

Genetics of Coenzyme Q₁₀ Deficiency

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Abstract

Coenzyme Q₁₀ (CoQ₁₀) is an essential component of eukaryotic cells and is involved in crucial biochemical reactions such as the production of ATP in the mitochondrial respiratory chain, the biosynthesis of pyrimidines, and the modulation of apoptosis. CoQ₁₀ requires at least 13 genes for its biosynthesis. Mutations in these genes cause primary CoQ₁₀ deficiency, a clinically and genetically heterogeneous disorder. To date mutations in 8 genes (*PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ6*, *ADCK3*, *ADCK4*, and *COQ9*) have been associated with CoQ₁₀ deficiency presenting with a wide variety of clinical manifestations. Onset can be at virtually any age, although pediatric forms are more common. Symptoms include those typical of respiratory chain disorders (encephalomyopathy, ataxia, lactic acidosis, deafness, retinitis pigmentosa, hypertrophic cardiomyopathy), but some (such as steroid-resistant nephrotic syndrome) are peculiar to this condition. The molecular bases of the clinical diversity of this condition are still unknown. It is of critical importance that physicians promptly recognize these disorders because most patients respond to oral administration of CoQ₁₀.

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Coenzyme Q₁₀ (CoQ₁₀) is an essential component of eukaryotic cells and participates in different crucial cellular processes. It is a co-factor of several enzymes involved in different pathways such as the mitochondrial respiratory chain, where it shuttles electrons from complexes I and II to complex III, beta oxidation of lipids and the biosynthesis of pyrimidines; it is also an important antioxidant and a regulator of the mitochondrial permeability transition pore, thereby modulating apoptosis [Trevisson et al., 2011].

CoQ₁₀ is a small lipophilic molecule composed of a quinone group joined to a polyisoprenoid tail of different length in different species, 10 units in humans (CoQ₁₀), 9 in mice (CoQ₉), 8 in *Caenorhabditis elegans* (CoQ₈), and 6 in *Saccharomyces cerevisiae* (CoQ₆) [Crane and Navas, 1997].

Biosynthesis of Coenzyme Q in Eukaryotes

Biosynthesis of CoQ

The biosynthesis of CoQ is still an incompletely characterized process which involves a large number of enzymes and takes place in different subcellular compartments.

In higher eukaryotes, the synthesis of the polyisoprenoid tail occurs mainly in the cytosol through the mevalon-

Table 1. Yeast and human genes involved in CoQ biosynthesis

Yeast	Human	Function	Notes
<i>COQ1</i>	<i>COQ1-PDSS1</i> <i>COQ1-PDSS2</i>	synthesis of polyprenyl-diphosphate	homotetramer in yeast and heterotetramer in humans
<i>COQ2</i>	<i>COQ2</i>	4HB prenyl-transferase	
<i>COQ3</i>	<i>COQ3</i>	O-methyltransferase	
<i>COQ4</i>	<i>COQ4</i>	organization of the multienzyme complex	possible role in the maturation of other COQ proteins
<i>COQ5</i>	<i>COQ5</i>	C-methyltransferase	
<i>COQ6</i>	<i>COQ6</i>	monooxygenase involved in C5-hydroxylation	
<i>COQ7</i>	<i>COQ7</i>	hydroxylase involved in C6-hydroxylation	
<i>COQ8</i>	<i>COQ8-ADCK3</i> <i>COQ8-ADCK4</i>	regulatory kinase	partially redundant function hypothesized, but precise individual roles are still unclear
<i>COQ9</i>	<i>COQ9</i>	chaperone for <i>COQ7</i> ?	
<i>COQ10</i>	<i>COQ10a</i> <i>COQ10b</i>	CoQ chaperone, not directly involved in biosynthesis	

ate pathway (which is shared by cholesterol and dolichol) [Ericsson and Dallner, 1993]. The precursor of the quinone group is 4-hydroxybenzoate (4HB, a catabolite of tyrosine), which is joined to the prenyl tail inside mitochondria. The ring is then modified by a set of enzymes that in yeast are grouped into a complex [Marbois et al., 2005]; the integrity of this complex is essential for the function of all its components. The mitochondrial reactions are thought to be the limiting steps of the biosynthetic pathway, and are catalyzed by a series of enzymes encoded by COQ genes [Tran and Clarke, 2007].

