Primary Coenzyme Q\textsubscript{10} Deficiency

**Synonyms:** Coenzyme Q Deficiency, CoQ Deficiency, Primary CoQ\textsubscript{10} Deficiency, Ubiquinone Deficiency

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


**Summary**

**Clinical characteristics.** Primary coenzyme Q\textsubscript{10} (CoQ\textsubscript{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\textsubscript{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\textsubscript{10} or by detection of reduced levels of CoQ\textsubscript{10} (ubiquinone) in skeletal muscle or reduced activities of complex I+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 Q<sub>10</sub>

<table>
<thead>
<tr>
<th>Gene</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>Heart</td>
</tr>
<tr>
<td>COQ2</td>
<td>SRNS</td>
</tr>
<tr>
<td>COQ4</td>
<td>Heart failure</td>
</tr>
<tr>
<td>COQ6</td>
<td>SRNS&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>COQ7</td>
<td></td>
</tr>
<tr>
<td>COQ8A</td>
<td></td>
</tr>
<tr>
<td>COQ8B</td>
<td>SRNS&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>COQ9</td>
<td>Tubulopathy</td>
</tr>
<tr>
<td>PDSS1</td>
<td></td>
</tr>
<tr>
<td>PDSS2</td>
<td>SRNS</td>
</tr>
</tbody>
</table>

[View in own window]
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 COQB-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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Number of Families w/Coenzyme Q10 Deficiency Attributed to Mutation of This Gene</th>
<th>Proportion of Pathogenic Variants Detected by Test Method</th>
<th>Sequence analysis</th>
<th>Gene-targeted deletion/duplication analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>COQ2</td>
<td>10</td>
<td>All pathogenic variants reported to date</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>COQ4</td>
<td>9</td>
<td>All pathogenic variants reported to date</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>COQ6</td>
<td>5</td>
<td>All pathogenic variants reported to date</td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>
### Primary Coenzyme Q10 Deficiency

<table>
<thead>
<tr>
<th>Gene</th>
<th>N. of Variants</th>
<th>Pathogenicity</th>
<th>Chromosome Locus and Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>COQ7</td>
<td>9</td>
<td>All pathogenic variants reported to date</td>
<td>Unknown</td>
</tr>
<tr>
<td>COQ8A</td>
<td>14</td>
<td>All pathogenic variants reported to date</td>
<td>Unknown 11</td>
</tr>
<tr>
<td>COQ8B</td>
<td>34</td>
<td>Most pathogenic variants reported to date</td>
<td>Unknown</td>
</tr>
<tr>
<td>COQ9</td>
<td>2</td>
<td>All pathogenic variants reported to date</td>
<td>Unknown</td>
</tr>
<tr>
<td>PDSS1</td>
<td>2</td>
<td>All pathogenic variants reported to date</td>
<td>Unknown</td>
</tr>
<tr>
<td>PDSS2</td>
<td>2</td>
<td>All pathogenic variants reported to date</td>
<td>Unknown</td>
</tr>
<tr>
<td>Unknown</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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
A deletion from exon 3 to exon 15 has been described [Lagier-Tourenne et al 2008].

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].

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 encephalopathy 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 [Röting 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


The main clinical features include SRNS, which can be:

- 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];

**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].

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 coenzyme Q10 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.

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
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- 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.

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.

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.
### Table A.

