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Abstract

Primary Coenzyme Q deficiencies represent a group of rare conditions caused by mutations in one of the genes required in its biosynthetic pathway at the enzymatic or regulatory level. The associated clinical manifestations are highly heterogeneous and mainly affect central and peripheral nervous system, kidney, skeletal muscle and heart. Genotype-phenotype correlations are difficult to establish, mainly because of the reduced number of patients and

the large variety of symptoms. In addition, mutations in the same *COQ* gene can cause different clinical pictures. Here we present an updated and comprehensive review of the clinical manifestations associated to each of the pathogenic variants causing primary CoQ deficiencies.

Abbreviation list

2,4-dHB, 2,4-dihydroxybenzoic acid; 3,4-dHB, 3,4-dihydroxybenzoate; 4-HB, 4-hydrozybenzoate; CNS, central nervous system; CoQ, Coenzyme Q; EEG, electroencephalography; ESRD, end-stage renal disease; ETFDH, electron transport flavoprotein dehydrogenase; HHB, hexaprenyl-hydroxybenzoate; ID, intellectual disability; LDL, low density lipoproteins; mETC, mitochondrial electron transport chain; MRI, magnetic resonance imaging; OXPHOS, oxidative phosphorylation; pABA, para-aminobenzoic acid; PNS, peripheral nervous system; ROS, reactive oxygen species; SNHL, sensorineural hearing loss; SRNS, steroid-resistant nephrotic syndrome; VA, vanillic acid.

Please, refer to table 3 for symptoms abbreviations.

Coenzyme Q structure and function

Coenzyme Q (CoQ) or ubiquinone is the only endogenously synthetized redox-active lipid that is found in virtually all endomembranes, plasma membrane and serum lipoproteins, being especially abundant in mitochondria. It is composed of a benzoquinone ring as a head group, and a polyisoprenoid chain, which inserts the molecule into the phospholipid bilayer and varies in length depending on the species (figure 1A). In humans, it has 10 isoprene units (CoQ_{10}), 6 in *Saccharomyces cerevisiae* (CoQ_6) and the main form found in mice has 9 units (CoQ_9), although low amounts of CoQ_{10} can be also detected in their membranes.

Soon after the first description by Cain and Morton in 1955 (1), the main function of CoQ in the mitochondrial electron transport chain (mETC) was proposed by Crane and cols., who also demonstrated its redox proprieties (2). In the mETC CoQ is an essential mobile electron

transport component, shuttling electrons from complex I (NADH-ubiquinone oxidoreductase) or complex II (succinate-ubiquinone oxidoreductase) to complex III (succinate-cytochrome c oxidoreductase).

CoQ is permanently going through oxidation-reduction cycles. It can be found in a completely reduced form ($CoQH_2$ or ubiquinol), after receiving two electrons, or in a completely oxidized form (CoQ or ubiquinone). When, as in the mETC, this redox cycle occurs by a two-step transfer of one electron each, a semiquinone (or semi-ubiquinone, $CoQ\bullet^-$) intermediate is produced (figure 1B).

Computational prediction models have recently confirmed studies describing how, in the inner mitochondrial membrane, CoQ is mainly located either close to the membrane-water interface, with its relatively small head group being shadowed by the bigger polar heads of phospholipids, or stabilized in the middle of the bilayer. During the process of electron transfer, CoQ rapidly translocates from one side to the other of the inner membrane bilayer, with a rate that varies depending on the redox state of the molecule. This process enables the interaction with the reducing and oxidizing sites in the proteins of the mETC complexes, located close to the membrane surfaces (3).

After the discovery of its role in the mETC, new functions have emerged for CoQ, being the electron acceptor for different dehydrogenases. Among others, in mitochondria CoQ accepts electrons from:

(i) dihydroorotate dehydrogenase, a key enzyme for pyrimidine biosynthesis (4) ,

(ii) mitochondrial glycerol-3-phosphate dehydrogenase (5), a tissue-specific component of mitochondria connecting glycolysis, oxidative phosphorylation and fatty acid metabolism (6),

(iii) electron transport flavoprotein dehydrogenase (ETFDH), a key enzyme involved in the fatty acid β-oxidation and branched-chain amino acid oxidation pathways (7),

(iv) proline dehydrogenase 1, an enzyme required for proline and arginine metabolism (8),

(v) probably, from hydroxyproline dehydrogenase (or proline dehydrogenase 2), involved in the glyoxylate metabolism (9)

(vi) sulphide-quinone oxidoreductase (10) during sulphide detoxification, a gas modulator of relevant cellular processes but toxic when in excess (11).

