**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 59757

**Manuscript Type:** CASE REPORT

***Crumbs homolog 2* mutation in two siblings with steroid-resistant nephrotic syndrome: Two case reports**

Lu J *et al*. Siblings with *CRB2* mutation

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**Author contributions:** Lu J and Dong LQ contributed to the conceptualization of the report, drafted, and revised the article; Lu J, Guo YN, and Dong LQ contributed to data curation.

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**Received:** November 3, 2020

**Revised:** February 22, 2021

**Accepted:** March 11, 2021

**Published online:**

**Abstract**

BACKGROUND

*Crumbs homolog 2* (*CRB2*) is a recently discovered gene that is closely related to the maintenance of normal polarity in podocytes; mutations can directly lead to steroid-resistant nephrotic syndrome (SRNS). However, the characteristics of nephrotic syndrome (NS) caused by *CRB2* mutations have not been described.

CASE SUMMARY

We report a novel compound heterozygous mutation of the *CRB2* gene in two siblings with SRNS. The two siblings had edema, proteinuria, hypoproteinemia and hyperlipidemia. Both their father and mother had normal phenotypes (no history of NS). Whole exon sequencing (WES) of the family showed a novel compound heterozygous mutation, c.2290 (exon 8) C > T and c.3613 (exon 12) G > A. Glucocorticoid therapy (methylprednisolone pulse therapy or oral prednisone) and immunosuppressive agents (tacrolimus) had no effect. During a 3-year follow-up after genetic diagnosis by WES, proteinuria persisted, but the patient was healthy.

CONCLUSION

*CRB2* mutations related to SRNS often occur in exons 7, 10, and 12. Clinical manifestations of SRNS caused by *CRB2* mutations are often less severe than in other forms of SRNS.

**Key Words:** Steroid-resistant nephrotic syndrome; *Crumbs homolog 2*; Proteinuria; Compound heterozygous mutation; Glomerulosclerosis; Renal biopsy; Case report

Lu J, Guo YN, Dong LQ. *Crumbs homolog 2* mutation in two siblings with steroid-resistant nephrotic syndrome: Two case reports. *World J Clin Cases* 2021; In press

**Core Tip:** *Crumbs homolog 2* (*CRB2*)mutation is related to early-onset steroid-resistant nephrotic syndrome (SRNS). We here report two siblings with a novel compound heterozygous *CRB2* mutation. We also reviewed the literature and found that *CRB2* mutations related to SRNS often occur in exons 7, 10 and 12. Clinical manifestations of SRNS caused by *CRB2* mutations, such as edema, are often less severe than in other forms of SRNS.

**INTRODUCTION**

Primary nephrotic syndrome (NS) is a common urinary system disease in children. According to its sensitivity to corticosteroids, it can be divided into steroid-sensitive and steroid-resistant NS (SRNS). The majority of children with NS are sensitive to steroids and have a good prognosis, but 10%–20% of them have SRNS, and 30%-40% of children with SRNS progress to end-stage renal disease (ESRD) within 10 years[1]. Studies of primary NS confirm the importance of genetic testing to find mutations. A number of studies have shown that some cases of SRNS are caused by mutations of genes encoding glomerular podocyte cytoskeletal proteins. NS with gene mutations is now called hereditary NS. So far, more than 20 different single-gene mutations such as *WT1*, *NPHS1*, *NPHS2* and *PLCE1*[2-5] have been reported to cause SRNS, and those mutations are the cause of most hereditary NS.

Podocytes are highly polarized and specialized cells that play an important role in renal glomerular filtration. Many gene mutations affecting the kidneys are related to podocyte proteins, such as mutation of the *Crumbs homolog* *2* (*CRB2*) gene. *CRB2* belongs to the Crumbs family, which includes *CRB1*, *CRB2* and *CRB3*. The latter two are found in mammals[6]. The *CRB2* gene is located on chromosome 9q33.3, consists of 13 exons, and encodes a 1285 amino acid transmembrane protein. It is a recently discovered gene that is closely associated with SRNS, prenatal onset ventriculomegaly, and retinitis pigmentosa. By characterization of a loss-of-function mutation in zebrafish *crb2b*, Ebarasi *et al*[7] demonstrated that the *CRB2* gene is important for correct podocyte foot process arborization, slit diaphragm formation, and proper nephrin trafficking[7]. It may be that different manifestations are related to the location of the mutation.

This report describes two siblings diagnosed with SRNS and carrying a novel compound heterozygous mutation of *CRB2* gene that was inherited from their parents. We reviewed the literature on *CRB2* gene mutations reported in recent years, summarize their clinical manifestations, pathology and management; and suggest corresponding exon mutations related to NS.

