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Primary Coenzyme Q_{10} Deficiency

Synonyms: Coenzyme Q Deficiency, CoQ Deficiency, Primary CoQ_{10} Deficiency, Ubiquinone Deficiency

Leonardo Salviati, MD, PhD,[1] Eva Trevisson, MD, PhD,[1] Mara Doimo, PhD,[1] and Placido Navas, PhD[2]

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Summary

Clinical characteristics

Primary coenzyme Q_{10} (CoQ_{10}) deficiency is usually associated with multisystem involvement, including neurologic manifestations such as fatal neonatal encephalopathy with hypotonia; a late-onset slowly progressive multiple-system atrophy-like phenotype (neurodegeneration with autonomic failure and various combinations of parkinsonism and cerebellar ataxia, and pyramidal dysfunction); and dystonia, spasticity, seizures, and intellectual disability. Steroid-resistant nephrotic syndrome (SRNS), the hallmark renal manifestation, is often the initial manifestation either as isolated renal involvement that progresses to end-stage renal disease (ESRD), or associated with encephalopathy (seizures, stroke-like episodes, severe neurologic impairment) resulting in early death. Hypertrophic cardiomyopathy (HCM), retinopathy or optic atrophy, and sensorineural hearing loss can also be seen.

Diagnosis/testing

The diagnosis of primary CoQ_{10} deficiency in a proband is established by identification of biallelic pathogenic variants in one of the nine genes encoding proteins directly involved in the synthesis of coenzyme Q_{10} or by detection of reduced levels of CoQ_{10} (ubiquinone) in skeletal muscle or reduced activities of complex I+III and II+III of the mitochondrial respiratory chain on frozen muscle homogenates.

Management

Treatment of manifestations: In individuals with primary CoQ_{10} deficiency early treatment with high-dose oral CoQ_{10} supplementation (ranging from 5 to 50 mg/kg/day) can limit disease progression and reverse some manifestations; however, established severe neurologic and/or renal damage cannot be reversed. ACE inhibitors may be used in combination with CoQ_{10} supplementation in persons with proteinuria; renal transplantation is

Author Affiliations: 1 Clinical Genetics Unit Department of Woman and Child Health University of Padova Padova, Italy; Email: leonardo.salviati@unipd.it; Email: eva.trevisson@unipd.it; Email: mara.doimo@umu.se. 2 Centro Andaluz de Biología del Desarrollo Universidad Pablo de Olavide Sevilla, Spain; Email: pnavas@upo.es.

an option for those with ESRD. Treatment of hypertrophic cardiomyopathy, retinopathy, and sensorineural hearing loss is per usual practice.

Prevention of primary manifestations: Supplementation with high-dose oral CoQ_{10} can prevent progression of the renal disease and onset of neurologic manifestations.

Surveillance: Periodic neurologic evaluation, urine analysis (for proteinuria) and renal function tests, ophthalmologic evaluation, and audiometry.

Evaluation of relatives at risk: Presymptomatic diagnosis for the purpose of early treatment with CoQ_{10} supplementation is warranted for relatives at risk.

Genetic counseling

Primary coenzyme Q_{10} deficiency is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are possible if the pathogenic variants in a family are known.

Diagnosis

Primary deficiency of coenzyme Q_{10}, a lipid component of the mitochondrial respiratory chain, is classified as a mitochondrial respiratory chain disorder [DiMauro et al 2013].

For this *GeneReview* the term "primary coenzyme Q_{10} deficiency" refers to the group of conditions characterized by a reduction of coenzyme Q_{10} (CoQ_{10}) levels in tissues or cultured cells associated with mutation of the nine genes involved in the biosynthesis of coenzyme Q_{10} (collectively called "*COQ* genes").

There are no formal diagnostic criteria for primary coenzyme Q_{10} deficiency.

Suggestive Findings

Primary coenzyme Q_{10} deficiency, which is associated with an extremely heterogeneous group of clinical manifestations, should be suspected in individuals with the following clinical findings (Table 1).

Clinical findings

- Steroid-resistant nephrotic syndrome (SRNS) without mutation of *NPHS1* (encoding nephrin) or *NPHS2* (encoding podocin), especially when accompanied by deafness, retinopathy, and/or other CNS manifestations [Emma et al 2012, Desbats et al 2015a]
- Clinical features of a mitochondrial encephalomyopathy, including neurologic findings (hypotonia, seizures, dystonia, nystagmus, cerebellar ataxia or pyramidal dysfunction, spasticity, peripheral neuropathy, and intellectual disability), myopathy, retinopathy, or optic atrophy, sensorineural hearing loss, and/or hypertrophic cardiomyopathy (Table 1).
- Unexplained ataxia (especially if family history suggests autosomal recessive inheritance) [Rahman et al 2012]
- Subacute exercise intolerance (with onset usually between ages 6 and 33 years) with proximal muscle weakness and elevated CK (≤20 times upper limit of the control range) [Rahman et al 2012]

Table 1. Clinical Manifestations Associated with Mutation of Genes Encoding Proteins Directly Involved in the Synthesis of Coenzyme Q_{10}

Gene	Clinical Manifestations					
	Renal	Heart	Eye	Hearing	Neurologic	Muscle
COQ2	SRNS	HCM	Retinopathy	SNHL	Encephalopathy [1]; seizures; other [2]	Myopathy
COQ4		Heart failure; HCM			Encephalopathy; seizures; other [3]	Myopathy
COQ6	SRNS [4]			SNHL	Encephalopathy; seizures	
COQ7					Encephalopathy; ID; peripheral neuropathy	Muscle weakness
COQ8A					Encephalopathy; cerebellar ataxia; dystonia; spasticity; seizures	Exercise intolerance
COQ8B	SRNS [4]				ID	
COQ9	Tubulopathy	HCM			Encephalopathy	Myopathy
PDSS1			Optic atrophy		Encephalopathy; peripheral neuropathy	
PDSS2	SRNS		Retinopathy	SNHL	Leigh syndrome; ataxia	

Table contents are ordered by gene.
HCM = hypertrophic cardiomyopathy; ID = intellectual disability; SNHL = sensorineural hearing loss; SRNS = steroid-resistant nephrotic syndrome
1. Encephalopathy comprises a wide spectrum of brain involvement with different clinical and neuroradiologic features, often not further explicated by the reporting authors.
2. Adult-onset multisystem atrophy-like phenotype [Desbats et al 2016]
3. Severe hypotonia, respiratory insufficiency, cerebellar hypoplasia, slowly progressive neurologic deterioration
4. Because individuals with *COQ6*- and *COQ8B*- related coenzyme Q_{10} deficiency were ascertained by the presence of SRNS, the authors cannot exclude the possibility that biallelic pathogenic variants in these two genes could also cause a broader phenotype.

Laboratory findings. Serum or plasma lactate concentration may be high in those individuals with severe neonatal onset. Of note, normal lactate levels do not exclude the possibility of coenzyme Q_{10} deficiency [Rahman et al 2012].

CSF lactate concentration may be more sensitive than serum/plasma levels, but can be normal.

Establishing the Diagnosis

The diagnosis of primary coenzyme Q_{10} deficiency in a proband **is established** by identification of biallelic pathogenic variants in one of the nine genes encoding proteins directly involved in the synthesis of coenzyme Q_{10} (Table 2).

