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Human CoQ_{10} deficiencies

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Abstract

Coenzyme Q_{10} (CoQ_{10} or ubiquinone) is a lipid-soluble component of virtually all cell membranes and has multiple metabolic functions. A major function of CoQ_{10} is to transport electrons from complexes I and II to complex III in the respiratory chain, which resides in the mitochondrial inner membrane. Deficiencies of CoQ_{10} (MIM 607426) have been associated with four major clinical phenotypes: 1) encephalomyopathy characterized by a triad of recurrent myoglobinuria, brain involvement, and ragged-red fibers; 2) infantile multisystemic disease typically with prominent nephropathy and encephalopathy; 3) cerebellar ataxia with marked cerebellar atrophy; and 4) pure myopathy. Primary CoQ_{10} deficiencies due to mutations in ubiquinone biosynthetic genes (*COQ2, PDSS1, PDSS2,* and *ADCK3* [*CABC1*]) have been identified in patients with the infantile multisystemic and cerebellar ataxic phenotypes. In contrast, secondary CoQ_{10} deficiencies, due to mutations in genes not directly related to ubiquinone biosynthesis (*APTX, ETFDH*, and *BRAF*), have been identified in patients with cerebellar ataxia, pure myopathy, and cardiofaciocutaneous syndrome. In many patients with CoQ_{10} deficiencies, the causative molecular genetic defects remain unknown; therefore, it is likely that mutations in additional genes will be identified as causes of CoQ_{10} deficiencies.

Coenzyme Q_{10} (CoQ_{10}), the predominant human form of endogenous ubiquinone, is synthesized in the mitochondrial inner membrane and is composed of a benzoquinone and a decaprenyl side chain. Whereas the quinone ring is derived from tyrosine or phenylalanine, the isoprenoid side chain is produced by addition of isopentenyl diphosphate molecules, derived from the mevalonate pathway, to farnesyl diphosphate in multiple steps catalyzed by decaprenyl diphosphate synthase. Decaprenyl diphosphate and para-hydroxybenzoate are condensed in a reaction catalyzed by PHB-polyprenyl transferase or COQ2, and the benzoate ring is then modified by at least six enzymes, which catalyze methylation, decarboxylation, and hydroxylation reactions to synthesize CoQ_{10} (Fig.1). In addition to its central role in the mitochondrial respiratory chain as the carrier of electrons from complexes I and II to complex III, CoQ_{10} participates in other cellular functions [33]. In the reduced form (ubiquinol), is one of the most potent lipophilic antioxidants in all cell membranes [4]. CoQ_{10} is also required for pyrimidine nucleoside biosynthesis and may modulate apoptosis and the mitochondrial uncoupling protein [33]. Thus, deficiency of CoQ_{10} may have multiple biochemical effects, which could produce different clinical diseases.

In fact, CoQ_{10} deficiency has been associated with four major clinical phenotypes: 1) an encephalomyopathic form, reported the first time by Ogasahara in 1989, characterized by mitochondrial myopathy, recurrent myoglobinuria and central nervous system signs, associated with decrease of complex I+III and II+III activity and CoQ_{10} in muscle [3, 6, 24, 32]; 2) a pure myopathic form, with lipid storage myopathy and respiratory chain dysfunction [9, 12, 15]; 3) a cerebellar form, with cerebellar ataxia and atrophy variably

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associated with other manifestations as neuropathy, seizures, mental retardation and muscle weakness, hypogonadism [2, 11, 16, 23]; and 4) a multisystemic infantile form [5, 18, 28, 30, 31]. Moreover, CoQ_{10} deficiency has been reported in 2 adults sisters with Leigh syndrome encephalopathy, growth retardation, infantilism, ataxia, deafness and lactic acidosis [34] and with cardiofaciocutaneous syndrome [1]. In most of these phenotypes, family history suggests an autosomal recessive mode of inheritance because siblings are often affected while parents are typically unaffected and sometimes consanguineous.

