Coenzyme Q

Subjects: Biochemistry & Molecular Biology
Contributor: Alfonso Varela-López

Coenzyme Q (CoQ), ubiquinone or 2,3-dimethoxy-5-methyl-6-polyprenyl-1,4-benzoquinone is a two-part molecule composed of a benzoquinone ring, which has redox active sites, and a long polyisoprenoid lipid chain that positions the molecule in the mid-plane of a membrane bilayer. It is an essential endogenously synthesized molecule that links different metabolic pathways to mitochondrial energy production thanks to its location in the mitochondrial inner membrane and its redox capacity, which also provide it with the capability to work as an antioxidant.

Keywords: mitohormesis ; antioxidant ; mitochondria ; anti-aging ; diet ; aging-related diseases

1. CoQ Biosynthesis

Coenzyme Q (CoQ), ubiquinone or 2,3-dimethoxy-5-methyl-6-polyprenyl-1,4-benzoquinone is a two-part molecule composed of a benzoquinone ring, which has redox active sites, and a long polyisoprenoid lipid chain that positions the molecule in the mid-plane of a membrane bilayer. The length of the chain depends on the species, i.e., 10 isoprene units (CoQ_{10}) in humans and *S. pombe*, eight units (CoQ_8) in *Escherichia coli*, six units (CoQ_6) in *Saccharomyces cerevisiae* and nine units (CoQ_9) in rodents. Nevertheless, some species have more than one CoQ form, e.g., human cells and tissues also contain CoQ_9 and rodent cells and tissues also contain CoQ_{10} as minor forms.

The synthesis of CoQ in eukaryotes mainly occurs in mitochondria by a set of nuclear-encoded CoQ proteins through a biochemical pathway that has not been fully defined. Moreover, some authors have suggested that CoQ may also be produced outside of mitochondria, mainly in the endoplasmic reticulum-Golgi [1][2]. On the other hand, recent studies suggest that the endoplasmic reticulum mitochondria encounter structure (ERMES) might promote CoQ biosynthesis and the movement of CoQ and its precursors and intermediates between these organelles [3]. Thus, the mitochondrial production of CoQ could contribute to extramitochondrial pools of CoQ. The known steps required for CoQ production were first identified in *S. cerevisiae* and later confirmed in mammals. Specifically, *S. cerevisiae* CoQ (CoQ1–CoQ9) mutants, but also *E. coli* ubi (ubiA-J and ubiX) mutants, have allowed identifying the CoQ genes and biosynthetic intermediaries of the biosynthetic pathway of CoQ [4][5][6][7][8][9]. At least 11 genes (ubiA, B, C, D, E, F, G, H, I, J, and X) in *E. coli* and 13 genes (YAH1, ARH1, and CoQ1–CoQ11) in *S. cerevisiae* are involved in CoQ biosynthesis. Human and mouse orthologues for almost all of these genes have already been identified (with the possible exception of *CoQ11*). In the cases of *CoQ8* and *CoQ10*, humans have two orthologues for each one: *ADCK3* (*CoQ8A*) and *ADCK4* (*CoQ8B*), and *CoQ10A* and *CoQ10B*, respectively. In *Homo sapiens* the polypernyl diphosphate synthase is a heterotetramer formed by the dimer of PDSS1 and PDSS2 proteins [10][11]. The expression of the human homologs (*CoQ1–CoQ10*) for yeast genes restores CoQ_6 biosynthesis in the corresponding *S. cerevisiae CoQ* mutants, indicating the profound functional conservation in human cells [12]. Structurally, CoQ biosynthesis could be divided into four stages: quinone synthesis, isoprenoid tail synthesis, both molecules condensation and ring modification.

1.1. Quinone Synthesis

The primary aromatic precursor of the benzoquinone ring is 4-hydroxybenzoic acid (4HB). For the biosynthesis of 4HB, human cells utilize phenylalanine or tyrosine as ring precursors. Many of the steps involved in the generation of 4HB from tyrosine are not completely understood and the responsible enzymes are unidentified [13][14]. Current studies have identified the first and last reactions of this pathway and the enzymes involved in these reactions in yeast. Thus, 4HB synthesis starts with the deamination of tyrosine to 4-hydroxyphenylpyruvate by Aro8 and Aro9 and finishes with the oxidation of 4-hydroxybenzaldehyde to 4HB by Hfd1. Human Hdf1 homolog ALDH3A1 plays a role in CoQ biosynthesis and is able to rescue CoQ deficiency in yeast with the inactivated *HFD1* gene [15][16]. Aro8 and Aro9 human homolog remain unidentified, but α-aminoadipate aminotransferase (AADAT) and the tyrosine aminotransferase (TAT) have been postulated as candidates [17].

Although 4HB is depicted as the main precursor of CoQ, other aromatic ring precursors may be incorporated into CoQ biosynthesis. The 2,4-dihydroxybenzoic acid (2,4-diHB), 3,4-dihydroxybenzoic acid (3,4-diHB) and vanillic acid are analogs of 4HB that may allow the stimulation and/or bypass of CoQ biosynthesis defects in yeast *CoQ6* and *CoQ7* mutants, as well as in *CoQ7* conditional knockout mice, *CoQ9*^{R239X} mice and human skin fibroblasts from patients with mutations in *CoQ7* and *CoQ9* [18][19][20][21][22][23]. Para-coumarate and resveratrol also can be used as CoQ ring precursors in *E. coli*, *S. cerevisiae*, and human and mouse cells [24]. Moreover, in mouse and human kidney cells, kaempferol is able to increase CoQ levels. This phenolic compound apparently acts as a biosynthetic ring precursor competing with 4HB [25].

1.2. Polyisoprenyl Tail Synthesis

The lipophilic polyprenyl tail is synthetized by the addiction of dimethylally pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP) to form decaprenyl diphosphate and nonaprenyl diphosphate via PDSS1/PDSS2 in humans and mice. Consequently, the heterotetramer PDSS1/PDSS2 is responsible for the length of the polyprenyl tail. The polyprenyl precursors come from the mevalonate pathway and are generated in the cytosol. The mechanism by which these precursors are transported from the cytosol to mitochondria is unknown, and it has been suggested that some transporters may exist in the inner mitochondrial membrane [17].

1.3. Attachment of the Ring/Chain

Furthermore, 4HB and polyprenyl tail are condensed in a reaction catalyzed by human or mice CoQ2 to form 3-decaprenyl-4HB and 3-nonaprenyl-4HB (**Figure 1**a).

1.4. Next Steps of CoQ Biosynthesis-Ring Modifications

Then, 3-decaprenyl-4HB or 3-nonaprenyl-4HB undergoes subsequent modifications of the ring through a set or reactions of methylations, decarboxylation and hydroxylations to finally generate the molecule of CoQ_{10} or CoQ_9.

The first reaction is the C5-hydroxylation, catalyzed by CoQ6, to produce 3-decaprenyl-4,5-dihydroxybenzoic acid and 3-nonaprenyl-4,5-dihydroxybenzoic acid. In yeast, this step requires two enzymes, ferredoxin Yah1p and ferredoxin reductase Arh1p, which provide electrons for CoQ6 activity. It is unknown whether the mammalian orthologs, ferredoxin reductase (FDXR) and ferredoxin 2 (FDX2), respectively, act in mammalian CoQ biosynthesis. CoQ6 is characterized as a flavin-dependent monooxygenase peripherally associated with inner mitochondrial membrane on the matrix face [26][27].

