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Primary Coenzyme Q deficiencies: A literature review and online platform of clinical features to uncover genotype-phenotype correlations

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ABSTRACT

Primary Coenzyme Q (CoQ) deficiencies are clinically heterogeneous conditions and lack clear genotype-phenotype correlations, complicating diagnosis and prognostic assessment. Here we present a compilation of all the symptoms and patients with primary CoQ deficiency described in the literature so far and analyse the most common clinical manifestations associated with pathogenic variants identified in the different *COQ* genes. In addition, we identified new associations between the age of onset of symptoms and different pathogenic variants, which could help to a better diagnosis and guided treatment.

To make these results useable for clinicians, we created an online platform (https://coenzymeQbiology.github.io/clinic-CoQ-deficiency) about clinical manifestations of primary CoQ deficiency that will be periodically updated to incorporate new information published in the literature. Since CoQ primary deficiency is a rare disease, the available data are still limited, but as new patients are added over time, this tool could become a key resource for a more efficient diagnosis of this pathology.

1. Introduction

Primary Coenzyme Q (CoQ) deficiencies are a group of rare autosomal recessive and clinically heterogeneous mitochondrial conditions caused by defects in one of the proteins involved in the biosynthesis of this lipidic molecule [1]. Although only approximately 280 patients have been diagnosed to date, it is predicted that about 125,000 individuals would be affected by this condition worldwide (1 in 50,000). The disease occurrence is probably underestimated, mainly in countries where next-generation sequencing is not implemented [2].

1.1. The CoQ molecule

CoQ is a lipidic molecule conserved from proteobacteria to humans and virtually present in all cell membranes and serum lipoproteins [3–6]. Structurally, CoQ is composed of a redox-active fully substituted benzoquinone ring and a highly hydrophobic polyisoprenoid tail that anchors the molecule to the lipid bilayer [3,7]. The number of isoprene units is species-specific and probably responds to the particular lipidic environment that characterises the membranes of the different species. CoQ from *Saccharomyces cerevisiae* contains six units, and so it is called CoQ_6. *Escherichia coli*, instead, has eight isoprene units and so it has CoQ_8. Humans and *Saccharomyces pombe* have ten isoprene units, and thus they have CoQ_{10}. Mice have mostly CoQ_9 but also some CoQ_{10}, with nine and ten isoprene units, respectively [8,9]. The CoQ head group is subjected to continuous oxidation/reduction cycles, being able to accept or donate two electrons and two protons. When it is completely reduced, it is called ubiquinol ($CoQH_2$). When it is fully oxidised, instead, it is called ubiquinone (CoQ). A partially reduced semiquinone radical is formed when electron transfer occurs in two steps of one electron each ($CoQH^{\bullet -}$, semiubiquinone) [3,10].

1.2. CoQ biological functions

Functionally, CoQ is an essential link in the mitochondrial electron transport chain (mETC), shuttling electrons from complexes I and II to complex III and therefore, contributing to the generation of the mitochondrial electrochemical gradient that permits the production of ATP

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by the ATP synthase [11–14] (Fig. 1A). Importantly, a number of other mitochondrial dehydrogenases also donate electrons to CoQ, feeding the electron transport chain as well. CoQ is essential for the *de novo* pyrimidine biosynthesis, receiving electrons from the dihydroorotate dehydrogenase (DHODH) [15,16]. Also, CoQ participates in the beta-oxidation of fatty acids and oxidation of branched-chain amino acids, as it is an electron acceptor from the electron transport flavoprotein dehydrogenase (ETFDH) in the mitochondria [17]. It can also be considered an essential part of the system linking carbohydrate and lipidic metabolism by receiving electrons from the mitochondrial glycerol-3-phosphate dehydrogenase (G3PDH) [18,19]. Besides, CoQ is involved in the metabolism of some amino acids as the electron acceptor of proline dehydrogenase 1 (PROD1) [20], and probably proline dehydrogenase 2 (PROD2) [21]. Notably, by receiving electrons from the sulfide:quinone oxidoreductase (SQOR) it participates in the detoxification of sulfides which are signalling molecules critical for some cellular processes, but toxic when in excess [22–27]. Reduced CoQ ($CoQH_2$) generated by all these processes transfers its electrons to complex III in the mETC. Importantly, owing to its redox properties, CoQ is the only lipidic antioxidant endogenously synthesised by cells [28]. It has been shown to directly prevent both the initiation and propagation of lipoperoxidation in membranes [28]. Moreover, being an essential component of the plasma membrane antioxidant system, CoQ is able to regenerate other antioxidants such as alpha-tocopherol and ascorbate [4,29]. As part of the extracellular antioxidants regeneration process, CoQ becomes oxidised. Subsequent $CoQH_2$ regeneration is performed in

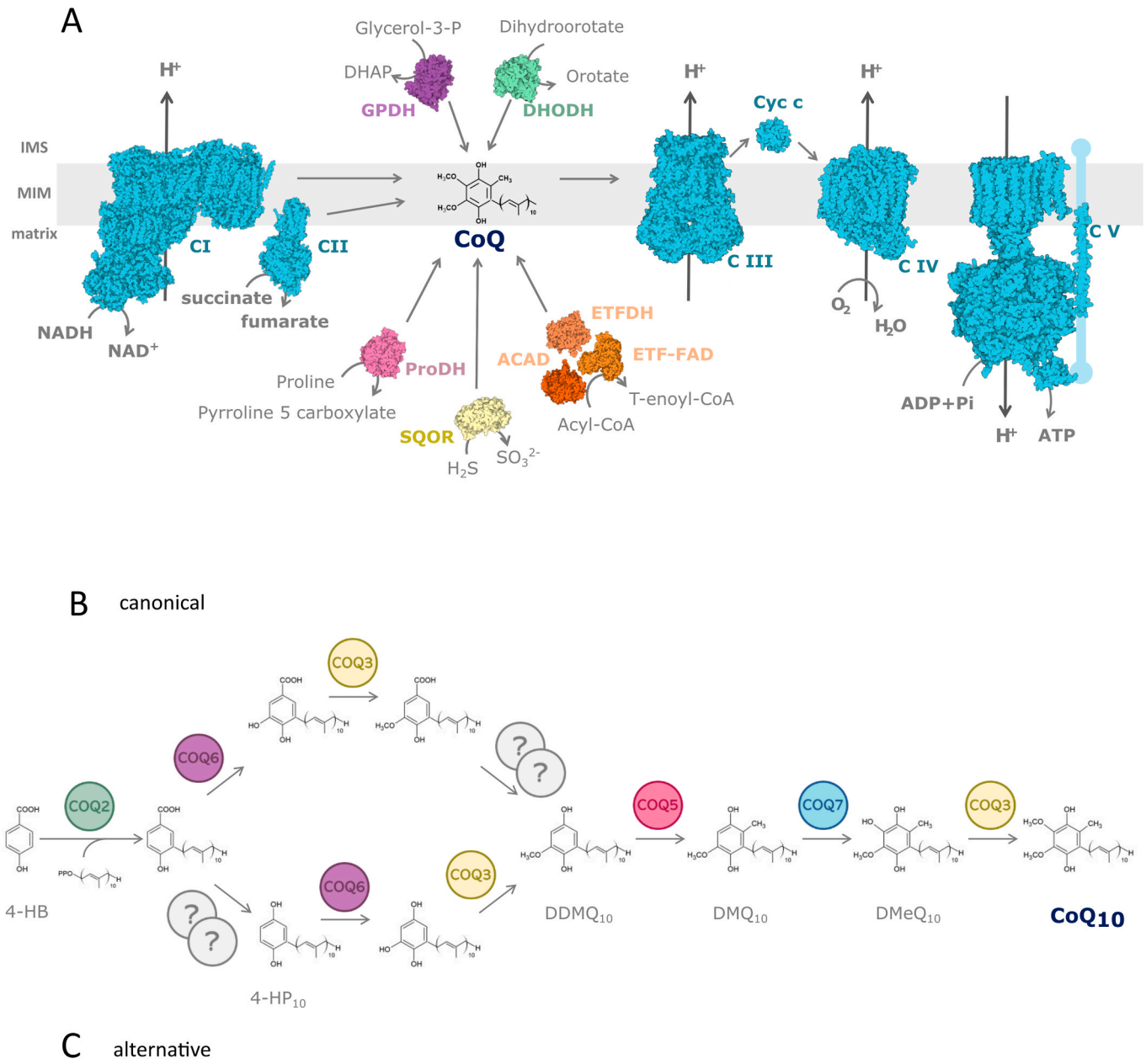

Fig. 1. (A) OXPHOS system showing complexes I and II, and other dehydrogenases that reduce CoQ in the inner mitochondrial membrane. Depicted using Illustrate [246]. CI: NADH:CoQ oxidoreductase; CII: succinate dehydrogenase; CIII: CoQ:cytochrome *c* oxidoreductase; CIV: Cytochrome *c* oxidase; CV: ATP 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.; (B) classical CoQ biosynthesis pathway; (C) Alternative CoQ biosynthesis pathway, as suggested by Acosta et al. [51].

the plasma membrane by either a one-electron reaction mechanism that involves the cytochrome *b*5 reductase or a two-electron reaction that involves NAD(P)H-quinone oxidoreductase 1 (NQO1) [30,31]. Both the selenoprotein thioredoxin reductase (TrxR1) and thioredoxin have also been reported to extramitochondrially regenerate the reduced form of CoQ in a selenocysteine-dependent manner, which has been proposed to explain the relationship between CoQ and selenium levels [32–34]. Recently, CoQ has also been shown to be reduced by FSP1 in the plasma membrane avoiding the propagation of iron-triggered lipid peroxidation and contributing to the protection against ferroptosis, a form of regulated cell death [35,36].

Moreover, CoQ has been shown to participate in other processes such as the regulation of uncoupling proteins (UCPs) [37] and the modulation of the mitochondrial permeability transition pore (mPTP) [38–43]. The biological meaning of CoQ involvement in mPTP modulation remained rather obscure for a long time, but recently it has been demonstrated to be essential for cardiomyocyte maturation. High levels of CoQ are associated with reduced proton leak and mPTP opening in the developing heart of a model of an excess of CoQ [44]. However, a mechanistic explanation is still lacking. Tumour growth dependence on CoQ oxidation has also been recently demonstrated, with potential implications for anticancer development targeting mitochondrial metabolism. CoQ oxidation would be necessary for the regeneration of mitochondrial NAD^+ and FAD, which enables oxidative TCA cycle flux [45].

Although CoQ can be incorporated from the diet, probably due to its reduced bioavailability and distribution to tissues [46], human cells strongly depend on its endogenous synthesis by a set of nuclear-encoded proteins called COQ proteins [3,47]. CoQ biosynthesis probably starts in the cytosol and the endoplasmic reticulum. Still, the central part of the process takes part in the mitochondria by means of a possibly dynamic biosynthetic complex, the CoQ synthome [48,49]. It is then distributed to other membranes in an endomembrane system-dependent way by mechanisms which have not yet been wholly characterised [6].

1.3. CoQ biosynthesis and regulation

CoQ biosynthetic genes (*COQ* genes) were first discovered as a complementation group in *Saccharomyces cerevisiae* [50]. Since then, most of the work has been performed in this model, not only because of its short life cycle and easy genetic manipulation, but also due to the capacity of yeast to grow in both fermentable and non-fermentable carbon sources. Only the growth in non-fermentable carbon sources depends on CoQ. Yeast null mutants for almost all the *coq* genes recover their ability to grow in non-fermentable media when the corresponding human orthologues are expressed [48]. This is one of the reasons why, for a long time, the CoQ biosynthesis pathway was considered to be highly conserved between yeasts and humans. However, recent work has revealed some differences that remain to be clarified [51–54].

In humans, the precursor of the benzoquinone ring is 4-Hydrozybenzoate (4-HB), which derives from tyrosine and possibly phenylalanine, by a yet not completely known pathway [3,55,56]. Recently, the dietary flavonol kaempferol has also been proved to be a precursor of the quinone head, especially in the kidney [57,58]. In yeasts, *para*-aminobenzoic acid (pABA) can be a precursor of CoQ as well [53,59]. In mammalian cell cultures, pABA acts instead as a competitive inhibitor of CoQ synthesis, but in mice, it does not show any effect [54]. Further work is needed to completely decipher whether pABA could act as a precursor in humans. The isoprenoid units required to build the polyisoprenoid chain come from the mevalonate pathway, which is shared with the synthesis of dolichol, heme A, cholesterol and components for protein prenylation [60–62]. By a process still to be defined, tail subunits are shepherded to the mitochondria and assembled by a heterotetramer composed of PDSS1 and PDSS2 (in yeast homodimeric Coq1p) [63,64]. Next, head and tail are condensed through C3 by COQ2 (Coq2p in yeasts) in the inner mitochondrial membrane [65,66]. Subsequent ring modifications are performed by other COQ proteins. First, the hydroxylase COQ6 (Coq6p in yeasts) introduces a hydroxyl group in C5 [67,68], a necessary step for COQ3 (Coq3p in yeasts), which is an O-methylase, to further modify this carbon [69,70]. Next, a C1 decarboxylation is followed by a C1 hydroxylation by one or more enzymes that have not yet been identified. COQ5 (Coq5p in yeasts) then performs a methylation in C2 [71,72] and COQ7 (Coq7p in yeasts) catalyses a C6-hydroxylation [73,74]. Finally, a C6 O-methylation is carried out by COQ3 to obtain the final and completely functional CoQ molecule (Fig. 1B). COQ9 (Coq9p in yeasts) would participate in CoQ biosynthesis by accessing, selecting, and presenting membrane intermediaries to the peripheral membrane COQ7 protein for its appropriated modification [75–78]. Interestingly, an alternative pathway has been proposed for mammals in which the decarboxylation and hydroxylation of C1 would occur independently or before the action of COQ6, since the loss-of-function of this enzyme produces an accumulation of the 3-decaprenyl-1,4-benzoquinone intermediary [51] (Fig. 1C). In yeasts, Coq6p also performs a C4-deamination when pABA is used as a precursor [52]. Yeast mitochondrial ferredoxin Yah1 (human ortholog FDX1) and ferredoxin reductase Arh1 (human ortholog FDX2) have been shown to transfer electrons to Coq6p but whether this also occurs in humans is still unknown [59].

After PDSS1/PDSS2 and COQ2, the head-modifying COQ proteins together with COQ9 have been proposed to sequentially work in association in the so-called CoQ biosynthetic complex or CoQ synthome. This configuration would ensure CoQ biosynthesis processivity by preventing the leakage of potentially not-fully substituted reactive intermediates [3,48]. In fact, it has been recently shown that head-modifying CoQ pathway components, but not Coq1p and Coq2p, selectively colocalise to multiple resolvable domains adjacent to ER-mitochondria contact sites in yeasts [49,79,80]. Whether this organisation is also functionally relevant in mammals remains to be elucidated.

COQ4 has been demonstrated to be essential for CoQ biosynthesis both in yeasts and humans [81–84]. However, no enzymatic activity has been assigned to this protein yet. Neither the yeast nor the human protein has yet been crystallised, and structural predictions models do not give clear clues about a putative catalytic activity for COQ4. It has been suggested instead, that COQ4 would act as a nucleator factor or a scaffolding element for the CoQ synthome, behaving as an essential structural component of this complex [81].

Other COQ proteins are proposed to participate as regulators in CoQ biosynthesis, although whether they are directly and stably associated with the complex is yet unclear. Coq8p was first proposed to phosphorylate and stabilise the CoQ complex and activity in yeast [85–87], since phosphorylation of Coq3p, Coq5p and Coq7p was altered in a *coq8* null mutant yeast. However, the crystallisation of one of its human orthologs, COQ8A (ADCK3), revealed a protein kinase-like fold with unique UbiB-specific features demonstrated to inhibit protein kinase activity [88]. Moreover, further investigations have demonstrated that COQ8A lacks canonical protein kinase activity in *trans* [89] and has instead an ATPase activity that is activated by cardiolipin and other lipids, like small phenolic molecules resembling CoQ pathway intermediates in the mitochondrial membranes [90]. It has thus been hypothesised that it would couple the hydrolysis of ATP to the extraction of the quinone heads of CoQ intermediates out of the membrane and allow their chemical modification [49,90]. The human lipid-binding proteins COQ10A and B, homologs to the yeast Coq10p START protein, would act as chaperone-like proteins, helping CoQ to localise into the appropriated places within the mitochondrial inner membrane [91,92]. Yeast Coq11p protein would be necessary for Coq10p activity, but no clear ortholog in humans has yet been reported [93,94].

Other proteins belonging to the ADCK family have been suggested to participate in CoQ biosynthesis, but diverse functions have recently arisen for some of them. For instance, ADCK1 has been proposed to be involved in the structural maintenance of mitochondrial membranes in the muscle through a signalling pathway composed of ADCK1, YME1L1,

OPA1 and IMMT [95]. Also, ADCK2 has been suggested to participate not only in CoQ biosynthesis but also in the fatty acid metabolism in skeletal muscle [96]. Very recently, ADCK2 has been proposed to participate in the distribution of CoQ from mitochondria to other membranes [97].

So far, only fragmented pieces of information are available regarding *COQ* genes expression, coordination and CoQ biosynthesis regulation. Specifically, very little is still known about how CoQ biosynthesis is coordinated and balanced with the mETC components and the rest of the systems where the molecule exerts a central role [10]. At the transcriptional level, it has been shown that NF-kB binds *COQ7* promoter and regulates CoQ biosynthesis under stress conditions [98], and Sp1 is responsible for the constitutive expression of *PDSS2* [99]. At the post-transcriptional level, the polyribosomal associated transcriptional repressor FMRP, whose loss-of-function causes Fragile X syndrome, has been shown to bind the mRNA from most of the mouse brain *Coq* genes. However, it is unknown how this factor actually influences CoQ biosynthesis [100]. Also, the mRNA protein binding HuR has been shown to specifically associate and regulate *COQ7* expression [101]. In yeast, Puf3p binds and controls Coq5 mRNA translation, strongly influencing CoQ biosynthesis [102]. However, the conservation of this mechanism in humans is currently unknown.

On the other hand, phosphorylation/dephosphorylation cycles or protease processing of COQ proteins have been proposed to regulate the pathway as well. Mammalian COQ7 has been shown to be modulated by PPTC7, a mitochondrial phosphatase involved in mitochondrial biogenesis [103–105]. Oct1p mitoprotease has been shown to control Coq5p stability in yeast [106], but whether protease modification of COQ proteins in mammals regulates CoQ biosynthesis is currently unknown. Several pieces of information support the idea that the CoQ biosynthetic complex would assemble dynamically, responding to energy demands or antioxidant needs. The mechanism of controlling such an assembly remains currently unknown.

2. Primary CoQ deficiencies

Primary CoQ deficiencies are autosomal recessive conditions caused by biallelic mutations in any of the *COQ* genes that are characterised by clinical heterogeneity with a wide spectrum of clinical manifestations [1]. Secondary deficiencies are caused by defects in mitochondrial or non-mitochondrial processes, associated with a reduction of CoQ levels in tissues, possibly by adaptive mechanisms [107].

Symptoms associated with primary deficiencies have been traditionally classified in 5 groups: encephalomyopathy, cerebellar ataxia, severe infantile multisystemic disease, nephropathy, and isolated myopathy [108], but were based on a small number of patients. However, this classification is currently probably outdated since a growing number of cases are continuously reported with a broader and overlapping clinical spectrum of manifestations, even in patients harbouring pathogenic variants in individual genes [1,109,110]. Moreover, so far isolated myopathy has been described only in individuals with secondary CoQ deficiencies [109,111].

Primary CoQ deficiency is a rare condition affecting less than 1 in 2000 people, according to the European definition. Up to date, around 280 patients from 180 families have been reported in the literature [1], but CoQ primary deficiencies are largely underdiagnosed. Taking into account the reported pathogenic variants and the allelic frequency of predicted loss-of-function and missense changes in the population databases, it has been estimated that a worldwide total of 123,789 individuals suffer from primary CoQ deficiency [2]. The limited general knowledge of the disease, the broad range of associated symptoms, involving multiple systems with different presentations (acute, subacute, etc.) and with variable age of onset and different clinical courses, probably explain why these conditions are overlooked.

Traditionally, the diagnosis of CoQ relied on biochemical assays and later also on genetic linkage or homozygous mapping analysis in consanguineous families [109,112,113]. Today, as for other genetic conditions, Next Generation Sequencing (NGS) has become a key achievement for the screening and diagnosis of genetic diseases, including primary CoQ deficiencies. During the last ten years, an increasing number of genetically diagnosed patients have been identified. To date, defects in *PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ5*, *COQ6*, *COQ7*, *COQ8A*, *COQ8B* and *COQ9* have been found to cause human CoQ deficiency and disease. The set of reported symptoms are numerous and varies widely among individual genes, affecting diverse organs and systems, including the central (CNS) and peripheral (PNS) nervous systems, skeletal muscle, heart, and the sensory system [1], with onset ranging from birth to adulthood [114].

The clinical scenario for CoQ deficiencies caused by defects in the different *COQ* genes is rather complex. Patients harbouring different pathogenic variants in a particular gene can manifest a highly heterogeneous combination of symptoms with different age of onset. Moreover, specific pathogenic variants of some *COQ* genes cause multisystemic defects (e.g. *COQ2* and *COQ4*) while variations of others clearly display a more specific phenotype (e.g. *COQ8A* and *COQ8B*) [1,114]. Not surprisingly, a recent analysis of *COQ8A*-related CoQ deficiency showed that there is more intra-familial phenotype correlation than inter-familial correlation [115]. A correlation between the residual activity of the mutant protein and the severity of the disease observed in patients has been demonstrated for some genes, as *COQ2* [116], but not for others, as *COQ8A* [117,118].

One of the difficulties in explaining the high heterogeneity of clinical manifestations is the limited number of available patients that impedes getting a general picture of the disease. This is affected by ascertainment biases in most studies, since many of the cases were identified in cohorts of patients manifesting specific symptoms [119–122]. In addition, a series of factors, including a different sensitivity to CoQ defects in distinct tissues or during development could determine the severity or the age-of-onset of the disease. Another factor determining the heterogeneity could be related to different potential physiological impacts of the intermediates that accumulate when specific steps of the biosynthetic pathway are compromised [123,124]. Also, putative additional roles for COQ proteins that could be differentially modulated during development might be responsible for the diversity of clinical presentations of primary CoQ deficiencies.

3. Pathogenesis of primary CoQ deficiencies

The pathogenesis of CoQ deficiencies is poorly understood. The different presentations of the condition depending on the affected gene, the varied age of onset, and the differences in severity make the existence of a common pathogenetic mechanism unlikely for the whole group of patients. It has been proposed that this could be partially the consequence of the diverse roles of CoQ in different cell processes [110]. Notwithstanding, it could be related to putative additional unknown functions for *COQ* genes that could even not pertain to CoQ biosynthesis. A differential role for those genes during development could also be responsible for the differential age of onset and severity of the disease in different cases.

Certainly, the impairment of the OXPHOS system and the increased levels of reactive oxygen species (ROS) make a significant contribution to the development of the disease. In cultured skin fibroblasts harbouring *COQ2* and *PDSS2* mutations, it has been observed that a severe reduction in CoQ levels, which is typically associated with the early onset multisystemic forms of the disease, results in an evident bioenergetic impairment [125]. However, mild CoQ defect would primarily contribute to an increase in ROS production [125,126], which would possibly not only increase oxidative stress but also unbalance cellular signalling pathways with variable consequences on the disease development [127].

It has been demonstrated that reduction in CoQ biosynthesis impacts other processes where CoQ is involved such as de *novo* pyrimidine

biosynthesis [128], or sulfide metabolism [24,26,27] further contributing to the pathology. Mitophagy has been found to be increased in primary deficiency disease models and has been proposed as a protective mechanism for CoQ biosynthesis-defective cells [129], that could have variable consequences for the pathogenesis of the disease. More recently, however, it has been found that mitophagy inhibition significantly ameliorates respiratory chain pathologies, specifically CoQ deficiencies [130]. Although less studied, genetic background, epigenetic regulation, compensation mechanisms, maternal effect and conceivably, environmental factors could influence the outcome of each genetic defect in single individuals. We speculate that the combination of specific defects in *COQ* genes with the diverse factors mentioned above during embryonic development could determine the degree of deterioration of the tissues and the severity of the disease. Further studies are warranted to confirm these hypotheses.

