

An Unusual Genetic Etiology For Adult-Onset FSGS

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Introduction:

Focal segmental glomerulosclerosis (FSGS) is a histological pattern that is commonly associated with nephrotic syndrome and characterized by damage to the podocyte cytoskeleton. Genetic FSGS results from mutations in genes encoding podocyte proteins, particularly those predominantly expressed in the slit diaphragm. Here we discuss a case of genetic FSGS associated with mutation of a gene predominantly expressed in the proximal tubules.

Case Report:

A 31-year-old African American male was referred to the renal clinic for evaluation of stage IV chronic kidney disease (CKD) and nephrotic range proteinuria. He had a history of well-controlled hypertension (not on any antihypertensives) and non-obstructive nephrolithiasis. Given proteinuria of more than 3 grams, suggesting glomerular disease and uncertain etiology of his CKD, a renal biopsy was performed. Biopsy revealed focal segmental glomerulosclerosis and severe interstitial fibrosis with tubular atrophy (Figure). Given the patient's age and the unclear etiology of his FSGS, genetic testing was conducted, which revealed a homozygous mutation in the CLCN5 gene, consistent with Dent Disease type 1.

Discussion:

Dent Disease type-1 is a rare X-linked recessive disease due to mutations in the CLCN5 gene that encodes for the electrogenic Cl⁻/H⁺ exchanger. It usually manifests with proximal tubular dysfunction including low-molecular-weight proteinuria, hypercalciuria, nephrolithiasis, and progressive CKD. A novel mutation (L521F) in the CLCN5 gene has been reported to cause defects in podocyte transport and 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.