Note: If a diagnosis of primary coenzyme Q_{10} deficiency cannot be established by molecular genetic testing, biochemical testing may be considered.

Molecular Genetic Testing

Molecular testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

Serial single-gene testing based on clinical findings (see Table 1). Sequence analysis is performed first, followed by deletion/duplication analysis if only one or no pathogenic variant is identified.

Use of a multigene panel that includes the nine genes in Table 2 and some or all of the other genes of interest may be considered; for example, genes:

- Known (or suspected) to be required for CoQ_{10} biosynthesis but not identified to date as a cause of primary CoQ_{10} deficiency (i.e., *ADCK1*, *ADCK2*, *ADCK5*, *COQ3*, *COQ10a*, *COQ10b*, *FDXR*, and *FDX2* (*FDX1L*) [Desbats et al 2015a])
- Associated with secondary deficiencies of coenzyme Q_{10} (*APTX*, *BRAF*, *ETFDH*) (See Differential Diagnosis.)
- Associated with a specific phenotype (e.g., steroid-resistant nephrotic syndrome, ataxia)

Note: (1) The choice of the specific panel depends on the phenotype observed in the patient. (2) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (3) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (4) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (5) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

More comprehensive genomic testing. Because of the large (and still growing) number of genes involved, the rarity of primary coenzyme Q_{10} deficiency, the incomplete knowledge of the coenzyme Q_{10} biosynthetic pathway, and the continuous reduction in the cost of genomic testing, exome sequencing is an alternative to the use of single-gene testing and specific multigene panels [Desbats et al 2015a, Desbats et al 2015b]. In fact, exome sequencing may also be able to detect all possible genetic causes of both primary and secondary coenzyme Q_{10} deficiency (see Differential Diagnosis).

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 2. Molecular Genetic Testing Used in Primary Coenzyme Q_{10} Deficiency

Gene [1]	Number of Families with Coenzyme Q_{10} Deficiency Attributed to Mutation of Gene	Proportion of Pathogenic Variants [2] Detected by Method	
		Sequence analysis [3]	Gene-targeted deletion/duplication analysis [4]
COQ2	10 [5]	All pathogenic variants reported to date	Unknown
COQ4	9 [6]	All pathogenic variants reported to date	Unknown [7]
COQ6	5 [8]	All pathogenic variants reported to date	Unknown
COQ7	1 [9]	All pathogenic variants reported to date	Unknown
COQ8A	14 [10]	All pathogenic variants reported to date	Unknown [11]
COQ8B	34 [12]	Most pathogenic variants reported to date	Unknown

Table 2. continued from previous page.

Gene [1]	Number of Families with Coenzyme Q_{10} Deficiency Attributed to Mutation of Gene	Proportion of Pathogenic Variants [2] Detected by Method	
		Sequence analysis [3]	Gene-targeted deletion/duplication analysis [4]
COQ9	2 [13]	All pathogenic variants reported to date	Unknown
PDSS1	2 [14]	All pathogenic variants reported to date	Unknown
PDSS2	2 [15]	All pathogenic variants reported to date	Unknown
Unknown [16]	NA	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. Quinzii et al [2006], Diomedi-Camassei et al [2007], Mollet et al [2007], Dinwiddie et al [2013], Jakobs et al [2013], McCarthy et al [2013], Mitsui et al [2013], Scalais et al [2013], Desbats et al [2015b], Desbats et al [2016]
6. Salviati et al [2012], Brea-Calvo et al [2015], Chung et al [2015]
7. To date only one individual has had a heterozygous deletion encompassing *COQ4* [Salviati et al 2012].
8. Heeringa et al [2011], Doimo et al [2014]
9. Freyer et al [2015]
10. 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], Mignot et al [2013], Blumkin et al [2014], Liu et al [2014]
11. A deletion from exon 3 to exon 15 has been described [Lagier-Tourenne et al 2008].
12. Ashraf et al [2013], Korkmaz et al [2016]
13. Duncan et al [2009], Rahman et al [2012], Danhauser et al [2016]
14. Mollet et al [2007], Vasta et al [2012]
15. Rötig et al [2000], Rahman et al [2012]
16. To date many individuals with reduced CoQ_{10} in cells or tissues lack a clear genetic diagnosis, making it impossible to distinguish between primary and secondary CoQ_{10} deficiency [Trevisson et al 2011].

Biochemical Testing

The following findings on biochemical testing can differentiate coenzyme Q_{10} deficiency from other mitochondrial disorders with similar clinical findings, but cannot differentiate primary from secondary coenzyme Q_{10} deficiency (see Differential Diagnosis).

- Reduced levels of CoQ_{10} in skeletal muscle [Montero et al 2008]. Note: While coenzyme Q_{10} measurements may be performed on cultured skin fibroblasts or blood mononuclear cells, these tissues may not be reliable in detecting secondary coenzyme Q_{10} defects [Yubero et al 2015].
- Reduced activities of complex I+III and II+III of the mitochondrial respiratory chain on frozen muscle homogenates. These enzymatic activities, which depend on endogenous coenzyme Q_{10}, are reduced in persons with a defect in CoQ_{10} even when isolated complex II and III respiratory chain activities are normal [Rahman et al 2012].

Clinical Characteristics

Clinical Description

The manifestations of primary coenzyme Q_{10} deficiency vary (Table 1). Traditionally, clinical presentations have been classified into five distinct phenotypes: encephalomyopathy, cerebellar ataxia, severe infantile multisystem disease, steroid-resistant nephrotic syndrome, and isolated myopathy [Emmanuele et al 2012]. This classification is probably now outdated because the range of clinical phenotypes is much wider, and different combinations of findings with significant overlap have been identified. Furthermore, no individuals with molecularly confirmed primary CoQ_{10} deficiency with isolated myopathy have been reported [Authors, personal observation], since most individuals reported with predominantly muscle disease have secondary coenzyme Q_{10} deficiency [Doimo et al 2014] (see Differential Diagnosis).

The broad age of onset of primary coenzyme Q_{10} deficiency is exemplified by *COQ2*-related coenzyme Q_{10} deficiency, in which onset ranges from birth to the seventh decade.

The principal clinical manifestations of primary CoQ_{10} deficiency (regardless of genetic cause) are summarized below [Desbats et al 2015a], and followed by a summary of the phenotypes of *COQ2*-, *COQ8A*-, and *COQ8B*-related CoQ_{10} deficiencies, the three most common causes of primary coenzyme Q_{10} deficiency.

Principal Clinical Manifestations

Neurologic. Central nervous system (CNS) manifestations include encephalopathy (a wide spectrum of brain involvement with different clinical and neuroradiologic features often not further specified). In some individuals encephalopathy is associated with findings on neuroimaging resembling Leigh syndrome [López et al 2006] or MELAS (with stroke-like episodes) [Salviati et al 2005]. CNS manifestations often include seizures, dystonia, spasticity, and/or intellectual disability [López et al 2006, Mollet et al 2007, Heeringa et al 2011].

The age of onset and clinical severity range from fatal neonatal encephalopathy with hypotonia [Mollet et al 2007, Jakobs et al 2013] to a late-onset slowly progressive multiple-system atrophy (MSA)-like phenotype, a neurodegenerative disorder characterized by autonomic failure associated with various combinations of parkinsonism, cerebellar ataxia, and pyramidal dysfunction. This clinical picture resembling MSA with onset in the seventh decade was reported in two multiplex families with *COQ2*-related coenzyme Q_{10} deficiency [Mitsui et al 2013].