COQ Genes

These genes have been initially characterized in yeast, and subsequently their human counterparts have been identified. The nomenclature (*COQ1*, *COQ2*, *COQ3*, etc.) does not correspond to a sequential role within the biosynthetic pathway, but rather the order in which the yeast complementation groups that allowed their identification were originally classified [Tzagoloff and Dieckmann, 1990].

In humans, at least 13 genes (table 1) are involved in CoQ₁₀ biosynthesis [Trevisson et al., 2011]. In the case of *COQ1*, *COQ8* and *COQ10*, 2 human paralogues of the yeast gene exist. Only some of the COQ gene products directly catalyze the CoQ₁₀ biosynthetic reactions, others are required for the formation of the multienzymatic

complex [Casarin et al., 2008], for the transport of CoQ₁₀ and for the overall regulation of the process [Tran and Clarke, 2007].

The enzymes that catalyze at least 2 steps of the pathway are still unknown, and the sequence of reactions that generate 4HB from tyrosine is not completely clear [Ozeir et al., 2011]. Furthermore, the involvement of 3 other genes (*ADCK1*, *ADCK2* and *ADCK5*) in CoQ₁₀ biosynthesis has been postulated but not yet demonstrated.

CoQ₁₀ Deficiency

The reduction of CoQ₁₀ levels in tissues or cells is a biochemical finding first reported in 1989 [Ogasahara et al., 1989]; since then, it has been associated with a large number of different clinical phenotypes. These clinical entities can be divided into primary and secondary forms [Trevisson et al., 2011]. Primary CoQ₁₀ deficiency is caused by mutations in COQ genes, while secondary deficiencies are related to defects in genes not directly involved in CoQ₁₀ biosynthesis, or to non-genetic factors such as fibromyalgia [Cordero et al., 2009].

Primary CoQ₁₀ Deficiency

Primary CoQ₁₀ deficiency is a clinically and genetically heterogeneous disorder. To date, mutations in 8 of

Table 2. COQ genes involved in human disease

Gene	Kindreds, n	Patients, n	Clinical manifestations	Onset	Response to therapy	Mouse model
<i>PDSS1</i>	1	2	mild mental retardation, macrocephaly, mild lactic acidosis, peripheral neuropathy, livedo reticularis, optic atrophy, cardiac valvulopathy	early childhood	data not available	no
<i>PDSS2</i>	2	4	SRNS, hypotonia, Leigh syndrome, epilepsy, encephalomyopathy and ataxia, deafness, retinitis pigmentosa	neonatal to early childhood	++++	yes
<i>COQ2</i>	9	14	fatal neonatal multisystemic disorder, lactic acidosis, Leigh syndrome, seizures, hypertrophic cardiomyopathy, nystagmus, SRNS, MELAS-like encephalomyopathy, stroke-like episodes, deafness, retinitis pigmentosa, adult-onset multisystem atrophy	neonatal to 7th decade	++++	no
<i>COQ4</i>	1	1	encephalomyopathy	early childhood	++++	no
<i>COQ6</i>	5	11	SRNS, deafness, seizures	early childhood	++++	no
<i>ADCK3</i>	15	21	cerebellar ataxia, encephalopathy, seizures, dystonia, spasticity	early childhood to 2nd decade	+/-	no
<i>ADCK4</i>	7	14	SRNS, mild mental retardation	early childhood to 2nd decade	++++	no
<i>COQ9</i>	1	2	fatal neonatal multisystemic disorder, lactic acidosis, encephalomyopathy	neonatal	+	yes

these genes (table 2) have been reported, which cause a variety of clinical phenotypes ranging from fatal infantile multisystem disorders to adult onset encephalopathy. Some clinical manifestations resemble those found in other respiratory chain disorders (encephalomyopathy, ataxia, lactic acidosis, sensorineural deafness, retinitis pigmentosa, hypertrophic cardiomyopathy), while others are peculiar to CoQ₁₀ deficiency, such as steroid-resistant nephrotic syndrome (SRNS), which is rarely found in respiratory chain disorders [Emma et al., 2012].