4. Diagnosis of primary CoQ deficiencies

Traditionally, when a CoQ deficiency was suspected, biochemical studies were conducted: if they specifically showed a decrease in CoQ levels or a reduced combined enzymatic activity of complexes I + III or II + III in skeletal muscle biopsies [109,131], a genetic study was performed through genetic linkage or homozygous mapping and sequencing of *COQ* genes. Nowadays, the availability of NGS technologies in many genetic laboratories has allowed to diagnose an increasing number of patients with mitochondrial diseases (including CoQ deficiency) in a fast and non-invasive way. These technologies, which may cover gene panels, the whole exome (WES) or the whole genome (WGS), may pose the problem of variants interpretation, thus requiring subsequent functional validation.

The diagnosis of a primary CoQ deficiency is confirmed when biallelic pathogenic variants in any of the *COQ* genes are found in a patient, and they segregate with the genetic profile of the parents. Identification of a new pathogenic variant needs to be functionally validated to prove the genetic aetiology of the disease. Of course, beyond the biochemical identification of reduced levels of CoQ [110,131], genetic rescue experiments or *de novo* CoQ biosynthesis rate measurements by radioactive precursor incorporation can be performed if skin-derived fibroblasts are available [132–135]. Although muscular biopsies have been traditionally used for the biochemical diagnosis of patients, measurement of CoQ levels in plasma samples, white blood cells (lymphoblastoid cell lines or lymphocytes), urine or skin-derived fibroblasts, which are obtained through less invasive techniques, have been proposed as alternatives. Still, fibroblasts are the most reliable option and also permit functional studies [115,131,134,136], although it has been observed that sometimes fibroblasts do not show reduction while the muscle does [137].

One of the main difficulties that clinicians face in the diagnosis of a primary CoQ deficiency is the highly heterogeneous clinical manifestations and the lack of clear genotype-phenotype correlations. Moreover, an overview of the whole clinical manifestations associated with the different forms of primary CoQ deficiency is missing. Such an examination might help to unveil novel genotype-phenotype correlations and to improve the diagnostic yield for this condition, which is still overlooked.

5. Genotype-phenotype correlations for primary CoQ deficiencies

Although the mere reduction of the levels of CoQ in tissues would be the logical consequence of pathogenetic variations of *COQ* genes, clinical and biochemical findings associated with these mutations are far from being uniform, and genotype-phenotype correlations remain difficult to delineate. Reasons for the clinical variability of patients with CoQ deficiency can be diverse: on the one hand, CoQ deficiencies have, for long, been diagnosed mainly on the bases of biochemical findings and, only recently, direct genetic tests and family linkage. This has hampered the distinction between primary and secondary forms, which relies on molecular analysis. In addition, so far only a few families have been found to harbour pathogenic variants of some *COQ* genes, as is the case of *PDSS1* (2 families, 3 patients), *PDSS2* (5 families, 7 patients), *COQ5* (1 family, 3 patients), *COQ7* (3 families, 3 patients) or *COQ9* (4 families, 7 patients). For this reason, any attempt to establish a definitive genotype-phenotype correlation in these cases could be misleading. Up to now, no *COQ3* patient has been identified.

Due to the low number of patients described, animal or yeast models of primary CoQ deficiencies are especially useful to attempt to establish some genotype-phenotype correlations of the disease.

For example, in the case of *COQ2*, which is associated with the broadest clinical spectrum and age-of-onset among *COQ* patients, it has been proposed that the severity of the disease caused by mutations in this gene correlates with the residual enzymatic activity of the COQ2 protein and, consequently, with CoQ levels, as shown by expressing mutant proteins in yeast: mutant proteins retaining the highest residual activity were found in patients with the mildest phenotype, whereas all patients with the neonatal multisystemic disease harboured mutations with detrimental effects on protein function [116]. In spite of the possible involvement of many other factors and the small number of patients, these data showed that residual activity of COQ2 may influence the phenotype.

The highest number of patients with primary CoQ defect have been reported to harbour pathogenic variants in *COQ8A* and *COQ8B*. Some studies have focused on genotype-phenotype correlations for *COQ8A* patients, but there are still no clear conclusions [117,118,138]. In a recent report, mutations were grouped in two according to the heterogeneity of clinical presentation, severity and age-of-onset. Multisystemic involvement beyond ataxia was found to be more prevalent in missense than biallelic truncating or splicing variants, cases whose phenotype was more frequently found to be isolated ataxia [118]. Also, preliminary associations between missense variants in specific domains and certain phenotypic outcomes have been proposed. For example, missense variants within the COQ8 protein-specific KxGQ domain seem to be associated with cortical (developmental delay and epilepsy) and pyramidal tract dysfunction [118]. Residual activity of mutant versions of *COQ8B* from some patients have been analysed in yeast, but no correlations between CoQ levels and the severity of the symptoms were found [139].

Limited studies on *COQ7* patients' fibroblasts and *COQ7*-deficient MEFs (mouse embryonic fibroblasts) have suggested a correlation between the residual of COQ7 protein and CoQ levels, and the severity of the disease [140,141]. Analysis of two different knock-in mouse models of *COQ9* pathogenic variants [142,143] suggested that the degree of stability of the CoQ complex determines the disease severity in *COQ9* cases, being less severe when the complex is more stable. To date, no clear correlations have been proposed for *COQ6* and *COQ4* patients.

6. CoQ primary deficiency general clinical manifestations

Currently, over 280 patients from approximately 180 families have been reported to have a primary CoQ deficiency with mutations in one of the *COQ* genes. Pathogenic variants of *PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ5*, *COQ6*, *COQ7*, *COQ9*, *COQ8A* and *COQ8B* have been associated with primary CoQ deficiency in the literature.

Clinical phenotypes derived from primary CoQ deficiency can affect different organs, tissues, and systems [1]. A complete picture of the frequency of the clinical manifestations depending on the affected gene may help to diagnose this condition. We have exhaustively compiled all the symptoms reported in all published cases of primary CoQ deficiency. Figs. 2 and 3 show the frequency of reported manifestations grouped by organs and systems. It is important to note that the number of primary CoQ deficiency patients reported is small, and the number of patients harbouring pathogenic variants in individual genes varies widely. This number is significantly reduced for *PDSS1*, *PDSS2*, *COQ5*, *COQ7* and

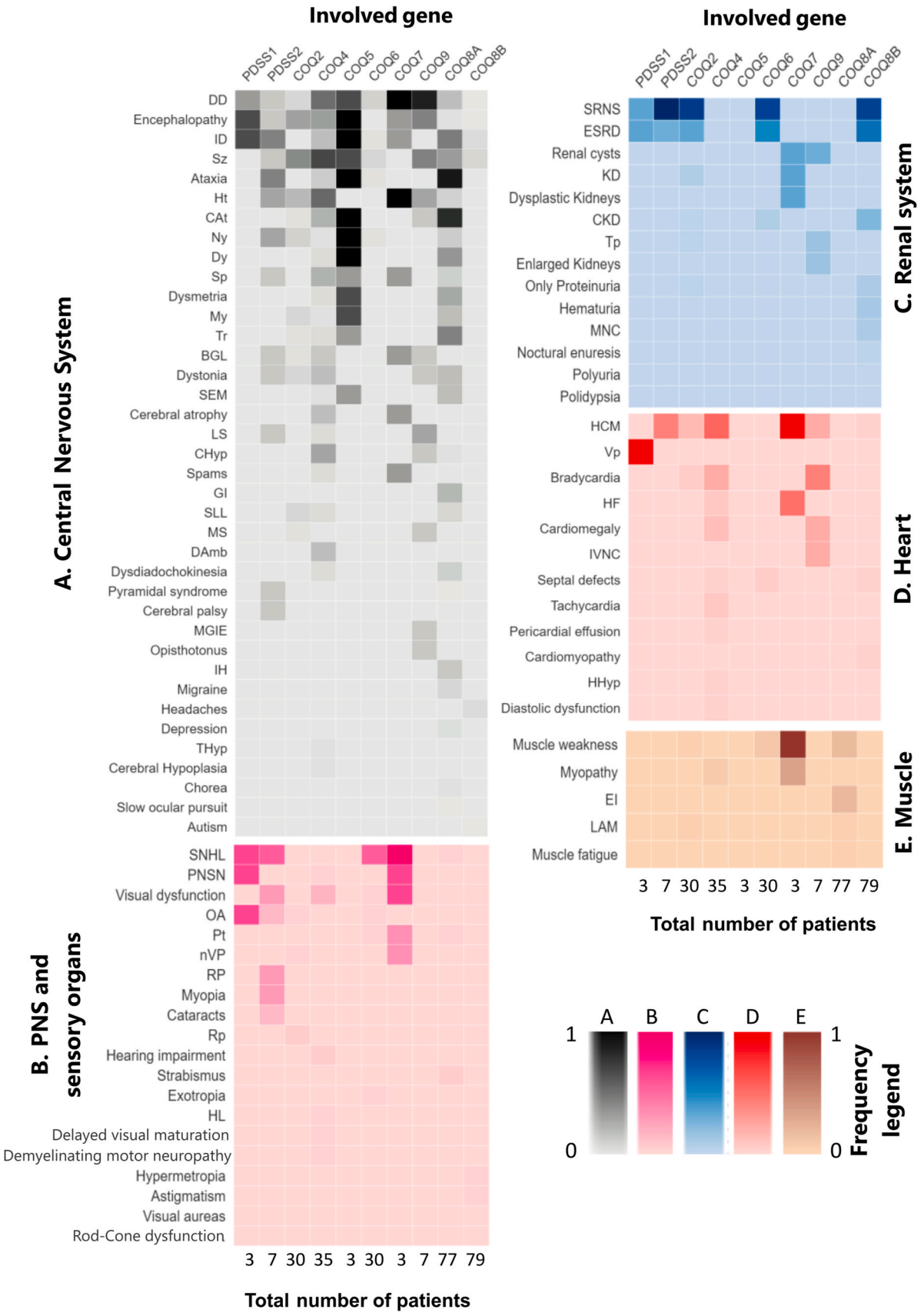

Fig. 2. Frequency of manifestations related to the most commonly affected organs and systems in primary CoQ deficiency, for each *COQ* gene involved. Symptoms related to central nervous system (CNS) (A), peripheral nervous system (PNS) and sensory organs (B), renal system (C), heart (D) and muscle (E) are sorted in a decreasing order of frequencies. Total number of patients for each gene is indicated at the bottom of the heatmaps.

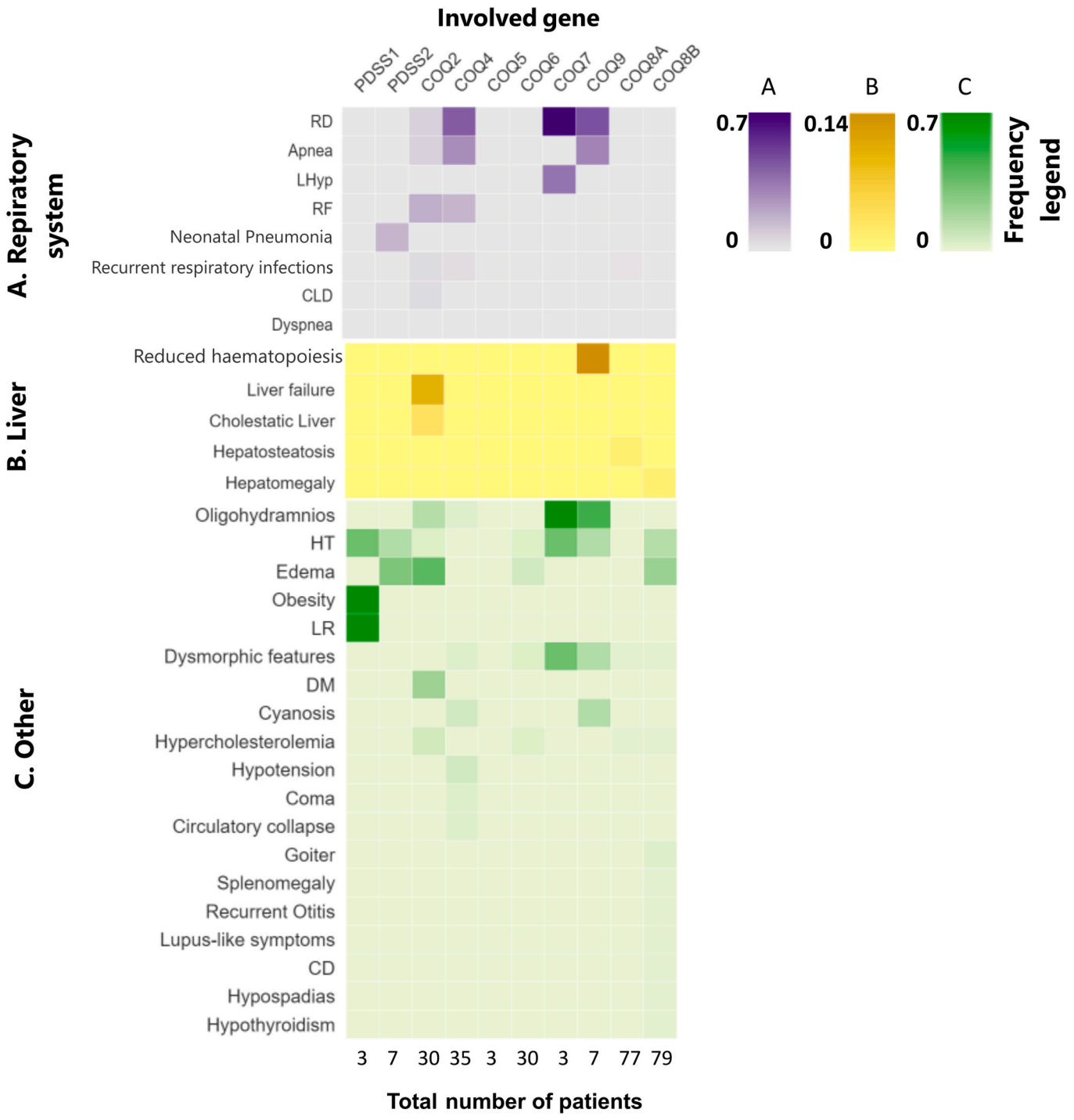

Fig. 3. Frequency of manifestations related to the less commonly affected organs and systems in primary CoQ deficiency, for each *COQ* gene involved. Symptoms related to respiratory system (A), liver (B) and other symptoms (C) are sorted in a decreasing order of frequencies. Total number of patients for each *COQ* gene is indicated at the bottom of the heatmaps.

COQ9 genes, so higher frequencies found for some symptoms in these cases can be due to the sampling effect. The most frequently affected systems are the central and peripheral nervous system, kidney, heart, and skeletal muscle.

To make these analyses of frequency openly available to the community, we have created a web-based platform that will be periodically updated with the new literature: https://coenzymeQbiology.github.io/clinic-CoQ-deficiency. Heatmap representation of the frequency of symptoms will give a visual and convenient overview of the disease according to the affected gene. The continuous update of the platform will permit a *quasi*-real-time overview of the research in the field. With this resource, we aim to contribute not only to a better understanding of the genotype-phenotype correlations of the disease, but also to a more efficient diagnosis of primary CoQ deficiencies.

6.1. CNS manifestations

CNS symptoms have been observed in patients with pathogenic variants in any of the disease-associated *COQ* genes, being less frequent in *COQ6* and *COQ8B* patients (Fig. 2A). The most common features

reported are the following:

6.1.1. Disorders or conditions

The most frequently CNS-related disorder reported are encephalopathy and ARCA2 (autosomal recessive cerebellar ataxia-2, or autosomal recessive ataxia due to Coenzyme Q_{10} deficiency). Other conditions less often reported are cerebral palsy or sporadic multisystem atrophy (MSA).

Encephalopathy is defined as a broad spectrum of brain clinical and neuroradiological manifestations, that are often not further described in case reports. It has been observed in patients with variants identified in each of all the ten genes involved in primary CoQ deficiency, mainly in *COQ4* (11/35, 31%) [83,144–149], *COQ2* (9/30, 30%) [113,150–154], *COQ5* (3/3, 100%) [155] and *COQ9* (3/7, 43%) [156–158] patients. It has also been observed in some *PDSS1* (2/3, 67%) [152], *PDSS2* (1/7, 14%) [159], *COQ6* (1/30, 3%) [160,161], *COQ7* (1/3, 33%) [162], *COQ8A* (2/77, 2.6%) [117,163] and *COQ8B* (1/79, 1.3%) [164] probands. Notably, findings on magnetic resonance imaging (MRI) resembling Leigh syndrome (LS) [165] or MELAS (with stroke-like episodes) are observed in some cases of encephalopathy [154].

Progressive cerebellar atrophy and ataxia, also called ARCA2, is a neurodegenerative disorder defined by an ataxic phenotype with movement disorders, sometimes accompanied by intellectual disability (ID), epileptic seizures (Sz), tremor (Tr), dysarthria (Dy), dysmetria, dysdiadochokinesia, saccadic eye movements (SEM), dystonia or spasticity (Sp) [118,138]. ARCA2 is found in *COQ8A* patients (70/77, 91%). Besides, the only family affected by a mutation in *COQ5* identified so far showed a cerebellar ataxic phenotype similar to *COQ8A* patients (3/3, 100%) [155]. A subgroup of *COQ4* patients with childhood-onset presents this phenotype as well (5/35 14%) [83,166,167]. Cerebellar ataxia has also been observed in some patients harbouring pathologenic variants of *PDSS2* (3/7, 43%) [168,169] and *COQ6* (1/30, 3%) [119] genes.

6.1.2. Cognitive and behavioural deficits

Developmental delay (DD) is defined as a delay in reaching one or more milestones, categorised into motor, cognitive, speech, emotional, social and communication skills [170]. Specific or global developmental delay has been reported in patients with mutations in each of the ten genes involved in primary CoQ deficiency, mainly in *COQ4* (18/35, 51%) [83,144,145,149,171,172], *COQ5* (2/3, 67%) [155], *COQ7* (3/3, 100%) [140,141,162] and *COQ9* (6/7, 86%) [156–158,173] patients. It has also been observed in some probands with mutations in *PDSS1* (1/3, 33%) [174], *COQ8A* (13/77, 17%) [115,163,175,176], *PDSS2* (1/7, 14%) [159], *COQ6* (4/30, 13%), *COQ2* (2/30, 7%) [150,177] and *COQ8B* (1/79, 1.3%) [120].

Intellectual disability (ID) is a generalized neurodevelopmental disorder characterised by significantly impaired intellectual and adaptive functioning [178]. It was reported in a variable number of cases but in patients of almost all the *COQ* genes: *PDSS1* (2/3, 67%) [152], *PDSS2* (3/7, 43%) [121,169], *COQ4* (6/35, 17%) [83,148,166,167], *COQ5* (3/3, 100%) [155], *COQ6* (1/30, 3%) [179], *COQ7* (1/3, 33%) [140], *COQ8A* (35/77, 45%) [115,117,122,138,163,175,180–187] and *COQ8B* (4/79, 5%) [164,188,189].

6.1.3. Epilepsy

Epilepsy and seizures have been reported mainly in *COQ4* (24/35, 69%) [83,144–147,149,167,190], *COQ2* (12/30, 40%) [150,152,153,191–193], *COQ5* (2/3, 67%) [155] and *COQ9* (3/7, 43%) [156,158,194] patients, generally associated with encephalopathy, but also without such association in some *COQ8A* (25/77, 32%) [117,138,176,181,182,184,185], *PDSS2* (1/7, 14%) [165], *COQ6* (2/30, 7%) [119] and *COQ8B* (6/79, 8%) [164,195] patients.

6.1.4. Others

Hypotonia (Ht) is a state of low muscle tone. It can be caused by central or peripheral nervous system, as well as by muscle involvement. This feature has been reported mainly in *COQ4* (19/35, 54%) [83,144,145,147,148], some *COQ2* (6/30, 20%) [150,153,191,192] and in all the three published *COQ7* patients (3/3, 100%) [140,141,162]. Ht has also been observed in several other *COQ* patients. However, the exact frequency might be especially misleading because of the low number of reported cases (*PDSS2* (2/7, 29%) [159,165], *COQ9* (2/7, 29%) [194]). Other groups of *COQ* patients apparently present a lower frequency of Ht, such as *COQ8A* (7/77, 9%) [115,163,184,196] and *COQ6* (3/30, 10%).

Other alterations of the CNS reported with variable frequency in the literature include movement disorders (dysarthria, dystonia, dysmetria, dysdiadochokinesia, myoclonus (My), gait instability (GI), Tr, spasticity, etc.) and eye movement disorders (nystagmus (Ny), SEM, slow ocular pursuit), among others.

Brain imaging techniques revealed in some cases CNS lesions (cerebral atrophy, cerebellar atrophy (CAt), cerebellar hypoplasia (CHyp), basal ganglia lesions (BGL), stroke-like lesions (SLL), etc.). Particularly, CAt, which is a hallmark of the ARCA2 phenotype, is a relevant diagnostic feature since it was universally found at brain MRI of a large worldwide cohort of 59 *COQ8A* patients [118].

6.2. Peripheral nervous system and sensory organs manifestations

PNS and sensory organ manifestations have also been reported in several cases of primary deficiencies (Fig. 2B). Eye and ear are the main sensory organs reported to be affected in CoQ primary deficiencies patients. Sensorineural hearing loss (SNHL) is the most frequent phenotype in this group of symptoms. SNHL is present in over half of the reported cases of *COQ6* (18/30, 60%) and *PDSS2* (4/7, 57%) patients [159,168,169], being in all those cases associated with steroid-resistant nephrotic syndrome (SRNS) [119,179,193,197–199]. Some probands with *PDSS1* (2/3, 67%) [152], *COQ7* (3/3, 100%) [140,141,162] and *COQ8A* (2/77, 2.6%) [186] pathogenic variants presented SNHL as well, which in these cases was not linked to SRNS. The *PDSS1* patients with SNHL were two siblings that were reported to suffer peripheral neuropathy (PNSN), associated with optic nerve atrophy (OA) and early-onset SNHL [152]. All the three *COQ7* reported patients presented SNHL, and in two cases, they also showed PNSN and visual dysfunction (2/3, 67%) [140,141,162]. Visual dysfunction was also reported in some *COQ4* (6/35, 17%) [147,149], *PDSS2* (2/7, 29%) [169], *COQ6* (1/30, 3%) [160], *COQ8A* (1/77, 1.3%) [180] and *COQ8B* (1/79, 1.3%) [164] probands. OA was reported in very few individuals with *PDSS1* (2/3, 67%) [152], *PDSS2* (1/7, 14%) [169], *COQ2* (1/30, 3%) [113,150,154] and *COQ6* (1/30, 3%) [198] pathogenic variants. Other less frequent visual impairments such as cataracts [169,185], retinopathy (Rp) [150,191], retinitis pigmentosa (RP) [159,164,169] or delayed visual maturation [145] have been observed in several cases of *COQ* patients.

6.3. Renal manifestations

Renal dysfunction, altered morphology and specific signs and symptoms of renal disease are also observed in CoQ deficiency. Particularly, SRNS is very frequent in primary CoQ deficiency patients (Fig. 2C), specifically in those with pathogenic variants of *PDSS2* (7/7, 100%) [121,159,165,169], *COQ2* (26/30, 87%) [113,121,136,150,152–154,177,192,193,200–202], *COQ6* (26/30, 87%) [119,179,193,198,199,203–205] and *COQ8B* (65/79, 82%) [120,164,189,206–209]. Importantly, it evolves to end-stage renal disease (ESRD) within childhood, if not treated.

