Chapter 6
Coenzyme Q Biosynthesis Disorders

Gloria Brea-Calvo, María Alcázar-Fabra, Eva Trevisson, and Plácido Navas

Abstract Coenzyme Q (CoQ) is a lipidic molecule that transfers electrons between complexes I and II to complex III in the mitochondrial respiratory chain. It is also essential for processes mediated by other mitochondrial dehydrogenases, such as those involved in pyrimidine nucleotides biosynthesis, beta-oxidation and sulfide biosynthesis. A nuclear-encoded multiprotein complex at the inner mitochondrial membrane drives CoQ biosynthesis, which requires at least 13 proteins, leastways in yeasts. Mutations in the genes (*COQ* genes) coding for these proteins cause a decrease of CoQ biosynthesis rate leading to primary CoQ deficiency, a very heterogeneous group of mitochondrial diseases affecting different tissues and organs, and showing variable severity and age of onset. In general, this primary condition shows a good response to the supplementation with high doses of CoQ, but early diagnosis is compulsory to limit tissue damage. However, sometimes effectiveness is reduced, possibly due to its low bioavailability and, probably, difficulties crossing the blood-brain barrier. Secondary CoQ deficiency is a more common condition, in which defects of diverse mitochondrial processes induce an adaptive CoQ decrease. Secondary deficiency can be caused by oxidative phosphorylation (OXPHOS) defects, such as complex III dysfunction or mitochondrial DNA (mtDNA) depletion, or even non-OXPHOS mitochondrial defects. Here, we review the current knowledge of CoQ biosynthesis pathway, the genetic defects leading to primary deficiency and those conditions in which mitochondrial defects cause secondary deficiency.

G. Brea-Calvo · M. Alcázar-Fabra · P. Navas (✉)
Centro Andaluz de Biología del Desarrollo and CIBERER, Instituto de Salud Carlos III, Universidad Pablo de Olavide-CSIC-JA, Sevilla, Spain
e-mail: pnavas@upo.es

E. Trevisson
Clinical Genetics Unit, Department of Women's and Children's Health, University of Padova, Padova, Italy

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6.1 CoQ Structure and Functions

Coenzyme Q (CoQ) is a lipidic molecule formed by a benzoquinone ring attached to an isoprenoid chain at position 3, whose length is species-specific (Fig. 6.1a). The chain has 6 isoprenoid groups in the yeast *Saccharomyces cerevisiae* (CoQ_6), eight in *Escherichia coli* (CoQ_8), nine and ten in mice and rats (CoQ_9, CoQ_{10}) and mostly 10 in humans. The diversity in the side chain length is interpreted as a requirement for its stability inside the bilayer of different phospholipids composition (Bentinger et al. 2010). CoQ oxidized form (ubiquinone) is an electron carrier that can be reduced to ubiquinol with two electrons. This reduction can occur directly by one reaction of two electrons, or it can pass through two steps of one electron each, producing the semiquinone intermediate (Mitchell 1975; Wang and Hekimi 2016). CoQ is present in all cells, being mainly located in the mitochondrial inner membrane as a component of the respiratory chain, driving electrons from complex I and complex II, to complex III (Fig. 6.1b) (Alcázar-Fabra et al. 2016; Crane et al. 1957; Kozlov et al. 1998; Lenaz et al. 2007). Mitochondrial CoQ can also be reduced by other different dehydrogenases, such as the electron transfer flavoprotein dehydrogenase (ETFDH), a component of the β–oxidation of fatty acids (Watmough and Frerman 2010); the mitochondrial dihydroorotate dehydrogenase, responsible of

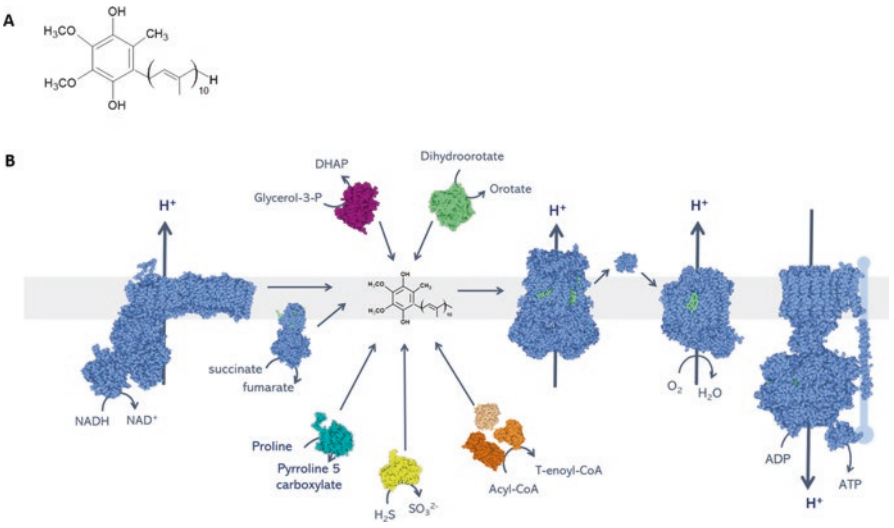

Fig. 6.1 (**a**) Chemical structure of Coenzyme Q; (**b**) OXPHOS system showing complexes I and II, and other dehydrogenases that reduce CoQ in the inner mitochondrial membrane. Depicted using Illustrate (Goodsell et al. 2019). *CI* NADH:CoQ oxidoreductase, *CII* succinate dehydrogenase, *CIII* CoQ: cytochrome c oxidoreductase, *CIV* Cytochrome c oxidase, *CV* ATP synthetase, *DHODH* Dihidroorotate dehydrogenase, *GPDH* Glycerol 3 phosphate dehydrogenase, *ProDH* Proline dehydrogenase, *ACAD* Acyl-CoA dehydrogenase, *ETF-FAD* Electron Transfer Flavoprotein, *ETFDH* Electron Transfer Flavoprotein Coenzyme Q reductase, *SQOR* sulfide: quinone oxidoreductase, *Cyt c* cytochrome *c*, *IMS* inter membrane space, *MIM* mitochondrial inner membrane

pyrimidine nucleotides biosynthesis (Evans and Guy 2004) and the glycerol-3-phosphate dehydrogenase, an enzyme involved in lipid metabolism (Harding et al. 1975). Additionally, CoQ is a substrate for the sulfide: quinone oxidoreductase (SQOR), which oxidizes hydrogen sulfide (H_2S) in the first step of its catabolism in the mitochondria. SQOR levels and activity have been recently reported to be severely decreased in CoQ deficiency (Luna-Sánchez et al. 2017; Quinzii et al. 2017; Ziosi et al. 2017).

CoQ has also been shown to be a structural component of Complex III–at least in yeasts- contributing to both its assembly and stability. This integral location optimizes the efficiency of the electron transport from $CoQH_2$ throughout the CoQ cycle, which is an essential step for proton translocation and hence energy conservation (Cramer et al. 2011; Santos-Ocaña et al. 2002). Complex III can be associated with complexes I and IV in a super assembly manner, constituting several types of respiratory chain supercomplexes (Letts and Sazanov 2017; Lobo-Jarne and Ugalde 2018; Schägger and Pfeiffer 2000). One of these assemblies is the so-called respirasome that contains complexes I, III and IV, which can transfer electrons from NADH to O_2 (Enríquez 2016; Gu et al. 2016; Guo et al. 2016, 2017). CoQ has been proposed to be an essential component in respiratory-active respirasome and other associations (Acín-Pérez et al. 2008), being organised in different pools according to the complexes involved in the superassembly (Enriquez and Lenaz 2014; Lapuente-Brun et al. 2013). However, it has been recently suggested that CoQ constitutes one single pool that can be reduced either by complexes I or II. CoQ can be experimentally reoxidized more rapidly by alternative quinol oxidases outside the supercomplexes than by complex III inside these superstructures. This would indicate that substrate channeling does not occur, but instead CoQ diffuses freely (Fedor and Hirst 2018; Hirst 2018). Thus, the existence of a single or various CoQ pools in the mitochondrial respiratory chain is still controversial.

Being an integral part of the system, CoQ biosynthesis rate must be linked to balanced electron transport chain components. Thus, secondary deficiencies can be derived from defects in OXPHOS components (Yubero et al. 2016). Mutations in other genes, such as *ETFDH*, involved in the fatty acids oxidation pathway (Gempel et al. 2007) could also cause secondary deficiencies due to the functional link between processes. Secondary deficiencies have also been linked to other OXPHOS defects by extensive omics analysis in tissues of several knockout mouse strains defective in essential nuclear DNA-encoded factors involved in mtDNA expression (Kühl et al. 2017). Secondary CoQ deficiency in these cases could indicate that these mtDNA expression defects would provoke an imbalance of the OXPHOS system components that would lead to the downregulation of the CoQ biosynthesis in an attempt to adjust the CoQ levels to the rest of the components of the system.

Mitochondrial respiratory chain is the primary source of reactive oxygen species (ROS) (Murphy 2009) and the structural organization of supercomplexes has been proposed to modulate ROS production (Genova and Lenaz 2015; Lenaz et al. 2016). High levels of ROS cause macromolecular damage, whereas low levels of mitochondrial ROS act as a signal to enhance systemic defense mechanisms by inducing an adaptive response (Gonzalez-Freire et al. 2015). High ROS cause accumulation

of mtDNA damage, leading to a defective mitochondrial protein synthesis, which ultimately impacts on mitochondrial physiology, and may lead to premature senescence and ageing (Larsson 2010; Sgarbi et al. 2014; Teshima et al. 2014). CoQ is also involved in ROS production, which can reconfigure electron transport after complex I disorganization, increasing electron flow through complex II (Guarás et al. 2016). Mutations or knock-down of CoQ biosynthesis genes in *C. elegans* increase longevity associated with lower levels of ROS, despite decreasing mitochondrial function (Asencio et al. 2003; Wong et al. 1995). Thus, CoQ-dependent ROS production would be rather acting as signaling to modulate longevity as it acts in other cellular protection pathways (Scialò et al. 2016; Yee et al. 2014).

CoQ is the only lipidic antioxidant endogenously synthesized by the cell. It can directly avoid lipid peroxidation in membranes (Bentinger et al. 2007; Maroz et al. 2009) and, in plasma membrane, it acts as an antioxidant, recycling ascorbic acid and α-tocopherol (Arroyo et al. 2004; Mukai 2001; Navas et al. 2007). Extramitochondrial CoQ role has recently recovered relevance as part of the plasma membrane antioxidant system that inhibits ferroptosis, a form of regulated cell death induced by the iron-dependent peroxidation of lipids, through the NAD(P)H/CoQ oxidoreductase FSP1 (Bersuker et al. 2019; Doll et al. 2019).

Participation of CoQ in all these functions would pleiotropically influence the cellular physiology leading to mitochondrial health or disease depending on its concentration and/or biosynthesis rate under genetic or environmental conditions. Here, we review the underlying mechanisms modulating cellular CoQ levels and those that affect the optimum concentration leading to CoQ deficiency syndrome.

6.2 Primary CoQ Deficiency

CoQ deficiencies are characterized by reduced levels of CoQ in tissues due to either impairment of it biosynthesis or as a consequence of defects not directly involved with this process, the so called primary and secondary deficiencies, respectively.