Individuals with *COQ8A*-related coenzyme Q_{10} deficiency display progressive cerebellar atrophy and ataxia with intellectual disability and seizures [Lagier-Tourenne et al 2008, Mollet et al 2008].

Peripheral neuropathy with absent deep tendon reflexes has been reported in the two sibs with *PDSS1*-related coenzyme Q_{10} deficiency; the age at onset and frequency of this manifestation are not known.

Given the small number of affected individuals described to date, clinical data are insufficient to make any generalizations about other neurologic manifestations (e.g., dystonia, spasticity, seizures, intellectual disability).

Renal. Steroid-resistant nephrotic syndrome (SRNS), an unusual feature of mitochondrial disorders, is a hallmark of primary CoQ_{10} deficiency. If not treated with coenzyme Q_{10} (see Management), SRNS usually progresses to end-stage renal disease (ESRD).

Renal involvement usually manifests as proteinuria in infancy. Affected individuals often present initially with SRNS that leads to ESRD, followed by an encephalomyopathy with seizures and stroke-like episodes resulting in severe neurologic impairment and ultimately death [Rötig et al 2000, Salviati et al 2005, Heeringa et al 2011].

Some affected individuals manifest only SRNS with onset in the first or second decade of life and slow progression to ESRD without extrarenal manifestations.

One of the two individuals in a family with *COQ9*-related coenzyme Q_{10} deficiency manifested tubulopathy within a few hours after birth.

Cardiac. Hypertrophic cardiomyopathy (HCM) has been reported in:

- Neonatal-onset *COQ2*-related coenzyme Q_{10} deficiency [Scalais et al 2013];
- *COQ4*-related coenzyme Q_{10} deficiency manifesting as prenatal-onset HCM [Brea-Calvo et al 2015];
- *COQ9*-related coenzyme Q_{10} deficiency manifesting as neonatal-onset lactic acidosis followed by a multisystem disease that included HCM [Duncan et al 2009]. The cardiac disease worsened despite treatment with CoQ_{10}.

Ocular. Retinopathy is observed in some persons with *COQ2*-related coenzyme Q_{10} deficiency [Desbats et al 2016].

Optic atrophy is present in some individuals with *PDSS1*-related coenzyme Q_{10} deficiency [Mollet et al 2007] and *PDSS2*-related coenzyme Q_{10} deficiency [Rötig et al 2000, Rahman et al 2012]. Data regarding age of onset and course of the eye manifestations are not available.

Hearing. Sensorineural hearing loss, which is common in individuals with *COQ6*-related coenzyme Q_{10} deficiency, is also observed in some individuals with *COQ2*-related coenzyme Q_{10} deficiency [Author, personal observation].

Muscle findings include weakness and exercise intolerance. Muscle biopsy may show nonspecific signs of lipid accumulation and mitochondrial proliferation [Trevisson et al 2011, Desbats et al 2015b].

Prognosis. Data on the prognosis of primary CoQ_{10} deficiency are limited due to the small number of affected individuals reported to date. It is a progressive disorder, with variable rates of progression and tissue involvement depending on the gene that is mutated and the severity of the CoQ_{10} deficiency.

Children with severe multisystem CoQ_{10} deficiency generally die within the neonatal period or in the first year of life.

The only child reported with *COQ9*-related coenzyme Q_{10} deficiency died before age two years of a progressive multisystem disorder [Duncan et al 2009].

Of note, supplementation with high-dose oral CoQ_{10} can change the natural history of the disease by blocking progression of the renal disease and preventing the onset of neurologic manifestations in persons with biallelic pathogenic variants in *COQ2*, *COQ6*, *COQ8B*, and *PDSS2* [Montini et al 2008; Author, personal communication].

Phenotypes of *COQ2*-, *COQ8A*-, and *COQ8B*-Related Coenzyme Q_{10} Deficiency

COQ2. The findings in affected individuals from the ten families described to date differ in severity and age of onset [Mollet et al 2007, Diomedi-Camassei et al 2007, Dinwiddie et al 2013, Jakobs et al 2013, McCarthy et al 2013, Mitsui et al 2013, Scalais et al 2013, Desbats et al 2015b, Desbats et al 2016].

The main clinical features include SRNS, which can be:

- Isolated [Salviati et al 2005, Diomedi-Camassei et al 2007, McCarthy et al 2013];
- Associated with encephalomyopathy [Salviati et al 2005] or severe multiple-system disease [Diomedi-Camassei et al 2007, Mollet et al 2007, Jakobs et al 2013];

- Associated with late-onset multiple-system atrophy with retinitis pigmentosa [Mitsui et al 2013, Desbats et al 2016].

COQ8A. Affected individuals experience onset of muscle weakness and reduced exercise tolerance between ages 18 months and three years, followed by cerebellar ataxia (the predominant clinical feature) with severe cerebellar atrophy on MRI. The disease course varies, including both progressive and apparently self-limited ataxia. The ataxia may be:

- Isolated [Lagier-Tourenne et al 2008];
- Progressive with cerebellar atrophy in addition to intellectual disability, epilepsy, stroke-like episodes, and/or exercise intolerance [Auré et al 2004, Lagier-Tourenne et al 2008, Mollet et al 2008, Terracciano et al 2012].

COQ8B. Affected individuals generally manifest SRNS in the second decade, and frequently evolve to end-stage renal disease [Ashraf et al 2013, Korkmaz et al 2016]. In addition, four affected individuals were reported with mild intellectual disability, two with occasional seizures, and one with retinitis pigmentosa.

Genotype-Phenotype Correlations

To date the limited number of affected individuals reported for each related gene complicates the delineation of genotype-phenotype correlations.

The factors that determine the clinical variability observed in primary CoQ_{10} deficiency are unknown. One possibility is that the residual activity of the mutated protein modulates the phenotype; however, experimental data to evaluate this hypothesis are lacking.

Prevalence

The estimated overall incidence of primary coenzyme Q_{10} deficiency is less than 1:100,000; no precise epidemiologic data are available [Desbats et al 2015a].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *COQ2*, *COQ4*, *COQ7*, *COQ8A*, *COQ8B*, *COQ9*, *PDSS1*, or *PDSS2*.

COQ6. Heterozygous germline pathogenic variants in *COQ6* have been associated with susceptibility to schwannomatosis, a finding that has been disputed [Trevisson et al 2015].

