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Kemp House - 152 City Road
London EC1V 2NX - Greay-Britain
Phone: +33 (0)6 83 16 60 78



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Pagon RA, Adam MP, Ardinger HH, et al.,
editors.
Seattle (WA): [University of Washington, Seattle](https://www.ncbi.nlm.nih.gov/pubs/books/ncbi1222/);
1993-2017.

Primary Coenzyme Q₁₀ Deficiency

Synonyms: Coenzyme Q Deficiency, CoQ Deficiency, Primary CoQ₁₀ Deficiency, Ubiquinone Deficiency

Leonardo Salviati, MD, PhD, Eva Trevisson, MD, PhD, Mara Doimo, PhD, and Placido Navas, PhD.

Initial Posting: January 26, 2017.

Summary

Clinical characteristics. Primary coenzyme Q₁₀ (CoQ₁₀) 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 CoQ₁₀ 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 Q₁₀ or by detection of reduced levels of CoQ₁₀ (ubiquinone) in skeletal muscle or reduced activities of complex I+II and II+III of the mitochondrial respiratory chain on frozen muscle homogenates.

Management. *Treatment of manifestations:* In individuals with primary CoQ₁₀ deficiency early treatment with high-dose oral CoQ₁₀ 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 CoQ₁₀ supplementation in persons with proteinuria; renal transplantation is 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 CoQ₁₀ 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 CoQ₁₀ supplementation is warranted for relatives at risk.

Genetic counseling. Primary coenzyme Q₁₀ 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 diagnosis](#) are possible if the pathogenic variants in a family are known.

Diagnosis

Primary deficiency of coenzyme Q₁₀, 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 Q₁₀ deficiency’ refers to the group of conditions characterized by a reduction of coenzyme Q₁₀ (CoQ₁₀) levels in tissues or cultured cells associated with mutation of the nine genes involved in the biosynthesis of coenzyme Q₁₀ (collectively called ‘*COQ* genes’).

There are no formal diagnostic criteria for primary coenzyme Q₁₀ deficiency.

Suggestive Findings

Primary coenzyme Q₁₀ 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 Q₁₀

[View in own window](#)

| Gene | Clinical Manifestations | | | | | |
|--------------|-------------------------|----------------------|---------------|---------|---|----------------------|
| | Renal | Heart | Eye | Hearing | Neurologic | Muscle |
| <i>COQ2</i> | SRNS | HCM | Retinopathy | SNHL | Encephalopathy ¹ Seizures Other ² | Myopathy |
| <i>COQ4</i> | | Heart failure HCM | | | Encephalopathy Seizures Other ³ | Myopathy |
| <i>COQ6</i> | SRNS ⁴ | | | SNHL | Encephalopathy Seizures | |
| <i>COQ7</i> | | | | | Encephalopathy ID Peripheral neuropathy | Muscle weakness |
| <i>COQ8A</i> | | | | | Encephalopathy Cerebellar ataxia Dystonia Spasticity Seizures | Exercise intolerance |
| <i>COQ8B</i> | SRNS ⁴ | | | | ID | |
| <i>COQ9</i> | Tubulopathy | HCM | | | Encephalopathy | Myopathy |
| <i>PDSS1</i> | | | Optic atrophy | | Encephalopathy Peripheral neuropathy | |
| <i>PDSS2</i> | 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 Q₁₀ 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 Q₁₀ 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 Q₁₀ 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 Q₁₀ ([Table 2](#)).

Note: If a diagnosis of primary coenzyme Q₁₀ 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 **multi-gene 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 multi-gene panel** that includes the nine genes in [Table 2](#) and some or all of the other genes of interest; for example, genes:
 - Known (or suspected) to be required for CoQ₁₀ biosynthesis but not identified to date as a cause of primary CoQ₁₀ deficiency (i.e., *ADCK1*, *ADCK2*, *ADCK5*, *COQ3*, *COQ10a*, *COQ10b*, *FDXR*, and *FDX2* (*FDX1L*) [Desbats et al 2015a])
 - Associated with secondary deficiencies of coenzyme Q

(*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 over time.

For more information on multi-[gene](#) panels click [here](#).

