The Kidney in Mitochondrial Diseases

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Abstract

Mitochondria are small dynamic intracellular organelles with critical roles in energy generation and other aspects of cellular homeostasis. Mitochondrial disorders, which are estimated to have a population prevalence of at least 1 in 4300, are monogenic diseases associated with dysfunction of the oxidative phosphorylation system, mitochondrial ultrastructure and dynamics, production of cofactors and vitamins, or other metabolic processes within the mitochondrion. Renal manifestations are a relatively frequent complication of mitochondrial disease and include Fanconi-type tubulopathy, chronic tubulointerstitial nephritis, steroid-resistant nephrotic syndrome, and cystic glomerular disease. Isolated kidney disease is a rare presentation of mitochondrial disease, although it does occur, particularly in some types of coenzyme Q_{10} (CoQ_{10}) deficiency. More frequently, renal involvement is part of a complex multisystemic disease. The genetics of mitochondrial disease is complex and includes mutations of the intrinsic mitochondrial DNA (mtDNA) as well as more than 300 nuclear-encoded Mendelian disorders affecting mitochondrial function. The most frequent causes of mitochondrial nephropathy are point mutations and large-scale rearrangements of the mtDNA and autosomal recessive disorders of CoQ_{10} biosynthesis. Increasingly, exome and genome sequencing of large cohorts is leading to the identification of novel genetic causes of mitochondrial kidney disease, including disorders of mtDNA maintenance, mitochondrial translation, mitochondrial dynamics, and biosynthesis of membrane lipids and iron-sulfur clusters. Diagnosis is challenging, as there may be few clues from renal or muscle biopsy and biochemical testing, and the approach to diagnosis increasingly involves genome-wide next generation sequencing.

Keywords

Mitochondria · Kidney · Mitochondrial DNA · Nuclear DNA encoding mitochondrial proteins · Oxidative phosphorylation · Coenzyme Q_{10} deficiency

Introduction

Mitochondria are small dynamic intracellular organelles that play a central role in cellular homeostasis. Their principal function is the generation of ATP through oxidative phosphorylation (OXPHOS). The OXPHOS system comprises five enzymatic complexes and two electron carriers, cytochrome *c* and coenzyme Q_{10} (CoQ_{10}). Mitochondria host several other metabolic pathways and control intracellular calcium homeostasis and the intrinsic apoptotic pathway [1, 2]. Mitochondria possess their own genome (the mitochondrial DNA, mtDNA) that is a 16,569 base pairs long circular molecule, lacks introns, and has its own genetic code (different from the universal code) for protein synthesis. However, the vast majority of genes needed for mitochondrial function are encoded in the nucleus. MtDNA is present in multiple copies per mitochondrion (and in hundreds of copies in each cell), and its transmission does not follow the laws of Mendel. Firstly, mtDNA is inherited only from the mother

(**Maternal Inheritance**). Both males and females may be affected by a mtDNA-related disorder, but only females will transmit it to their offspring. Secondly, wild type and mutant mtDNA molecules coexist in different proportions within cells of the same tissue, or within different tissues of the same individual (**Heteroplasmy**). Thirdly, mutations must affect a critical proportion of the total mtDNA in order to cause a biochemical or clinical phenotype (**Threshold Effect**). Fourthly, mtDNA molecules segregate randomly in daughter cells at cell division (**Random Drift**). Tissues with high cell turnover, such as the bone marrow, are more likely to be relatively spared because cells with higher mutation loads are cleared during proliferation. Conversely, postmitotic cells, such as neurons or renal cells, tend to accumulate mutations and are more likely to develop mitochondrial dysfunction [3].

MtDNA encodes 37 genes, including 13 OXPHOS subunits, and the 22 transfer RNAs (tRNAs) and 2 ribosomal RNAs (rRNAs) required for mitochondrial protein synthesis. OXPHOS complexes contain more than 80 subunits in total. Hundreds of other proteins are required for mtDNA maintenance, replication, transcription, and for mitochondrial protein synthesis and cofactor biosynthesis, all of which are encoded by nuclear genes, synthesized in the cytosol and then imported into mitochondria. Hence, OXPHOS biogenesis requires the coordinated action of two distinct genomes, and its dysfunction may result from mutations in either mitochondrial or nuclear genes (Fig. 1) [4].