Primary CoQ deficiencies are rare autosomal recessive conditions caused by mutations in any of the genes directly involved in the CoQ biosynthesis pathway at the enzymatic or the regulatory level. CoQ, which is structurally composed by a redox-active benzoquinone ring and a polyisoprenoid tail that anchors the molecule to the membrane (Fig. 6.1a), can be incorporated by the diet, but it is mainly endogenously synthesized in mitochondria and subsequently distributed to other membranes (Fernandez-Ayala et al. 2005).

The information available on CoQ biosynthesis mainly derives from studies of intermediates of the pathway in bacteria and mutant yeasts. In *Saccharomyces cerevisiae*, the synthesis of CoQ depends on at least 13 nuclear-encoded genes called coq genes (coq1–coq11, Yah1 and Arh1) that are evolutionarily highly conserved. Some of the products of these genes assemble in a multienzymatic complex (the CoQ Synthome) located in the mitochondrial inner membrane (Allan et al. 2015; Belogrudov et al. 2001; Gonzalez-Mariscal et al. 2014; Marbois et al. 2005, 2009).

Currently, the exact enzymatic role of the different components of the route is only partially known. Orthologues of most of the yeast coq genes have been identified in humans (Awad et al. 2018), but the assembly and regulation of the CoQ Synthome have not yet been wholly demonstrated in humans, although a more complete evidence of the existence of a complex by BN-PAGE experiments has recently been reported (Floyd et al. 2016; Lohman et al. 2014; Nguyen et al. 2014; Reidenbach et al. 2018; Stefely et al. 2016; Yen et al. 2016; 2020). In yeast, the CoQ biosynthetic complex is spatially and functionally related to ERMES (endoplasmic reticulum-mitochondria encounter structure) complex, also known as ER-mitochondria contacts, and the loss of this structure impairs respiration through reduction of CoQ levels (Eisenberg-Bord et al. 2019). This complex requires the CoQ lipid intermediates for its formation, and it seems to be conserved from yeast to human cells (Subramanian et al. 2019).

CoQ main head precursor is 4-Hydrozybenzoate (4-HB). Yeast and bacteria can synthetize it *de novo* through the shikimate pathway (Clarke 2000), while mammals and yeast can use tyrosine to produce 4-HB by a yet poorly known pathway (Payet et al. 2016; Stefely and Pagliarini 2017; Stefely et al. 2016). Mammals can also use phenylalanine, which is converted to tyrosine, and then to 4-HB. Interestingly, yeast but not mammals or bacteria can use para-aminobenzoic acid (pABA) as an alternative ring precursor for CoQ_6 synthesis (Marbois et al. 2010; Pierrel et al. 2010). Resveratrol and para-coumarate can also be used as alternative ring precursors by bacteria, yeast and mammals, probably through 4-HB transformation (Xie et al. 2015). The isoprene units are synthesized through the mevalonate pathway in extramitochondrial membranes and then condensed by Coq1p (PDSS1/PDSS2 heterotetramer in mammals) in mitochondria (Ashby and Edwards 1990). Next, head and tail are conducted to the mitochondria inner membrane by unknown mechanisms, and there are linked together by Coq2p (COQ2 in mammals) (Ashby et al. 1992; Forsgren et al. 2004). Additional modifications of the head are performed by different Coq proteins in mitochondria (Fig. 6.2) Coq3p (COQ3 in mammals) is an O-methylase which modifies C5 and C6 (Hsu et al. 1996; Jonassen and Clarke 2000; Poon et al. 1999); Coq5p (COQ5 in mammals) methylates C2 (Barkovich et al. 1997; Nguyen et al. 2014) and Coq6p (COQ6 in mammals) (Gin et al. 2003; Ozeir et al. 2011) and Coq7p (COQ7 in mammals) (Marbois and Clarke 1996; Tran et al. 2006) are hydroxylases modifying C5 and C6 respectively. It has been shown that Coq6p acts as a deaminase in yeast as well, whenever pABA is used as a precursor (Ozeir et al. 2015). The yeast mitochondrial ferredoxin and ferredoxin reductase (Yah1 and Arh1) are required for CoQ synthesis by transferring electrons to Coq6p (Pierrel et al. 2010). Still, there is no evidence that it occurs in humans as well. CoQ synthesis requires a C1-decarboxylation and hydroxylation catalyzed by enzymes that have not yet been identified. Coq4p (COQ4 in mammals) does not have any catalytic activity assigned, but it has been proposed to participate in the stabilization of the CoQ Synthome (Belogrudov et al. 2001; Marbois et al. 2009). In yeasts, Coq8p (COQ8A (or ADCK3/CABC1) and COQ8B (or ADCK4) in mammals) has been proposed to regulate CoQ biosynthesis by phosphorylation of Coq3p, Coq5p

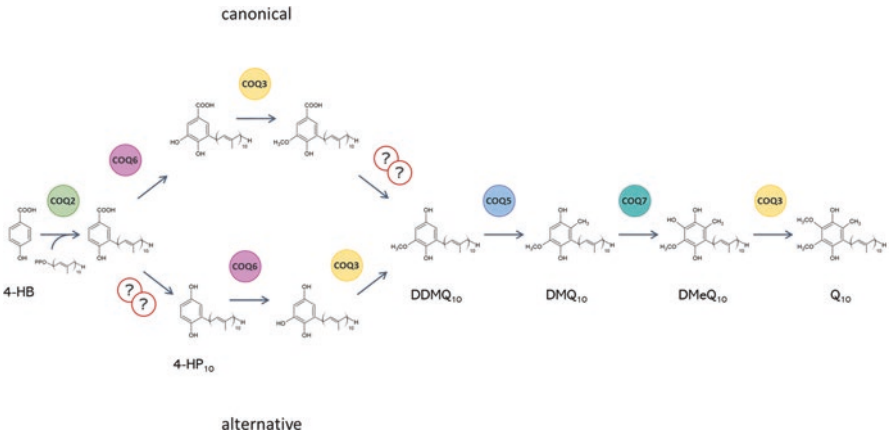

Fig. 6.2 Human CoQ biosynthesis pathway. The classical and alternative routes (suggested in (Acosta-López et al. 2019)) are depicted

and Coq7p (Stefely et al. 2015; Tauche et al. 2008; Xie et al. 2011, 2012). Recently, however, an ATPase activity has been assigned to COQ8A/ADCK3, whose role in CoQ biosynthesis pathway still needs to be further clarified (Reidenbach et al. 2018). Coq9p (COQ9 in humans) is a lipid-binding protein that binds to Coq7p. It would enable CoQ synthesis probably by lipid presentation of the substrate (He et al. 2017; Hsieh et al. 2007; Lohman et al. 2014, 2019). Coq10p (COQ10A and COQ10B in humans) probably chaperones CoQ to the sites where it is needed within the mitochondrial membranes (Barros et al. 2005; Cui and Kawamukai 2009; Tsui et al. 2019). Coq11p is essential for CoQ synthesis in yeast, but a clear human orthologue is still lacking (Allan et al. 2015; Bradley et al. 2020). Moreover, three other genes of the *ADCK* family (*ADCK1*, *ADCK2* and *ADCK5*) have been suggested to be involved in the biosynthetic process, although currently, there is no experimental evidence for this (Doimo et al. 2014; Stefely et al. 2015; Vázquez-Fonseca et al. 2019). The phosphatase Ptc7 has been demonstrated to regulate CoQ biosynthesis by activating Coq7 in yeast (Martín-Montalvo et al. 2013; González-Mariscal et al. 2018). In mammals, its orthologue PPTC7 is thought to regulate mitochondrial biogenesis and metabolism, by a process linked to CoQ content modulation. The specificity of this link is controversial, though (González-Mariscal et al. 2018; Niemi et al. 2019).

The exact order of reactions involved in the modifications of the aromatic ring of CoQ is still unclear in eukaryotes. The accepted model starts with a C5 hydroxylation of the head group performed by COQ6 (Fig. 6.2) (Kawamukai 2016). However, yeast and human *COQ6* knockout cells accumulate 4-HP, a compound that is decarboxylated and hydroxylated in position C1 of the ring. Therefore, these reactions (which are catalyzed by still unidentified enzymes) must occur before or independently on C5 hydroxylation by COQ6 (Acosta-López et al. 2019; Ozeir et al. 2011).

6.2.1 Clinical Manifestations of Primary CoQ Deficiencies

Primary deficiencies are very rare conditions. In the last years, next-generation sequencing advances have allowed the identification of an increasing number of pathogenic variants in *COQ* genes. Approximately 277 patients from 184 families with primary CoQ deficiency caused by homozygous or compound heterozygous pathogenic variants of some but not all *COQ* genes (*PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ5*, *COQ6*, *COQ7*, *COQ8A*, *COQ8B* and *COQ9*) have been identified up to date (Alcázar-Fabra et al. 2018) (Table 6.1). Primary CoQ deficiencies are mainly of early-onset, ranging from birth to early childhood (*PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ5*, *COQ6*, *COQ7* and *COQ9*), or from childhood to adolescence (*COQ8A* and *COQ8B*). However, there are reports for some adult-onset cases harboring mutations in *COQ2* (Mitsui et al. 2013), *COQ8A* (Horvath et al. 2012; Terracciano et al. 2012) or *COQ8B* (Atmaca et al. 2017) (Table 6.2).

Symptoms of CoQ deficiencies have been traditionally grouped into five categories: encephalomyopathy, cerebellar ataxia, severe infantile multisystemic disease, nephropathy, and isolated myopathy (Emmanuele et al. 2012). However, this classification is currently dismissed since a growing number of patients have been studied lately and show a broader and overlapping clinical spectrum (Acosta-López et al. 2019; Salviati et al. 2017). Also, it has become more evident that only patients affected by secondary CoQ deficiency have isolated myopathy (Salviati et al. 2017; Trevisson et al. 2011).

Impairment of CoQ biosynthesis caused by mutations in *COQ* genes are clinically highly diverse and manifest with defects in different tissues and systems, mainly skeletal muscle, central and peripheral nervous system, kidney and heart (Fig. 6.3). Not only the clinical manifestations, but also the specific phenotypic consequences of mutations in *COQ* genes are very heterogeneous. Mutations in some *COQ* genes affect particular tissues (e.g. *COQ8A* (Mignot et al. 2013) and *COQ8B* (Ashraf et al. 2013)), while others' pathological variations are more pleiotropic (e.g. *COQ2* (Desbats et al. 2016) and *COQ4* (Brea-Calvo et al. 2015)). Also, mutations in the same *COQ* gene can cause very variable clinical phenotypes with different age of onset, as it occurs with *COQ2* or *COQ4* patients. Genotype-phenotype correlations are currently difficult to establish, mainly because of the low number of patients identified and the highly complex set of symptoms associated with them. The diversity of clinical manifestations suggests that different pathomechanisms may exist. Genetic background, compensation mechanisms, maternal effect and maybe, environmental factors, could determine the moment and the tissues affected during development and thus, influence the outcome of each genetic defect in each individual.

