Variation of the clinical spectrum and genotype-phenotype associations in Coenzyme Q10 deficiency associated glomerulopathy

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Primary Coenzyme Q10 deficiency is a rare mitochondriopathy with a wide spectrum of organ involvement, including steroid-resistant nephrotic syndrome mainly associated with disease-causing variants in the genes *COQ2*, *COQ6* or *COQ8B*. We performed a systematic literature review, PodoNet, mitoNET, and CCGKDD registries queries and an online survey, collecting comprehensive clinical and genetic data of 251 patients

spanning 173 published (47 updated) and 78 new cases. Kidney disease was first diagnosed at median age 1.0, 1.2 and 9.8 years in individuals with disease-causing variants in *COQ2, COQ6 and COQ8B*, respectively. Isolated kidney involvement at diagnosis occurred in 34% of *COQ2*, 10.8% of *COQ6* and 70.7% of *COQ8B* variant individuals. Classic infantile multiorgan involvement comprised 22% of the *COQ2* variant cohort while 47% of them developed neurological symptoms at median age 2.7 years. The association of steroid-resistant nephrotic syndrome and sensorineural hearing loss was confirmed as the distinctive phenotype of *COQ6* variants, with hearing impairment manifesting at average age three years. None of the patients with *COQ8B* variants, but 50% of patients with *COQ2* and *COQ6* variants progressed to kidney failure by age five. At adult age, kidney survival was equally poor (20-25%) across all disorders. A number of sequence variants, including putative local founder mutations, had divergent clinical presentations, in terms of onset age, kidney and non-kidney manifestations and kidney survival. Milder kidney phenotype was present in those with biallelic truncating variants within the *COQ8B* variant cohort. Thus, significant intra- and inter-familial phenotype variability was observed, suggesting both genetic and non-genetic modifiers of disease severity.

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Steroid-resistant nephrotic syndrome (SRNS) is one of the main causes of kidney failure in the first 2 decades of life.[1,2] More than 60 causative genes, encoding podocyte-associated proteins, have been identified, explaining the disease etiology in up to 30% of pediatric SRNS cases. Primary coenzyme Q10 (CoQ10, ubiquinone) deficiency is the underlying disease cause in 1%–2.7% of SRNS cases, and in up to 10% of those in whom a genetic cause is identified.[3,4] The term *primary CoQ10 deficiency* defines a group of rare mitochondrial disorders caused by recessive disease-causing variants in genes encoding proteins of the CoQ10 biosynthesis pathway. CoQ10 is a lipid component of the respiratory chain. Its deficiency leads to bioenergetic defects, H2S depletion, and oxidative stress in multiple cell types with a wide and variable spectrum of organ involvement and disease severity, ranging from single-organ disease to complex syndromic phenotypes. Defects of the podocyte lead to proteinuria and progressive loss of glomerular function. Among the 10 genes encoding proteins involved in CoQ10 biosynthesis, a kidney phenotype has mainly been associated with biallelic disease-causing variants in *COQ2*, *COQ6*, and *COQ8B* (previously referred to as *ADCK4*).[5–7] The CoQ10 deficiency–associated glomerulopathies are of particular interest as they are potentially amenable to therapeutic intervention with oral CoQ10 supplementation, through targeting of the underlying molecular defect. Up to now, the rarity of the primary CoQ10 deficiency disorders has limited the assessment of their spectrum of clinical presentation, their genotype–phenotype correlation, and their natural history. To advance the state of knowledge, we systematically reviewed 251 (173 published and 78 previously unreported) cases of CoQ10 deficiency–associated glomerulopathy.

METHODS

Data collection

A comprehensive search strategy was applied to compile the study cohort from different sources (for details, see Figure 1). A systematic search of the PubMed database yielded 44 published articles with 174 patients. Three patient registries were queried: the international PodoNet registry[8] for children with primary steroid-resistant nephrotic syndrome,[3] the Chinese Children Genetic Kidney Disease Database[9] (CCGKDD); and the German Network for Mitochondrial Disorders (mitoNET[10]).[11] A total of 20, 17, and 7 new cases, respectively, were identified in these registries, and updated information was provided on 20,13, and 2 previously published cases.

Finally, invitations to an online survey were sent to all members of the European Rare Kidney Disease Network (ERKNet), the PodoNet Consortium, the ESCAPE Clinical Research Network, and the European and Asian Societies for Pediatric Nephrology (ESPN and AsPN). Through this effort, 34 novel and 32 previously published patients, in 24 countries, were identified and documented.

All patient-related data were collected in a completely deidentified manner. Names, initials, birth dates, and hospital-specific patient identifiers were not retrieved. Center identifiers were deleted from the database after checking for duplicate entries was completed, and only the country or residence was retained for demographic studies. Also, times and ages (e.g., age at diagnosis, time since diagnosis) were reported instead of calendar dates. As a result of these measures, all analyses were performed on completely anonymized datasets.

Verification and unification of genetic diagnoses

All molecular diagnoses were re-evaluated by an expert geneticist, following the best practice recommendations of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) for the interpretation of sequence variants.[12] Variants classified as (likely) pathogenetic, per ACMG criteria, were considered causative and were included in the study. Two *COQ2* variants with conflicting interpretations of pathogenicity according to the ClinVar database—namely *NM_015697.8:c.288dupC [rs759310292]* and *c.683A>G [rs121918232]*—were considered disease-causing due to their increased prevalence among affected individuals, compared to that among the general population, their presence in *trans* with another (likely) pathogenic variant in patients with highly specific phenotype, and the absence of homozygous cases in control databases. A previously published case with a homozygous *COQ6 NM_182476.3:c.41G>A [rs17094161]* variant was excluded from the analysis, as the variant was reclassified as benign because it is relatively frequent, is also in a homozygous state, in general populations, has been reported as benign in the CliniVar database, and is located

