An Unusual Genetic Etiology For Adult-Onset FSGS

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Introduction

Focal segmental glomerulosclerosis (FSGS) is not a distinct disease but a histological pattern frequently associated with nephrotic syndrome in adults and children. It is characterized by the presence of sclerosis in parts of some glomeruli under light microscopy. Damage to the podocyte cytoskeleton is the pathologic hallmark in the pathogenesis of FSGS.

Genetic FSGS can arise from various genetic mutations occurring in genes responsible for encoding proteins predominantly expressed in the podocytes and slit diaphragms.

This case report aims to focus on CLCN5 gene mutation as an unusual etiology for FSGS in adults, to highlight the utility of genetic testing and when it should be considered as the next step in management.

Case Presentation

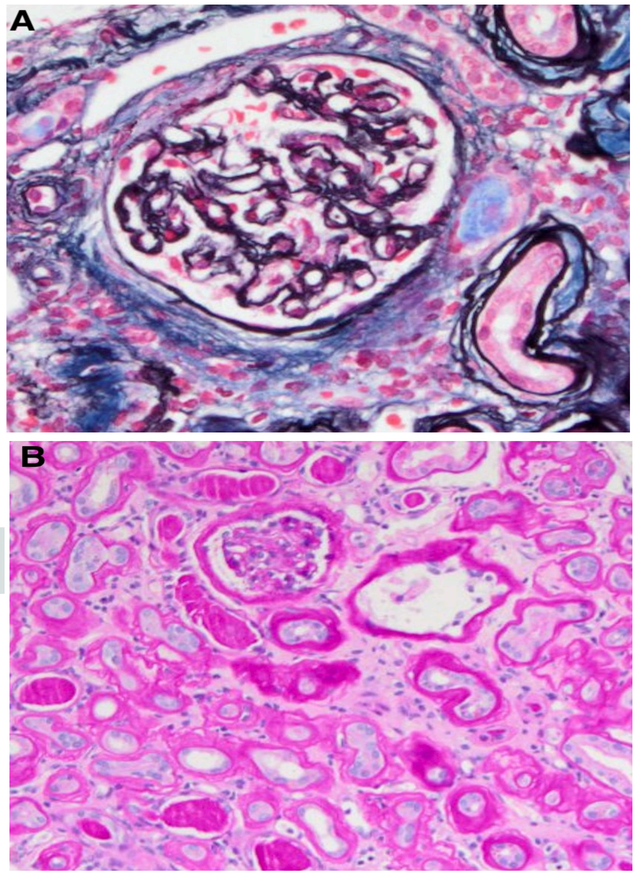
This is a case of a 31-year-old African American male with a history of well-controlled hypertension, non-obstructive nephrolithiasis, and remote history of cocaine use, who was referred to the renal clinic due to stage IV chronic kidney disease (CKD) and nephrotic range proteinuria. His blood pressure was well-managed without antihypertensive medications.

Initial laboratory tests revealed a serum creatinine of 3.19 mg/dl, blood urea nitrogen (BUN) of 27 mg/dl, and an estimated glomerular filtration rate (eGFR) of 25 mL/min. Importantly, his urine protein: creatinine ratio was significantly elevated at 3200 mg/g, suggesting glomerular disease.

Given the patient's nephrotic range proteinuria and the uncertain etiology of his CKD, a renal biopsy was performed. The biopsy result demonstrated focal segmental glomerulosclerosis (FSGS) with severe interstitial fibrosis and tubular atrophy.

In light of his young age and the fact that his blood pressure was well-controlled, the possibility of a genetic cause for his CKD was explored. Genetic testing was conducted and revealed a homozygous mutation in the CLCN5 gene, consistent with Dent Disease type-1, and a heterozygous genetic variant of APOL-1.

Image 1: Renal Biopsy



A. Trichrome staining under light microscopy (40x) showing segmental sclerotic changes.

B. Periodic-acid-Schiff (PAS) staining under light microscopy (10x) showing severe interstitial fibrosis and tubular atrophy, with a single glomerulus showing ischemic-type changes.