Traditionally, primary CoQ₁₀ deficiency was associated with 4 main clinical phenotypes: encephalomyopathy, infantile multisystem disorder, an ataxic form with cerebellar atrophy, and pure myopathy [Quinzii et al., 2007]. This classical subdivision is probably now updated, since it has become clear that the phenotypic spectrum associated with COQ gene mutations is much wider. Moreover, mutations in the same gene may cause markedly different phenotypes.

Secondary CoQ₁₀ Deficiency

CoQ₁₀ deficiency may also be observed in other situations as a secondary event. In fact, there are patients who harbor defects in genes unrelated to CoQ₁₀ biosynthesis but display CoQ₁₀ deficiency in muscle or skin fibroblasts. Examples are mutations in aprataxin (*APTX*) [Quinzii et al., 2005], *BRAF* [Aeby et al., 2007] and *ETFDH* [Gempel et al., 2007], as well as many mtDNA mutations [Montero et al., 2005; Miles et al., 2008; Sacconi et al., 2010]. CoQ₁₀ deficiency has been observed in cells of patients with methylmalonic aciduria [Haas et al., 2009], but the clinical relevance of this finding is unclear. The mech-

anisms by which these genetic defects cause CoQ₁₀ deficiency are still unknown. It should be noted, however, that CoQ₁₀ deficiency is not a constant clinical feature in these patients, as there are patients with *ETFDH* or *APTX* mutations and normal CoQ₁₀ content in muscle or fibroblasts [Trevisson et al., 2011]. The biological base of this clinical variability is still unknown.

Pathogenesis of CoQ₁₀ Deficiency

The pathogenesis of CoQ₁₀ deficiency is still incompletely understood, and it is probably related to the bioenergetic defect (especially in the severe forms) but also to other physiological functions of CoQ₁₀ that are not directly linked to mitochondrial ATP synthesis. In fact, knockdown of *COQ6* in cultured podocytes causes an increase in apoptosis [Heeringa et al., 2011], while the impaired growth of CoQ₁₀-deficient fibroblasts can be rescued by uridine alone, indicating that impairment of pyrimidine metabolism (CoQ₁₀ is a cofactor of dihydroorotate dehydrogenase, an enzyme required for biosynthesis of pyrimidines) also plays a role in this disorder [Lopez-Martin et al., 2007]. The antioxidant effect of CoQ₁₀ is also important; interestingly, there is an inverse relationship between the severity of CoQ₁₀ deficiency in cultured fibroblasts and reactive oxygen species (ROS) production. Relatively mild defects (30–50% residual CoQ₁₀) are harmful to the cell because of increased ROS rather than because of a reduction in ATP production [Quinzii et al., 2010]. It should be noted that quinone analogues such as idebenone, that are good antioxidants but do not rescue mitochondrial respiration, are not effective in the treatment of this disease, indicat-

ing that both aspects (bioenergetic defect and increased ROS production) are relevant for the pathogenesis of the disorder [Lopez et al., 2010]. CoQ₁₀-deficient cells also display increased autophagy. This is likely a protective mechanism because pharmacological inhibition of CoQ₁₀ biosynthesis in cells lacking components of the autophagic pathway results in cell death [Rodriguez-Hernandez et al., 2009]. Autophagy is present also in cells with secondary CoQ₁₀ deficiency [Cotan et al., 2011].