The central nervous system (CNS) is very often affected in primary CoQ deficiency patients. CNS symptoms may be present in individuals with mutations in any of the *COQ* genes, but they are less frequent in patients with pathogenic variants of *COQ6* and *COQ8B*, in whom the central phenotype is renal involvement (Table 6.3). **Encephalopathy**, defined as a broad spectrum of brain manifestations,

Table 6.1 Pathogenic variants of *COQ* genes found in primary CoQ deficiency patients reported in the literature

Gene	Length (AA)	Exons	RefSeq[1]	Pathogenic Variants				
				F (P)	cDNA Mutation	AA Modification	Exon	Reference
PDSS1	415	12 exons	NM_014317.5 NP_055132.2	1 (1)	c.661_662insT	p.Arg221Leufs*	7	Vasta (2012)
				1 (2)	c.924T > G	p.Asp308Glu	10	Mollet (2007)
				1 (1)	c.1108A > C	p.Ser370Arg	12	Vasta (2012)
PDSS2	399	8 exons	NM_020381.4 NP_065114.3	1 (1)	c.485A > G	p.His162Arg	3	Iványi (2018)
				1 (1)	c.964C > T	p.Gln322*	6	López (2006)
				1 (1)	c.1042_1148-2816del	p.?	8	Iványi (2018)
				2 (2)	c.1145C > T	p.Ser382Leu	8	López (2006) and Sadowski (2015)
				1 (1)	c.1151C > A	p.Ala384Asp	8	Sadowski (2015)
				1 (3)	NK	NK	NK	Rötig et al. (2000) and Rahman et al. (2012)
COQ2[2]	371	7 exons	NM_001358921.2 NP_001345850.1	1 (1)	c.26dupT	p.Ala10Argfs*33	1	Starr (2018)
				1 (1)	c.232A>G	p.Met78Val	1	Mitsui (2013) and Desbats et al. (2016)
				5 (7)	c.287G > A[4]	p.Ser96Asn	2	Diomedi-Camassei et al. (2007), Dinwiddie (2013), Desbats et al. (2016), Scalais (2013) and Eroglu (2018)
				2 (3)	c.368G > A	p.Arg123His	2	Sadowski (2015) and Xu (2018)
				1 (1)	c.395T > G	p.Met132Arg	2	Desbats et al. (2015a, b)
				1 (1)	c.440G > A	p.Arg147His	3	Diomedi-Camassei et al. (2007) and Desbats et al. (2016)
				8 (9)	c.533A > G	p.Asn178Ser	3	Diomedi-Camassei et al. (2007), Mccarthy (2013), Desbats et al. (2016), Sadowski (2015), Starr (2018) and Bezdíčka et al. (2018)
				1 (1)	c.551delT	p.Leu184fs*14	4	Mccarthy (2013) and Desbats et al. (2016)

				1 (1)	c.682T > C[5]	p.Cys228Arg	5	Wu (2019)
				1 (1)	c.706C > T	p.Leu236Phe	5	Sadowski (2015)
				1 (1)	c.731C > T	p.Thr244Ile	5	Starr (2018)
				2 (3)	c.740A > G	p.Tyr247Cys	5	Diomedi-Camassei et al. (2007), Salviati (2005), Quinzii (2006), Desbats (2016) and Sadowski (2015)
				1 (2)	c.755C > T	p.Ala252Val	5	Jakobs (2013) and Desbats (2016)
				2 (3)	c.823A > G	p.Thr275Ala	6	Starr (2018) and Xu (2018)
				2 (2)	c.1009C > T[4]	p.Arg337*	7	Dinwiddie (2013), Desbats (2016) and Starr (2018)
				1 (2)	c.1019G > C	p.Gly340Ala	7	Gigante (2017)
				1 (2)	c.1047delT	p.Asn351Ilefs*15	7	Mollet (2007)
COQ4	265	7 exons	NM_016035.5 NP_057119.3	1 (1)	c.23_33delTCCTCCGTCGG	p.Val8Alafs*19	1	Sondheimer (2017)
				1 (2)	c.155T > C	p.Leu52Ser	2	Brea-Calvo (2015)
				1 (2)	c.164G > T	p.Gly55Val	2	Caglayan (2019)
				1 (1)	c.190C > T	p.Pro64Ser	2	Brea-Calvo (2015)
				1 (2)	c.197_198delGCinsAA	p.Arg66Gln	2	Chung (2015)
				2 (3)	c.202G > C	p.Asp68His	2-3	Chung (2015) and Helbig (2016)
				1 (2)	c.230C > T	P.Thr77Ile	3	Bosch (2018)
				1 (2)	c.245T > A	p.Leu82Gln	3	Chung (2015)
				1 (1)	c.311G > T	p.Asp111Tyr	4	Sondheimer (2017)
				1 (1)	c.356C > T	p.Pro119Leu	4	Sondheimer (2017)
				12 (16)	c.370G > A[6]	p.Gly124Ser	4	Lu (2019), Ling (2019) and Yu (2019)

(continued)

Table 6.1 (continued)

Gene	Length (AA)	Exons	RefSeq[1]	Pathogenic Variants				
				F (P)	cDNA Mutation	AA Modification	Exon	Reference
				2 (2)	c.371G > T	p.Gly124Val	4	Ling (2019) and Yu (2019)
				4 (5)	c.402+1G > C	?	Intron 4	Yu (2019)
				1 (1)	c.421C > T	p.Arg141*	5	Brea-Calvo (2015)
				1 (1)	c.433C > G	p.Arg145Gly	5	Brea-Calvo (2015)
				1 (1)	c.469C>A	p.Gln157Lys	5	Helbig (2016)
				1 (2)	c.473G > A	p.Arg158Gln	5	Chung (2015)
				1 (2)	c.521_523delCCA	p.Thr174del	5	Brea-Calvo (2015)
				1 (1)	c.533G > A	p.Gly178Glu	6	Ling (2019)
				1 (1)	c.550T > C	p.Trp184Arg	6	Yu (2019)
				3 (3)	c.718C > T	p.Arg240Cys	7	Brea-Calvo (2015) and Chung (2015)
				1 (1)	3.9 Mb deletion of chromosome 9q34.13, including COQ4 gene			Salviati (2012)
COQ5	327	7 exons	NM_032314.4 NP_115690.3	1 (3)	9590 pb tandem duplication of the last 4 exons of COQ5 after 1Kb of 3′UTR (modifies the 3′UTR) (base pair positions on Chr 12: 120,940,150-120,949,950/hg19)			Malicdan (2018)
COQ6	468	12 exons	NM_182476.3 NP_872282.1	Isoform 1				
				1 (1)	c.145G > T	p.Ala49Ser	1	Schoonen (2019) and Louw (2018)
				6 (6)	c.189_191delGAA	p.Lys64del	2	Park et al. (2017a, b)
				1 (1)	c.484C > T[3]	p.Arg162*	5	Heeringa (2011)
				1 (1)	c.564G > A[3]	p.Trp188*	5	Heeringa (2011)
				1 (1)	c.686A > C	p.Gln229Pro	6	Park et al. (2017a, b)
				2 (7)	c.763G > A	p.Gly255Arg	7	Heeringa (2011) and Doimo (2014)

				6 (6)	c.782C > T	p.Pro261Leu	7	Gigante (2017) and Park et al. (2017a, b)
				1 (1)	c.804delC	p.Leu269Trpfs*13	8	Stańczyk et al. (2018)
				5 (8)	c.1058C > A	p.Ala353Asp	9	Heeringa (2011), Doimo (2014), Sadowski (2015), Koyun (2018) and Yuruk Yildirim et al. (2019)
				3 (3)	c.1078C > T	p.Arg360Trp	9	Cao (2017), Li (2018) and Stańczyk et al. (2018)
				1 (1)	c.1154A > C	p.Asp385Ala	11	Sadowski (2015)
				2 (2)	c.1235A>G[3]	p.Tyr412Cys	11	Doimo (2014) and Sadowski (2015)
				1 (1)	c.1341G > A	p.Trp447*	11	Heeringa (2011) and Doimo (2014)
				1 (1)	c.1383delG	p.Gln461fs*478	12	Heeringa (2011) and Doimo (2014)
				Isoform 2				
				2 (2)	c.41G > A[3]	p.Trp14*	1	Schoonen (2019), Louw (2018) and Song et al. (2018)
COQ7	217	6 exons	NM_016138.5 NP_057222.2	1 (1)	c.319C > T	p.Arg107Trp	3	Kwong (2019)
				1 (1)	c.332T > C (and c.308C > T)[7]	p.Leu111Pro (and p.Thr103Met)	3	Wang (2017)
				1 (1)	c.422T > A	p.Val141Glu	4	Freyer (2015) and Wang (2017)
				1 (1)	c.599_600delinsTAATGCATC	p.(Lys200Ilefs*56	6	Kwong (2019)
COQ9	318	9 exons	NM_020312.4 NP_064708.1	1 (1)	c.384delG	p.Gly129Valfs*17	4	Kaya Ozcora et al. (2017)
				1 (1)	c.521 + 1delG	p.Ser127_Arg202del	Intron 5	Danhauser (2016)
				1 (4)	c.521 + 2T>C	p.Ser127_Arg202del	Intron 5	Smith (2018)
				1 (4)	c.711 + 3G>C	p.Ala203_Asp237del	Intron 7	Smith (2018)
				1 (1)	c.730C > T	p.Arg244*	7	Rahman et al. (2001) and Duncan (2009)

(continued)

Table 6.1 (continued)

Gene	Length (AA)	Exons	RefSeq[1]	Pathogenic Variants				
				F (P)	cDNA Mutation	AA Modification	Exon	Reference
COQ8A/ ADCK3	647	15 exons	NM_020247.5 NP_064632.2	1 (1)	c.500_521del22insTTG	p.Gln167Leufs*36	3	Lagier-Tourenne et al. (2008)
				4 (5)	c.589-3C > G[8]	p.Leu197Valfs*20	Intron 3	Mignot (2013), Schirinzi (2019) and Galosi (2019)
				1 (2)	c.637C > T	p.Arg213Trp	4	Mollet (2008) and Mignot (2013)
				1 (3)	c.685-690delCTGGCA	p.Leu229_Ala230del	5	Hajjari (2019)
				2 (3)	c.811C > T	p.Arg271Cys	6	Horvath (2012), Mignot (2013) and Sun (2019)
				1 (2)	c.815G > T	p.Gly272Val	6	Mollet (2008) and Mignot (2013)
				1 (1)	c.815G>A	p.Gly272Asp	6	Mollet (2008) and Mignot (2013)
				1 (1)	c.827A > G	p.Lys276Arg	6	Pronicka (2016)
				1 (2)	c.830T > C	p.Leu277Pro	6	Jacobsen (2017)
				5 (7)	c.895C > T	p.Arg299Trp	7	Horvath (2012), Mignot (2013) and Hikmat (2016)
				3 (3)	c.901C > T	p.Arg301Trp	7	Sun (2019)
				1 (2)	c.910G > A	p.Ala304Thr	7	Horvath (2012)
				1 (1)	c.911C > T	p.Ala304Val	7	Horvath (2012)
				1 (1)	c.913G > T	p.Asp305Tyr	7	Chang (2018)
				1 (1)	c.993C > T[9]	p.Lys314_Gln360del	8 (del of exon8?)	Lagier-Tourenne et al. (2008), Anheim (2010) and Mignot (2013)
				1 (1)	c.1000C > T	p.Arg334Trp	8	Sun (2019)
				1 (1)	c.1013C > T	p.Ala338Val	8	Kaya Ozcora et al. (2017)
				3 (6)	c.1027C > T	p.Gln343*	8	Shalata (2019)