C5-hydroxylation is followed by O-methylation catalyzed by CoQ3 to form 3-decaprenyl-4-hydroxy-5-methoxybenzoic acid and 3-nonaprenyl-4-hydroxy-5-methoxybenzoic acid. CoQ3 is an S-adenosylmethionine-dependent methyltransferase that is involved in two O-methylation reactions in the CoQ biosynthetic pathway. This polypeptide is also peripherally associated with the mitochondrial inner membrane on the matrix face [28][29].

The proteins involved in the subsequent steps, C1-decarboxylation and C1-hydroxylation, have not been identified in the eukaryotes. However, in prokaryotes the decarboxylation and hydroxylation in prokaryotes are catalyzed by the 3-Octaprenyl-4-hydroxybenzoate decarboxylase UbiD and the 2-octaprenyl-6-methoxyphenol hydroxylase UbiH, respectively [30][31]. In prokaryotic decarboxylation, the flavin prenyltransferase UbiX is important for synthesizing prenylated flavin, which is used as a cofactor for UbiD [32]. Nevertheless, there is no sequence homolog for UbiD or UbiX in humans, suggesting that the C1-hydroxylation could be part of the decarboxylation mechanism.

The ring is then further modified by C2-methylation in a reaction catalyzed by CoQ5. In this reaction, 2-decaprenyl-6-methoxy-1,4-benzenediol and 2-nonaprenyl-6-methoxy-1,4-benzenediol is converted to 2-decaprenyl-3methyl-6-methoxy-1,4-benzenediol and 2-nonaprenyl-3methyl-6-methoxy-1,4-benzenediol ($DMQH_2$) [33]. CoQ5 is an S-adenosyl methionine (SAM)-dependent methyltransferase (SAM-MTase) that is peripherally associated with the mitochondrial inner membrane on the matrix face [34]. $DMQH_2$ is converted to 2-decaprenyl-3methyl-6methoxy-1,4,5-benzenetriol and 2-nonaprenyl-3methyl-6methoxy-1,4,5-benzenetriol ($DMeQH_2$) in a C6-hydroxylation catalyzed by CoQ7, which is a carboxylate bridged diiron hydroxylase peripherally associated with the mitochondrial inner membrane on the matrix side [35].

The final step of the CoQ biosynthetic pathway is an O-methylation also catalyzed by CoQ3.

1.5. Other Mitochondrial Proteins Involved in CoQ Biosynthesis

There are additional proteins needed for CoQ biosynthesis since their dysfunctions induce a decline in the levels of CoQ. However, their molecular exact functions are yet unclear. These are the cases of CoQ8A, CoQ8B, CoQ9, CoQ_{10}A,

CoQ_{10}B and CoQ4.

CoQ8A (=ADCK3) and CoQ8B (=ADCK4) have been related with CoQ_{10} biosynthesis and mutations in these proteins are associated with CoQ_{10} deficiency [36][37][38][39]. These two proteins are considered the human orthologues of yeast CoQ8p because CoQ_6 biosynthesis is rescued by the expression of human CoQ8A and CoQQB in CoQ8-mutant yeast strains [39][40]. However, the precise biochemical activity and the role of CoQ8 in CoQ biosynthesis remains unknown. Although initially CoQ8 was hypothesized to be a protein kinase that may phosphorylate other CoQ biosynthetic proteins, recent studies have demonstrated that CoQ8A shows ATPase activity that is essential for CoQ biosynthesis. In any case, it seems that the activity of CoQ8A could stabilize Complex Q [41].

CoQ9 is a lipid-binding protein associated with the inner mitochondrial membrane, on the matrix face [42]. This protein binds aromatic isoprenes with high specificity, including CoQ intermediates that likely reside within the bilayer. Therefore, CoQ9 seems to present the intermediates of the CoQ biosynthetic pathway directly to CoQ enzymes [43]. CoQ9 is also necessary for the stability and activity of CoQ7, so *CoQ9* mutant mice and human cells show reduced levels of CoQ7 and accumulation of $DMQH_2$, the substrate of the reaction catalyzed by CoQ7 [23][27][44][45][46].

CoQ_{10}A and CoQ_{10}B in humans [47] are homologues of the yeast CoQ_{10}, a protein that contains a lipid-binding domain that binds CoQ and CoQ intermediates, and that is required for efficient biosynthesis of CoQ_6 and electron transport in the mitochondrial respiratory chain. The molecular basis for these effects is unknown, but CoQ_{10} probably directs to CoQ from synthesis site to function sites [48][49][50].

Finally, the function of the CoQ4 is still unknown, although some studies suggest that it is required for the assembly and stability of Complex Q, as it is associated with CoQ3, CoQ5, CoQ6 and CoQ9 [28][51][52]. Also, it is speculated that CoQ4 could bind to CoQ and CoQ intermediates and it could organize the enzymes that perform the ring modifications. In humans, there are two different isoforms of the CoQ4 polypeptide but only one is localized in mitochondria [53].

1.6. Complex Q

CoQ biosynthesis depends on a multi-subunit CoQ polypeptide complex formed by several CoQ biosynthetic proteins and by non-proteinaceous components, including some CoQ intermediates and CoQ itself. It is widely accepted that CoQ3–CoQ9 assembly into a high molecular mass complex called Complex Q. These complexes are peripherally associated with the matrix-side of the inner mitochondrial membrane and are essential feature for the de novo biosynthesis of CoQ [17][51][54][55]. In fact, the lack of a single CoQ polypeptide in yeasts, mice and human cells results in the degradation of several CoQ proteins [23][40][42][45][56].

The functional role of Complex Q is to enhance the catalytic efficiency, optimizing the orientation of the substrates and active sites of the enzymes, and to minimize the escape of intermediates, which could be toxic due to their redox or electrophilic properties [17][45][54]. However, many questions about Complex Q remain unknown, including its regulation and the key components involved in its formation and stability.

2. Functions of CoQ

The lipophilic characteristic of CoQ together with its redox capacity allows this molecule to participate in multiple cellular pathways and functions.

2.1. The Role of CoQ in the Mitochondrial Respiratory Chain

The best-known role of CoQ is its function as an essential electron carrier in the mitochondrial respiratory chain (MRC). CoQ passes electrons between complex I (NADH-ubiquinone oxidoreductase) or Complex II (succinate-ubiquinone oxidoreductase) and Complex III (succinate-cytochrome c oxidoreductase) [57]. Thus, CoQ can be found in both oxidized (CoQ or ubiquinone) and reduced forms ($CoQH_2$ or ubiquinol), and the conversion between these oxidized-reduced states allows it to act as a cofactor of enzymatic reactions transferring electrons to substrates. This oxidation–reduction cycle may occur by a two-step transfer of electrons producing a semiquinone (CoQH·) intermediate.

