Mitochondrial Disease and the Kidney With a Special Focus on CoQ\textsubscript{10} Deficiency

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Mitochondrial cytopathies include a heterogeneous group of diseases that are characterized by impaired oxidative phosphorylation, leading to multi-organ involvement and progressive clinical deterioration. Most mitochondrial cytopathies that cause kidney symptoms are characterized by tubular defects, but glomerular, tubulointerstitial, and cystic diseases have also been described. Mitochondrial cytopathies can result from mitochondrial or nuclear DNA mutations. Early recognition of defects in the coenzyme Q\textsubscript{10} (CoQ\textsubscript{10}) biosynthesis is important, as patients with primary CoQ\textsubscript{10} deficiency may be responsive to treatment with oral CoQ\textsubscript{10} supplementation, in contrast to most mitochondrial diseases. A literature search was conducted to investigate kidney involvement in genetic mitochondrial cytopathies and to identify mitochondrial and nuclear DNA mutations involved in mitochondrial kidney disease. Furthermore, we identified all reported cases to date with a CoQ\textsubscript{10} deficiency with glomerular involvement, including 3 patients with variable renal phenotypes in our clinic. To date, 144 patients from 95 families with a primary CoQ\textsubscript{10} deficiency and glomerular involvement have been described based on mutations in \textit{PDSS1}, \textit{PDSS2}, \textit{COQ2}, \textit{COQ6}, and \textit{COQ8B/ADCK4}. This review provides an overview of kidney involvement in genetic mitochondrial cytopathies with a special focus on CoQ\textsubscript{10} deficiency.

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manifestation at presentation. CoQ10 deficiency is highly relevant for clinicians because, in contrast to most mitochondrial disorders, patients with primary CoQ10 deficiency may respond to treatment with CoQ10 supplementation.11 Early diagnosis is crucial, as oral supplementation of CoQ10 can limit disease progression, prevent neurological deterioration, and improve clinical symptoms.12 As established neurologic and/or kidney damage is irreversible, this underlines the importance of early diagnosis and treatment. In this review, an overview of kidney involvement in genetic mitochondrial cytopathies is provided with a special focus on CoQ10 deficiency.

**MITochondrial (DYS)FUNCTION**

The mitochondrial genome is composed of a single, double-stranded, circular loop that lacks introns and contains 37 genes, encoding 2 ribosomal RNA, 22 transfer RNAs, and 13 structural protein subunits of the respiratory chain complexes I, III, and IV, and protein complex V.13–15 Complex II contains only nDNA-encoded subunits, whereas the other respiratory chain complexes and complex V comprise both mtDNA-encoded and nDNA-encoded subunits.8 The mitochondrial respiratory chain is composed of 4 protein complexes and 2 electron carriers: CoQ10 and cytochrome c (Figure 1). CoQ10, also known as ubiquinone, is present in all cell membranes as a lipid molecule with a variety of biological functions. Besides its function as electron carrier, CoQ10 is involved in the β-oxidation of fatty acids, pyrimidine synthesis, detoxification of hydrogen sulfide, and protection from reactive oxygen species (ROS).16–19 Mitochondrial cytopathies refer to inherited or sporadic mtDNA or nDNA mutations in genes that affect mitochondrial functions. Different from nDNA, various amounts of mtDNA copies are present in a cell depending on its energy demand. mtDNA is highly susceptible to damage and mutations, with a 10- to 1000-fold greater mutation rate than nDNA.20 The threshold level for mitochondria to become dysfunctional can vary between tissues due to differences in energy dependence. The threshold for disease is lower in tissues that are highly dependent on oxidative metabolism, such as kidney tubules.2,21 Defects in oxidative metabolism.

![Figure 1. Mitochondrial energy-generating system. Acetyl-CoA, the terminal product of carbohydrate and lipid metabolism, enters the Krebs cycle to generate CO₂, NADH, and FADH₂. Electrons derived from cellular dehydrogenases in the Krebs cycle are passed along 4 protein complexes and 2 small carriers. The flow of electrons from NADH or FADH₂ through the protein complexes leads to the pumping of protons from the mitochondrial matrix to the intermembrane space. The electrons are shuttled from complex I and II to complex III by the electron carrier CoQ₁₀ and then transferred to complex IV by cytochrome c. These processes create an electrochemical gradient that is used by ATP synthase (complex V) to synthesize ATP from inorganic phosphate and ADP. Acetyl-CoA, acetyl coenzyme A; ADP, adenosine diphosphate; ATP, adenosine triphosphate; C, cytochrome c; e, electron; FADH₂, reduced form of flavin adenine dinucleotide; NADH, nicotinamide adenine dinucleotide hydrogen; CoQ₁₀, coenzyme Q₁₀; I, complex I; II, complex II; III, complex III; IV, complex IV; V, complex V.](image-url)
phosphorylation cause 1 major problems: a reduction in ATP production, and an increase in ROS production. In approximately one-third of patients, the first symptoms of mitochondrial defects develop within the first weeks of life, and more than 80% of patients are symptomatic by the age of 2 years.22