Image 2: Renal Ultrasound

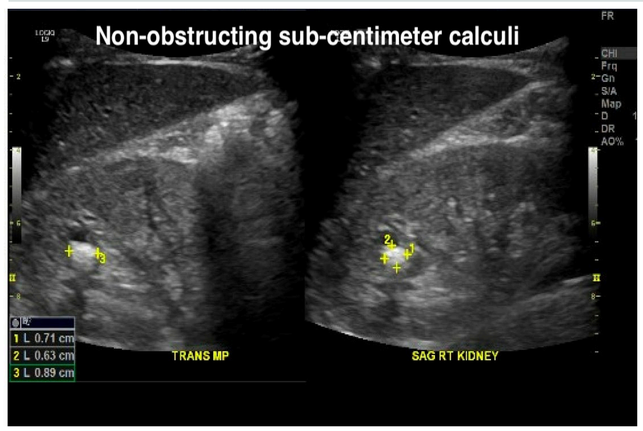
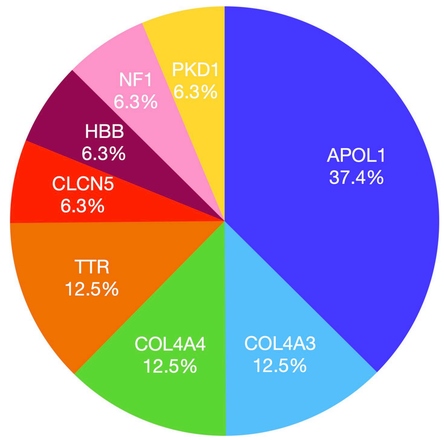


Image 3: LSU Nephrology Genetic Testing Metrics



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- Apolipoprotein L1 (APOL1)
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- Polycystic Kidney Disease type 1 (PKD1)

Renasight genetic testing:

13 positive results out of 35 to date (37 % positive yield)

Most common findings:

- APOL1-mediated kidney disease (38%)
- COL4A3/4-related Alport syndrome (25%)

Discussion

Dent Disease type-1, is a rare X-linked recessive disease that affects males more predominantly than females and is considered a partial Fanconi syndrome since it primarily affects the proximal tubules. It is associated with increased rates of nephrolithiasis as well as low molecular weight proteinuria, hypercalciuria, progressive CKD, and rickets.

Dent Disease type-1 is due to mutations in the CLCN5 gene that encodes for the endosomal electrogenic Cl-/H+ exchanger, which plays a critical role in organizing the components of the podocyte slit diaphragm to help maintain normal cell physiology and a functional filtration barrier. A novel mutation (L521F) in the CLCN5 gene has been reported to cause defects in podocyte transport and subsequent FSGS.

However, the L521F mutation is usually not associated with hypercalciuria or nephrolithiasis. Our patient had evidence of both glomerular and tubular involvement. Our case demonstrates the value of genetic testing in patients with CKD of uncertain etiology, particularly in younger patients or those with unusual presentations. Understanding the genetic basis of kidney disease can lead to novel discoveries in renal physiology.