OXPHOS dysfunction causes a wide spectrum of clinical phenotypes that may present at any age and may affect virtually any tissue, although those that rely the most on aerobic metabolism (nervous system, skeletal and cardiac muscle) are usually most severely affected. In recent years, it has become evident that renal involvement is not at all rare in these disorders.

Mitochondrial DNA Defects Associated with Kidney Disorders

Primary mtDNA defects comprise point mutations (the most frequent is the m.3243A>G in *MT-TL1*-encoding $tRNA^{Leu(UUR)}$, present in 1 in 400 of the population) and gross rearrangements (essentially deletions) which typically span from 2 to 8 kb in size [5]. Point mutations may affect the 13 structural subunits, and tRNA or rRNA genes. Mutations of tRNAs and rRNAs impair mitochondrial protein synthesis as a whole. This is true also for large deletions, since they always include at least one tRNA gene (Table 1).

Because some residual OXPHOS activity is essential for development, pathogenic mtDNA variants are usually heteroplasmic, i.e., a certain proportion of wild type mtDNA molecules are still present. Conversely, polymorphisms are usually homoplasmic (i.e., they affect all mtDNA molecules in an individual), although a few bona fide homoplasmic mtDNA-pathogenic variants causing renal dysfunction have been reported (and confirmed by subsequent reports or functional studies) such as the m.616T>C in *MT-TF* encoding $tRNA^{Phe}$ (Table 1) [4, 6].

MtDNA mutations have been associated with proximal or distal tubular dysfunction, and with glomerulopathies; more rare phenotypes are tubulointerstitial nephritis (TIN) and cystic glomerular disease (Table 1) [7]. Renal involvement can be an isolated manifestation or, more frequently, a part of a complex syndrome, affecting other tissues. The most common mtDNA-related syndromes associated with renal involvement are Kearns-Sayre (KSS) and Pearson syndromes, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), and maternally inherited diabetes and deafness (MIDD), but there are also patients whose symptoms do not fit into any of these syndromic diagnoses. In some cases, renal manifestations are the presenting symptom, and extrarenal involvement may become evident only after months or years (leading to significant diagnostic delay), and in other cases the renal disease remains the only manifestation [8, 9]. The complexity of inheritance and transmission of mtDNA explains only

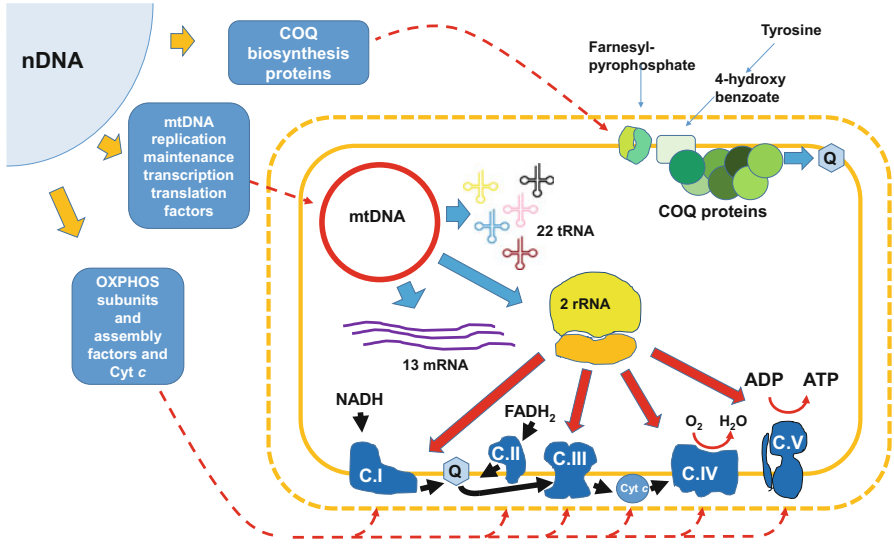

Fig. 1 Relationships between the nuclear (nDNA) and mitochondrial (mtDNA) genomes in the biogenesis of the mitochondrial oxidative phosphorylation (OXPHOS) system. mtDNA provides 13 mRNAs encoding OXPHOS structural subunits [7 of complex I (C.I), 1 of C.III, 3 of C.IV, and 2 of C.V) and the ribosomal RNA (rRNA) and transfer RNA (tRNA) molecules required for mitochondrial protein synthesis. nDNA provides more than 70 other subunits of OXPHOS complexes, as well as cytochrome *c* (Cyt *c*), assembly factors, and all other factors required for mtDNA replication, maintenance, transcription, and translation. nDNA also encodes the proteins required for Coenzyme Q_{10} (COQ, Q) biosynthesis. The black arrows depict the flow of electrons between the different complexes and electron carriers