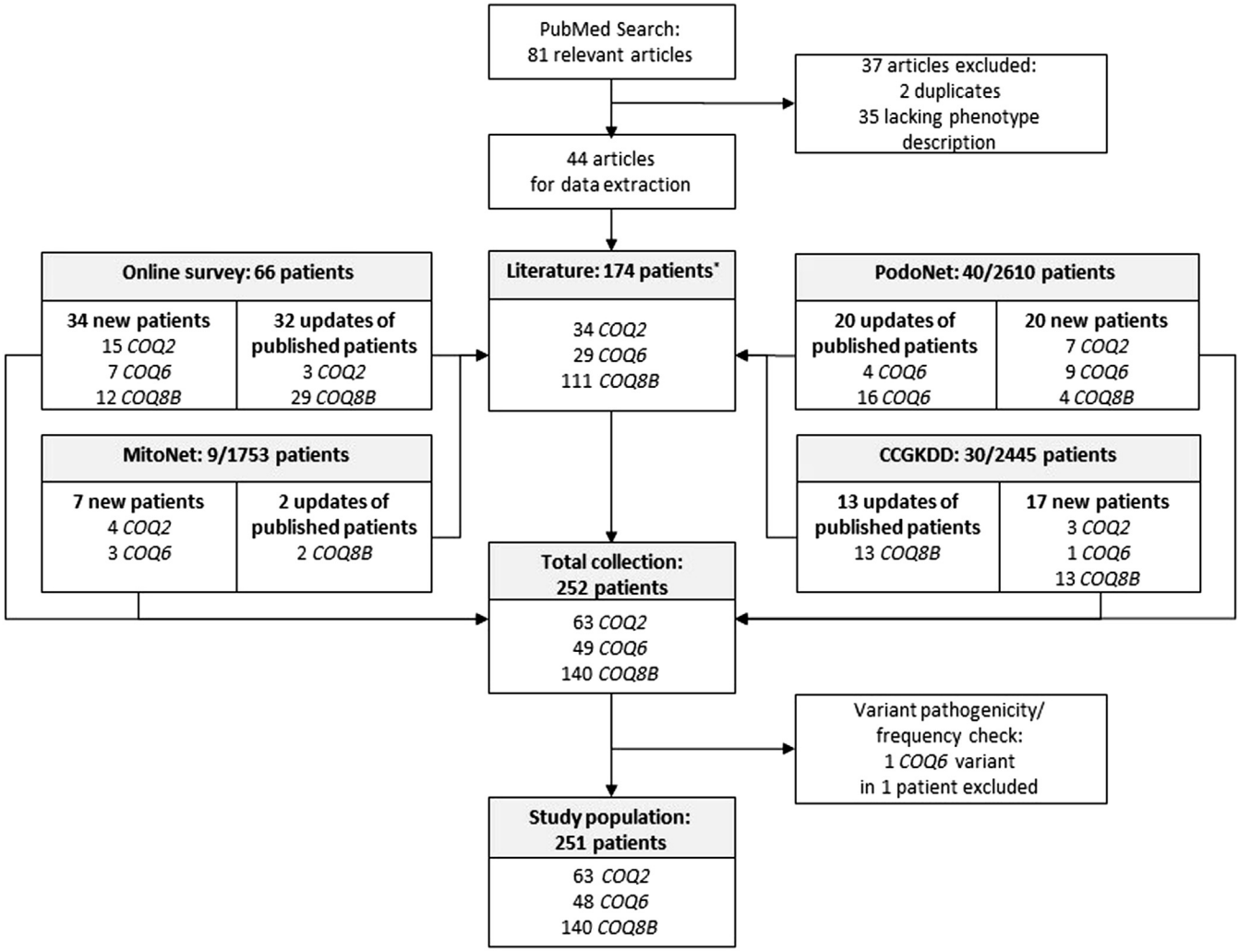


Figure 1 | Schematic representation of case selection process. CCGKDD, Chinese Children Genetic Kidney Disease Database[9]; mitoNET[10]; PodoNet.[8]

upstream of the standard start codon of the canonical isoform of the gene.

Statistical analysis

Descriptive data are presented as median and interquartile range. Patient and kidney survival rates were calculated using Kaplan–Meier lifetable analysis, with log–rank testing for analysis of significant differences. Fisher's exact test was performed for genotype-based pairwise comparisons, with 2 × 2 and 2 × 3 contingency tables of dichotomized data. Intra- and interfamilial phenotype variability was assessed by the coefficient of variation (CV = SD/mean) of the age at kidney-disease onset.

A value of $P < 0.05$ was considered statistically significant. Statistical analyses were performed using Prism, version 8, data analysis software system (GraphPad Software).

RESULTS

Clinical data were available for 63, 48, and 140 patients with disease-causing variants in *COQ2*, *COQ6*, and *COQ8B*, respectively. A summary of the phenotype characteristics and clinical outcomes per genetic diagnosis is given in Table 1. Patient-level genotype and phenotype characteristics are provided in Supplementary Table S1.

Mortality

Patient survival was markedly compromised with *COQ2* deficiency (Table 1), with 77.3% (95% confidence interval [CI], 67.8%–84.2%) of patients being alive at 1 year of age, and 69.9% (95% CI, 55.1%–80.6%) being alive at 10 years of age. Ten-year survival from birth was 90.8% (95% CI, 67.7%–97.6%) for *COQ6*, and 99.2% (95% CI, 94.7%–99.8%) for *COQ8B* disease ($P < 0.0001$; Figure 2). The leading cause of death in *COQ2* disease patients was severe multisystemic involvement leading to multiorgan failure ($n = 13$) or progressive neurologic deterioration ($n = 2$). In patients with *COQ6* and *COQ8B*, disease sepsis was the most common cause of death.