Reduced CoQ ($CoQH_2$) generated by all these processes is efficiently reoxidised by complex III in the mETC (figure 1C).

The ability to sustain continuous oxidation/reduction cycles makes CoQ not only a great electron carrier for different cellular processes, but also a potent membrane antioxidant, which protects lipids, proteins and nucleic acids from harmful oxidative damage (12,13). In membranes, $CoQH_2$ has been shown to prevent both initiation and propagation of lipid peroxidation (14,15) and, indirectly, to regenerate other antioxidants, such as α-tocopherol and ascorbate (16). The high efficiency of CoQ against oxidative stress may be related to its ubiquitous distribution, its localization in the core of membranes and the availability of diverse dehydrogenases, able to efficiently regenerate the molecule.

CoQ biosynthesis and regulation in eukaryotes/human

Levels of CoQ are quite stable in cells but its concentration varies among different tissues and organs, depending on dietary conditions and age (17–20). Although CoQ is mainly endogenously synthetized in mitochondria and then distributed to other cell membranes (21), cells can incorporate a certain amount from dietary sources. CoQ is synthesized by a set of nuclear-encoded COQ proteins, through a pathway that is not completely understood. Most of the work on CoQ biosynthesis has been done in *Saccharomyces cerevisiae*, and at least 13 yeast genes (*coq1* – *coq11*, *Yah1*, *Arh1*) have been identified as players of this process.

Information about the human pathway is very scarce, but orthologues of almost all of these genes have been already identified (see Dr. Clark review in this same number).

4-Hydrozybenzoate (4-HB), precursor of the benzoquinone ring, is synthesized from tyrosine, phenylalanine, or also para-aminobenzoic acid (pABA) in yeast, through a poorly characterized set of reactions (22–24). The isoprenoid tail comes from the mevalonate pathway, which is shared with cholesterol, among other molecules, and takes place in extra-mitochondrial membranes. This side chain is assembled by Coq1p (PDSS1 and PDSS2, acting as a heterotetramer, are the human orthologues), which also determines its length. Coq2p (human orthologue COQ2) condensates head and tail and the resulting molecule undergoes subsequent modifications of the ring moiety: C5-hydroxylation (yeast Coq6p, human COQ6) (25), O-methylations (yeast Coq3p, human COQ3) (26,27), C1-hydroxylation and C1-decarboxylation (unidentified), C2-methylation (yeast Coq5p, human COQ5) (28,29), and C6-hydroxylation (yeast Coq7p, human COQ7) (30), but also C4-deamination (Coq6p), in the case of yeast using pABA as precursor (24). Yah1 and Arh1 (human orthologues, FDXR and FDX2), mitochondrial ferredoxin and ferredoxin reductase, have been shown to transfer electrons to Coq6p (31). Mammalian pathway is still incompletely defined and significant efforts are required in order to determine whether it coincides with the yeast one (figure 2).

Other Coq proteins are thought to have regulatory functions. Coq8p (two human orthologues: COQ8A (or ADCK3/CABC1) and COQ8B (or ADCK4)), displays features of an atypical kinase that possibly phosphorylates Coq3p, Coq5p and Coq7p in yeast (32–34). However, COQ8A/ADCK3 has recently been shown to have a more clear ATPase activity (35) whose role in CoQ biosynthesis still needs to be further studied. Coq4p (human orthologue COQ4) function has not been elucidated yet, but it seems to be required for the formation and maintenance of the CoQ biosynthetic complex (36). Coq9p (human orthologue COQ9) is a lipid-binding protein stabilizing Coq7p (37,38). Coq10p (human orthologues COQ10A and COQ10B) probably

controls CoQ correct localization within the mitochondrial membranes (39). Coq11p is thought to be essential for CoQ synthesis in yeast, but lacks a clear human orthologue (40). Additionally, three other genes of the ADCK family (human *ADCK1*, *ADCK2* and *ADCK5*) have been proposed to participate in the biosynthetic process, but there is no experimental evidence for this (34,41).

It is widely accepted that yeast Coq3p-Coq9p proteins are organized in a multiprotein complex, possibly containing some intermediates of the biosynthesis and CoQ itself (40,42,43). The complex would probably optimize the orientation of the substrates and active sites of the enzymes as well as their functional coordination (36,44–47) (figure 2). Evidence supporting the existence of a conserved complex also in mammals has been recently reported by different groups through diverse approaches (23,29,35,38,48–52). However, functional organization and regulation of mammalian biosynthetic complex is still elusive and could be different from the yeast one.