- **More comprehensive [genomic testing](#).** Because of the large (and still growing) number of genes involved, the rarity of primary coenzyme Q₁₀ deficiency, the incomplete knowledge of the coenzyme Q₁₀ 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 multi-gene 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 Q₁₀ deficiency (see [Differential Diagnosis](#)). For more information on comprehensive [genome sequencing](#) click [here](#).

Table 2.

Summary of Molecular Genetic Testing Used in Primary Coenzyme Q₁₀ Deficiency

| Gene ¹ | Number of Families w/Coenzyme Q ₁₀ Deficiency Attributed to Mutation of This Gene | Proportion of Pathogenic Variants ² Detected by Test Method | |
|-------------------|--|--|--|
| | | Sequence analysis ³ | Gene-targeted deletion/duplication analysis ⁴ |
| <i>COQ2</i> | 10 ⁵ | All pathogenic variants reported to date | Unknown |
| <i>COQ4</i> | 9 ⁶ | All pathogenic variants reported to date | Unknown ⁷ |
| <i>COQ6</i> | 5 ⁸ | All pathogenic variants reported to date | Unknown |

| | | | |
|-----------------------|------------------|---|-----------------------|
| <i>COQ7</i> | 1 ⁹ | All pathogenic variants reported to date | Unknown |
| <i>COQ8A</i> | 14 ¹⁰ | All pathogenic variants reported to date | Unknown ¹¹ |
| <i>COQ8B</i> | 34 ¹² | Most pathogenic variants reported to date | Unknown |
| <i>COQ9</i> | 2 ¹³ | All pathogenic variants reported to date | Unknown |
| <i>PDSS1</i> | 2 ¹⁴ | All pathogenic variants reported to date | Unknown |
| <i>PDSS2</i> | 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. 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 that may be used 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 CoQ₁₀ in cells or tissues lack a clear genetic diagnosis, making it impossible to distinguish between primary and secondary CoQ₁₀ deficiency [[Trevissan et al 2011](#)].

Biochemical Testing

The following findings on biochemical testing can differentiate coenzyme Q₁₀ deficiency from other mitochondrial disorders with similar clinical findings, but cannot differentiate primary from secondary coenzyme Q₁₀ deficiency (see [Differential Diagnosis](#)).

- Reduced levels of CoQ₁₀ in skeletal muscle [[Montero et al 2008](#)].
Note: While coenzyme Q₁₀ measurements may be performed on cultured skin fibroblasts or blood mononuclear cells, these tissues may not be reliable in detecting secondary coenzyme Q₁₀ 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 Q₁₀, are reduced in persons with a defect in CoQ₁₀ even when [isolated](#) complex II and III respiratory chain activities are normal [[Rahman et al 2012](#)].

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Clinical Characteristics

Clinical Description

The manifestations of primary coenzyme Q₁₀ 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 CoQ₁₀ deficiency with isolated myopathy have been reported [Authors, personal observation], since most individuals reported with predominantly muscle disease have secondary coenzyme Q₁₀ deficiency [[Doimo et al 2014](#)] (see [Differential Diagnosis](#)).

The broad age of onset of primary coenzyme Q₁₀ deficiency is exemplified by *COQ2*-related coenzyme Q₁₀ deficiency, in which onset ranges from birth to the seventh decade.

The [principal clinical manifestations](#) of primary CoQ₁₀ 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 CoQ₁₀ deficiencies](#), the three most common causes of primary coenzyme Q₁₀ 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 Q₁₀ deficiency [[Mitsui et al 2013](#)].

Individuals with *COQ8A*-related coenzyme Q₁₀ 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 Q₁₀ 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 CoQ₁₀ deficiency. If not treated with coenzyme Q₁₀ (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 Q₁₀ deficiency manifested tubulopathy within a few hours after birth.

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

- Neonatal-onset *COQ2*-related coenzyme Q₁₀ deficiency [[Scalais et al 2013](#)];
- *COQ4*-related coenzyme Q₁₀ deficiency manifesting as prenatal-onset HCM [[Brea-Calvo et al 2015](#)];
- *COQ9*-related coenzyme Q₁₀ 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 CoQ₁₀.

Ocular. Retinopathy is observed in some persons with *COQ2*-related coenzyme Q₁₀ deficiency [[Desbats et al 2016](#)].