part of the phenotypic variability. Genotype phenotype correlations are still not clearly understood. Our knowledge of the pathophysiology of these conditions is still limited, and we lack animal models for these diseases, although the recent discovery of enzymes capable of mtDNA base editing may finally allow the generation of mouse models harbouring specific mtDNA mutations [10].

The proximal and distal tubules have high energetic demands and are rich in mitochondria. Tubular involvement is observed frequently in mitochondrial disorders and is linked to ATP deficiency. Proximal tubular dysfunction may range in severity from complete Fanconi syndrome with low-molecular-weight proteinuria, to partial defects, such as isolated renal tubular acidosis, glycosuria, aminoaciduria, a Bartter-like phenotype, or even isolated hypermagnesuria. In the majority of cases, these manifestations are seen in the context of a multisystemic disorder (such as KSS). Most of these patients harbored deletions of mtDNA, more rarely point mutations such as the m.8344A>G in *MT-TK* encoding $tRNA^{Lys}$ which has been associated with aminoaciduria (Table 1) [11].

Several patients have been reported in the literature with dysfunction of the distal convoluted tubule, presenting with specific electrolyte alterations, most frequently hypomagnesaemia and hypokalemia. Again, patients displayed in most cases a multisystemic phenotype and harbored mtDNA deletions.

The glomerulus relies less on OXPHOS since anaerobic glycolysis maintains glomerular filtration independent of mitochondrial metabolism [12]. Nevertheless, glomerular involvement is often observed in MELAS and MIDD, associated with the m.3243A>G mutation [13]. Clinical manifestations may range from proteinuria, often

Table 1 Mitochondrial kidney disease: examples of molecular mechanisms

Molecular defect	Gene(s)	Inheritance	Renal manifestations	Other clinical phenotypes
mtDNA-encoded				
Large-scale rearrangements of mtDNA	Multiple	Sporadic	Fanconi-type tubulopathy, tubulointerstitial nephritis	Pearson and Kearns-Sayre syndromes, PEO
mtDNA point mutations (selected examples)	*MT-TL1*	Maternal	FSGS	MELAS, MIDD
	MT-TK	Maternal	Tubulointerstitial nephritis	MERRF
	MT-TF	Maternal/ sporadic	Tubulointerstitial nephritis	Encephalomyopathy
	MT-ND5	Maternal/ sporadic	Glomerulocystic disease	Leigh syndrome, MELAS
Nuclear-encoded				
Coenzyme Q_{10} biosynthesis	*COQ2, COQ6, COQ8B, PDSS1, PDSS2*	AR	Steroid resistant nephrotic syndrome	Seizures, ataxia, hearing loss, and multisystem disease
	COQ9	AR	Tubulopathy	Encephalomyopathy, HCM
Complex I assembly	*NDUFAF2*	AR	Renal tubular acidosis	Leigh syndrome
Complex III subunits	*UQCC2, UQCRC2*	AR	Tubular dysfunction	Neonatal lactic acidosis
Complex III assembly	*BCS1L*	AR	Proximal tubulopathy	GRACILE, encephalopathy, and hepatopathy
Complex IV assembly	*COX10*	AR	Tubulopathy	Leigh syndrome
	SURF1		Distal renal tubular acidosis	Leigh syndrome
Complex V subunit	*ATP5A1*	AR	Renal cysts	Fatal neonatal encephalopathy
Complex V assembly	*ATPAF2*	AR	Hypoplastic kidneys	Cerebral and skeletal abnormalities, lactic acidosis
	TMEM70	AR	Proximal tubulopathy	HCM, lactic acidosis, hyperammonaemia, and 3MGA
mtDNA maintenance	*RRM2B, DGUOK, TK2, SUCLA2, MPV17*	AR	Proximal tubulopathy	Mitochondrial DNA depletion syndrome (hepatocerebral, myopathic, and encephalomyopathic)
	POLG	AR	Renal tubular acidosis	Epilepsy, ataxia, and PEO
Mitochondrial tRNA aminoacylation	*SARS2*	AR	Tubulo-interstitial disease with salt wasting and hypomagnesaemia	HUPRA
Mitochondrial ribosome	*MRPS16, MRPS22, MRPS34, MRPL44*	AR	Tubulopathy	HCM, encephalomyopathy
Mitochondrial translation	*TFSM*	AR	Tubulopathy	IUGR, hepatic insufficiency, hypotonia
	RMND1	AR	End-stage kidney disease	Multisystem disease
Iron-sulfur cluster biogenesis	*NFS1*	AR	End-stage kidney disease	Multisystem disease