The majority of *COQ2* patients manifested early-onset nephrotic syndrome (24/30, 80%) [113,121,136,150,152–154,177,192,200–202], and there was also one family with adolescent onset and slow progression of the isolated renal disease (2/30, 7%) [193]. Also, for *COQ6* patients, the hallmark manifestation is childhood-onset SNRS (26/30, 87%) [119,179,193,198,199,203–205], which in around half of the cases is associated with SNHL (17/30, 57%) [119,179,198,199].

COQ8B patients mainly manifest SRNS (65/79, 82%) [120,164,189,206–209] due to focal segmental glomerulosclerosis (FSGS), some of them associated with oedema (16/79, 20%) [120,164,208,209] and hypertension (HT) (11/79, 14%) [164,189], which in most of the cases progressed to ESRD (47/79, 59%). All of the patients with *PDSS2* (7/7, 100%) [121,159,165,169] mutations and one of those with *PDSS1* (1/3, 33%) [174] variants also manifested SRNS.

Other less frequent renal involvements reported are chronic kidney disease (CKD) (*COQ2* (1/30, 3%) [210], *COQ6* (2/30, 7%) [211,212], *COQ8B* (18/79, 23%) [164,188,189,209]), renal cysts (*COQ7* (1/3, 33%) [162], *COQ9* (2/7, 29%) [157,158]) or tubulopathy (Tp) (*COQ2* (1/30, 3%) [151], *COQ9* (1/7, 14%) [156,173]).

6.4. Cardiac manifestations

The heart is often affected in primary CoQ deficiency (Fig. 2D). Arrhythmia and functional and morphological defects have been reported with variable frequency. The most commonly reported heart defect is hypertrophic cardiomyopathy (HCM), which is particularly frequent in *COQ4* (13/35, 37%) [83,144,149] and *COQ7* (2/3, 67%) [140,162] patients. It has also been reported in some *PDSS2* (2/7, 29%) [159,169], *COQ2* (3/30, 10%) [151,192,213], *COQ9* (1/7, 14%) [156,173] and *COQ8B* (2/79, 2.5%) [189,208] patients. Other morphological or functional heart defects less frequently found are valvulopathies (*PDSS1* (2/3, 67%) [152]), cardiomegaly (*COQ4* (3/35, 9%) [144,146,149], *COQ9* (1/7, 14%) [157]), septal defects (*COQ4* (1/35, 3%) [148], *COQ6* (1/30, 3%), *COQ8A* (1/77, 1%) [163] and *COQ8B* (2/79, 3%) [164,207]) or heart hypoplasia (*COQ4* (1/35, 3%) [83]). Also, arrhythmia (bradycardia) has been observed (*COQ4* (5/35, 14%) [83,144,147], *COQ9* (2/7, 29%) [157,194] and *COQ2* (1/30, 3%) [153]). In some cases, heart failure has been reported as a fatal outcome (*COQ4* (2/35, 5.7%) [83,144], *COQ7* (1/3, 33%) [162] and *COQ8B* (1/79, 1.3%) [164]).

6.5. Muscle manifestations

Muscle is less commonly affected in these patients (Fig. 2E). Isolated myopathy has been found in patients affected by secondary forms so far, but not in primary CoQ deficiency [108,109]. Instead, myopathy is always reported in association with a broader multisystemic phenotype (*COQ4* (2/35, 6%) [148,149], *COQ7* (1/3, 33%) [162], *COQ8A* (1/77, 1%) [214]). Muscular symptoms include exercise intolerance (EI) (*COQ8A* (14/77, 18%) [115,180,184,186]), muscle weakness (MW) (*COQ2* (1/30, 3%) [113,150,154], *COQ6* (3/30, 10%) [160,198], *COQ7* (3/3, 100%) [140,141,162], *COQ8A* (13/77, 17%) [115,184,185,215], *COQ8B* (1/79, 1%) [208]) and muscle fatigue (MF) (*COQ8A* (3/77, 4%) [180,185,216] and *COQ8B* (1/79, 1%) [164]). Also hypotonia and respiratory alterations may depend on muscular involvement. Some muscle biopsies have shown lipid accumulation (*COQ8A* (3/77, 4%) [184,185], *COQ2* (1/30, 3%) [213]), but probably this type of study has not been performed for all primary CoQ deficiency patients, so the information is still vastly incomplete.

6.6. Other manifestations

Other more heterogeneous clinical findings have also been reported in patients affected by mutations in the different *COQ* genes (Fig. 3). Among them, respiratory system alterations are the most frequent (Fig. 3B). Respiratory distress (RD) and apnea seem to be characteristic of *COQ4* (14/35, 40%; 9/35, 26%) [83,144,149], and have been observed in *COQ7* (2/3, 67%; None) [140,162], *COQ9* (3/7, 43%; 2/7, 29%) [157,158,194] and some *COQ2* (2/30, 7%; 2/30, 7%) [153] patients. Respiratory failure (RF) occurred in few cases of *COQ2* (5/30, 17%) [150,153,191] and *COQ4* (5/35, 14%) [83,145,147,149].

The liver is affected in a few patients harbouring mutant versions of *COQ2* (liver failure in 3/30, 10% [152,213] and cholestatic liver in 1/30, 3% [151]), *COQ9* (reduced haematopoiesis in the liver in 1/7, 14% [157]), *COQ8A* (hepatosteatosis in 1/77, 1.3% [217]) and *COQ8B* (hepatomegaly in 1/79, 1.3%) (Fig. 3A). Oedema is only reported in cases with nephrotic syndrome, so it is frequent in probands with pathogenic variants in genes characterized by renal involvement, such as *COQ8B* (16/79, 20%), *COQ2* (11/30, 37%) [136,150,153,177,191–193,200], *COQ6* (2/30, 7%) [119,211] and *PDSS2* (2/7, 29%) [159,165]. A more exhaustive comprehension of these disorders might derive from long-term follow-up studies of patients affected by primary CoQ deficiencies. Less frequent clinical findings include dysmorphic features [119,148,158], metabolic pathologies (diabetes mellitus, obesity and hypercholesterolemia) [151–153,203], thyroid disease (goiter, hypothyroidism) [120,189] or circulatory problems (cyanosis, HT, livedo reticularis (LR)) [83,147,164], among others (Fig. 3C). It should be considered that some of these symptoms could be secondary and not directly related to the primary cause of the disease.

7. Treatment of primary CoQ deficiency

Exogenous CoQ supplementation is the only therapeutic option currently available for CoQ deficiency. In general, patients respond positively to CoQ supplementation, but this is not always the case. Barriers for tissues CoQ delivery have been found due to its high molecular weight and low aqueous solubility, but at high doses, dietary supplementation increases CoQ levels in all tissues, including heart and brain, especially with specific formulations [218,219]. It also increases in circulating low-density lipoproteins (LDL), where it functions as an efficient antioxidant together with α-tocopherol [5,220]. Recently, the EMA approved ubiquinol as an orphan drug to treat primary CoQ deficiency [221].

CoQ supplementation at high doses has been shown to be effective for treating some cases of both primary and secondary CoQ deficiencies [222]. Still, it is crucial to start the supplementation as soon as possible to get favourable outcomes and to limit irreversible damage in critical tissues such as the kidney or the CNS [109]. Different doses of CoQ have been administered to treat primary CoQ deficiencies, ranging from 5 mg/kg/day [169] to 30–50 mg/kg/day for both adults and children [223]. In mouse models of this condition, even higher doses (up to 200 mg/kg/day) have been used [224]. Regarding safety, the highest dose for CoQ supplementation is 1200 mg/day according to well-designed randomized, controlled human trials, although doses as high as 3000 mg/day have been used in shorter clinical trials [221,225].

118 cases of the 276 reported ones (43%) were treated with CoQ supplementation. Except for COQ8A patients, most individuals with primary forms show an acceptable response to CoQ treatment, which is usually evident after 10–20 days [223]. Different formulations of CoQ are now available, both in the oxidised and the reduced forms, although most of the data available have been obtained in patients treated with ubiquinone (the oxidised form).

Some 4-HB analogues have been proposed as potential bypass molecules with higher bioavailability than CoQ [54]. These molecules provide the lacking chemical group due to defects in specific enzymes and can reactivate endogenous CoQ biosynthesis. They have only been tested in yeast, mammalian cell cultures and mouse models of primary CoQ deficiency, but they are promising for patients' treatment.

Early-onset CoQ deficiencies can cause mortality in a 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 new-borns (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 increase the survival of new-borns until they can be fed with supplements.

8. Age of onset and age of death

The age of onset in primary CoQ is very variable, but each of the affected genes seems to have a distinguishable onset age interval (Fig. 4). Moreover, even for the same gene, this range can be extensive (Fig. 4B). The age of onset generally falls between birth and childhood (*PDSS1*, *PDSS2*, *COQ2*, *COQ4*, *COQ5*, *COQ6*, *COQ7*, *COQ9*), or between childhood and adolescence (*COQ8A*, *COQ8B*), but there are also some adult-onset cases (*COQ8A* [185], *COQ8B* [189]) (Fig. 4B). Of note, some *COQ2* variants have been reported to increase susceptibility to adult-onset multisystem atrophy (MSA) [226–229].

Neonatal onset is more frequent in *COQ4* (19/35, 54% of the cases) [83,145,147–149,162], *COQ7* (2/3, 67% of the cases) [140,162] and *COQ9* (6/7, 86% of the cases) [156,157,194] patients. Also, many *COQ2* (11/30, 37% of the cases) [151–153,177,191,213], and some *PDSS1* (1/3, 33%) [174] and *PDSS2* (3/7, 43%) [121,159,165] patients presented neonatally. A significant lethality in the group of neonatal-onset patients is evident, almost all of them dying in the neonatal or infantile period, and some of them during childhood (Fig. 4A).

The majority of the *COQ2* patients presented before the age of 2 years (14/30, 47%) [121,136,150,201,202]. This is also true for *PDSS1* (2/3, 67%) [152], *PDSS2* (4/7, 57%) [121,169] and *COQ6* (15/30, 50%)

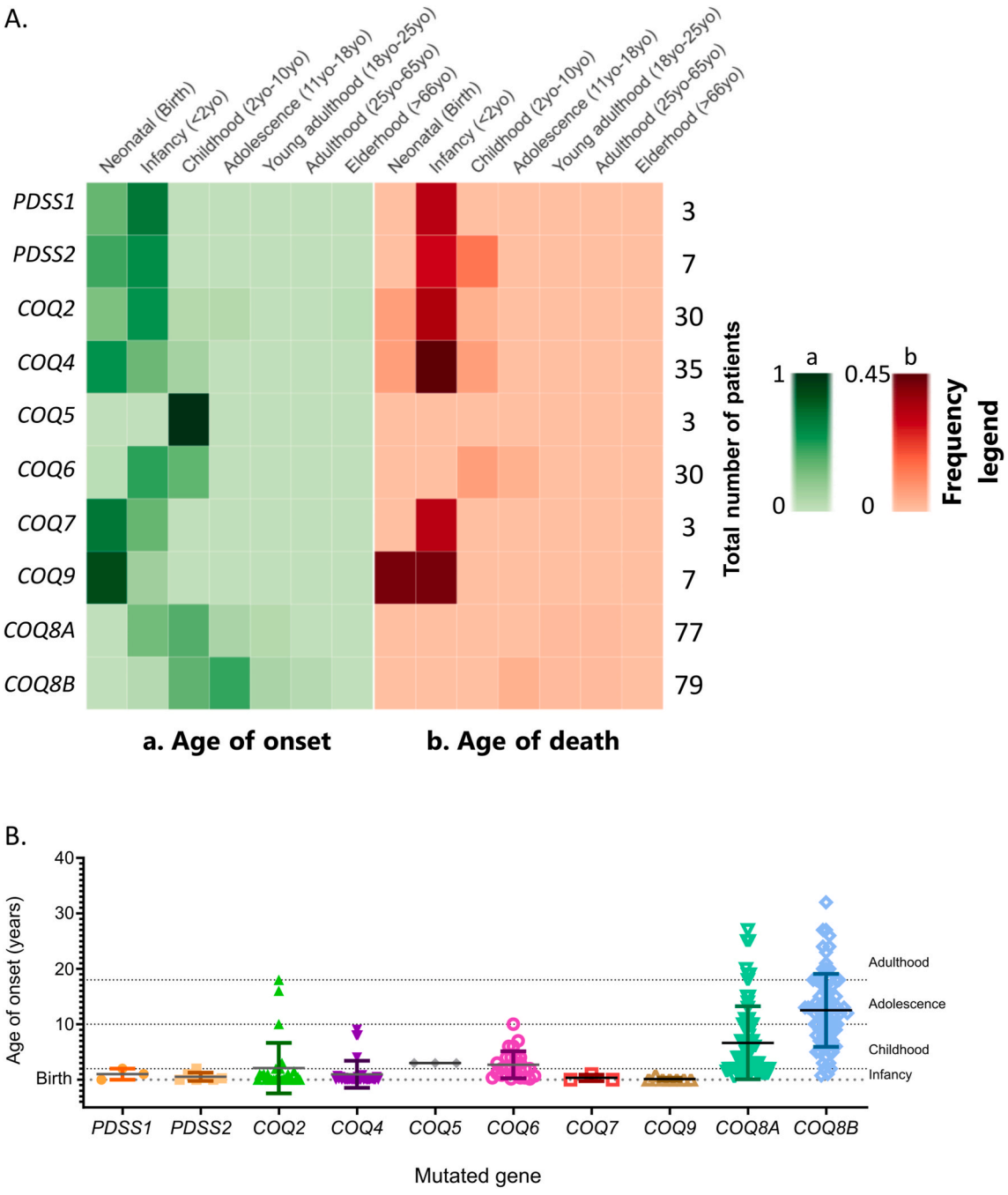

Fig. 4. (A) Heatmaps representing the age in which patients first manifested (a) or died (b), as described in publications, for each *COQ* gene involved. The age has been represented as percentage of patients belonging to seven different age groups: neonatal (birth), infancy (before 2 years of age), childhood (2–10 years old), adolescence (11–18 years old), young adulthood (18–25 years old), adulthood (25–65 years old) and elderhood (after 66 years old). Total number of patients for each *COQ* gene is indicated at the right of the heatmaps. (B) Age of onset of patients with primary CoQ deficiency, for each *COQ* gene involved. Each point represents one patient, and mean age of onset and standard deviation is calculated for each mutated gene. yo: years old.

[119,179,193,198,203,211] patients. Some probands with pathogenic variants of *COQ4* (11/35, 31%) [83,147,149], *COQ7* (1/3, 33%) [141], *COQ9* (1/7, 14%) [158], *COQ8A* (23/77, 30%) [115,117,163,180, 184–186] and *COQ8B* (4/79, 5%) [120,188] also presented when they were 2 years old or before.

COQ8A patients generally first manifest during childhood (29/77, 38%) [117,118,138,181,186]. Childhood-onset also occurs in a significant number of *COQ8B* (28/79, 35%) [164,189,207] and *COQ6* (11/30, 37%) [119,198,199] patients, and in the only reported family with *COQ5* defects (3/3, 100%) [155]. Some patients with *COQ2* (2/30, 7%) [136,202] and *COQ4* (4/35, 11%) [166,167] mutations also presented during childhood.

Adolescent-onset is the hallmark of *COQ8B* patients' presentation (35/79,44%) [120,164,189], while also some *COQ8A* (7/77, 9%) [117, 138,216] and *COQ2* (2/30, 7%) [193] patients presented between 11 and 18 years old. Adult-onset is rare, but some patients with *COQ8B* (11/79, 14%) [120,164,189] and *COQ8A* (6/77, 7%) [117,138,185, 230] mutations presented when they were adults.

9. Primary CoQ deficiency due to mutations in the different *COQ* genes

To shed light on the plethora of symptoms associated with the different cases of primary CoQ reported, we will discuss here the patterns of symptoms at onset (Fig. 5) and the general clinical manifestations for each *COQ* gene. For the genes for which the total number of families with affected patients was sufficiently high (>20), the clinical cases were additionally stratified by age-at-onset. The groups were the following: 0/birth: neonatal-onset; 0–2 years old (yo): infantile-onset; 2–10 years old (yo): childhood-onset; 11–18 years old (yo): adolescence onset; 19–65 years old (yo): adult-onset. We classified patients with mutations in *COQ2* (30 patients from 22 families), *COQ4* (35 patients from 26 families), *COQ6* (30 patients from 22 families), *COQ8A* (77 patients from 55 families) and *COQ8B* (79 patients from 41 families) (Fig. 6). With this classification, in some cases, patients belonging to the same family were split into different groups. This happened mainly with *COQ8B* patients, in which siblings from the same family first manifested at different ages. The number of patients with mutations in *PDSS1* (3 patients from 2 families), *PDSS2* (7 patients from 5 families), *COQ5* (3 patients from 1 family), *COQ7* (3 patients from 3 families) and *COQ9* (7 patients from 4 families) was too low to do the same. Still, we will equally discuss global clinical features.

We have also compiled the information about the pathogenicity of the mutations in the literature, reviewing three aspects: (i) the segregation of the mutation in the family; (ii) the biochemical characterisation of the disturbance of CoQ biosynthesis (measuring CoQ levels, synthesis rate, levels of COQ proteins or *COQ* transcripts, etc.); (iii) or the functional demonstration of the pathogenesis using a model (yeast, human or mouse cells). We analysed *in silico* the predicted pathogenicity of the mutations found in these patients. We used SIFT and PolyPhen-2 tools to predict the effects of the missense mutations on protein function, and SPiCE tool to predict the spliceogenicity of the variant; furthermore, a pathogenicity score for single nucleotide variants and small insertion/deletions variants was calculated using the Combined Annotation Dependent Depletion (CADD v1.6) tool, which integrates multiple annotations (Table 1). Most variants analysed display a CADD score higher than 20, the cut-off of deleteriousness that is usually considered.

Additionally, we analysed how the pathogenic variants were distributed concerning the age of onset of the disease (Fig. 7). All the pathogenic variants of each gene were classified in the onset-age stratified groups, to investigate if some variants could be linked to different phenotypic outcomes. Of note, the majority of variants have been described only in one family, whereas some of them are more represented within the patient cohort. It is not possible to draw definite conclusions for variants that have only been described in a reduced number of families. What is more, for compound heterozygous genotypes, both variants are considered, but in the absence of functional data, it is not possible to establish which of them contributes more to the phenotype. Only for those few variants that are represented in more than one family, we have analysed the possible link to different clinical pictures. In the cases of frameshift or nonsense mutations, when they occur early in the sequence, they could be considered as loss of function alleles.

9.1. *PDSS1*

The *PDSS1* gene (MIM*607429) encodes the decaprenyl diphosphate synthase subunit 1, involved in the elongation of the prenyl side-chain of CoQ, [3,48]. Defects in this gene are a cause of primary CoQ deficiency (COQ10D2, MIM#614651).

9.1.1. *CoQ deficiency due to PDSS1 mutations*

Only 3 patients from 2 families with *PDSS1* mutations have been reported so far, so little information is known to draw a complete disease picture (Figs. 2 and 3). The mean age of onset was 1 yo (range birth-2 yo) (Fig. 4B). These two families manifested very different clinical symptoms.

One family had a birth-onset disease with mainly renal involvement, with a severe SRNS that progressed in an ESRD, with death at 16 months old (mo). The patient from this family also had a marked developmental delay. The reported clinical picture could be considered as a severe multisystem disorder, similar to the primary phenotype of *COQ2* patients. This patient had two compound heterozygous mutations, one frameshift mutation in exon 7 (c.661_662insT), producing an early truncated protein (p.Arg221Leufs*16), and one missense mutation in exon 12, c.1108A > C (p.Ser370Arg) [174].

The other family had two siblings with an infancy onset (1–2 yo), who developed a milder disease. They presented with SNHL and later, in their childhood and adolescence, they developed mild ID and associated PNSN with OA. They also presented a valvulopathy, LR and obesity. They did not display any renal involvement, at least at the age of the last examination (14 and 22 yo respectively). They had a homozygous mutation in exon 10 of PDSS1, c.924T > G (p.Asp308Glu) [152].

9.1.2. *Pathogenicity of the mutations*

Only one of the 3 reported mutations in *PDSS1*, the c.924T > G (p.Asp308Glu) missense variant, has been demonstrated to have detrimental consequences in a yeast model, [152]. The other two are classified as pathogenic because of the low levels of CoQ found in patient's cells. The frameshift mutations would probably lead to a loss-of-function allele. The two missense mutations have been predicted as pathogenic by SIFT, PolyPhen-2 and CADD tools (Table 1).

9.2. *PDSS2*

Three different protein-coding transcripts are annotated for *PDSS2* gene (MIM*610564), but only the longest one is thought to produce PDSS subunit 2. Together with PDSS1, PDSS2 forms the heterotetramer that assembles the complete polyisoprenoid side chain, the first step in CoQ biosynthesis [48]. Defects in this gene are a cause of CoQ deficiency (COQ10D3, MIM#614652).

9.2.1. *CoQ deficiency due to PDSS2 mutations*

Seven patients from 5 families with *PDSS2* mutations have been reported so far. Strikingly, the pathology of *PDSS2* deficiency seems to be different from that of *PDSS1* deficiency (Figs. 2 and 3). *PDSS2* patients showed a multisystemic disorder with mainly renal involvement, all of them having SRNS and some of them ending in an ESRD. However, a wide range of neurological manifestations within the different families was reported (Leigh-like syndrome (LS), ataxia, cerebral palsy, encephalopathy). What is clear is that when SNHL was present (in 4 patients of 2 families), it was the first symptom to appear, similar to one of

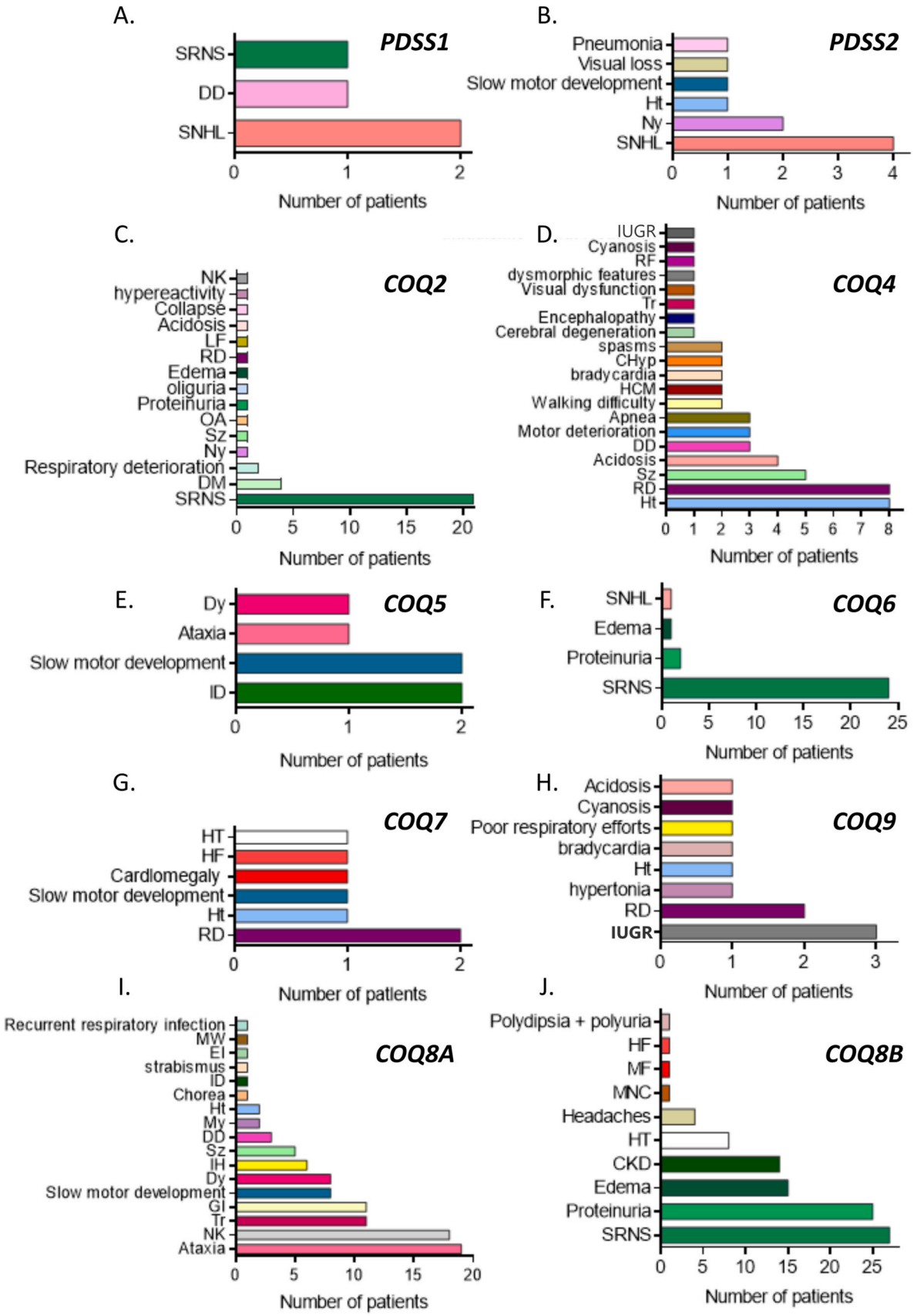

Fig. 5. Symptoms at onset in patients with mutations in the different *COQ* genes and number of patients associated with each first symptom. Each graph represents each gene involved in primary CoQ deficiency. (A) *PDSS1*, 3 patients in total; (B) *PDSS2*, 7 patients in total; (C) *COQ2*, 30 patients in total; (D) *COQ4*, 35 patients in total; (E) *COQ5*, 3 patients in total; (F) *COQ6*, 32 patients in total; (G) *COQ7*, 3 patients in total; (H) *COQ9*, 7 patients in total; (I) *COQ8A*, 77 patients in total and (J) *COQ8B*, 79 patients in total.