Kidney phenotypes

The age at disease onset differed markedly depending on the gene involved. Whereas 50% of the *COQ2* and *COQ6* cohort manifested first symptoms of kidney disease within the first

Table 1 | Patient characteristics and clinical outcomes

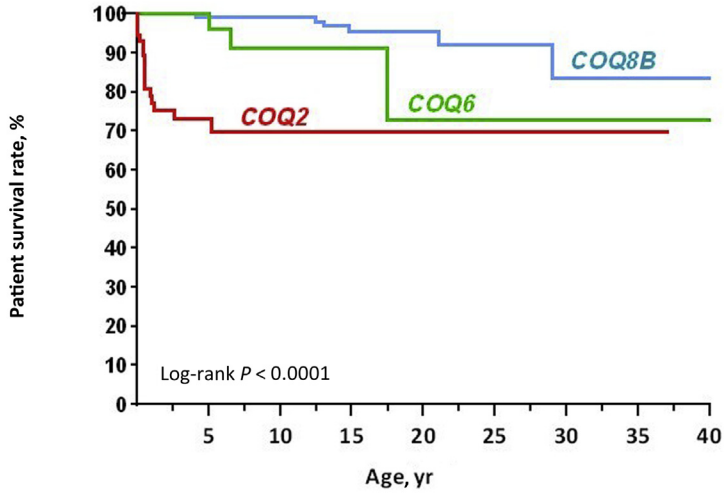
Patient characteristic	*COQ2*	*COQ6*	*COQ8B*
Total number of patients (females)	63 (30)	48 (16)	140 (65)
First disease manifestation			
Age at first symptoms, yr	1 (0.3–2)	1.2 (0.6–3.4)	9.8 (5–15)
Kidney involvement	93.6 (59/63)	97.9 (47/48)	100 (140/140)
Kidney disease presentation			
Age at first kidney disease manifestation, yr	1 (0.5–2)	2 (0.9–4.5)	9.9 (5.3–14.4)
Nephrotic range proteinuria	85.7 (36/42)	86.1 (31/36)	71.7 (86/120)
Non–nephrotic range proteinuria	14.3 (6/42)	13.9 (5/36)	28.3 (34/120)
Asymptomatic proteinuria	0 (0/63)	18.7 (9/48)	23.6 (33/140)
Hypertension	28.6 (12/42)	21 (4/19)	39 (32/82)
Oedema	86.6 (39/45)	47.8 (11/23)	40.2 (33/82)
Microhematuria	6.8 (4/59)	8.5 (4/47)	18 (13/72)
CKD stage 1	71.8 (23/32)	42.1 (8/19)	34.3(35/102)
CKD stage 2–4	18.7 (6/32)	36.8 (7/19)	32.3 (33/102)
ESKD	9.4 (3/32)	21 (4/19)	33.3 (34/102)
Renal histopathologic findings			
FSGS	69.4 (25/36)	72.2 (26/36)	77.1 (64/83)
FSGS, not otherwise specified	76 (19/25)	88.4 (23/26)	89 (57/64)
FSGS, collapsing subtype	24 (6/25)	11.5 (3/26)	9.4 (6/64)
FSGS, tip-lesion	0 (0/25)	0 (0/26)	1.5 (1/64)
Global glomerulosclerosis	11.1 (4/36)	8.3 (3/36)	15.6 (13/83)
Mesangioproliferative glomerulonephritis	11.1 (4/36)	5.6 (2/36)	7.2 (6/83)
Minimal change disease	5.6 (2/36)	5.6 (2/36)	0 (0/83)
Dysmorphic mitochondria	30.5 (11/36)	25 (9/36)	10.8 (9/83)
Extrarenal features			
Any extrarenal involvement	77.9 (46/59)	89.1 (41/46)	29.3 (41/140)
Intrauterine abnormalities/preterm delivery	13.6 (8/59)	2.2 (1/46)	0.7 (1/140)
Infantile multisystemic disease/multi-organ failure	22 (13/59)	0 (0/46)	0 (0/140)
Neurologic findings	47 (28/59)	21.7 (10/46)	12.1 (17/140)
Encephalopathy/seizures	42 (25/59)	8.7 (4/46)	7.1 (10/140)
Developmental delay/cognitive impairment	5 (3/59)	13 (6/46)	5 (7/140)
Retinopathy/ocular abnormalities	20.3 (12/59)	17.4 (8/46)	5 (7/140)
Hearing abnormalities	1.7 (1/59)	73.9 (34/46)	0 (0/140)
Myopathy	20.3 (12/59)	8.7 (4/46)	0 (0/140)
Cardiovascular abnormalities	15.2 (9/59)	8.7 (4/46)	7.1 (10/140)
Liver dysfunction	13.6 (8/59)	2.2 (1/46)	0 (0/140)
Growth retardation	11.8 (7/59)	8.7 (4/46)	3.6 (5/140)
Facial/body dysmorphisms	3.4 (2/59)	4.3 (2/46)	1.4 (2/140)
Clinical outcome (status at last follow-up)			
Median follow-up time, yr	1.5 (0.3–4.5)	1.7 (0–5.4)	3.9 (1.3–6.9)
Deceased	25.4 (16/63)	10.4 (5/48)	4.3 (6/140)
Median age at death, yr	0.5 (0.3–0.9)	6.5 (5.7–12)	13.9 (12.6–19.5)
Survival rate at age 1 yr, %	77.2	100	100
Survival rate at age 10 yr, %	69.9	90.8	99.2
ESKD	50.8 (32/63)	56.2 (27/48)	66.4 (93/140)
Median age at ESKD, yr	2.5 (0.7–5.8)	3.4 (1.7–6.3)	13 (10–16.7)
Median time from first manifestation to ESKD, yr	0.5 (0–1.6)	1.0 (0.3–2.1)	1.0 (0–4.2)
Probability of ESKD at age 5 yr, %	47.6	47.8	3.1
Probability of ESKD at age 18 yr, %	80.8	72.3	74.2
Kidney transplantation	26.9 (17/63)	29.2 (14/48)	26.4 (37/140)
Median age at kidney transplantation, yr	8.3 (5.2–17.2)	6.4 (5.1–7.5)	15.1 (11–16)

CKD, chronic kidney disease; ESKD, end-stage kidney disease; FSGS, focal segmental glomerulosclerosis.
Values are % (number of affected patients/informative number of patients) or median (interquartile range), as appropriate.

15 months of life, and 85% were symptomatic at 3 and 5 years of age, respectively, 50% of *COQ8B* disease patients remained asymptomatic until age 9 years (Figure 3a). A total of 14.3% of all patients presented kidney disease beyond 16 years of age.