Primary Coenzyme Q10 Deficiency: Genes and Databases

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome Locus</th>
<th>Protein</th>
<th>Locus Specific</th>
<th>HGMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>COQ2</td>
<td>4q21.22-21.23</td>
<td>Para-hydroxybenzoate-poly-prenyltransferase, mitochondrial</td>
<td>COQ2 database</td>
<td>COQ2</td>
</tr>
<tr>
<td>COQ4</td>
<td>9q34.11</td>
<td>Ubiquinone biosynthesis protein COQ4 homolog, mitochondrial</td>
<td></td>
<td>COQ4</td>
</tr>
<tr>
<td>COQ6</td>
<td>14q24.3</td>
<td>Ubiquinone biosynthesis monooxygenase COQ6, mitochondrial</td>
<td></td>
<td>COQ6</td>
</tr>
<tr>
<td>COQ7</td>
<td>16p12.3</td>
<td>5-demethoxyubiquinone hydroxylase, mitochondrial</td>
<td></td>
<td>COQ7</td>
</tr>
<tr>
<td>COQ8A</td>
<td>1q42.13</td>
<td>Atypical kinase ADCK3, mitochondrial</td>
<td>ADCK3 database</td>
<td>COQ8A</td>
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<tr>
<td>COQ8B</td>
<td>19q13.2</td>
<td>Atypical kinase COQ8B, mitochondrial</td>
<td></td>
<td>COQ8B</td>
</tr>
<tr>
<td>COQ9</td>
<td>16q21</td>
<td>Ubiquinone biosynthesis protein COQ9, mitochondrial</td>
<td>COQ9 database</td>
<td>COQ9</td>
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<tr>
<td>PDSS1</td>
<td>10p12.1</td>
<td>Decaprenyl-diphosphate synthase subunit 1</td>
<td>PDSS1 database</td>
<td>PDSS1</td>
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<tr>
<td>PDSS2</td>
<td>6q21</td>
<td>Decaprenyl-diphosphate synthase subunit 2</td>
<td>PDSS2 database</td>
<td>PDSS2</td>
</tr>
</tbody>
</table>

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](https://www.omim.org/))

<table>
<thead>
<tr>
<th>OMIM Entry</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>601683</td>
<td>COQ7, S. CEREVISIAE, HOMOLOG OF; COQ7</td>
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<tr>
<td>606980</td>
<td>COENZYME Q8A; COQ8A</td>
</tr>
<tr>
<td>Gene ID</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>607426</td>
<td>COENZYME Q10 DEFICIENCY, PRIMARY, 1; COQ10D1</td>
</tr>
<tr>
<td>607429</td>
<td>PRENYL DIPHOSPHATE SYNTHASE, SUBUNIT 1; PDSS1</td>
</tr>
<tr>
<td>609825</td>
<td>COQ2, S. CEREVISIAE, HOMOLOG OF; COQ2</td>
</tr>
<tr>
<td>610564</td>
<td>PRENYL DIPHOSPHATE SYNTHASE, SUBUNIT 2; PDSS2</td>
</tr>
<tr>
<td>612016</td>
<td>COENZYME Q10 DEFICIENCY, PRIMARY, 4; COQ10D4</td>
</tr>
<tr>
<td>612837</td>
<td>COQ9, S. CEREVISIAE, HOMOLOG OF; COQ9</td>
</tr>
<tr>
<td>612898</td>
<td>COENZYME Q4, S. CEREVISIAE, HOMOLOG OF; COQ4</td>
</tr>
<tr>
<td>614647</td>
<td>COQ6, S. CEREVISIAE, HOMOLOG OF; COQ6</td>
</tr>
<tr>
<td>614650</td>
<td>COENZYME Q10 DEFICIENCY, PRIMARY, 6; COQ10D6</td>
</tr>
<tr>
<td>614651</td>
<td>COENZYME Q10 DEFICIENCY, PRIMARY, 2; COQ10D2</td>
</tr>
<tr>
<td>614652</td>
<td>COENZYME Q10 DEFICIENCY, PRIMARY, 3; COQ10D3</td>
</tr>
<tr>
<td>614654</td>
<td>COENZYME Q10 DEFICIENCY, PRIMARY, 5; COQ10D5</td>
</tr>
<tr>
<td>615567</td>
<td>COENZYME Q8B; COQ8B</td>
</tr>
<tr>
<td>616276</td>
<td>COENZYME Q10 DEFICIENCY, PRIMARY, 7; COQ10D7</td>
</tr>
<tr>
<td>616733</td>
<td>COENZYME Q10 DEFICIENCY, PRIMARY, 8; COQ10D8</td>
</tr>
</tbody>
</table>