Differential Diagnosis

Note: It is important to consider primary CoQ_{10} deficiency in individuals with the following diverse presentations because primary CoQ_{10} deficiency is potentially treatable:

- **Mitochondrial encephalomyopathies.** See Mitochondrial Disorders Overview. The clinical manifestations of mitochondrial encephalomyopathies and primary coenzyme Q_{10} deficiency can often be indistinguishable, especially in the severe phenotypes.
- **Steroid-resistant nephrotic syndrome (SRNS)** that results from mutation of other genes important for podocyte function (including *DGKE*, *LAMB2*, *NPHS1*, *NPHS2*, *PLCE1*, *PTPRO*, and WT1); clinically indistinguishable from the SRNS resulting from primary CoQ_{10} deficiency. See Genetic Steroid-Resistant Nephrotic Syndrome Overview.
- **Early onset ataxia.** See Hereditary Ataxia Overview.
- **Muscle disease/myopathy**

- **Secondary coenzymeQ_{10} deficiencies.** Disorders in which reduction in CoQ_{10} levels is caused by mutation of genes not directly related to coenzyme Q_{10} biosynthesis [Trevisson et al 2011]. Molecular genetic testing is the only way to distinguish primary coenzyme Q_{10} deficiency from secondary coenzyme Q_{10} deficiencies.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with primary coenzyme Q_{10} deficiency, the following evaluations are recommended:

- Neurologic evaluation including brain MRI
- Renal evaluation with particular attention to the presence of proteinuria
- Cardiac evaluation including echocardiography with particular attention to possible hypertrophic cardiomyopathy
- Ophthalmologic evaluation with particular attention to possible retinopathy and optic atrophy
- Audiometry with particular attention to possible sensorineural hearing loss
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Pharmacologic Treatment

Coenzyme Q_{10} supplementation. Individuals with primary CoQ_{10} deficiency may respond well to high-dose oral CoQ_{10} supplementation (ranging from 5 to 50 mg/kg/day). Soluble formulations are apparently more bioavailable [Desbats et al 2015a].

Treatment should be instituted as early as possible [Montini et al 2008] because it can limit disease progression and reverse some manifestations; however, established severe neurologic and/or renal damage cannot be reversed.

Individuals with the following genetic causes of primary CoQ_{10} deficiency apparently respond well to CoQ_{10} supplementation:

- *COQ4*-related coenzyme Q_{10} deficiency. Neurologic signs responded to CoQ_{10} supplementation in a single individual reported to date with a heterozygous deletion encompassing *COQ4* [Salviati et al 2012]; no response was observed in patients reported by Chung et al [2015].
- *COQ6*-related coenzyme Q_{10} deficiency. Homozygotes for the pathogenic variants p.Gly255Arg or p.Ala353Asp responded [Heeringa et al 2011].
- *COQ8B*-related coenzyme Q_{10} deficiency. In a patient homozygous for a truncating pathogenic variant, edema resolved and proteinuria was significantly improved.
- *PDSS2*-related coenzyme Q_{10} deficiency. The only kindred reported responded [Rötig et al 2000].

Data for response to CoQ_{10} supplementation in individuals with mutation of other genes causing primary coenzyme Q_{10} deficiency are limited or lacking:

- *COQ8A*-related coenzyme Q_{10} deficiency. While most affected individuals respond poorly to CoQ_{10} supplementation, three individuals had a favorable response: one had objective stabilization of ataxia [Lagier-Tourenne et al 2008]; one had a dramatic and long-lasting improvement of dystonia and myoclonus after six months of treatment; and in one tremor and drawing ability improved [Mignot et al 2013].

- *COQ9*-related coenzyme Q_{10} deficiency. One patient with multiple-system disease characterized by intractable seizures, developmental delay, hypertrophic cardiomyopathy, and renal tubular dysfunction did not respond to CoQ_{10} supplementation; however, this may be due to late diagnosis [Duncan et al 2009].

Ineffective treatments (or those without validated effects) for individuals with primary coenzyme Q_{10} deficiency include the following CoQ_{10} derivatives:

- Ubiquinol, the reduced form of CoQ_{10}, has recently become commercially available; however, data on the therapeutic dosage and its efficacy are still lacking.
- Short chain quinone analogs such as idebenone [Rötig et al 2000, López et al 2010] have been reported to cause clinical deterioration in individuals with CoQ_{10} deficiency [Hargreaves 2014].

Renal Disease

ACE inhibitors may be used in combination with CoQ_{10} supplementation in individuals with proteinuria [Heeringa et al 2011].

Renal transplantation is an option for those with end-stage renal disease [Salviati et al 2005].

Other

Treatment of hypertrophic cardiomyopathy, retinopathy, and sensorineural hearing loss is routine (see Hypertrophic Cardiomyopathy and Hereditary Hearing Loss and Deafness).

Prevention of Primary Manifestations

Early CoQ_{10} supplementation may prevent the onset of manifestations of primary CoQ_{10} deficiency (see Treatment of Manifestations).

Surveillance

While surveillance depends on the specific genetic defect and on the clinical manifestations (see Table 1), it should always include periodic evaluations of the following: neurologic findings, urine analysis (for proteinuria) and renal function, ophthalmologic findings, and hearing.

Note: Because cardiomyopathy to date has been found only in the most severe phenotype (i.e., neonatal onset), cardiac evaluation should be performed at the time of diagnosis, but not periodically unless cardiac involvement has been documented.

Evaluation of Relatives at Risk

Given the importance of early CoQ_{10} supplementation, it is appropriate to evaluate the sibs of a proband who has primary coenzyme Q_{10} deficiency in order to identify as early as possible those sibs who would benefit from early initiation of treatment.

- If the pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the pathogenic variants in the family are not known and the diagnosis has been established by biochemical findings, one can consider measuring CoQ_{10} levels in skin fibroblasts of at-risk sibs [Desbats et al 2015b].

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Primary coenzyme Q_{10} deficiency is generally inherited in an autosomal recessive manner.

Primary coenzyme Q_{10} deficiency associated with a *de novo* contiguous gene deletion encompassing *COQ4* was reported in one individual [Salviati et al 2012].

Risk to Family Members (Autosomal Recessive Inheritance)

Parents of a proband

- The parents of an individual with a confirmed molecular genetic diagnosis of primary coenzyme Q_{10} deficiency are obligate heterozygotes (i.e., carriers of a pathogenic variant in *COQ2*, *COQ4*, *COQ6*, *COQ7*, *COQ8A*, *COQ8B*, *COQ9*, *PDSS1*, or *PDSS2*).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with a confirmed molecular genetic diagnosis of primary coenzyme Q_{10} deficiency are obligate heterozygotes (i.e., carriers of a pathogenic variant in *COQ2*, *COQ4*, *COQ6*, *COQ7*, *COQ8A*, *COQ8B*, *COQ9*, *PDSS1*, or *PDSS2*).

Other family members. Each sib of the parents of a proband with a confirmed molecular genetic diagnosis of primary coenzyme Q_{10} deficiency is at a 50% risk of being a carrier of a pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *COQ2*, *COQ4*, *COQ6*, *COQ7*, *COQ8A*, *COQ8B*, *COQ9*, *PDSS1*, or *PDSS2* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *COQ2*, *COQ4*, *COQ6*, *COQ7*, *COQ8A*, *COQ8B*, *COQ9*, *PDSS1*, or *PDSS2* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for primary coenzyme Q_{10} deficiency are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**
  Primary coenzyme Q10 deficiency

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Primary Coenzyme Q10 Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
COQ2	4q21.23	Para-hydroxybenzoate--polyprenyltransferase, mitochondrial	COQ2 database	COQ2	COQ2
COQ4	9q34.11	Ubiquinone biosynthesis protein COQ4 homolog, mitochondrial		COQ4	COQ4
COQ6	14q24.3	Ubiquinone biosynthesis monooxygenase COQ6, mitochondrial		COQ6	COQ6
COQ7	16p12.3	5-demethoxyubiquinone hydroxylase, mitochondrial		COQ7	COQ7
COQ8A	1q42.13	Atypical kinase ADCK3, mitochondrial	ADCK3 database	COQ8A	COQ8A
COQ8B	19q13.2	Atypical kinase COQ8B, mitochondrial		COQ8B	COQ8B

Table A. continued from previous page.