**KIDNEY MANIFESTATIONS OF GENETIC MITOCHONDRIAL CYTOPATHIES**

Kidney symptoms caused by mitochondrial dysfunction are often characterized by tubular or glomerular defects. Tubulointerstitial and cystic kidney diseases have also been described; however, the molecular mechanisms remain to be elucidated.20

**Tubular Defects**

Tubular disorders are frequently reported in patients with mitochondrial cytopathies. Mutations in both mitochondrial and nuclear genes have been described to cause tubular defects (Tables 1 and 2, Figure 2).10,21–71 Excellent overviews of mitochondrial and nuclear gene mutations causing tubular defects are provided in various reviews.8,20,72–74 The most commonly reported problem is a proximal tubular defect, as proximal tubular cells are relatively vulnerable to oxidative stress. Most patients present with partial defects, including renal tubular acidosis (RTA), aminoaciduria, glycosuria, hypermagnesuria, or a combination of the above.8,73 Renal Fanconi syndrome has been reported in children with specific mitochondrial syndromes, including Kearns–Sayre syndrome, Pearson syndrome, Leigh syndrome, and CoQ10 deficiency.70,75–79 Kearns–Sayre syndrome typically includes chronic progressive external ophthalmoplegia, ptosis, and pigmentary retinopathy in individuals less than 20 years of age.80 Pearson syndrome occurs in infancy, and characteristically includes sideroblastic anemia and exocrine pancreatic dysfunction.81 Hypomagnesemia has been described in different mitochondrial syndromes, for instance in patients with Kearns–Sayre syndrome.82,83 Moreover, Wilson et al. describe a cluster of metabolic defects, including hypomagnesemia, caused by a mitochondrial tRNAleu mutation.44

**Glomerular Diseases**

Podocytes are highly differentiated cells with limited regenerative capacity.84 The main metabolic pathway for podocytes is anaerobic glycolysis and the fermentation of glucose to lactate.85 Therefore, the mechanism of glomerular dysfunction is probably different from that of tubular dysfunction in patients with mitochondrial cytopathies. Brinkkoetter et al. hypothesize that a change in podocyte metabolism rather than the loss of mitochondrial oxidative phosphorylation is essential for damage to the podocyte.85 Two major mitochondrial cytopathies associated with glomerular dysfunction are due to a m.3243A>G mutation in tRNAleu gene or to genetic defects in the CoQ10 biosynthesis pathway8 (Tables 1 and 2, Figure 2).

**m.3243A>G Mutation in tRNAleu Gene**

The m.3243A>G mutation in the tRNAleu gene is one of the most common mtDNA point mutations, but the phenotypic expression can be highly variable. This mutation is associated with a wide range of clinical extrarenal manifestations including deafness, diabetes mellitus, neuromuscular involvement, hypertrophic

| Gene | mtDNA point mutation | Predominant kidney phenotype | Extrarenal symptoms | Ref |
|------|---------------------|------------------------------|---------------------|-----|
| tRNAAsn | m.5728A>G | FSGS | Failure to thrive, neurological involvement | 45 |
| tRNATyr | m.5843A>G | FSGS | Dilated cardiomyopathy | 46 |
| MT-ND5 | m.12425delA | Chronic kidney failure, glomerulocystic disease | Myopathy | 48 |
| tRNAleu | m.3243A>G | Tubulopathy | Myclonic epilepsy and ragged-red fiber disease (MERRF), hearing loss, Kearns–Sayre syndrome, mitochondrial myopathy | 49 |