**CASE PRESENTATION**

***Chief complaints***

**Case 1:** An 11-year-old girl presented with repeated edema of the eyelids and lower extremities for > 9 years. She had been taking oral prednisone, tripterygium, and dipyridamole without regular follow-up.

**Case 2:** A 9-year-old boy, who is the younger brother of case 1, was admitted to hospital with the chief complaint of repeated proteinuria for > 5 years. Eyelid edema appeared at the onset of the disease. He was diagnosed with NS 1 year before and was started on long-term oral steroid therapy, but there was no significant improvement in his proteinuria.

***History of present illness***

SRNS

***History of past illness***

Both cases had no history of significant past illnesses.

***Personal and family history***

Their parents had normal phenotypes and had no history of NS. Their father and grandfather had histories of renal calculi.

***Physical examination***

**Case 1:** The patient had a Cushing-like appearance, edema of both eyelids, and mild edema of both lower extremities.

**Case 2:** The patient presented with slight swelling of the eyelids.

***Laboratory examinations***

**Case 1:** Routine blood tests showed a white blood cell (WBC) count of 9.68 × 109/L, neutrophils 69.7%, hemoglobulin (Hb) 145 g/L, a platelet (PLT) count of 286 × 109/L, and C-reactive protein 6.45 mg/L. Routine urinalysis revealed protein 3+, 24 h urinary protein 1.46 g, serum albumin 19.8 g/L, and cholesterol 9.78 mmol/L. Serum creatinine, urea nitrogen, and complement C3 and C4 were all normal. Doppler ultrasound showed slightly enhanced echogenicity of the bilateral renal parenchyma. Renal biopsy revealed mild mesangial proliferative glomerulonephritis.

**Case 2:** Routine blood tests showed a WBC count of 6.16 × 109/L, neutrophils 36.7%, Hb 130 g/L, PLT count of 362 × 109/L, 24 h urinary protein 1.73 g, albumin 17.3 g/L, triglyceride 2.76 mmol/L, and cholesterol 10.07 mmol/L. Serum creatinine, urea nitrogen, complement C3 and C4 and chest radiography were all normal.

***Whole exon sequencing***

The two siblings and their parents all underwent whole exon sequencing, which showed that both siblings had a novel compound heterozygous mutation on exon 8, c.2290C>T and exon 12, c.3613G>A of *CRB2*. The mother had a heterozygous mutation on exon 8, c.2290C>T, and the father had a heterozygous mutation on exon 12, c.3613G>A (Figures 1 and 2).

**FINAL DIAGNOSIS**

SRNS with *CRB2* mutation

**TREATMENT**

The two siblings were treated with methylprednisolone pulse therapy (400 mg × 3 d and 300 mg × 3 d, respectively) followed by oral prednisone (25 mg bid), and tacrolimus. Other therapies included low molecular-weight heparin calcium, captopril, multivitamins, and dipyridamole.

**OUTCOME AND FOLLOW-UP**

During a 3-year follow-up, their proteinuria and mild edema persisted; the girl underwent surgery for hormone-related glaucoma.

**DISCUSSION**

NS is a common kidney disease in childhood. Although most cases are sensitive to steroids, 10%-20% of them are resistant, and 30%-40% of children with SRNS will develop ESRD within the next 10 years. Genetic diagnosis is important in SRNS and can avoid excessive use of steroids and immunosuppressants, thereby preventing adverse effects such as infection and cytotoxicity and improving quality of life. SRNS with a monogenic cause is known as hereditary NS[8], which can result in an isolated glomerular disease or syndrome with renal and extrarenal manifestations. Genes encoding podocyte proteins play an important role, such as *WT1*, *NPHS1*, *PLCE1*, *CRB2*, *LAMB2*, *EXT1* and*COL4A5*[9].