(continued)

Table 1 (continued)

Molecular defect	Gene(s)	Inheritance	Renal manifestations	Other clinical phenotypes
Membrane lipid remodeling	*SERAC1*	AR	Tubular dysfunction	MEGDEL
Mitochondrial homeostasis	*CLPB*	AR	Nephrocalcinosis	Cataracts, 3MGA, and multisystem disease
Mitochondrial chaperone	*TRAP1*	AR	CAKUT	VACTERL association
Other disease mechanisms	*C1QBP*	AR	Congenital nephrosis	HCM, multisystem disease

Key: 3MGA, 3-methylglutaconic aciduria; AR, autosomal recessive; CAKUT, congenital abnormalities of the kidney and urinary tract; FSGS =; GRACILE, growth retardation, amino aciduria, cholestasis, iron overload, lactic acidosis, and early death; HCM, hypertrophic cardiomyopathy; HUPRA, hyperuricaemia, pulmonary hypertension, renal failure, and alkalosis; IUGR, intrauterine growth restriction; MEGDEL, 3-methylglutaconic aciduria, deafness, and Leigh-like encephalomyopathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibres; MIDD, maternally inherited diabetes-deafness; and PEO, progressive external ophthalmoplegia

without haematuria, to overt nephrotic syndrome, with progression to renal failure. The histological picture is usually characterized by focal and segmental glomerulosclerosis. These patients are often misdiagnosed with Alport syndrome due to coexistence of sensorineural hearing loss (SNHL). However, absence of haematuria and typical histopathological features characterizing Alport syndrome facilitates ascertainment of the correct diagnosis. Other mtDNA point mutations, and occasionally deletions, may present with glomerular involvement [5]. The pathogenesis of glomerular dysfunction is still not clear. In general, defects in OXPHOS produce two major effects: a decrease in ATP production and an increase in generation of reactive oxygen species, each of which has been implicated in the pathogenesis of the renal manifestations of mitochondrial disease. In addition, defects in electron carriers such as CoQ_{10} and cytochrome *c* also affect apoptosis as they have important roles in this process by modulating the mitochondrial permeability transition pore, which acts as a gating channel for apoptosis [1, 9].

Chronic TIN is a histopathological rather than clinical diagnosis, and it is characterized by the presence of tubulointerstitial inflammatory cell infiltrates and interstitial edema. Clinically, patients present with nonspecific symptoms such as renal failure and low molecular weight proteinuria. TIN has been associated with mtDNA deletions, and with several point mutations, especially in *MT-TF*. Finally, glomerulocystic disease has been associated with a mutation in the *MT-ND5* gene (Table 1) [5].

Nuclear-Encoded Mitochondrial Kidney Disorders

Coenzyme Q_{10} Deficiencies and Related Nephropathies

Primary CoQ_{10} deficiencies are unique among mitochondrial disorders, as they are amenable to treatment with exogenous supplementation of CoQ_{10}. They therefore deserve special emphasis since early diagnosis and CoQ_{10} supplementation are essential to prevent sustained organ damage. In common with all mitochondrial diseases, this group of autosomal recessive disorders is clinically and genetically heterogeneous. Kidney involvement may be isolated or occur as part of a multisystemic disease [9]. In many affected