Treatment of CoQ₁₀ Deficiency

The peculiarity of CoQ₁₀ deficiency among mitochondrial disorders is that patients respond well to oral supplementation with CoQ₁₀, making this the only currently treatable mitochondrial disorder. High-dose oral CoQ₁₀ supplementation can stop the progression of the encephalopathy [Salviati et al., 2005] and also of the renal manifestations in patients with *COQ2* [Montini et al., 2008], *COQ6* [Heeringa et al., 2011] and *ADCK4* [Ashraf et al., 2013] mutations. The muscular symptoms in the single patient with *COQ4* mutation significantly improved after CoQ₁₀ supplementation [Salviati et al., 2012] and relapsed after it was inadvertently stopped. In *ADCK3* patients the clinical response is much less striking for still unknown reasons. Data obtained from mice with *Pdss2* mutations further support the efficacy of CoQ₁₀ supplementation [Saiki et al., 2008]. Conversely, quinone analogues, such as idebenone, which are good antioxidants but do not rescue mitochondrial respiration are not effective in the treatment of this condition [Rotig et al., 2000; Lopez et al., 2010]. It is essential to start treatment as early as possible in the course of the disease, because, although it is possible to stop the progression of the disease, once damage in critical organs such as the kidney or the CNS is established, only minimal recovery is possible [Montini et al., 2008].

In 2011, it has been shown that probucol, an antioxidant and hypolipidemic drug, has beneficial effects in *Pdss2*-mutant mice [Falk et al., 2011], but no data on humans are available.

Also patients with secondary deficiencies may respond well to CoQ₁₀ supplementation, even though the response is often less striking [Trevissan et al., 2011].

Gene Mutations and Phenotypes

Below is a detailed description of the clinical phenotypes that have been associated with mutations in COQ genes. With the exception of *COQ4*, all other defects are inherited as autosomal recessive traits.

COQ1-PDSS1

Mutations in *PDSS1* have been reported in 2 siblings from a single family with mild mental retardation, macrocephaly, mild lactic acidosis, peripheral neuropathy and livedo reticularis, and optic atrophy. They also presented valvulopathy consisting of mild aortic and mitral regurgitation. One patient displayed bulimia and obesity. Apparently they did not present with nephrotic syndrome. It is not reported if they responded to CoQ₁₀ treatment [Mollet et al., 2007].

COQ1-PDSS2

Only 2 families are reported. The first patient presented with hypotonia, Leigh syndrome, epilepsy, and nephrotic syndrome. He died at 8 months of refractory status epilepticus [Lopez et al., 2006]. He did not respond to treatment. The second family was initially reported in 2000 [Rotig et al., 2000], but the actual genetic defect was reported only later [Rahman et al., 2011]. Three siblings presented with nephrotic syndrome, encephalomyopathy and ataxia, deafness, and retinitis pigmentosa. They responded well to CoQ₁₀ supplementation.

A naturally occurring mouse model with *Pdss2* defect is the *kd* mouse. It harbors a homozygous mutation in *Pdss2*, presents with a glomerulopathy that recapitulates the human disease, and responds well to CoQ₁₀ supplementation [Saiki et al., 2008]. Conditional ablation of *Pdss2* in the cerebellum causes ataxia in mice [Lu et al., 2012].

COQ2

COQ2 is the first mutated gene identified in patients with primary CoQ₁₀ deficiency [Quinzii et al., 2006]. Mutations in this gene have been reported in 14 patients from 9 different kindreds and have been associated with the widest range of clinical presentations. The most severe form is a devastating multisystemic disorder (which includes glomerular dysfunction and lactic acidosis) with onset at birth and death in the first days of life. It has been reported in 4 patients from 2 different families [Diomedici-Camassei et al., 2007; Mollet et al., 2007]. Other patients had a relatively less dramatic course with mainly encephalopathic features and death within the first 6 months of life [Jakobs et al., 2013]. Two patients did not present with SRNS, and one developed it only after the other manifestations (including a severe hypertrophic cardiomyopathy) had developed [Scalais et al., 2013], one had severe oligohydramnios, cardiomyopathy and dysmorphic features [Dinwiddie et al., 2013].

