PERSPECTIVE

The changing role of diagnostic genomics in kidney transplantation

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ABSTRACT

Chronic Kidney Disease (CKD), which affects both juvenile and adult patient populations, is largely caused by monogenic forms of heritable kidney disease, with up to 11% of patients under the age of 40 developing end-stage Kidney Failure (KF) and needing a kidney transplant. The subject of diagnostic genomics in nephrology is constantly developing, and it now plays a crucial part in the evaluation and management of kidney transplant recipients and the linked donor pairs. Genomic testing can aid in the diagnosis of KF in kidney transplant patients and help predict the prognosis for graft survival and the likelihood of primary kidney disease recurrence. At-risk relatives who are donors can be tested for a gene mutation that has been found in the recipient and rejected if it is present.

INTRODUCTION

With 5% of KF patients in Australia having an unidentified primary kidney diagnosis, end-stage KF or KF with an unknown etiology continues to make up a sizable minority of patients undergoing kidney transplant assessment. However, it is frequently avoided in patients with advanced CKD due to increased complication rates or risk of disease misclassification when performed at such a late stage. Kidney biopsy has historically been the gold standard for diagnosing many kidney diseases. As a result, many renal diagnoses given are erroneous or assumed. In the context of kidney transplantation, understanding the underlying cause of KF is crucial. It can help identify and rule out at-risk related donors in the context of heritable disease and offer some insight into transplant survival and recurrence rates of primary kidney disease. About 70% of pediatric and 10% of adult cases of Chronic Kidney Disease (CKD) are caused by recognized monogenic forms of kidney disease. The availability of diagnostic genomic testing has increased dramatically during the past ten years, along with the number of genes linked to Genetic Kidney Disease (GKD). Diagnostic yield from genetic testing varies from 10% to 73% depending on the presumed monogenic kidney illness. Similar to kidney transplantation, clinical practice in the field of kidney genetics can be challenging to manage without a multidisciplinary team. The right test selection, pre-test counseling, interpretation and delivery of results, and counseling and management of worried family members are among the practical problems. Multidisciplinary renal genetics clinics, which are increasingly common in Australia, the UK, Canada, and the United States of America, are crucial for streamlining a number of these procedures and managing these difficult patients by combining the skills of nephrologists, clinical geneticists, and genetic counselors. Numerous clinical reasons should motivate the idea of genetic testing to identify the underlying genetic causes of primary renal disease. Strong family history, early illness onset, syndromic presentation, or extrarenal symptoms of a known genetic renal disease are a few examples of these. When testing is made available and a positive outcome is obtained, it is possible to diagnose the patient's kidney disease, which aids in planning for kidney transplantation, cascade testing in their relatives (including live related donors), and planning for the proband and their relative's future children. Pharmacogenetics may also play a part in transplantation-related mainstream practice in the future. When the cause of the possible kidney transplant recipient's kidney illness is unknown, genetic testing should be taken into account. The recipient should be phenotyped in this instance, and the genetic test should use either

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Exome Sequencing (ES) or Genome Sequencing (GS). These testing platforms should be used to analyze a panel of illness-specific genes or all genes related to monogenic kidney disease, as detailed in PanelApp Australia. The management of a patient post-transplant requires an understanding of the underlying cause of KF because the primary kidney disease may impair graft survival by increasing the likelihood of recurrence or rejection. For instance, genetic testing for the Steroid-Resistant Nephrotic Syndrome (SRNS) aids in prognosticating around risk of relapse after transplant and provides useful information regarding other manifestations like malignancy, already a significant post-transplant issue, which may be exacerbated in the case of potential WT1 mutations. A heritable kidney disease diagnosis may also help potential live related donors because they are more likely to have the same symptoms. When there is a clear family history of kidney illness but no known pathogenic mutation, the possible receiver is evaluated initially on the basis of phenotype, and if the test is successful, further testing can be done on the affected family members. Despite largely positive outcomes, kidney donors are more likely to develop CKD, KF, and hypertension. If the donor and recipient are genetically related, this risk may be substantially enhanced. In this case, it is important to determine the root cause of the recipient's main kidney disease. According to Kidney Disease: Improving Global Outcomes recommendations, related recipient and donor pairs should undergo genetic testing for recipient kidney diseases with a high rate of identifying pathogenic variants, such as atypical hemolytic uremic syndrome, Alport syndrome, and focal segmental glomerular sclerosis. Alpha-galactosidase A levels in these at-risk people could not completely rule out a diagnosis of Fabry disease, so it would be crucial to test prospective related female donors in the case of a condition like Fabry disease. There have been instances where females have donated a kidney to a relative only to later learn that they also have Fabry disease. The American College of Medical Genetics list of secondary findings, which calls for reporting if a pathogenic mutation is unintentionally discovered, includes Fabry disease as one of the six identified renal phenotypes. One such complementary field of medicine is kidney transplantation, which has significant promise for enhancing safe living-related kidney transplantation access as well as enhancing multidisciplinary care for impacted families. The ever-evolving field of kidney genetics presents some difficulties, such as an incomplete understanding of how specific gene variants are related to disease (as is the case with the APOL1 gene variants), unequal access to a service for kidney genetics in some regions of the world, and the cost of tests to the patient when funding is not covered. Additionally, genetic testing can prolong the time to transplant owing to the testing process, but it may provide insight on the main kidney disease in recipients and help identify prospective donors.