individuals, progressive kidney disease is characterized by proteinuria or steroid-resistant nephrotic syndrome (SRNS) with or without haematuria clinically and by focal segmental glomerulosclerosis (FSGS) lesions, particularly its collapsing variants and rarely diffuse mesangial sclerosis, histopathologically. Light microscopic findings are not specific; however, although not always visible in electron microscopy, high numbers of dysmorphic mitochondria in the cytoplasm of podocytes might be indicative of an underlying mitochondrial disease [1]. After the identification of the first link between CoQ_{10} deficiency and renal disease in the year 2000 [14], several genes involving endogenous CoQ_{10} biosynthesis including *COQ2, COQ6, COQ8B, PDSS1, PDSS2,* and *COQ9* have been discovered to cause mainly glomerular but rarely tubular disorders when mutated and altogether are responsible for 1% of SRNS (Table 1) [9, 15].

COQ2 Nephropathy

COQ2-encoding 4-para-hydroxybenzoate polyprenyltransferase, an enzyme that catalyzes the second step in the mitochondrial biosynthesis of endogenous CoQ_{10}, was the first gene defect linked to primary CoQ_{10} deficiency [16]. It is a rare disorder, with 27 patients with biallelic *COQ2* variants reported in the literature to date [17, 18]. The disease manifests with three clinical presentations: (a) isolated nephrotic syndrome, (b) cerebrorenal disease, and (c) multisystemic disease. Reported extrarenal findings include progressive ataxia, generalized amyotrophy, retinitis pigmentosa, nystagmus, bilateral SNHL, psychomotor delay or progressive psychomotor regression, optic atrophy, hypotonia, seizure, acute respiratory distress, hypertrophic cardiomyopathy, liver failure, anaemia, pancytopaenia, insulin-dependent diabetes mellitus, and metabolic acidosis [9]. Onset is usually before the age of 2.5 years, but adolescent onset SRNS has also been reported [19]. In the initial reports of COQ2 deficiency, CoQ_{10} supplementation was suggested to improve neurological symptoms but not the renal findings. However, these initial patients had advanced kidney disease at the time of commencing CoQ_{10} supplementation, and subsequent studies showed beneficial effects of CoQ_{10} supplementation on proteinuria if started immediately after onset of renal symptoms [17, 18, 20] but no improvement of progressive encephalopathy [17].

COQ6 Nephropathy

COQ6 encodes a monooxygenase enzyme that catalyzes the C5 hydroxylation step of the quinone ring during endogenous CoQ_{10} biosynthesis [9]. To date, 21 patients with biallelic *COQ6* variants have been reported. The main clinical presentation is progressive SRNS resulting in end stage kidney disease (ESKD) and SNHL. The median age of diagnosis is 1.2 (range 0.2–7) years [21]. Extrarenal findings including seizure, white matter abnormalities, ataxia, facial dysmorphism, growth retardation, muscle weakness, exotrophia, nystagmus, and bilateral optic nerve atrophy have been reported [22]. Untreated, ESKD develops between 0.4–9 years of age. Exogenous CoQ_{10} supplementation may be beneficial and should be considered for protecting renal function; however, its beneficial effect on SNHL and other extrarenal findings does not seem to be promising [9, 21].

PDSS1 and PDSS2 Nephropathies

PDSS1 encodes decaprenyl-diphosphate synthase subunit 1, which is required for the synthesis of the polyisoprenoid chain, while *PDSS2* encodes decaprenyl-diphosphate synthase subunit 2, which is required for the elongation of the prenyl side chain during biosynthesis of CoQ_{10}. These disorders are extremely rare, manifest as infantile-onset multisystemic disease, and are generally fatal despite exogenous CoQ_{10} therapy. In 2000, three siblings with similar symptoms but different degrees of severity characterized by nephrotic syndrome, ataxia, dystonia, muscle weakness, retinitis pigmentosa, SNHL, and cardiomyopathy were reported in whom *PDSS2* mutation as an underlying etiology was subsequently identified [14, 23]. Since

then, *PDSS2*-related disorders have been reported in four further patients, all with SRNS [15, 24, 25]. Associated findings in these patients include neonatal pneumonia, hypotonia, seizure, changes in the basal ganglia consistent with Leigh syndrome, encephalomyopathy, hypertrophic cardiomyopathy, SNHL, and retinitis pigmentosa. *PDSS1*-related nephropathy has been described in only one patient with infantile SRNS, developmental delay, leukoencephalopathy, lactate peak, and faltering growth [26].