Little is known about CoQ biosynthesis regulation, which may occur at the transcriptional, post-transcriptional and post-translational level, or even during the assembly of the putative multisubunit complex. Transcriptionally, several factors have emerged as possible candidates (53–55). However, a deep study of promoters and regulation sequences of the *COQ* genes is lacking currently. At the post-transcriptional level, several RNA binding proteins that modulate the stability of COQ transcripts have also been identified (56,57). At the post-translational level, processing by proteases, phosphorylation and dephosphorylation have been suggested to have a role in the regulation of some COQ proteins' activity, but only a very fragmented piece of information is currently available (33,34,58,59).

Clinical manifestations of CoQ deficiencies.

CoQ deficiencies have been associated with a wide range of clinical manifestations. Patients with CoQ deficiency have reduced levels of CoQ in tissues, which can be caused either by

mutations in the genes participating in CoQ biosynthesis, the so-called primary CoQ deficiencies, or by defects not directly linked CoQ biosynthesis, the secondary CoQ deficiencies.

Primary deficiencies.

Primary CoQ deficiencies are very rare conditions, usually associated with highly variable multisystemic manifestations (figure 3), and genetically caused by autosomal recessive mutations. Approximately 200 patients from 130 families have been described in the literature so far (Supplementary Table 1).

It has been estimated a worldwide total of 123,789 individuals (1 in 50,000) affected by primary CoQ deficiencies, being only 1,665 (less than 1 in 3,000,000) due to known pathogenic variants, taking into account the frequency of the different known or predicted pathogenic variants in given populations (60).

To date, ten genes encoding CoQ biosynthetic proteins have been shown to have pathogenic variants causing human CoQ deficiency: *PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ5*, *COQ6*, *COQ7*, *COQ8A*, *COQ8B* and *COQ9* (Table 1, supplementary table 1). They affect multiple organ systems in a highly variable way, including central nervous system (CNS) (encephalopathy, seizures, cerebellar ataxia, epilepsy or intellectual disability (ID)), peripheral nervous system (PNS), kidney (steroid-resistant nephrotic syndrome (SRNS)), skeletal muscle (myopathy), heart (hypertrophic cardiomyopathy) and sensory system (sensorineural hearing loss (SNHL), retinopathy or optic atrophy) (Table 2). While mutations in some *COQ* genes can affect different organs (e.g. *COQ2*, *COQ4*), pathogenic variants of other *COQ* genes show a more specific phenotype (e.g. *COQ8A*, *COQ8B*). Even more, mutations in the same *COQ* gene can cause very variable clinical phenotypes with different age of onset. The age of onset may generally range from birth to early childhood (*PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ5*, *COQ6*,

170 *COQ7*, *COQ9*), or from childhood to adolescence (*COQ8A*, *COQ8B*), but there are also some
171 adult-onset cases (*COQ2* (61); *COQ8A* (62,63); *COQ8B* (64)).

172 *CNS manifestations:*

173 Central nervous system is often affected in these patients, showing a wide range of clinical
174 manifestations, including encephalopathy, hypotonia, seizures, dystonia, cerebellar ataxia,
175 epilepsy, stroke-like episodes, spasticity or ID. These symptoms may be present in patients
176 with mutations in one of the reported COQ genes, but they are less prominent in patients with
177 pathogenic variants of *COQ6* and *COQ8B*, in whom the more frequent phenotype is renal
178 involvement. *COQ2* patients manifested early-onset nephrotic syndrome (17/22) which in
179 some cases may be accompanied by encephalopathy and seizures (7/22) (65–76). *COQ4*
180 patients generally show a severe CNS involvement, with encephalopathy and seizures (9/14),
181 hypotonia (10/14) and cerebellar hypoplasia (6/14); and often a fatal outcome with death in
182 the first days (6/14) or months (5/14) of life (77–81). The hallmark phenotype in *COQ8A*
183 patients is slow progressive cerebellar atrophy and ataxia (43/45), associated with ID (19/45),
184 epileptic seizures (18/45), tremor (18/45), dysarthria (16/45), saccadic eye movements
185 (10/45), dystonia (9/45) or spasticity (8/45), among others (62,63,82–93). The only *COQ5*
186 family described shows a phenotype similar to *COQ8A* patients (94). Some *COQ8A* patients
187 (6/45) (62,84,85,87) and one *COQ2* patient (1/19) (66) suffered one stroke-like episode, that
188 contributed significantly to deterioration of the neurological status and may explain the
189 heterogeneity of the functional outcome among affected siblings (84). Some *COQ2* variants
190 have also been predicted to increase susceptibility to adult-onset multisystem atrophy (MSA),
191 but this issue is still under debate (61,95).

