patient requires kidney transplantation or regular dialysis.

ADPKD results from the dysregulation of two main genes: *PKD1* and *PKD2*, which encode the proteins, polycystin 1 and 2, respectively. These polycystins are associated with ciliary function; thus, defective polycystins result in abnormal formation or function of cilia. When cilia malfunction, the levels of the antidiuretic hormone vasopressin increase, resulting in increased water reabsorption by the kidneys. Eventually this results in cyst formation. The novel treatment, recently approved worldwide – Tolvaptan, blocks the action of vasopressin in the collecting ducts of the kidney, leading to a reduction of cyst proliferation and improved fluid secretion. Even though Tolvaptan is a major step forward, it only slows down disease progression but will not prevent eventually reaching ESRD.

The presence of non-functional genes which are very similar to *PKD1* and the very large size of the *PKD1* gene, represent a diagnostic challenge for ADPKD, as conventional diagnostic methods are not effective. The novel High Throughput Sequencing (HTS) technique overcomes these issues, while allowing the simultaneous testing of other genes.

In this research project we applied HTS to identify the genetic changes causing ADPKD in the Maltese. Definite pathogenic mutations were identified in 14 pedigrees (87.5%) whilst no causative variants were identified in 2 pedigrees (12.5%). Twelve pedigrees had *PKD1* variants (75%) and the remaining two pedigrees (12.5%), harboured the same splice variant in *PKD2*. Of the identified DNA variants, 6 are novel and have never been reported before.

This study demonstrates that laborious long-range PCRs (the traditional diagnostic methods) can be avoided, since HTS with stringent mapping parameters is an effective method for detecting variants in *PKD1*. This strategy significantly reduces the cost and time for simultaneous *PKD1* and *PKD2* sequence analysis, facilitating routine genetic diagnostics of ADPKD. This master's degree was supported by the Tertiary Education Scholarship Scheme (TESS) managed by the Ministry of Education and Employment.