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Clinical Application of Genetic Testing in Nephrology

Dear Editor,

Chronic kidney disease (CKD) is an increasingly prevalent global health problem. It can be identified by well-established clinical biomarkers, such as serum creatinine, cystatin C, estimated glomerular filtration rate, proteinuria estimation, etc. The etiological diagnosis is often obscure without a biopsy and is relevant for prognosis and transplantation planning. Presently, ~625 genes have been identified for CKD development. Genetic evaluation is an essential component of precision medicine and can reduce the clinical uncertainty of CKD.[1] This retrospective study was conducted to identify the prevalence of genetic abnormalities in renal diseases at the VPS Lakeshore Hospital, Kochi [Supplementary Material]. Data were collected from the hospital database. Eighty participants were included, of whom 60 had CKD, 18 were renal transplant recipients, and 2 had childhood nephrotic syndrome. Whole exome sequencing (WES) showed gene mutations in 18.8% (n=15). This is comparable with published literature, which reports gene mutations in 19% of all screened patients.[2] The prevalance of identified gene mutations, cause of renal function impairement, and indications for genetic testing has been given in Supplementary Tables 1-3. Next-generation sequencing (NGS) can detect 39 genes, including those involved in steroid-resistant nephrotic syndrome (SRNS), collagen type IV mutations, Alport's syndrome, thin basement membrane nephropathy, and collagen gene mutations.[3] Genetic studies are warranted in patients with a family history of CKD, extra-renal manifestations, young age of onset, unusual disease course, unclear etiology, and for guiding therapeutic decisions.[2] WES, with the ability to identify 13 genetic disorders, found 24% of patients with one or more abnormalities.[4] WES can identify mutations in diseases like nephronophthisis, medullary cystic kidney disease and tubulointerstitial fibrosis.[5] Another NGS modality used to detect rare genetic disorders is whole genome sequencing (WGS).[6] Chronic glomerulonephritis (CGN) is the reported leading cause of CKD in developing countries, followed by diabetes mellitus and systemic hypertension.[S1] Among participants with CGN, 33.3% (n=6) had clinically and therapeutically significant mutations and four (22.2%) with CKD had Alport's syndrome. Alport's syndrome has been recognized as one of the most common causes of CKD. It is responsible for end stage renal disease (ESRD) in 0.2-3% patients, varying significantly by age, ethnicity, and the presence of co-morbidities all of which are etiological factors for CKD too.[S2-S6] *COL4A4* & 5 (Alport's gene) are X chromosomal genes that form collagen chains of the glomerular basement membrane.[S7] Mutations of this

gene are detected in 18-89% of people with renal failure, depending on the number of symptoms present under the classical Alport diagnostic criteria.[S8] Two participants (3.3%) had atypical hemolytic uremic syndrome, a rare etiological factor affecting ~2% and 8% of participants with CKD and acute kidney injury (AKI), respectively.[S9] Complement factor H-related protein (*CFHR*) genes are of five subtypes. Deletions, duplication of *CFHR* 1 & 5 genes, and generation of hybrid genes like hybrid *CFHR* 3/1 & hybrid *CFHR* 2/5, are associated with CRF.[S10]

CFHR mutations leading to atypical hemolytic uremic syndrome (HUS) were observed in 6.7% (n=1) of participants. One also had CFH mutations.

Nephrocystin 1 (*NPHP1*) gene deletions, the most prevalent (15%) genetic cause for end-stage renal disease, are associated with nephronophthisis.[S11] One participant had *NPHP1* mutations. This relatively small number could be attributed to regional variations in the prevalence of these mutations.

Three participants with focal segmental glomerulosclerosis (FSGS) (37.5%) had mutations of the *INF2* gene, two (25%) had unexpected yet clinically significant mutations, and three (37.5%) had variants of uncertain significance (VUS). Many genes, including *NPHS 1 & 2, CD2AP, TRPC6, ACTN4, ANLN, ARHGAP24, ARHGDIA, WT1, LMX1B, LAMB2, PAX2, COQ 2 & 6, PDSS2, ADCK4,* and *COL4A4* have been implicated in FSGS.[S12]

Five participants (8.3%) <25 years had CKD. This was quite alarming as the quality of life is considerably lower than their peers for young patients with CKD.[S13] By identifying genetic abnormalities in younger patients, we can avoid long term immunosuppression, thereby reducing the possibility of serious infections and mortality. It is unlikely for genetic FSGS to recur after renal transplantation. Rare cases of recurrence are reported in patients with NPHS1 mutation due to anti-nephrin antibody development.[S14]

Renal transplant patients who developed post-transplant thrombotic microangiopathy (TMA) were tested for gene mutations. TMA has an incidence of 5.6 cases per 1000 patients undergoing renal transplant per year and mortality rate of 50%.[S15] Fourteen participants who underwent renal transplantation developed TMA, of whom two had mutations in *ADAMTS13*. Four participants were planning for second transplantaion who had features of chronic TMA on intial biopsies had tested negative.

Variants of uncertain significance were found in 18 participants. Computational prediction algorithms were utilized to predict the potential impact of the genetic variants on the mature protein. Based on these, most variants were reported as VUS.[S7] The presence of such variants is particularly vexing for clinical management.[S16] Therefore, laboratories specializing in functional analysis of genetic variants need to be contacted for assistance in defining the significance of the variant.[S17]

Genetic testing is helpful in guiding post-transplant treatment strategies, especially in cases with TMA. We had successfully transplanted two cases of atypical HUS by adapting Netherlands protocol.[S18] Genetic analysis helps nephrologists in proceeding with transplants. It should be considered in young patients with otherwise unexplained renal failure, FSGS, suspected TMA, and SRNS. It also helps stratify the treatment strategies and predicts the recurrence of the disease after transplantation.

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