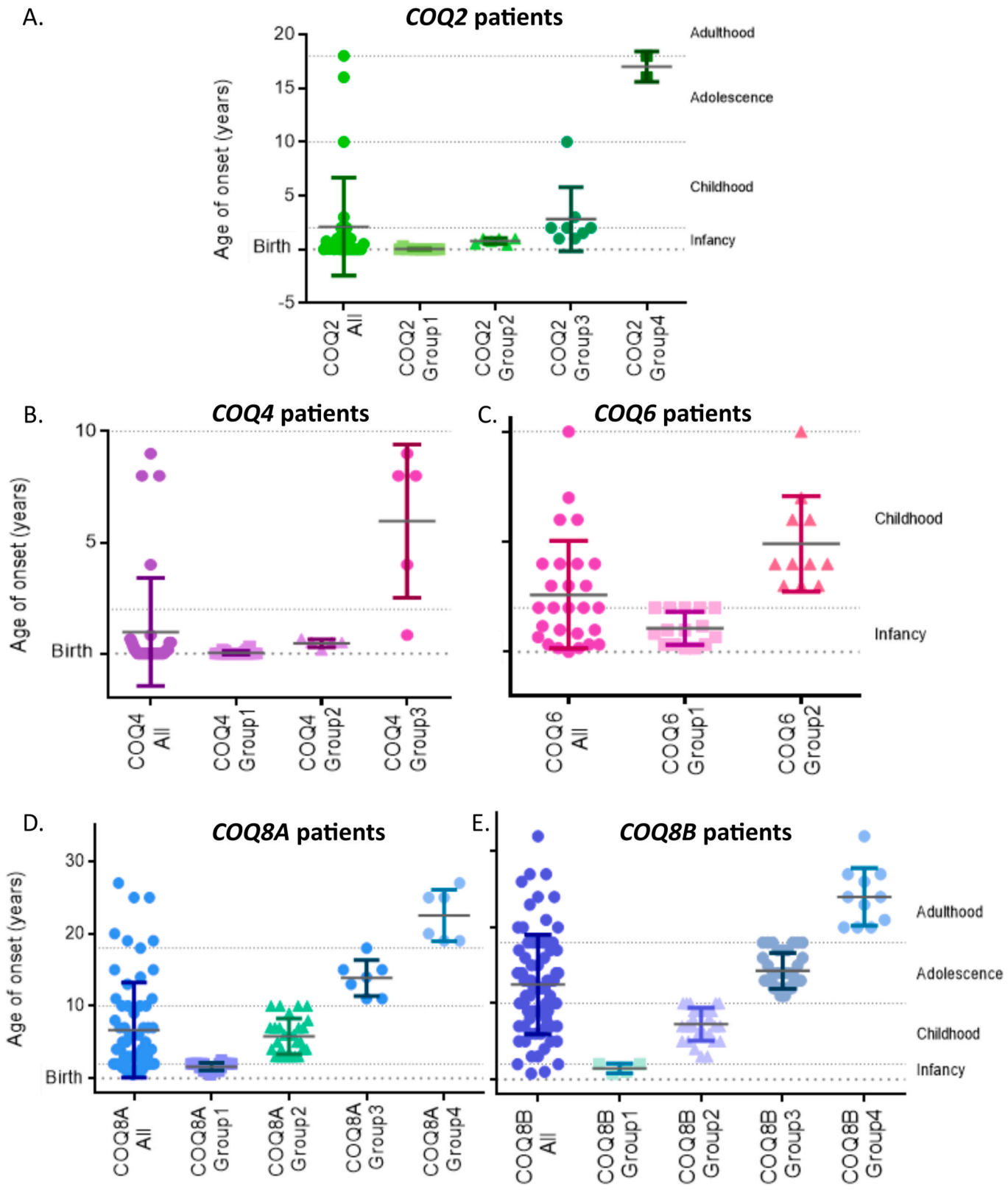

Fig. 6. Age of onset of patients with pathogenic variants of (A) *COQ2* (30 patients), (B) *COQ4* (35 patients), (C) *COQ6* (32 patients), (D) *COQ8A* (77patients) and (E) *COQ8B* (79 patients). In each graph, the whole group of patients is represented (All), as well as different groups of patients resulting of age-of-onset stratification of the cases (groups 1–4). Each point represents one patient, and mean age-of-onset and standard deviation is calculated for each mutated gene.

Table 1
Pathogenic variants of *COQ* genes identified in primary CoQ deficiency patients reported in the literature.

Gene/protein	F (P)	Pathogenic variants			Validation				*In silico* mutagenesis prediction				Ref.
		Genomic Coordinate (hg19) (Chr: position)	cDNA mutation	aa modification	Exon	Segregation (S),	Biochemical (B),	Functional (F)	SIFT Patho-genic?	PolyPhen-2 Damaging?	SPiCE Probability to alter splicing?	CADD score	
PDSS1 12 exons, 415 aa	1 (1)	10:27012786	c.661_662insT	p.Arg221Leufs*	7		B		-	-	-	33	[174]
NM_014317.5[a]	1 (2)	10:27024406	c.924T>G	p.Asp308Glu	10	S	B	F	Pathog.	Probably	-	22.1	[152]
NP_055132.2	1 (1)	10:27035262	c.1108A>C	p.Ser370Arg	12		B		Pathog.	Probably	low	26.4	[174]
PDSS2 8 exons 399 aa	1 (1)	6:107595378	c.485A>G	p.His162Arg	3	S			Pathog.	Probably	-	25.1	[159]
NM_020381.4[a]	1 (1)	6:107531687	c.964C>T	p.Gln322*	6	S	B		-	-	-	43	[165]
NP_065114.3	1 (1)	NA	c.1042_1148-2816del	p.?	8	S			-	-	low	- [15]	[159]
	2 (2)	6:107475878	c.1145C>T	p.Ser382Leu	8	S	B		Pathog.	Probably	-	31	[121, 165]
	1 (1)	6:107475872	c.1151C>A	p.Ala384Asp	8	S			Tolerated	Probably	-	29.0	[121]
	1 (3)	NA	NA	NA	NA		B		Pathog.	Probably	-	-	[168, 169]
COQ2[b] 7 exons 371 aa	1 (1)	4:84205892	c.26dupT	p.Ala10Argfs*33	1				-	-	-	21.8	[136]
NM_001358921.2 NP_001345850.1	5 (7)	4:84200234	c.287G>A[d]	p.Ser96Asn	2	S	B	F	Pathog.	Probably	-	25.1	[116, 150,151, 153, 192]
	2 (3)	4:84200153	c.368G>A	p.Arg123His	2	S			Pathog.	Probably	-	25.4	[121, 177]
	1 (1)	4:84200126	c.395T>G	p.Met132Arg	2	S	B	F	Pathog.	Probably	-	27.7	[213]
	1 (1)	4:84194751	c.440G>A	p.Arg147His	3	S	B	F	Pathog.	Probably	-	31	[116, 150]
	8 (9)	4:84194658	c.533A>G	p.Asn178Ser	3	S	B	F	Tolerated	Probably	-	26.5	[121, 136,150, 201, 210]
	1 (1)	4:84193317	c.551delT	p.Leu184fs*14	4	S	B		-	-	-	32	[116, 201]
	1 (1)	4:84191093	c.682T>C[e]	p.Cys228Arg	5	S			Pathog.	Probably	-	25.3	[200]
	1 (1)	4:84191069	c.706C>T	p.Leu236Phe	5	S			Pathog.	Probably	-	25.1	[121]
	1 (1)	4:84191044	c.731C>T	p.Thr244Ile	5				Tolerated	Probably	-	25.2	[136]
	2 (3)	4:84191035	c.740A>G	p.Tyr247Cys	5	S	B	F	Pathog.	Possibly	-	25.0	[113, 116,121, 150, 154]
	1 (2)	4:84191020	c.755C>T	p.Ala252Val	5	S	B	F	Pathog.	Probably	-	26.5	[116, 191]
	2 (3)	4:84188867	c.823A>G	p.Thr275Ala	6	S			Tolerated	Possibly	-	23.7	[136, 177]
	2 (2)	4:84185459	c.1009C>T[d]	p.Arg337*	7				-	-	-	38	[116, 136, 151]
	1 (2)	4:84185449	c.1019G>C	p.Gly340Ala	7	S	B	F	Pathog.	Possibly	-	22.9	[193]
	1 (2)	4:84185421	c.1047delT	p.Asn351Ilefs*15	7	S	B	F	-	-	-	25.7	[152]
COQ4 7 exons 265 aa	1 (1)	9:131085158	c.23_33delTCCTCCGTCGG	p.Val8Alafs*19	1	S			-	-	-	21.1	[145]
NM_016035.5[a]	1 (2)	9:131085379	c.155T>C	p.Leu52Ser	2	S			Pathog.	Probably	-	28.6	[83]
NP_057119.3	1 (2)	9:131085388	c.164G>T	p.Gly55Val	2	S			Pathog.	Probably	-	24.4	[166]
	1 (1)	9:131085414	c.190C>T	p.Pro64Ser	2	S	B		Pathog.	Probably	-	26.8	[83]

(*continued on next page*)

Table 1 (*continued*)

Gene/protein	F (P)	Pathogenic variants			Validation				*In silico* mutagenesis prediction				Ref.
		Genomic Coordinate (hg19) (Chr: position)	cDNA mutation	aa modification	Exon	Segregation (S), Biochemical (B), Functional (F)			SIFT Patho-genic?	PolyPhen-2 Damaging?	SPiCE Probability to alter splicing?	CADD score	
	1 (2)	9:131085421	c.197_198delGCinsAA	p.Arg66Gln	2	S	B		Pathog.	Probably	-	32	[144]
	2 (3)	9:131085426	c.202G>C	p.Asp68His	2	S	B		Pathog.	Probably	high	35	[144, 190]
	1 (2)	9:131087449	c.230C>T	P.Thr77Ile	3	S	B		Pathog.	Possibly	-	28.7	[167]
	1 (2)	9:131087464	c.245T>A	p.Leu82Gln	3	S	B		Pathog.	Benign	-	24.6	[144]
	1 (1)	9:131088069	c.311G>T[f]	p.Asp111Tyr	4		B		Pathog.	Probably	-	27.2	[145]
	1 (1)	9:131088114	c.356C>T[f]	p.Pro119Leu	4	S		F	Pathog.	Probably	-	26.0	[145]
	12 (16)	9:131088128	c.370G>A[g]	p.Gly124Ser	4	S	B	F	Pathog.	Probably	-	24.7	[146, 147, 149]
	2 (2)	9:131088129	c.371G>T	p.Gly124Val	4	S			Pathog.	Probably	-	24.4	[147, 149]
	4 (5)	9:131088161	c.402+1G>C	?	Intron 4	S	B		-	-	high	33	[149]
	1 (1)	9:131094450	c.421C>T	p.Arg141*	5	S	B	F	-	-	-	41	[83]
	1 (1)	9:131094462	c.433C>G	p.Arg145Gly	5				Pathog.	Possibly	-	25.1	[83]
	1 (1)	9:131094498	c.469C>A	p.Gln157Lys	5		B		Tolerated	Possibly	-	23.5	[190]
	1 (2)	9:131094502	c.473G>A	p.Arg158Gln	5	S			Pathog.	Probably	-	29.7	[144]
	1 (2)	9:131094546	c.521_523delCCA	p.Thr174del	5	S			-	-	-	22.1	[83]
	1 (1)	9:131095129	c.533G>A	p.Gly178Glu	6	S			Pathog.	Probably	medium	33	[147]
	1 (1)	9:131095146	c.550T>C	p.Trp184Arg	6	S	B		Pathog.	Probably	-	26.2	[149]
	3 (3)	9:131095844	c.718C>T	p.Arg240Cys	7	S		F	Pathog.	Probably	-	32	[83,144]
	1 (1)	9:130491179-134533179	3.9 Mb deletion on 9q34.13, including *COQ4*[c]		B		-	-	-	- [o]	[148]		
COQ5 7 exons, 327 aa NM_032314.4[a] NP_115690.3	1 (3)	12:120940150-120949950	9590 bp tandem duplication including the last 4 exons of *COQ5*	S	B		-	-	-	- [o]	[155]		
COQ6 12 exons 468 aa NM_182476.3[a] NP_872282.1	6 (6)	14:74420160	c.189_191delGAA	p.Lys64del	2	S			-	-	-	22.4	[198]
	1 (1)	14:74424852	c.484C>T[c]	p.Arg162*	5			F	-	-	-	38	[119]
	1 (1)	14:74424932	c.564G>A[c]	p.Trp188*	5			F	-	-	-	39	[119]
	1 (1)	14:74425747	c.686A>C	p.Gln229Pro	6	S			Tolerated	Probably	-	27.5	[198]
	2 (7)	14:74425907	c.763G>A	p.Gly255Arg	7	S		F	Pathog.	Probably	-	32	[119, 205]
	6 (6)	14:74425926	c.782C>T	p.Pro261Leu	7	S		F	Pathog.	Probably	low	33	[193, 198]
	1 (1)	14:74426137	c.804delC	p.Leu269Trpfs*13	8				-	-	-	32	[203]
	5 (8)	14:74428042	c.1058C>A	p.Ala353Asp	9	S		F	Pathog.	Probably	-	31	[119, 121,197, 199, 205]
	3 (3)	14:74428062	c.1078C>T	p.Arg360Trp	9	S			Pathog.	Probably	-	32	[179, 203, 211]
	1 (1)	14:74428217	c.1154A>C	p.Asp385Ala	11				Pathog.	Probably	-	29.8	[121]
	2 (2)	14:74428464	c.1235A>G[c]	p.Tyr412Cys	11			F	Pathog.	Probably	-	25.5	[121, 205]
	1 (1)	14:74428570	c.1341G>A	p.Trp447*	11	S		F	-	-	-	41	[119, 205]
	1 (1)	14 74429677	c.1383delG	p.Gln461fs*478	12	S		F	-	-	-	33	[119, 205]

(*continued on next page*)

Table 1 (*continued*)

Gene/protein	F (P)	Pathogenic variants			Validation				*In silico* mutagenesis prediction				Ref.
		Genomic Coordinate (hg19) (Chr: position)	cDNA mutation	aa modification	Exon	Segregation (S), Biochemical (B), Functional (F)			SIFT Patho-genic?	PolyPhen-2 Damaging?	SPiCE Probability to alter splicing?	CADD score	
COQ7 6 exons 217 aa NM_016138.5[a] NP_057222.2	1 (1)	16:19085309	c.319C>T	p.Arg107Trp	3	S	B		Pathog.	Probably	-	33	[162]
	1 (1)	16:19085322 (16:19085298)	c.332T>C (and c.308C>T)[h]	p.Leu111Pro (and p. Thr103Met)	3	S	B	F	Pathog.	Probably	-	28.5 (23.1)	[141]
	1 (1)	16:19087097	c.422T>A	p.Val141Glu	4	S	B	F	Pathog.	Probably	-	28.8	[140, 141]
	1 (1)	16:19089425	c.599_600delinsTAATGCATC	p.Lys200Ilefs*56	6	S	B		-	-	-	27.1	[162]
COQ9 318 aa 9 exons NM_020312.4[a] NP_064708.1	1 (1)	16:57490420	c.384delG	p.Gly129Valfs*17	4	S			-	-	-	23.2	[158]
	1 (1)	16:57490559	c.521+1delG	p.Ser127_Arg202del	Intron 5	S	B	F	-	-	high	24.4	[194]
	1 (4)	16:57490560	c.521+2T>C	p.Ser127_Arg202del	Intron 5	S	B		-	-	high	33	[157]
	1 (4)	16:57492265	c.711+3G>C	p.Ala203_Asp237del	Intron 7	S	B		-	-	high	23.6	[157]
	1 (1)	16:57493495	c.730C>T	p.Arg244*	7		B	F	-	-	-	46	[156, 173]
COQ8A/ ADCK3 15 exons 647 aa NM_020247.5[a] NP_064632.2	1 (1)	1:227153023	c.500_521del22insTTG	p.Gln167Leufs*36	3		B		-	-	-	33	[186]
	4 (5)	1:227153369	c.589-3C>G[i]	p.Leu197Valfs*20	Intron 3	S			-	-	high	23.0	[117, 138, 187]
	1 (2)	1:227153420	c.637C>T	p.Arg213Trp	4		B	F	Pathog.	Probably	-	32	[117, 184]
	1 (3)	1:227165178	c.685_690delCTGGCA	p.Leu229_Ala230del	5	S			-	-	-	21.1	[231]
	2 (3)	1:227169808	c.811C>T	p.Arg271Cys	6	S	B		Pathog.	Probably	-	27.1	[117, 176, 185]
	1 (2)	1:227169812	c.815G>T	p.Gly272Val	6		B	F	Pathog.	Probably	-	26.0	[117, 184]
	1 (1)	1:227169812	c.815G>A	p.Gly272Asp	6		B	F	Pathog.	Probably	-	26.5	[117, 184]
	1 (1)	1:227169824	c.827A>G	p.Lys276Arg	6				Pathog.	Probably	-	29.0	[214]
	1 (2)	1:227169827	c.830T>C	p.Leu277Pro	6	S	B		Pathog.	Probably	-	28.2	[196]
	5 (7)	1:227170420	c.895C>T	p.Arg299Trp	7	S	B		Pathog.	Probably	-	31	[117, 181, 185]
	3 (3)	1:227170426	c.901C>T	p.Arg301Trp	7	S	B		Pathog.	Probably	-	23.5	[176]
	1 (2)	1:227170435	c.910G>A	p.Ala304Thr	7	S			Pathog.	Probably	-	24.8	[185]
	1 (1)	1:227170436	c.911C>T	p.Ala304Val	7	S	B		Pathog.	Probably	-	25.0	[185]
	1 (1)	1:227170438	c.913G>T	p.Asp305Tyr	7		B		Pathog.	Benign	-	24.8	[175]
	1 (1)	1:227170648	c.993C>T[j]	p.Lys314_Gln360del	8		B		-	-	-	9.753	[117, 186, 239]
	1 (1)	1:227170655	c.1000C>T	p.Arg334Trp	8	S			Pathog.	Probably	-	29.7	[176]
	1 (1)	1:227170668	c.1013C>T	p.Ala338Val	8				Pathog.	Probably	-	24.8	[217]
	3 (6)	1:227170682	c.1027C>T	p.Gln343*	8	S			-	-	-	49	[115]
	5 (8)	1:227170697	c.1042C>T	p.Arg348*	8	S	B		-	-	-	40	[138, 176,180, 182]
	1 (1)	1:227171252	c.1081-1_1082dupGTA	p.Gln360_Tyr361ins*	Intron 8				-	-	low	18.65	[117]
	1 (2)	1:227171308	c.1136T>A	p.Leu379*	9	S	B		-	-	-	43	[180]
	1 (2)	1:227171527	c.1228C>T	p.Arg410*	10	S	B		-	-	-	40	[117]
	1 (1)	1:227171528	c.1229G>A	p.Arg410Gln	10	S			Pathog.	Possibly	-	26.8	[176]
	1 (2)	1:227171824	c.1286A>G[c]	p.Tyr429Cys	11	S	B		Tolerated	Benign	-	22.1	[185]

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Table 1 (*continued*)

Gene/protein	F (P)	Pathogenic variants			Validation				*In silico* mutagenesis prediction				Ref.
		Genomic Coordinate (hg19) (Chr: position)	cDNA mutation	aa modification	Exon	Segregation (S), Biochemical (B), Functional (F)			SIFT Patho-genic?	PolyPhen-2 Damaging?	SPiCE Probability to alter splicing?	CADD score	
	3 (3)	1:227171870	c.1331_1332insCACAG	p.Glu446Alafs*33	11	S			-	-	-	33	[138, 187]
	1 (1)	1:227171869	c.1334_1335del[c]	p.Thr445Argfs*52	11	S			-	-	-	32	[176]
	1 (1)	1:227171895	c.1358delT	p.Leu453Argfs*24	11				-	-	-	33	[117]
COQ8A/ ADCK3 15 exons 647 aa NM_020247.5[a] NP_064632.2	3 (4)	1:227171933	c.1396delG	p.Glu466Argfs*11	11	S			-	-	low	33	[122]
	1 (4)	1:227171938	c.1398+2T>C[k]	p.Asp420Trpfs*40; p. Ile467Alafs*22	Exons 11-12	S	B		-	-	high	32	[186]
	1 (1)	1:227172244	c.1399-3_1408del	p.?	Intron 11- Exon 12	S	B		-	-	high	33	[175]
	1 (2)	1:227172357	c.1506+1G>A	p.Val503Metfs*21	Intron 12	S	B		-	-	high	35	[196]
	1 (1)	1:227172580	c.1511_1512delCT	p.Ala504fs*	13		B		-	-	-	33	[240]
	1 (1)	1:227172593	c.1523T>C	p.Phe508Ser	13				Pathog.	Probably	-	29.9	[117]
	2 (2)	1:227172602	c.1532C>T	p.Thr511Met	13	S	B		Pathog.	Probably	-	24.9	[175, 176]
	1 (1)	1:227172604	c.1534C>T[l]	p.Arg512Trp	13	S			Pathog.	Probably	-	23.4	[163]
	1 (1)	1:227172611	c.1541A>G	p.Tyr514Cys	13		B	F	Pathog.	Probably	-	22.9	[186]
	1 (1)	1:227173027	c.1645G>A	p.Gly549Ser	14		B	F	Pathog.	Probably	-	26.3	[117, 186, 239]
	2 (2)	1:227173033	c.1651G>A	p.Glu551Lys	14		B	F	Pathog.	Probably	-	31	[176, 184]
	1 (1)	1:227174192	c.1702delG	p.Glu568Argfs*	15				-	-	-	34	[214]
	1 (2)	1:227174226	c.1732T>G	p.Phe578Val	15		B		Pathog.	Probably	-	28.3	[181]
	4 (5)	1: 227174240	c.1750_1752delACC[m]	p.Thr584del	15	S	B	F	-	-	-	22.5	[175, 176,183, 186]
	1 (2)	1:227174299	c.1805C>G	p.Pro602Arg	15				Pathog.	Probably	-	27.3	[183]
	1 (1)	1:227174306	c.1813dupG	p.Glu605Glyfs*125	15		B		-	-	-	34	[117, 184]
	2 (3)	1:227174317	c.1823C>T	p.Ser608Phe	15	S			Pathog.	Probably	-	31	[115]
	3 (4)	1:227174338	c.1844G>A[i]	p.Gly615Asp	15	S			Pathog.	Probably	-	29.9	[117, 138, 187]
	1 (2)	1:227174338	c.1844dupG	p.Ser616Leufs*114	15	S	B		-	-	-	33	[216]
	1 (1)	1:227125 473-227151023	27.6 kb deletion at 1q42.3 including exons 1-2 of *COQ8A*		B		-	-	-	- [o]	[138]		
	1 (1)	1:227150977-227195656	29 kb partial deletion including at least exons 3 to 15 of *COQ8A*[c]				-	-	-	- [o]	[117]		
	1 (1)	NA	2.9Mb duplication at 1q42.11q42.13 (including *COQ8A*)				-	-	-	- [o]	[215]		
COQ8B/ ADCK4 15 exons 544 aa NM_024876.4[a] NP_079152.3	1 (1)	19:41220437	c.101G>A	p.Trp34*	2				-	-	low	34	[120]
	4 (8)	19: 41216038	c.293T>G	p.Leu98Arg	5				Pathog.	Probably	-	28.6	[164, 189]
	1 (2)	19:41211271	c.449G>A	p.Arg150Gln	6				Pathog.	Probably	-	29.0	[207]
	3 (5)	19:41211045	c.532C>T	p.Arg178Trp	7	S	B	F	Pathog.	Probably	-	25.9	[120, 139,164, 188]

