



Genetic vs non-genetic kidney disease: prognosis insights from a multi-cohort study

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Monogenic kidney disorders (MKDs) have a wide clinical spectrum and are among the leading causes of kidney failure (KF). In recent years, MKDs have become increasingly important because next-generation sequencing studies, including large multinational cohorts, have revealed that nearly 10% of patients with KF have MKDs [1, 2]. In addition to autosomal dominant polycystic kidney disease (especially PKD1, PKD2 and IFT140 variants), Alport syndrome/Alport kidney disease (COL4A3-4-5 variants) and autosomal dominant tubulointerstitial diseases, mostly due to UMOD and MUC1 variants, account for a significant proportion of the KF etiology. Also, APOL1 high-risk variants (G1 and G2) are closely associated with KF development in the African-American population [2]. A family history of kidney disease is a strong predictor of monogenic kidney disorders. Therefore, a proper assessment of family history is crucial in nephrology practice. In addition to patients with a family history of kidney disease or consanguinity, genetic screening should be particularly considered in cases of early onset, cystic or congenital kidney diseases, unknown etiology of kidney disease, unexplained multisystemic findings, immunosuppressive treatment responsiveness and risk stratification in kidney transplantation (e.g. living relative donor screening or post-transplant recurrence of atypical hemolytic uremic syndrome). Genetic screening is also valuable for prognostic guidance in conditions such as Alport syndrome or autosomal dominant polycystic kidney disease [3].

However, there is a lack of knowledge regarding the differences in kidney disease progression between the underlying genetic and non-genetic conditions in patients with KF. The UK National Registry of Rare Kidney Diseases (RaDaR) cohort study

[4], which included 27 285 patients with rare kidney disorders, predominantly glomerular or genetic diseases, showed that the 5-year risk of KF was higher in RaDaR participants compared with 2.81 million UK patients with all-cause chronic kidney disease (CKD) (28% vs 1%, $P < .0001$). However, the study group showed better survival rates than other patients with stage 3–5 CKD, with a standardized mortality rate of 0.42 (95% confidence interval 0.32–0.52; $P < .0001$).

Accordingly, in a recent publication by Elliott et al. [5], the authors aimed to investigate the prognostic differences between genetic and non-genetic kidney diseases in three different cohorts (1913 patients in prospective CureGN, 1098 patients in retrospective Columbia-GN and 2716 patients in retrospective Columbia-CKD cohorts) that included 5727 patients who underwent genome or exome sequencing. CureGN [baseline median estimated glomerular filtration rate (eGFR) and urine protein-creatinine ratio (UPCR) were 83.33 mL/min and 3.39 g/g, respectively] and Columbia-GN (baseline median eGFR and UPCR were 48.16 mL/min and not available, respectively) cohorts consisted of patients with immunoglobulin A nephropathy (IgAN), minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) and membranous nephropathy (MN). Columbia-CKD (baseline median eGFR and UPCR were 27.24 mL/min and not available, respectively) cohort included patients with different etiologies of kidney diseases other than IgAN, MCD, FSGS and MN.

As a result, 12% of 5727 patients had genetic kidney diseases (6.5% had MKDs, and 5.5% had high-risk APOL1 variants) (Fig. 1). In total, 371 patients were diagnosed with MKDs in the cohorts [53/1913 (2.8%), 39/1098 (3.6%) and 279/2716 (10.3%)

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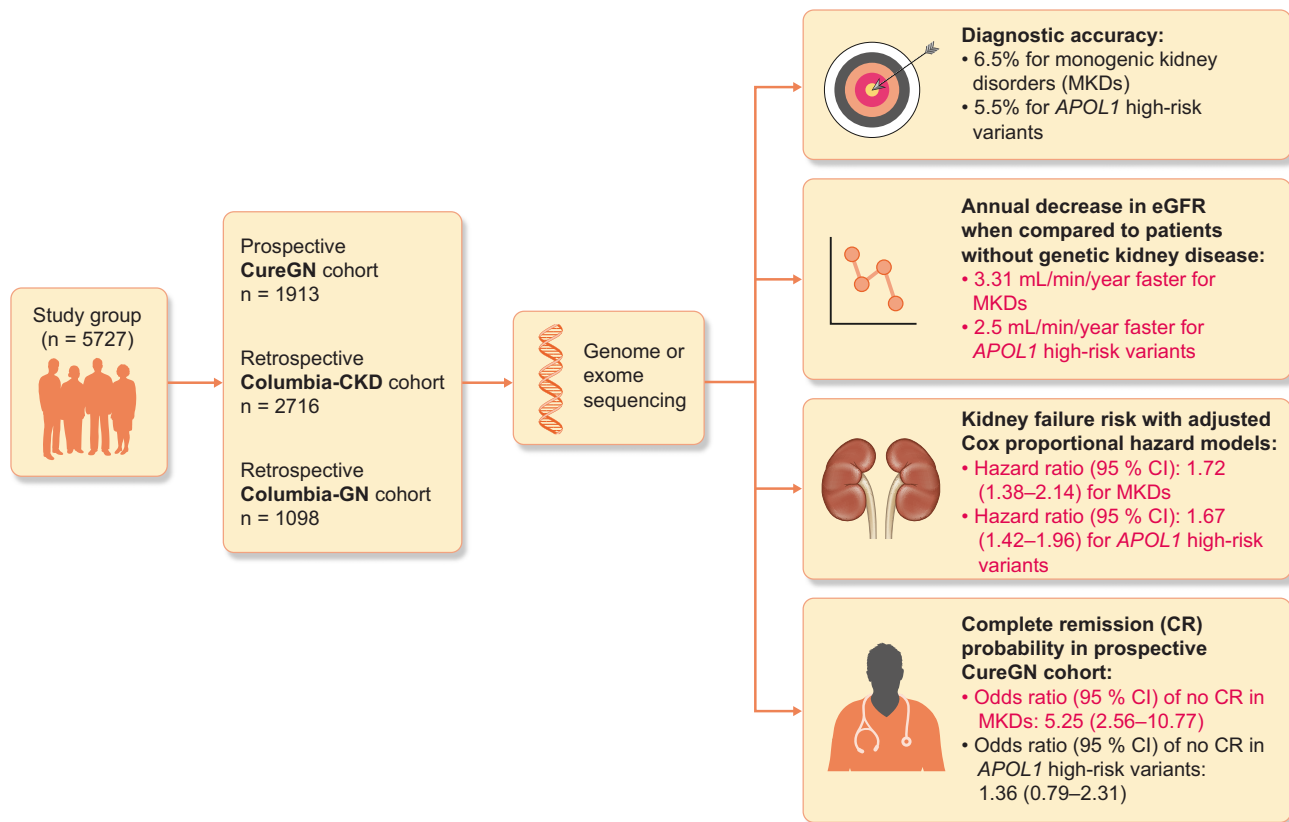