Asn, Asparagine; DNA, deoxyribonucleic acid; FSGS, focal segmental glomerulosclerosis; HSP, heavy strand promotor; HUPRA, hyperuricemia, pulmonary hypertension, kidney failure
cardiomyopathy, and macular dystrophy. The m.3243A>G mutation was initially described in mitochondrial myopathy encephalopathy with lactic acidosis and stroke like episodes (MELAS) syndrome, a mitochondrial syndrome manifested in patients who are typically less than 40 years of age. Low m.3243A>G mutation heteroplasmy levels cause maternally inherited diabetes and deafness (MIDD) syndrome. The m.3243A>G mutation is associated with focal segmental glomerulosclerosis (FSGS),

| Gene                        | nDNA mutation                                  | Consequences on protein level | Predominant kidney phenotype                  | Extrarenal symptoms                                  | Ref |
|-----------------------------|------------------------------------------------|-------------------------------|-----------------------------------------------|------------------------------------------------------|-----|
| Respiratory chain assembly and function |                                                                                          |                                |                                               |                                                      |     |
| BCS1L                       | c.830G→A, c.286G→T                            | p.Ser277Asp, p.Pro99Leu       | Proximal tubulopathy                          | Hepatic involvement, encephalopathy                  | 50-52|
| SURF1                       | c.312del10insAT, c.688C>T                      | p.Pro104_Leu105insTer, p.Arg230Ter p.Thr278Ter | Tubulopathy                                   | Hypotonia, developmental regression, encephalopathy | 53  |
| COX10                       | c.612C→A                                      | p.Asn204Iys                   | Tubulopathy                                   | Neurological deterioration, leukodystrophy           | 54  |
| TMEM70                      | c.317-2A→G, c.317-2A→G                        | Splice site mutation, (ND, p.Thr210Pro, p.Ser402Tyr, p.Thr193Serfs p.Tyr179His, ND) | Renal tubular acidosis, hydropneumos, kidney failure | Neurological involvement, cardiomyopathy             | 55-56|
| UQCC2                       | c.214-3C→G                                    | Splice site mutation          | Tubular dysfunction                            | Severe intrauterine growth retardation, lactic acidosis | 57  |
| ETHE1                       | c.505→1G>T                                    | Splice site mutation          | Crescentic glomerulonephritis                 | Ethylmalonic encephalopathy                          | 58  |
| NDUFAF2                     | c.114G→G                                      | p.Tyr36Ter                    | Renal tubular acidosis                         | Muscular hypotonia, developmental delay               | 59  |
| Mitochondrial protein translation |                                                                                          |                                |                                               |                                                      |     |
| S4HS2                       | c.1169A→G, c.12050A                           | p.Arg390Gly, p.Arg402His      | Tubulopathy, hypomagnesemia, progressive kidney failure | Pulmonary hypertension (HUPRA syndrome)              | 60, 61|
| YARS2                       | c.1303A→G                                     | p.Ser435Gly                   | Myopathy, lactic acidosis, enemia              |                                                      | 62  |
| MRP2S2                      | c.509G→A                                      | p.Arg170His                   | Tubulopathy                                   | Hypertrophic cardiomyopathy                          | 63  |
| Post-translational modification of mitochondrial proteins |                                                                                          |                                |                                               |                                                      |     |
| XPNPEP3                     | c.1357G→T                                     | p.Gly453Cys                   | Kidney failure                                | Limited to mild neurologic involvement with sensoryneural hearing loss and essential tremor Mental retardation, seizures, cardiomyopathy | 64  |
| DGUKO                       | c.931_934delAACA                               | p.Asn311LysX5                 |                                               |                                                      |     |
| TTMF                        | c.1650C→A, c.487_490dupGACA, c.627A→G, c.952-3delTT | p.Tyr65Ter, frame shift mutation p.His226Arg, splice site mutation | Tubulopathy                                   | Developmental delay, hypotonia                         | 65  |
| SULCA2                      | c.534→1G→A                                    | Splice site mutation, multiple exon skipping | Tubulopathy, renal Fanconi syndrome | Progressive hearing loss, epilepsy                    | 67  |
| TK2                         | c.547C→G, c.780C→T                            | p.Asp183Gly, p.Asp254Ter      | Tubulopathy                                   | CNS and skeletal muscle involvement                  | 68  |
| COQ2                        | Various (Supplementary Table S1)               | Various (Supplementary Table S1) | (steroid-resistant) nephrotic syndrome         | Neurological, cardiovascular, and ocular involvement, diabetes mellitus | Supplementary Table S1 |
| COQ6                        | Various (Supplementary Table S1)               | Various (Supplementary Table S1) | (steroid-resistant) nephrotic syndrome         | Sensoryneural deafness, occasional neurological involvement | Supplementary Table S1 |
| COQ8B/AOCX4                 | Various (Supplementary Table S1)               | Various (Supplementary Table S1) | (steroid-resistant) nephrotic syndrome         | Occasional (mild) neurological, ocular, and cardiovascular involvement | Supplementary Table S1 |
| COQ9                        | c.730G→T                                      | p.Arg244Ter                   | Tubular dysfunction                            | Neonatal lactic acidosis, seizures, global developmental delay, hypertrophic cardiomyopathy | 69, 70|

