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Case Report

Adult-Onset Focal Segmental Glomerulosclerosis Associated with CRB2 Gene Variants, a Case Report

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ABSTRACT

Focal segmental glomerulosclerosis (FSGS) is a common pathological lesion in kidney biopsies with diverse etiologies, including genetic mutations.

This is a case of a 39-year-old man presenting with proteinuria of 2 g/day, normal kidney function, and no nephrotic syndrome. A kidney biopsy revealed findings consistent with FSGS (not otherwise specified (NOS) type), and whole-exome sequencing (WES) identified two heterozygous variants in the CRB2 gene: c.3219C>G (likely pathogenic) and c.1864G>A (variant of uncertain significance). The patient was managed conservatively with renin-angiotensin-aldosterone system (RAAS) inhibitor and Sodium-Glucose cotransporter 2 (SGLT2) inhibitor, resulting in sustained proteinuria reduction and preservation of kidney function over a three-year follow-up. This report highlights a suspected association between CRB2 mutation and adult-onset FSGS without steroid resistance or nephrotic syndrome, that was successfully managed without immunosuppression.

Keywords: FSGS; Glomerulonephritis; Genetics

Introduction

Focal segmental glomerulosclerosis (FSGS) represents a heterogeneous group of glomerular disorders that share histological patterns of segmental sclerosis affecting less than half of the glomeruli (focal). FSGS usually presents with proteinuria with or without nephrotic syndrome. There are four etiological causes of FSGS classified: primary, secondary, genetic, and unclassifiable [1–3]. The differentiation between these etiologies plays a crucial role in decision of management protocol, benefits of immunosuppression and kidney transplantation outcomes and possibility of recurrence after transplantation.

Primary FSGS results from an unidentified circulating podocyte-toxic permeability factor and classically manifests itself as nephrotic syndrome, which may, or may not, respond to steroids. Secondary FSGS results from adaptive structural–functional changes, viral infections, or drugs leading to glomerular hyperfiltration. Diffuse foot process effacement is classically associated with primary FSGS but may also occur in some genetic forms; therefore, electron microscopy (EM) findings alone are insufficient to reliably distinguish primary, genetic, and adaptive etiologies [3].

Genetic FSGS can be sporadic or familial. It could be renal limited or syndromic. There are over 50 FSGS-associated genes so far, most of them have a role in regulating the structure and function of podocytes or the composition of the glomerular basement membrane (GBM) [3–5]. The clinical presentation varies from patient to patient; however, a fully blown nephrotic syndrome is uncommon.

CRB2 encodes Crumbs homolog 2, a critical protein for maintaining podocyte integrity. CRB2 mutations, while previously implicated in steroid-resistant nephrotic syndrome (SRNS) [6,7], have not been documented in association with non-nephrotic syndrome FSGS. This case report presents a unique clinical course of possible CRB2-related FSGS managed successfully with conservative therapy, underscoring the evolving spectrum of CRB2-associated glomerular disease.

Case Presentation

A 39-year-old man weighing 50 kg presented with persistent proteinuria of 2 g/day, detected incidentally during routine occupational laboratory testing. He has no relevant family history. He denied edema, oliguria, or systemic symptoms. There were no previous laboratory or clinical evaluations related to kidney function or proteinuria documented before the current presentation. Physical examination was unremarkable. Blood pressure was normal (130/80 mmHg). Laboratory investigations revealed normal kidney function (serum creatinine 0.6 mg/dL, blood urea nitrogen: 9 mg/dL, uric acid 6.1 mg/dL), normal serum albumin (4 g/dL), and negative autoimmune and infectious workups.

The autoimmune workup included negative antinuclear antibodies (ANA), anti-double-stranded DNA (Anti-DNA), antineutrophil cytoplasmic antibodies (ANCA p and c), with normal complement levels (C3: 127 mg/dL; C4: 25 mg/dL). Serological testing for hepatitis B (HBV) surface antigen and hepatitis C (HCV) antibodies was negative. Blood glucose (82 mg/dL), HbA1c (5.4%), and thyroid-stimulating hormone (TSH: 0.8 IU/mL) were within normal limits. Helicobacter pylori antigen testing was negative. Serum lipids revealed mild hypercholesterolemia (226 mg/dL) and hypertriglyceridemia (179 mg/dL). A urine dipstick test and microscopy showed +3 proteinuria without hematuria, casts or other abnormalities.

