Title: Coenzyme $Q_{10}$ Deficiency *GeneReview* – Model Organisms
Authors: Salviati L, Trevisson E, Doimo M, Navas P
Initial posting: January 2017
Note: The following information is provided by the authors and has been minimally reviewed by *GeneReviews* staff.

# Coenzyme $Q_{10}$ Deficiency – Model Organisms



## *PDSS1*

The p.Asp308Glu missense variant in *PDSS1* causes a loss of function of the protein as proved by the lack of complementation in a yeast model: the respiratory defective phenotype of a yeast strain with a deletion of the gene coq1 can be restored by the wild-type but not by the mutant yeast gene harboring the variant equivalent to human p.Asp308Glu pathogenic variant [Mollet et al 2007].

## *PDSS2*

A spontaneous mutant mouse model kd (kidney disease) harbors a homozygous pathogenic missense variant in *PDSS2* changing the highly conserved Val177 residue with a methionine [Peng et al 2008]. The *Pdss2*$^{kd/kd}$ mouse developed a glomerulopathy in early adulthood with CoQ deficiency in the kidney that dramatically responds to CoQ supplementation, recapitulating the human disease [Saiki et al 2008]. Another mouse model with conditional knockout of *PDSS2* in the cerebellum developed severe cerebellar hypoplasia with disorganized cell arrangement and ataxia [Lu et al 2012]; the effect of CoQ supplementation was not analyzed.

## *COQ2*

**Normal gene product.** In vitro import studies in yeast demonstrated that Coq2 is imported and fully processed within mitochondria [Leuenberger et al 1999].

## *COQ6*

**Normal gene product.** Isoform *a* -but not isoform *b* -can complement the deletion of the yeast orthologue *Coq6* [Doimo et al 2014]. The *S. cerevisiae* orthologue *Coq6* is responsible for the C5-hydroxylation in CoQ biosynthesis. Its deficiency could be

bypassed by the use of hydroxylated 4-hydroxybenzoic acid (4HB) analogs such as vanillic acid (VA) or 3-4 di-hydroxybenzoic acid (3,4-diHB) [Ozier et al 2011]. Moreover, Coq6 is part of the COQ biosynthetic complex and it is downregulated in other Coq mutant strains [Tran & Clarke 2007]. Its expression can be rescued to steady state levels by overexpression of Coq8 kinase protein [Xie et al 2012].

### *ADCK3*

**Normal gene product.** The yeast homologs Cabc1/Coq8 encode a putative protein kinase (based on presence of kinase motifs in its amino acid sequence). In yeast this mitochondrial protein is not part of the COQ complex but affects its stability [Tauche et al 2008]. Expression of a mitochondrial targeted ADCK3 protein rescues CoQ biosynthesis and COQ protein phosphorylation in coq8 yeast mutants [Xie et al 2011]. Moreover it has been shown that Coq8 overexpression can stabilize the Coq complex [He et al 2014] and could be instrumental for analyzing the intermediates of CoQ that accumulates in coq mutant strains [Xie et al 2012]. However, the exact mechanism by which this protein enables CoQ biosynthesis is still unclear.

**Abnormal gene product.** These pathogenic variants were introduced in the homologous yeast gene and caused a respiratory phenotype with no or decreased growth on glycerol medium and a severe reduction in ubiquinone synthesis, with a linear correlation between yeast growth and residual CoQ content in yeast (lower CoQ content for most severe yeast phenotype, except for p.Arg177Trp corresponding to p.Arg213Trp human variant).

Patients with p.Arg213Trp and p.Gly272Val pathogenic variants (which have the mildest effect in yeast) display the milder CII+CIII reduction [Mollet et al 2008]. Also p.Tyr514Cys, p.Gly549Ser, and p.Thr584del alleles were introduced in yeast and caused impaired growth on non-fermentable carbon source that could be partially rescued by exogenous CoQ6 supplementation, as well as impaired oxygen consumption and increased in $H_2O_2$ production [Lagier-Tourenne et al 2008].

### *ADCK4*

**Normal gene product.** Co-immunoprecipitation in cultured podocytes shows that ADCK4 interacts with a complex containing COQ6 and COQ7 proteins. Protein ablation in zebrafish or *Drosophila* causes a phenotype reminiscent of human nephrotic syndrome. In humans protein KD causes defect in podocyte migration that is reversed by the addition of CoQ but does not reduce cell proliferation or increase apoptosis [Ashraf et al 2013].