There are a few clinical reports of NS caused by *CRB2* gene mutation. *CRB2* is a recently discovered gene that is closely related to the maintenance of normal podocyte polarity, and its mutation can directly lead to SRNS[10]. The family of Crumbs proteins including *CRB1*, *CRB2* and *CRB3*, includes human homologs of drosophila *Crb* and plays a key role in the establishment and maintenance of epithelial polarity[11]. Katoh and Kotah[13] first identified *CRB2*, localized on 9q33.3, consisting of 13 exons and encoding 1285 amino acid transmembrane protein, containing large extracellular domains with epidermal growth factor[13,14]. Ebarasi *et al*[7] suggested that in zebrafish, *crb2b* has important effects on the correct podocyte foot process arborization, slit diaphragm formation, and proper renin trafficking[7]. The *CRB2*-null zebrafish presents with pronephric cysts, pericardial edema and smaller eyes, which demonstrates that the *CRB2* gene mutation can cause the corresponding loss-of-function of podocytes, and that *CRB2* mutations in humans can lead to NS. Jaron *et al*[15] presented two cases with ventriculomegaly and hydronephrosis and concluded that *CRB2*-associated disease is a new ciliopathy[15]. *CRB2* is a member of the Crumbs family of proteins implicated in planar cell polarity and is highly expressed in brain, retina and kidney[14]. *CRB2* missense mutation of different domains can lead to different clinical manifestations, and exons related to SRNS include 7, 10 and 13[7,16]. The *CRB2* gene has 13 exons in total, and mutation of this gene can cause NS, hydrocephalus, and retinitis pigmentosa. Whether a patient with *CRB2* gene mutation presents with NS, hydrocephalus or retinitis pigmentosa depends on the mutation sites. In the literature review, we found that *CRB2* mutations related to SRNS often occur in exons 7, 10 and 12 (Figure 3).

We found that the two siblings had a novel compound heterozygous mutation that led to SRNS. Their parents were carriers of *CRB2* gene mutation, but the mutation sites were different. The mother’s mutation site was chromosome 9, *CRB2* gene exon 8 c.2290C>T, while the father’s mutation site was chromosome 9, *CRB2* gene exon 12 c.3613G>A. The siblings presented clinical phenotypes as SRNS. The two mutation sites are reported here for the first time.

As *CRB2* is mainly expressed in the brain, retina and kidney,the main manifestations include ventriculomegaly, hydronephrosis, and SRNS (Table 1). Jaron *et al*[15] reported two Ashkenazi Jewish siblings clinically diagnosed with severe congenital hydrocephalus and mild urinary tract anomalies[15]. Lamont *et al*[16] reported five individuals with biallelic variants in *CRB2* presenting with lateral ventriculomegaly and bilateral echogenic kidneys, loss of corticomedullary differentiation, and multiple small cysts in both kidneys[16]. Ebarasi *et al*[7] identified recessive mutations of *CRB2* in four different families affected by SRNS[7]. Watanabe *et al*[10]reported the long-term clinicopathological observation of a Japanese female patient with SRNS caused by a compound heterozygous mutation of *CRB2*[10]. Udagawa *et al*[17] analyzed the expression of *CRB2* and slit diaphragm molecules in a 3-year-old girl with SRNS and concluded that *CRB2* mutations were the mechanism of SRNS[17]. Fan *et al*[18] reported a 7-year-old boy with SRNS who had heterozygous mutations of *CRB2*[18]. Chen *et al*[19] reported the identification of *CRB2* as a novel retinitis pigmentosa causative gene in a Chinese consanguineous family[19]. Slavotinek *et al*[20] reported five fetuses and a child from three families who shared a phenotype comprising cerebral ventriculomegaly and echogenic kidneys with histopathological findings of congenital nephrosis[20].

Renal biopsy findings from SRNS patients with *CRB2* mutations range from minor glomerular abnormalities to advanced focal segmental glomerulosclerosis (FSGS). Ebarasi *et al*[7]reported four individuals with renal histology of FSGS. In a 3-year-old girl, renal pathology showed FSGS with effaced podocyte foot processes in a small area. Fan reported renal histology of FSGS in a 7-year-old boy[7]. In a case report by Watanabe, six sequential renal biopsy specimens revealed histological alteration ranging from minor glomerular abnormalities to FSGS[10]. In our case, renal biopsy showed mild mesangial proliferative glomerulonephritis. It seems that renal biopsy in SRNS patients caused by *CRB2* mutation is related to the stage of the disease course.

For children with *CRB2* mutations, treatment is difficult. A Japanese girl reported by Udagawa *et al*[17] was unresponsive to corticosteroids, immunosuppressants, and rituximab[17]. Fan *et al*[18]suggested that high-dose methylprednisolone pulses and cyclosporine were effective[18]. Watanabe suggested presumptive podocyte-protective therapy including low-dose tacrolimus and angiotensin receptor blocker[10]. The two siblings in our report presented with SRNS, and immunosuppressive agents had no effect. In a 2-year follow-up, proteinuria remained, along with slight edema. Judging from the SRNS cases reported above as well as the two siblings reported here, although proteinuria is difficult to control in NS caused by *CRB2* mutation, the patients looked healthy and their renal function remained normal during 2–16.5 years of follow-up. Thus, it may be that in SRNS patients with *CRB2* mutations, regular follow-up is more important than treatment with corticosteroids and immunosuppressant agents, which may induce adverse effects such as infection, short stature, and glaucoma.