192 Very few patients with mutations in *PDSS1* (70,96), *PDSS2* (71,97–100), *COQ5* (94), *COQ7*
193 (101,102) and *COQ9* (103–106) have been identified to define a specific phenotype, but they
194 presented encephalopathy (*PDSS1*, *COQ9*), Leigh-like syndrome (*PDSS2*, *COQ9*), ataxia (*PDSS2*,

COQ5), ID (*PDSS1*, *PDSS2*, *COQ5*, *COQ7*), seizures (*PDSS2*, *COQ5*, *COQ9*) or spasticity (*PDSS2*, *COQ5*, *COQ7*).

Peripheral nervous system and sensory organs manifestations:

Peripheral neuropathy has been described in 2 siblings with *PDSS1* mutations, associated with optic atrophy and early-onset SNHL (70). Also, the 2 *COQ7* patients described showed peripheral polyneuropathy, again with SNHL and one of them with visual dysfunction (101,102). SNHL is very frequent, especially in *COQ6* patients (16/26) (69,71,107–109), associated with SRNS in all cases, and with optic atrophy (1/18) (109). One *COQ8A* patient (1/45) also showed early-onset bilateral SNHL (82–84), as well as patients with *PDSS2* mutations (4/7), who manifested retinitis pigmentosa (2/7) and optic atrophy (1/7), too (98,100). One patient with *COQ4* mutations (1/14) manifested bilateral hearing loss as well (77). Visual impairment was also a symptom in some patients with optic atrophy (*PDSS1* (70), *PDSS2* (98,100), *COQ2* (66), *COQ6* (109)), retinopathy (*COQ2*) (74), retinitis pigmentosa (*PDSS2* (100), *COQ2* (61), *COQ8B* (110)) and cataracts (*PDSS2* (98), *COQ8A* (62)).

Renal manifestations:

SRNS is frequent in primary CoQ deficiency patients, specifically in patients with pathogenic variants of *COQ2*, *COQ6* and *COQ8B*. It generally starts as proteinuria and if untreated evolves to end-stage renal disease (ESRD) within childhood (71).

COQ2 patients displayed early-onset nephrotic syndrome (15/22) (65–68,70,71,73,76), isolated (9/22) or with encephalopathy and seizures (6/22), but there was also one family with onset in adolescence, slow progression of the renal disease and mild neurological symptoms (69). The hallmark of *COQ6* pathogenic variants is childhood-onset SNRS (23/26) associated with SNHL (16/26) (69,71,107–109,111). *COQ8B* patients mainly presented with an adolescence-onset SRNS due to focal segmental glomerulosclerosis, associated with edema (15/74) and

hypertension (10/74), which generally progressed to ESRD (50,64,110,112–116). Onset of SRNS may be before 10 years of age (29/74).

Patients with *PDSS1* (1/3) (96) and *PDSS2* (7/7) (71,97–100)mutations also showed SRNS. One *COQ9* (1/6) (104) and one *COQ2* (1/22) (75) patient displayed a tubulopathy.

Muscle manifestations:

Isolated myopathy has not been found in individuals with molecularly confirmed primary CoQ deficiency. The majority of the patients with a predominantly muscular phenotype have been associated with secondary CoQ deficiency. Myopathy has been described in some patients with a multisystemic phenotype (*COQ4* (1/14) (81), *COQ8A* (1/45) (91)). Other muscular manifestations include exercise intolerance (*COQ8A* (8/45) (82,84–86)), muscle weakness (*COQ2* (1/22) (66), *COQ6* (2/26) (109), *COQ7* (2/2) (101,102), *COQ8A* (7/45) (62,85,87,92), *COQ8B* (1/74) (113)) and muscle fatigue (*COQ8A* (2/45) (62,90) and *COQ8B* (1/74) (110)). Some muscle biopsies have shown lipid accumulation in muscle (*COQ4* (1/14) (81), *COQ8A* (3/45) (62,85), *COQ2* (1/22) (72)).

Cardiac manifestations:

The most frequent heart manifestation is hypertrophic cardiomyopathy, often present in *COQ4* patients with a prenatal onset (7/14) (77–79), whereas *COQ2* (3/22) (65,72,75), *COQ8B* (2/74) (64,112,113), *COQ7* (1/2) (101) and *COQ9* patients (1/6) (104) show a neonatal onset. Other less frequently reported cardiac manifestations are valvulopathies (*PDSS1* (2/3) (70)), heart hypoplasia (*COQ4* (1/14) (78)), septal defects (*COQ4* (1/14) (81), *COQ8B* (2/74) (110,116)), heart failure (*COQ4* (2/14) (78,79) and *COQ8B* (1/74) (110)), bradycardia (*COQ4* (4/14) (77–79), *COQ9* (2/6) (105,106), or pericardial effusion (*COQ8B* (1/74) (64,112)). However, it is questionable whether some manifestations such as heart failure, bradycardia or pericardial effusion are primary events or are secondary manifestations of some other general

phenomena.