### *COQ9*

**Normal gene product.** The protein has been extensively studied in the yeast *S. cerevisiae* and in mouse [Johnson et al 2005, Duncan et al 2009, García-Corzo et al 2013, Lohman et al 2014]. Coq9 is peripherally associated to the inner mitochondrial membrane facing the matrix and is part of the coenzyme Q biosynthetic complex [Johnson et al 2005, Lohman et al 2014]. Its ablation or mutation causes reduction of CoQ in yeast and in several mouse tissues and the accumulation of

demothoxyubiquinone, the precursor of the reaction catalyzed by Coq7 [Hsieh at al 2007, García-Corzo et al 2013]. Based on these data, Coq9 seems to specifically regulate Coq7 protein [García-Corzo et al 2013].

**Abnormal gene product.** When introduced in the yeast gene, the pathogenic variant causes the impairment of the respiratory phenotype [Duncan et al 2009].

A mouse model harboring the p.Arg239Ter homozygous allele, corresponding to the human pathogenic variant, displays progressive encephalomyopathy associated with CoQ deficiency and neuronal death [García-Corzo et al 2013]. This mouse model presents decreased level of Coq7 protein and accumulates the substrate for its reaction. In the brain mice show a reduction of Complex I and an increase of free complex III leading to the decrease in mitochondrial respiration and ATP synthesis. Neuronal degeneration is due to caspase-independent apoptosis [García-Corzo et al 2013].

Based on the protein structure, the pathogenic variant truncates the binding site for Coq7-Coq9 interaction and the lipid-binding domain probably blocking the Coq7 reaction [Lohman et al 2014].

The phenotype of the mice with the pathogenic variant ameliorates after treatment with a water soluble form of ubiquinol-10, the reduced form of ubiquinone. This compound increases CoQ levels in all tissues and the CoQ-dependent respiratory chain activity in brain cells leading to the reduction of astrogliosis, vacuolization and oxidative damage in neuronal tissue and to an increase in the animal body weight [García-Corzo et al 2014].

## References


Ashraf S, Gee HY, Woerner S, Xie LX, Vega-Warner V, Lovric S, Fang H, Song X, Cattran DC, Avila-Casado C, Paterson AD, Nitschké P, Bole-Feysot C, Cochat P, Esteve-Rudd J, Haberberger B, Allen SJ, Zhou W, Airik R, Otto EA, Barua M, Al-Hamed MH, Kari JA, Evans J, Bierzynska A, Saleem MA, Böckenhauer D, Kleta R, El Desoky S, Hacihamdioglu DO, Gok F, Washburn J, Wiggins RC, Choi M, Lifton RP, Levy S, Han Z, Salviati L, Prokisch H, Williams DS, Pollak M, Clarke CF, Pei Y, Antignac C, Hildebrandt F. ADCK4 mutations promote steroid-resistant nephrotic syndrome through CoQ10 biosynthesis disruption. J Clin Invest. 2013;123:5179-89.

Doimo M, Trevisson E, Airik R, Bergdoll M, Santos-Ocaña C, Hildebrandt F, Navas P, Pierrel F, Salviati L. Effect of vanillic acid on COQ6 mutants identified in patients with coenzyme Q10 deficiency. Biochim Biophys Acta. 2014;1842:1-6.

Duncan AJ, Bitner-Glindzicz M, Meunier B, Costello H, Hargreaves IP, López LC, Hirano M, Quinzii CM, Sadowski MI, Hardy J, Singleton A, Clayton PT, Rahman S.A nonsense mutation in COQ9 causes autosomal-recessive neonatal-onset primary coenzyme Q10 deficiency: a potentially treatable form of mitochondrial disease. Am J Hum Genet. 2009;84:558-66.

García-Corzo L, Luna-Sánchez M, Doerrier C, García JA, Guarás A, Acín-Pérez R, Bullejos-Peregrín J, López A, Escames G, Enríquez JA, Acuña-Castroviejo D, López LC. Dysfunctional Coq9 protein causes predominant encephalomyopathy associated with CoQ deficiency. Hum Mol Genet. 2013;22:1233-48.

García-Corzo L, Luna-Sánchez M, Doerrier C, Ortiz F, Escames G, Acuña-Castroviejo D, López LC. Ubiquinol-10 ameliorates mitochondrial encephalopathy associated with CoQ deficiency. Biochim Biophys Acta. 2014;1842:893-901.

He CH, Xie LX, Allan CM, Tran UC, Clarke CF. Coenzyme Q supplementation or over-expression of the yeast Coq8 putative kinase stabilizes multi-subunit Coq polypeptide complexes in yeast coq null mutants. Biochim Biophys Acta. 2014;1841:630-44

Hsieh EJ, Gin P, Gulmezian M, Tran UC, Saiki R, Marbois BN, Clarke CF. Saccharomyces cerevisiae Coq9 polypeptide is a subunit of the mitochondrial coenzyme Q biosynthetic complex. Arch Biochem Biophys. 2007;463:19-26.