COQ8B Nephropathy

COQ8B (previously known as *ADCK4*) encodes an atypical kinase that interacts with components of the CoQ_{10} biosynthesis pathway. Patients with *COQ8B* mutations have reduced cellular CoQ_{10} content [27]. Among the CoQ_{10}-related nephropathies, recessive mutations in *COQ8B* account for the highest number of patients and constitute an important differential diagnosis in adolescents with SRNS/FSGS and/or chronic kidney disease (CKD) of unknown origin [28, 29]. The renal phenotype of *COQ8B* disease is characterized by an insidious onset at adolescence with mild-to-moderate proteinuria and absence of apparent edema in the majority of cases. As a consequence of the oligosymptomatic early course, advanced CKD is often present at the time of diagnosis. Haematuria may be present at presentation in 25% of patients, and FSGS is the main histopathological diagnosis [28]. In contrast to other CoQ_{10} deficiencies, *COQ8B* disease typically manifests as an isolated nephropathy with only occasional extrarenal symptoms, which have been described in only a few patients and include seizure, intellectual impairment, defects of visual field, retinitis pigmentosa, agoraphobia, hypertrophic cardiomyopathy, autism, and pulmonary hypertension [28, 29]. Although clinical presentation is not usually seen until the adolescent period, asymptomatic proteinuria may actually be present at any age between 4.4 and 39 years [29]. *COQ8B*-related nephropathies are among the CoQ_{10} deficiencies that appear to benefit most from exogenous CoQ_{10} supplementation. In animal models, knocking out *Coq8b* resulted in reduced podocyte motility in vitro, which could be reversed by adding CoQ_{10} to the culture medium [27]. In humans, exogenous CoQ_{10} supplementation has been shown to decrease proteinuria while preserving glomerular filtration rate [27–30]. In view of its insidious nature, screening of apparently asymptomatic individuals for early diagnosis and avoidance of progressive renal disease by early initiation of CoQ_{10} treatment are recommended in families with at least one affected individual with *COQ8B* nephropathy [29, 30].

COQ9 Nephropathy

COQ9 is necessary for the stability and function of COQ7. Mutations in *COQ9* are extremely rare and have been reported in only a few individuals. Reported findings include neonatal lactic acidosis, intractable seizures, global developmental delay, microcephaly, dystonia, left ventricular hypertrophy, Leigh-like syndrome, truncal hypotonia, dysmorphic features, cardiomyopathy, tubulopathy, abnormal appearing kidneys, and cystic kidneys [9, 31]. Limited clinical benefit of exogenous CoQ_{10} supplementation was observed in these patients.

Other Nuclear-Encoded Mitochondrial Disorders Associated with Renal Involvement

Approaching 1500 nuclear-encoded proteins are needed for mitochondrial function, and more than 350 of these have now been linked to mitochondrial disease [2]. In addition to the CoQ_{10} biosynthesis disorders described above, pathogenic variants in dozens of nuclear genes have been reported to cause significant renal dysfunction, usually in the context of complex multisystem disorders presenting in childhood [32]. Renal manifestations of these gene defects include

tubulopathy, ESKD, nephrocalcinosis, and congenital kidney abnormalities. Detailed discussion of all of these gene defects is beyond the scope of this chapter, but we describe the pathological mechanisms of nuclear-encoded mitochondrial disease and some of the more common disorders linked to renal manifestations.

Disorders of OXPHOS Subunits and Assembly Factors

Mutations of nuclear-encoded structural OXPHOS proteins have rarely been reported to cause renal disease. Exceptions include two complex III subunits, UQCC2 and UQCRC2, mutations of which have been linked to tubular dysfunction and neonatal-onset lactic acidosis [33, 34]. Mutations of a complex V subunit ATP5A1 caused a fatal neonatal encephalopathy with renal cysts [35].

