ChiKD CHILDHOOD KIDNEY DISEASES

Editorial

Child Kidney Dis 2024;28(3):87-89
pISSN 2384-0242 · eISSN 2384-0250
https://doi.org/10.3339/ckd.24.019

CUBN mutation, a genetic cause of persistent proteinuria in children

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See "*CUBN* mutation: a benign genetic cause of proteinuria?" by Lee. on page 19, Vol. 27, No. 1, 2023

The *CUBN* gene encodes cubilin, an albumin-binding protein essential for renal tubular albumin reabsorption [1]. Albumin is filtered to a limited extent through the glomerular filtration barrier, and most of the filtered albumin is reabsorbed in the proximal tubules via megalin-cubilin receptor complexes. Therefore, a mutation in the *CUBN* gene can impair albumin reabsorption, leading to persistent proteinuria without affecting glomerular filtration function [2].

Persistent proteinuria is an important sign possibly indicating glomerular diseases. Hence, clinicians should consider a renal biopsy for a definitive diagnosis in patients with persistent proteinuria, even in the absence of hematuria, hypertension, or decreased renal function. Furthermore, it is a prognostic factor associated with adverse outcomes, such as chronic kidney disease, cardiovascular disease, and mortality. The Kidney Disease: Improving Global Outcomes guidelines recommend aggressive treatment to maintain the urine protein-to-creatinine ratio within the normal range in children with proteinuria, regardless of the underlying cause [3].

Although renal biopsy is the gold standard for diagnosing glomerular diseases, it is an invasive procedure, particularly in children, and even more so in young children who require general anesthesia. With increasing identification of the genetic causes of various kidney diseases, genetic testing is now widely used as a diagnostic tool for identifying the underlying causes of proteinuria, replacing kidney biopsy as the definitive method. Notable examples include steroid-resistant nephrotic syndrome (SRNS), polycystic kidney disease and Alport syndrome [4].

In a recent issue of *Childhood Kidney Diseases*, Lee [5] introduced a genetic kidney disease that causes persistent proteinuria, specifically the *CUBN* mutation. This review discusses the findings of large-scale cohort studies on the genetic diagnosis of patients with proteinuria with *CUBN* mutations. It highlights the clinical features of patients with *CUBN* mutations and outlines the indications for genetic testing to diagnose this condition.

In the study by Bedin et al. [6], when next-generation sequencing was performed for renal disease genes in 107 patients with chronic asymptomatic proteinuria in the chronic proteinuria cohort and in 2,109 patients in the genetic kidney disease cohorts I and II with suspected hereditary kidney diseases such as SRNS, Alport syndrome, nephronophthisis, polycystic kidney disease, congenital anomalies of the kidney and urinary tract, and tubular diseases, *CUBN* mutations were identified in 39 of the total 2,216 patients. The diagnostic rate of *CUBN* mutations was significantly higher in the chronic proteinuria cohort than in the two genetic kidney disease cohorts I and II (11.2% vs. 1.3%).

Received: October 1, 2024; Revised: October 14, 2024; Accepted: October 15, 2024

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Regarding the renal function outcomes of the 39 patients with *CUBN* mutations, none progressed to end-stage kidney disease. The median ages at the first presentation and at the last follow-up for patients in the chronic proteinuria cohort (n=12), genetic kidney disease cohort I (n=14), and genetic kidney disease cohort II (n=13) were 7.8/26 years, 10.8/19.8 years, and 6.3/10.4 years, respectively, and their last estimated glomerular filtration rate (eGFR) was 105.6, 114.2, and 128.1 mL/min/1.73 m^2, respectively, all of which indicated normal kidney function.

In another multicenter cohort study by Domingo-Gallego et al. [7], 347 families with proteinuria of a suspected monogenic cause underwent next-generation sequencing, and *CUBN* mutations were detected in 15 patients from 12 unrelated families. The median age at diagnosis was 4 years, with a follow-up duration of 7 years. Of these 15 patients, 13 presented with chronic isolated non-nephrotic range proteinuria and normal serum albumin levels. Additionally, at the last follow-up, the eGFR of all 13 patients was greater than 85 mL/min/1.73 m^2. Compared with other patients, the remaining two patients exhibited a more severe phenotype than expected, owing to the *CUBN* mutation. One patient presented with SRNS at the age of 3 years, with kidney biopsy showing minimal changes in the disease and requiring cyclophosphamide treatment in addition to steroids. However, after 6.6 years of follow-up, the patient had a normal eGFR of 101 mL/min/1.73 m^2. Another patient was diagnosed with a *CUBN* mutation at the age of 35 years owing to chronic proteinuria, and a biopsy showed focal segmental glomerulosclerosis. At the last follow-up, at the age of 51 years, the patient's eGFR decreased to 70.2 mL/min/1.73 m^2. However, the patient also had type 2 diabetes mellitus, obesity, and hypertensive cardiomyopathy, and these comorbidities were suspected to be the cause of the patient's decreased kidney function.

The common characteristics observed in patients with *CUBN* mutations across multiple cohort studies, such as normal serum albumin levels, preserved kidney function in adulthood, and renal pathology findings showing normal or minimal lesions with only a small subset exhibiting glomerular sclerosis, reflect the benign nature of *CUBN* mutations. Most patients do not progress to chronic kidney disease unless additional comorbidities that affect renal function, such as diabetes mellitus or obesity, are present [7,8]. Based on these characteristics, *CUBN* mutations should be suspected in patients with chronic proteinuria who do not present with hypertension or hypoalbuminemia and who exhibit glomerular proteinuria with >50% albuminuria. This review emphasizes that awareness of *CUBN* mutations as a differential diagnosis for persistent proteinuria could help clinicians care for pediatric patients with proteinuria and make accurate diagnoses without resorting to invasive kidney biopsies.

Furthermore, several cohort studies have demonstrated that patients with *CUBN* mutations do not respond to treatment with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) treatment [6,7]. Thus, ACEi or ARB therapy for kidney protection may not be necessary in patients with *CUBN* mutations. However, long-term follow-up studies are needed to definitively determine whether this condition is truly benign, particularly in pediatric patients who experience proteinuria for longer durations than adults.

In conclusion, Lee's study is significant because it introduces the clinical features, diagnosis, and treatment considerations of *CUBN* mutations, which are important genetic diseases that should be considered in pediatric patients with proteinuria. As genetic kidney diseases become increasingly important in pediatric nephrology, a new paradigm for diagnosing and treating patients with proteinuria is emerging [9]. Clinicians treating pediatric and adolescent patients with proteinuria should consider that new diagnostic and therapeutic approaches may be needed in some cases instead of traditional tools. We look forward to future cohort studies of *CUBN* mutations in Korean children and adolescents.

Conflicts of interest

Jin-Soon Suh is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No potential conflicts of interest relevant to this article were reported.

Funding

None.

Author contributions

All the work was done by JSS.

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