Kidney ultrasound was unremarkable. A kidney biopsy (figures 1-3) revealed 17 glomeruli, one of which was globally sclerosed, with three exhibiting segmental sclerosis and hyalinosis. Tubules, interstitium, and vasculature were unremarkable. Immunohistochemistry and Congo red staining showed no deposits. Electron microscopy revealed diffuse podocyte foot process effacement without electron-dense deposits, confirming FSGS (NOS type). Genetic FSGS was suspected due to the non-nephrotic syndrome presentation, together with the absence of any apparent secondary causes. The patient was counselled about genetic testing and whole exome sequencing (WES) was performed.

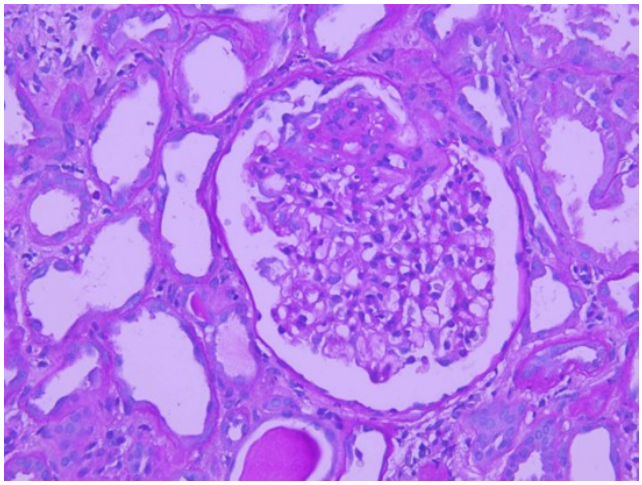

Figure 1. PAS stained section featuring one glomerulus with segmental tuft sclerosis (arrow) (x400).

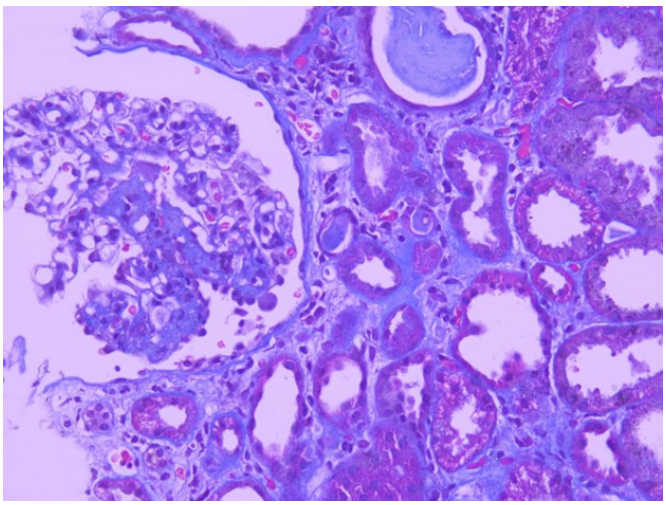

Figure 2. A Trichrome stained section reveals the presence of segmental tuft sclerosis with mesangial matrix expansion. (x400).

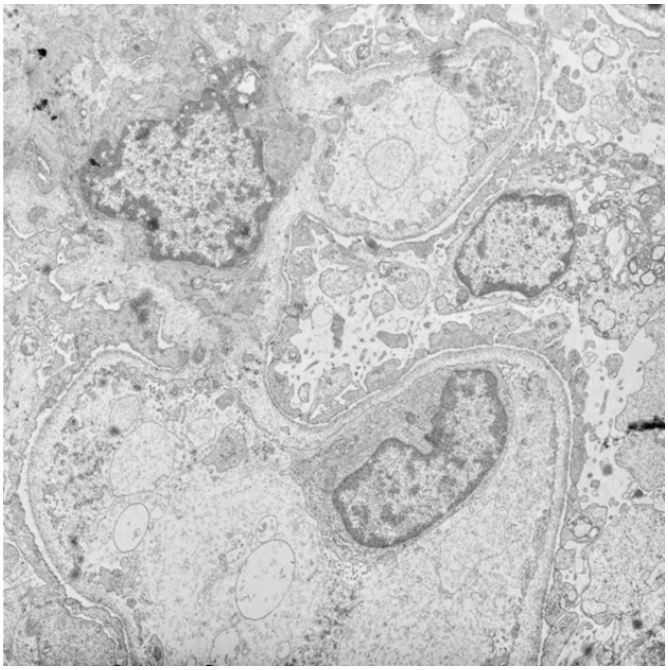

Figure 3. Ultrathin section stained by Uranyl acetate and lead citrate examined by TEM featuring diffuse effacement and fusion of podocyted foot processes with focally thickened an crenated GBM with no electron dense deposits.