Optic atrophy is present in some individuals with *PDSS1*-related coenzyme Q₁₀ deficiency [[Mollet et al 2007](#)] and *PDSS2*-related coenzyme Q₁₀ 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 Q₁₀ deficiency, is also observed in some individuals with *COQ2*-related coenzyme Q₁₀ 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 CoQ₁₀ 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 CoQ₁₀ deficiency.

Children with severe multisystem CoQ₁₀ deficiency generally die within the neonatal period or in the first year of life.

The only child reported with *COQ9*-related coenzyme Q₁₀ deficiency died before age two years of a progressive multisystem disorder [[Duncan et al 2009](#)].

Of note, supplementation with high-dose oral CoQ₁₀ 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 Q₁₀ 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 kidney 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 CoQ₁₀ 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 Q₁₀ 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](#)].

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Differential Diagnosis

Note: It is important to consider primary CoQ₁₀ deficiency in individuals with the following diverse presentations because primary CoQ₁₀ deficiency is potentially treatable.

Mitochondrial encephalomyopathies. See [Mitochondrial Disorders Overview](#). The clinical manifestations of mitochondrial encephalomyopathies and primary coenzyme Q₁₀ 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*) is clinically indistinguishable from the SRNS resulting from primary CoQ₁₀ deficiency.

Early onset ataxia. See [Hereditary Ataxia Overview](#).

Muscle disease/myopathy. See [Limb-Girdle Muscular Dystrophy Overview](#) and [Congenital Muscular Dystrophy Overview](#).

Secondary coenzymeQ₁₀ deficiencies are those disorders in which reduction in CoQ₁₀ levels is caused by mutation of genes not directly related to coenzyme Q₁₀ biosynthesis [[Trevisson et al 2011](#)]. Molecular genetic testing is the only way to distinguish primary coenzyme Q₁₀ deficiency from secondary coenzyme Q₁₀ deficiencies.

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Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with primary coenzyme Q₁₀ 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 Q₁₀ supplementation. Individuals with primary CoQ₁₀ deficiency may respond well to high-dose oral CoQ₁₀ 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 CoQ₁₀ deficiency apparently respond well to CoQ₁₀ supplementation:

- *COQ4*-related coenzyme Q₁₀ deficiency. Neurologic signs responded to CoQ₁₀ 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 Q₁₀ deficiency. Homozygotes for the pathogenic variants p.Gly255Arg or p.Ala353Asp responded [[Heeringa et al 2011](#)].
- *COQ8B*-related coenzyme Q₁₀ deficiency. In a patient [homozygous](#) for a truncating [pathogenic variant](#), edema resolved and proteinuria was significantly improved.
- *PDSS2*-related coenzyme Q₁₀ deficiency. The only kindred reported responded [[Rötig et al 2000](#)].

Data for response to CoQ₁₀ supplementation in individuals with mutation of other genes causing primary coenzyme Q₁₀ deficiency are limited or lacking:

- *COQ8A*-related coenzyme Q₁₀ deficiency. While most [affected](#) individuals respond poorly to CoQ₁₀ 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 Q₁₀ deficiency. One patient with multiple-system disease characterized by intractable seizures, global developmental delay, hypertrophic cardiomyopathy, and renal tubular dysfunction did not respond to CoQ₁₀ 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 Q₁₀ deficiency include the following CoQ₁₀ derivatives:

- Ubiquinol, the reduced form of CoQ₁₀, 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 CoQ₁₀ deficiency [[Hargreaves 2014](#)].

Renal Disease

ACE inhibitors may be used in combination with CoQ₁₀ 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 CoQ₁₀ supplementation may prevent the onset of manifestations of primary CoQ₁₀ 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 CoQ₁₀ supplementation, it is appropriate to evaluate the sibs of a [proband](#) who has primary coenzyme Q₁₀ 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 CoQ₁₀ 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](#) 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.

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Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Primary coenzyme Q₁₀ deficiency is generally inherited in an [autosomal recessive](#) manner.

Primary coenzyme Q₁₀ 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 Q₁₀ 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 Q₁₀ 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 Q₁₀ deficiency is at a 50% risk of being a [carrier](#) of a [pathogenic variant](#).