References

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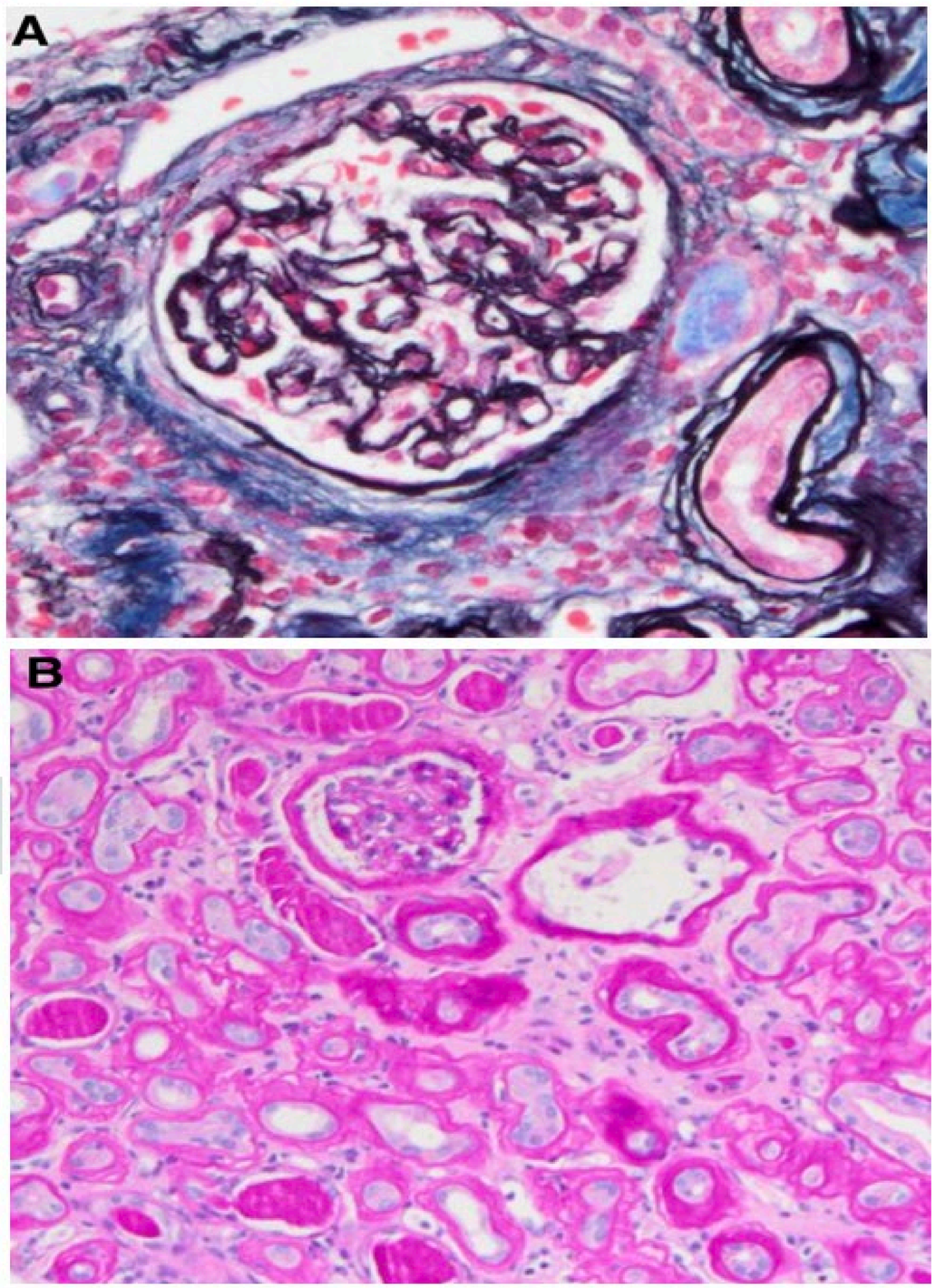