The oldest documented ages at kidney disease diagnosis were 11.6 years, 27 years, and 32.2 years in patients with *COQ6*-, *COQ2*-, and *COQ8B*-related disease, respectively. Isolated kidney involvement at diagnosis was found in 34% of the *COQ2* cohort, 10.8% of the *COQ6* cohort, and 70.7% of the *COQ8B* cohort.

Kidney involvement was observed in 98% (246 of 251) of patients (Figure 3b). In 4 of 63 children with *COQ2* disease, no kidney manifestations were reported; 3 were deceased within the first 6 months of life. Additionally, 1 of 48 with confirmed *COQ6* disease, a subject diagnosed by family screening at 10 years of age, presented with hearing impairment but still had no renal symptoms at last observation at



Number at risk	Time, yr				
	0	5	10	20	30
COQ2	54	23	17	10	4
COQ6	32	24	12	4	3
COQ8B	140	135	115	29	10
Total	226	182	144	43	17

Figure 2 | Overall survival of patients with biallelic causative variants in (red) *COQ2*, (green) *COQ6*, and (blue) *COQ8B*.

age 17 years. With the term end-stage kidney disease (ESKD), we identified patients with a glomerular filtration rate <15/ml per 1.73 m^2 (chronic kidney disease [CKD] stage 5, as delineated by Kidney Disease: Improving Global Outcomes [KDIGO]).

Nephrotic-range proteinuria was reported in 85.7% of the *COQ2* disease patients, 86.1% of the *COQ6* disease patients, and 71.7% of the *COQ8B* disease patients. Although the *COQ2* group typically presented with edema and hypertension but normal kidney function, nearly 40% of children with *COQ6* disease presented with mild-to-moderate CKD (CKD 2–4), and up to 20% presented with ESKD (CKD 5) at the time of diagnosis. Children with *COQ8B* disease presented with the most-advanced CKD, with one third already in ESKD at the time of diagnosis. Notably, asymptomatic proteinuria was present in 18.7% and 23.6% of children with *COQ6* and *COQ8B* disease, respectively, including a few younger siblings of index cases (2 of 9 with *COQ6* disease and 5 of 33 with *COQ8B* disease). Concomitant hematuria was reported at diagnosis in only 6.8% and 8.5%, respectively, of *COQ2* and *COQ6* disease patients, but in 18% of the *COQ8B* cohort.

Kidney biopsy was performed in 155 patients (61.7%). Focal segmental glomerulosclerosis accounted for 74.2% of the histopathologic diagnoses. Among those patients with focal segmental glomerulosclerosis in whom a specific subtype was reported, 94% displayed collapsing variant and 6% displayed tip lesions. Dysmorphic mitochondria were observed in 80.5% of biopsies in which electron microscopy results were reported (18.7% of all biopsies), namely in 30% of the *COQ2* cohort, 25% of the *COQ6* cohort, and 10% of the *COQ8B* cohort patients. In 3 cases, mitochondrial abnormalities identified by electron microscopy of kidney tissue led to the diagnosis of a mitochondriopathy prior to genetic testing.

Approximately 60% of individuals progressed to ESKD during follow-up (Table 1). Although the *COQ2* and *COQ6* cohorts tended to progress faster than the *COQ8B* cohort in the first decade of life, *COQ8B* disease patients were more likely to develop ESKD in the second decade (Figure 4). Interestingly, for all 3 groups, a significant probability of ESKD persists beyond 25 years of age. Overall, 70 surviving patients were on dialysis at last observation (7 in the *COQ2* cohort, 8 in the *COQ6* cohort, and 55 in the *COQ8B* cohort), and 68 had received a kidney transplant. Disease recurrence in the allograft was never observed.

Extrarenal manifestations

Extrarenal disease manifestations were most frequent and severe in the *COQ2* cohorts and least common in *COQ8B* disease (Table 1; Figure 3). Neurologic manifestations occurred in 47% of the *COQ2* cohort patients (60.8% of patients with extrarenal manifestations); these included encephalopathy, ataxia, seizures, nystagmus, and any degree of psychomotor delay or intellectual disability. Although neurologic symptoms manifested within the first 3 years of