CNS, central nervous system; CoQ10, coenzyme Q10; DNA, deoxyribonucleic acid; n, nuclear; ND, no data (not reported); Ref, reference. All mutations are described as pathogenic in the literature.
tubulointerstitial nephritis, and cystic kidney disease (Table 1). The kidney disease associated with the m.3243A>G mutation generally corresponds to a glomerulopathy with proteinuria, which is below the nephrotic range in two-thirds of patients. The majority of patients are diagnosed with kidney disease in their second or third decade of life, and CKD is present in one-half of these cases.

**CoQ10 Deficiency**

Primary CoQ10 deficiency is a clinically and genetically heterogeneous disorder. Clinical phenotypes range from fatal infantile multisystem disorders to isolated glomerular involvement. In addition, variability exists regarding the age of onset, the different organs involved, and clinical response to CoQ10 supplementation. CoQ10 is present in the normal diet, but at insufficient levels to supply mitochondria. Therefore, de novo biosynthesis in mitochondria is needed, a complex pathway that involves several proteins encoded by COQ genes (Figure 3). Currently, mutations in 10 different genes involved in the CoQ10 pathway have been reported (PDSS1, PDSS2, COQ2, COQ4, COQ5, COQ6, COQ7, COQ8A/ADCK3, COQ8B/ADCK4, COQ9). A literature search was conducted to identify all reported cases with glomerular involvement to date (February 2020). References of the identified articles were used to search for additional case reports. In total, approximately 200 patients from 130 families with a primary CoQ10 deficiency have been described in the literature. Mutations in PDSS1, PDSS2, COQ2, COQ6, and COQ8B/ADCK4 have been associated with glomerular involvement. Supplementary Table S1 summarizes clinical and genetic data of all 144 patients with a PDSS1, PDSS2, COQ2, COQ6, and COQ8B/ADCK4 mutation with glomerular involvement reported to date. An overview of the clinical characteristics of these mutations is provided in Table 3. Three cases from our tertiary referral center are described in detail in the Supplementary Case Description, Supplementary Table S2, and Supplementary Figures S1 and S2.

PDSS1 and PDSS2 encode a subunit of the enzyme required for synthesis of the decaprenyl tail of CoQ10 (Figure 3). Only 1 patient with a PDSS1 mutation and glomerular involvement has been reported in literature. The patient presented before the age of 6 months with nephrotic syndrome, failure to thrive, and developmental delay. She rapidly developed kidney failure and died at the age of 16 months. To date, PDSS2 mutations have been identified in 7 patients with glomerular mitochondrial cytopathies associated with CoQ10 deficiency.
with CoQ10 deficiency from 5 unrelated families. Gasser et al. showed that a PDSS2 haplotype was associated with a significantly increased risk of FSGS and collapsing glomerulopathy in European American patients. Although the number of reported patients with a PDSS2 mutation is limited, the patients
Table 3. Overview of clinical characteristics of patients with a PDSS2, COQ2, COQ6, or COQ8B/ADCK4 mutation and kidney involvement reported in literature

| Clinical characteristics | PDSS2 gene | COQ2 gene | COQ6 gene | COQ8B/ADCK4 gene |
|--------------------------|------------|-----------|-----------|------------------|
| Patients reported, n     | 7 patients | 28 patients | 26 patients | 82 patients      |
| Families reported, n     | 5 families | 23 families | 19 families | 47 families      |
| Median age of onset (range) | 6 mo (birth to 3 yr) | 9 mo (birth to 18 yr) | 2.5 yr (2 mo to 16 yr) | 12 yr (10 days to 32 yr) |
| Reported extrarenal symptoms, % of patients (proportion) | 100% (6/6) | 68% (17/25) | 90% (20/22) | 40% (26/65) |
| Kidney failure, % of patients (proportion) | 100% (3/3) | 63% (12/19) | 72% (16/22) | 73% (54/74) |
| Median age at kidney failure (range) | 8 yr (6 mo to 9 yr) | 2.1 yr (3 wk to 19 yr) | 3.2 yr (6 mo to 9 yr) | 14.9 yr (6 to 35 yr) |
| Time to kidney failure (range) | 8 yr (2 wk to 7 yr) | 5 mo (0 to 2.5 yr) | 1 yr (1 mo to 3 yr) | 1 yr (0 to 13 yr) |
| Histopathology, % of patients (proportion) | Glomerulonephritis | 100% (3/3) | 5% (1/21) | 98% (43/44) |
| | Membranoproliferative glomerulonephritis | 69% (11/16) | 86% (18/21) | 13% (8/65) |
| | FSGS | 10% (2/21) |
| | MPGN | 13% (8/5) |
| | Nephrocalcinosis | 37.5% (30/82) |
| | Dosing range | 5–20 mg/kg per day | 5–60 mg/kg per day | 20–100 mg/kg per day | 3.3–30 mg/kg per day |