In mitochondria, CoQ also accepts electrons from sulfide quinone oxidoreductase (SQOR) during sulfide detoxification [58][59][60][61]; proline dehydrogenase 1 (PDH), an enzyme required for proline and arginine metabolism [62]; coline dehydrogenase (CHDH), required for glycine metabolism; mitochondrial glycerol-3-phosphate dehydrogenase (G3PDH), which connects oxidative phosphorylation, fatty acid metabolism and glycolysis [63]; dihydroorotate dehydrogenase (DHOH), an enzyme involved in pyrimidine biosynthesis [64][65][66]; electron transport flavoprotein dehydrogenase

(ETFDH), a key enzyme involved in the fatty acid β-oxidation [67]; and hydroxylproline dehydrogenase, involved in the glyoxylate metabolism [68]. All these processes generate $CoQH_2$, which is re-oxidized by complex III. Therefore, CoQ is an excellent redox carrier involved in different cellular processes since it has the ability to sustain continuous oxidation–reduction cycles.

2.2. The Antioxidant Capacity

Reactive Oxygen Species (ROS) formed in the cell are able to damage lipids, proteins and DNA. The mitochondrion is the compartment considered to be the major source of ROS production in the cell and, therefore, this organelle is highly susceptible to suffer oxidative damage. To avoid this harmful effect, the mitochondrion possesses antioxidant compounds and systems, being CoQ one of them. CoQ is one of the most powerful endogenously synthesized membrane antioxidants, being present in all membranes. Its antioxidant function efficiently protects lipids from harmful oxidative damage, but also DNA and proteins [69][70].

CoQ is able to prevent lipid peroxidation in most subcellular membranes and its effectiveness to inhibit lipid peroxidation depends on its complex interaction during the peroxidation process. $CoQH_2$ has the ability to both prevent production and eliminate directly lipid peroxyl radicals (LOO), while vitamin E acts by quenching these radicals. Also, $CoQH_2$ regenerates vitamin E from the α-tocopheroxyl radical [71]. CoQ is considered an efficient antioxidant against radicals produced in membranes for its regeneration capacity, its lipid solubility and because of its involvement in the initiation and propagation of lipid peroxidation [72].

CoQ is effective in the prevention of DNA damage as shown by the decreased strand breaks in DNA and other oxidative DNA damage markers in mitochondria [73], which is important for mitochondrial DNA since its oxidative damage is approximately 10-fold higher than nuclear DNA and is not easily reparable. These data are supported by Tomasetti and colleagues [74][75] who showed that CoQ_{10} supplementation inhibits DNA strand break formation and oxidative damage and enhances DNA repair enzyme activities in lymphocytes. Both the antioxidant activity of CoQ_{10} and the role that CoQ_{10} may play in the redox mechanism implicated in the transactivation of DNA repair enzymes could explain the capability of CoQ_{10} to protect DNA from oxidative damage. However, the precise mechanism under these effects remains unclear.

The high efficiency of CoQ as an antioxidant is related to its effective reactivation redox, its ubiquitous distribution, its localization in membranes, its relatively high concentration and the large capacity of the cell to regenerate CoQ at all its locations [76][77].

2.3. Other Controversial Functions

It has been suggested that CoQ is one of the compounds influencing the mitochondrial permeability transition pore (PTP). Studies about the regulation of the PTP by ubiquinone analogues show that ubiquinone inhibits the Ca^{2+} dependent PTP opening, which is mediated through a ubiquinone-binding site directly involved in PTP regulation rather than through redox reactions [78]. However, further details about the organization, structure, components and regulation of the PTP are required to understand whether CoQ has a primary function in the PTP. Other mitochondrial components susceptible to being regulated by redox reactions are the uncoupling proteins (UCPs). However, controversial results have been reported regarding to the involvement of CoQ in the regulation of the UCPs [79][80][81][82][83].

3. Pathologic Conditions with Decreased Levels of CoQ

The levels of CoQ are quite stable in cells. However, CoQ levels can be severely reduced in a group of mitochondrial diseases called CoQ deficiencies, which are clinically and genetically heterogeneous disorders characterized by a decrease in the levels of CoQ in tissues or cells. If the deficiency is caused by pathogenic mutations in the genes required for CoQ_{10} biosynthesis, it is classified as primary CoQ_{10} deficiencies. Nevertheless, secondary CoQ_{10} deficiencies are caused by mutations in genes unrelated to CoQ biosynthesis or are derived from other physiological processes or pharmacological treatments. The secondary forms are probably more frequent than the primary defects.

CoQ deficiencies cause the inhibition of oxidative phosphorylation and ATP production, since CoQ is an essential component of the mitochondrial respiratory chain. Because CoQ has other roles unrelated to ATP production, CoQ deficiency can impair other vital cellular functions, such as sulfide metabolism [58][59][60], and may induce oxidative damage [46][84][85][86].

3.1. Primary CoQ_{10} Deficiencies

Primary ubiquinone deficiency is a subset of mitochondrial diseases caused by autosomal recessive mutations in CoQ genes. Ogasahara et al. [87] described the first patients with primary CoQ_{10} deficiency as two sisters with progressive muscle weakness, fatigability and central nervous system dysfunction, learning disability, and seizures in one and cerebellar syndrome in the other [87]. Since then, approximately 200 patients have been described with pathogenic mutations in PDSS1 [88], PDSS2 [89][90], CoQ2 [88][89][91], CoQ6 [89][92], CoQ7 [22], CoQ4 [93][94][95], CoQ5 [96], CoQ8A [36][37][38], CoQ8B [89][97] and CoQ9 [98] genes. The clinical manifestations are very heterogeneous among different genes and among patients with mutations in individual genes. Multiple organs may be affected and lead to different symptomatology; when the central nervous system (CNS) is affected the clinical manifestations are variable, including encephalopathy, seizures, cerebellar ataxia, epilepsy, intellectual disability, hypotonia, dystonia, spasticity; in kidney, the most common manifestations is steroid-resistant nephrotic syndrome (SRNS); myopathy in muscle and hypertrophic cardiomyopathy in heart. Many symptoms are common to other mitochondrial diseases [99].

3.2. Secondary CoQ_{10} Deficiencies

Secondary CoQ deficiencies may affect any of the multiple CoQ biological functions and its connection to other metabolic pathways [100][101]. Low CoQ levels have been observed in a wide spectrum of diseases, such as oxidative phosphorylation (OXPHOS) diseases due to defects in nDNA-encoded proteins, OXPHOS diseases due to defects in mtDNA-encoded proteins and non-OXPHOS diseases (mitochondrial energy metabolism disorders and other non-mitochondrial diseases). Examples of diseases that may display secondary CoQ deficiencies include mitochondrial myopathies, mitochondrial DNA depletion syndrome, multiple acyl-CoA dehydrogenase deficiency (by mutations in *ETFDH*), ataxia-oculomotor apraxia syndrome (by mutations in *APTX*), cardiofaciocutaneous syndrome (by mutations in *BRAF*), methylmalonic aciduria, GLUT1 deficiency syndrome, mucopolysaccharidosys type III, spinocerebellar ataxia-10 (by mutations in *ANO10*) or multisystem atrophy (MSA) [102][103][104][105][106]. The symptoms are highly dependent on the original pathology and the most common symptoms are muscular and central nervous system manifestations. The exact mechanisms by which CoQ deficiency occurs are still unknown but it has been speculated that the low CoQ values in patients with mitochondrial diseases may be explained by a combination of different mechanisms, such as an incomplete or abnormal respiratory chain that may affect the formation of Complex Q linked to the respiratory chain (resulting in alterations in CoQ biosynthesis); an increase in CoQ degradation as a consequence of the oxidative stress derived from OXPHOS dysfunction; an interference with signaling pathways that potentially regulate CoQ biosynthesis; or a general deterioration of mitochondrial function [55][107].