COQ9	16q21	Ubiquinone biosynthesis protein COQ9, mitochondrial	COQ9 database	COQ9	COQ9
PDSS1	10p12.1	All trans-polyprenyl-diphosphate synthase PDSS1	PDSS1 database	PDSS1	PDSS1
PDSS2	6q21	All trans-polyprenyl-diphosphate synthase PDSS2	PDSS2 database	PDSS2	PDSS2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Primary Coenzyme Q10 Deficiency (View All in OMIM)

601683	COENZYME Q7, HYDROXYLASE; COQ7
606980	COENZYME Q8A; COQ8A
607426	COENZYME Q10 DEFICIENCY, PRIMARY, 1; COQ10D1
607429	PRENYL DIPHOSPHATE SYNTHASE, SUBUNIT 1; PDSS1
609825	COENZYME Q2, POLYPRENYLTRANSFERASE; COQ2
610564	PRENYL DIPHOSPHATE SYNTHASE, SUBUNIT 2; PDSS2
612016	COENZYME Q10 DEFICIENCY, PRIMARY, 4; COQ10D4
612837	COENZYME 9; COQ9
612898	COENZYME Q4; COQ4
614647	COENZYME Q6, MONOOXYGENASE; COQ6
614650	COENZYME Q10 DEFICIENCY, PRIMARY, 6; COQ10D6
614651	COENZYME Q10 DEFICIENCY, PRIMARY, 2; COQ10D2
614652	COENZYME Q10 DEFICIENCY, PRIMARY, 3; COQ10D3
614654	COENZYME Q10 DEFICIENCY, PRIMARY, 5; COQ10D5
615567	COENZYME Q8B; COQ8B
616276	COENZYME Q10 DEFICIENCY, PRIMARY, 7; COQ10D7
616733	COENZYME Q10 DEFICIENCY, PRIMARY, 8; COQ10D8

Molecular Pathogenesis

The pathogenesis of primary CoQ_{10} deficiency is still not clear and the molecular basis of the locus heterogeneity of this group of disorders remains to be elucidated. Although the bioenergetic defect plays a crucial role in the pathophysiology of CoQ_{10} deficiency, CoQ_{10} carries out a number of fundamental functions in cells (it is a cofactor of other mitochondrial dehydrogenases, an essential antioxidant, and a modulator of apoptosis), suggesting that other mechanisms are involved.

In fact, it has been shown in cells that severe CoQ_{10} deficiency causes a marked reduction in ATP production without increased production of reactive oxygen species (ROS), while mild CoQ_{10} deficiency is associated with high ROS production without significant impairment of cellular bioenergetics [Quinzii et al 2010].

In addition, CoQ_{10} deficiency impairs *de novo* pyrimidine synthesis, further contributing to disease pathogenesis [López-Martín et al 2007].

Note: In this section the genes associated with primary CoQ_{10} deficiency are ordered by gene.

COQ2

Gene structure. *COQ2* consists of seven exons [Forsgren et al 2004]. The open reading frame contains four in-frame ATG initiation codons (termed ATG1-4 [López-Martín et al 2007]); the third one produces a transcript similar to yeast *COQ2.* Human *COQ2* cDNA originating from ATG1, ATG2, and ATG3 (but not from ATG4) can complement the defective respiratory phenotype of yeast *COQ2*-null strains [Forsgren et al 2004, López-Martín et al 2007, Mollet et al 2007].

Note: The presence of multiple possible initiation codons has generated confusion in naming *COQ2* pathogenic variants. The majority of reports consider the most 5' ATG (ATG1) as the initiation codon and the longer transcript NM_015697.7 as reference. *GeneReviews* adheres to this nomenclature. However, changes to this convention are possible; it was recently proposed to transition from legacy nomenclature to nucleotide 1 corresponding to the A of ATG4 [Desbats et al 2016].

Benign variants. Multiple rare benign *COQ2* variants have recently been associated with sporadic multiple-system atrophy [Mitsui et al 2013]; however, this finding is still under debate and further confirmation is needed [Mitsui et al 2013, Jeon et al 2014, Schottlaender & Houlden 2014, Sharma et al 2014].

The p.Val393Ala *COQ2* variant, which is relatively common in the Japanese population, has not been found in European or North American populations.

Pathogenic variants. *COQ2* was the first gene found to be mutated in individuals with primary CoQ_{10} deficiency [Quinzii et al 2006]. *COQ2* pathogenic variants include mainly missense alleles; truncating variants have also been reported (Table 3).

To date *COQ2* pathogenic variants have been reported in ten families with primary CoQ_{10} deficiency [Quinzii et al 2006, Diomedi-Camassei et al 2007, Mollet et al 2007, Dinwiddie et al 2013, Jakobs et al 2013, McCarthy et al 2013, Mitsui et al 2013, Scalais et al 2013, Desbats et al 2015b, Desbats et al 2016].

Table 3. Selected Pathogenic *COQ2* Variants that Cause Primary CoQ_{10} Deficiency

DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Reference Sequences
c.382A>G (232A>G)	p.Met128Val (Met78Val)	NM_015697.7 NP_056512.5
c.437G>A	p.Ser146Asn	
c.545T>G	p.Met182Arg	
c.590G>A	p.Arg197His	
c.683A>G	p.Asn228Ser	
c.890A>G	p.Tyr297Cys	
c.905C>T	p.Ala302Val	
c.1159C>T	p.Arg387Ter	
c.1197delT (1198delT)	p.Asn401IlefsTer15	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. *COQ2* encodes a 421-amino acid para-hydroxybenzoate:polyprenyltransferase (NP_056512.5) required for the second step of the final reaction sequence of CoQ biosynthesis. COQ2 catalyzes

the condensation of 4-hydroxybenzoate with polyprenyl-pyrophosphate, generating the first membrane-bound CoQ intermediate [Ashby et al 1992].

The COQ2 enzyme is highly conserved throughout evolution. The human protein contains a N-terminal mitochondrial leader sequence, two conserved putative substrate-binding domains (which are rich in aspartic acid residues) and six predicted trans-membrane helices [Forsgren et al 2004].

For information on yeast studies, see Coenzyme Q_{10} Deficiency – Model Organisms, ***COQ2***.

Abnormal gene product. All coenzyme Q_{10} deficiency-related *COQ2* pathogenic variants reported to date act through a loss-of-function mechanism, reducing the polyprenyl-transferase activity, as proved by the lack of complementation in yeast strains harboring deletion in the *COQ2* ortholog [Mollet et al 2007] or by a reduced incorporation of radiolabeled substrates into CoQ_{10} [Quinzii et al 2006]. Although genotype-phenotype correlations are still unclear, most *COQ2* pathogenic variants behave as hypomorphic alleles, retaining residual activity that may contribute to the phenotype.

All known *COQ2* pathogenic variants affect highly conserved amino acid residues. The variant c.890A>G changes a highly conserved tyrosine to cysteine at amino acid 297 within the third predicted transmembrane domain. Variants p.Ser146Asn and p.Arg197His are located in the putative substrate-binding site (UbiA), whereas p.Asn228Ser is located in the first putative transmembrane domain.