Other manifestations:

Less frequent clinical findings include dysmorphic features (81,107), metabolic pathologies (diabetes mellitus (70,75), obesity (70) and hypercholesterolemia (69,113) -although the latest is often observed during SRNS, independently of its aetiology-), thyroid disease (goiter (50,112), hypothyroidism (64)), lung involvement (respiratory distress -very frequent in *COQ4* patients (9/14) (75,78,79,101,105)-, apnea (74,77–79,105) or respiratory failure (66,74,75,77,78)), circulatory problems (cyanosis (78,105), hypertension, livedo reticularis (70)), liver abnormalities (hepatic insufficiency (70,72), cholestatic liver (75)), among others.

Biochemical findings:

Primary CoQ deficiency patients, particularly those with neonatal onset, can show higher levels of lactate in plasma or serum. CoQ levels in skeletal muscle biopsies or fibroblasts may be reduced (117), as well as the enzymatic activities of complex I+III and/or II+III (118).

Pathogenesis

The pathogenesis of CoQ deficiency is complex and not completely understood. The bioenergetic defect and the increased reactive oxygen species (ROS) production may have a crucial role. However the wide spectrum of CoQ functions, the unclear roles of some COQ gene products and the considerable phenotypic variability, suggest that other mechanisms contribute to the pathogenesis of the disease. In cultured cells it has been found that, while severe CoQ deficiencies lead to great defects in energy production with no major increase in oxidative stress, mild CoQ defects cause a significant increase in ROS production without affecting ATP production, but yielding increased cell death levels (119). In addition, as expected, CoQ deficiency impairs *de novo* pyrimidine synthesis, further contributing to disease pathogenesis (120). CoQ deficiency cells also show increased mitophagy, being proposed as a

protective mechanism in disease pathogenesis (121), although other authors defined it as detrimental (122). Recently, sulfide oxidation pathway impairment has been proposed as an additional pathomechanism in primary CoQ deficiency, as different *in vivo* and *in vitro* models of the disease show a tissue-specific defect in the metabolism of H_2S, leading to the accumulation of this molecule, that may alter protein S-sulfhydrilation, inducing changes such as vasorelaxation, inflammation and ROS production (123). Finally, CoQ deficiency has been linked to development of insulin resistance in human and mouse adipocytes, as a result of increased ROS production via complex II (124).

Genotype-phenotype correlation

Due to the small number of patients harbouring mutations in COQ genes and the wide range of clinical manifestations, it is arduous to define genotype-phenotype correlations. In fact, only a few families with pathogenic variants of *PDSS1*, *PDSS2*, *COQ5* or *COQ9* have been published, being unachievable to establish any correlation. In the case of *COQ9*, studies in two mouse models suggest that a key factor appears to be the different degree of impairment of formation of the CoQ complex (49). Even though only 2 patients with *COQ7* mutations have been described, there seems to be a correlation between the residual levels of CoQ (and levels of COQ7 protein) and the severity of the disease: fibroblasts from patient with the most severe phenotype show a drastic CoQ deficiency (101), while the patient with the milder phenotype has a 30% decrease in CoQ levels in skin fibroblasts (102). Interestingly, only fibroblasts with a severe deficiency benefit from 2,4-dihydroxybenzoic acid (2,4-dHB) supplementation, while CoQ biosynthesis was inhibited in those with the milder defect treated with 2,4-dHB.

COQ8A and *COQ8B* have the highest number of families with pathogenic variants reported (29 and 38), and in neither case there is any correlation between the mutations and the clinical phenotype (84,112). In the case of *COQ2* patients (18 families described), who show the widest clinical spectrum, it has been proposed that the severity of the disease correlates with the

293 enzymatic residual activity and hence CoQ levels, as shown by expressing mutant proteins in
294 yeast (125). It is worth to mention that most of the *COQ6* patients were diagnosed during
295 screening for SNRS, so there may be a reference bias in these cases (71,107,109). To date, no
296 other clear correlations have been observed for *COQ4* patients.