				5 (8)	c.1042C > T	p.Arg348*	8	Gerards (2010), Terracciano (2012), Sun (2019) and Galosi (2019)
				1 (1)	c.1081-1_1082dupGTA	p.Gln360_ Tyr361ins*	Intron 8/ Exon 9	Mignot (2013)
				1 (2)	c.1136T > A	p.Leu379*	9	Gerards (2010)
				1 (2)	c.1228C > T	p.Arg410*	10	Mignot (2013)
				1 (1)	c.1229G > A	p.Arg410Gln	10	Sun (2019)
				1 (2)	c.1286A > G[3]	p.Tyr429Cys	11	Horvath (2012)
				3 (3)	c.1331_1332insCACAG	p.Glu446Alafs*33	11	Schirinzi (2019) and Galosi (2019)
				1 (1)	c.1334–1335del[3]	p.Thr445Argfs*52	11	Sun (2019)
				1 (1)	c.1358delT	p.Leu453Argfs*24	11	Mignot (2013)
				3 (4)	c.1396delG	p.Glu466Argfs*11	11	Mutlu-Albayrak et al. (2020)
				1 (4)	c.1398 + 2T > C[10]	p.Asp420Trpfs*40; p.Ile467Alafs*22	Exons 11-12	Lagier-Tourenne et al. (2008)
				1 (1)	c.1399-3_1408del	Exon 12 skipping?	Exons 11-12	Chang (2018)
				1 (2)	c.1506 + 1G>A	p.Val503Metfs*21	Intron 12	Jacobsen (2017)
				1 (1)	c.1511_1512delCT	p.Ala504fs*	13	Barca et al. (2016a)
				1 (1)	c.1523T > C	p.Phe508Ser	13	Mignot (2013)
				2 (2)	c.1532C > T	p.Thr511Met	13	Sun (2019) and Chang (2018)
				1 (1)	c.1534C > T[11]	p.Arg512Trp	13	Nair (2018)
				1 (1)	c.1541A > G	p.Tyr514Cys	13	Lagier-Tourenne et al. (2008)
				1 (1)	c.1645G > A	p.Gly549Ser	14	Lagier-Tourenne et al. (2008), Anheim (2010) and Mignot (2013)

(continued)

Table 6.1 (continued)

Gene	Length (AA)	Exons	RefSeq[1]	Pathogenic Variants				
				F (P)	cDNA Mutation	AA Modification	Exon	Reference
				2 (2)	c.1651G > A	p.Glu551Lys	14	Mollet (2008) and Sun (2019)
				1 (1)	c.1702delG	p.Glu568Argfs*	15	Pronicka (2016)
				1 (2)	c.1732T > G	p.Phe578Val	15	Hikmat (2016)
				1 (1)	c.1749_1751delCAC	p.Thr584del	15	Chang (2018)
				3 (4)	c.1750_1752delACC	p.Thr584del	15	Lagier-Tourenne et al. (2008), Blumkin et al. (2014) and Sun (2019)
				1 (2)	c.1805C > G	p.Pro602Arg	15	Blumkin et al. (2014)
				1 (1)	c.1813dupG	p.Glu605Glyfs*125	15	Mollet (2008) and Mignot (2013)
				2 (3)	c.1823C > T	p.Ser608Phe	15	Shalata (2019)
				3 (4)	c.1844G > A[8]	p.Gly615Asp	15	Mignot (2013), Schirinzi (2019) and Galosi (2019)
				1 (2)	c.1844dupG	p.Ser616Leufs*114	15	Liu (2014)
				1 (1)	27.6 kb deletion of 1q42.3 including Exons 1–2			Galosi (2019)
				1 (1)	29 kb partial deletion of the gene including exons 3 to 15 (base pair position: 227,150,977-227,195,656, hg19)			Mignot (2013)
				1 (1)	2.9Mb duplication at chromosome region 1q42.11q42.13 (including ADCK3)			Malgireddy (2016)
COQ8B/ ADCK4	544	15 exons	NM_024876.4 NP_079152.3	1 (1)	c.101G > A	p.Trp34*	2	Ashraf (2013)
				4 (8)	c.293T > G	p.Leu98Arg	5	Korkmaz (2016) and Atmaca (2017)
				1 (2)	c.449G > A	p.Arg150Gln	6	Park et al. (2017a, b)
				3 (5)	c.532C > T	p.Arg178Trp	7	Ashraf (2013), Korkmaz (2016), Vazquez-Fonseca et al. (2017) and Feng (2017)
				3 (4)	c.645delT	p.Phe215Leufs*14	8	Ashraf (2013), Korkmaz (2016) and Vazquez-Fonseca et al. (2017)

				1 (1)	c.649G > A	p.Ala217Thr	8	Lolin (2017)
				6 (7)	c.737G > A	p.Ser246Asn	9	Feng (2017), Park et al. (2017a, b) and Kakiuchi et al. (2019)
				1 (2)	c.748G > A	p.Asp250Asn	9	Korkmaz (2016)
				1 (1)	c.748G > T	p.Asp250Tyr	9	Lolin (2017)
				4 (5)	c.748G > [12]	p.Asp250His	9	Zhang (2017), Feng (2017) and Yang et al. (2019)
				2 (3)	c.759C > A	p.Asn253Lys	9	Park et al. (2017b)
				1 (3)	c.857A > G	p.Asp286Gly	10	Ashraf (2013) and Vazquez-Fonseca et al. (2017)
				1 (1)	c.929C > T	p.Pro310Leu	10	Korkmaz (2016)
				1 (1)	c.954_956dupGAC	p.Thr319dup	11	Ashraf (2013)
				1 (2)	c.958C > T	p.Arg320Trp	11	Ashraf (2013) and Vazquez-Fonseca et al. (2017)
				1 (2)	c.1027C > T	p.Arg343Trp	11	Ashraf (2013)
				1 (1)	c.1041G > T	p.Cys347*	12	Yang et al. (2019)
				5 (13)	c.1199dupA	p.His400Glnfs*11	13	Ashraf (2013), Korkmaz (2016), Vazquez-Fonseca et al. (2017) and Atmaca (2017)
				7 (20)	c.1339dupG	p.Glu447Glyfs*10	15	Korkmaz (2016), Atmaca (2017) and Vazquez-Fonseca et al. (2017)
				1 (2)	c.1356_1362delGGGCCCT	p.Gln452Hisfs*	15	Ashraf (2013)
				2 (3)	c.1430G > A	p.Arg477Gln	15	Ashraf (2013), Vazquez-Fonseca et al. (2017) and Atmaca (2017)
				1 (3)	c.1447G > T	p.Glu483*	15	Ashraf (2013) and Vazquez-Fonseca et al. (2017)
				1 (1)	c.1468C > T	p.Arg490Cys	15	Park et al.(2017b)
				1 (1)	c.1493_1494CC > AA	p.Ala498Glu	15	Korkmaz (2016)

(continued)

Table 6.1 (continued)

[1]Reference sequences correspond to longest transcript
[2]COQ2: Several initiation codons. The last proposed nomenclature is used, corresponding to a 371 aa length protein (Desbats et al. 2016)
[3]These pathogenic variants were found in simple heterozygosis in at least one patient(Doimo et al. 2014; Heeringa et al. 2011; Horvath et al. 2012; Song et al. 2018; Sun et al. 2019)
The patient with these two mutations also carries a novel mutation in *MT-ND1* (3754C > A) with 22% of heteroplasmy in peripheral blood, which may contribute to the disease (Dinwiddie et al. 2013)
[5]The patient with this mutation in homozygosis also carries an additional homozygous mutation in *ARSB* gene (c.1213 + 1G > A), which may contribute to the disease (Wu et al. 2019)
[6]c.370G > A, p.Gly124Ser mutation in *COQ4* has been described as a founder mutation in southern Chinese population, being found in 16 patients of 12 Chinese families (Ling et al. 2019; Lu et al. 2019; Yu et al. 2019)
[7]*COQ7* c.308C > T polymorphism seems to increase COQ7 protein instability and intensify the effect of the mutation. The patient also has a 1555A>G mutation in mtDNA, not previously reported, which may contribute to the disease (Wang et al. 2017)
[8]A patient with these two mutations in heterozygosis in *COQ8A* also carries two compound heterozygous mutations in *PAH* gene, which may contribute to the disease (Galosi et al. 2019)
[9]Pathogenic variant c.993C > T of *COQ8A* shows a conflicting protein change. Based on the sequence, it should be a synonymous change (p.Phe331=) (Lagier-Tourenne et al. 2008)
[10]*COQ8A* c.1398 + 2T > C6 variant affects a splice donor site, different splice variants are expressed: p.Asp420Trpfs*40 and p.Ile467Alafs*22 (Lagier-Tourenne et al. 2008)
[11]The patient with this *COQ8A* mutation in homozygosis also carries an additional homozygous mutation in *MED25* gene (c.518T > C; p.Ile173Thr), which may contribute to the disease (Nair et al. 2018)
[12]Two siblings with this *COQ8B* variant in homozygosis also had an homozygous mutation in *NPHS1* gene (c.1339G > A; p.Glu447Lys) (Zhang et al. 2017)
Abbreviations: *F* number of families with each mutation, *P* number of patients with each mutation, *AA* amino acid

Table 6.2 Age of onset, biochemical findings and CoQ treatment response of primary CoQ deficiency patients in the literature

Gene	Families	Patients	Sex	Age		Biochemical Findings		CoQ Treatment		References
				Onset	Last Examination (*death)	Lactic Acidosis	CoQ Deficiency	CoQ Treatment	Effect	
PDSS1	2	3	F (2)	<2yo (3)	1,5yo* (1)	3	F (2)			Mollet et al. (2007) and Vasta et al. (2012)
			M (1)		14–22yo (2)		WBC (1)			
PDSS2	5	7	F (2)	<1yo (6)	8mo* (2)	2	M (1)	Yes (2)	No benefits (2)	Iványi et al. (2018), López et al. (2006), Rahman et al. (2012), Rötig et al. (2000) and Sadowski et al. (2015)
			M (5)	2yo (1)	8yo* (1)		F (1)			
					8-12yo (2)					
					NK (2)					
COQ2	23	31	F (16)	<3yo (26)	<3yo* (15)	12	M (5)	Yes (14)	Neuromuscular functions restored (2)	Bezdíčka et al. (2018, 2020), Desbats et al. (2015, 2016), Dinwiddie et al. (2013), Diomedi-Camassei et al. (2007), Eroglu et al. (2018), Gigante et al. (2017), Jakobs et al. (2013), McCarthy et al. (2013), Mitsui et al. (2013), Mollet et al. (2007), Quinzii et al. (2006), Sadowski et al. (2015), Salviati et al. (2005), Scalais et al. (2013), Starr et al. (2018), Wu et al. (2019) and Xu et al. (2018)
			M (15)	10yo (1)	2-4yo (5)		F (3)		No benefits (2)	
				16–18yo (2)	12yo (1)				No benefits on neuromuscular function (3)	
				70yo (1)	23-37yo (2)				No benefits on renal function (1)	
				NK (1)	71yo (1)				No deterioration (2)	
					NK (7)				Renal function restored (6)	

(continued)

Table 6.2 (continued)