| Treatment effect, % of patients (proportion) | No effect | Improvement clinical condition | Improvement neurological condition | Neurological deterioration | Improvement kidney symptoms | No effect on kidney symptoms |
|---------------------------------------------|-----------|-------------------------------|---------------------------------|--------------------------|----------------------------|-----------------------------|
| | 50% (2/4) | 50% (2/4) | 14% (2/14) | 29% (4/14) | 43% (6/14) | 29% (4/14) |
| | No effect | Improvement sensorineural deafness | 83% (5/6) | 37% (13/30) | 57% (17/30) |
| | No effect on sensorineural deafness | 17% (1/6) |

AarF, AarF Domain Containing Kinase-4; COQ2, Coenzyme Q2; COQ6, Coenzyme Q6; COQ8B, Coenzyme Q8B; (c)FSGS, (collapsing) focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; PDSS2, decaprenyl-diphosphate synthase subunit 2. Proportion in parenthesis represents the number of patients with the characteristic/total number of patients for whom this characteristic was reported in literature. Only 1 patient with a PDSS7 mutation and glomerular involvement was reported in literature and is therefore not included in Table 3. This patient is reported in Supplementary Table S1. Three patients from our clinic are described in detail in the Supplementary File, including Supplementary Case Description, Supplementary Table S2, and Supplementary Figures S1 and S2.

generally presented at a young age and rapidly developed kidney failure. Furthermore, severe extrarenal involvement was reported in these patients, resulting in a poor prognosis. Saiki et al. showed that CoQ10 supplementation rescued proteinuria and interstitial nephritis in PDSS2-deficient mice.96 In clinical practice, CoQ10 supplementation (5–20 mg/kg per day) was started in 4 patients, and 2 of them showed improvement in their clinical condition.97

COQ2 encodes the enzyme para-hydroxybenzoate-polyprenyl-transferase required for the second step of the final pathway of CoQ10 biosynthesis (Figure 3).98 Steroid-resistant nephrotic syndrome (SRNS) usually develops within the first 2 years of life and often represents the first symptom of the disease, with or without neurologic symptoms. As shown in Table 3, 12 of 19 patients showed a rapid decline in kidney function. Furthermore, 17 of 25 patients showed some degree of extrarenal involvement. Patients who presented with decreased kidney function did not show improvement of kidney function after CoQ10 supplementation. In patients presenting with nephrotic syndrome, a decrease in proteinuria may occur. Patients with severe neurological involvement showed neurological deterioration irrespective of treatment with CoQ10, even when started immediately after birth (Supplementary Table S1). As expected, no recurrence of proteinuria occurred after kidney transplantation. In contrast to other genes involved in the CoQ10 biosynthesis, there is a genotype—phenotype correlation for mutations in the COQ2 gene.99 Mutations in the COQ2 gene have been associated with a wide spectrum of phenotypes, including a rapidly fatal, neonatal onset, multisystemic disease100; SRNS, which can be associated with encephalopathy; and late-onset encephalopathy with retinopathy mimicking multiple system atrophy.8,99,101,102 As previously described by Desbats et al., patients with severe phenotypes harbored 2 alleles that significantly impaired CoQ10 production.103 In contrast, patients harboring a compound heterozygous COQ2 mutation showed a milder clinical phenotype, including a higher age of onset, less severe clinical symptoms, and absence of extrarenal manifestations.