297 ## Diagnosis

298 The diagnosis of primary CoQ deficiency is established with the identification of biallelic
299 pathogenic variants in any of the genes coding for one of the proteins directly involved in CoQ
300 biosynthesis. Genome or specific gene sequencing is performed when decreased levels of CoQ
301 or reduced combined activities of complex I+III and II+III in mitochondria of skeletal muscle
302 biopsies are detected in patients (126,127). It is important to note that biochemical analysis is
303 not able to distinguish between primary and secondary CoQ deficiencies (127). Genetic
304 identification of new pathogenic variants is usually followed by functional validation.

305 CoQ levels can also be measured on plasma samples, white blood cells or skin fibroblasts
306 obtained after skin biopsy from patients (128). However, there are concerns about CoQ plasma
307 measurements for diagnosis, since it seems to be influenced by the amount of plasma
308 lipoproteins (carriers of CoQ in circulation) and the dietary intake. Muscle or fibroblasts
309 represent the preferred diagnosis tissues, although sometimes fibroblasts do not show
310 reduction while muscle does (129).It has been shown that white blood cells CoQ levels alone
311 are not reliable to diagnose primary CoQ deficiency in the setting of nephrotic syndrome (76).
312 *De novo* synthesis can also be measured by radioactive precursor incorporation in fibroblasts
313 (130) which is especially useful to discriminate between primary and secondary deficiencies.
314 Recently, urine CoQ measurement as non-invasive approach has been proposed (131) .

315 ## Management

316 Considering the wide clinical spectrum of this condition, any individual with a diagnosis of
317 primary CoQ deficiency should be assessed, in order to establish the severity of the disease.

318 Importantly, a genetic consultation is recommended for other family members and for
319 recurrence risk of patient's parents. Based on the genetic defect identified in the patient, a
320 specific follow-up should be programmed.

321 Being CNS manifestations very frequent, every patient with a diagnosis of CoQ deficiency
322 should undergo periodical neurological examinations, even if normal at diagnosis. In fact, the
323 age of onset of these symptoms is highly variable, ranging from the first hours or days of life
324 (as in patients with *COQ4* mutations), up to the seventh decade of life (as in *COQ2* patients
325 with the adult-onset multisystem atrophy-like phenotype). Evaluation should include an EEG
326 analysis and a brain MRI. In addition, peripheral nervous system should be assessed for the
327 possible presence of peripheral neuropathy in patients with *PDSS1* and *COQ7* mutations.

328 Patients with mutations in *PDSS1*, *PDSS2*, *COQ2*, *COQ6*, *COQ7*, *COQ8A* and *COQ8B* may have
329 eye involvement due to optic atrophy, retinopathy, retinitis pigmentosa and even cataracts
330 and should therefore be screened at diagnosis and during the follow-up. Audiometry is
331 necessary in *COQ6* patients who almost invariably manifest SRNS, but should be performed
332 also in patients with mutations in *PDSS1*, *COQ8A* and *COQ4* who may sometimes manifest this
333 phenotype.

334 Individuals harbouring mutations in *COQ2*, *PDSS1*, *PDSS2*, *COQ6*, and *COQ8B* may manifest
335 renal involvement with SRNS, whose onset may vary from early childhood to adolescence.
336 Tubulopathy has been reported rarely. These patients thus need to undergo periodical renal
337 function tests with urine analysis for proteinuria and nephrological evaluations for the risk of
338 evolving to ESRD.

339 A cardiologist examination with echocardiogram should be performed in patients with *COQ4*
340 mutations (who may present with a severe prenatal-onset cardiomyopathy) and should also be
341 considered in individuals with mutations in *PDSS1* and *COQ8B* to exclude the presence of a
342 valvulopathy or septal defects.

Treatment

Barriers for tissues CoQ delivery have been found due to its high molecular weight and poor aqueous solubility, but at high doses, dietary supplementation increases CoQ levels in all tissues, including heart and brain, especially with certain formulations (132,133). It also increases in circulating low density lipoproteins (LDL), where it functions as an efficient antioxidant together with α-tocopherol (134,135). CoQ supplementation at high doses has been demonstrated to be effective for treatment of both primary and secondary CoQ deficiencies (136). It is crucial to start the supplementation as soon as possible to get favorable outcomes and to limit irreversible damage in critical tissues such as the kidney or the CNS (126). Different doses of CoQ have been employed for the treatment of primary CoQ deficiencies, ranging from 5 mg/kg/day (98) to 30-50 mg/kg/day for both adults and children (137) but in mouse models of this condition even higher doses (up to 200 mg/kg/day) have been used (138). Except for *COQ8A* patients, most individuals with primary forms show a good response to CoQ treatment, which is usually evident after 10-20 days (137). Different formulations of CoQ are now available, both in the oxidized and the reduced forms, although most of the data available have been obtained in patients treated with ubiquinone.