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Table 1 (*continued*)

Gene/protein	F (P)	Pathogenic variants			Validation				*In silico* mutagenesis prediction				Ref.
		Genomic Coordinate (hg19) (Chr: position)	cDNA mutation	aa modification	Exon	Segregation (S), Biochemical (B), Functional (F)			SIFT Patho-genic?	PolyPhen-2 Damaging?	SPiCE Probability to alter splicing?	CADD score	
	3 (4)	19:41209691	c.645delT	p.Phe215Leufs*14	8	S		F	-	-	-	31	[120, 139, 164]
	1 (1)	19:41209688	c.649G >A	p.Ala217Thr	8	S			Pathog.	Probably	-	28.9	[195]
	6 (7)	19:41209508	c.737G>A	p.Ser246Asn	9	S			Pathog.	Probably	-	27.0	[188, 206, 207]
	1 (2)	19:41209497	c.748G>A	p.Asp250Asn	9				Pathog.	Probably	-	26.1	[164]
	1 (1)	19:41209497	c.748G>T	p.Asp250Tyr	9	S			Pathog.	Probably	-	26.3	[195]
	5 (7)	19:41209497	c.748G>C[n]	p.Asp250His	9	S			Pathog.	Probably	-	25.6	[188, 208,209, 241]
	2 (3)	19:41209486	c.759C>A	p.Asn253Lys	9				Pathog.	Probably	-	24.4	[207]
	1 (3)	19:41208541	c.857A>G	p.Asp286Gly	10	S		F	Pathog.	Probably	-	29.7	[120, 139]
	1 (1)	19:41206321	c.929C>T	p.Pro310Leu	10				Pathog.	Probably	-	32	[164]
	1 (1)	19:41206294	c.954_956dupGAC	p.Thr319dup	11				-	-	-	23.5	[120]
	1 (2)	19:41206292	c.958C>T	p.Arg320Trp	11	S		F	Pathog.	Probably	-	25.5	[120, 139]
	1 (2)	19:41206223	c.1027C>T	p.Arg343Trp	11	S			Pathog.	Probably	-	29.0	[120]
	2 (3)	19:41206074	c.1041C>A	p.Cys347*	12	S			-	-	-	38	[209, 241]
	5 (13)	19:41201904	c.1199dupA	p.His400Glnfs*11	13	S	B	F	-	-	-	33	[120, 139,164, 189]
	7 (20)	19:41198236	c.1339dupG	p.Glu447Glyfs*10	15			F	-	-	-	34	[139, 164, 189]
	1 (2)	19:41198212	c.1356_1362delGGGCCCT	p.Gln452Hisfs*	15	S	B		-	-	-	34	[120]
	2 (3)	19:41198145	c.1430G>A	p.Arg477Gln	15	S		F	Pathog.	Probably	-	29.7	[120, 139, 189]
	1 (3)	19:41198128	c.1447G>T	p.Glu483*	15	S		F	-	-	-	40	[120, 139]
	1 (1)	19:41198107	c.1468C>T	p.Arg490Cys	15	S			Pathog.	Probably	-	29.5	[207]
	1 (1)	19:41198081	c.1493_1494delCCinsAA	p.Ala498Glu	15				Pathog.	Benign	-	24.0	[164]

Different complementary online software for pathogenicity prediction were employed: SIFT [242] (available at https://sift.bii.a-star.edu.sg/) and PolyPhen-2 [243] (available at http://genetics.bwh.harvard.edu/pph2/) for missense variants; SPiCEv2.1 [244] (available at https://sourceforge.net/projects/spicev2-1/) for splicing variants; and CADD v1.6 [245] (available at https://cadd.gs.washington.edu/). SIFT score <0.05 was considered pathogenic. PolyPhen-2 score >0.05 was considered probably/possibly damaging (using the HumVar data set). SPiCE probability to alter splicing (p) was considered high when $p > 0.749$, medium when $0.115 < p < 0.749$ and low when $p < 0.115$. CADD score >20 was considered pathogenic.

Abbreviations: F: Number of families with each variant, P: Number of patients with each variant, Chr: chromosome, aa: amino acid, Ref: references, NA: not available, Pathog: Pathogenic.

[a] Reference sequences correspond to the longest transcript.

[b] The *COQ2* gene has four in-frame initiation codons. The last proposed nomenclature is used, corresponding to the 371 aa long COQ2 protein (starting from ATG4) [116].

[c] These pathogenic variants were found in heterozygosis in at least one patient [117,119,148,176,185,205].

[d] The patient with these two variants also carries a novel variant in *MT-ND1* (m.3754C > A) with 22% of heteroplasmy in peripheral blood, which may contribute to the disease [151].

[e] The patient with this homozygous mutation also carries an additional homozygous variant in *ARSB* (c.1213 + 1G > A), which may contribute to the phenotype [200].

[f] These two missense variants were identified in a patient in the same allele, paternally inherited. The maternally inherited *COQ4* allele carried the c.22_33delTCCTCCGTCGG deletion (p.Val8Alafs*19) [145].

[g] The c.370G > A p.(Gly124Ser) variant in *COQ4* has been described as a founder mutation in southern Chinese population, being identified in 16 patients from 12 Chinese families [146,147,149].

[h] The c.308C > T substitution in *COQ7* seems to increase COQ7 protein instability and to intensify the effect of the pathogenic variant. The patient also harbours a 1555A > G mutation in mtDNA, which may contribute to the phenotype [141].

[i] A patient with these two heterozygous variants in *COQ8A* also carries two compound heterozygous mutations in the *PAH* gene, which may contribute to the disease [138].

[j] The variant c.993C > T in *COQ8A*, which was identified in a patient in *trans* with the c.1645G > A missense change, was shown to partially affect splicing, leading to the production of an abnormal transcript with exon 8 skipping [186]. However, this variant showed an allelic frequency of approximately 1.6% with 38 homozygous individuals in the European non-Finnish population in the gnomAD population database (https://gnomad.broadinstitute.org/) and it is reported in the ClinVar database as likely benign.

[k] The c.1398+2T > C6 *COQ8A* variant affects a splice donor site, leading to the expression of different splice variants: p.Asp420Trpfs*40 and p.Ile467Alafs*22 [186].

[l] The patient with this homozygous *COQ8A* variant also carries an additional homozygous mutation in *MED25* (c.518T > C; p.Ile173Thr), which may contribute to the disease [163].

[m] This variant is named as c.1749_1751delCAC in Chang et al., 2018 [175].

[n] Two siblings with this homozygous *COQ8B* variant also had an homozygous mutation in *NPHS1* (c.1339G > A; p.Glu447Lys) [208].

[o] Large rearrangement, not included in CADD analysis.

the two *PDSS1* families [152] (Fig. 5). The two families with SNHL also had an HCM. The disease manifested at a mean age of 6 mo (range birth-2 yo) (Fig. 4B). Three families had a birth onset (3/7 patients, 43%), while two families (4/7 patients, 57%) had an infancy onset (Figs. 4B and 5B).

Two patients with a birth onset died during infancy (8mo), but from different causes (epilepsy or ESRD), while the age of the third one is not available. One of these patients presented with Ht and developed LS with BGL (basal ganglia lesions) and Sz, passing away because of a complication of the epileptic status. He had two compound heterozygous mutations, one nonsense variant in exon 6 (c.964C > T), producing an early truncated protein (p.Gln322*), and one missense change in exon 8, c.1145C > T (p.Ser382Leu) [165]. The other patient initially presented with hearing loss, and developmental delay, and later manifested an encephalopathy with Ht, RP and HCM, dying because of a renal dysfunction. He had two compound heterozygous mutations in *PDSS2*, one missense mutation in exon 3, c.485A > G (p.His162Arg), and a 2923bp deletion that affected the 5‘ end of exon 8 [159]. The third patient was described with no other presentation than the SRNS, and had a homozygous missense mutation in exon 8, c.1151C > A (p.Ala384Asp) [121].

There were two families with an infancy onset, and with a less severe phenotype. One of them had three siblings who presented with Ny and HL, and then developed visual impairment and an ataxic phenotype, with ID. One of them had HCM. The mutations in these patients were not specified [168,169]. The other family had one patient with cerebral palsy and ID who harboured a homozygous missense substitution in exon 8, c.1145C > T (p.Ser382Leu), the same as the one that was found in the patient with LS [121].

9.2.2. Pathogenicity of the mutations

Five pathogenic variants of *PDSS2* have been related to primary CoQ deficiency in published patients (Fig. 7). All of them were confirmed to correctly segregate within families. Only the variants identified in the patient with LS (c.964C > T (p.Gln322*) and c.1145C > T (p.Ser382-Leu)) were analysed biochemically and revealed low levels of CoQ biosynthesis rate in patient fibroblasts [165]. This missense mutation was also found in an unrelated patient [121], showing a different disease course. The deletion c.1042_1148-2816del involves the 3’ portion of the last exon with an uncertain molecular effect [159]. The missense change found in *trans* with this deletion, c.485A > G (p.His162Arg), was predicted to be pathogenic by SIFT, PolyPhen-2 and CADD tools. Finally, *in silico* analysis of the missense c.1151C > A (p.Ala384Asp) change in exon 8 [121], which was identified in homozygous state in another patient, yielded contrasting results, being predicted as tolerated by SIFT, probably damaging by Polyphen-2, but reaching a pathogenicity score (29) with CADD. This finding supports a deleterious effect of this substitution, which, however, should be experimentally validated (Table 1).

9.3. COQ2

The open reading frame of the *COQ2* gene (MIM*609825) contains four in-frame ATG initiation codons (termed ATG1-4). Traditionally, ATG1 was considered as the first translated codon, generating a 421 aa protein with 7 exons. Still, recently, it has been shown that the most abundant *COQ2* transcript in human cells includes only the most downstream initiation codon (ATG4, 1641 bp), giving rise to a 371 aa protein with 7 exons [116]. The gene product, the *para*-hydroxybenzoate polyprenyl transferase, is the enzyme that catalyses the condensation of 4- hydroxybenzoate with polyprenyl-pyrophosphate, generating the first membrane-bound CoQ intermediate [48]. Defects in this gene are a cause of CoQ deficiency (COQ10D1, MIM#607426).

9.3.1. CoQ deficiency due to COQ2 mutations

30 patients from 22 families with *COQ2* pathogenic variants have

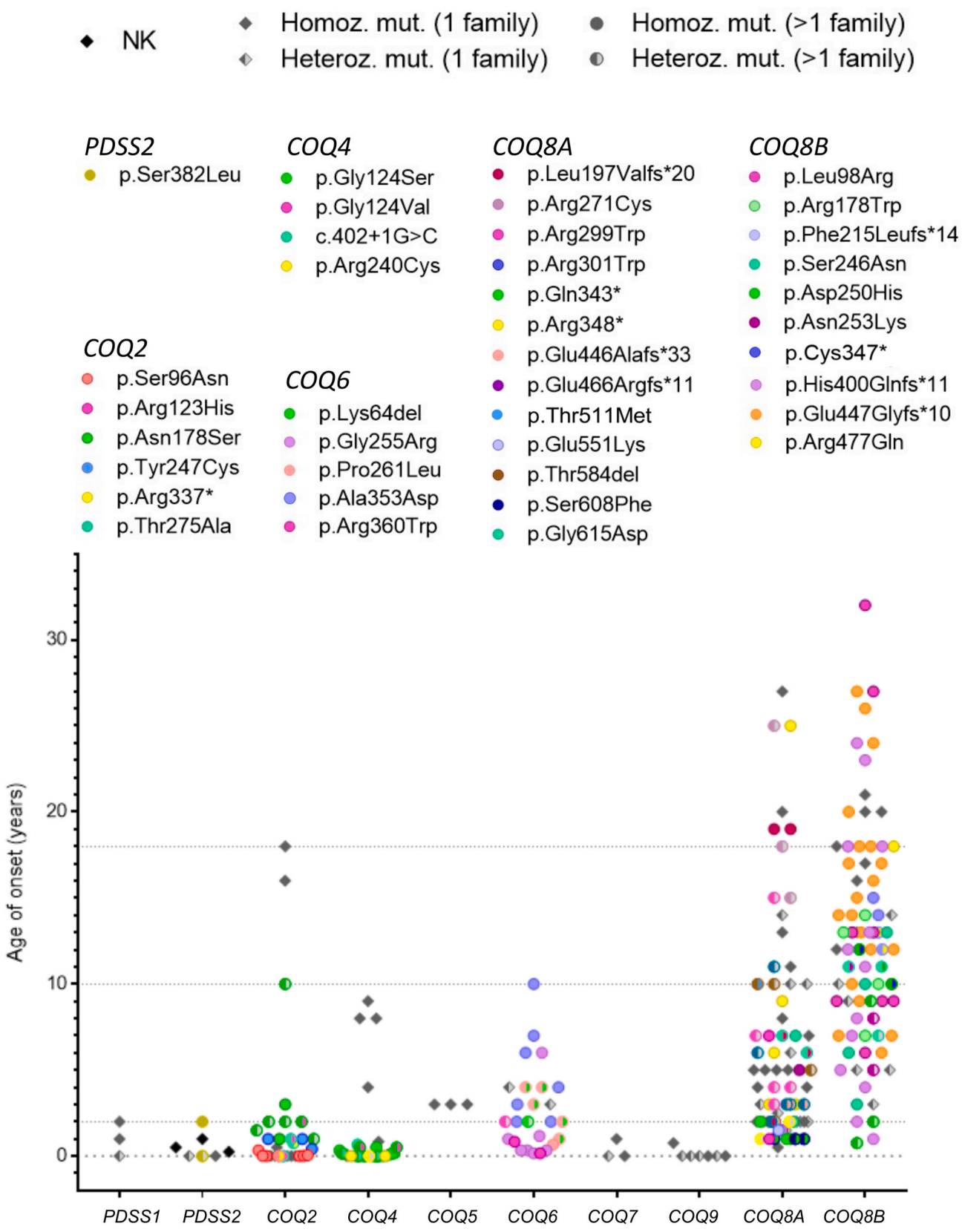

Fig. 7. Age of onset of patients with pathogenic variants of the ten genes involved in primary CoQ deficiency. Each point represents one patient. Coloured circles represent mutations that were found in more than one family (each mutation in a different colour, depicted in the legend). Rhombus represent patients with mutations that appeared only in one family (in gray) or unknown mutations (in black). Full-filled symbols represent homozygous mutations, while half-filled ones design heterozygous mutations. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

been reported up to date. *COQ2* patients manifested a nephrotic syndrome with different degrees of severity (Figs. 2 and 3), that could be either isolated, associated with central nervous system affections, or as a part of a more severe multisystemic disorder.

9.3.1.1. Age of onset. The mean age of onset for *COQ2* patients is 25 mo (range birth-18 yo) (Fig. 4B). We classified the clinical cases by the age of onset in 4 different groups, each of them showing a different clinical picture (Figs. 7A and 8A and B).

Group 1 is the largest one (13/30, 43% of the total number of *COQ2* patients). The mean age of onset in this group was 2 weeks old (wo) (range birth-4 mo). Group 2 is a small group (6/30, 20% of the total number of *COQ2* patients), and includes 6 patients from 5 different families, in whom the mean age of onset was 9 mo (range 5 mo- 1 yo). Group 3 is composed of patients (9/30, 30% of the total number of *COQ2* patients) who had an infancy (6/9, 78%) or childhood (2/9, 22%) -onset, whose mean age of presentation was almost 3 yo (34 mo) (range 1 yo-10 yo). Only one family (Group 4, 2/30, 6.7% of the total number of *COQ2* patients) manifested during adolescence, with a mean age of presentation of 17 yo (range 16–18 yo).

9.3.1.2. Symptoms at onset. *COQ2* patients mainly displayed a pleiotropic presentation at onset, with a combination of different clinical manifestations (Fig. 5). However, the hallmark symptom at onset was SRNS (21/30, 70%). Other relatively common symptoms at onset were diabetes mellitus (DM) (4/30, 13%) [153] or respiratory defects (3/30, 10%) [151,191], among others, that were present in combination. Particularly, all the three *COQ2* patients reported to have respiratory symptoms were born prematurely and presented with a multisystemic involvement; one also showed HCM.

When sorted by age at onset, patients with the earliest onset (group 1) first presented with a broad spectrum of different symptoms (SRNS (5/13, 38%) [152,153], respiratory defects (3/13, 23%) [151,191], DM (4/13, 31%) [153], liver failure (1/13, 8%) [152], Sz (1/13, 8%) [192], acidosis (1/13, 8%) [213], collapse (1/13, 8%) [152] or hyperreactivity (1/13, 8%) [213]) (Fig. 8C). For group 2 patients, SRNS was the first symptom in the majority of the cases (5/6, 83%) [113,121,136,150,154,200]. One patient also presented with Ny and OA [113,154], and another one with oedema and proteinuria, which are signs of SRNS (Fig. 8D) [177]. The rest of the patients (groups 3 and 4) first presented with SRNS (9 and 2, respectively) (Fig. 8E and F) [121,136,150,193,201,210].

9.3.1.3. Clinical manifestations of the disease. Considering the general disease course of *COQ2* patients in more detail, the main phenotype is an early-onset severe multisystemic disorder (group 1), mainly with renal disorders (SRNS (9/13, 69%) and CNS (Encephalopathy (7/13, 54%), Sz (10/13, 77%), Ht (5/13, 38%), dystonia (2/13, 15%), SLL (2/13, 15%), Ny (2/13, 15%), but also with other affected organs and systems (HCM (3/13, 23%), LF (3/13, 23%), DM (6/13, 46%), RF (5/13, 38%) [150–153,177,192,213]. All patients from group 1 died (13/13, 100%) mainly because of multiorgan failure (7/13, 54%) [151,153,192], or a complication of the renal (2/13, 15%) [150,200] or neurological (3/13, 23%) status [153,213]. Infections caused the death of the rest of the patients (2/13, 15%) [191].

Some patients presented an infancy-onset SRNS that was accompanied by some neurological involvement (group 2), manifesting as encephalopathy (2/6, 33%), DD (2/6, 33%), and Sz, Ny, Ht, My, CAt, Tr, OA and Rp (1/6, 17% each symptom) [113,121,150,154,177].

Group 3 is composed of patients who had infancy (6/9, 67%) or childhood (2/9, 22%) -onset isolated SRNS (9/9, 100%), sometimes associated with oedema (2/9, 22%) [121,136,150,201,210]. Only one family (group 4) manifested SRNS during adolescence, with a mild CNS involvement (epilepsy, mild neurological symptoms) [193].

9.3.2. Pathogenicity of the mutations

There are 16 reported *COQ2* variants that have been associated with primary CoQ deficiency in the literature (Figs. 7 and 8G). Almost all the mutations (13/16, 81%) were confirmed to segregate within the different families, except the variants c.26dupT (p.Ala10Argfs*33), c.731C > T (p.Thr244Ile) and c.1009C > T (p.Arg337*) where parental DNA was not available. Some of the mutations (8/16, 50%) were tested in a yeast model in a study in which a genotype-phenotype correlation for *COQ2* patients is established [116].

Following the stratification based on the age-of-onset previously mentioned, we analysed the pathogenic variations that were represented within the different groups (Fig. 8G). We observed a correlation in which some variants are associated with a more severe phenotype, while others with a less severe disease. This is in agreement with previous studies in which *COQ2* variants conferring residual CoQ synthesis were found to correlate with the severity of the disease [116].

Although no clear conclusions can be drawn for variants described in a reduced number of families, we will discuss the phenotypic features of those most represented in each group (c.287G > A (p.Ser96Asn), c.740A > G (p.Tyr247Cys), c.533A > G (p.Asn178Ser), c.1019G > C (p.Gly340Ala)).

The p.Ser96Asn variation is present in 7 patients from 5 different families corresponding to group 1, in homozygous (6/7 patients) [113,150,153,154,192] or compound heterozygous state (1/7 patients, with the nonsense mutation p.Arg337*) [151]. Its pathogenicity has been confirmed in a yeast model, where it showed to have very low levels of residual CoQ biosynthesis [116], thus leading to a severe infantile multisystemic disorder.

Two families were diagnosed as having p.Tyr247Cys variant homozygously, and presented SRNS with neurological symptoms (Group 2) [113,116,121,154]. However, the number of cases is too small to be able to conclude anything further. The functional consequence of this amino acid substitution was assessed on a yeast model that showed 30% residual CoQ content [116].

On the other hand, p.Asn178Ser variant is present in 9 patients from 8 families grouped in the isolated SRNS clinical group 3, in homozygosis (2/9 patients) [136,210] or compound heterozygosis (7/9 patients, with different missense and frameshift mutations) [121,136,150,201]. Its pathogenicity was confirmed in a yeast model, where it showed to have 50% of residual CoQ biosynthesis, compared to the WT allele [116]. This pathogenic variant seems to be less severe.

Only one family manifested SRNS during adolescence (Group 4) with a mild CNS involvement. These two siblings had p.Gly340Ala variant in homozygosis. The pathogenicity of this mutation has been confirmed in a yeast model, where it showed to have a mild effect, retaining almost 50% of residual CoQ biosynthesis, compared to the WT allele [193].

Finally, some variants were found in heterozygous state in patients belonging to different groups (p.Arg123His, p.Thr275Ala, p.Arg337*), and predicted pathogenic by CADD (Table 1) [121,136,151,177]. However, with the available data, it is hard to establish the extent to which each of the heterozygous mutations would contribute to the disease pathogenesis. The p.Arg337* is a nonsense change, but since it is in the last exon, the protein only lacks the last 34 amino acids, and its effect on protein function is unknown.

Of note, two patients presented in the seventh decade of life with a late onset encephalopathy with Rp mimicking multiple system atrophy without any signs of renal involvement [227]. Furthermore, some studies predict that specific *COQ2* variants increase susceptibility to adult-onset MSA, with Parkinson's-like symptoms, particularly in the East Asian population, but not in the Caucasian one [226–229], however this finding must still be confirmed.