Heterozygote (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 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 is the storage of DNA (typically extracted from white blood cells) for possible future use. 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 of [affected](#) individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

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 diagnosis](#) for primary coenzyme Q₁₀ deficiency are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Go to: Go to:

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](#).

- **Medline Plus**

[Coenzyme Q-10](#)

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 | HGMD |
|-----------------------|--------------------------------|---|--------------------------------|-----------------------|
| COQ2 | 4q21.22-q21.23 | Para-hydroxybenzoate--polyprenyltransferase, mitochondrial | COQ2 database | COQ2 |
| COQ4 | 9q34.11 | Ubiquinone biosynthesis protein COQ4 homolog, mitochondrial | | COQ4 |
| COQ6 | 14q24.3 | Ubiquinone biosynthesis monooxygenase COQ6, mitochondrial | | COQ6 |
| COQ7 | 16p12.3 | 5-demethoxyubiquinone hydroxylase, mitochondrial | | COQ7 |
| COQ8A | 1q42.13 | Atypical kinase ADCK3, mitochondrial | ADCK3 database | COQ8A |
| COQ8B | 19q13.2 | Atypical kinase COQ8B, mitochondrial | | COQ8B |
| COQ9 | 16q21 | Ubiquinone biosynthesis protein COQ9, mitochondrial | COQ9 database | COQ9 |
| PDSS1 | 10p12.1 | Decaprenyl-diphosphate synthase subunit 1 | PDSS1 database | PDSS1 |
| PDSS2 | 6q21 | Decaprenyl-diphosphate synthase subunit 2 | PDSS2 database | PDSS2 |

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus, locus name, critical region, complementation group from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD) to which links are provided, click [here](#).

Table B.

OMIM Entries for Primary Coenzyme Q10 Deficiency ([View All in OMIM](#))

| | |
|------------------------|---------------------------------------|
| 601683 | COQ7, S. CEREVISIAE, HOMOLOG OF; COQ7 |
| 606980 | COENZYME Q8A; COQ8A |

| | |
|------------------------|--|
| 607426 | COENZYME Q10 DEFICIENCY, PRIMARY, 1; COQ10D1 |
| 607429 | PRENYL DIPHOSPHATE SYNTHASE, SUBUNIT 1; PDSS1 |
| 609825 | COQ2, <i>S. CEREVISIAE</i> , HOMOLOG OF; COQ2 |
| 610564 | PRENYL DIPHOSPHATE SYNTHASE, SUBUNIT 2; PDSS2 |
| 612016 | COENZYME Q10 DEFICIENCY, PRIMARY, 4; COQ10D4 |
| 612837 | COQ9, <i>S. CEREVISIAE</i> , HOMOLOG OF; COQ9 |
| 612898 | COENZYME Q4, <i>S. CEREVISIAE</i> , HOMOLOG OF; COQ4 |
| 614647 | COQ6, <i>S. CEREVISIAE</i> , HOMOLOG OF; 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 Genetic Pathogenesis

The pathogenesis of primary CoQ₁₀ 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 CoQ₁₀ deficiency, CoQ₁₀ 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 CoQ₁₀ deficiency causes a marked reduction in ATP production without increased production of reactive oxygen species (ROS), while mild CoQ₁₀ deficiency is associated with high ROS production without significant impairment of cellular bioenergetics [[Quinzii et al 2010](#)].

In addition, CoQ₁₀ 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 CoQ₁₀ 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 CoQ10 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 CoQ10 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 CoQ10 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 | |

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *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 Q₁₀ Deficiency – Model Organisms](#), *COQ2*.

Abnormal gene product. All coenzyme Q₁₀ 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 CoQ₁₀ [[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 CoQ₁₀ deficiency in fibroblasts had encephalomyopathic manifestations [[Salviati et al 2012](#)].

Table 4.Selected *COQ4* Pathogenic Variants that Cause Primary CoQ₁₀ 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 | |

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *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. *COQ4* transcript [NM_016035.4](#) encodes coq4 isoform 1, which consists of 265 amino acids, localizes to mitochondria, and is required for CoQ₁₀ 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 CoQ₁₀ 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 CoQ₁₀ 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 missense](#) pathogenic variants, c.763G>A and c.1058C>A, and two [heterozygous nonsense](#) pathogenic

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

Table 5.