Alternatively to CoQ_{10} supplementation, some 4-HB analogues have been proposed as potential bypass molecules with higher bioavailability than CoQ. These water-soluble CoQ head precursors would bypass enzymatic steps disrupted by mutations in *COQ* genes, but their efficacy may differ depending on the stability of the CoQ biosynthetic complex. Some examples are vanillic acid (VA) and 3,4-dihydroxybenzoate (3,4-dHB), able to bypass *COQ6* mutations, or 2,4-dHB for COQ7 defects (figure 2C and 2D). The effectivity of VA and 3,4-dHB in restoring CoQ biosynthesis has been demonstrated in *coq6* yeast mutant strains expressing pathogenic versions of human *COQ6* (111). Notably, VA also stimulates CoQ synthesis and

improves cell viability in *COQ9* patient fibroblasts (139). 2,4-dHB was able to increase CoQ levels and lifespan in Coq7 (140) and Coq9 defective mice (49), as well as to bypass the reaction in human fibroblasts with *COQ7* (101,102,139) and *COQ9* mutations (139). Remarkably, the effectivity of 2,4-dHB depends on the nature of the *COQ7* mutation and the residual activity of the protein (102). It has also been reported that treatment with high doses of 4-HB, thus increasing COQ2 substrate availability, restores CoQ synthesis in *COQ2* deficient cell lines, which also suggests that these enzyme variants retain some residual activity (141).

Early onset CoQ deficiencies can cause mortality in few days. We have observed that CoQ is efficiently incorporated in different tissues by breastfeeding and placenta in mice (unpublished data). We propose treatment of pregnant mothers of high-risk newborns (high probability of CoQ deficiency after genetic screening or due to family history) with CoQ supplementation, in order to reduce tissue damage during embryonic/fetal development and to increase the survival of newborns until they can be fed with supplements.

Secondary deficiencies

CoQ levels can also be reduced secondary to conditions not directly linked to CoQ biosynthesis, but related to oxidative phosphorylation (OXPHOS), other non-OXPHOS mitochondrial processes, or even to non-mitochondrial functions (142). Remarkably, secondary CoQ deficiencies are proved to be more common than primary deficiencies (142,143), probably because of the diversity of biological functions and metabolic pathways in which CoQ is involved in mitochondrial and non-mitochondrial membranes, highlining the importance of CoQ homeostasis in human health. However, there is a lack of consistency of CoQ deficiency presence among different patients, which could suggest different susceptibility to the development of secondary deficiencies among different individuals. Currently, there is not any general explanation for this, although genetic factors, such as certain polymorphisms, have been proposed to be involved (112,142–144). A comprehensive analysis of muscle and

393 fibroblasts samples from patients affected by a wide range of mitochondrial diseases, showed
394 that secondary deficiencies were more frequent in depletion syndromes than in any other
395 mitochondrial disease (142), supporting previous observations (145). The same study analysed
396 CoQ levels in samples of patients affected by different OXPHOS diseases, but were unable to
397 find any difference between them. Further studies on wider cohorts are needed in order to
398 understand whether certain diseases are more prone to develop secondary deficiencies than
399 others, as well as the underlying molecular mechanism. Nonetheless, it is clear that
400 mitochondrial myopathies are frequently associated with CoQ secondary deficiencies (144).
401 Besides its reduction in many mitochondrial OXPHOS disorders, other diseases may display
402 secondary CoQ deficiency, including ataxia and oculomotor apraxia syndrome (MIM #208920),
403 multiple acyl-CoA dehydrogenase deficiency (MIM #231680), cardiofaciocutaneous syndrome
404 (MIM #115150), methylmalonic aciduria (# 251000), GLUT-1 deficiency syndrome (MIM
405 #606777), mucopolysaccharidosys type III (MIM #605270) or multisystem atrophy
406 (142,143,146). The mechanisms underlying CoQ secondary defects remain largely unknown,
407 but several explanations have been proposed that are related to: (i) an increased rate of CoQ
408 degradation due to oxidative damage caused by a non-functional respiratory chain; (ii) a
409 decrease in CoQ through the interference with the signalling pathways involved in the process
410 of biosynthesis; (iii) the reduction of the stability of the CoQ biosynthetic complex or (vi) a
411 general deterioration of mitochondrial function (142,143).