WES identified two heterozygous variants in the CRB2 gene: c.3219C>G in exon 10, classified as likely pathogenic, and c.1864G>A in exon 7, classified as a variant of uncertain significance (VUS) per ACMG guidelines (Table 1). Although these variants are located on different exons, compound heterozygosity could not be definitively confirmed in the absence of segregation analysis. Segregation analysis was not feasible as both parents were deceased. This limitation should be considered when interpreting the potential pathogenic contribution of these variants.

The patient was initiated on ramipril (2.5 mg daily) with dietary sodium restriction, achieving a reduction in proteinuria to 1781 mg/g after one month. Ramipril was increased to 5 mg daily, and SGLT2 inhibition with dapagliflozin (10 mg daily) was introduced. Over the next three years, Ramipril was increased to 10 mg daily, proteinuria progressively declined to 633 mg/g with no deterioration in kidney function or adverse events. Serial lipid monitoring necessitated statin therapy for hypercholesterolemia. At the latest follow-up, kidney function remained stable with normal serum creatinine (0.67 mg/dL) and blood pressure (120/80 mmHg).

Table 1: Variant interpretation according to ACMG guidelines.

Variant	Location	Inheritance	Variant type	Protein change	In silico prediction	Population Frequency (gnomAD)	Interpretation
c.3219C>G	CRB2 gene Exon 10	AR	missense	AA change from Aspartic acid to Glutamic acid (p.Asp1073Glu)	Damaging by SIFT, PolyPhen, and Mutation Taster	0.0009	Likely pathogenic
c.1864G>A	CRB2 gene Exon 7	AR	missense	AA change from Aspartic acid to Aspargine (p.Asp622Asn)	Damaging by SIFT, PolyPhen, LRT and Mutation Taster	Not reported	variant of uncertain significance

AR: Autosomat Recessive, AA: Aminoacid

Discussion and Conclusion

FSGS represents a diverse pattern of kidney injury with multiple underlying etiologies. In Egypt, FSGS is among the most prevalent types of glomerulonephritis (8). However, the prevalence of adult-onset genetic FSGS is likely to be underrecognized, and its clinical and histological characteristics remain inadequately defined (6,9–11).

The clinical classification of FSGS remains challenging due to its many variable etiologies, limited understanding of its pathophysiology, and the poor correlation between histopathology, treatment responses, and clinical outcomes. Initially, a morphological classification system, the Columbia classification, proposed five variants: collapsing, tip, cellular, perihilar, and not otherwise specified (NOS). However, depending only on this classification for treatment decisions often led to overlooking genetic factors or syndromic presentations (5).

To address these limitations, a holistic, clinicopathologic classification has been developed, categorizing FSGS into primary, secondary, genetic, and undetermined forms (1).

Genetic FSGS can present either in childhood or in adulthood, according to the gene involved. It presents with variable degrees of proteinuria and effacement of podocyte foot process. In some cases, such as those involving APOL1 mutations, appearance of clinical manifestation requires a secondary trigger, such as drug toxicity, or infection.

Genetic FSGS can be further divided into renal-limited and syndromic forms. Syndromic cases are characterized by extrarenal manifestations, such as hearing or vision impairment, which help guide diagnosis (12). Genetic mutations can induce injury in FSGS through affecting the podocyte's architecture, Actin cytoskeleton, calcium signaling, and lysosomal and mitochondrial function. There are many gene mutations that have been identified in both familial and sporadic cases. For example, mutations in genes such as NPHS1, NPHS2, PLCε1, CD2AP, and MYO1E (autosomal recessive) and ACTN4, TRPC6 and INF2 (autosomal dominant) are associated with non-syndromic steroid resistant nephrotic syndrome (SRNS) and FSGS (13–15). On the other hand, mutations in genes like WT1, LAMB2, ITGB4, CD151, SCARB, and LMX1b, which encode proteins expressed in both renal and extrarenal tissues (16) are associated with Syndromic FSGS.