Gene	Families	Patients	Sex	Age		Biochemical Findings		CoQ Treatment		References
				Onset	Last Examination (*death)	Lactic Acidosis	CoQ Deficiency	CoQ Treatment	Effect	
COQ4	26	35	F (20)	Birth (19)	<4do* (7)	24	M (7)	Yes (20)	No benefits (7)	Bosch et al. (2018), Brea-Calvo et al. (2015), Caglayan et al. (2019), Chung et al. (2015), Helbig et al. (2016), Ling et al. (2019), Lu et al. (2019), Salviati et al. (2012), Sondheimer et al. (2017) and Yu et al. (2019)
			M (14)	<1yo (11)	1mo-3yo* (12)		F (10)		Improvement of Sz or Ep (3)	
			NK (1)	4–10yo (4)	9mo-4yo (8)				Improvement in development (2)	
				NK (1)	7yo* (1)				Improvement of cardiac function (2)	
					8–28yo (6)				Stable condition (2)	
					NK (1)				Subjective response improvement (2)	
									Improvement of ataxia (1)	
									Improvement of lactic acidosis (1)	
									Muscle improvement (1)	

COQ5	1	3	F (3)	Early childhood (3)	14–22yo (3)		WBC (3)	Yes (3)	Improvement of ataxia (3)	Malicdan et al. (2018)
							M (1)			
COQ6	24	32	F (13)	<3yo (19)	5–6yo* (2)		M (1)	Yes (10)	Improved proteinuria (6)	Cao et al. (2017), Doimo et al. (2014), Gigante et al. (2017), Heeringa et al. (2011), Koyun et al. (2018), Li et al. (2018), Louw et al. (2018), Park et al. (2017a), Sadowski et al. (2015), Schoonen et al. (2019), Stańczyk et al. (2018) and Yuruk Yildirim et al. (2019)
			M (10)	4–10yo (8)	17yo* (1)				Improved renal function (3)	
			NK (12)	NK (5)	NK* (2)				Improved growth retardation (2)	
					0.5–17yo (20)				Improved SNHL (1)	
					NK (7)					
COQ7	3	3	F (1)	<1yo (3)	1yo*(1)	3	M (1)	Yes (3)	No deterioration (2)	Freyer et al. (2015), Kwong et al. (2019) and Wang et al. (2017)
			M (2)		6–9yo (2)		F (3)		No benefits (1)	
COQ9	4	7	F (2)	Birth (6)	Birth*(2)	5	M (1)	Yes (4)	No benefits (3)	Danhauser et al. (2016), Duncan et al. (2009), Olgac et al. (2020), Rahman et al. (2001) and Smith et al. (2018)
			M (5)	9mo (1)	12ho*(1)		F (3)		Plasma lactate reduced (1)	
					3do*(1)					
					18do* (1)					
					2yo* (1)					
					3yo (1)					

(continued)

Table 6.2 (continued)

Gene	Families	Patients	Sex	Age		Biochemical Findings		CoQ Treatment		References
				Onset	Last Examination (*death)	Lactic Acidosis	CoQ Deficiency	CoQ Treatment	Effect	
COQ8A	55	77	F (41)	1–4yo (35)	22yo*(1)	7	M (15)	Yes (29)	No benefits (13)	Anheim et al. (2010), Barca et al. (2016a, b), Blumkin et al. (2014), Chang et al. (2018), Galosi et al. (2019), Gerards et al. (2010), Hajjari et al. (2019), Hikmat et al. (2016), Horvath et al. (2012), Jacobsen et al. (2017), Kaya Ozcora et al. (2017), Lagier-Tourenne et al. (2008), Liu et al. (2014), Malgireddy et al. (2016), Mignot et al. (2013), Mollet et al. (2008), Mutlu-Albayrak et al. (2020), Nair et al. (2018), Pronicka et al. (2016), Schirinzi et al. (2019), Shalata et al. (2019), Sun et al. (2019) and Terracciano et al. (2012)
			M (33)	5–11yo (19)	26yo*(1)		F (4)		Improvement of ataxia (9)	
			NK (3)	13–27yo(11) NK (12)	3–11yo (14)		WBC (1)		Improvement of tremor and myoclonus (5)	
					13–25yo (22)				Improvement in motor abilities (5)	
					26–54yo (32)				Slight improvement of cerebellar signs (2)	
					81yo (1)				Stabilization of the ataxia (2)	
					NK (6)				Improvement in fatigue and speech (1)	
									Improvement of cognitive abilities (1)	

COQ8B	41	79	F (32)	<1yo-10yo (32)	13–15yo* (2)		F (5)	Yes (29)	No benefits (7)	Ashraf et al. (2013), Atmaca et al. (2017), Feng et al. (2017), Kakiuchi et al. (2019), Korkmaz et al. (2016), Lolin et al. (2017), Park et al. (2017b), Vazquez-Fonseca et al. (2017), Yang et al. (2018), Yang et al. (2019) and Zhang et al. (2017)
			M (31)	11yo-21yo (39)	25yo* (1)				Improvement of proteinuria (18)	
			NK (16)	23–32yo (7)	29yo* (1)				Better physical fitness and reduced fatigue (1)	
				NK (1)	1–9yo (6)				Improvement of edema (1)	
					10–20yo (54)				Stabilization of renal function (1)	
					21–39yo (14)					
					NK (1)					

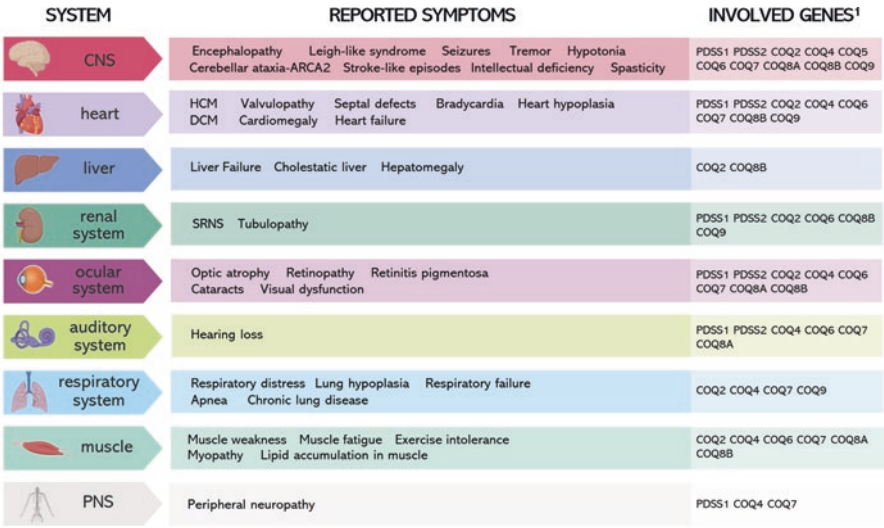

Fig. 6.3 Main tissues affected in individuals with primary CoQ deficiency. Compilation of the more common clinical manifestations and the genes whose mutations have been associated with one or several of the referred symptoms. For the number of patients showing each symptom refer to Table 6.3. Abbreviations are also indicated in Table 6.3. [1]Symptoms are reported at different frequencies for patients harboring pathogenic variants of the different *COQ* genes

which are often not described in detail in case reports, has been mainly found in *COQ2* (Dinwiddie et al. 2013; Diomedi-Camassei et al. 2007; Eroglu et al. 2018; Mollet et al. 2007), *COQ4* (Brea-Calvo et al. 2015; Chung et al. 2015; Ling et al. 2019; Lu et al. 2019; Salviati et al. 2012; Sondheimer et al. 2017; Yu et al. 2019), *COQ5* (Malicdan et al. 2018) and *COQ9* (Duncan et al. 2009; Olgac et al. 2020; Smith et al. 2018) patients. However, it has also been observed in some *PDSS1* (Mollet et al. 2007), *PDSS2* (Iványi et al. 2018), *COQ6* (Louw et al. 2018; Schoonen et al. 2019), *COQ7* (Kwong et al. 2019), *COQ8A* (Mignot et al. 2013; Nair et al. 2018) and *COQ8B* (Korkmaz et al. 2016) probands. Most of the *COQ2* patients presented early-onset nephrotic syndrome, accompanied in one-third of the cases with encephalopathy and seizures (Bezdíčka et al. 2018; Desbats et al. 2015a, b, 2016; Dinwiddie et al. 2013; Diomedi-Camassei et al. 2007; Eroglu et al. 2018; Gigante et al. 2017; Jakobs et al. 2013; McCarthy et al. 2013; Mollet et al. 2007; Quinzii et al. 2006; Sadowski et al. 2015; Salviati et al. 2005; Scalais et al. 2013; Starr et al. 2018; Xu et al. 2018). *COQ4* cases generally present encephalopathy accompanied by seizures, hypotonia and cerebellar hypoplasia, and almost half of the diagnosed patients had a fatal outcome with death in the postnatal period (Brea-Calvo et al. 2015; Chung et al. 2015; Helbig et al. 2016; Ling et al. 2019; Lu et al. 2019; Salviati et al. 2012; Sondheimer et al. 2017). Likewise *COQ2*, one third of the *COQ8A* patients also suffered **seizures** (Galosi et al. 2019; Hikmat et al. 2016; Horvath et al. 2012; Mignot et al. 2013; Mollet et al. 2008; Sun et al. 2019; Terracciano et al. 2012), and it has also been reported in cases of *PDSS2* (López

Table 6.3 Clinical manifestations and number of patients affected by symptom in primary CoQ deficiency

Affected Gene		*PDSS1*	*PDSS2*	*COQ2*	*COQ4*	*COQ5*	*COQ6*	*COQ7*	*COQ9*	*COQ8A*	*COQ8B*
Total Number of Patients		3	7	31	35	3	32	3	7	77	79
CNS	Autosomal recessive cerebellar ataxia 2 (ARCA2)	–	3	–	4	3	1	–	–	70	–
	Basal ganglia lessions (BGL)	–	1	1	5	–	–	1	1	–	–
	Cerebellar atrophy (CAt)	–	–	1	8	3	–	–	1	63	–
	Cerebellar hypoplasia (CHyp)	–	–	–	10	–	–	–	1	2	–
	Cerebral atrophy	–	–	–	6	–	–	1	–	–	–
	Cerebral Hypoplasia	–	–	–	1	–	–	–	–	–	–
	Cerebral palsy	–	1	–	–	–	–	–	–	–	–
	Chorea	–	–	–	–	–	–	–	–	2	–
	Depression	–	–	–	–	–	–	–	–	3	–
	Deteriorated ambulation (DAmb)	–	–	–	6	–	–	–	–	–	–
	Developmental delay(DD)	1	1	2	18	2	3	3	6	11	1
	Dysarthria (Dy)	–	–	–	2	3	–	–	–	26	–
	Dysdiadochokinesia	–	–	–	2	–	–	–	–	8	–
	Dysmetria	–	–	–	2	2	–	–	–	20	–
	Dystonia	–	1	2	6	–	–	–	1	15	–
	Encephalopathy	2	1	10	11	3	1	1	3	2	1
	Epilepsy (Ep)	–	–	4	9	1	–	–	–	15	2
	Gait instability (GI)	–	–	–	–	–	–	–	–	12	–
	Hypotonia (Ht)	–	2	6	19	–	1	3	2	7	–
	Impaired Handwriting (IH)	–	–	–	–	–	–	–	–	7	–
	Intellectual deficiency (ID)	2	3	–	6	3	1	1	–	35	4