412 In addition, CoQ seems to be reduced in the process of aging (147) and a secondary deficiency
413 of CoQ may be a side effect of hypercholesterolemia treatment with statins, since both
414 cholesterol and CoQ share part of their biosynthetic pathways (148,149).

415 Of course, particular symptoms of secondary CoQ deficiencies are highly dependent on the
416 original pathology. Myopathies presented as muscular weakness, hypotonia, exercise
417 intolerance or myoglobinuria are commonly reported as muscular manifestations in diseases

418 associated to secondary CoQ deficiencies. Neurological decline and ataxia are also often
419 reported (143,150). It is possible that the primary disease symptoms are potentiated by the
420 lack of CoQ (143). In fact, many of these patients partially improve their condition by CoQ
421 supplementation, which supports the importance of an early diagnosis also in these cases
422 (150). From the point of view of the molecular diagnosis, it is necessary to perform a genetic
423 analysis to distinguish between primary and secondary deficiencies (126).

424 Concluding remarks

425 The deficiency in CoQ is a genetically and clinically heterogeneous syndrome. Primary
426 deficiency diagnosis is a great challenge due to the number of genes involved, the poor
427 knowledge of CoQ biosynthesis pathway and its regulation in humans, the small number of
428 patients described and the great variety of associated symptoms. Moreover, secondary
429 deficiencies can be consequences of many other mitochondrial dysfunctions adding a layer of
430 complexity to the diagnosis. Observation of the clinical manifestations here described and /or
431 the molecular identification of potentially pathological variants of *COQ* genes should be
432 complemented by the biochemical determination of CoQ levels, biosynthesis rate if possible,
433 and the combined enzymatic activities of complexes I+III and I+II in muscle or fibroblast. It is
434 important to identify potential cases as early as possible because high-dose CoQ oral
435 supplementation is a very effective treatment in most cases, blocking the progression of the
436 disease.

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440 Declaration of interest

441 The authors report no conflicts of interest.

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Author contribution statement

MA-F exhaustively compiled the mutations and symptoms data from literature and elaborated the tables. MA-F and GB-C made the figures. MA-F, ET and GB-C wrote and edited the text and GB-C coordinated the work.

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Summary

- CoQ is an endogenously synthesized lipid that is essential for the electron transport in the mitochondrial respiratory chain.
- Primary CoQ deficiencies are rare diseases caused by mutations in genes of the CoQ biosynthesis pathway.
- CoQ deficiencies are characterized by reduced levels of CoQ affecting energy production.
- Primary CoQ deficiencies show highly heterogeneous manifestations mainly affecting CNS, PNS, sensory organs, kidney, skeletal muscle and heart.
- Currently, it is hard to establish any genotype-phenotype correlations for these diseases, partially due to the low amount of studied patients.
- It is essential to biochemically determine CoQ deficiency since supplementation has positive therapeutic effects.

Figure legends

Figure1. (A) Chemical structure of Coenzyme Q (CoQ) and (B) redox cycle of its head group. (C) Integration of CoQ reduction by different dehydrogenases in the mETC. DHODH: Dihidroorotate dehydrogenase; G3PDH: Glycerol 3 phosphate dehydrogenase; ETF-FAD: Electron Transfer Flavoprotein; ETF-Qase: Electron Transfer Flavoprotein cCenzyme Q reductase; Cyt c: cytochrome *c*; SQR: sulphide-quinone oxidoreductase; PROD: proline dehydrogenase.

Figure 2. (A) Schematic model of human CoQ biosynthesis pathway. Blue arrows represent enzymatic reactions and circled numbers represent the different COQ proteins that participate in each step. Brown arrows indicate regulatory mechanisms. Circled question mark shows currently unidentified enzymes. (B) Model of human CoQ biosynthetic complex, containing at least COQ3-COQ9 and lipids, such as CoQ itself. (C) and (D) green boxes contain 4-HB analogues, defined as unnatural CoQ precursors, which are able to lead to CoQ production, bypassing defective COQ enzymes such as COQ6 (3,4-dihydroxybenzoate (3,4-dHB) or vanillic acid (VA)) or COQ7 (2,4-dihydroxybenzoate (2,4-dHB). COQ9 patient fibroblasts can also benefit from 2,4-dHB and VA. DDMQ: demethoxy-demethyl-Coenzyme Q; DMQ: demethoxy-Coenzyme Q; DMeQ: demethyl-Coenzyme Q

Figure 3. Organs and systems affected in individuals with primary CoQ deficiency, associating specific clinical manifestations with the genes involved in each one. For abbreviations go to Table 3. For frequency of each symptom linked to a specific gene go to Table 2.