9.4. COQ4

The gene product of *COQ4* (MIM*612898) appears to play a structural role in stabilising the CoQ synthome [48,81,82]. *COQ4* deficiency

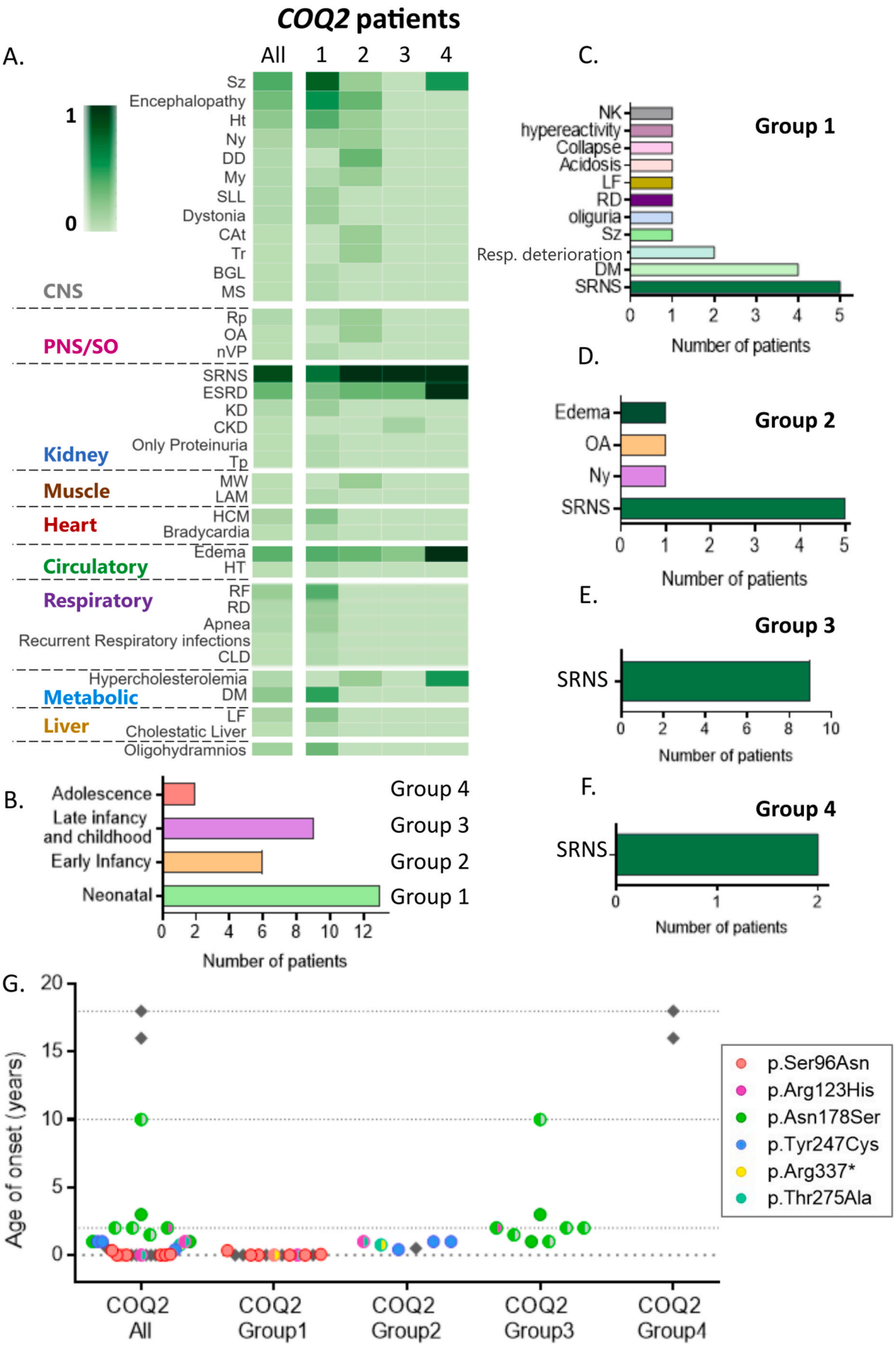

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Fig. 8. Clinical manifestations and genotype of *COQ2* patients. (A) Heatmap representing symptom frequency found in *COQ2* patients, for each age-of-onset group 1–4. (B) Total number of patients in each age-of-onset group. (C–F) Bar graphs represent the first symptoms the patients manifested at onset, and the number of patients manifesting them, for each age-of-onset group. (G) Age-of-onset and pathogenic variants of *COQ2* patients. Each point represents one patient. Coloured circles represent mutations found in more than one family (each mutation in a different colour, see the legend). Rhombus represent patients with mutations only present in one family (gray) or unknown mutations (black). Full-filled symbols represent homozygous mutations, half-filled ones design heterozygous mutations. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

leads to a form of primary CoQ deficiency (COQ10D7, MIM#616276).

9.4.1. CoQ deficiency due to COQ4 mutations

35 patients from 26 families with *COQ4* mutations have been reported so far. *COQ4* patients mainly showed a severe neurological affection, associated with cardiomyopathy (18/35, 51%) and RD (14/35, 40%) in the majority of the cases (Figs. 2 and 3).

9.4.1.1. Age of onset. The mean age of presentation was 1 yo (range birth-9 yo) (Fig. 4B), most of them being neonatal or infancy (19/35, 54% and 11/35, 31%; respectively) presentations (Fig. 9B). Likewise *COQ2*, *COQ4* patients present different clinical pictures, and we can classify them in 3 different groups when stratified by the age of onset (Figs. 6B and 9).

Group 1 is constituted by 25 patients from 18 families (25/35, 71% of the total number of *COQ4* patients), which include all the birth-onset ones and some presenting the disease within the first months of life. The mean age of onset of patients in this group is 2 weeks old (wo) (range birth −4 mo). Group 2 is composed of four patients from four Chinese families (4/35, 11% of the total number of *COQ4* patients), with a mean age of presentation of 6 mo (range 6–8 mo). Group 3 is the one with the less severe phenotype (5/35, 14% of the total number of *COQ4* patients), manifesting at a mean age of 6 yo (range 10 mo-9 yo).

9.4.1.2. Symptoms at onset. Patients generally first presented with a combination of 1, 2 or 3 clinical manifestations, typical of a severe multisystemic disorder (Figs. 5D and 9C-E). The most common symptoms at onset were Ht (8/35, 23%), RD (8/35, 23%), Sz (5/35, 14%), acidosis (4/35, 11%), developmental delay (3/35, 9%), motor deterioration (3/35, 9%) and apnea (3/35, 9%). Other less frequent symptoms at onset were walking difficulty, HCM, bradycardia, cerebellar hypoplasia or spasms (2/35, 6% each of them).

If analysed at onset, different patterns of symptoms are revealed. The majority of *COQ4* patients presented at birth (group 1) with a collection of different symptoms affecting variable systems and organs (RD (8/25, 32%), Ht (7/25, 28%), acidosis (4/25, 16%), Sz (4/25, 16%), apnea (3/25, 12%), bradycardia (2/25, 8%), HCM (2/25, 8%) [83,144,145,147,149] (Fig. 9C). Infantile-onset patients (group 2) presented with developmental delay (2/4, 50%), spasms (1/4, 25%), visual dysfunction (1/4, 25%) and Ht (1/4, 25%) (Fig. 9D) [147,149]. Some patients presented during childhood (group 3) and their first symptoms were motor deterioration or walking difficulties (3/5, 60%), Tr (1/5, 20%) and Sz (1/5, 20%), as this onset is typical of a cerebellar disorder (Fig. 9E) [83,166,167].

9.4.1.3. Clinical manifestations of the disease. During the course of the disease, *COQ4* patients mainly showed a severe CNS affection, with encephalopathy (11/35, 31%), Sz (24/35, 69%), Ht (19/35, 54%) and cerebellar hypoplasia (10/35, 29%), associated to HCM (13/35, 37%) and RD (14/35, 40%) (Fig. 9A); and a fatal outcome with death within the first days (2/35, 6%), months (16/35, 46%) or years of life (2/35, 6%). Of note, the majority of the identified *COQ4* patients in this group are Chinese (17/35, 49%) [146,147,149].

The main phenotype of *COQ4* deficiency is a neonatal-infantile onset encephalo-cardiomyopathy (group 1) [83,144–149]. The most common cardiac manifestations were HCM (13/25, 52%), bradycardia (5/25, 20%), cardiomegaly (3/25, 12%), heart failure (2/25, 8%), tachycardia (2/25, 8%); while CNS was mainly affected by Ht (16/25, 64%), Sz (16/25, 64%), DD (13/25, 52%), encephalopathy (9/25, 36%), CHyp (9/25, 36%), BGL (5/25, 20%), amongst other implications. Additionally to cardiac and CNS involvement, these patients very often presented RD (14/25, 56%) and apnea (9/25, 36%). Almost all these patients died (19/25, 76%) (Fig. 4A) mainly because of a multiorgan failure (7/25, 28%), a complication of the cardiac (4/25, 16%) or respiratory (4/25, 16%) functions, or a severe episode of acidosis (3/25, 12%).

Some patients had a slightly milder outcome (group 2), with an infantile-onset encephalopathy mainly with DD (4/4, 100%), dystonia (4/4100%), visual dysfunction (4/4, 100%), Sp (3/4, 75%) and Sz (2/4, 50%). The clinical picture for group 2 is characterised by the lack of cardiac and respiratory involvement (Fig. 9A) [147,149].

The less severe phenotype is that of patients manifesting a childhood-onset progressive spinocerebellar ataxia (group 3), similar to *COQ8A* patients' clinical presentation [83,166,167]. After onset, during their childhood and adolescence, they developed ataxia (4/5, 80%), with deteriorated ambulation (5/5, 100%), ID (5/5, 100%), Sz (5/5, 100%), Sp (4/5, 80%), CAt (3/5, 60%), Dy (2/5, 40%), Dysdiadochokinesia (2/5, 40%), dysmetria (2/5, 40%), Tr (2/5, 40%), SLL (2/5, 40%), Ht (1/5, 20%) and PNSN (1/5, 20%).

9.4.2. Pathogenicity of the mutations

Among the 26 families, 22 *COQ4* pathogenic variants associated with primary CoQ deficiency have been reported in the literature (Figs. 7 and 9F). Nearly all of them were confirmed to segregate within the different families (18/22, 82%), except for the mutations c.402+1G > C and c.533G > A (p.Gly178Glu) where no data were available. The pathogenicity of some of the variants (6/22, 38%) was confirmed in a yeast model [83].

We classified the mutations into the three age-of-onset groups (Fig. 9F). Here, we will only discuss the most represented variants, which are the c.718C > T (p.Arg240Cys) mutation, found in 3 families; and 3 mutations identified in Chinese families, c.370G > A (p.Gly124Ser), c.402+1G > C and c.371G > T (p.Gly124Val).

Three families were diagnosed with the p.Arg240Cys missense change, in homozygosis (2/3) [144] or heterozygosis (1/3) with the nonsense variant p.Arg141* [83,171], and they all presented a fatal neonatal-onset encephalo-cardiomyopathy.

The p.Gly124Ser mutation has been described as a founder mutation in the southern Chinese population, and it has been found in 16 patients from 12 different families [147,149]. Most of them (13 patients from 9 families) were associated to the most severe phenotype (group 1), in homozygosis (8/13 patients) or heterozygosis (5/13 patients) with the probably spliceogenous variant c.402+1G > C in 4 of the cases [149]. This variant has a high probability of altering splicing, according to the SPiCE prediction software (Table 1). The remaining patients with the p.Gly124Ser mutation (3 patients from 3 families) were classified within the phenotypic group 2, in homozygosis (1/3 patients) or heterozygosis (2/3 patients) with c.371G > T (p.Gly124Val) variant [147,149]. These three pathogenic variants have all been described in patients with a neonatal-infantile onset encephalo-cardiomyopathy or an infancy-onset encephalopathy.

One patient with haploinsufficiency of *COQ4* due to a *de novo* heterozygous 3.9-Mb deletion of chromosome 9q34 presented encephalomyopathic manifestations and CoQ deficiency in fibroblasts [148].

All the 5 patients from 3 families with 3 different mutations in homozygosis (p.Pro64Ser, p.Thr77Ile and p.Gly55Val) [83,166,167] had a childhood-onset progressive spinocerebellar ataxia (group 3). These

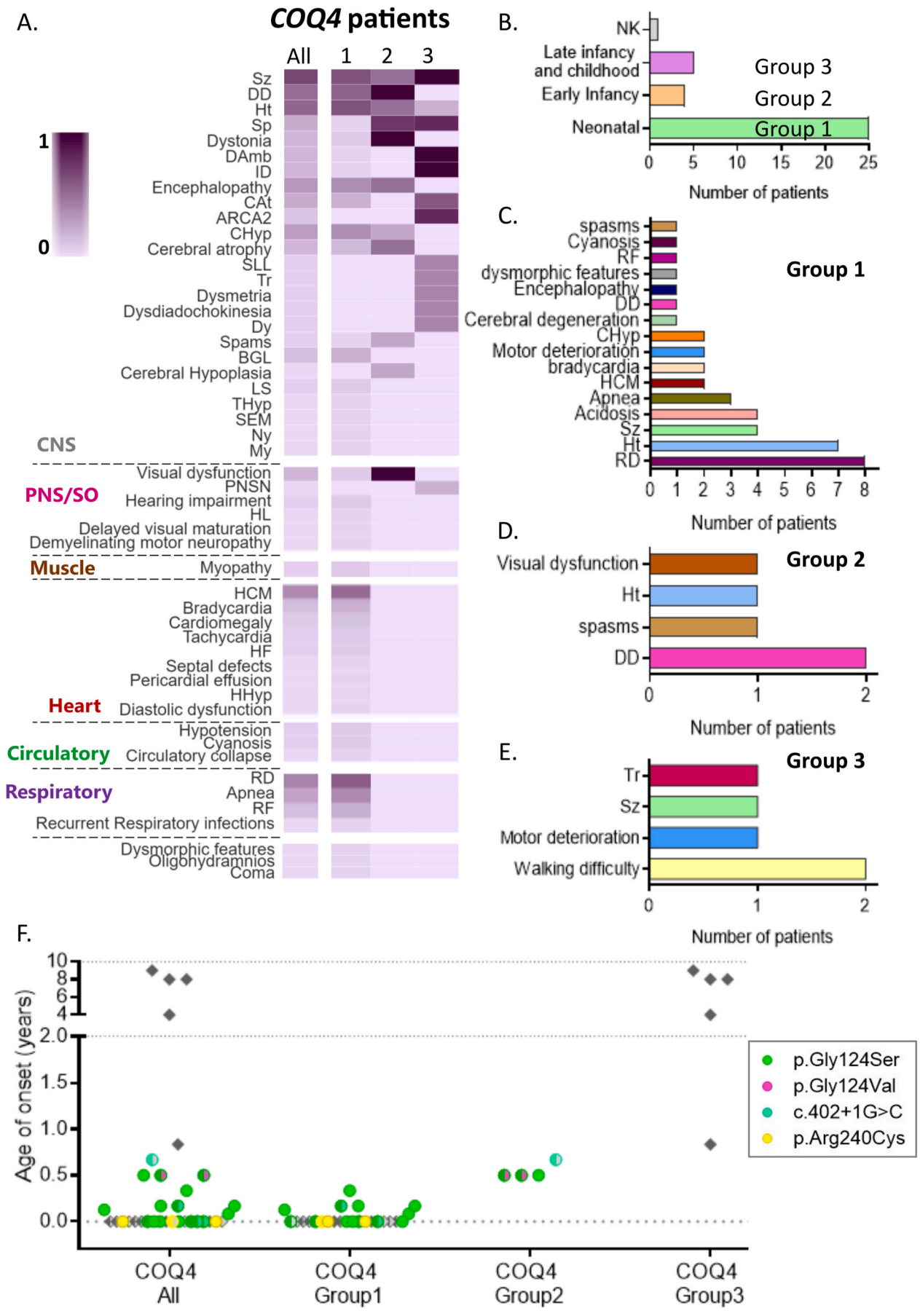

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Fig. 9. Clinical manifestations and genotype of *COQ4* patients. (A) Heatmap representing symptom frequency found in *COQ4* patients, for each age-of-onset group 1–3. (B) Total number of patients in each age-of-onset group. (C–E) Bar graphs represent the first symptoms the patients manifested at onset, and the number of patients manifesting them, for each age-of-onset group. (F) Age of onset and pathogenic variants of *COQ4* patients. Each point represents one patient. Coloured circles represent mutations found in more than one family (see the legend). Rhombus represent patients with mutations only present in one family (gray) or unknown mutations (black). Full-filled symbols represent homozygous mutations, half-filled ones design heterozygous mutations.

mutations could be considered less severe than the rest of the described *COQ4* mutations, but the number of cases is again too small to reach any sound conclusion.

Finally, there are some other variants (either in homozygous or heterozygous state) identified in patients belonging to the different groups. We have predicted they are pathogenic and classified them, but we cannot be certain of how they would contribute to the disease pathogenesis because of their low representation (Table 1).

9.5. *COQ5*

COQ5 gene (MIM*616359) encodes a methyltransferase required for the methylation of 2-polyprenyl-6-methoxy-1,4-benzoquinol ($DDMQH_2$) to get 2-polyprenyl-3-methyl-6-methoxy-1,4-benzoquinol ($DMQH_2$). Defects in this gene have been found to cause primary CoQ deficiency (COQ10D9, MIM#619028).

9.5.1. *CoQ deficiency due to COQ5 mutations*

Only 3 patients from 1 family with *COQ5* defects have been reported so far. These three female siblings presented varying degrees of an early childhood cerebellar ataxic phenotype similar to *COQ8A* patients [155] (Figs. 2 and 3). The first symptoms they manifested were a slow motor development (2/3) with ID (2), ataxia (1) or Dy (1). The age of the last examination was between 14 and 22 years old. They mainly presented cerebellar ataxia (3), encephalopathy (3), generalized tonic-clonic seizures (2), and cognitive disability (3) (Figs. 4B and 5E).

9.5.2. *Pathogenicity of the mutations*

The probands had a biallelic duplication of 9590 bp in the *COQ5* gene, spanning the last four exons of the gene (4–7) and part of the 3' UTR. This duplication creates an abnormal isoform due to an altered splicing event, where the original 3′UTR is partially deleted and fused with duplicated exons (exons 4–7), thus creating a new 3′UTR that appears abnormally long [155].

9.6. *COQ6*

The isoform 1 (or *a*) of the *COQ6* gene (MIM*614647) encodes an evolutionarily conserved FAD-dependent monooxygenase that is required for the C5-ring hydroxylation during CoQ biosynthesis. It catalyses the hydroxylation of 3-decaprenyl-4-hydroxybenzoic acid (HHB) to 3-decaprenyl-4,5-dihydroxybenzoic acid (DHHB) [48,67,68]. The electrons required for the hydroxylation reaction may be obtained indirectly from NADPH via a ferredoxin/ferredoxin reductase system [59]. There are two additional transcripts (isoforms 2 or *b*; and 3 or *c*), which are present at lower levels in cells and encode different proteins. Transcript variant 2 (1538 bp) contains an alternative first exon (exon 1b) and lacks exon 3. It is thought that it is not active [205]. Transcript variant 3 (1608 bp) differs from isoform 1 only for the first exon, but it does not rescue CoQ biosynthesis in human cells lacking *COQ6* [51]. Mutations in this gene are associated with autosomal recessive CoQ deficiency (COQ10D6, MIM#614650), which manifests as nephrotic syndrome with SNHL.

9.6.1. *CoQ deficiency due to COQ6 mutations*

30 patients from 22 families with *COQ6* pathogenic variants have been reported in the literature up to date. *COQ6* patients mainly showed a nephrotic syndrome (26/30, 87%), associated in most of the cases with SNHL (18/30, 60%) (Figs. 2 and 3).

9.6.1.1. *Age of onset.*

The disease was first presented in patients at a mean age of almost 3 yo (32 mo) (range 2 mo–10 yo) (Fig. 4B), with mostly infancy or childhood-onset (15/30, 50% and 11/30, 37%; respectively) (Fig. 10B). When classified by the age of onset, the cases were sorted into 2 different groups, each of them having a slightly different clinical picture (Figs. 6C and 10A).

Group 1 includes 15 patients from 11 families (15/30, 50% of the total number of *COQ6* patients), who first manifested before the age of 2 years old (mean age of onset of 1 yo, range 2 mo-2 yo). Patients with childhood-onset are grouped together in group 2, which includes 12 probands from 10 families (12/30, 40% of the total number of *COQ6* patients). The mean age of presentation was almost 5 yo (range 3–10 yo).

9.6.1.2. *Symptoms at onset.*

Patients with *COQ6* pathogenic variants mainly first presented with SRNS (24/30, 80%) [119,198], but in some cases, proteinuria (2/30, 7%), oedema (1/30, 3%), CKD (1/30, 3%), HT (1/30, 3%) or SNHL (1/30, 3%) were found as first manifestations of the disease (Figs. 5 and 10C and D).

When stratified by the age of onset, patients with infancy onset (group 1) mainly presented with SRNS (12/15, 80%), but some patients were first found having proteinuria (2/15, 13%) [119,203] or oedema (1/15, 7%) [211] (Fig. 10C). Patients with childhood-onset (group 2) presented with SRNS as the first symptom (11/12, 92%) [119,121,198]. Only one of them first showed SNHL (1/12, 8%), and did not develop SRNS afterwards [199] (Fig. 10D).

9.6.1.3. *Clinical manifestations of the disease.*

COQ6 patients mainly showed a nephrotic syndrome (26/30, 87%), associated in most of the cases with SNHL (18/30, 60%). Some of them also presented a CNS affection, with Sz (2/30, 7%), ataxia (1/30, 3%), exotropia (1/30, 3%), ID (1/30, 3%), Ny (1/30, 3%), or Pt (1/30, 3%). These neurological manifestations occur mostly in patients manifesting earlier in life (Fig. 10A).

Group 1 had an infantile-onset nephrotic syndrome (14/15, 93%) that evolved, in most of the cases, to an ESRD (10/15, 67%). These patients also developed SNHL (8/15, 53%) [119,121,198]. Some of the patients (7/15, 47%) also presented a CNS affection, with developmental delay (3/15, 20%) [119,179,211], Sz (2/15, 13%) [119], ataxia (1/15, 7%) [119], exotropia (1/15, 7%) [198], ID (1/15, 7%) [179], Ny (1/15, 7%) [198] or ptosis (1/15, 7%) [179]. Other less frequent manifestations are OA, MW, cardiovascular abnormalities, septal defects, oedema, dysmorphic features or hypercholesterolemia.

Patients with childhood-onset (group 2) had SRNS (11/12, 92%), associated with SNHL (8/12, 67%) [119,121,198,199]. Some of the patients developed an ESRD (6/12, 50%). Also cases of MW (1/12, 8%) or oedema (1/12, 8%) were reported.

9.6.2. *Pathogenicity of the mutations*

Primary CoQ deficiency due to *COQ6* mutations has been associated with 13 different variants in *COQ6* (Figs. 7 and 10E). Most of them were confirmed to correctly segregate within the different families (8/13, 62%). Their pathogenicity was predicted (Table 1), and confirmed in some cases (8/13, 62%) in a yeast model [193,205].