Other diseases such as liver cirrhosis, phenylketonuria, fibromyalgia and cardiomyopathies also present a decrease in plasma CoQ levels [101][108], although this parameter is not reliable for a diagnostic purpose [109]. The use of statins to treat hypercholesterolemia can cause secondary CoQ deficiency because statins inhibit the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) in the mevalonate pathway, which is required to produce farnesyl pyrophosphate, an intermediate in CoQ biosynthesis [110]. Also, a decrease in the levels of the components of Complex Q has recently been related to secondary CoQ deficiency in various mouse models of mitochondrial diseases [111], as well as in muscle and adipose tissue of patients and a mouse model with insulin resistance [112].

References

1. Kalén, A.; Appelkvist, E.L.; Chojnacki, T.; Dallner, G. Nonaprenyl-4-hydroxybenzoate transferase, an enzyme involved in ubiquinone biosynthesis, in the endoplasmic reticulum-Golgi system of rat liver. J. Biol. Chem. 1990, 265, 1158–1164.
2. Kalén, A.; Norling, B.; Appelkvist, E.; Dallner, G. Ubiquinone biosynthesis by the microsomal fraction from rat liver. Biochim. Biophys. Acta 1987, 926, 70–78.
3. Eisenberg-Bord, M.; Tsui, H.S.; Antunes, D.; Fernandez-Del-Rio, L.; Bradley, M.C.; Dunn, C.D.; Nguyen, T.P.T.; Rapaport, D.; Clarke, C.F.; Schuldiner, M. The Endoplasmic Reticulum-Mitochondria Encounter Structure Complex Coordinates Coenzyme Q Biosynthesis. Contact 2019, 2.
4. Turunen, M.; Olsson, J.; Dallner, G. Metabolism and function of coenzyme Q. Biochim. Biophys. Acta 2004, 1660, 171–199.
5. Tzagoloff, A.; Akai, A.; Needleman, R.B.; Zulch, G. Assembly of the mitochondrial membrane system. Cytoplasmic mutants of Saccharomyces cerevisiae with lesions in enzymes of the respiratory chain and in the mitochondrial ATPase. J. Biol. Chem. 1975, 250, 8236–8242.
6. Tzagoloff, A.; Dieckmann, C.L. PET genes of Saccharomyces cerevisiae. Microbiol. Rev. 1990, 54, 211–225.

7. Meganathan, R. Ubiquinone biosynthesis in microorganisms. FEMS Microbiol. Lett. 2001, 203, 131–139.
8. Hajj Chehade, M.; Loiseau, L.; Lombard, M.; Pecqueur, L.; Ismail, A.; Smadja, M.; Golinelli-Pimpaneau, B.; Mellot-Draznieks, C.; Hamelin, O.; Aussel, L.; et al. ubiI, a new gene in Escherichia coli coenzyme Q biosynthesis, is involved in aerobic C5-hydroxylation. J. Biol. Chem. 2013, 288, 20085–20092.
9. Aussel, L.; Loiseau, L.; Hajj Chehade, M.; Pocachard, B.; Fontecave, M.; Pierrel, F.; Barras, F. ubiJ, a new gene required for aerobic growth and proliferation in macrophage, is involved in coenzyme Q biosynthesis in Escherichia coli and Salmonella enterica serovar Typhimurium. J. Bacteriol. 2014, 196, 70–79.
10. Awad, A.M.; Bradley, M.C.; Fernández-Del-Río, L.; Nag, A.; Tsui, H.S.; Clarke, C.F. Coenzyme Q10 deficiencies: Pathways in yeast and humans. Essays Biochem. 2018, 62, 361–376.
11. Saiki, R.; Nagata, A.; Kainou, T.; Matsuda, H.; Kawamukai, M. Characterization of solanesyl and decaprenyl diphosphate synthases in mice and humans. FEBS J. 2005, 272, 5606–5622.
12. Hayashi, K.; Ogiyama, Y.; Yokomi, K.; Nakagawa, T.; Kaino, T.; Kawamukai, M. Functional Conservation of Coenzyme Q Biosynthetic Genes among Yeasts, Plants, and Humans. PLoS ONE 2014, 9, e99038.
13. Kawamukai, M. Biosynthesis of coenzyme Q in eukaryotes. Biosci. Biotechnol. Biochem. 2016, 80, 23–33.
14. Marbois, B.; Xie, L.X.; Choi, S.; Hirano, K.; Hyman, K.; Clarke, C.F. para-Aminobenzoic Acid Is a Precursor in Coenzyme Q6 Biosynthesis in Saccharomyces cerevisiae. J. Biol. Chem. 2010, 285, 27827–27838.
15. Payet, L.-A.; Leroux, M.; Willison, J.C.; Kihara, A.; Pelosi, L.; Pierrel, F. Mechanistic Details of Early Steps in Coenzyme Q Biosynthesis Pathway in Yeast. Cell Chem. Biol. 2016, 23, 1241–1250.
16. Stefely, J.A.; Kwiecien, N.W.; Freiberger, E.C.; Richards, A.L.; Jochem, A.; Rush, M.J.P.; Ulbrich, A.; Robinson, K.P.; Hutchins, P.D.; Veling, M.T.; et al. Mitochondrial protein functions elucidated by multi-omic mass spectrometry profiling. Nat. Biotechnol. 2016, 34, 1191–1197.
17. Stefely, J.A.; Pagliarini, D.J. Biochemistry of Mitochondrial Coenzyme Q Biosynthesis. Trends Biochem. Sci. 2017, 42, 824–843.
18. 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.
19. Hidalgo-Gutierrez, A.; Barriocanal-Casado, E.; Bakkali, M.; Diaz-Casado, M.E.; Sanchez-Maldonado, L.; Romero, M.; Sayed, R.K.; Prehn, C.; Escames, G.; Duarte, J.; et al. beta-RA reduces DMQ/CoQ ratio and rescues the encephalopathic phenotype in Coq9 (R239X) mice. EMBO Mol. Med. 2019, 11, e9466.
20. Pierrel, F. Impact of Chemical Analogs of 4-Hydroxybenzoic Acid on Coenzyme Q Biosynthesis: From Inhibition to Bypass of Coenzyme Q Deficiency. Front. Physiol. 2017, 8, 436.
21. Wang, Y.; Oxer, D.; Hekimi, S. Mitochondrial function and lifespan of mice with controlled ubiquinone biosynthesis. Nat. Commun. 2015, 6, 6393.
22. Wang, Y.; Smith, C.; Parboosingh, J.S.; Khan, A.; Innes, M.; Hekimi, S. Pathogenicity of two COQ7 mutations and responses to 2,4-dihydroxybenzoate bypass treatment. J. Cell. Mol. Med. 2017, 21, 2329–2343.
23. Luna-Sánchez, M.; Díaz-Casado, E.; Barca, E.; Ángel, T.M.; Ángeles, M.-G.; Cobos, E.J.; Escames, G.; Acuña-Castroviejo, D.; Quinzii, C.M.; López, L.C. The clinical heterogeneity of coenzyme Q10 deficiency results from genotypic differences in the Coq9 gene. EMBO Mol. Med. 2015, 7, 670–687.
24. Xie, L.X.; Williams, K.J.; He, C.H.; Weng, E.; Khong, S.; Rose, T.E.; Kwon, O.; Bensinger, S.J.; Marbois, B.N.; Clarke, C.F. Resveratrol and para-coumarate serve as ring precursors for coenzyme Q biosynthesis[S]. J. Lipid Res. 2015, 56, 909–919.
25. Fernandez-Del-Rio, L.; Nag, A.; Gutierrez Casado, E.; Ariza, J.; Awad, A.M.; Joseph, A.I.; Kwon, O.; Verdin, E.; de Cabo, R.; Schneider, C.; et al. Kaempferol increases levels of coenzyme Q in kidney cells and serves as a biosynthetic ring precursor. Free Radic. Biol. Med. 2017, 110, 176–187.
26. Gin, P.; Hsu, A.Y.; Rothman, S.C.; Jonassen, T.; Tzagoloff, A.; Clarke, C.F.; Lee, P.T. TheSaccharomyces cerevisiae COQ6Gene Encodes a Mitochondrial Flavin-dependent Monooxygenase Required for Coenzyme Q Biosynthesis. J. Biol. Chem. 2003, 278, 25308–25316.
27. 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, 1134–1142.
28. Marbois, B.; Gin, P.; Faull, K.F.; Poon, W.W.; Strahan, J.; Clarke, C.F.; Lee, P.T.; Shepherd, J.N. Coq3 and Coq4 Define a Polypeptide Complex in Yeast Mitochondria for the Biosynthesis of Coenzyme Q. J. Biol. Chem. 2005, 280, 20231–20238.