COQ4

Gene structure. *COQ4* spans a region of about 12 kb and has two transcript variants (details in Table A, **Gene**, *COQ4*). The longer transcript NM_016035.4 has seven exons. An alternate transcript (NM_001305942.1) is shorter and has four exons.

COQ4 is ubiquitously expressed, with higher levels in liver, lung, and pancreas [Casarin et al 2008].

Pathogenic variants. *COQ4* pathogenic variants have been reported in eleven affected individuals from eight unrelated families [Brea-Calvo et al 2015, Chung et al 2015].

A patient with haploinsufficiency of *COQ4* due to a *de novo* 3.9-Mb deletion of chromosome 9q34 and documented CoQ_{10} deficiency in fibroblasts had encephalomyopathic manifestations [Salviati et al 2012].

Table 4. Selected Pathogeneic *COQ4* Variants that Cause Primary CoQ_{10} Deficiency

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.155T>C	p.Leu52Ser	NM_016035.4 NP_057119.2
c.190C>T	p.Pro64Ser	
c.421C>T	p.Arg141Ter	
c.433C>G	p.Arg145Gly	
c.521_523delCCA	p.Thr174del	
c.718C>T	p.Arg240Cys	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
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Normal gene product. *COQ4* transcript NM_016035.4 encodes coq4 isoform 1, which consists of 265 amino acids, localizes to mitochondria, and is required for CoQ_{10} biosynthesis since it efficiently restores both growth in glycerol and CoQ content when expressed in a *COQ4*-null yeast strain.

An alternate transcript (NM_001305942.1) encodes coq4 isoform 2, which has 100 amino acids and unknown function; it lacks the first 24 amino acids that specify the predicted mitochondrial targeting sequence [Casarin et al 2008].

The precise function of ubiquinone biosynthesis protein COQ4 in CoQ_{10} biosynthesis is still unknown: the protein lacks enzymatic activity but in yeast it is thought to organize proteins encoded by other genes involved in the synthesis of CoQ_{10} into a multi-enzymatic complex [Marbois et al 2009].

Abnormal gene product. Missense *COQ4* pathogenic variants expressed in yeast failed to complement a $COQ4^{null}$ yeast strain [Brea-Calvo et al 2015].

COQ6

Gene structure. *COQ6* transcript variant 1 has 12 exons.

Among the 18 putative isoforms resulting from alternative splicing, two full-length transcript variants NM_182476.2 and NM_182480.2 (designated transcript variants 1 and 2, respectively) were found to be expressed in several tissues including kidney; however, the longer transcript variant 1 is more abundant than variant 2. The two isoforms differ in the use of alternative exon 1a or 1b and the splicing of exon 3 (absent in isoform *b*) [Heeringa et al 2011, Doimo et al 2014] (see details in Table A, **Gene**, *COQ6*).

Pathogenic variants. Two homozygous pathogenic missense variants, c.763G>A and c.1058C>A, and two heterozygous pathogenic nonsense variants, c.1341G>A and c.1383delG, were found in four different families with steroid-resistant nephrotic syndrome (SRNS) [Heeringa et al 2011].

Variant c.763G>A was found in one family from northern Lebanon and one from southern Turkey, suggesting a possible founder effect [Heeringa et al 2011].

Two pathogenic nonsense variants, c.484C>T and c.564G>A, were found as single heterozygous pathogenic variants in two individuals with cyclosporine A-dependent nephrotic syndrome and diffuse mesangial sclerosis, respectively [Heeringa et al 2011].

The pathogenic missense variant c.1235A>G was found in the heterozygous state in another individual with SRNS [Doimo et al 2014].

Table 5. Selected Pathogenic *COQ6* Variants that Cause Primary CoQ_{10} Deficiency

DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Reference Sequences
c.484C>T	p.Arg162Ter	NM_182476.2 NP_872282.1
c.564G>A	p.Trp188Ter	
c.763G>A	p.Gly255Arg	
c.1058C>A	p.Ala353Asp	
c.1235A>G	p.Tyr412Cys	
c.1341G>A	p.Trp447Ter	
c.1383delG	p.Ile462LeufsTer18 (Gln461fsTer478)	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. COQ6 protein is a flavin-dependent monooxygenase involved in CoQ_{10} synthesis [Ozeir et al 2011]. *COQ6* transcript variant 1 encodes isoform *a* (NP_872282.1), a 468-amino acid protein (54 kd) containing a mitochondrial import sequence. Transcript variant 2 encodes isoform *b* (NP_872286.2), a 443-amino acid protein (51 kd).

The human COQ6 isoform *a* localizes to mitochondria when overexpressed in several cell lines including podocytes. Under endogenous conditions it is expressed in glomeruli but not in tubules and localizes within cellular processes and Golgi apparatus [Heeringa et al 2011].

A pathogenic variant that reduced COQ6 expression (knockdown) in podocytes caused mitochondrial depolarization and increased the apoptotic rate through the intrinsic pathway, leading to growth defect. This phenotype was rescued by treating cells with CoQ_{10} [Heeringa et al 2011].

For information on yeast studies, see Coenzyme Q_{10} Deficiency – Model Organisms, ***COQ6***.

Abnormal gene product. Alleles p.Trp447Ter, p.Gly255Arg, and p.Tyr412Cys did not rescue the respiratory deficiency of the *COQ6*-null yeast strain as did the wild-type, and p.Ala353Asp, and p.Ile462LeufsTer18 [Doimo et al 2014]. However, in vitro experiments suggest that all the alleles, with the exception of the nonsense allele p.Trp447Ter, are thought to be hypomorphic, because modeling of the human pathogenic variant on the correspondent yeast amino acid residue did not completely abolish the respiratory growth of the yeast strain. Finally, the phenotype of yeast expressing the human pathogenic alleles recovers after addition of vanillic acid or 3,4 dihydroxybenzoic acid [Doimo et al 2014].

The pathogenic variants p.Tyr412Cys and p.Ala353Asp affect an amino acid located at the flavin adenine dinucleotide (FAD) binding domain and may negatively interfere with COQ6 binding to FAD. The p.Gly255Arg variant, which affects a residue located in the active site pocket, and the p.Trp447Ter and p.Ile462LeufsTer18 variants, affecting residues located at the C-terminal tail, may cause perturbation of the active site [Doimo et al 2014].

COQ7

Gene structure. *COQ7* has two transcript variants each comprising six exons. They differ in the first exon; the longer transcript (NM_016138.4) encodes a 217-amino acid long protein (NP_057222.2), whereas the shorter transcript (NM_001190983.1) uses an alternate 5' exon, resulting in a downstream AUG start codon with a shorter N-terminus resulting in a 170-amino acid protein (NP_001177912.1). See Table A, **Gene**, *COQ7* for a detailed summary of gene and protein information.

Pathogenic variants. A single affected individual born to consanguineous parents has been reported to date [Freyer et al 2015] harboring a homozygous c.422T>A missense variant. The patient manifested mild learning disabilities, muscular hypotonia, and hearing and visual impairment.

Table 6. Selected Pathogenic *COQ7* Variants that Cause Primary CoQ_{10} Deficiency

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.422T>A	p.Val141Glu	NM_016138.4 NP_057222.2

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. COQ7 is a mitochondrial di-iron oxidase responsible for the penultimate step of CoQ synthesis, hydroxylating 5-demethoxyubiquinol (DMQH2) in the presence of NADH.