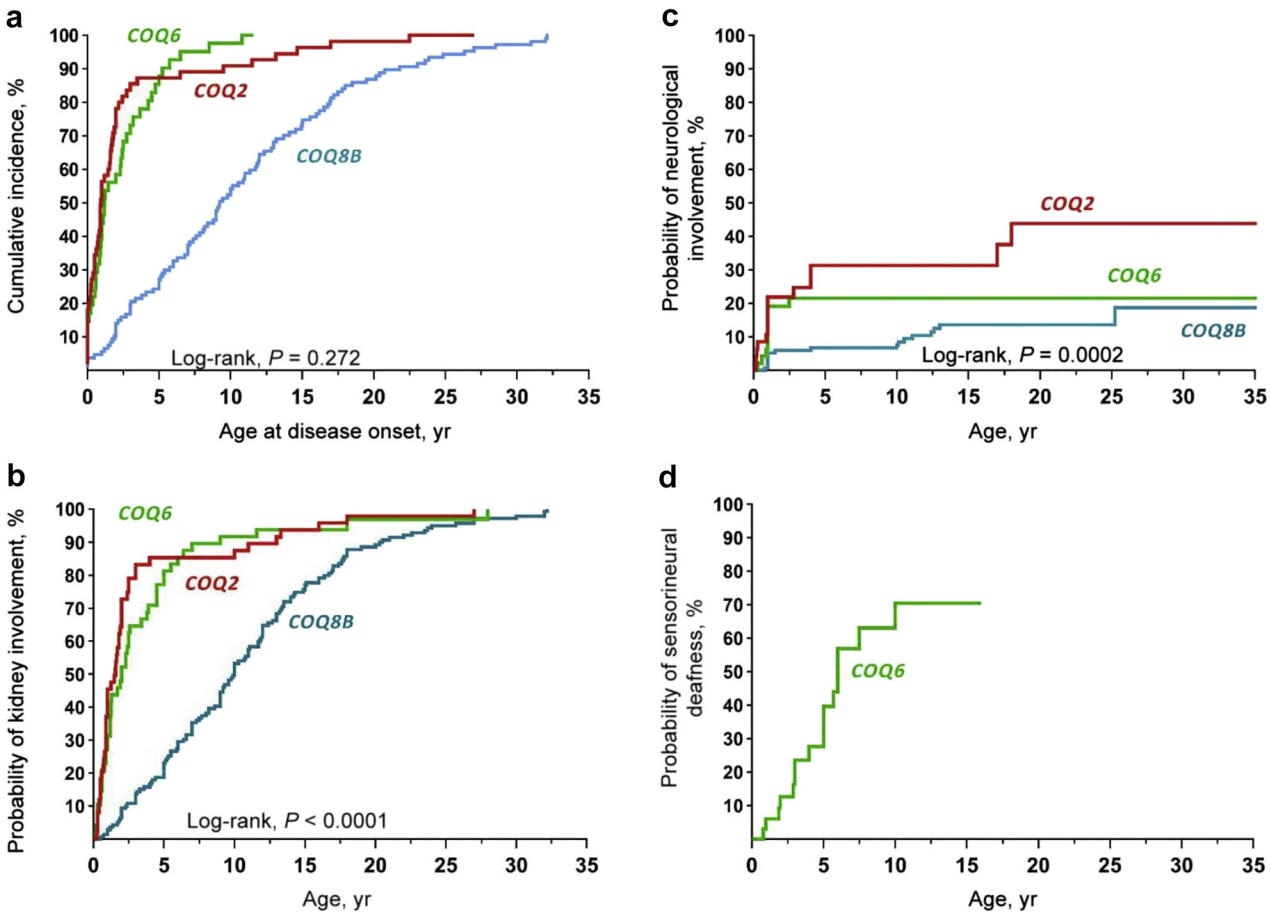


Figure 3 | (a) Incidence of disease manifestations (any clinical symptoms*); (b) probability of kidney disease onset; (c) probability of neurologic disease onset; (d) probability of sensorineural deafness (SND) onset in patients with biallelic causative variants in (red) *COQ2*, (green) *COQ6*, and (blue) *COQ8B*. *First symptoms related to coenzyme Q10 deficiency (i.e., kidney disease/neurological disease/sensory organs disease/myopathy/cardiomyopathy).

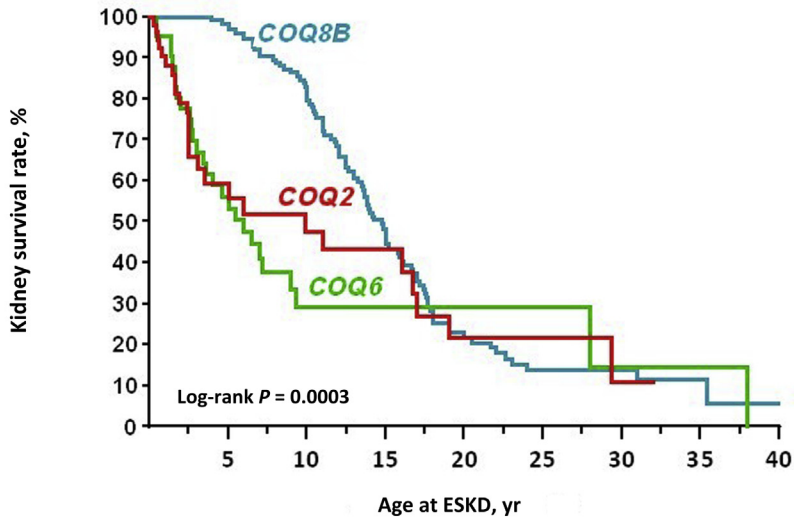
life in 87% of patients (Figure 3c), 2 subjects showed late-onset symptoms—that is, headache with phono- and photophobia at 17 years, and myoclonic epilepsy at 18 years. Neuroimaging revealed a wide spectrum of abnormalities, including cerebral or cerebellar cortical atrophy, stroke-like lesions, basal ganglia involvement, hemorrhage (1 of 42), and intracranial calcifications (1 of 42). Thirteen *COQ2* disease cases (20.6%) were characterized by severe infantile multiorgan disease, encompassing some degree of encephalopathy, myopathy, cardiomyopathy, retinopathy, and/or metabolic disorders (hyperlactatemia and/or diabetes mellitus), which led to rapidly progressive clinical deterioration and death at a median age of 6 months. In contrast to these severe courses, 22 patients (34%) were reported as not showing any extrarenal symptoms at the time of diagnosis. However, extrarenal symptoms developed in 9 of 22 patients with initially isolated kidney disease—specifically, in 6 patients within 3 years, and in a further 3 patients after up to 20 years of follow-up.

The association of SRNS and sensorineural hearing loss was confirmed as the distinct phenotype of *COQ6* disease. Hearing impairment was present in 73.9% (34 of 48) of the *COQ6* cohort, but in only one child with *COQ2*, and in none of those with *COQ8B* disease. Among *COQ6* disease patients, 4 cases had congenital deafness and 19 (19.6%) showed later-onset sensorineural hearing loss, with a median age at diagnosis of 5 years (interquartile range: 2.9–6 years; Figure 3d). In 11 patients (24%), hearing loss preceded the onset of renal symptoms. Almost a quarter of the *COQ6* cohort showed other neurologic abnormalities, namely seizures and/or cognitive impairment; severe encephalopathy was reported in one case. If present, neurologic symptoms usually occurred within the first 2 years of life (Figure 3c).

Individuals with *COQ8B* disease showed a much milder extrarenal phenotype; the most common findings were neurologic abnormalities (12.1%), including mostly moderate neurocognitive impairment, developmental delay, and seizures.

Genetic characteristics

A total of 39 (21 novel, hitherto unreported as [likely] pathogenic) different variants in *COQ2*, 16 (5 novel) variants plus one deletion encompassing the entire gene sequence in



Number at risk	Time, yr				
	0	5	10	20	30
COQ2	58	17	11	4	1
COQ6	42	20	10	2	1
COQ8B	134	127	98	19	7
Total	234	164	119	25	9

Figure 4 | End-stage kidney disease (ESKD)–free survival of patients with causative variants in (red) *COQ2*, (green) *COQ6*, and (blue) *COQ8B*.