Selected *COQ6* Pathogenic Variants that Cause Primary CoQ₁₀ Deficiency

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

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *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 CoQ₁₀ 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 CoQ₁₀ [[Heeringa et al 2011](#)].

For information on yeast studies, see [Coenzyme Q₁₀ 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 *COQ7* Pathogenic Variants that Cause Primary CoQ₁₀ Deficiency

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

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *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 CoQ₁₀ 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, CABCI) 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 [[Iizumi 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 COQ8A Pathogenic Variants that Cause Primary CoQ₁₀ Deficiency

| DNA Nucleotide Change (Alias ¹) | Predicted Protein Change | Reference Sequences |
|---|--------------------------|---------------------|
| c.637C>T (636C>T) | p.Arg213Trp | |
| 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 | | NM_020247.4 |
| c.1523T>C | p.Phe508Ser | NP_064632.2 |
| 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 | |
| g.227150977_227195656del144680 See footnote 4 | | NC_000001.10 ⁵ |

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *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 CoQ₁₀ 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 (Mg²⁺)-dependent ATPase activity [[Wheeler & Jia 2015](#)].

For information on yeast studies, see [Coenzyme Q₁₀ 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 CoQ₁₀ deficiency and reduced mitochondrial respiratory chain enzyme activity.

The two [nonsense](#) pathogenic 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 hypothetical 17 putative alternative [splicing](#) variants, the longest transcript [NM_024876.3](#) contains 15 exons; [exon 1](#) is non-coding [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 CoQ₁₀ deficiency [Ashraf et al 2013].

Table 8.

Selected *COQ8B* Pathogenic Variants that Cause Primary CoQ₁₀ Deficiency

| DNA Nucleotide Change | Predicted Protein Change | Reference Sequences |
|-----------------------|--------------------------|---------------------|
| c.101G>A | p.Trp34Ter | |

| | | |
|-----------------------|---------------------|-----------------------------|
| c.532C>T | p.Arg178Trp | |
| c.645delT | p.Phe214LeufsTer14 | |
| c.857A>G | p.Asp286Gly | |
| c.954_956dup | p.Thr319dup | |
| c.958C>T | p.Arg320Trp | NM_024876.3 |
| c.1027C>T | p.Arg343Trp | NP_079152.3 |
| c.1199dupA | p.His400AsnfsTer11 | |
| c.1356_1362delGGGCCCT | p.Gln452HisfsTer261 | |
| c.1430G>A | p.Arg477Gln | |
| c.1447G>T | p.Glu483Ter | |

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *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. 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 CoQ₁₀ 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 Q₁₀ Deficiency – Model Organisms](#), *COQ8B*.

Abnormal gene product. All the reported [missense](#) pathogenic variants affect conserved residues. Patients have reduced levels of CoQ₁₀ 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, global 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 *COQ9* Pathogenic Variants that Cause Primary CoQ₁₀ Deficiency

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

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *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 CoQ₁₀ [[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 CoQ₁₀ or CoQ₁₀ precursor) and a binding surface crucial for protein-protein interaction with Coq7 [[Lohman et al 2014](#)].

See also [Coenzyme Q₁₀ 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 Q₁₀ 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 CoQ₁₀ 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 *PDSS1* Pathogenic Variants that Cause Primary CoQ₁₀ Deficiency

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

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *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 CoQ₁₀ 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 CoQ₁₀ 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 CoQ₁₀.

For information on yeast studies, see [Coenzyme Q₁₀ Deficiency – Model Organisms](#), *PDSSI*.

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 *PDSS2* Pathogenic Variants that Cause Primary CoQ₁₀ Deficiency

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

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *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 CoQ₁₀. 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 *PDSSI* 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 CoQ₁₀. 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 CoQ₁₀ 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 Q₁₀ Deficiency – Model Organisms](#), *PDSS2*.

Go to: Go to:

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Chapter Notes

Acknowledgments

This work is supported by Telethon Italy Grants GGP13222 and GGP14187, a grant from Fondazione CARIPARO, and University of Padova Grant CPDA123573/12 (to LS) and from Ministry of Health Grant GR-2009-1578914 to (ET).

Revision History

- 26 January 2017 (bp) Review posted live
- 20 February 2015 (ls) Original submission

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