The enzyme CoQ10 monoxygenase 6 (COQ6) is required for biosynthesis of CoQ10 and catalyzes the C5 hydroxylation step of the quinine ring (Figure 3). Ozeir et al. showed that Coq6 is not required for the C1-hydroxylation.104 As shown in Table 3, most of the...
affected children presented with SRNS and sensorineural deafness, generally at older ages than those reported for patients with COQ2 mutations.104 The effect of CoQ10 supplementation was not easy to evaluate, as most reported patients rapidly developed kidney failure. However, patients who did not rapidly develop kidney failure showed improvement of proteinuria (Table 3, Supplementary Table S1). In contrast, CoQ10 supplementation did not improve sensorineural deafness in most patients.

COQ8B/ADCK4 (AarF Domain Containing Kinase-4) interacts with components of the CoQ10 biosynthesis pathway (Figure 3).105–107 COQ8B/ADCK4 is expressed in podocytes and localized to mitochondria and foot processes.106 A total of 82 patients with a COQ8B/ADCK4 mutation and kidney involvement have been reported to date (Table 3). Symptoms typically present in puberty, and CKD was diagnosed at presentation in one-fourth of the reported patients. Moreover, 54 of 74 patients (73%) developed kidney failure, with a median time to kidney failure of 1 year. In most patients, a kidney biopsy showed FSGS. Interestingly, Park et al. reported accompanying medullary nephrocalcinosis in 6 Korean patients.108 Treatment with CoQ10 was started in less than 50% of the reported patients. In 17 of 30 patients (57%), no improvement of kidney function was seen, especially in patients who already presented with impaired kidney function. However, if started early, patients did show a decrease in proteinuria (Table 3).

**CoQ10 IN DEPTH**

Primary CoQ10 deficiency is a clinically and genetically highly variable disorder, as illustrated by the patients reported in Supplementary Table S1. Early diagnosis is crucial, as oral supplementation of CoQ10 can limit disease progression and improve clinical symptoms.

**Diagnostic Methods and Monitoring**

The diagnosis of primary CoQ10 deficiency is established with the identification of pathogenic variants in any of the genes encoding for the proteins directly involved in CoQ10 biosynthesis (Figure 3). Nowadays, genetic testing using next-generation sequencing is substantially less time intensive than a few years ago; however, because treatment should be started as early as possible, additional diagnostic tests are still indispensable to enable rapid identification of CoQ10 deficiency. Classic biochemical analyses remain important in the diagnostics of mitochondrial cytopathies. Specifically for CoQ10 deficiency, analysis of the combined activity of complex I to III and/or II and III is important. Furthermore, initial diagnostic testing should include measurement of blood lactate and alanine (as a measure of impaired energy production in skeletal muscle and long-standing pyruvate accumulation, respectively), even though normal levels do not exclude CoQ10 deficiency.109,110 In addition, assessment of CoQ10 levels may be helpful in diagnosis and follow-up. Measurement of CoQ10 in skeletal muscle is considered the gold standard test for diagnosing CoQ10 deficiency; however, with the availability of relatively rapid genetic diagnostics, muscle biopsies are not routinely performed anymore.105,111 Measurement of CoQ10 levels in skin fibroblasts may be another option in patients with a primary CoQ10 deficiency.112 Nevertheless, a less invasive screening test is desirable. CoQ10 levels can be measured in different biological specimens.113,114–116 CoQ10 levels in plasma appear to be highly dependent on dietary intake and are therefore not reflective of the levels in tissues.117 Moreover, CoQ10 levels in peripheral cells do not seem to accurately reflect the amount of CoQ10 in tissues, and the exact value of other biological specimens in the diagnostics of CoQ10 deficiency remains to be elucidated.