These syndromes can be also classified as primary, if associated with mutations in genes involved in the biosynthesis of CoQ_{10}; or secondary with genes not directly related to ubiquinone synthesis. Primary CoQ_{10} deficiency has been molecularly confirmed in 8 patients (6 families) with infantile-onset diseases [7] and in 11 patients (7 families) with cerebellar ataxia [14, 21] (Table). In 2006, the first missense mutation in the *COQ2* gene, encoding para-hydroxybenzoate-polyprenyl transferase, was identified in two siblings of consanguineous parents with infantile steroid-resistant nephropathy, encephalomyopathy in the older child, and deficiency of CoQ_{10} in muscle and fibroblasts [25, 31]. In 2007, Mollet and colleagues reported a homozygous base pair deletion in exon 7 of the *COQ2* gene in a patient with neonatal neurologic distress, nephrotic syndrome, hepatopathy, pancytopenia, diabetes, seizures and lactic acidosis, who died at 12 days of multiorgan failure [20]. Later that year, Diomedi-Cassadei and colleagues reported two patients with early-onset glomerular lesions that harbored mutations in the *COQ2* gene [8]. The first patient presented with steroid-resistant nephrotic syndrome at the age of 18 months as a result of collapsing glomerulopathy, with no extra-renal syntoms. The second patient presented at five days of life with oliguria, had severe extracapillary proliferation on renal biopsy, rapidly developed end-stage renal disease, and died at the age of 6 months after a course complicated by progressive epileptic encephalopathy. Combined complex II+III activity and CoQ_{10} level were decreased in renal cortex as well as skeletal muscle [8].

Moreover, mutations in the 2 subunits of PDSS, which encodes decaprenyl diphosphate synthase, the first enzyme of the CoQ_{10} biosynthetic pathway, have been reported: two non-synonymous nucleotide changes in *PDSS2* in a male infant with nephrotic syndrome and Leigh syndrome who died at age 8 months due to severe refractory focal status epilepticus [18] and a homozygous missense mutation in *PDSS1* in an consanguineous family with CoQ_{10} deficiency manifesting as a multisystem disease with early-onset deafness, encephaloneuropathy, obesity, livedo reticularis, and valvulopathy [20]. In all of the infantile multisystemic syndromes, levels of CoQ_{10} were decreased in muscle and fibroblasts.

Finally, mutations in *ADCK3* (also called *CABC1*), a mitochondrial kinase involved in ubiquinone biosynthesis [13], have been described in 11 patients from 7 families with cerebellar phenotype. All patients presented with childhood-onset cerebellar ataxia variably associated with exercise intolerance that improved with years, mild psychomotor delay and neuropathy [14, 21]. None had kidney disease. Partial CoQ_{10} deficiency was documented in muscle and in some patients' fibroblasts [14, 21].

Secondary CoQ_{10} deficiency has been genetically proven in the cerebellar and myopathic phenotypes. In 2001, Musumeci and colleagues reported for the first time 6 patients presenting with cerebellar ataxia, pyramidal signs and seizures, and low level of CoQ_{10} in muscle and fibroblasts [23]. In the 3 of those patients who were siblings, we found a homozygous W279X mutation in the *APTX* gene, encoding aprataxin, a protein involved in DNA single strand break repair and known to be cause of ataxia-oculomotor-apraxia 1 (AOA1) [22, 29].

Le Ber and colleagues confirmed that aprataxin gene mutations are associated with decreased CoQ_{10} levels in muscle and that the decrease correlates with the genotype. They noted low levels of CoQ10 in muscle from 5 unrelated patients with AOA1 and the lowest levels of CoQ10 were seen in the patients with the homozygous W279X mutation [17]. The CoQ_{10} deficiency was not correlated with duration, severity, and/or progression of the disease or with biologic measures, indicating that CoQ_{10} deficiency is not the primary or the only cause of neurological decline in AOA1; nevertheless, patients improved considerately after CoQ10 supplementation [17, 26].