Establishing a molecular genetic diagnosis in FSGS is crucial for guiding management decisions, such as benefits of immunosuppression and predicting the risk of post-transplant recurrence. Genetic mutations have been identified in 24% of patients with early childhood onset of SRNS, 36% with late childhood onset, 25% with adolescent onset, and 14% with adult onset (17). Despite advances in identifying many genetic mutations resulting in abnormal podocytes and FSGS, routine genetic screening is not yet universally standard practice but should be considered in selected cases.

Adult-onset FSGS has been associated with a limited range of genetic mutations. For example, Sadowski et al (18) identified monogenic causes in 21.4% of cases with an onset between 19–25 years. Among autosomal dominant mutations, INF2, which encodes a protein involved in the actin and microtubule cytoskeletal remodeling, is the most common, accounting for up to 17% of familial cases with early adulthood onset (19,20). TRPC6 mutations, which affect calcium-permeable cation channels, are found in approximately 6% of familial and 2% of sporadic FSGS cases (6,21–23). Autosomal recessive mutations most frequently involve NPHS2, with a prevalence ranging from 4%–30% in familial cases (24–26).

The Crumbs gene was first characterized in Drosophila melanogaster (27). Subsequently, a human member of the Crumbs family, CRB2, was identified through bioinformatics approaches. The CRB2 gene, is located on chromosome 9q33.3 and comprises 13 exons encoding a transmembrane protein of 1285 amino acid (28). CRB2 encodes Crumbs homolog 2, a protein that plays a key role in preserving the integrity of the glomerular filtration barrier, regulating cell polarity and facilitating cell–cell adhesion (16,29). It is also critical for the structural differentiation of podocyte foot processes (30).

Defects in CRB2 impair the function of slit diaphragm–associated proteins in podocytes, including podocin, nephrin, and zonula occludens-1 (ZO-1). This disruption is mediated, at least in part, through decreased phosphorylation of sphingosine 1-phosphate receptor 1 (S1PR1).

CRB2 knockdown in zebrafish disrupts apical membrane differentiation and the trafficking of slit diaphragm proteins, leading to cytoplasmic mis-localization of nephrin and reduced expression of ZO-1 in podocytes (30,31). Likewise, biallelic mutations in CRB2 gene have been identified in humans with CRB2-related syndrome and isolated SRNS. These mutations may also result in ventriculomegaly associated with cystic kidney disease, representing a more severe clinical phenotype.

Mutations in CRB2 have been established as a monogenic cause of SRNS (10,11). In CRB2 knockout mouse model disruption of the coordinated trafficking between CRB2 and nephrin has been observed, leading

to retention of mutant CRB2 within the endoplasmic reticulum (ER). This intracellular accumulation induce ER stress, which may partially explain the pathophysiological mechanisms underlying glomerular filtration barrier (GFB) dysfunction in CRB2-associated disease (32). Moreover, loss of CRB2 in murine podocytes results in reduced expression of key genes, including WT1, NPHS2, PODXL, and NPHS1 likely mediated through downregulating F- actin. These findings suggest that CRB2 plays an essential role in slit diaphragm (SD) assembly and cytoskeletal organization (33). In contrast, a patient harbouring a heterozygous CRB2 variant did not demonstrate significant changes in the expression of nephrin, podocin, or ZO-1(34). Overall, the precise mechanisms by which CRB2 mutations induce podocyte injury remain incompletely understood, particularly with respect to slit diaphragm assembly and maintenance of cytoskeletal integrity, warranting further investigation.

This case underscores a challenge commonly encountered in adult-onset genetic kidney diseases, where confirmatory testing (e.g. parental genotyping) is not always feasible. As in our case, this absence limits definitive genetic classification. Still, the overall clinical context; non-nephrotic proteinuria, lack of systemic features, absence of identifiable causes of secondary adaptive FSGS, and the presence of CRB2 variants raised suspicion for a possible genetic contribution to the disease phenotype. We acknowledge that diffuse foot process effacement is not specific for genetic FSGS and may also be observed in primary forms.

We understand that the definitive diagnosis of compound heterozygosity requires segregation analysis. In our case, this was not feasible due to the unavailability of parental samples. We acknowledge this limitation, however, CRB2 gene mutation have been previously reported to be associated with SRNS and FSGS phenotypes.