The complex nature of the OXPHOS enzymes means that their assembly is an intricate process involving many assembly factors. Renal tubulopathy has been documented in defects of the assembly of complexes I, III, IV, and V (Table 1). The most prevalent of these disorders is BCS1L deficiency, a disorder of complex III assembly that has been linked to a wide clinical spectrum. The most severe phenotype of BCS1L deficiency is GRACILE (Growth Retardation, Aminoaciduria, Cholestasis, Iron overload, Lactic acidosis, and Early death) syndrome, but tubulopathy is a frequent feature in patients with *BCS1L* mutations leading to other clinical presentations, typically including encephalopathy and hepatopathy [36]. Mutations of two factors needed for complex V assembly have also been reported to cause renal manifestations. An infant with ATPAF2 deficiency had hypoplastic kidneys [37], while renal involvement was present in 34% of a large cohort of children with biallelic variants in *TMEM70*, in association with neonatal onset cardiomyopathy, lactic acidosis, hyperammonaemia, and 3-methylglutaconic aciduria, with a progressive neurological course [38].

Mitochondrial DNA Maintenance Defects

Disorders of mtDNA maintenance may be divided broadly into defects of the mitochondrial replication apparatus and defects of nucleoside supply for mtDNA synthesis. Mutations of *POLG* encoding the catalytic subunit of DNA polymerase gamma, the only enzyme able to replicate mtDNA, are the most prevalent single gene cause of mitochondrial disease. *POLG* mutations result in mtDNA depletion and/or multiple mtDNA deletions and present with neurological disease, usually epilepsy, ataxia, or ophthalmoplegia but can occasionally be associated with renal tubular acidosis [39]. Two defects of mitochondrial nucleoside salvage, DGUOK and MPV17 deficiencies, cause mtDNA depletion syndromes manifesting with liver failure, encephalomyopathy, and renal tubulopathy [40, 41]. A third disorder, RRM2B deficiency, is a defect of cytosolic de novo nucleoside synthesis. Infantile-onset RRM2B deficiency now appears to be a relatively homogeneous condition with neonatal onset muscle weakness leading to feeding difficulties and respiratory failure, frequently associated with SNHL and gastro-intestinal manifestations, and with renal tubulopathy reported in 55% of cases [42].

Disorders of Mitochondrial Translation

The burgeoning group of disorders of mitochondrial gene expression, which includes defects of mitochondrial RNA modification, aminoacyl tRNA synthetases, ribosomal proteins, and translation elongation factors, is frequently accompanied by renal manifestations (Table 1). Mutations of *SARS2*, encoding the mitochondrial aminoacyl tRNA synthetase for serine, were initially linked to a syndrome of hyperuricemia, pulmonary hypertension, and renal failure in infancy with alkalosis (HUPRA) [43] but more recently have been reported to cause spastic paraparesis without renal involvement. Defects of several other mitochondrial aminoacyl tRNA synthetases are associated with tubular dysfunction, as are mutations of four

mitochondrial ribosomal proteins (Table 1). One of the most frequently reported mitochondrial translation defects resulting in ESKD is RMND1 deficiency, which initially manifests with a neonatal pseudohypoaldosteronism type picture associated with SNHL, with later progressive renal disease associated with myopathy and lactic acidosis [44].

Defects of Mitochondrial Lipid Membranes and Dynamics

Another growing subgroup of mitochondrial disorders includes defects of proteins needed for the synthesis of mitochondrial membrane lipids and for mitochondrial dynamics (fission and fusion). SERAC1 deficiency, a defect of mitochondrial membrane lipid remodelling, causes a syndrome of 3-methylglutaconic aciduria, deafness, and Leigh-like encephalomyopathy (MEGDEL). Impaired tubular function was noted in the neonatal period in 12% (8/66) of cases in one large series of patients with *SERAC1* mutations, and was a transient problem in most cases, who went on to have a progressive neurodegenerative disorder dominated by dystonia (Table 1) [45].

Disorder of Iron-Sulfur Cluster Biosynthesis

Iron-sulfur (Fe-S) clusters are essential components of several mitochondrial enzyme complexes, and numerous defects of Fe-S cluster biosynthesis have been linked to mitochondrial disease. Examples of Fe-S cluster defects associated with renal disease include NFS1 deficiency, which was reported to cause ESKD in two infants (Table 1) [46].