(continued)

Table 6.3 (continued)

Affected Gene		*PDSS1*	*PDSS2*	*COQ2*	*COQ4*	*COQ5*	*COQ6*	*COQ7*	*COQ9*	*COQ8A*	*COQ8B*
Total Number of Patients		3	7	31	35	3	32	3	7	77	79
	Leigh-like Syndrome (LS)	–	1	–	2	–	–	–	2	–	–
	Migraine	–	–	–	–	–	–	–	–	5	–
	Multifocal global ischemic events (MGIE)	–	–	–	–	–	–	–	1	–	–
	Muscle stiffness (MS)	–	–	1	–	–	–	–	1	–	–
	Myoclonus (My)	–	–	2	1	2	–	–	–	14	–
	Non-visual pursuit (nVP)	–	–	1	–	–	–	1	–	–	–
	Nystagmus (Ny)	–	1	3	1	3	1	–	–	9	–
	Opisthotonus	–	–	–	–	–	–	–	1	–	–
	Ptosis (Pt)	–	–	–	–	–	1	1	–	3	–
	Pyramidal syndrome	–	1	–	–	–	–	–	–	1	–
	Saccadic eye movements (SEM)	–	–	–	1	1	–	–	–	14	–
	Seizures (Sz)	–	1	11	19	2	2	–	3	17	4
	Slow ocular pursuit	–	–	–	–	–	–	–	–	1	–
	Spams	–	–	–	2	–	–	1	–	–	–
	Spasticity (Sp)	–	1	–	9	1	–	1	–	8	–
	Sporadic Multisystem Atrophy (MSA)	–	–	1	–	–	–	–	–	–	–
	Strabismus	–	–	–	–	–	–	–	–	4	–
	Stroke-like lessions (SLL)	–	–	2	2	–	–	–	–	6	–
	Thalamic hypoplasia (THyp)	–	–	–	1	–	–	–	–	–	–
	Tremor (Tr)	–	–	1	2	1	–	–	–	33	–

PNS/ sensory organs	Astigmatism	–	–	–	–	–	–	–	–	–	2
	Cataracts	–	1	–	–	–	–	–	–	1	–
	Delayed visual maturation	–	–	–	1	–	–	–	–	–	–
	Hearing impairment	–	–	–	2	–	–	–	–	–	–
	Hearing Loss (HL)	–	–	–	1	–	–	–	–	–	–
	Hypermetropia	–	–	–	–	–	–	–	–	–	2
	Myopia	–	2	–	–	–	–	–	–	–	–
	Optic Nerve Atrophy (OA)	2	1	1	–	–	1	–	–	–	–
	Peripheral Neuropathy (PNSN)	2	–	–	1	–	–	2	–	–	–
	Retinitis Pigmentosa (RP)	–	2	1	–	–	–	–	–	–	1
	Retinopathy (Rp)	–	–	2	–	–	–	–	–	–	–
	Rod-Cone dysfunction	–	–	–	–	–	–	–	–	1	–
	Sensorineural hearing loss (SNHL)	2	4	–	–	–	18	3	–	2	–
	Visual aureas	–	–	–	–	–	–	–	–	1	–
	Visual dysfunction	–	2	–	6	–	–	2	–	1	1
Kidney	Chronic kidney disease (CKD)	–	–	1	–	–	2	–	–	–	18
	Dysplastic kidneys	–	–	–	–	–	–	1	–	–	–
	End-stage Renal Disease (ESRD)	1	2	10	–	–	16	–	–	–	47
	Enlarged kidneys	–	–	–	–	–	–	–	1	–	1
	Hematuria	–	–	–	–	–	–	–	–	–	8
	Kidney dysfunction (KD)	–	–	2	–	–	–	1	–	–	1
	Medullary nephrocalcinosis (MNC)	–	–	–	–	–	–	–	–	–	6
	Only Proteinuria	–	–	1	–	–	1	–	–	–	9
	Renal cysts	–	–	–	–	–	–	1	1	–	–
	Steroid resistant nephrotic syndrome (SRNS)	1	7	25	–	–	25	–	–	–	66
	Tubulopathy (Tp)	–	–	1	–	–	–	–	1	–	–

(continued)

Table 6.3 (continued)

Affected Gene		*PDSS1*	*PDSS2*	*COQ2*	*COQ4*	*COQ5*	*COQ6*	*COQ7*	*COQ9*	*COQ8A*	*COQ8B*
Total Number of Patients		3	7	31	35	3	32	3	7	77	79
Muscle	Exercise intolerance (EI)	–	–	–	–	–	–	–	–	14	–
	Lipid accumulation in muscle (LAM)	–	–	1	–	–	–	–	–	3	–
	Muscle fatigue (MF)	–	–	–	–	–	–	–	–	3	1
	Muscle weakness (MW)	–	–	1	–	–	3	3	–	13	1
	Myopathy	–	–	–	2	–	–	1	–	1	–
Heart	Bradycardia	–	–	–	5	–	–	–	2	–	–
	Cardiomegaly	–	–	–	3	–	–	–	1	–	–
	Cardiomyopathy	–	–	–	–	–	–	–	–	1	2
	Heart Failure(HF)	–	–	–	2	–	–	1	–	–	1
	Heart hypoplasia (HHyp)	–	–	–	1	–	–	–	–	–	–
	Hypertrophic Cardiomyopathy (HCM)	–	2	3	13	–	–	2	1	–	2
	Isolated ventricular non-compactation (IVNC)	–	–	–	–	–	–	–	1	–	–
	Pericardial effusion	–	–	–	1	–	–	–	–	–	1
	Septal defects	–	–	–	1	–	1	–	–	1	2
	Tachycardia	–	–	–	2	–	–	–	–	–	–
	Valvulopathy (Vp)	2	–	–	–	–	–	–	–	–	–
	Diastolic dysfunction	–	–	–	1	–	–	–	–	–	–
Other clinical features	Dysmorphic features	–	–	–	1	–	1	1	1	1	1
	Edema	–	2	11	–	–	2	–	–	–	16
	Diabetes Mellitus (DM)	–	–	6	–	–	–	–	–	–	–
	Obesity	2	–	–	–	–	–	–	–	–	–
	Hypercholesterolemia	–	–	2	–	–	1	–	–	1	1
	Goiter	–	–	–	–	–	–	–	–	–	2
	Hypothyroidism	–	–	–	–	–	–	–	–	–	1

	Respiratory distress (RD)	–	–	2	14	–	–	2	2	–	–
	Neonatal Pneumonia	–	1	–	–	–	–	–	–	–	–
	Respiratory failure (RF)	–	–	5	5	–	–	–	–	–	–
	Apnea	–	–	2	9	–	–	–	2	–	–
	Chronic Lung Disease (CLD)	–	–	1	–	–	–	–	–	–	–
	Recurrent Respiratory infections	–	–	1	1	–	–	–	–	1	–
	Lung Hypoplasia (LHyp)	–	–	–	–	–	–	1	–	–	–
	Cyanosis	–	–	–	2	–	–	–	1	–	–
	Hypertension (HT)	1	1	1	–	–	1	1	–	–	10
	Hypotension	–	–	–	2	–	–	–	–	–	–
	Livedo Reticularis (LR)	2	–	–	–	–	–	–	–	–	–
	Dyspnea	–	–	–	–	–	–	–	–	–	1
	Noctural enuresis	–	–	–	–	–	–	–	–	–	2
	Polyuria	–	–	–	–	–	–	–	–	–	1
	Polidypsia	–	–	–	–	–	–	–	–	–	1
	Cholestatic Liver	–	–	1	–	–	–	–	–	–	–
	Hepatomegaly	–	–	–	–	–	–	–	–	–	1
	Hepatosteatosis	–	–	–	–	–	–	–	–	1	–
	Liver failure (LF)	–	–	3	–	–	–	–	–	–	–
	Reduced hematopoiesis in liver	–	–	–	–	–	–	–	1	–	–
	Coma	–	–	–	1	–	–	–	–	–	–
	Hypospadias	–	–	–	–	–	–	–	–	–	1
	Lupus-like symptoms	–	–	–	–	–	–	–	–	–	1
	Oligohydramnios	–	–	3	1	–	–	1	3	–	–
	Recurrent Otitis	–	–	–	–	–	–	–	–	–	1
	Splenomegaly	–	–	–	–	–	–	–	–	–	1
	Crohn's Disease (CD)	–	–	–	–	–	–	–	–	–	1

et al. 2006), *COQ5* (Malicdan et al. 2018), *COQ6* (Heeringa et al. 2011), *COQ9* (Danhauser et al. 2016; Duncan et al. 2009; Olgac et al. 2020) and *COQ8B* (Korkmaz et al. 2016; Lolin et al. 2017). Again, **hypotonia** is a feature that has been reported mainly in *COQ4* (Brea-Calvo et al. 2015; Chung et al. 2015; Ling et al. 2019; Salviati et al. 2012; Sondheimer et al. 2017), some *COQ2* patients (Diomedi-Camassei et al. 2007; Eroglu et al. 2018; Jakobs et al. 2013; Scalais et al. 2013) and the three published cases of *COQ7* (Freyer et al. 2015; Kwong et al. 2019; Wang et al. 2017). However, it has been observed in several other *COQ* patients (*PDSS2* (Iványi et al. 2018; López et al. 2006), *COQ9* (Danhauser et al. 2016) and *COQ8A* (Jacobsen et al. 2017; Mollet et al. 2008; Nair et al. 2018; Shalata et al. 2019)) with lower frequency. **Dystonia** has been observed in some *COQ8A* patients (Chang et al. 2018; Gerards et al. 2010; Horvath et al. 2012; Liu et al. 2014; Mignot et al. 2013; Mollet et al. 2008; Sun et al. 2019), but also in a lower proportion in *PDSS2* (Rahman et al. 2012; Rötig et al. 2000), *COQ2* (Jakobs et al. 2013), *COQ4* (Yu et al. 2019) and *COQ9* ones (Duncan et al. 2009). **Cerebellar ataxia** and **cerebellar atrophy** seem to be hallmarks for *COQ8A* patients since they have been reported in 70 and 63 out of the 77 identified subjects respectively. In almost half of the described cases these symptoms have been associated with intellectual disability and tremor, or seizures, dysarthria, dysmetria, saccadic eye movements, dystonia, dysdiadochokinesia or spasticity in other instances (Anheim et al. 2010; Barca et al. 2016a; Blumkin et al. 2014; Chang et al. 2018; Gerards et al. 2010; Hajjari et al. 2019; Hikmat et al. 2016; Horvath et al. 2012; Jacobsen et al. 2017; Kaya Ozcora et al. 2017; Lagier-Tourenne et al. 2008; Liu et al. 2014; Malgireddy et al. 2016; Mignot et al. 2013; Mollet et al. 2008; Nair et al. 2018; Pronicka et al. 2016; Shalata et al. 2019; Sun et al. 2019; Terracciano et al. 2012). The only family affected by a mutation in *COQ5* up to now also shows a cerebellar ataxic phenotype similar to *COQ8A* patients (Malicdan et al. 2018). Cerebellar ataxia has also been observed in some patients harboring pathological variations of *PDSS2* (Rahman et al. 2012; Rötig et al. 2000), *COQ4* (Bosch et al. 2018; Caglayan et al. 2019; Yu et al. 2019) and *COQ6* (Heeringa et al. 2011) genes. **Cerebellar hypoplasia** has been annotated in one third of the *COQ4* reported probands (Brea-Calvo et al. 2015; Chung et al. 2015; Yu et al. 2019), in one *COQ9* (Olgac et al. 2020) and in two *COQ8A* patients (Shalata et al. 2019). It should be noted that sometimes it could be challenging to differentiate cerebellar hypoplasia from cerebellar atrophy, especially if the progression of the latter cannot be proven by repeated MRI. **Epilepsy** is another CNS symptom associated with CoQ primary deficiency that has been mainly found in *COQ8A* (Gerards et al. 2010; Hikmat et al. 2016; Horvath et al. 2012; Malgireddy et al. 2016; Mignot et al. 2013; Mollet et al. 2008; Pronicka et al. 2016; Schirinzi et al. 2019; Terracciano et al. 2012), *COQ4* (Brea-Calvo et al. 2015; Caglayan et al. 2019; Chung et al. 2015; Ling et al. 2019) and *COQ2* (Diomedi-Camassei et al. 2007; Gigante et al. 2017; Scalais et al. 2013), but also in *COQ5* cases (Malicdan et al. 2018) and some *COQ8B* patients (Korkmaz et al. 2016; Vazquez-Fonseca et al. 2017). In some *COQ8A* (Hikmat et al. 2016; Horvath et al. 2012; Mignot et al. 2013; Mollet et al. 2008), *COQ2* (Diomedi-Camassei et al. 2007; Eroglu et al. 2018) and *COQ4* (Bosch et al. 2018) cases, epilepsy was accompanied by **stroke-like**

