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Case Report

COQ6 Mutations in Children With Steroid-Resistant Focal Segmental Glomerulosclerosis and Sensorineural Hearing Loss

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The phenotypic combination of steroid-resistant focal segmental glomerulosclerosis (SR-FSGS) and sensorineural hearing loss has been mainly reported in patients with mitochondrial cytopathies, including primary coenzyme Q10 (CoQ10) deficiency. In this report of 10 children with SR-FSGS and sensorineural hearing loss, we found 6 patients with biallelic *COQ6* mutations. Median age at the onset of nephrotic syndrome was 29 (range, 15-47) months. All patients progressed to end-stage renal disease within a median of 13 (range, 1-27) months after the onset. Kidney biopsy revealed abnormal mitochondrial proliferation in podocytes in all 6 patients. None of the 5 patients who underwent kidney transplantation developed recurrence of FSGS. Primary CoQ10 deficiency due to *COQ6* mutations should be considered in children presenting with both SR-FSGS and sensorineural hearing loss. An early diagnosis of *COQ6* mutations is essential because the condition is treatable when CoQ10 supplementation is started at the early stage. We recommend early kidney biopsy because detection of abnormal mitochondrial proliferation in podocytes might provide an earlier diagnostic clue.

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INDEX WORDS: Steroid-resistant focal segmental glomerulosclerosis (SR-FSGS); sensorineural hearing loss; mitochondrial cytopathy; coenzyme Q10 deficiency; *COQ6* mutation; mitochondrial proliferation in podocytes; kidney biopsy; pediatric; children; end-stage renal disease (ESRD); case report.

Steroid-resistant nephrotic syndrome (SRNS), which occurs mostly in association with focal segmental glomerulosclerosis (FSGS), is the second most frequent cause of end-stage renal disease in children. Genetic diagnosis of SRNS or FSGS through traditional Sanger sequencing is expensive and time consuming because of the high genetic heterogeneity and phenotypic variability of this disease. Although massively parallel next-generation sequencing technology has drastically increased the sequencing throughput and reduced the cost per nucleotide sequenced as compared to Sanger sequencing, the current overall rate of mutation detection from using targeted next-generation sequencing of a broad panel of NS-related genes has been reported to be ~30%.[1-4]

Conversely, the candidate genes can be pinpointed and standard Sanger sequencing can be readily performed if patients with SRNS/FSGS also present a typical extrarenal manifestation, such as disproportional growth retardation in Schimke immuno-osseous dysplasia,[5] microcoria in Pierson syndrome,[6] dystrophic nails and absence of patella in nail-patella syndrome,[7] megathrombocytopenia in Fechtner syndrome,[8] and genitalia abnormalities in Denys-Drash syndrome.[9]

In this report, we focus on the association of sensorineural hearing loss in children with SR-FSGS. Such a phenotypic combination has been mainly reported in patients with mitochondrial cytopathies, including those resulting from the 3243A>G mutation in *MT-TL1* (leading to MELAS [mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes] syndrome)[10] and mutations in the genes involved in the biosynthesis of coenzyme Q10 (CoQ10).[11-14] Moreover, this combination can develop in certain patients with mutations in *COL4A3/COL4A4* (autosomal recessive Alport syndrome),[15] *MYH9* (Fechtner syndrome),[16] *ARHGDIA* (nephrotic syndrome type 8),[17] and *INF2* (FSGS5 with autosomal dominant inheritance).[18]

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Table 1. Clinical Course of Kidney Diseases and Genotypes in 6 Patients With Biallelic *COQ6* Mutations Manifesting With Steroid-Resistant Focal Segmental Glomerulosclerosis and Sensorineural Hearing Loss

	Age, mo, at			Duration, mo, Between Onset and		Kidney Function at the Time of Biopsy			Sclerosed Glomeruli			
Pt/Sex	Onset	ESRD	Tx	ESRD	Biopsy	Proteinuria[a]	eGFR	Kidney Biopsy Findings	Segmental	Global	*COQ6* Mutations[b]	Other Extrarenal Manifestations
1/M	46	73	137	27	1	38.0	72	cFSGS	28/57 (49%)	29/57 (51%)	c.189_191delGAA, p.Lys64del (♀) c.782C>T, p.Pro261Leu (♂)	Mild muscle weakness in the lower extremities
2/F	23	31	—	8	7	57.6	14	FSGS	19/27 (70%)	8/27 (30%)	c.189_191delGAA, p.Lys64del (♀) c.686A>C, p.Gln229Pro (♂)	Exotropia with nystagmus on both eyes
3/F	47	48	76	1	1	5.1	16	cFSGS	11/21 (52%)	10/21 (48%)	c.189_191delGAA, p.Lys64del (♀) c.782C>T, p.Pro261Leu (♂)	None
4/F	32	55	87	23	1	27.5	167	cFSGS	4/34 (12%)	1/34 (3%)	c.189_191delGAA, p.Lys64del (?) c.782C>T, p.Pro261Leu (?)	None
5/F	15	17	77	2	1	12.5	70	FSGS	13/60 (22%)	0	c.189_191delGAA, p.Lys64del (♂) c.782C>T, p.Pro261Leu (♀)	Bilateral optic nerve atrophy
6/M	25	43	60	18	13	13.6	89	FSGS	1/28 (4%)	11/28 (38%)	c.189_191delGAA, p.Lys64del (♂) c.782C>T, p.Pro261Leu (♀)	Mild muscle weakness in the lower extremities

Note: All patients exhibited mitochondrial proliferation in podocytes.

Abbreviations: cFSGS, focal segmental glomerulosclerosis, collapsing variant; eGFR, estimated glomerular filtration rate calculated using the Schwartz formula (mL/min/1.73 m^2); ESRD, end-stage renal disease; F, female; FSGS, focal segmental glomerulosclerosis, not-otherwise-specified variant; M, male; Pt, patient; Tx, kidney transplantation.

[a]Protein-creatinine ratio (mg/mg) in random urine samples.

[b]Mutations were annotated according to a *COQ6* complementary DNA reference sequence (GenBank Accession No. NM_182476.2). ♀ indicates mutation was inherited from mother; ♂ indicates mutation was inherited from father; ? indicates origin of the mutation is unknown.