Other Disease Mechanisms

Novel molecular mechanisms of mitochondrial disease are increasingly recognized, and frequently associated with renal abnormalities. For example, mutations of *TRAP1*, encoding tumor necrosis factor receptor-associated protein 1, a mitochondrial chaperone, have been linked to congenital abnormalities of the kidney and urinary tract (CAKUT) and VACTERL association [47]. Deficiency of CLPB, an enzyme needed for mitochondrial homeostasis, was reported to cause cataracts, renal cysts, and nephrocalcinosis with 3-methylglutaconic aciduria [48] but has also been linked to more complex infantile onset multisystem disorders, occasionally with ESKD [49]. Mutations of *C1QBP*-encoding complement component 1 Q subcomponent-binding protein caused mitochondrial cardiomyopathy with congenital nephrosis in one case (Table 1) [50]. Other disease mechanisms associated with mitochondrial kidney disease include mitochondrial toxicity and disorders of antioxidant defense.

Approach to Diagnosis of Mitochondrial Kidney Disease

The diagnosis of these conditions remains complex. Routine renal histology is usually not specific for mitochondrial diseases. It is possible to perform histochemical studies assessing cytochrome *c* oxidase and succinate dehydrogenase activities on frozen sections, similarly to what is routinely performed on skeletal muscle samples. These tests, however, have never gained popularity, partly due to technical issues, and in part because abnormal histochemical staining patterns are often observed in acquired disorders. Electron microscopy can be useful to exclude other conditions, particularly Alport syndrome. The presence of abnormally shaped mitochondria in podocytes and/or tubular cells, or signs of mitochondrial proliferation, may provide important clues to the diagnosis [51].

Next generation sequencing has revolutionized the diagnosis of Mendelian disorders, including nuclear-encoded mitochondrial disorders. It is now possible to study panels comprising hundreds of genes in a nuclear mitochondrial gene panel, which can also be adapted to capture the mtDNA. Furthermore, reduction in costs is making the analysis of the entire exome or genome a realistic alternative in the routine diagnostic setting.

The identification of causative mtDNA mutations can be more problematic due to heteroplasmy and random drift events. However, next generation sequencing is also an attractive tool for analyzing low-level heteroplasmic mtDNA mutations. The high throughput allows great breadth of coverage (analyzing whole mtDNA genomes across multiple samples) and great depth of coverage (resolution of very low-level variants).

Analysis of DNA extracted from muscle was considered the gold standard, but it requires an invasive procedure. In recent years, analysis of DNA extracted from urinary sediment cells has become popular. It is possible to screen for mtDNA deletions and for the common point mutations, or sequence the entire mitochondrial genome.

Management and Treatment

Individuals with mitochondrial disorders should be managed by a multidisciplinary team depending on the spectrum of renal and extrarenal findings. Early diagnosis is particularly important for CoQ_{10}-related disorders as early supplementation of CoQ_{10} may prevent these individuals from progressive disease. No evidence-based study regarding dosage has been published. Therefore, CoQ_{10} has been given to patients with empirical doses 30–50 mg/kg per day [9, 20, 29, 30]. Since the bioavailability and the correlation between plasma and tissue levels of CoQ_{10} are poor, observing clinical response is the only practical method to monitor the efficacy of therapy. Regular surveillance for and supportive management of extrarenal manifestations is important; such supportive measures may include antiepileptic drugs, hearing aids, cochlear implants, brow suspension for ptosis, pacing for heart block, medical management of cardiomyopathy, blood transfusions in Pearson syndrome, hormone replacement, and appropriate nutritional support.

Cross-References

- ▶ Aminoaciduria and Glycosuria in Children
- ▶ Approach to the Child with Hematuria and/or Proteinuria
- ▶ Clinical Aspects of Genetic forms of Nephrotic Syndrome
- ▶ Congenital Abnormalities of the Kidneys
- ▶ Congenital Nephrotic Syndrome
- ▶ Ethical Issues in Pediatric Nephrology
- ▶ Genetic Bases of Nephrotic Syndrome
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- ▶ Pediatric Tubulointerstitial Nephritis
- ▶ Renal Manifestations of Metabolic Disorders in Children
- ▶ Renal Transplantation: Evaluation of Children and Donors
- ▶ Renal Tubular Acidosis

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