We classified the variants into the two age-of-onset groups. Only the most represented variants will be discussed here: c.189_191delGAA (p.Lys64del), c.763G > A (p.Gly255Arg), c.782C > T, (p.Pro261Leu), c.1058C > A (p.Ala353Asp) and c.1078C > T (p.Arg360Trp). Some of these variants appear more frequently in group 1, others in group 2,

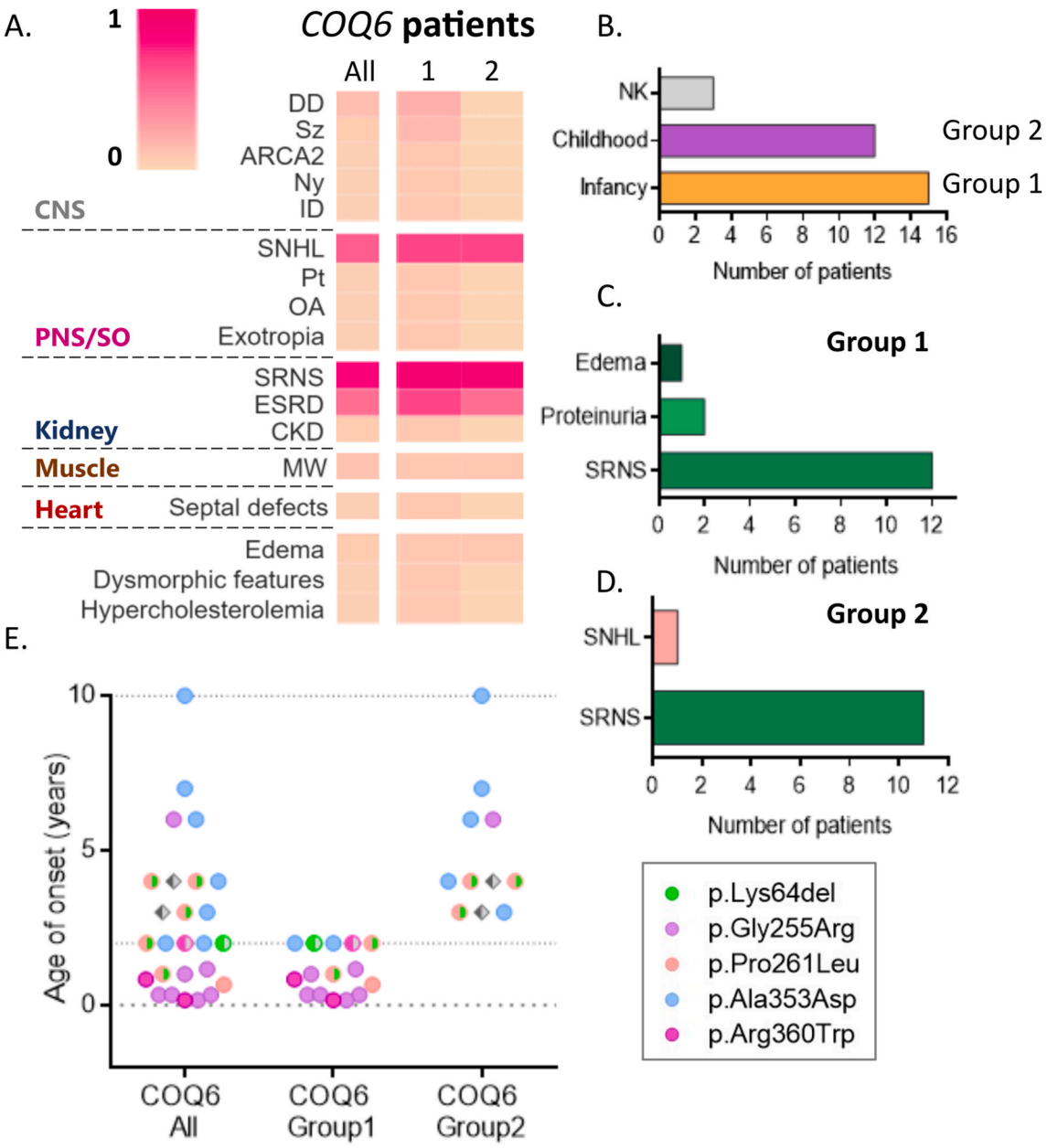

Fig. 10. Clinical manifestations and genotype of *COQ6* patients. (A) Heatmap representing symptom frequency found in *COQ6* patients, for each age-of-onset group 1 and 2. (B) Total number of patients in each age-of-onset group. (C–D) Bar graphs represent the first symptoms the patients manifested at onset, and the number of patients manifesting them, for each age-of-onset group. (E) Age-of-onset and pathogenic variants of *COQ6* patients. Each point represents one patient. Coloured circles represent mutations found in more than one family (see the legend). Rhombus represent patients with mutations only present in one family (gray) or unknown mutations (black). Full-filled symbols represent homozygous mutations, half-filled ones design heterozygous mutations.

while some of them are equally represented in the two age-on-onset groups (Fig. 11E).

The p.Gly255Arg missense change was found in 7 patients from 2 families, 6 of them classified in group 1 and only 1 in group 2 [119]. They presented an infantile-onset nephrotic syndrome with SNHL and a slight CNS involvement. Again, the number of cases is small to be able to define possible genotype-phenotype correlations. The pathogenicity of this mutation was confirmed in a yeast model [205], in which the mutant allele retained a low residual CoQ biosynthetic activity (only 15% of the WT levels).

The p.Arg360Trp substitution was reported in 3 patients of 3 different families, in homozygosis in 2 cases [179,211], and in heterozygosis with a frameshift mutation in the other [203]. This variant has been associated with the most severe phenotype (group 1), but the number of patients is still too low to be able to define a correlation.

The p.Ala353Asp variant was reported in 8 patients from 5 families, always in homozygosis. They were classified mostly in group 2 (6/8 patients) [119,121,199], while two patients belonged to group 1 (in the upper limit of group 1, being 2 years old) [119]. These patients mainly presented childhood-onset SRNS, associated with SNHL. The pathogenicity of this mutation was confirmed in a yeast model [205], in which the mutant allele retained 30% of the WT CoQ biosynthetic function.

The p.Lys64del variation is described in 6 patients from 6 different families, in heterozygosis with the missense mutations p.Pro261Leu (5/6) [193,198] or p.Gln229Pro (1/6) [198]. p.Pro261Leu was also found in homozygosis in 1 patient [193]. Patients with these mutations are equally found in group 1 or 2, so they might not contribute to the differences in age of onset or clinical presentation. However, the age of

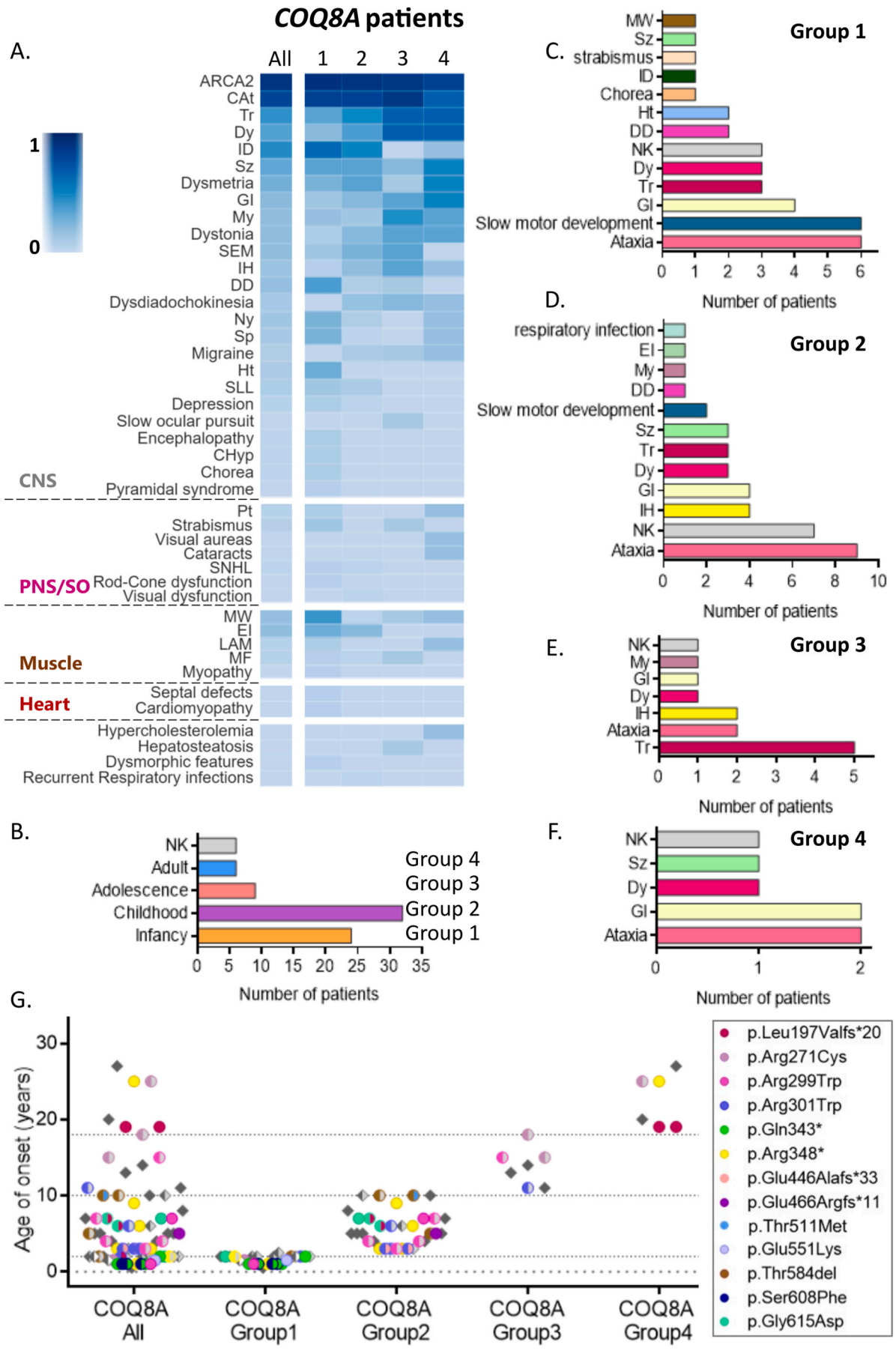

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Fig. 11. Clinical manifestations and genotype of *COQ8A* patients. (A) Heatmap representing symptom frequency found in patients, for each age-of-onset group 1–4. (B) Total number of patients in each age-of-onset group. (C–F) Bar graphs represent the first symptoms the patients manifested at onset, and the number of patients manifesting them, for each age-of-onset group. (G) Age-of-onset and pathogenic variants of *COQ8A* patients. Each point represents one patient. Coloured circles represent mutations found in more than one family (each mutation in a different colour, see the legend). Rhombus represent patients with mutations only present in one family (gray) or unknown mutations (black). Full-filled symbols represent homozygous mutations, half-filled ones design heterozygous mutations. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

presentation of these patients in group 1 is closer to the upper limit, 2 years old, while in group 2 it is closer to the lower limit, 3 years old. The pathogenicity of the p.Pro261Leu mutation was confirmed in a yeast model [193], in which the mutant allele retained a low residual CoQ biosynthetic function (only 10% of the WT levels).

Finally, there are some variants found in homozygosis or heterozygosis in patients belonging to the different groups, but it is still hard to infer how they could contribute to the disease pathogenesis because of their low representation.

9.7. COQ7

The *COQ7* gene (MIM*601683) encodes a mitochondrial di-iron oxidase responsible for hydroxylating 5-demethoxyubiquinol ($DMQH_2$) in the presence of NADH, during CoQ biosynthesis. Mutations in this gene are a cause of primary CoQ deficiency (COQ10D8, MIM#616733).

9.7.1. CoQ deficiency due to COQ7 mutations

Only 3 patients from 3 families with *COQ7* defects have been reported so far. These patients presented varying degrees of a neonatal-infancy onset multisystemic disorder, with CNS, PNS, renal, muscle and heart involvement (Figs. 2 and 3). The mean age of onset was 4 mo (range birth −1 yo), and they first presented with RD (2/3, 67%) and other symptoms, such as cardiomegaly, heart failure, HT, Ht or slow motor development (1/3, 33% for each symptom) (Figs. 4B and 5G). The main manifestations were Ht (3/3), DD (3/3), SNHL (3/3), PNSN (2/3), MW (3/3), HCM (2/3) and RD (2/3). However, the three families manifested different clinical pictures.

The most severe case was a Chinese patient, who presented at birth with cardiomegaly, heart failure and RD. He developed an encephalopathy with developmental delay, Ht, basal ganglia lesions and ptosis. He had SNHL and visual impairment, as well as renal cysts and MW, with low muscle bulk. The heart was also affected by an HCM, and he experienced HF. He passed away at 1 year of age due to an episode of sepsis. He had two compound heterozygous mutations in *COQ7*, a missense mutation (c.319C > T, p.Arg107Trp) and a frameshift variant (c.599_600delinsTAATGCATC, p.Lys200Ilefs*56) [162].

The second case was a Syrian patient who presented at birth, with Ht, RD and HT. The patient developed a complex clinical picture with multiorgan involvement, including mild ID, Ht, DD. He also had a PNSN, with SNHL and visual impairment. He had MW and HCM. Kidney dysplasia resolved alone within the first year of life. The age of the last examination was 9 years old. He had a missense homozygous mutation (c.422T > A, p.Val141Glu) in *COQ7* gene [140].

The third family presented a less severe phenotype. The patient, a 1-year-old girl, debuted with slow motor development and showed Sp, Ht and DD. She also presented a PNSN, with SNHL and MW. The age of the last examination was 6 years old. She had a missense homozygous mutation (c.332T > C, p.Leu111Pro) in the *COQ7* gene [141].

9.7.2. Pathogenicity of the mutations

Four pathogenic variants of *COQ7* have been associated with primary CoQ deficiency in the literature so far (Fig. 7). All the mutations were confirmed to correctly segregate in each family. The pathogenicity of the homozygous mutations from the two less severe cases was confirmed by expressing the variants in mouse cells KO in *Coq7*. The levels of residual CoQ synthesis were consistent with the severity of the disease observed in the patients. The missense mutation from the most severe case, c.319C > T (p.Arg107Trp), was predicted to be pathogenic with SIFT, PolyPhen and CADD tools (Table 1).

9.8. COQ9

The gene product of the *COQ9* gene (MIM*612837) is a lipid-binding protein thought to bind CoQ and present it to COQ7 during CoQ biosynthesis. Defects in this gene are a cause of CoQ deficiency (COQ10D5, MIM#614654).

9.8.1. CoQ deficiency due to COQ9 mutations

Only 7 patients from 4 families with *COQ9* mutations have been reported so far. These patients presented varying degrees of a severe neonatal-infancy onset multisystemic disorder, with CNS, renal and cardiac involvement [156–158,173,194]. The mean age of onset was 1 mo (range birth-9 mo) (Figs. 4B and 5H). COQ9 probands presented with intrauterine growth restriction (3/7, 43%), RD (2/7, 29%), poor respiratory efforts accompanied by Ht, bradycardia and cyanosis (1/7, 14%) or acute acidosis (1/7, 14%). Most of them had a profound DD (6/7, 86%), with encephalopathy (3/7, 43%), Sz (3/7, 43%), Ht (2/7, 29%) and LS (2/7, 29%), among others. In some cases, there was also renal involvement, with renal cysts (2/7, 29%) and tubulopathy (1/7, 14%). The heart was also affected with bradycardia (2/7, 29%), cardiomegaly (1/7, 14%) and HCM (1/7, 14%). Some patients presented RD (3/7, 43%) and apnea (2/7, 29%).

9.8.2. Pathogenicity of the mutations

There are 5 pathogenic variants of *COQ9* that have been described in the literature in patients with primary CoQ deficiency (Fig. 7). Among them, there are three intronic mutations, one frameshift and one nonsense mutation. All the mutations were confirmed to correctly segregate in the different families [157,158,194], except for the nonsense mutation, whose pathogenicity was confirmed biochemically and by heterologous expression of the variant in yeast [156]. All the variants were predicted to be pathogenic by CADD, and the three intronic mutations showed a high probability to affect splicing by *in silico* analysis (Table 1). The pathogenicity of one of these three was confirmed by rescuing the patient's fibroblasts with the expression of WT *COQ9* [194].

9.9. ADCK/COQ8 proteins

In humans there are five paralogs belonging to the aarF domain-containing protein kinase or UbiB protein kinase-like family (ADCK1-5); among them, COQ8A (ADCK3) and COQ8B (ADCK4) are highly similar, and both are involved in CoQ biosynthesis. Human COQ8A and COQ8B protein sequences have a 44.23% of identity and a 66.12% of similarity. COQ8A has a longer N-terminal region of 117 aa, while COQ8B has an extended C-terminal region of 18 aa. Both proteins contain a conserved kinase motif in the domain responsible for ATP binding and phosphotransfer reaction. Still, they lack the conserved kinase C-terminal motif, not having canonical protein kinase activity in trans. Instead, they have ATPase activity, whose role in CoQ biosynthesis still needs to be further studied [88]. They have also been proved to interact with lipid CoQ intermediates and are thought to have a regulatory function, probably redundant as each of them are specialised in different tissues. In humans, *COQ8A* expression exceeds *COQ8B* in

several tissues with the exception of kidney, in which *COQ8B* is highly expressed [88].

9.10. COQ8A

Defects in *COQ8A* gene (MIM*606980) are a cause of CoQ deficiency (COQ10D4, MIM#612016).

9.10.1. CoQ deficiency due to COQ8A mutations

77 patients from 55 families with *COQ8A* mutations have been reported so far. *COQ8A* patients have traditionally been diagnosed to have ARCA2 (70/77, 91%), a slowly progressive ataxic syndrome with CAt (62/77, 81%). After the elaboration of this study, a multicentre study of 59 *COQ8A* patients (39 novel) was published, aiming to establish genotype-phenotype correlations in this disease [118]. These patients are not included in this study, but the results will be discussed and compared.

9.10.1.1. Age of onset. The mean age of onset for COQ8A patients was 6.6 yo (range 6 mo–27 yo) (Fig. 4B), as it is mostly an infancy or childhood presentation (23/77, 30% and 29/77, 38%; respectively). When classified by the age of onset, *COQ8A* cases were sorted into 4 different groups (Figs. 6 and 11).

Group 1 includes 24 patients from 17 families (24/77, 31% of the total number of *COQ8A* patients), which are all infancy-onset cases. The mean age of onset of patients in this group is 1.6 yo (19 mo) (range 6 mo-2.5 yo). The majority of the *COQ8A* patients was classified in group 2, with 32 patients from 24 families (32/77, 42% of the total number of *COQ8A* patients) presenting the first signs of the disease during childhood (mean age of presentation of almost 6 yo, range 3–10 yo). Group 3 includes 9 patients from 8 families (9/77, 12% of the total number of *COQ8A* patients) who first manifested at a mean age of 14 yo (range 11–18 yo). 6 patients from 5 families with *COQ8A* mutations (group 4) presented when they were adults (6/77, 8% of the total number of COQ8A patients). This group of patients first manifested at a mean age of 22.5 yo (range 19–27 yo).

9.10.1.2. Symptoms at onset. Patients typically first presented with 1, 2 or 3 clinical manifestations (Figs. 5I and 11C-FF) including ataxia (19/77, 25%), gait instability (11/77, 14%), Tr (11/77, 14%), Dy (8/77, 10%) or slow motor development (8/77, 10%). Other less frequent symptoms at onset were IH (6/77, 8%), Sz (5/77, 6%), DD (3/77, 4%).

When stratified by age of onset, patients with infancy-onset (group 1) mainly first presented with slow motor development (6/24, 25%) and ataxia (6/24, 25%), but also with GI (4/24, 17%), Tr (3/24, 13%), Dy (3/24, 13%), DD (2/24, 8%) or Ht (2/24, 8%)) (Fig. 11C) [115,117,163,181,183–187,196,214]. Probands with childhood-onset (group 2) had ataxia (9/32, 28%), GI (4/32, 13%), IH (4/32, 13%), Dy (3/32, 9%), Tr (3/32, 9%), Sz (3/32, 9%) or slow motor development (2/32, 6%) as first symptoms (Fig. 11D) [117,122,138,175,176,180–184,186,187,215,216,231]. In the case of an adolescence-onset of the disease, the first symptoms were mainly Tr (5/9, 56%), ataxia (2/9, 22%), IH (2/9, 22%), myoclonus (1/9, 11%), GI (1/9, 11%) or Dy (1/9, 11%) (Fig. 11E) [117,138,175,176,185,186,216,217]. Some patients presented when they were adults with GI (2/6, 33%), gait ataxia (2/6, 33%), Dy (1/6, 17%) or Sz (1/6, 17%) (Fig. 11F) [117,138,176,185,230].

Ataxia, as the first symptom, is equally frequent in all disease onset groups. From this grouping, it is evident that impaired developmental and cognitive manifestations were more common when the disease manifested earlier. In contrast, Tr, gait instability, handwriting or speech difficulties become more frequent as first symptoms when the onset of the disease happens later in life (Fig. 11C–F).

9.10.1.3. Clinical manifestations of the disease. *COQ8A* deficiency results in an autosomal-recessive cerebellar ataxia type 2 (ARCA2) (70/77, 91%), a slowly progressive ataxic syndrome with cerebellar atrophy (62/77, 81%), with variable associated clinical features: intellectual deficiency (35/77, 45%), Tr (33/77, 43%), Dy (27/77, 35%), Sz (25/77, 32%) and EI (14/77, 18%), among others. The clinical severity of the disease varies with its age of onset, the earlier the disease appears, the more severe it becomes, as it can be clearly seen when patients are stratified by the age of onset (Fig. 11A).

Patients with the earliest onset (group 1) manifested an infantile-onset cerebellar ataxic syndrome with ID (15/24, 63%) and DD (9/24, 38%) [115,117,163,181,183–187,196,214]. Probands also had Tr (8/24, 33%), Ht (7/24, 29%), dysmetria (6/24, 25%), Sz (8/24, 33%), Sp (6/24, 25%) and Ny (6/24, 25%). Other less frequent manifestations were Dy (5/24, 21%), My (4/24, 17%), SLL (3/24, 13%), strabismus (3/24, 13%), GI (3/24, 13%) or SEM (3/23, 13%). Some of them had other systems and tissues affected, with MW (10/24, 42%), EI (7/24, 29%), SNHL (1/24, 4%) or cardiac abnormalities (2/24, 8%).

The majority of the *COQ8A* patients (group 2) presented a childhood-onset cerebellar ataxic syndrome with cognitive impairment (16/32, 50%), Tr (15/32, 47%) and speech difficulties (12/32, 38%) [117,122,138,175,176,180–184,186,187,215,216,231]. Dysmetria (11/32, 34%), Sz (11/32, 34%), SEM (8/32, 25%), GI (7/32, 22%) and dystonia (7/32, 22%) were also reported. Other less frequent manifestations in this group were IH (6/32, 19%), dysdiadochokinesia (5/32, 16%), My (4/32, 13%) or SLL (3/32, 9%). Other systems were also affected in some patients, exhibiting EI (7/32, 22%), MW (1/32, 3%), SNHL (1/32, 3%) or visual dysfunction (1/32, 3%).

Some patients (group 3) manifested an adolescence-onset cerebellar ataxic syndrome with Tr (6/9, 67%), speech difficulties (6/9, 67%) and myoclonus (4/9, 44%) [117,138,175,176,185,186,216,217]. They also manifested GI (3/9, 33%), IH (3/9, 33%), dystonia (3/9, 33%), SEM (3/9, 33%), Sz (2/9, 22%) and Dysdiadochokinesia (2/9, 22%). Some of them also suffered from MF (1/9, 11%) or MW (1/9, 11%). Other less frequent manifestations in this group were DD, dysmetria, migraine, strabismus, slow ocular pursuit or hepatosteatosis (1/9, 11% each).

A few patients (group 4) had an adult-onset cerebellar ataxic syndrome with Tr (4/6, 67%) and speech difficulties (4/6, 67%) [117,138,176,185,230]. These patients also manifested Sz (3/6, 50%), GI (3/6, 50%), dysmetria (3/6, 50%), dystonia (2/6, 33%) and My (2/6, 33%). Other less frequent manifestations reported in this group were IH, dysdiadochokinesia, migraine, ID, Ny, Pt, Sp, cataracts, visual aureas or MW (1/6, 17% each).

Generally, *COQ8A* patients had an ataxic syndrome with cerebellar atrophy, displaying multiple cerebellar and non-cerebellar features whose frequency varies when patients are stratified by the age of onset. Developmental delay and cognitive impairment are more frequent with the youngest ages of onset. Muscle or heart involvement is also more frequent in patients that had an earlier presentation. Other symptoms, such as dysarthria, dystonia, gait instability, myoclonus or Tr, become more frequent the later in life the disease manifests (Fig. 11A).

9.10.2. Pathogenicity of the mutations

There are almost 50 reported *COQ8A* pathogenic variants associated with primary CoQ deficiency (Figs. 7 and 11G). Approximately half of them were confirmed to correctly segregate within the different families (27/49, 55%), while the rest of the variants were mostly functionally evaluated through biochemical studies (by measuring CoQ levels) (29/49, 57%). The pathogenicity of some of the variations (7/49, 14%) was confirmed in a yeast model [184,186]. *In silico* predictions classified almost all of them as pathogenic (Table 1).