Johnson A, Gin P, Marbois BN, Hsieh EJ, Wu M, Barros MH, Clarke CF, Tzagoloff A. COQ9, a new gene required for the biosynthesis of coenzyme Q in Saccharomyces cerevisiae. J Biol Chem. 2005;280:31397-404.

Lagier-Tourenne C, Tazir M, López LC, Quinzii CM, Assoum M, Drouot N, Busso C, Makri S, Ali-Pacha L, Benhassine T, Anheim M, Lynch DR, Thibault C, Plewniak F, Bianchetti L, Tranchant C, Poch O, DiMauro S, Mandel JL, Barros MH, Hirano M, Koenig M. ADCK3, an ancestral kinase, is mutated in a form of recessive ataxia associated with coenzyme Q10 deficiency. Am J Hum Genet. 2008;82:661-72.

Leuenberger D, Bally NA, Schatz G, Koehler CM. Different import pathways through the mitochondrial intermembrane space for inner membrane proteins. EMBO J. 1999;18:4816-22.

Lohman DC, Forouhar F, Beebe ET, Stefely MS, Minogue CE, Ulbrich A, Stefely JA, Sukumar S, Luna-Sánchez M, Jochem A, Lew S, Seetharaman J, Xiao R, Wang H, Westphall MS, Wrobel RL, Everett JK, Mitchell JC, López LC, Coon JJ, Tong L, Pagliarini DJ. Mitochondrial COQ9 is a lipid-binding protein that associates with COQ7 to enable coenzyme Q biosynthesis. Proc Natl Acad Sci U S A. 2014;111:E4697-705.

Lu S, Lu LY, Liu MF, Yuan QJ, Sham MH, Guan XY, Huang JD. Cerebellar defects in Pdss2 conditional knockout mice during embryonic development and in adulthood. Neurobiol Dis. 2012;45:219-33.

Mollet J, Giurgea I, Schlemmer D, Dallner G, Chretien D, Delahodde A, Bacq D, de Lonlay P, Munnich A, Rötig A. Prenyldiphosphate synthase, subunit 1 (PDSS1) and OH-benzoate polyprenyltransferase (COQ2) mutations in ubiquinone deficiency and oxidative phosphorylation disorders. J Clin Invest. 2007;117:765-72.

Mollet J, Delahodde A, Serre V, Chretien D, Schlemmer D, Lombes A, Boddaert N, Desguerre I, de Lonlay P, de Baulny HO, Munnich A, Rötig A. CABC1 gene mutations cause ubiquinone deficiency with cerebellar ataxia and seizures. Am J Hum Genet. 2008;82:623-30.

Ozeir M, Mühlenhoff U, Webert H, Lill R, Fontecave M, Pierrel F. Coenzyme Q biosynthesis: Coq6 is required for the C5-hydroxylation reaction and substrate analogs rescue Coq6 deficiency. Chem Biol. 2011;18:1134-42

Peng M, Falk MJ, Haase VH, King R, Polyak E, Selak M, Yudkoff M, Hancock WW, Meade R, Saiki R, Lunceford AL, Clarke CF, Gasser DL. Primary coenzyme Q deficiency in Pdss2 mutant mice causes isolated renal disease. PLoS Genet. 2008;4:e1000061.

Saiki R, Lunceford AL, Shi Y, Marbois B, King R, Pachuski J, Kawamukai M, Gasser DL, Clarke CF. Coenzyme Q10 supplementation rescues renal disease in Pdss2kd/kd mice with mutations in prenyl diphosphate synthase subunit 2. Am J Physiol Renal Physiol. 2008;295:F1535-44.

Tauche A, Krause-Buchholz U, Rödel G. Ubiquinone biosynthesis in Saccharomyces cerevisiae: the molecular organization of O-methylase Coq3p depends on Abc1p/Coq8p. FEMS Yeast Res. 2008;8:1263-75.

Tran UC, Clarke CF. Endogenous synthesis of coenzyme Q in eukaryotes. Mitochondrion. 2007;7 Suppl:S62-71

Xie LX, Hsieh EJ, Watanabe S, Allan CM, Chen JY, Tran UC, Clarke CF. Expression of the human atypical kinase ADCK3 rescues coenzyme Q biosynthesis and phosphorylation of Coq polypeptides in yeast coq8 mutants. Biochim Biophys Acta. 2011;1811:348-60.

Xie LX, Ozeir M, Tang JY, Chen JY, Jaquinod SK, Fontecave M, Clarke CF, Pierrel F. Overexpression of the Coq8 kinase in Saccharomyces cerevisiae coq null mutants allows for accumulation of diagnostic intermediates of the coenzyme Q6 biosynthetic pathway. J Biol Chem. 2012;287:23571-81.