In 2007, Gempel and colleagues reported mutations in the *ETFDH* (electron-transferring-flavoprotein dehydrogenase) gene, previously associated with glutaric aciduria type II, in patients with pure myopathy and CoQ_{10} deficiency [9]. In this report, all seven patients, from five families, presented with exercise intolerance, fatigue, proximal myopathy, and high serum creatine kinase (CK) and muscle histology showed lipid storage and subtle signs of mitochondrial myopathy. All of the patients showed dramatic improvements after CoQ_{10} supplementation [9]. A single patient with cardiofaciocutaneous syndrome due to a *BRAF* gene mutation also had CoQ_{10} deficiency and improvement with CoQ_{10} supplementation [1].

Despite the aforementioned advances, primary and secondary CoQ_{10} deficiencies have been defined biochemically and genetically in less than half of the reported patients and their pathogenic mechanisms remain unclear. In skeletal muscle of patients, CoQ_{10} deficiency has been associated with variable defects of the mitochondrial respiratory chain, increased apoptosis, and up-regulation of antioxidant defenses [6, 12, 18, 24, 31, 32]. By contrast, studies of cultured fibroblasts from two siblings with infantile-onset CoQ_{10}-deficiency of known genetic etiology showed mild respiratory chain defects, but no evidence of increased superoxide anions, lipid peroxidation, or apoptosis-mediated cell death [10]. Moreover, Lopez-Martin and colleagues showed that *COQ2* mutant cells require uridine to maintain growth and proposed that deficiency of CoQ_{10} caused a defect of pyrimidines biosynthesis because of the dependence of dihydro-orotate dehydrogenase on ubiquinol [19].

Thus, lack of CoQ_{10} may cause human diseases by one or multiple processes including: reduced respiratory chain activity; enhanced reactive oxygen species (ROS) production, increased ROS susceptibility, or both; or impairment of *de novo* pyrimidines synthesis. In a recent study, we investigated the consequence of severe CoQ_{10} deficiency on bioenergetics, oxidative stress, and antioxidant defenses in cultured skin fibroblasts harboring *COQ2* and *PDSS2* mutations and found that defects in the first two committed steps of the CoQ_{10} biosynthetic pathway produce different biochemical alterations, which may contribute to the clinical heterogeneity of patients. *PDSS2* mutant fibroblasts have markedly reduced CoQ_{10} (12% of normal) and CII+III activity (28% of normal) and markedly reduced ATP synthesis, but do not show increased reactive oxygen species (ROS) production, signs of oxidative stress, or increased antioxidant defense markers. In contrast, *COQ2* mutant fibroblasts have milder reductions of CoQ_{10} (30% of normal) and CII+III activity (48% of normal) with moderate defects in ATP synthesis, but significantly increased ROS production and oxidation of lipids and proteins. Curiously, in both mutant fibroblasts lines, we observed small subpopulations of cells with decreased mitochondrial membrane potential that was more prominent in cells grown in glucose-rich than galactose medium and in *COQ2* mutant than *PDSS2* mutant cells [27].

In conclusion, identification of additional disease-causing genes is necessary to further elucidate the pathogenesis of CoQ_{10} deficiencies and may lead to new insights into the biosynthesis and regulation of CoQ_{10}. Treatment response has been remarkable in most cases, highlighting the importance of an early diagnosis of these disorders.