**Pathophysiology**

The pathogenesis of CoQ10 deficiency involves different aspects. Interestingly, variable degrees of CoQ10 deficiency appear to cause different defects of ATP synthesis and oxidative stress. Quinzii et al. show that severe CoQ10 deficiency (<20% of normal) results in significant bioenergetic defects without oxidative stress. In contrast, intermediate CoQ10 deficiency (30%–40% of normal) causes moderate bioenergetic defects but a significant increase in ROS production, indicating that residual activity of the respiratory chain is indispensable to produce ROS.118 Podocytes are known to be susceptible to oxidative damage,119 whereas impaired mitochondrial biogenesis did not result in a developmental or pathological change in podocytes.85 This supports the concept that podocytes are independent of mitochondrial ATP production but susceptible to oxidation. In line with this, Desbats et al. show that patients with a severe presentation of CoQ10 deficiency (presentation at birth with multi-organ failure) due to a COQ2 mutation harbored 2 alleles that markedly impaired CoQ10 production. In contrast, patients with a milder phenotype including isolated nephrotic syndrome had at least 1 allele that allowed significant residual CoQ10 biosynthesis for ROS production.119 Zhu et al. used a Drosophila model to investigate COQ2 nephropathy. Silencing coq2 led to abnormal localization of slit diaphragms, collapse of lacunar channels, and dysmorphic mitochondria. Furthermore, increased levels of ROS were found in this model, and dietary supplementation with CoQ10 partially rescued these defects.120 Mutations in COQ8B/ADCK4 account for the highest number of patients with kidney disease secondary to CoQ10 deficiency (Supplementary Table S1). Ashraf et al. showed that knockdown of
COQ8B/ADCK4 in zebrafish resulted in the characteristic triad of nephrotic syndrome. Moreover, COQ8B/ADCK4 is required for CoQ10 biosynthesis and mitochondrial function in podocytes. Compared to other CoQ10 biosynthesis defects, mutations in COQ8B/ADCK4 seem to result in a less severe clinical entity, with a more prominent kidney phenotype, higher age at onset of SRNS, and good patient survival owing to the lack of extrarenal manifestations. The selective glomerular phenotype of patients with COQ8B/ADCK4 mutations may be the result of relative enrichment of COQ8B/ADCK4 and lacking expression of the related protein COQ8A/ADCK3 in podocytes, whereas COQ8A/ADCK3 expression exceeds that of COQ8A/ADCK4 in most other body tissues. Ashraf et al. showed that knockdown of COQ8B/ADCK4 in podocytes reduced their migration phenotype, which could be reversed by the addition of CoQ10. The relatively mild phenotype observed in patients with COQ8B/ADCK4 defects is probably related to the fact that the encoded enzyme has a modulatory function without catalytic activity, enabling residual CoQ10 synthesis even in the complete absence of this protein. Moreover, other genes may partially compensate for the absence of COQ8A/ADCK4.

Treatment
Oral administration of CoQ10 is the treatment strategy for affected individuals with a CoQ10 deficiency. As was previously shown by Montini et al. and various other clinical reports, CoQ10 can block the progression of the disease. Although severe neurological and kidney damage cannot be reversed, treatment may also be initiated to prevent development of additional extrarenal symptoms. Different formulations of CoQ10 are available, including an oxidized form (ubiquinone), a reduced form (ubiquinol), and analogs such as idebenone. Recently, Kleiner et al. proposed that CoQ10 supplementation causes an increase in CoQ10 levels, rescuing sulfide oxidation and thereby preventing kidney failure. Unfortunately, clinical studies regarding efficacy are lacking, and the optimal dose and form of oral CoQ10 are still under debate. In the literature, the daily dose of CoQ10 ranges from 5 to 100 mg/kg (Supplementary Table S1), with most clinicians describing a dose between 30 and 50 mg/kg per day. Atmaca et al. recently published long-term follow-up results of CoQ10 supplementation in patients with a COQ8B/ADCK4 mutation, and observed maximum reduction of proteinuria at 6 months of treatment. After a median follow-up duration of 25.3 months following CoQ10 administration (20–30 mg/kg per day), proteinuria was significantly decreased, whereas kidney function was preserved. Of note, 4 of 8 reported patients received angiotensin-converting enzyme inhibitors or an angiotensin receptor blocker in addition to CoQ10, which may have contributed to the decrease in proteinuria. For patients with mutations in the COQ2 gene, however, results were less favorable. Eroglu et al. reported 4 patients of 2 different families, in which 2 patients were started on CoQ10 supplementation immediately after birth or at first presentation. Despite early treatment and an initial good response in terms of nephrotic syndrome and hyperglycemia, the patients still developed severe neurological problems and eventually died at 31 and 14 months of age, respectively.

Interestingly, 3 patients with a COQ6 mutation reported in the literature and 1 of the patients with a homozygous pathogenic COQ2 mutation from our clinic (Supplementary File) showed a response to cyclosporine therapy with regard to the nephrotic syndrome. CoQ10 deficiency can directly lead to the opening of the mitochondrial permeability transition pore (MPTP). Moreover, an increased amount of ROS can also induce mitochondrial permeability transition. Cyclosporine has the capacity to inhibit MPTP through interaction with cyclophilin D, an essential component of the MPTP, and thereby reduce permeability. In line with this, Heeringa et al. showed that incubation of COQ6 knockout podocytes with cyclosporine had a mild rescue effect. Our additional hypothesis is that the increase in ROS due to CoQ10 deficiency may have an impact on the cytoskeleton of the podocytes. Cyclosporine is known for its podocyte-stabilizing capacities and might therefore cause a partial response in these patients.