The original *COQ2* patient developed nystagmus in the first months of life, presented with SRNS at age 12 months and 6 months later developed a MELAS-like encephalopathy with stroke-like episodes and seizures, deafness and retinopathy [Salviati et al., 2005]. His sister presented only with SRNS at 12 months but was treated before she developed significant neurological manifestations [Montini et al., 2008]. Two patients presented with isolated SRNS at a later age [Diomedi-Camassei et al., 2007; McCarthy et al., 2013]. Finally, 2 siblings presented in the seventh decade of life with multisystem atrophy and retinitis pigmentosa without renal involvement [Multiple-System Atrophy Research Collaboration, 2013].

Polymorphisms in *COQ2* have been linked to multisystem atrophy, but this finding still needs to be confirmed [Multiple-System Atrophy Research Collaboration, 2013].

COQ4

A single patient with haploinsufficiency of *COQ4* was reported by our group. He had encephalomyopathic manifestations which responded to CoQ₁₀ supplementation [Salviati et al., 2012]. This is the only example of an autosomal dominant defect.

COQ6

Mutations in *COQ6* have been reported in 11 patients from 5 kindreds. The main clinical manifestations were nephrotic syndrome and deafness, but some had also encephalopathic features such as seizures [Heeringa et al., 2011]. A good response to treatment was reported in some patients.

COQ8-ADCK3

Mutations in *ADCK3* have been identified in 21 patients from 15 different kindreds [Lagier-Tourenne et al., 2008; Mollet et al., 2008; Anheim et al., 2010; Gerards et al., 2010; Horvath et al., 2012; Terracciano et al., 2012]. All presented with a predominantly ataxic phenotype with cerebellar atrophy. These manifestations are associated with other encephalopathic signs such as seizures, dystonia, spasticity, and migraine. Onset was usually during childhood, but later-onset cases were also reported [Horvath et al., 2012]. Cognitive impairment has been described in severe forms. Response to treatment is usually poor. This form is also known as autosomal recessive ataxia type 2 (ARCA2).

COQ8-ADCK4

Mutations in *ADCK4* have been identified in 14 patients from 7 kindreds presenting with SRNS [Ashraf et al., 2013]. Onset is often in the second decade. Only 1 patient, who had the earliest onset of the disease (at ~1 year of age), presented also with developmental delay. A single patient was treated with oral CoQ₁₀ and responded well to treatment.

COQ9

COQ9 mutations were reported only in 2 patients from a single kindred who presented with a severe neonatal-onset multisystem disorder with renal tubulopathy but not nephrotic syndrome.

One patient died at birth, but the other survived until 2 years of age [Rahman et al., 2001; Duncan et al., 2009]. Clinical response to CoQ₁₀ administration was partial: lactic acidosis improved, but the neurological picture was unaffected.

A knockout mouse model recapitulated the encephalopathic phenotype and did not present with renal involvement [Garcia-Corzo et al., 2013].

Conclusion

The biological basis of the different clinical presentations associated with *COQ* gene defects is still unknown. It is possible that the residual amount of CoQ₁₀ produced in the patients (a complete block of the biosynthetic pathway is embryonically lethal [Levavasseur et al., 2001; Peng et al., 2008]) may determine the clinical phenotype, but there are no comprehensive studies on this issue. Environmental factors also play an important role as demonstrated by studies performed in mice [Fernandes et al., 1978; Hallman et al., 2006].

The fact that some genes (such as *COQ6* and *ADCK4*) seem to be associated with a relatively homogeneous phenotype (SRNS) probably reflects selection bias, since the studies that led to the discovery of these 2 genes selected the patients for the presence of this particular manifestation.

The reasons of the variable response to CoQ₁₀ supplementation are also still puzzling. The reduced number of patients treated and the lack of controlled studies are critical issues, that are, however, difficult to address. The lack of an apparent clinical response in some patients is probably due to delayed institution of the treatment, when damage to critical tissues had progressed beyond the possibility of recovery [Salviati et al., 2005; Lopez et al., 2006].

To further complicate matters, not all CoQ₁₀ formulations are equally absorbed (for example, tablet preparations have a very poor bioavailability [Bhagavan et al., 2007]); therefore, it is possible that at least in some cases the lack of response could be due to the insufficient dosage administered.

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