29. Zhu, Y.; Wu, B.; Zhang, X.; Fan, X.; Niu, L.; Li, X.; Wang, J.; Teng, M. Structural and biochemical studies reveal UbiG/Coq3 as a class of novel membrane-binding proteins. Biochem. J. 2015, 470, 105–114.

30. Cox, G.B.; Young, I.G.; McCann, L.M.; Gibson, F. Biosynthesis of Ubiquinone in Escherichia coli K-12: Location of Genes Affecting the Metabolism of 3-Octaprenyl-4-hydroxybenzoic Acid and 2-Octaprenylphenol. J. Bacteriol. 1969, 99, 450–458.

31. Young, I.G.; Stroobant, P.; Macdonald, C.G.; Gibson, F. Pathway for Ubiquinone Biosynthesis in Escherichia coli K-12: Gene-Enzyme Relationships and Intermediates. J. Bacteriol. 1973, 114, 42–52.

32. White, M.D.; Payne, K.A.P.; Fisher, K.; Marshall, S.A.; Parker, D.; Rattray, N.J.W.; Trivedi, D.K.; Goodacre, R.; Rigby, S.E.J.; Scrutton, N.S.; et al. UbiX is a flavin prenyltransferase required for bacterial ubiquinone biosynthesis. Nature 2015, 522, 502–506.

33. Dai, Y.N.; Zhou, K.; Cao, D.D.; Jiang, Y.L.; Meng, F.; Chi, C.B.; Ren, Y.M.; Chen, Y.; Zhou, C.Z. Crystal structures and catalytic mechanism of the C-methyltransferase Coq5 provide insights into a key step of the yeast coenzyme Q synthesis pathway. Acta Crystallogr. D Biol. Crystallogr. 2014, 70, 2085–2092.

34. Nguyen, T.P.; Casarin, A.; Desbats, M.A.; Doimo, M.; Trevisson, E.; Santos-Ocaña, C.; Navas, P.; Clarke, C.F.; Salviati, L. Molecular characterization of the human COQ5 C-methyltransferase in coenzyme Q10 biosynthesis. Biochim. Biophys. Acta 2014, 1841, 1628–1638.

35. Stenmark, P.; Grunler, J.; Mattsson, J.; Sindelar, P.J.; Nordlund, P.; Berthold, D.A. A new member of the family of di-iron carboxylate proteins. Coq7 (clk-1), a membrane-bound hydroxylase involved in ubiquinone biosynthesis. J. Biol. Chem. 2001, 276, 33297–33300.

36. Gerards, M.; Bosch, B.V.D.; Calis, C.; Schoonderwoerd, K.; Van Engelen, K.; Tijssen, M.; De Coo, R.; Van Der Kooi, A.; Smeets, H. Nonsense mutations in CABC1/ADCK3 cause progressive cerebellar ataxia and atrophy. Mitochondrion 2010, 10, 510–515.

37. Horváth, P.O.; Czermin, B.; Gulati, S.; Pyle, A.; Hassani, A.; Foley, C.; Taylor, R.W.; Chinnery, P.F. 003 Adult-onset cerebellar ataxia due to mutations in the CABC1/ADCK3 gene. J. Neurol. Neurosurg. Psychiatry 2012, 83.

38. Lagier-Tourenne, C.; Tazir, M.; López, L.C.; Quinzii, C.M.; Assoum, M.; Drouot, N.; Busso, C.; Makri, S.; Ali-Pacha, L.; Benhassine, T.; et al. ADCK3, an Ancestral Kinase, Is Mutated in a Form of Recessive Ataxia Associated with Coenzyme Q10 Deficiency. Am. J. Hum. Genet. 2008, 82, 661–672.

39. Vazquez Fonseca, L.; Doimo, M.; Calderan, C.; Desbats, M.A.; Acosta, M.J.; Cerqua, C.; Cassina, M.; Ashraf, S.; Hildebrandt, F.; Sartori, G.; et al. Mutations in COQ8B (ADCK4) found in patients with steroid-resistant nephrotic syndrome alter COQ8B function. Hum. Mutat. 2018, 39, 406–414.

40. Xie, L.X.; Ozeir, M.; Tang, J.Y.; Chen, J.Y.; Jaquinod, S.-K.; Fontecave, M.; Clarke, C.F.; 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, 23571–23581.

41. Reidenbach, A.G.; Kemmerer, Z.A.; Aydin, D.; Jochem, A.; McDevitt, M.T.; Hutchins, P.D.; Stark, J.L.; Stefely, J.A.; Reddy, T.; Hebert, A.S.; et al. Conserved Lipid and Small-Molecule Modulation of COQ8 Reveals Regulation of the Ancient Kinase-like UbiB Family. Cell Chem. Biol. 2018, 25, 154–165 e111.

42. Hsieh, E.J.; Gin, P.; Gulmezian, M.; Tran, U.C.; Saiki, R.; Marbois, B.N.; Clarke, C.F. Saccharomyces cerevisiae Coq9 Polypeptide is a Subunit of the Mitochondrial Coenzyme Q Biosynthetic Complex. Arch. Biochem. Biophys. 2007, 463, 19–26.

43. Lohman, D.C.; Aydin, D.; Von Bank, H.C.; Smith, R.W.; Linke, V.; Weisenhorn, E.; McDevitt, M.T.; Hutchins, P.; Wilkerson, E.M.; Wancewicz, B.; et al. An Isoprene Lipid-Binding Protein Promotes Eukaryotic Coenzyme Q Biosynthesis. Mol. Cell 2019, 73, 763–774.e10.