episodes, which contributed significantly to the deterioration of the neurological status and could explain the heterogeneity of the functional outcome among affected siblings (Mignot et al. 2013). **Spasticity** has been observed in some *COQ8A* (Anheim et al. 2010; Gerards et al. 2010; Horvath et al. 2012; Lagier-Tourenne et al. 2008; Mignot et al. 2013; Mollet et al. 2008) and *COQ4* (Bosch et al. 2018; Brea-Calvo et al. 2015; Caglayan et al. 2019; Ling et al. 2019; Yu et al. 2019) cases and a few *PDSS2* (Rahman et al. 2012; Rötig et al. 2000), *COQ5* (Malicdan et al. 2018) and *COQ7* (Wang et al. 2017) patients. **Intellectual disability** is a feature found in a variable number of cases but in patients of almost all the *COQ* genes (*PDSS1*, *PSDD2*, *COQ4* to *COQ7*, *COQ8A* and *B*). Some studies predict that specific *COQ2* variants increase susceptibility to adult-onset **multisystem atrophy** (MSA), particularly in East Asian population, but not in the Caucasian one (Katzeff et al. 2019; Mitsui et al. 2013; Ogaki et al. 2014; Procopio et al. 2019).

Peripheral nervous system (PNS) and sensory organs manifestations are less common, but related symptoms have been reported in several cases of primary deficiencies (Table 6.1). **Sensorineural hearing loss** (SNHL) is the most frequent PNS phenotype in *COQ6* patients, in whom it was associated with Steroid Resistant Nephrotic Syndrome (SRNS) in all cases (Cao et al. 2017; Gigante et al. 2017; Heeringa et al. 2011; Koyun et al. 2018; Park et al. 2017a, b; Yuruk Yildirim et al. 2019). Some probands with *PDSS1* (Mollet et al. 2007), *PDSS2* (Iványi et al. 2018; Rahman et al. 2012; Rötig et al. 2000), *COQ7* (Freyer et al. 2015; Kwong et al. 2019; Wang et al. 2017) and *COQ8A* (Lagier-Tourenne et al. 2008) pathological variants presented SNHL as well. Two siblings with *PDSS1* pathological variations were reported to suffer **peripheral neuropathy**, associated with **optic atrophy** and early-onset SNHL (Mollet et al. 2007). All the three *COQ7* patients presented SNHL, and in two cases, they also showed peripheral **polyneuropathy** and/or **visual dysfunction** (Freyer et al. 2015; Kwong et al. 2019; Wang et al. 2017). **Optic nerve atrophy** was reported in very few individuals with *PDSS1* (Mollet et al. 2007), *PDSS2* (Rötig et al. 2000), *COQ2* (Diomedi-Camassei et al. 2007) and *COQ6* (Park et al. 2017a) pathogenic variants. Other visual impairments such as **cataract** (Horvath et al. 2012; Rötig et al. 2000), **retinopathy** (Diomedi-Camassei et al. 2007; Jakobs et al. 2013), **retinitis pigmentosa** (Iványi et al. 2018; Korkmaz et al. 2016; Mitsui et al. 2013; Rötig et al. 2000) or **delayed visual maturation** (Sondheimer et al. 2017) have been observed in several cases of *COQ* patients.

Renal involvement has also been reported for several of the *COQ* patients (Table 6.1). S**teroid resistant nephrotic syndrome** (SRNS) is often found in primary CoQ deficiency patients, specifically in those with pathogenic variants of *PDSS2*, *COQ2*, *COQ6* and *COQ8B*. It has generally been reported in patients starting as proteinuria that, when untreated, evolved to **end-stage renal disease** (ESRD) during childhood (Sadowski et al. 2015).The majority of the identified *COQ2* patients displayed early-onset nephrotic syndrome, isolated or associated with encephalopathy and seizures (Bezdíčka et al. 2018; Diomedi-Camassei et al. 2007; Eroglu et al. 2018; Gigante et al. 2017; McCarthy et al. 2013; Mollet et al. 2007; Quinzii et al. 2006; Sadowski et al. 2015; Salviati et al. 2005; Scalais et al. 2013; Starr et al. 2018; Wu et al. 2019; Xu et al. 2018). Of note, the hallmark of *COQ6*

pathogenic variants is childhood-onset SNRS associated with SNHL (Cao et al. 2017; Gigante et al. 2017; Heeringa et al. 2011; Park et al. 2017a, b; Yuruk Yildirim et al. 2019). *COQ8B* patients mainly presented with an adolescence-onset SRNS due to focal segmental glomerulosclerosis, associated with oedema and hypertension, which generally progressed to ESRD (Ashraf et al. 2013; Atmaca et al. 2017; Feng et al. 2017; Hughes et al. 2017; Korkmaz et al. 2016; Lolin et al. 2017; Park et al. 2017b; Vazquez-Fonseca et al. 2017; Yang et al. 2018; Zhang et al. 2017). All the 7 reported patients of *PDSS2* (Iványi et al. 2018; López et al. 2006; Rahman et al. 2012; Rötig et al. 2000; Sadowski et al. 2015) and 1 of the three reported *PDSS1* patients (Vasta et al. 2012) presented SNRS as well. Two cases of *COQ2* and *COQ9* patients displayed a tubulopathy (Dinwiddie et al. 2013; Duncan et al. 2009).

Skeletal muscle manifestations are not common in these patients (Table 6.1). **Isolated myopathy** has not been found in patients with molecular confirmation of primary CoQ deficiency (Salviati et al. 2017). Most of the patients with a predominant muscular clinical phenotype are affected by secondary CoQ defects (see next section). **Muscle weakness** and **muscle fatigue** are the most frequent symptoms associated with this tissue in primary deficiencies, but in combination with other affectations and, in any case, reported in very few cases of each of the genes (Alcázar-Fabra et al. 2018).

Heart conditions are, instead, more frequent, being **hypertrophic cardiomyopathy** possibly a hallmark for *COQ4* patients with prenatal-onset, specifically (Brea-Calvo et al. 2015; Chung et al. 2015; Ling et al. 2019; Sondheimer et al. 2017; Yu et al. 2019). Some patients with *PDSS2* (Iványi et al. 2018; Rötig et al. 2000), *COQ2* (Desbats et al. 2015a, b; Dinwiddie et al. 2013; Scalais et al. 2013), *COQ7* (Freyer et al. 2015; Kwong et al. 2019), *COQ9* (Duncan et al. 2009) and *COQ8B* mutations (Atmaca et al. 2017; Vazquez-Fonseca et al. 2017; Zhang et al. 2017) also presented hypertrophic cardiomyopathy. Less frequently found cardiac manifestations include **valvulopathies** (Mollet et al. 2007), **heart hypoplasia** (Brea-Calvo et al. 2015), **septal defects** (Korkmaz et al. 2016; Li et al. 2018; Nair et al. 2018; Park et al. 2017a, b; Salviati et al. 2012), **heart failure** (Brea-Calvo et al. 2015; Chung et al. 2015; Korkmaz et al. 2016; Kwong et al. 2019), **bradycardia** (Brea-Calvo et al. 2015; Chung et al. 2015; Danhauser et al. 2016; Eroglu et al. 2018; Ling et al. 2019; Smith et al. 2018; Sondheimer et al. 2017) or **pericardial effusion** (Atmaca et al. 2017; Vazquez-Fonseca et al. 2017; Yu et al. 2019). It should be taken into account that some of these symptoms could be secondary consequences of a more general defect.

Other symptoms, more heterogeneous, have also been reported in some patients affected by mutations in all the different *COQ* genes. Among them, **respiratory distress** and **apnea** seem to be characteristic of *COQ4* patients (Brea-Calvo et al. 2015; Chung et al. 2015). **Oedema** is always present in cases with nephrotic syndrome, so it is more frequent in pathogenic variants of genes with renal involvement, such as *COQ8B*, *COQ2* and *COQ6*. For more details on this type of affections, refer to Table 6.1 and bibliography (Alcázar-Fabra et al. 2018).

It is essential to note that this non-detailed list of symptoms associated with variants of different *COQ* genes has a limited validity due to the small number of

patients described for each of them (Table 6.1). It should also be considered that the number of patients with pathological variations in the different genes varies widely, so the higher frequency found for some symptoms in some cases can be due to the sampling effect.

6.2.2 Biochemical Findings

Biochemically, primary CoQ deficiency patients, in particular those with neonatal-onset, can show higher levels of lactate in plasma or serum (Table 6.3), although normal lactate levels do not exclude the possibility of a CoQ deficiency (Rahman et al. 2012). Skeletal muscle biopsies typically show decreased CoQ steady-state levels and reduced combined enzymatic activity of complexes I + III and/or II + III. Still, these tests are unable to differentiate between primary and secondary CoQ deficiencies (Salviati et al. 2017). *In vivo* assessment of CoQ biosynthetic rate is possible, by measuring the incorporation of a labelled CoQ precursor in skin fibroblast cultures. This technique allows to biochemically discriminate between primary and secondary deficiencies (Rodríguez-Aguilera et al. 2017). The biochemical determination of CoQ levels is a useful and quick strategy for the identification of primary CoQ deficiencies. However, only a genetic test (using next-generation sequencing (NGS) approaches, either genetic panels or whole-exome and–genome sequencing) will definitively determine the molecular diagnosis of these pathologies. It should bear in mind, that for each new potentially pathogenic variants of the *COQ* genes that are identified by NGS, a molecular validation is necessary.