A new potential therapeutic approach was recently reported for mitochondrial dysfunction due to CoQ10 deficiency. The treatment of Coq6 knockout mice with 2,4-dihydroxybenzoic acid (4-diHB), an analog of a CoQ precursor molecule, prevented kidney dysfunction and reversed podocyte migration rate impairment. A potential role for 2,4-diHB was suggested for the treatment of CoQ10 deficiency caused by COQ8B/ADCK4 mutations as well. Moreover, Ozeir et al. demonstrated that analogs of 4-HB can bypass a deficient CoQ biosynthetic enzyme. In addition, hydroxylated analogs of 4-HB, 3,4-dihydroxybenzoic acid and/or vanillic acid were marked as a potential therapeutic intervention for CoQ10 deficiency due to a COQ6 mutation.

Currently, no curative treatment options for mitochondrial cytopathies are available, besides CoQ10 supplementation for patients with a CoQ10 deficiency. Typically, patients receive supportive treatment, and other treatment options involve dietary supplements, vitamins, and antioxidants. A 2012 Cochrane review of mitochondrial therapies has found little evidence supporting the use of any vitamin or cofactor intervention. Furthermore, there is early evidence for a
therapeutic role of L-arginine and citrulline therapy for MELAS-related strokes. The evidence supporting the use of CoQ10 in mitochondrial diseases other than primary CoQ10 is sparse.133

CONCLUSION
In this review, an overview of kidney involvement in genetic mitochondrial cytopathies is provided. Kidney manifestations reported in the setting of mitochondrial dysfunction include tubular dysfunction, interstitial nephritis, glomerular pathology, and, in rare cases, cystic disease. Special focus on CoQ10 deficiency was presented to emphasize early diagnosis of primary CoQ10 deficiency, as oral supplementation of CoQ10 may limit disease progression and improve clinical symptoms. A combination of genetic and metabolic diagnostics, including targeted whole-exome sequencing and blood lactate and alanine levels at presentation, should be performed in children with nephrotic syndrome presenting in adolescence or at a young age (<3 years) and in patients with nephrotic syndrome at any age with extrarenal symptoms. In case none of these criteria is present, we recommend awaiting steroid responsiveness for 4 weeks. In case patients do not respond to steroids after 4 weeks of treatment, we would advise performing genetic diagnostics. Moreover, starting CoQ10 treatment should be considered in expectation of the final genetic diagnosis. Lifelong CoQ10 supplementation should be considered, as sustained remission of nephrotic syndrome has been described and extrarenal symptoms may be prevented. Finally, a multidisciplinary approach is required, given the number of organs that can be involved in patients suffering from a mitochondrial cytopathy.

DISCLOSURE
All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL
Supplementary File (PDF)
Supplementary Case Description. Detailed description of 3 patients.
Supplementary References.
Table S1. Overview of patients reported in literature with a PDSS1, PDSS2, COQ2, COQ6, or COQ8B/ADCK4 mutation and glomerular involvement.

Table S2. Clinical characteristics of our 3 patients with a primary CoQ10 deficiency.

Figure S1. (A) Light microscopy image, patient 2. Many glomeruli show segmental (or sometimes global) collapse of the capillaries with epithelial hyperplasia in the Bowman space, consistent with collapsing type focal and segmental glomerulosclerosis (indicated with the arrow). There are no basement membrane abnormalities. There is tubulopathy with flattening of the cells, irregular vacuolation, and activated appearance of the nuclei, probably secondary to protein overload. Bar = 50 μm. (B) Electron microscopy patient 2. (C) Electron microscopy patient 3. Electron microscopy images for patients 2 and 3. There is extensive podocyte foot-process effacement (indicated with the arrow), and there are large areas of podocyte detachment from the glomerular basement membrane. Segmentally, accumulation of electron-lucent material in the subepithelial space was observed (indicated by the asterisks). This material sometimes appeared vaguely laminated but there was no evident organization. These findings were considered consistent with massive podocyte injury/collapsing focal and segmental glomerulosclerosis. Electron microscopy patient 2, bar = 5 μm; electron microscopy patient 3, bar = 2 μm.

Figure S2. Disease course of patient 3. In this graph the disease course of patient 3 is depicted. The patient went into remission with CsA treatment, and, after adequate CoQ10 intake was guaranteed, CsA was discontinued. CoQ10, coenzyme Q10; CsA, cyclosporine A.

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