44. He, C.W.; Black, D.S.; Nguyen, T.P.T.; Wang, C.; Srinivasan, C.; Clarke, C.F. Yeast Coq9 controls deamination of coenzyme Q intermediates that derive from para-aminobenzoic acid. Biochim. Biophys. Acta 2015, 1851, 1227–1239.

45. Lohman, D.C.; Forouhar, F.; Beebe, E.T.; Stefely, M.S.; Minogue, C.E.; Ulbrich, A.; Stefely, J.A.; Sukumar, S.; Luna-Sánchez, M.; Jochem, A.; et al. Mitochondrial COQ9 is a lipid-binding protein that associates with COQ7 to enable coenzyme Q biosynthesis. Proc. Natl. Acad. Sci. USA 2014, 111, E4697–E4705.

46. Garcia-Corzo, L.; Luna-Sanchez, M.; Doerrier, C.; Garcia, J.A.; Guaras, A.; Acin-Perez, R.; Bullejos-Peregrin, J.; Lopez, A.; Escames, G.; Enriquez, J.A.; et al. Dysfunctional Coq9 protein causes predominant encephalomyopathy associated with CoQ deficiency. Hum. Mol. Genet. 2013, 22, 1233–1248.

47. Wang, Y.; Hekimi, S. Molecular genetics of ubiquinone biosynthesis in animals. Crit. Rev. Biochem. Mol. Biol. 2013, 48, 69–88.

48. Allan, C.M.; Hill, S.; Morvaridi, S.; Saiki, R.; Johnson, J.S.; Liau, W.S.; Hirano, K.; Kawashima, T.; Ji, Z.; Loo, J.A.; et al. A conserved START domain coenzyme Q-binding polypeptide is required for efficient Q biosynthesis, respiratory electron transport, and antioxidant function in Saccharomyces cerevisiae. Biochim. Biophys. Acta 2013, 1831, 776–791.

49. Cui, T.Z.; Kawamukai, M. Coq10, a mitochondrial coenzyme Q binding protein, is required for proper respiration in Schizosaccharomyces pombe. FEBS J. 2009, 276, 748–759.

50. Tsui, H.S.; Pham, N.V.B.; Amer, B.R.; Bradley, M.C.; Gosschalk, J.E.; Gallagher-Jones, M.; Ibarra, H.; Clubb, R.T.; Blaby-Haas, C.E.; Clarke, C.F. Human COQ10A and COQ10B are distinct lipid-binding START domain proteins required for coenzyme Q function. J. Lipid Res. 2019, 60, 1293–1310.

51. Marbois, B.; Gin, P.; Gulmezian, M.; Clarke, C.F. The yeast Coq4 polypeptide organizes a mitochondrial protein complex essential for coenzyme Q biosynthesis. Biochim. Biophys. Acta 2009, 1791, 69–75.

52. Belogrudov, G.I.; Lee, P.T.; Jonassen, T.; Hsu, A.Y.; Gin, P.; Clarke, C.F. Yeast COQ4 Encodes a Mitochondrial Protein Required for Coenzyme Q Synthesis. Arch. Biochem. Biophys. 2001, 392, 48–58.

53. Casarin, A.; Jimenez-Ortega, J.C.; Trevisson, E.; Pertegato, V.; Doimo, M.; Ferrero-Gomez, M.L.; Abbadi, S.; Artuch, R.; Quinzii, C.; Hirano, M.; et al. Functional characterization of human COQ4, a gene required for Coenzyme Q10 biosynthesis. Biochem. Biophys. Res. Commun. 2008, 372, 35–39.

54. Allan, C.M.; Awad, A.M.; Johnson, J.S.; Shirasaki, D.I.; Wang, C.; Blaby-Haas, C.E.; Merchant, S.S.; Loo, J.A.; Clarke, C.F. Identification of Coq11, a New Coenzyme Q Biosynthetic Protein in the CoQ-Synthome in Saccharomyces cerevisiae. J. Biol. Chem. 2015, 290, 7517–7534.

55. He, C.H.; Xie, L.X.; Allan, C.M.; Tran, U.C.; Clarke, C.F. 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, 630–644.

56. Stefely, J.A.; Licitra, F.; Laredj, L.; Reidenbach, A.G.; Kemmerer, Z.A.; Grangeray, A.; Jaeg-Ehret, T.; Minogue, C.E.; Ulbrich, A.; Hutchins, P.D.; et al. Cerebellar Ataxia and Coenzyme Q Deficiency through Loss of Unorthodox Kinase Activity. Mol. Cell 2016, 63, 608–620.

57. Crane, F.; Hatefi, Y.; Lester, R.; Widmer, C. Isolation of a quinone from beef heart mitochondria. Biochim. Biophys. Acta 1957, 25, 220–221.

58. Quinzii, C.M.; Luna-Sanchez, M.; Ziosi, M.; Hidalgo-Gutierrez, A.; Kleiner, G.; Lopez, L.C. The Role of Sulfide Oxidation Impairment in the Pathogenesis of Primary CoQ Deficiency. Front. Physiol. 2017, 8, 525.

59. Ziosi, M.; Di Meo, I.; Kleiner, G.; Gao, X.H.; Barca, E.; Sanchez-Quintero, M.J.; Tadesse, S.; Jiang, H.; Qiao, C.; Rodenburg, R.J.; et al. Coenzyme Q deficiency causes impairment of the sulfide oxidation pathway. EMBO Mol. Med. 2017, 9, 96–111.

60. Luna-Sanchez, M.; Hidalgo-Gutierrez, A.; Hildebrandt, T.M.; Chaves-Serrano, J.; Barriocanal-Casado, E.; Santos-Fandila, A.; Romero, M.; Sayed, R.K.; Duarte, J.; Prokisch, H.; et al. CoQ deficiency causes disruption of mitochondrial sulfide oxidation, a new pathomechanism associated with this syndrome. EMBO Mol. Med. 2017, 9, 78–95.

61. Zhang, M.; Wakitani, S.; Hayashi, K.; Miki, R.; Kawamukai, M. High production of sulfide in coenzyme Q deficient fission yeast. BioFactors 2008, 32, 91–98.

62. Blake, R.L.; Hall, J.G.; Russell, E.S. Mitochondrial proline dehydrogenase deficiency in hyperprolinemic PRO/Re mice: Genetic and enzymatic analyses. Biochem. Genet. 1976, 14, 739–757.

63. Battino, M.; Fato, R.; Lenaz, G.; Drahota, Z. Coenzyme Q-pool function in glycerol-3-phosphate oxidation in hamster brown adipose tissue mitochondria. J. Bioenerg. Biomembr. 1992, 24, 235–241.

64. Evans, D.R.; Guy, H.I. Mammalian Pyrimidine Biosynthesis: Fresh Insights into an Ancient Pathway. J. Biol. Chem. 2004, 279, 33035–33038.

65. Jones, E.M. Pyrimidine Nucleotide Biosynthesis in Animals: Genes, Enzymes, and Regulation of UMP Biosynthesis. Annu. Rev. Biochem. 1980, 49, 253–279.