In general, primary CoQ deficiencies respond quite positively to CoQ supplementation, but it is not always the case (Table 6.3). Still, an early definitive diagnosis is compulsory, in order to start the treatment as soon as possible to limit the damage that the condition could cause to tissues (Montero et al. 2008; Yubero et al. 2015). However, due to its hydrophobicity and possibly low bioavailability, new approaches are being developed to increase CoQ levels. Bypass treatments have been tested in cellular models of *COQ6* and *COQ7* patients. Vanillic acid and 2,4-HB, that are analogues of the head precursors have been shown to induce recovery of endogenous CoQ synthesis in *COQ6* and *COQ7*-defective cells respectively (Acosta-López et al. 2019; Freyer et al. 2015; Wang et al. 2017).

6.2.3 Pathogenesis

The pathogenesis of primary CoQ deficiency is far from being simple, and our understanding is still scarce. It is highly probable that the reduced activity of the OXPHOS system and an increase of ROS would be crucial factors involved in the pathogenesis, but the role of CoQ in other mitochondrial processes, and even in other membranes, might also contribute to explain the origin of some affections in

primary deficiencies, at least partially. For example, de novo pyrimidine synthesis is impaired in CoQ deficiency, further contributing to the development of the disease (López-Martín et al. 2007). Moreover, sulphide oxidation pathway has been described to be tissue-specifically defective in primary CoQ deficiency, leading to an accumulation of H_2S, and thus, an alteration of protein S-sulphydrilation promoting changes in vasorelaxation, inflammation and ROS production. These changes have been proposed as another cause of pathogenesis in primary CoQ deficiencies (Quinzii et al. 2017). Besides, the disparity on the age of onset, the different tissues affected and the specificity of some of the symptoms associated to certain genes suggest that *COQ* genes may be involved in other processes and the molecular mechanism of the disease would also be dependent on these yet unknown functions. In any case, it should bear in mind that a complete picture is lacking since there are too few patients harboring mutations in each *COQ* gene.

6.3 Secondary CoQ Deficiency

Reduced levels of CoQ can also be found in patients due to conditions not directly related with CoQ biosynthesis malfunctioning, but with oxidative phosphorylation failure, other non-OXPHOS mitochondrial defects or even impairment of other non-mitochondrial processes (Yubero et al. 2016). The classification of patients with either primary or secondary CoQ deficiency strictly depends on their genetic analysis (Salviati et al. 2017).

Secondary CoQ defects are more common than the primary ones (Desbats et al. 2015a, b; Yubero et al. 2016). This fact could be explained by the variety of processes where CoQ is involved and, possibly, the existence of mechanisms for modulating CoQ levels in response to a failure in these processes.

Isolated myopathies presented as muscular weakness, hypotonia, exercise intolerance or myoglobinuria are commonly reported as muscular manifestations in diseases associated with secondary CoQ deficiencies, but also neurological decline and ataxia are also often reported (Sacconi et al. 2010; Salviati et al. 2017).

Analysis of CoQ levels in cohorts of patients affected by diverse OXPHOS pathologies shows that among the different mitochondrial defects, the most common conditions associated with secondary CoQ deficiency are depletion syndromes (Montero et al. 2013; Yubero et al. 2016). However, more studies on broader cohorts of patients affected by different conditions are needed to better understand if certain diseases are more likely to develop secondary deficiencies than others, as well as the underlying molecular mechanism involved. It has been hypothesized that severe mitochondrial deficiencies would cause secondary CoQ deficiency by inhibiting the maturation of COQ proteins in the mitochondria, although further research still needs to be done (Yen et al. 2020). Very interestingly, comparative omic studies performed in mouse models of OXPHOS dysfunction caused by nuclear-encoded essential factors for mtDNA maintenance showed association with secondary CoQ deficiency (Kühl et al. 2017). Other mitochondrial conditions are associated, at a

different degree, with a reduction in CoQ levels. For example, mutations in *MT-TL1*, causing MELAS syndrome, and *MT-TK*, causing MERFF syndrome, were also associated to a secondary CoQ deficiency in skeletal muscle (Cotán et al. 2011; Sacconi et al. 2010). Other examples are: mutations in the mitochondrial chaperone *BSC1L* leading to complex III deficiency, associated with isolated mitochondrial encephalopathy (Fernandez-Vizarra et al. 2007); complex I deficiency caused by mutations in *NDUFS4*, associated to multifocal dystonia and Leigh syndrome (Bris et al. 2017; Ortigoza-Escobar et al. 2016); or combined OXPHOS defects caused by mutations in *EARS2*, which encodes for the mitochondrial aminoacyl-tRNA synthetase specific for glutamate, causing either leukoencephalopathy or multisystem fatal infantile disease (Talim et al. 2013; Taskin et al. 2016).

The study of mouse models is instrumental in predicting secondary CoQ deficiencies (Kühl et al. 2017), which can be exploited for human molecular diagnosis. One example is *Parl*$^{-/-}$ mouse model: *PARL* (coding for Presenilin Associated Rhomboid Like protein) is the only mitochondrial member known from the rhomboid family (Spinazzi and De Strooper 2016), a conserved group of intramembrane proteases. *Parl*$^{-/-}$ mouse model shows a phenotype similar to Leigh syndrome, with a severe complex III defect caused by the disappearance of mature Ttc19, a factor required for complex III stability (Bottani et al. 2017). Moreover, *Parl*$^{-/-}$ brain mitochondria show a significant decrease of CoQ biosynthesis associated with a reduction of Coq4 and other Coq peptides, independent to TTC19 defect. This suggests that the protease could be involved in CoQ biosynthesis complex regulation, compensating for complex III defect (Spinazzi et al. 2019). This adaptive mechanism, which should aim a balanced respiratory chain, would try to increase the survival of cells and tissues in CoQ deficiency conditions (Fernández-Ayala et al. 2013). The same rationale of a compensatory mechanism could be applied to the two cases with pyruvate dehydrogenase complex mutations showing CoQ overproduction (Asencio et al. 2016).

CoQ secondary deficiency has also been associated with non-OXPHOS gene defects, but the mechanisms involved are still elusive (Yubero et al. 2016). A pediatric patient with a defective GLUT1 transporter caused by a heterozygous variant in the *SLC2A1* gene showed significantly reduced CoQ levels (Yubero et al. 2014). However, this is not a common feature in GLUT1 deficiency syndrome (Barca et al. 2016b), indicating that possibly other factors would be involved in the CoQ defect in this patient.

CoQ is reduced by *ETFDH*-encoded flavoprotein-ubiquinone oxidoreductase as a critical step of mitochondrial fatty acid β-oxidation (Bentinger et al. 2010) (Fig. 6.1b). Mutations in this enzyme, and in the electron transfer flavoprotein, cause multiple acyl-CoA dehydrogenation deficiency (MADD)–also known as glutaric acidemia II or glutaric aciduria II- which is associated with decreased levels of CoQ (Buján et al. 2014; Gempel et al. 2007). It has been proposed that CoQ is distributed in specific pools within the mitochondrial inner membrane, which are dedicated to either NADH or $FADH_2$-mediated CoQ reduction in the respiratory chain (Lapuente-Brun et al. 2013). Specific modulation of CoQ levels in response to the decrease of the enzyme that reduces it would explain the secondary deficiency

associated with this condition. This could explain some of the secondary deficiencies associated with *ETFDH* mutations. However, it should be noted that not all MADD patients have CoQ deficiency (Liang et al. 2009; Wen et al. 2013).

Cerebellar ataxia has been found in some cases of primary CoQ deficiency, which can be explained by the high-energy requirement of the cerebellum (Salviati et al. 2017)–see previous section-. Mutations in other genes that cause cerebellar ataxia can also induce secondary CoQ deficiency. Mutations in *APTX* gene, for example, which encodes for the single-stranded DNA repair aprataxin, cause ataxia with ocular motor apraxia (Date et al. 2001; Moreira et al. 2001) and induce CoQ deficiency in muscle and fibroblasts of these patients (Quinzii et al. 2005; Yubero et al. 2016).

ANO10 gene encodes for a member of the anoctamin family of transmembrane proteins with calcium-activated chloride channel activities, whose mutations cause spinocerebellar ataxia associated to CoQ deficiency in skeletal muscle, plasma and cerebrospinal fluid (Balreira et al. 2014; Chamard et al. 2016; Nanetti et al. 2019).

Also, it has been shown that patients with Friedrich ataxia can show a decrease of CoQ content in skeletal muscle as a consequence of the mutation in *FXN* gene, which encodes for frataxin, a protein regulating iron transport into mitochondria (Yubero et al. 2016).

A secondary reduction of CoQ levels also seems to be associated with ageing (Hernández-Camacho et al. 2018). Some drugs, such as statins for hypercholesterolemia treatment, are reported to induce myopathy with secondary CoQ deficiency, since both cholesterol and CoQ share a part of their biosynthetic pathways (Marcoff and Thompson 2007; Uličná et al. 2012).

The mechanisms explaining CoQ secondary defects are still elusive. Several hypotheses, which depend on the specific primary mitochondrial or non-mitochondrial defect, have been proposed: (i) oxidative stress induced by non-functional respiratory chain could induce an increase in CoQ degradation rate; (ii) interference of the signaling pathways involved in CoQ biosynthesis could cause a decrease in CoQ biogenesis; (iii) a destabilization of the CoQ biosynthetic complex could be induced in response to the primary change or (vi) a general deterioration of mitochondrial function could be responsible for the reduced CoQ levels (Desbats et al. 2015a, b; Yubero et al. 2016).

Of course, the original pathology will influence the particular symptoms associated with secondary CoQ deficiencies and, probably, the lack of CoQ could even potentiate them (Desbats et al. 2015a, b). In fact, many of these patients partially improve their condition by CoQ supplementation, which supports the importance of an early diagnosis also in these cases (Quinzii and Hirano 2011).

6.4 Concluding Remarks

Next-generation sequencing approaches have allowed in the last years the genetic diagnoses of an increasing number of patients showing decreased levels of CoQ in tissues due to defects in CoQ biosynthesis pathway. Primary CoQ deficiencies are those caused by mutations in the *COQ* genes. Instead, secondary defects are caused by mutations in genes not directly involved in CoQ synthesis. Biochemically, both primary and secondary deficiencies present with decreased levels of CoQ in tissues. The only reliable way to distinguish primary from secondary CoQ deficiency is genetic analysis (Salviati et al. 2017).

The difficulties in the diagnosis and the proper addressing to the appropriated health service relay in the wide heterogeneity of clinical manifestations and the low number of patients identified. Here we present an overview of the different manifestations associated with the various mutations in the *COQ* genes in primary deficiencies and their frequency to serve as a diagnostic guide for clinicians who face the challenge of diagnosing rare mitochondrial diseases. A more significant coordinated effort at the level of the translational research is necessary to expand the cohorts of patients affected by mutations in the different *COQ* genes in order to better define the clinical spectrum associated with each genetic defect.

The variety of mitochondrial disorders showing a secondary deficiency and the comprehensive studies in mice models associated with secondary CoQ defects, clearly show the complexity of the pathogenic process of these mitochondrial conditions and the wide range of tissues, organs, and cellular functions affected. Specific efforts need to be done to better understand the–probably very diverse- pathomechanisms underlying CoQ reduction in other diseases.

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