**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, Icon 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).


**Table 3.**

Selected Pathogenic COQ2 Variants that Cause Primary CoQ10 Deficiency

<table>
<thead>
<tr>
<th>DNA Nucleotide Change (Alias)</th>
<th>Predicted Protein Change (Alias)</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.437G&gt;A</td>
<td>p.Ser146Asn</td>
<td></td>
</tr>
<tr>
<td>c.545T&gt;G</td>
<td>p.Met182Arg</td>
<td></td>
</tr>
<tr>
<td>c.590G&gt;A</td>
<td>p.Arg197His</td>
<td></td>
</tr>
<tr>
<td>c.683A&gt;G</td>
<td>p.Asn228Ser</td>
<td>NM_015697.7 NP_056512.5</td>
</tr>
<tr>
<td>c.890A&gt;G</td>
<td>p.Tyr297Cys</td>
<td></td>
</tr>
<tr>
<td>c.905C&gt;T</td>
<td>p.Ala302Val</td>
<td></td>
</tr>
<tr>
<td>c.1159C&gt;T</td>
<td>p.Arg387Ter</td>
<td></td>
</tr>
<tr>
<td>c.1197delT (1198delT)</td>
<td>p.Asn401IlefsTer15</td>
<td></td>
</tr>
</tbody>
</table>

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 polyprenylpyrophosphate, 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\textsubscript{10} Deficiency – Model Organisms, COQ2.

**Abnormal gene product.** All coenzyme Q\textsubscript{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\textsubscript{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\textsubscript{10} deficiency in fibroblasts had encephalomyopathic manifestations [Salviati et al 2012].
### Table 4.

Selected COQ4 Pathogenic Variants that Cause Primary CoQ10 Deficiency

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.155T&gt;C</td>
<td>p.Leu52Ser</td>
<td>NM_016035.4</td>
</tr>
<tr>
<td>c.190C&gt;T</td>
<td>p.Pro64Ser</td>
<td>NP_057119.2</td>
</tr>
<tr>
<td>c.421C&gt;T</td>
<td>p.Arg141Ter</td>
<td></td>
</tr>
<tr>
<td>c.433C&gt;G</td>
<td>p.Arg145Gly</td>
<td></td>
</tr>
<tr>
<td>c.521_523delCCA</td>
<td>p.Thr174del</td>
<td></td>
</tr>
<tr>
<td>c.718C&gt;T</td>
<td>p.Arg240Cys</td>
<td></td>
</tr>
</tbody>
</table>

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 CoQ_{10} Deficiency

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change (Alias 1)</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.484C&gt;T</td>
<td>p.Arg162Ter</td>
<td>NM_182476.2</td>
</tr>
<tr>
<td>c.564G&gt;A</td>
<td>p.Trp188Ter</td>
<td>NP_872282.1</td>
</tr>
<tr>
<td>c.763G&gt;A</td>
<td>p.Gly255Arg</td>
<td></td>
</tr>
<tr>
<td>c.1058C&gt;A</td>
<td>p.Ala353Asp</td>
<td></td>
</tr>
<tr>
<td>c.1235A&gt;G</td>
<td>p.Tyr412Cys</td>
<td></td>
</tr>
<tr>
<td>c.1341G&gt;A</td>
<td>p.Trp447Ter</td>
<td></td>
</tr>
<tr>
<td>c.1383delG</td>
<td>p.Ile462LeufsTer18 (Gln461fsTer478)</td>
<td></td>
</tr>
</tbody>
</table>

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 monoxygenase 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 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>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.422T&gt;A</td>
<td>p.Val141Glu</td>
<td>NM_016138.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NP_057222.2</td>
</tr>
</tbody>
</table>

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.
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, 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 [Iizumi et al 2002].