Abnormal gene product. The variant p.Val141Glu likely affects enzymatic function by impairing iron binding. Of note, supplementation of fibroblasts from the affected individual with 2,4-dihydroxybenzoic acid resulted in increased CoQ_{10} content and restored the combined activities of Complex I+III and II+III [Freyer et al 2015].

COQ8A

Gene structure. *COQ8A* (previous symbols: *ADCK3*, *COQ8*, *CABC1*) comprises 15 exons. Alternatively spliced transcript variants have been found; however, their full-length nature has not been determined. The gene is ubiquitously expressed, with greater abundance in heart and skeletal muscle [Iiizumi et al 2002].

Pathogenic variants. *COQ8A* pathogenic variants causing autosomal recessive ataxia associated with CoQ deficiency have been described extensively [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, Mignot et al 2013, Blumkin et al 2014, Liu et al 2014, Barca et al 2016, Hikmat et al 2016].

More than 20 pathogenic variants have been reported, including missense, nonsense, and frameshift variants and a multiexon deletion (from exon 3 to exon 15).

To date all pathogenic variants reported are private and no founder effect has been identified.

Table 7. Selected Pathogenic *COQ8A* Variants that Cause Primary CoQ_{10} Deficiency

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.637C>T (636C>T)	p.Arg213Trp	NM_020247.4 NP_064632.2
c.811C>T	p.Arg271Cys	
c.815G>A	p.Gly272Asp	
c.815G>T	p.Gly272Val	
c.895C>T	p.Arg299Trp	
c.993C>T [2]	p.Leu314_Gln360del	
c.1042C>T	p.Arg348Ter	
c.1081-1_1082dupGTA	--	
c.1136T>A	p.Leu379Ter	
c.1398+2T>C [3]		
c.1523T>C	p.Phe508Ser	
c.1541A>G	p.Tyr514Cys	
c.1645G>A	p.Gly549Ser	
c.1651G>A (1655G>A)	p.Glu551Lys	
c.1750_1752delACC	p.Thr584del	
c.1813dupG (1812_1813insG)	p.Glu605GlyfsTer125	
c.1844dupG (1844_1845insG)	p.Ser616LeufsTer114	
c.1844G>A	p.Gly615Asp	

Table 7. continued from previous page.

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
g.227150977_227195656del44680 [4]		NC_000001.10_ [5]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions
2. Causes the skipping of exon 8 leading to an in-frame deletion of 47 amino acids (p.Lys314_Gln360del) [Lagier-Tourenne et al 2008]
3. Results in the formation of at least two different abnormal splicing variants [Lagier-Tourenne et al 2008]
4. Mignot et al [2013]; 29-kb deletion of exons 3 to 15 (hg19)
5. Genome assembly hg19

Normal gene product. *COQ8A* encodes a 647-amino acid protein that belongs to the UbiB protein kinase-like family and contains the conserved kinase motif in the region responsible for ATP binding and phosphotransfer reaction, but lacks the conserved kinase C-term motif. Moreover, it presents an N-terminal domain that is absent in the other proteins of the kinase family and it appears to be specifically related to ubiquinone metabolism [Stefely et al 2015].

In humans there are five paralogs belonging to the aarF domain-containing protein kinase (ADCK1-5); among them, COQ8A and COQ8B are highly similar and both are involved in CoQ_{10} biosynthesis [Lagier-Tourenne et al 2008, Ashraf et al 2013]. COQ8A localizes in mitochondria.

Computational and in vitro analyses prove that COQ8A forms homodimers after dimerization at the level of the transmembrane alpha-helices [Khadria et al 2014] and that the kinase motif displays magnesium (Mg(2+))-dependent ATPase activity [Wheeler & Jia 2015].

For information on yeast studies, see Coenzyme Q_{10} Deficiency – Model Organisms, ***COQ8A***.

Abnormal gene product. The variants p.Arg213Trp, p.Gly272Val, p.Gly272Asp, and p.Glu551Lys predict changes in highly conserved amino acids of the protein, although none are in the kinase motifs [Mollet et al 2008].

The p.Tyr514Cys allele affects a residue proximal to the aspartates that bind the magnesium ions chelated by ATP [Lagier-Tourenne et al 2008].

The 1-bp frameshift insertion c.1813dupG results in the formation of a longer abnormal product (728 amino acids) and it is thought to modify an important domain of the protein altering the putative interaction or regulation between COQ8A and COQ9 [Mollet et al 2008].

The homozygous frameshift pathogenic variant p.Ser616LeufsTer114 causes the loss of the stop codon, leading to a 81-amino acid longer protein. The patient had significant CoQ_{10} deficiency and reduced mitochondrial respiratory chain enzyme activity.

The two pathogenic nonsense variants p.Arg348Ter and p.Leu379Ter cause a premature stop codon that triggers nonsense-mediated mRNA decay, leading to complete absence of functional COQ8A protein. Due to its regulatory role and to the presence of at least another ADCK protein with similar function (although patients with mutation of *COQ8A* do not have COQ8B up-regulation), the complete lack of residual functional protein is compatible with life [Gerards et al 2010].

The c.1081-1_1082dupGTA pathogenic variant does not alter the splicing of the transcript but causes insertion of three nucleotides, resulting in a stop codon [Mignot et al 2013].

The p.Phe508Ser variant is localized in one motif of the kinase domain [Mignot et al 2013].

The p.Gly549Ser and p.Gly615Asp pathogenic variants are in the C-terminal domain common to *COQ8A* and *COQ8B* [Lagier-Tourenne et al 2008, Mignot et al 2013].

COQ8B

Gene structure. *COQ8B* spans 12 kb. Among the hypothetic 17 putative alternative splicing variants, the longest transcript NM_024876.3 contains 15 exons; exon 1 is noncoding [Ashraf et al 2013].

Pathogenic variants. Recessive loss-of-function pathogenic variants in *COQ8B* have been described in patients with steroid-responsive nephrotic syndrome (SRNS) associated with primary CoQ_{10} deficiency [Ashraf et al 2013].

Table 8. Selected Pathogenic *COQ8B* Variants that Cause Primary CoQ_{10} Deficiency

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.101G>A	p.Trp34Ter	NM_024876.3 NP_079152.3
c.532C>T	p.Arg178Trp	
c.645delT	p.Phe214LeufsTer14	
c.857A>G	p.Asp286Gly	
c.954_956dup	p.Thr319dup	
c.958C>T	p.Arg320Trp	
c.1027C>T	p.Arg343Trp	
c.1199dupA	p.His400AsnfsTer11	
c.1356_1362delGGGCCCT	p.Gln452HisfsTer261	
c.1430G>A	p.Arg477Gln	
c.1447G>T	p.Glu483Ter	

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Normal gene product. Transcript variant NM_024876.3 encodes isoform *a*, which is a 60.1-kd protein that contains a helical domain, an ABC1 domain, and a kinase domain [Ashraf et al 2013]. COQ8B is one of the five ADCK paralogs and is highly similar to COQ8A, a putative kinase involved in CoQ_{10} biosynthesis [Lagier-Tourenne et al 2008]. It is conserved in several species and displays high sequence similarity with *S. cerevisiae* Coq8/Abc1 protein [Ashraf et al 2013].