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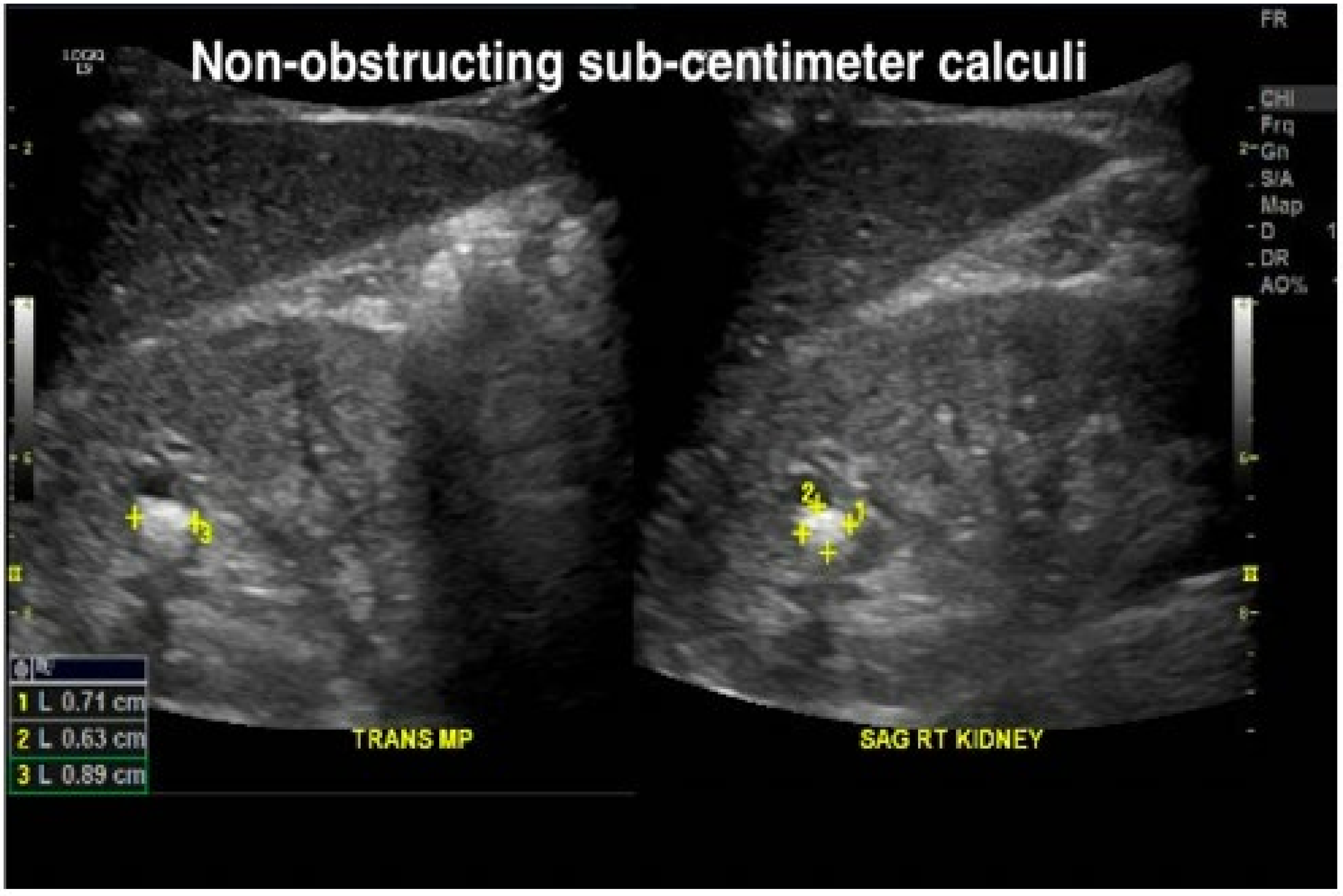

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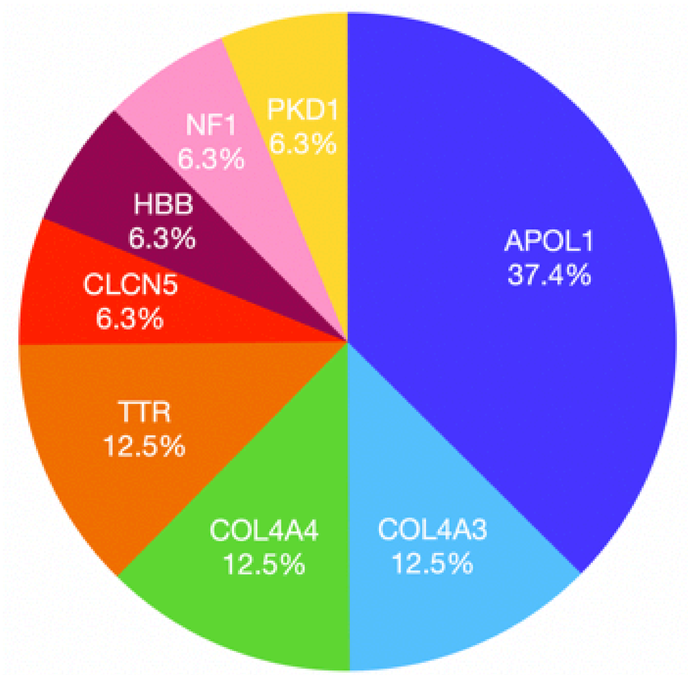

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