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

<table>
<thead>
<tr>
<th>DNA Nucleotide Change (Alias)</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.637C&gt;T (636C&gt;T) p.Arg213Trp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.811C&gt;T</td>
<td>p.Arg271Cys</td>
<td></td>
</tr>
<tr>
<td>c.815G&gt;A</td>
<td>p.Gly272Asp</td>
<td></td>
</tr>
<tr>
<td>c.815G&gt;T</td>
<td>p.Gly272Val</td>
<td></td>
</tr>
<tr>
<td>c.895C&gt;T</td>
<td>p.Arg299Trp</td>
<td></td>
</tr>
<tr>
<td>c.993C&gt;T</td>
<td>p.Leu314_Gln360del</td>
<td></td>
</tr>
<tr>
<td>c.1042C&gt;T</td>
<td>p.Arg348Ter</td>
<td></td>
</tr>
<tr>
<td>c.1081-1_1082dupGTA</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>c.1136T&gt;A</td>
<td>p.Leu379Ter</td>
<td></td>
</tr>
<tr>
<td>Variant</td>
<td>Description</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>c.1398+2T&gt;C</td>
<td>p.Phe508Ser</td>
<td></td>
</tr>
<tr>
<td>c.1523T&gt;C</td>
<td>p.Tyr514Cys</td>
<td></td>
</tr>
<tr>
<td>c.1541A&gt;G</td>
<td>p.Gly549Ser</td>
<td></td>
</tr>
<tr>
<td>c.1645G&gt;A</td>
<td>p.Glu551Lys</td>
<td></td>
</tr>
<tr>
<td>c.1750_1752delACC</td>
<td>p.Thr584del</td>
<td></td>
</tr>
<tr>
<td>c.1813dupG (1812_1813insG)</td>
<td>p.Glu605GlyfsTer125</td>
<td></td>
</tr>
<tr>
<td>c.1844dupG (1844_1845insG)</td>
<td>p.Ser616LeufsTer114</td>
<td></td>
</tr>
<tr>
<td>c.1844G&gt;A</td>
<td>p.Gly615Asp</td>
<td></td>
</tr>
<tr>
<td>g.227150977_227195656del44680</td>
<td>See footnote 4</td>
<td></td>
</tr>
</tbody>
</table>

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 (Mg(2+))-dependent ATPase activity [Wheeler & Jia 2015].

For information on yeast studies, see Coenzyme Q10 Deficiency – Model Organisms, COQ8A.

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].


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 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

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.101G&gt;A</td>
<td>p.Trp34Ter</td>
<td></td>
</tr>
</tbody>
</table>
### 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 CoQ\(_{10}\) Deficiency

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.521+1delG</td>
<td></td>
<td>NM_020312.3</td>
</tr>
<tr>
<td>c.730C&gt;T p.Arg244Ter</td>
<td></td>
<td>NP_064708.1</td>
</tr>
</tbody>
</table>

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 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].
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

<table>
<thead>
<tr>
<th>DNA Nucleotide Change (Alias 1)</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.661_662insT (661C&gt;CT)</td>
<td>p.Arg221LeufsTer16</td>
<td>NM_014317.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NP_055132.2</td>
</tr>
<tr>
<td>c.924T&gt;G (977T&gt;G)</td>
<td>p.Asp308Glu</td>
<td></td>
</tr>
<tr>
<td>c.1108A&gt;C (1108A&gt;AC)</td>
<td>p.Ser370Arg</td>
<td></td>
</tr>
</tbody>
</table>

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, 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 PDSS2 Pathogenic Variants that Cause Primary CoQ10 Deficiency

<table>
<thead>
<tr>
<th>DNA Nucleotide Change</th>
<th>Predicted Protein Change</th>
<th>Reference Sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.964C&gt;T</td>
<td>p.Gln322Ter</td>
<td>NM_020381.3</td>
</tr>
<tr>
<td>c.1145C&gt;T</td>
<td>p.Ser382Leu</td>
<td>NP_065114.3</td>
</tr>
</tbody>
</table>

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 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 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.

References

Literature Cited


Diomedi-Camassei F, Di Giandomenico S, Santorelli FM, Caridi G,


variability in ARCA2 and identification of a core ataxic phenotype with slow progression. Orphanet J Rare Dis. 2013;8:173. [PMC free article] [PubMed]


Quinzii CM, López LC, Gilkerson RW, Dorado B, Coku J, Naini AB,


Stefely JA, Reidenbach AG, Ulbrich A, Oruganty K, Floyd BJ, Jochem A, Saunders JM, Johnson IE, Minogue CE, Wrobel RL,


Chapter Notes

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