COQ6, and 40 variants (8 novel) in *COQ8B* were identified (Figure 5a–c; Supplementary Table S2).

For *COQ2*, the detected variants were distributed randomly throughout the coding sequence of the gene. By contrast, all *COQ6* missense variants clustered to 2 gene regions coding fragments involved directly in the binding of oxidized flavin adenine dinucleotide (FAD) (residues 194–300 and 340–425; NP_872282.1; Figure 5b). For *COQ8B*, 3 hotspot regions were recognized: residues 147–154 (loop between GQα1 and GQα2 helices), 174–184 (GQα3 helix), and 246–253 (GQα5 helix); NP_079152.3; Figure 5c (helices nomenclature according to Stefely *et al.*[13] The 2 former are also frequently mutated in the twin protein COQ8A,[14] whereas the variants located in the latter (GQα5) are specific for COQ8B. See Supplementary Material S1 and Supplementary Movie S1 for further COQ8B structural characteristics.

The geographical clustering of the recurrent variants to certain regions suggests founder effects in several populations (Figure 5d).

Genotype–phenotype correlations

Impact of genotype and relatedness on disease course. Intra- and interfamilial phenotype variability was globally assessed for variants identified in at least 2 homozygous individuals from at least 2 different families, which was the case in 60 patients from 16 *COQ8B* and 6 *COQ6* families harboring 7 different variants. A synopsis of the clinical timelines by gene, variant, and family is provided in Supplementary Figure S1. Age at disease onset was least variable among members of families sharing the same causative variant (intra-family, intra-variant CV: 35%) and similar among family members across families harboring a different causative variant (intra-family, inter-variant CV: 40%). Disease onset was more variable when different families shared the same variant (intra-variant, inter-family CV: 64%) and most diverse between families with different causative variants (inter-variant, inter-family CV: 106%; Figure 6).

Specific genotype–phenotype associations were explored for recurrent variants reported in at least 5 homozygous individuals or in at least 5 unrelated families (Supplementary Tables S3A–C).

COQ2. Patients who were homozygous for the most frequent *COQ2* variant *c.683A>G (p.Asn178Ser)* had a lower risk of disease onset in the first 2 years of life (odds ratio [OR] 0.07; 95% CI 0.0–0.56, $P = 0.0292$).

The homozygous variant *c.437G>A (p.Ser96Asn)*, present in 6 non-related Turkish children, was associated with a severe disease course characterized by higher risk of disease onset in the first 6 months of life ($P = 0.0006$), higher risk of death ($P < 0.0001$), obligate neurologic symptoms, and

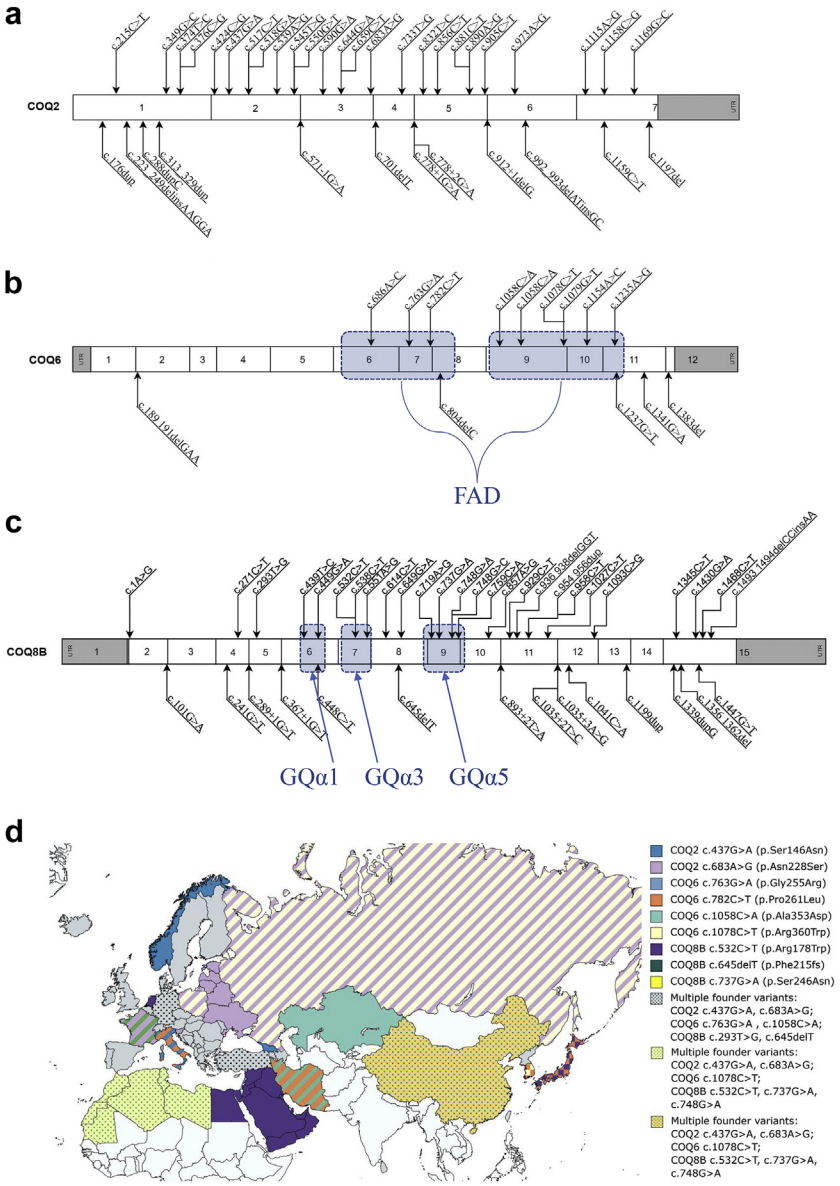


Figure 5 | Distribution of causative variants in (a) *COQ2*, (b) *COQ6*, and (c) *COQ8B*. Missense variants are depicted above, truncating variants below the gene sequence. Mutational hot-spots are indicated by shaded areas. In *COQ6,* residues 194–300 and 340–425 are involved in the binding of oxidized flavin adenine dinucleotide (FAD). In *COQ8B,* residues 147–154 and 174–184 represent GQα1 and GQα3 binding motifs and 246–253 GQα5 motif. (**d**) Geographical distribution of recurrent (founder) variants. Positions according to the reference sequences: *COQ2*: NM_015697.8, NP_001345850.1; *COQ6*: NM_182476.3, NP_872282.1; and *COQ8B*: NM_024876.4, NP_079152.3.

multiorgan failure, which was much less commonly observed in the rest of the *COQ2* cohort ($P < 0.0001$). Five of the 6 children received genetic testing due to a phenotype suggestive of mitochondriopathy, while SRNS was the leading complaint in the remaining *COQ2* disease patients.