66. López-Martín, J.M.; Salviati, L.; Trevisson, E.; Montini, G.; DiMauro, S.; Quinzii, C.; Hirano, M.; Rodriguez-Hernandez, A.; Cordero, M.D.; Sánchez-Alcázar, J.A.; et al. Missense mutation of the COQ2 gene causes defects of bioenergetics and de novo pyrimidine synthesis. Hum. Mol. Genet. 2007, 16, 1091–1097.

67. Watmough, N.J.; Frerman, F.E. The electron transfer flavoprotein: Ubiquinone oxidoreductases. Biochim. Biophys. Acta 2010, 1797, 1910–1916.

68. Summitt, C.B.; Johnson, L.C.; Jönsson, T.J.; Parsonage, D.; Holmes, R.P.; Lowther, W.T. Proline dehydrogenase 2 (PRODH2) is a hydroxyproline dehydrogenase (HYPDH) and molecular target for treating primary hyperoxaluria.

Biochem. J. 2015, 466, 273–281.

69. Forsmark-Andrée, P.; Dallner, G.; Ernster, L. Endogenous ubiquinol prevents protein modification accompanying lipid peroxidation in beef heart submitochondrial particles. Free Radic. Biol. Med. 1995, 19, 749–757.
70. Godic, A.; Poljsak, B.; Adamič, M.; Dahmane, R. The Role of Antioxidants in Skin Cancer Prevention and Treatment. Oxidative Med. Cell. Longev. 2014, 2014, 1–6.
71. Mukai, K.; Kikuchi, S.; Urano, S. Stopped-flow kinetic study of the regeneration reaction of tocopheroxyl radical by reduced ubiquinone-10 in solution. Biochim. Biophys. Acta 1990, 1035, 77–82.
72. Frei, B.; Kim, M.C.; Ames, B.N. Ubiquinol-10 is an effective lipid-soluble antioxidant at physiological concentrations. Proc. Natl. Acad. Sci. USA 1990, 87, 4879–4883.
73. Forsmark-Andree, P.; Ernster, L. Evidence for a protective effect of endogenous ubiquinol against oxidative damage to mitochondrial protein and DNA during lipid peroxidation. Mol. Asp. Med. 1994, 15, S73–S81.
74. Tomasetti, M.; Littarru, G.; Stocker, R.; Alleva, R. Coenzyme Q10 enrichment decreases oxidative DNA damage in human lymphocytes. Free Radic. Biol. Med. 1999, 27, 1027–1032.
75. Tomasetti, M.; Alleva, R.; Collins, A.R. In vivo supplementation with coenzyme Q10 enhances the recovery of human lymphocytes from oxidative DNA damage. FASEB J. 2001, 15, 1425–1427.
76. Bentinger, M.; Brismar, K.; Dallner, G. The antioxidant role of coenzyme Q. Mitochondrion 2007, 7, S41–S50.
77. Bentinger, M.; Dallner, G.; Chojnacki, T.; Swiezewska, E. Distribution and breakdown of labeled coenzyme Q10 in rat. Free Radic. Biol. Med. 2003, 34, 563–575.
78. Fontaine, E.; Ichas, F.; Bernardi, P. A Ubiquinone-binding Site Regulates the Mitochondrial Permeability Transition Pore. J. Biol. Chem. 1998, 273, 25734–25740.
79. Echtay, K.S.; Winkler, E.; Klingenberg, M.; Echtay, K.S.; Winkler, E.; Echtay, K.S.; Winkler, E.; Klingenberg, M. Coenzyme Q is an obligatory cofactor for uncoupling protein function. Nature 2000, 408, 609–613.
80. Echtay, K.S.; Winkler, E.; Frischmuth, K.; Klingenberg, M. Uncoupling proteins 2 and 3 are highly active H(+) transporters and highly nucleotide sensitive when activated by coenzyme Q (ubiquinone). Proc. Natl. Acad. Sci. USA 2001, 98, 1416–1421.
81. Jaburek, M.; Garlid, K.D. Reconstitution of recombinant uncoupling proteins: UCP1, -2, and -3 have similar affinities for ATP and are unaffected by coenzyme Q10. J. Biol. Chem. 2003, 278, 25825–25831.
82. Esteves, T.C.; Echtay, K.S.; Jonassen, T.; Clarke, C.F.; Brand, M.D. Ubiquinone is not required for proton conductance by uncoupling protein 1 in yeast mitochondria. Biochem. J. 2004, 379, 309–315.
83. Sluse, F.E.; Jarmuszkiewicz, W.; Navet, R.; Douette, P.; Mathy, G.; Sluse-Goffart, C.M. Mitochondrial UCPs: New insights into regulation and impact. Biochim. Biophys. Acta 2006, 1757, 480–485.
84. Quinzii, C.M.; Lopez, L.C.; Von-Moltke, J.; Naini, A.; Krishna, S.; Schuelke, M.; Salviati, L.; Navas, P.; DiMauro, S.; Hirano, M. Respiratory chain dysfunction and oxidative stress correlate with severity of primary CoQ10 deficiency. FASEB J. 2008, 22, 1874–1885.
85. Quinzii, C.M.; Lopez, L.C.; Gilkerson, R.W.; Dorado, B.; Coku, J.; Naini, A.B.; Lagier-Tourenne, C.; Schuelke, M.; Salviati, L.; Carrozzo, R.; et al. Reactive oxygen species, oxidative stress, and cell death correlate with level of CoQ10 deficiency. FASEB J. 2010, 24, 3733–3743.
86. Quinzii, C.M.; Garone, C.; Emmanuele, V.; Tadesse, S.; Krishna, S.; Dorado, B.; Hirano, M. Tissue-specific oxidative stress and loss of mitochondria in CoQ-deficient Pdss2 mutant mice. FASEB J. 2013, 27, 612–621.
87. Ogasahara, S.; Engel, A.G.; Frens, D.; Mack, D. Muscle coenzyme Q deficiency in familial mitochondrial encephalomyopathy. Proc. Natl. Acad. Sci. USA 1989, 86, 2379–2382.
88. Mollet, J.; Giurgea, I.; Schlemmer, D.; Dallner, G.; Chrétien, 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. Investig. 2007, 117, 765–772.
89. Sadowski, C.E.; Lovric, S.; Ashraf, S.; Pabst, W.L.; Gee, H.Y.; Kohl, S.; Engelmann, S.; Vega-Warner, V.; Fang, H.; Halbritter, J.; et al. A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome. J. Am. Soc. Nephrol. 2015, 26, 1279–1289.
90. López, L.C.; Schuelke, M.; Quinzii, C.M.; Kanki, T.; Rodenburg, R.J.T.; Naini, A.; DiMauro, S.; Hirano, M. Leigh Syndrome with Nephropathy and CoQ10 Deficiency Due to decaprenyl diphosphate synthase subunit 2 (PDSS2) Mutations. Am. J. Hum. Genet. 2006, 79, 1125–1129.