In humans, COQ8A expression exceeds COQ8B in several tissues with the exception of kidney. COQ8B is highly expressed in podocyte cell bodies and primary processes and, to a lesser extent, in renal glomeruli and in proximal tubules and collecting ducts. Analysis of subcellular fractions from cultured podocytes reveals that COQ8B resides both in mitochondria and cytosol, suggesting a localized function at ruffles and foot processes of podocytes besides its role in CoQ biosynthesis [Ashraf et al 2013].

See also Coenzyme Q_{10} Deficiency – Model Organisms, ***COQ8B***.

Abnormal gene product. All the reported pathogenic missense variants affect conserved residues. Patients have reduced levels of CoQ_{10} in both primary skin fibroblasts and lymphoblastoid-derived cells.

All individuals with biallelic pathogenic variants in *COQ8B* have SRNS; however, the phenotype depends on the genotype [Ashraf et al 2013]:

- The patient homozygous for the p.His400AsnfsTer11 truncating variant had the earliest onset and developmental delay.
- The patient homozygous for the p.Arg178Trp amino acid change had diffuse glomerulosclerosis.
- Homozygosity for the p.Gln452HisfsTer261 pathogenic variant was found in two sibs of Indian ancestry with renal histology and collapsing focal segmental glomerulosclerosis (cFSGS). Notably, cFSGS is common in individuals with mutation of *COQ8B* as well as in the pdss2 kd/kd mouse model [Saiki et al 2008, Ashraf et al 2013].

COQ9

Gene structure. *COQ9* has nine exons. No alternative splicing variants are known.

Pathogenic variants. One patient of Pakistani origin with multiple-system disease characterized by intractable seizures, developmental delay, hypertrophic cardiomyopathy, and renal tubular dysfunction was homozygous for the c.730C>T pathogenic variant in exon 7 resulting in a premature stop codon (p.Arg244Ter) [Duncan et al 2009].

The homozygous loss-of-function variant c.521+1del was reported in a child of Turkish origin with fatal neonatal lactic acidosis and encephalopathy [Danhauser et al 2016].

Table 9. Selected Pathogenic *COQ9* Variants that Cause Primary CoQ_{10} Deficiency

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.521+1delG		NM_020312.3 NP_064708.1
c.730C>T	p.Arg244Ter	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *COQ9* encodes a 318-amino acid protein that is involved in the synthesis of CoQ_{10} [Duncan et al 2009].

The crystal structure of the human protein reveals that COQ9 is homologous to the TetR family of transcriptional regulators but does not retain any DNA binding ability. It is organized as a homodimer and contains a hydrophobic pocket, responsible for binding of lipid molecules (likely CoQ_{10} or CoQ_{10} precursor) and a binding surface crucial for protein-protein interaction with Coq7 [Lohman et al 2014].

See also Coenzyme Q_{10} Deficiency – Model Organisms, ***COQ9***.

Abnormal gene product. The c.730C>T pathogenic variant is presumed to cause nonsense-mediated mRNA decay, as no transcript was detected in patient fibroblasts.

The c.521+1del pathogenic variant affects splicing with the skipping of exons 4 and 5 (p.Ser127_Arg202del), as shown by sequencing of the *COQ9* transcript in the patient's fibroblasts, with consequent degradation of the truncated protein [Danhauser et al 2016].

See also Coenzyme Q_{10} Deficiency – Model Organisms, ***COQ9***.

PDSS1

Gene structure. *PDSS1* spans more than 49.14 kb and comprises 12 exons. There is only one coding transcript, which is 1,679 bp long.

Pathogenic variants. *PDSS1* pathogenic variants have been identified in only two families with primary CoQ_{10} deficiency to date:

- Two sibs with encephalopathy, peripheral neuropathy, optic atrophy, cardiac valvulopathy, and mild lactic acidosis were homozygous for the c.924T>G missense variant in exon 10 [Mollet et al 2007].
- An individual with developmental delay, nephrotic syndrome, and failure to thrive was compound heterozygous for two novel variants: c.661_662insT and c.1108A>C [Vasta et al 2012].

Table 10. Selected Pathogenic *PDSS1* Variants that Cause Primary CoQ_{10} Deficiency

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.661_662insT (661C>CT)	p.Arg221LeufsTer16	NM_014317.3 NP_055132.2
c.924T>G (977T>G)	p.Asp308Glu	
c.1108A>C (1108A>AC)	p.Ser370Arg	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. *PDSS1* encodes decaprenyl-diphosphate synthase subunit 1 (previously reported as DPS1) which is required for the synthesis of the polyisoprenoid chain of the appropriate length, the first step in CoQ_{10} biosynthesis. The protein is composed of 415 amino acids.

It is an ortholog of *Schizosaccharomyces pombe* Dps1. Unlike in *S. cerevisiae* where the ubiquinone side chain is synthesized by the monomeric enzyme COQ1, in *S. pombe* and in mammals the PDSS1 polypeptide interacts with the product of *PDSS2* forming a heterotetramer that is responsible for the elongation of the prenyl side chain of CoQ_{10} and determines the isoprenoid chain length of ubiquinone [Saiki et al 2005].

Abnormal gene product. In the absence of *PDSS1*, decaprenyl-diphosphate synthase is not functional and does not produce CoQ_{10}.

For information on yeast studies, see Coenzyme Q_{10} Deficiency – Model Organisms, ***PDSS1***.

PDSS2

Gene structure. The gene has at least two different transcript variants that share the first three exons; only the longest (NM_020381.3), which has eight exons, is believed to encode a functional subunit of the decaprenyl diphosphate synthase [Saiki et al 2005].

Pathogenic variants. To date *PDSS2* pathogenic variants have been reported in two families; the phenotypes ranged from fatal Leigh syndrome and nephrotic syndrome to infantile-onset encephalomyopathy with ataxia, deafness, retinitis pigmentosa, and kidney disease [Rötig et al 2000, López-Martín et al 2007, Rahman et al 2012]. The patient reported by López-Martín et al [2007] was compound heterozygous for two novel variants, c.964C>T and c.1145C>T.

Table 11. Selected Pathogenic *PDSS2* Variants that Cause Primary CoQ_{10} Deficiency

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.964C>T	p.Gln322Ter	NM_020381.3 NP_065114.3
c.1145C>T	p.Ser382Leu	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The protein product of *PDSS2* (previously reported as DLP1) is the second subunit of decaprenyl diphosphate synthase, which is required for the elongation of the prenyl side chain of CoQ_{10}. The PDSS2 protein consists of 399 amino acids.

Unlike *S cerevisiae*, the prenyl diphosphate synthase in humans acts as a heterotetrameric complex, formed by two protein subunits encoded by *PDSS1* and two protein subunits encoded by *PDSS2* [Saiki et al 2005]. The same heterotetrameric complex is also found in mice and *S pombe*.

Abnormal gene product. In the absence of *PDSS2*, decaprenyl-diphosphate synthase is not functional and does not produce CoQ_{10}. The *PDSS2* pathogenic variants reported by López-Martín et al [2007] act through a loss-of-function mechanism, as suggested by substrate incorporation experiments showing a CoQ_{10} biosynthetic defect in fibroblasts from an affected individual when incubated with radioactive *para*-hydroxybenzoate (PHB), compared with normal synthesis in cells incubated with radiolabeled PHB and decaprenyl-PP.

For information on mouse studies, see Coenzyme Q_{10} Deficiency – Model Organisms, ***PDSS2***.

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Chapter Notes

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