COQ6. The subgroup carrying the most frequent variant *c.1058C>A (p.Ala353Asp)*, clustering in Kazak, Turkish, and Iranian populations, showed later disease onset, with a lower risk of symptoms within the first 15 months of life ($P = 0.0036$). Conversely, homozygosity for *c.1078C>T (p.Arg360Trp)*, present in Central/Eastern Europe and China, associated with a higher risk of neurologic involvement, myopathy, cardiomyopathy, and growth retardation ($P < 0.05$). The *c.763G>A (p.Gly255Arg)* variant, predominant in the Middle East, presented with severe phenotype, early disease onset ($P = 0.0207$), and early-onset ESKD (within the age of 2 years, OR 13.6, 95% CI 1.4–173, $P = 0.0297$), as well as higher odds of mortality ($P = 0.0104$).

COQ8B. Patients with the variant *NM_024876.4:c.748G>C (p.Asp250His)*, observed in China, showed a higher risk of developing kidney disease within the first 5 years of life (OR 5.7; 95% CI 1.5–18.7, $P = 0.0116$). Patients homozygous for variant *c.1339dupG*, common in

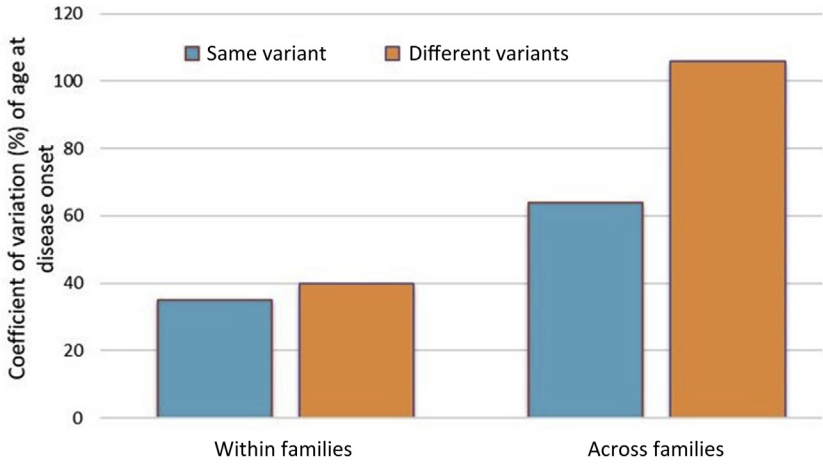


Figure 6 | Variability of age at disease onset according to variant type and relatedness of patients. Bars indicate intra- and inter-family coefficients of variation for patients affected by the same or different causative variants. 84 patients from 34 families with 5 causative variants in *COQ2* (c.437G>A, c.683A>G, c.890A>G, c.905C>T c.1169G>C), 3 causative variants in *COQ6* (c.763G>A, c.782C>T, c.1058C>A), and 10 causative variants in *COQ8B* (c.293T>G, c.532C>T, c.748G>C, c.748G>A, c.958C>T, c.1027C>T, c.1199dup, c.1339dup, c.1356_1362delGGGCCCT, c.1447G>T) were used for calculations.

patients of Turkish and Kurd descent, demonstrated later disease onset (>10 years, $P = 0.0044$) and later ESKD (>12 years, $P = 0.0055$), with higher odds of microhematuria at diagnosis ($P = 0.0497$). The variant *c.1199dup*, also common in patients of Turkish ancestry, associated with slower disease progression ($P = 0.0165$) and ESKD attained at a median age of 16 years (interquartile range: 14.4–17.6 years). Individuals with *c.293T>G (p.Leu98Arg)*, another variant prevalent in patients of Turkish descent, had a higher prevalence of extrarenal symptoms (OR 6.7; 95% CI 1.3–34.5, $P = 0.0228$). In individuals carrying *c.532C>T (p.Arg178Trp)*, ocular anomalies were reported more commonly.

Biallelic truncating variants. Patients with *COQ2* and *COQ6* disease carried at least one missense variant, except for 4 individuals with biallelic truncating variants located close to 3'UTR that are known to be associated with some residual enzymatic activity.[15] On the contrary, one third (47 of 140) of *COQ8B* disease patients had biallelic truncating variants (Supplementary Table S4). Patients without biallelic truncating alleles in *COQ8B* showed earlier disease onset (onset before age 10 years: OR = 2.2; 95% CI 1.0–4.8, $P = 0.0384$) and earlier kidney failure (ESKD before age 15 years: OR = 7.7; 95% CI 2.9–20.6, $P < 0.0001$).

Motifs GQα1/2 GQα3/GQα5 in COQ8B. Patients carrying at least one allele with a disease-causing missense variant affecting residues in the GQα1/2 or GQα3 motif were compared with the rest of the *COQ8B* population, excluding patients with biallelic truncating variants. ESKD was reached in 83% of patients with a variant in the GQα1/2 or GQα3 motif during the period of observation, as compared to 61% in the remaining population ($P = 0.0475$).

Similar analysis was performed for patients carrying a missense variant in the GQα5 motif on at least one allele. Patients with a missense variant affecting GQα5 reached ESKD at an earlier age; however, the observation was not confirmed in the restricted group of patients carrying biallelic missense variants affecting residues within the GQα5 motif.