Figure 1: Schematic representation of the patient group and study outcomes.

in the CureGN, Columbia-GN and Columbia-CKD cohorts, respectively]. A total of 318 patients had high-risk *APOL1* variants [122/1913 (6.4%), 66/1098 (6%) and 130/2716 (4.8%) in the CureGN, Columbia-GN and Columbia-CKD cohorts, respectively].

The risk of KF was evaluated using Cox proportional hazards models in the study groups.

- Two models were used for the Columbia-CKD group:
 - Unadjusted (disease start time at birth)
 - Adjusted (additional *APOL1* genotype, sex, hypertension, diabetes, renin-angiotensin-aldosterone system (RAAS) inhibitor or immunosuppression treatments at enrollment and genetic ancestry cluster)
- Three models were used for the Columbia-GN group:
 - Unadjusted (start time of kidney biopsy or clinical diagnosis)
 - Minimally adjusted (additional sex, pathologic diagnosis, age at diagnosis and *APOL1* genotype)
 - Matching adjusted model (additional diabetes, hypertension, use of immunosuppressive treatments at the time of renal biopsy, RAAS inhibitor usage at enrollment and genetic ancestry cluster)
- Four models were evaluated for the CureGN group:
 - Unadjusted (start time of kidney biopsy)
 - Minimally adjusted (additional sex, age at biopsy and *APOL1* genotype)
 - Matching adjusted (additional diabetes, hypertension, use of immunosuppressive treatments at the time of renal biopsy, RAAS inhibitor usage at enrollment and genetic ancestry cluster)

- Fully adjusted (additional eGFR and UPCR at the time of biopsy)

Hazard ratios (95% confidence intervals) for maximally adjusted models from all study groups were 1.72 (1.38–2.14) and 1.67 (1.42–1.96) for monogenic kidney disorders and high-risk *APOL1* variants, respectively.

Concurrently, MKDs and high-risk *APOL1* variants had 3.31 mL/min/year and 2.5 mL/min/year faster decreases in eGFR, respectively when compared with non-genetic disorders. Also, the possibility of complete remission (UPCR <0.3 g/g or 24-h proteinuria <0.3 g/day) of glomerular diseases was statistically lower in patients with MKD [odds ratio (95% confidence interval) for no remission 5.25 (2.56–10.77)], but not in patients with high-risk *APOL1* variants [odds ratio for no remission 1.36 (0.79–2.31)] within the prospective CureGN group, according to the covariates as fully adjusted Cox proportional hazard model.

The publication by Elliott *et al.* is one of the largest multicohort study to compare kidney outcomes between patients with and without MKDs or high-risk *APOL1* variants in the literature. Besides the high diagnostic accuracy of genetic kidney diseases via genomic/exomic sequencing, genetic screening also provided good prognostic information for kidney disease progression in this study. It should be taken into account that the lack of evaluation of intronic, intergenic and copy number variants, in addition to difficult regions for sequencing, such as the tandem repeat domain of *MUC1*, might have underestimated the diagnostic yield in some patients.

This study suggests that diagnosing genetic kidney diseases is crucial for medical care and predicting kidney survival, particularly within the framework of precision medicine. A

worse prognosis in genetic kidney disorders, compared with non-genetic causes, may be associated with severe structural dysfunction due to defective protein synthesis, resulting from the disrupted expression of relevant genes. Additionally, the resistance to immunosuppressive treatments and the need to avoid such drugs in genetic glomerular disorders should be considered during follow-up, as these treatments often come with severe side effects, lack of benefit and high costs.

Moreover, genetic testing and diagnosis can enable targeted therapies for a limited subset of genetic diseases and facilitate the recognition and screening of extrarenal manifestations of genetic disorders. This approach also supports the screening of family members and offers opportunities for genetic counseling.

According to the results of this study, genetic screening should be implemented in nephrology practice not only for diagnostic purposes but also as a prognostic tool.

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CONFLICT OF INTEREST STATEMENT

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