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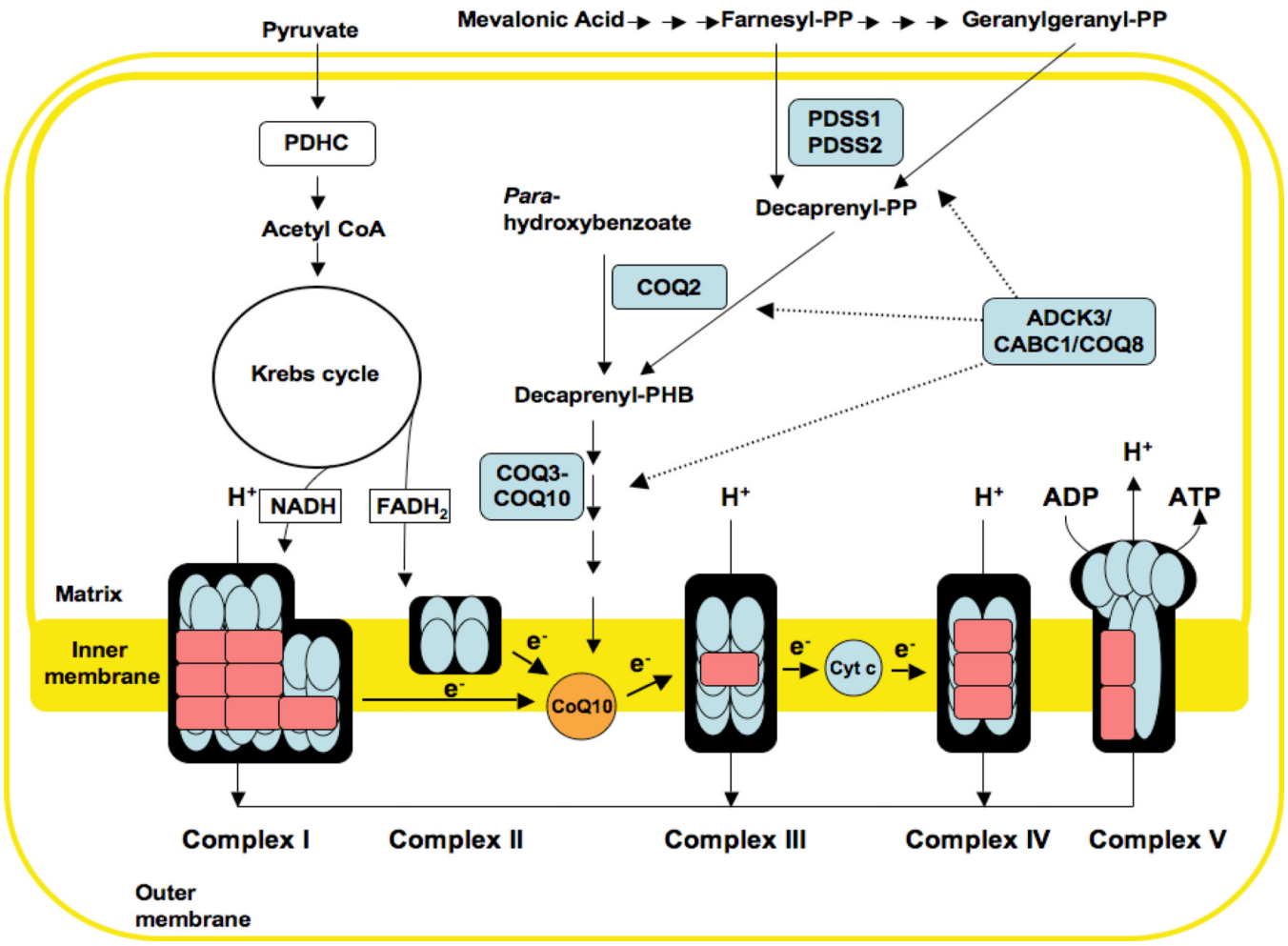

Figure.
Human CoQ_{10} biosynthesis pathway

Table

Mutations reported in genes involved in CoQ10 biosynthesis pathway

Gene	Nucleotide change	Amino acid change	Position	Reference
PDSS1	T977G	D308E	Exon 10	[20]
PDSS2	C964 T	Q322stop	Exon 6	[18]
	C1145T	S382L	Exon 8	
COQ2	G590A	R197H	Exon 4	[8, 20, 25]
	A683G	N228S	Exon 5	
	A890G	Y297C	Exon 6	
ADCK3	c.500_521delinsTTG	Q167LfsX36	Exon 3	[14, 21]
	c.636C>T	R213W	Exon 4	
	c.815G>T	G272V	Exon 6	
	c.815G>A	G272D	Exon 6	
	c.993C>T	K314_N360del	Exon 8	
	c.1398+2T>C	D420WfsX40, I467AfsX22	Intron 11	
	c.1541A>G	Y514C	Exon 13	
	c.1645G>A	G549S	Exon 14	
	c.1655G>A	E551K	Exon 14	
	c.1750_1752delACC	T584del	Exon 15	
	c.1812_1813insG	G272DfsX125	Exon 15	