Additionally, while CRB2 is classically associated with autosomal recessive inheritance, recent literature suggests that heterozygous variants in certain recessive genes may occasionally be associated with milder or late-onset phenotypes (35). Symptomatic heterozygotes have been identified across different disease types, including neurological, neuromuscular, hematological(36), endocrinal (37) and familial Mediterranean fever (FMF)(38).

Although the exact pathogenic mechanisms remain unclear, some mechanisms may explain phenotype expression in the absence of confirmed biallelic pathogenic variants including haploinsufficiency, dominant-negative effects, unidentified deep intronic or regulatory variants not captured by standard WES, epigenetic influences, or the influence of genetic or environmental modifiers. In our case, even in the absence of confirmed compound heterozygosity, it remains plausible that a single pathogenic or hypomorphic CRB2 variant could contribute to the phenotype of the patient.(35)

Ebarasi et al. have reported 5 patients from 4 families with an onset of SRNS between 9 months and 6 years of age and no additional systemic features. Renal biopsy was available in 4 patients and showed FSGS. Two of the families were consanguineous and of Turkish origin (6). Homozygous and compound heterozygous mutations in the CRB2 gene were identified. In the first two families, these variants were detected using homozygosity mapping and/or whole-exome sequencing (WES), whereas in the other two families, mutations were identified through targeted sequencing of the CRB2 gene in a cohort of 1,010 families with steroid-resistant nephrotic syndrome (SRNS). Yang et al have discovered two novel compound heterozygous mutations in the CRB2 gene (c.2905delinsGCCACCTCGCGCTGGCTG, p.T969Afs*179 and c.3268C > G, p.R1090G) in a family who presented with early-onset SRNS-FSGS (39). Another 3 year-old girl with SRNS and biopsy showed FSGS with small area of podocyte effacement, the WES identified novel compound heterozygous mutations in exons 10 and 12 of CRB2 (p.Trp1086ArgfsX64 and p.Asn1184Thr, each from different parents; Asn1184 within extracellular 15th EGF repeat domain) with significantly decreased Crb2 expression (40).

This case broadens the phenotypic spectrum of possible association between CRB2 mutations and genetic FSGS, highlighting a non-nephrotic syndrome presentation responsive to conservative therapy. While the c.3219C>G variant is classified as likely pathogenic, the presence of the (c.1864G>A) variant, classified as variant of uncertain significance (VUS), adds complexity. It is possible that this variant potentially contributes to the phenotype, or it may be a benign polymorphism. Importantly, our findings emphasize the utility of genetic testing in guiding management decisions, particularly in avoiding unnecessary immunosuppression in genetic FSGS.

In this case, the disease was associated with significant proteinuria reduction upon RAAS inhibition and SGLT2 inhibitor use. RAASi are known for their antiproteinuric effects and are considered cornerstone supportive treatment for any patient with proteinuria regardless the etiology (41,42). Similarly, SGLT2i are now becoming a standard of care for chronic kidney disease (43) as well as different glomerular diseases (44) especially after the publication of the prespecified analysis of the DAPA-CKD study in the FSGS cohort (45).

To conclude, this case demonstrates a suspected association of CRB2 mutations with FSGS, characterized by non-nephrotic syndrome, preserved kidney function and successful management with RAAS inhibitors and SGLT2 inhibitors. It underscores the need for genetic evaluation in atypical FSGS presentations to avoid unnecessary immunosuppression and highlights the therapeutic efficacy of conservative management in genetic FSGS.

Abbreviations

slit diaphragm (SD), endoplasmic reticulum (ER), human Crumbs family gene (*CRB2), Focal segmental glomerulosclerosis (FSGS), variant of uncertain significance (VUS), thyroid-stimulating hormone (TSH), hepatitis B (HBV), hepatitis C (HCV), antineutrophil cytoplasmic antibodies (ANCA), anti-double-stranded DNA (Anti-DNA), antinuclear antibodies (ANA), steroid-resistant nephrotic syndrome (SRNS), foot process effacement (FPE), Sodium-Glucose cotransporter 2 (SGLT2), renin-angiotensin-aldosterone system (RAAS), whole-exome sequencing (WES), not otherwise specified (NOS).*

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Consent for publication: The patient provided written informed consent for the publication of this case report,

Availability of data and materials: All the data for the current case are already provided.

Competing Interests: The authors declare that they have no competing interests.

Disclosure of AI Use: AI was used solely for English language editing and grammar refinement. All scientific content, data interpretation, and conclusions were developed entirely by the authors.

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