**CONCLUSION**

*CRB2* gene is related to early-onset SRNS. We report two siblings with a novel compound heterozygous *CRB2* mutation. In the literature review, we found that *CRB2* mutations related to SRNS often occur in exons 7, 10 and 12. Unlike other forms of SRNS caused by genetic mutations, clinical manifestations of SRNS caused by *CRB2* mutations, such as edema, are often less severe, but proteinuria is difficult to control. Regular follow-up is more important than drug therapy (*e.g*., corticosteroids and immunosuppressant agents). As more cases are reported, more information about the disease will be gathered and more appropriate treatments will be found.

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**Footnotes**

**Informed consent statement:** Informed consent was obtained from the guardian of the patient for the publication of this report.

**Conflict-of-interest statement:** The authors declare that they have no conflicts of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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**Manuscript source:** Unsolicited manuscript

**Peer-review started:** November 3, 2020

**First decision:** February 12, 2021

**Article in press:**

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Ali FEM, Wagner KD **S-Editor:** Fan JR **L-Editor:** Filipodia **P-Editor:**

**Figure Legends**



**Figure 1 Family pedigree indicating a compound heterozygosity for *Crumbs homolog 2* mutations.** Parents were unrelated. Genotype is indicated beneath each individual. Mutant alleles are shown in red: c.2290C>T and c.3613G>A.



**Figure 2 Whole exon sequencing of *Crumbs homolog 2* gene mutations in the two siblings and their parents.** The nucleotide exchange is marked by an arrow.



**Figure 3 Exons shown in red: Possible steroid-resistant nephrotic syndrome-related hotspot mutation region of *Crumbs homolog 2* gene.**

**Table 1 Literature review of previously reported *Crumbs homolog 2* mutation patients**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Reference** | **Age at diagnosis** | **Gender** | **Main Clinical manifestations** | **Nucleotide change** | **Exon** |
| Jaron *et al*[15] | 7 yr | Male | Ventriculomegaly and hydronephrosis | c.2400C>G; c.3089\_3104dup | 8; 10 |
|  | 5.5 yr | Male | Ventriculomegaly and hydronephrosis | c.2400C>G; c.3089\_3104dup | 8; 10 |
| Lamont *et al*[16] | 8 mo | Female | Ventriculomegaly and nephromegaly with multiple macrocysts | c.(3291\_3292delCT); c.(3343C>T) | 10; 10 |
|  | 2 mo | Male | Ventriculomegaly and increased echogenicity of kidney | c.(3385T>C); c.3108\_3109insCCGGCGCGGCCCCGGC | 10; 10 |
|  | 8 d | Female | persistent echogenicity of the kidneys and ventriculomegaly | c.(1494G>T); c.(3227A>C) | 7; 10 |
|  | 8 d | Female | persistent echogenicity of the kidneys and ventriculomegaly | c.(1494G>T); c.(3227A>C) | 7; 10 |
| Ebarasi *et al*[7] | 6 yr | ND | SRNS | c.1859G>C | 7 |
|  | 4 yr | ND | SRNS | c.1859G>C | 7 |
|  | 9 mo | ND | SRNS | c.1882C>T; (c.3089\_3104dup) | 7; 10 |
|  | 3 yr | ND | SRNS | c.1886G>C | 7 |
|  | NR | ND | SRNS | c.3746G>A | 13 |
| Watanabe *et al*[10] | 3.5 yr | Female | SRNS | c.1882C>T; c.2515G>T | 7; 9 |
| Udagawa *et al*[17] | 3 yr | Female | SRNS | c.3256\_3273del18insCGGCCCGGGGTGG; c.3551A>C | 10; 12 |
| Fan *et al*[18] | 7 yr | Male | SRNS | c.3190C>T; c.2705C>T | 10; 10 |
| Slavotinek *et al*[20] | 1 mo | Male | Cerebral ventriculomegaly and congenital nephrosis | c.1897C>T | 7 |
| Chen *et al*[19] | 51 yr | Female | Retinitis pigmentosa | c.3745C>G | 13 |
|  | 46 yr | Female | Retinitis pigmentosa | c.3745C>G | 13 |

ND: Not data; SRNS: Steroid-resistant nephrotic syndrome.