91. Quinzii, C.; Naini, A.; Salviati, L.; Trevisson, E.; Navas, P.; Dimauro, S.; Hirano, M. A mutation in para-hydroxybenzoate-polyprenyl transferase (COQ2) causes primary coenzyme Q10 deficiency. Am. J. Hum. Genet. 2006, 78, 345–349.
92. Heeringa, S.F.; Chernin, G.; Chaki, M.; Zhou, W.; Sloan, A.J.; Ji, Z.; Xie, L.X.; Salviati, L.; Hurd, T.W.; Vega-Warner, V.; et al. COQ6 mutations in human patients produce nephrotic syndrome with sensorineural deafness. J. Clin. Investig. 2011, 121, 2013–2024.
93. Sondheimer, N.; Hewson, S.; Cameron, J.M.; Somers, G.R.; Broadbent, J.D.; Ziosi, M.; Quinzii, C.M.; Naini, A.B. Novel recessive mutations in COQ4 cause severe infantile cardiomyopathy and encephalopathy associated with CoQ10 deficiency. Mol. Genet. Metab. Rep. 2017, 12, 23–27.
94. Chung, W.K.; Martin, K.; Jalas, C.; Braddock, S.R.; Juusola, J.; Monaghan, K.G.; Warner, B.; Franks, S.; Yudkoff, M.; Lulis, L.; et al. Mutations in COQ4, an essential component of coenzyme Q biosynthesis, cause lethal neonatal mitochondrial encephalomyopathy. J. Med. Genet. 2015, 52, 627–635.
95. Brea-Calvo, G.; Haack, T.B.; Karall, D.; Ohtake, A.; Invernizzi, F.; Carrozzo, R.; Kremer, L.; Dusi, S.; Fauth, C.; Scholl-Burgi, S.; et al. COQ4 mutations cause a broad spectrum of mitochondrial disorders associated with CoQ10 deficiency. Am. J. Hum. Genet. 2015, 96, 309–317.
96. Malicdan, M.C.V.; Vilboux, T.; Ben-Zeev, B.; Guo, J.; Eliyahu, A.; Pode-Shakked, B.; Dori, A.; Kakani, S.; Chandrasekharappa, S.C.; Ferreira, C.R.; et al. A novel inborn error of the coenzyme Q10 biosynthesis pathway: Cerebellar ataxia and static encephalomyopathy due to COQ5 C-methyltransferase deficiency. Hum. Mutat. 2018, 39, 69–79.
97. Ashraf, S.; Gee, H.Y.; Woerner, S.; Xie, L.X.; Vega-Warner, V.; Lovric, S.; Fang, H.; Song, X.; Cattran, D.C.; Avila-Casado, C.; et al. ADCK4 mutations promote steroid-resistant nephrotic syndrome through CoQ10 biosynthesis disruption. J. Clin. Investig. 2013, 123, 5179–5189.
98. Duncan, A.J.; Bitner-Glindzicz, M.; Meunier, B.; Costello, H.; Hargreaves, I.P.; López, L.C.; Hirano, M.; Quinzii, C.M.; Sadowski, M.I.; Hardy, J.; et al. 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, 558–566.
99. Alcázar-Fabra, M.; Trevisson, E.; Brea-Calvo, G. Clinical syndromes associated with Coenzyme Q10 deficiency. Essays Biochem. 2018, 62, 377–398.
100. Padilla, S.; González-Mariscal, I.; Martín-Montalvo, A.; Gonzalez-Mariscal, I.; García-Testón, E.; Martin-Montalvo, A.; Pomares-Viciana, T.; Vazquez-Fonseca, L.; Gandolfo-Domínguez, P.; Santos-Ocaña, C.; et al. Regulation of coenzyme Q biosynthesis in yeast: A new complex in the block. IUBMB Life 2014, 66, 63–70.
101. Yubero, D.; Montero, R.; Martin, M.A.; Montoya, J.; Ribes, A.; Grazina, M.; Trevisson, E.; Rodriguez-Aguilera, J.C.; Hargreaves, I.P.; Salviati, L.; et al. Secondary coenzyme Q10 deficiencies in oxidative phosphorylation (OXPHOS) and non-OXPHOS disorders. Mitochondrion 2016, 30, 51–58.
102. Montero, R.; Grazina, M.; López-Gallardo, E.; Montoya, J.; Briones, P.; Navarro-Sastre, A.; Land, J.M.; Hargreaves, I.P.; Artuch, R.; O'Callaghan, M.D.M.; et al. Coenzyme Q10 deficiency in mitochondrial DNA depletion syndromes. Mitochondrion 2013, 13, 337–341.
103. Quinzii, C.M.; Kattah, A.G.; Naini, A.; Akman, H.O.; Mootha, V.K.; DiMauro, S.; Hirano, M. Coenzyme Q deficiency and cerebellar ataxia associated with an aprataxin mutation. Neurology 2005, 64, 539–541.
104. Gempel, K.; Topaloglu, H.; Talim, B.; Schneiderat, P.; Schoser, B.G.H.; Hans, V.H.; Pálmafy, B.; Kale, G.; Tokatli, A.; Quinzii, C.; et al. The myopathic form of coenzyme Q10 deficiency is caused by mutations in the electron-transferring-flavoprotein dehydrogenase (ETFDH) gene. Brain 2007, 130, 2037–2044.
105. Aeby, A.; Sznajer, Y.; Cave, H.; Rebuffat, E.; Van Coster, R.; Rigal, O.; Van Bogaert, P.; Coster, R.; Bogaert, P. Cardiofaciocutaneous (CFC) syndrome associated with muscular coenzyme Q10 deficiency. J. Inherit. Metab. Dis. 2007, 30, 827.
106. Balreira, A.; Boczonadi, V.; Barca, E.; Pyle, A.; Bánsági, B.; Appleton, M.; Graham, C.; Hargreaves, I.P.; Rasic, V.M.; Lochmüller, H.; et al. ANO10 mutations cause ataxia and coenzyme Q10 deficiency. J. Neurol. 2014, 261, 2192–2198.
107. Miranda, S.; Foncea, R.; Guerrero, J.; Leighton, F. Oxidative Stress and Upregulation of Mitochondrial Biogenesis Genes in Mitochondrial DNA-Depleted HeLa Cells. Biochem. Biophys. Res. Commun. 1999, 258, 44–49.
108. Desbats, M.A.; Lunardi, G.; Doimo, M.; Trevisson, E.; Salviati, L. Genetic bases and clinical manifestations of coenzyme Q10 (CoQ10) deficiency. J. Inherit. Metab. Dis. 2015, 38, 145–156.
109. Rahman, S.; Clarke, C.F.; Hirano, M. 176th ENMC International Workshop: Diagnosis and treatment of coenzyme Q10 deficiency. Neuromuscul. Disord. 2012, 22, 76–86.

110. Marcoff, L.; Thompson, P.D. The role of coenzyme Q10 in statin-associated myopathy: A systematic review. J. Am. Coll. Cardiol. 2007, 49, 2231–2237.
111. Kühl, I.; Miranda, M.; Atanassov, I.; Kuznetsova, I.; Hinze, Y.; Mourier, A.; Filipovska, A.; Larsson, N.-G. Transcriptomic and proteomic landscape of mitochondrial dysfunction reveals secondary coenzyme Q deficiency in mammals. eLife 2017, 6, 6.
112. Fazakerley, D.J.; Chaudhuri, R.; Yang, P.; Maghzal, G.J.; Thomas, K.C.; Krycer, J.R.; Humphrey, S.J.; Parker, B.L.; Fisher-Wellman, K.H.; Meoli, C.C.; et al. Mitochondrial CoQ deficiency is a common driver of mitochondrial oxidants and insulin resistance. eLife 2018, 7, 7.