Only one variant, the c.993C > T, had a CADD score lower than the cut-off to be considered pathogenic (20). This variant was identified in a patient in *trans* with the c.1645G > A missense change, and it was shown to partially affect splicing, leading to an abnormal exon 8 skipping [186]. However, this variant showed an allelic frequency of approximately 1.6% with 38 homozygous individuals in the European non-Finnish population in the gnomAD population database (https

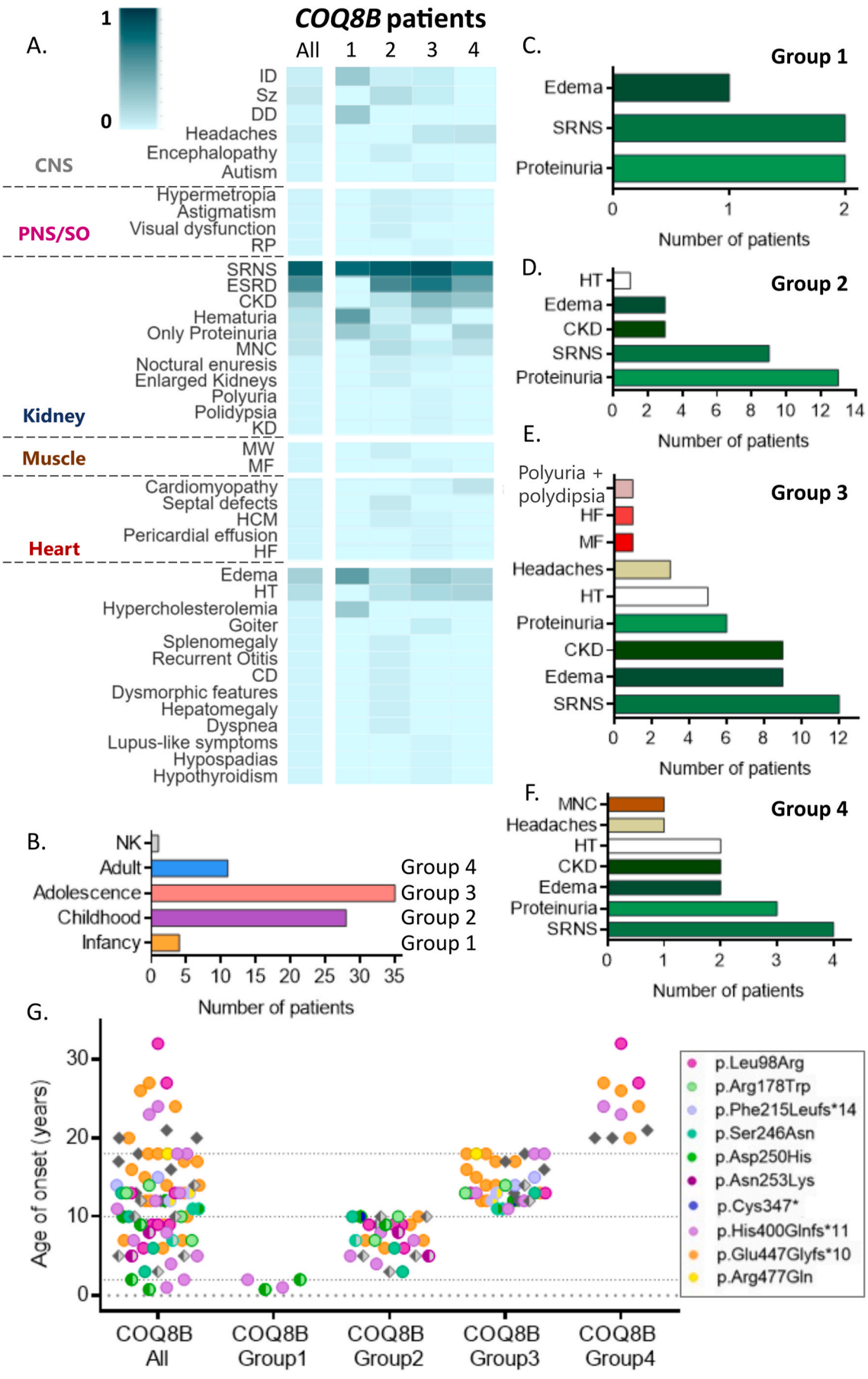

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Fig. 12. Clinical manifestations and genotype of COQ8B patients. (A) Heatmap representing symptom frequency found in patients, for each age-of-onset group 1–4. (B) Total number of patients in each age-of-onset group. (C–F) Bar graphs represent the first symptoms the patients manifested at onset, and the number of patients manifesting them, for each age-of-onset group. (G) Age of onset and pathogenic variants of *COQ8B* patients. Each point represents one patient. Coloured circles represent mutations found in more than one family (each mutation in a different colour, see the legend). Rhombus represent patients with mutations only present in one family (gray) or unknown mutations (black). Full-filled symbols represent homozygous mutations, half-filled ones design heterozygous mutations. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

://gnomad.broadinstitute.org/), and it is reported in the ClinVar database as likely benign. It is possible that this variant is a functional polymorphism that, when it appears in combination with other variants, may increase the susceptibility to develop a disease, but other studies are required to confirm this hypothesis.

We classified the variants in the 4 age-of-onset groups (Fig. 11G) and will only discuss the most represented variants.

The c.589-3C > G (p.Leu197Valfs*20) truncated allele in intron 3 was predicted as having a high probability of altering splicing by bioinformatics tools (Table 1). It was identified in 5 patients from 4 families; in heterozygosis with the p.Arg301Trp in one patient first presenting at 2 years of age (group 1) [187]; in heterozygosis with p.Gly615Asp mutation, in 2 families presenting during childhood (group 2) [138,187]; and in homozygosis in 2 sisters first presenting when they were 19 years old (group 4) [117]. It seems this splicing mutation is less severe when it is found in homozygosis, probably due to the pathogenicity of the mutation that accompanies it. The p.Gly615Asp variant was also found in homozygosis in a third family with 2 siblings, presenting at the age of 2 and 7 years old [117]. This mutation produces mainly a childhood-onset disease.

The c.895C > T (p.Arg299Trp) substitution was found in 7 patients from 5 families, having most of them a childhood-onset (group 2) (5 patients from 3 families) [117,181], but some of them with infancy (group 1) (1 patient) [181] or adolescence (group 3) (1 patient) onset [117].

The c.901C > T (p.Arg301Trp) change was described in 7 patients from 7 families. The majority of them (4) presented during childhood (group 2), in heterozygosis with the frameshift variant c.1331_1332insCACAG (p.Glu446Alafs*33) in 3 Italian families [138,187], and with a unique missense mutation (p.Arg410Gln) in one case [176]. Additionally, some of these patients had an infancy (group 1) (1 patient) [187] or adolescence (group 3) (1 patient) onset [175], having this variant in heterozygosis with other mutations.

The nonsense c.1027C > T (p.Gln343*) change was found in 6 patients from 3 families, all of them from Israel, with an infancy onset (group 1) [115]. In one family the mutation was homozygous, while in the other two, it was in compound heterozygosis with the p.Ser608Phe variant. A very similar nonsense mutation, c.1042C > T (p.Arg348*), was found in 8 patients from 5 families, mainly in homozygosis (5/8). Half of them presented during childhood [180,182], while some had infancy (group 1) (2 patients) [180], adult (group 4) (1 patient) [138] or unknown onset [176]. Due to *COQ8A* regulatory role and to the presence of at least another *COQ8* protein with a similar function, the lack of residual functional protein seems to be compatible with life.

The c.1750_1752delACC (p.Thr584del) deletion variant was found in 5 patients from 4 families, always in heterozygosis. 3 of them presented during childhood (group 2) [175,183,186], 1 of them at 2 years of age (group 1) [183] and the age of first presentation of the other patient is unknown [176].

Finally, there are some variants found in homozygous or heterozygous state in patients belonging to the different groups. We have classified them, but we cannot be certain of how they would contribute to the disease pathogenesis because of their low representation.

9.11. *COQ8B*

Defects in this *COQ8B* gene (MIM*615567) are a cause of nephrotic syndrome associated with primary CoQ deficiency (NPHS9, MIM#615573).

9.11.1. *CoQ deficiency due to COQ8B mutations*

79 patients from 41 families with *COQ8B* mutations have been reported until now. *COQ8B* deficiency typically leads to SRNS (65/79, 82%) with variable neurological involvement (13/79, 16.5%).

9.11.1.1. Age of onset. The general mean age of presentation was 12.5 yo (range 9 mo–32 yo) (Fig. 4B), as this is mostly a childhood or adolescent presentation (28/79, 35% and 35/79, 44%; respectively) (Fig. 12B). When classified by the age of onset, *COQ8B* cases were sorted in 4 different groups (Figs. 6E and 12).

Group 1 is the smallest one, including 4 patients from 4 families (4/79, 5% of the total number of *COQ8B* patients), who had an infancy-onset disease. The mean age of onset in this group is 1.4 yo (17 mo) (range 9 mo-2 yo). Group 2 includes 28 patients from 22 families (28/79, 35% of the total number of *COQ8B* patients) that manifested during childhood, at a mean age of 7.3 yo (range 3–10 yo). The majority of the *COQ8B* patients had an adolescent-onset (group 3), with 35 patients from 28 families (35/79, 44% of the total number of *COQ8B* patients). The mean age of presentation in this group was 14.3 yo (range 11–18 yo). Adult-onset is less frequent, with 11 patients from 10 families presenting after 20 years of age (group 4) (11/79, 14% of the total number of *COQ8B* patients). They manifested at a mean age of 24 yo (range 20–32 yo).

9.11.1.2. Symptoms at onset. COQ8B deficiency patients mainly presented with a renal manifestation (Figs. 5J and 12C–F). Patients typically present with SRNS (27/79, 34%), proteinuria (25/79, 32%), and to a lesser extent oedema (15/79, 19%), CKD (14/79, 18%), HT (8/79, 10%) or headaches (4/79, 5%). Early detection of proteinuria raised suspicion of a renal disease in many of them [195,204,232]. The majority of the patients first referred to the hospitals when they were suffering from nephrotic syndrome.

Patients with infancy-onset (group 1) mainly presented with proteinuria or SRNS (2/4 each, 50%), in one case with oedema (Fig. 12C) [120,139,188,208]. Childhood-onset (group 2) was mainly characterised by the detection of proteinuria upon scholar medical tests (13/28, 46%) [189,206–209], but also some other patients presented with SRNS (9/28, 32%) [120,139,189], oedema (3/28, 11%) [139,164,208], CKD (3/28, 11%) [139,189] or HT (1/28, 4%) [139,164] (Fig. 12D). The majority of the *COQ8B* patients had an adolescent-onset (group 3), mainly presenting with SRNS (12/35, 34%), CKD (9/35, 26%), oedema (9/35, 26%), proteinuria (6/35, 17%), HT (5/35, 14%) and headaches (3/35, 9%) [120,139,164,188,189,207,209]. Other less common adolescent-onset first symptoms were MF, heart failure and polydipsia plus polyuria (1/35, 3% each) (Fig. 12E). Adult-onset cases first manifested with SRNS (4/11, 36%), proteinuria (3/11, 27%), CKD (2/11, 18%), oedema (2/11, 18%), HT (2/11, 18%), MNC (1/11, 9%) and headaches (1/11, 9%) (Fig. 12F) [120,139,164,189].

SRNS as the first symptom is equally frequent in all disease onset groups for *COQ8B* cases. Early diagnosis was mainly characterised by the detection of proteinuria before the nephrotic syndrome was established. Oedema was found as the first manifestation in some cases, at any age of onset. Extrarenal symptoms as early symptoms were more common with a later onset of the disease. CKD or HT become more frequent as first symptoms when the beginning of the disease occurred later in life (Fig. 12C–F).

9.11.1.3. Clinical manifestations of the disease. *COQ8B* deficiency leads to a SRNS (65/79, 82%) with variable neurological involvement (13/79, 16.5%). Variable associated clinical features include oedema (16/79, 20%), HT (11/79, 14%), Sz (6/79, 8%), ID (4/79, 5%), headaches (4/79, 5%), HCM (2/79, 3%) or septal defects (2/79, 3%) (Fig. 12A).

Patients presenting the earliest (group 1) manifested an infantile-onset SRNS (3/4, 75%) with variable neurological involvement (2/4, 50%) [120,139,188,208]. They had oedema (2/4, 50%), developmental delay (1/4, 25%), ID (1/4, 25%) and hypercholesterolemia (1/4, 25%).

Childhood-onset patients (group 2) manifested SRNS (23/28, 82%) that progressed to an ESRD (17/28, 61%) in most of the cases [120,139,164,189,195,207–209]. Some of them also suffered from MNC (4/28, 14%), CKD (3/28, 11%), oedema (3/28, 11%), HT (3/28, 11%), Sz (4/28, 14%), encephalopathy (1/28, 4%), ID (1/28, 4%), HCM (1/28, 4%) or septal defects (2/28, 7%).

The majority of the *COQ8B* patients had an adolescence-onset (group 3) SRNS (31/35, 89%) that evolved to an ESRD in most of the cases (25/35, 71%) [120,139,164,188,189,207,209]. They had other renal affections, such as CKD (12/35, 34%), haematuria (5/35, 14%), MNC (2/35, 6%) or kidney dysfunction (1/35, 3%). Some of them also presented oedema (9/35, 26%), HT (6/35, 17%) or goiter (2/35, 6%). Some probands reported headaches (3/35, 9%), intellectual deficiency (2/35, 6%), Sz (2/35, 6%) or cardiac abnormalities (4/35, 11%).

Adult-onset is less frequent (group 4) (11/79, 14% of the total number of COQ8B patients). They presented an adult-onset SRNS (8/11, 73%) that evolved into an ESRD in some cases (5/11, 45%) [120,139,164,189]. They had other renal affections, such as CKD (3/11, 27%), MNC (1/11, 9%) or isolated proteinuria (2/11, 18%). Some of them also had oedema (2/11, 18%), HT (2/11, 18%) or dilated cardiomyopathy (1/11, 9%).

All these patients had SRNS, displaying multiple renal and some extrarenal features with variable frequency. Developmental delay and cognitive impairment are more frequent with the youngest ages of onset. Other symptoms, such as chronic kidney disease, HT or headaches, are more frequent the later in life the disease manifests itself (Fig. 12A).

9.11.2. Pathogenicity of the mutations

There are 24 reported *COQ8B* pathogenic variants (Figs. 7 and 12G). Most of these mutations were confirmed to be segregated on the different families (15/24, 63%). The pathogenicity of some of the mutations (8/24, 33%) was confirmed in a yeast model [139]. The molecular effect of other variations on the disease was not supported by any other evidence (8/24, 33%) than the *in silico* pathogenicity prediction, all of them being predicted pathogenic in the case of the missense variants, except for the p.Ala498Glu change, which was predicted as pathogenic by SIFT (0.03), but benign by Polyphen-2 (0.08). However, the integrated CADD score was above the threshold for pathogenicity, supporting a deleterious effect of this variant (Table 1).

We classified the variants into the 4 age-of-onset groups (Fig. 12G). We will only discuss the most represented variants.

The c.293T > G (p.Leu98Arg) was diagnosed in 8 patients from 4 unrelated families, all of them in homozygosis [164,189]. They mainly presented during late childhood (4/8), early adolescence (2/8) or adult age (2/8).

The c.532C > T (p.Arg178Trp) variant was found in 5 probands from 3 different families. When the mutation was in homozygosis, patients manifested between childhood (2/5) and adolescence (2/5) (7-14yo) [120,139,164], except for one case, in which it occurred in heterozygosis with the p.Asp250His variant, when the patient presented before 1 year of age [188].

This c.748G > C (p.Asp250His) substitution was present in 7 probands from 5 families. One homozygous patient also presented during infancy (2 yo), while his sister presented at 9 years old [208]. A heterozygous patient, with p.Ser246Asn mutation, presented when she was 11 years old [188], and two siblings with this variant in heterozygosis with the nonsense variant c.1041C > A (p.Cys347*) presented when they were 10 and 12 years old [209].

The c.737G > A (p.Ser246Asn) variant was identified in 7 patients from 6 families, the majority of them (4/7) presenting during childhood [206,207], while the rest (3/7) presented during early adolescence (11-13yo) [188,207].

The frameshift variants c.645delT (p.Phe215Leufs*14), c.1199dupA (p.His400Glnfs*11), and c.1339dupG (p.Glu447Glyfs*10) were respectively found in 4 patients from 3 families, 13 patients from 5 families and 20 patients from 7 families. All the patients with p.Phe215Leufs*14 allele presented during adolescence [120,139,164]. The c.1199dupA (p.His400Glnfs*11) was always found in homozygosis and patients presented in a wide range of ages, since infancy (2/13) to adulthood (2/13), but the majority of them presented during childhood (4/13) or adolescence (5/13) [120,139,164,189]. The c.1339dupG (p.Glu447Glyfs*10) variant was always found in homozygosis, and patients mainly presented during adolescence (11/20) [139,164,189]. Some probands with this mutation also presented during childhood (5/20) or when they were adults (4/20).

Finally, there are some variants found in homozygosis or heterozygosis in patients belonging to the different groups. We have classified them, but we cannot be sure of how they would contribute to the disease pathogenesis because of their low representation.

10. Discussion

As for other rare diseases, one of the main challenges clinicians face for the diagnosis of primary CoQ deficiencies is the still scarce information available. This mainly derives from the limited number of identified patients that prevents a more comprehensive analysis of the characteristic symptoms and natural history of the pathology. The current partial view and a probably complex aetiology of the disease hamper optimal management of primary CoQ deficiency patients. However, early diagnosis is of paramount importance since some patients could benefit from CoQ supplementation, limiting the extent of tissue damage and improving the disease course.

Heterogeneity of reported symptoms and the phenotypic pleiotropy observed in the up-to-now described patients are probably multicausal. On the one hand, the reduced number of available patients probably introduces a layer of variability due to their specific genetic background. Also, it is currently unknown how other factors different than the genetic ones would contribute to the disease. It is tempting to speculate that environmental factors, such as the nutritional status or the metabolic state of each organ and other stresses, could affect the development of the disease, its severity, and its outcome in every patient. On the other hand, malfunctioning of the various processes in which CoQ is involved, like pyrimidine biosynthesis or H_2S detoxification, probably differs depending on the specific tissue or system [27,128]. It seems that epigenetic factors are also important for the development of the disease and even for recovery after CoQ treatment [233]. Moreover, it is possible that all these above-mentioned factors may exert their modifying effects since the first stages of embryonic development [234]. Notably, it could even depend on each of the still-unknown roles of *COQ* genes during development or later, in different tissues or metabolic circumstances. It should also be considered that the heterogeneity and pleiotropic effect of decreased CoQ levels could have implications for ROS signalling, which is essential for the adequate mitochondrial physiology [127].

Next-generation sequencing has become a revolution for diagnosing rare genetic diseases, such as those in which the CoQ biosynthetic genes are affected. However, these technologies pose the problem of variant prioritization and interpretation. Furthermore, functional validation of candidate variants remains essential before a definitive link between the genetic variation and the disease can be established. The yeast model has been an instrumental one for this purpose since the expression of human proteins can recover growth in non-fermentable carbon sources [72,78,116,193,205]. More recently, the application of *in vitro* cell

culture, such as skin-derived fibroblasts, genome-edited cellular models (obtained by introducing or correcting specific variants, or generating knock-out models), or reprogrammed cells (such as induced pluripotent stem cells (iPSCs) or direct reprogrammed cells) has meant a breakthrough for the functional validation of new putative pathogenic variants [51,141,235].

Although new mutations are continuously described, the general picture of the disease is variable among patients and largely depends on the gene that is affected. Each *COQ* gene has a particular phenotypic spectrum of manifestations. However, even patients with pathogenic variants in the same gene can manifest differently in terms of clinical presentation, age of onset and course of the disease. Moreover, the low number of patients makes it difficult to visualise the specific manifestations and separate them from the effects of the differential genetic and epigenetic background. This fact, added to the high pleiotropy of the condition and the different set of symptoms, currently compromises the achievement of a complete genotype-phenotype correlation. This correlation would help to manage the disease at the clinical setting and foresee the severity of the disease in a given patient depending on the affected gene and the type of mutation. However, it should be noted that other factors may contribute to the phenotype establishment as additive variables to be considered for any correlations.

Efforts made on establishing such genotype-phenotype correlations have been challenging since the identification of the first patients. Important advances have been made since the first description in 1989 of a primary CoQ deficiency in two sisters with recurrent episodes of myoglobinuria and red-ragged fibres (RRF) and lipid storage in muscle biopsies, accompanied by encephalopathy and Sz [236]. After this first report, a growing number of patients with CoQ deficiency have been reported, presenting a wide range of symptoms. These clinical manifestations have been traditionally categorised into five groups: encephalomyopathy, cerebellar ataxia, severe infantile multisystemic disease, nephropathy, and isolated myopathy [108]. However, today this classification is thought to be outdated since the clinical picture of this syndrome has become much more complex. New cohorts of patients have been described, with a wider range of clinical manifestations sometimes overlapping between the already known phenotypic groups or even showing other combinations of phenotypes [51,109,237,238]. In fact, it now seems clear that isolated myopathy is rather associated with secondary deficiencies and not with primary ones [109]. Attempts to acquire an in-depth view of the disease linked to specific genes have been previously made. For example, for *COQ2* variants found in patients, the residual activity of the protein and therefore the CoQ levels are inversely related to the severity of the disease, as shown by expressing human COQ2 mutant proteins in a yeast model [116]. In the case of COA8A patients, multisystemic involvement was found more prevalently in missense than in biallelic loss-of-function variants, for which the most frequent phenotype was the isolated ataxia [118]. Currently, symptoms associated with primary CoQ deficiency have been proven to be broader and mainly affect central and peripheral nervous system, sensory organs, heart and kidney, although many others have also been less frequently reported.

Here, we present an exhaustive and complete study of all the up-to-date published cases of primary CoQ deficiency. Our aim was to show the frequency of the reported symptoms for each gene in a convenient format and to contribute to revealing specific features that could be generally considered to be characteristic for each of the *COQ* genes.

Interestingly, different clinical pictures emerge when patients harbouring mutations in each *COQ* gene are classified by the age-of-onset. In general, the earlier the disease manifests, the more severe it is. When specific mutations are also associated with the different age-of-onset groups, some variants seem to be more frequent in particular groups, especially for *COQ2* and *COQ6*. Some less evident associations can also be observed in *COQ4, COQ8A* and *COQ8B*. Instead, in the case of *PDSS2*, with fewer patients available, the picture is less clear.

Although clinical data reported in the literature may focus on specific issues and, thus, may be incomplete, a comprehensive analysis of the clinical manifestations observed in patients affected by primary CoQ deficiency may help clinicians to better understand this condition and, to increase its awareness, in order to improve the diagnostic yield. One of the main difficulties that arise when reviewing the literature for collecting clinical data is the heterogeneity in their description. For this reason, we propose to adopt the standardised HPO (human phenotype ontology) nomenclature for human phenotypic traits in a systematic way. In this way, all the community would have a uniform and understandable codification of symptoms. Also, bulk analysis could be performed more efficiently for a more meaningful overview of the disease.

As new patients are identified, the frequency of clinical manifestations associated with each *COQ* gene will certainly become more significant, thus helping to improve our understanding of the pathophysiology of primary CoQ deficiencies. Periodical reviews on the topic are very useful for clinicians and translational researchers involved in deciphering the pathogenesis of the disease at the molecular level. We have created an online platform that will be updated as new patients are identified. This tool, which offers an up-to-date frequency of clinical manifestations, will complement the diagnosis of new potential patients of primary CoQ, contributing to a *quasi*-real-time overview of state of the art for the diagnosis of primary CoQ deficiencies. Identifying specific variants of each gene that are grouped in early or later onset of the disease will also help clinicians to achieve a more efficient and earlier diagnosis that may improve the outcome of this pathology.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.freeradbiomed.2021.02.046.

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