DISCUSSION

We present the largest international cohort collected thus far of primary CoQ10-deficiency patients carrying biallelic disease-causing variants in *COQ2*, *COQ6*, and *COQ8B*, the 3 causative genes associated with kidney involvement and SRNS.

Although the estimation of the exact prevalence of CoQ10 deficiencies is beyond the scope of this study, published registry reports suggest that these disorders account for ~0.5% of mitochondriopathies, ~2% of childhood SRNS/persistent proteinuria, and up to 5% of molecularly confirmed genetic SRNS cases.[4,16] We found significant geographical divergence, with a globally higher incidence of CoQ10-related pathogenic variants observed in Asian populations. Given that these ethnicities are currently underrepresented in mostly Caucasian-based registries, global prevalence figures might differ notably. Already, the recent multicenter Chinese study reported *COQ8B* as the most common cause of SRNS in their region, accounting for 5.7% of cases.[11] This finding is in line with the proposed existence of several founder mutations in various regions of the world (Figure 5d). Our findings can serve to inform the development of focused gene panels and guide diagnostic expectations regarding the frequency and nature of causative variants in these regions.

Our study revealed an unexpectedly large variability in the spectrum and severity of phenotypes associated with abnormalities in each of the 3 genetic conditions associated with primary CoQ10 deficiency. Phenotypic heterogeneity was most remarkable for the *COQ2* cohort, a disorder

classically associated with severe and commonly lethal infancy-onset multisystem disease. We observed that more than 20% of patients with biallelic *COQ2* disease-associated variants manifest disease at an age older than 2 years, with a surprisingly high fraction of patients exhibiting isolated SRNS without any neurologic or other extrarenal manifestations at the time of disease diagnosis. Although 20% of the children died in the first year of life from multiorgan failure, no patients died after age 5 years, and long-term survival was 70%.

Likewise, although we confirmed the oto-renal disease phenotype as the characteristic clinical presentation of patients with *COQ6* disease, the degree of both kidney and hearing impairment varied substantially. Sensorineural hearing loss ranged from mild, late-onset hearing impairment to congenital deafness. Hearing loss could either precede or follow the renal symptoms, which typically consisted of nephrotic syndrome, but in almost one fifth of cases were limited to asymptomatic proteinuria. Notably, 1 in 12 *COQ6* disease patients exhibited hematuria, along with proteinuria and hearing impairment, suggesting that *COQ6* disease may present as a phenocopy of Alport syndrome.

Also, with regard to *COQ8B* disease, our findings imply a larger variability of disease onset and severity than suggested in previous reports.[17,18] Renal symptoms can appear from early childhood into adulthood (oldest reported age at onset: 32 years) and encompass a wide range of proteinuria level and glomerular filtration rate, with a quarter of patients presenting with asymptomatic proteinuria, and one third presenting with ESKD at the time of diagnosis.

Kidney disease progressed with all 3 monogenetic disorders. In line with their generally later onset of renal symptoms, none of the patients with *COQ8B* disease had progressed to ESKD by age 5 years, as compared to 50% of the children with *COQ2* and *COQ6* disease. However, at attainment of adult age, kidney survival was equally poor (20%–25%) with all underlying genetic disorders. Remarkably, in individual patients, ESKD was reached in the fourth decade of life.

The impact of clinical management, in particular oral CoQ10 supplementation, on proteinuria and kidney survival is beyond the scope of this article and will be discussed in a separate publication.[19] In the present study, we focused on the potential role of genetic determinants of the observed remarkable phenotypic variability of primary CoQ10 deficiency. We identified a number of sequence variants with divergent clinical presentations. Some of these are founder mutations that lead to regional variation of not only the incidence but also the typical clinical severity of the disease. Notably, we identified significant intra- and inter-familial phenotype variability among patients carrying the same underlying causative variant, suggesting additional effects of modifying variants and/or environmental factors on disease manifestation and evolution.

Variant analysis at the molecular level yielded important mechanistic insights. Given that a complete block in CoQ10 biosynthesis is considered lethal, all patients could be assumed to have some residual function of the enzyme complex.[15] In case of *COQ2* and *COQ6*, encoding key enzymes of the pathway, all patients had at least one hypomorphic allele. Conversely, one third of the *COQ8B* patients carried biallelic truncating (i.e., *null*) alleles. This implies that other proteins may compensate for this absence. The precise role of COQ8B and its potential redundancy is the subject of ongoing research. COQ8A is the most likely candidate for a functional substitute, as the 2 proteins have high (61.4%) sequence identity (Movie S1). The roles of *COQ8A/COQ8B* gene products remain largely unexplained. Their function is postulated to be essential for maintaining complex Q stability[13,20]; on the other hand, recent research points to a small molecule kinase activity or translocation of the CoQ precursor from the membrane.[21] Intriguingly, the ATPase activity of *COQ8A* is greatly enhanced by membrane interaction of GQα1 and GQα4.

We unexpectedly observed a milder kidney phenotype, with later disease onset and slower progression to ESKD, in patients with biallelic *COQ8B null* alleles. Remarkably, in patients with cerebellar ataxia due to *COQ8A* variants, multisystemic involvement also was more prevalent in carriers of missense, compared to those with loss-of-function, variants.[14] In both settings, residual CoQ10 biosynthesis in subjects with biallelic *null* alleles has been reported.[13,14] This implies that the 2 proteins possess redundant functions in a condition- or tissue-specific manner, and although absent protein can be substituted, misfolded proteins resulting from a missense variant would interfere with the CoQ10 biosynthesis pathway. This possibility is further supported by the fact that, in both disorders, disease-causing missense variants cluster to the same gene regions.

The high structural identity of COQ8B with the previously crystalized COQ8A protein[13,20] implies that both adopt a core fold similar to that of well-characterized protein kinase–like domains, with its invariant KxGQ motif (residues 155–158) completely occluding the typical substrate binding pocket (Supplementary Material S1). Variants located in the common functional cluster at the 2 regions neighboring the KxGQ motif (GQα1 and GQα3) are commonly involved in both *COQ8A*- and *COQ8B*-associated diseases. We identified a third motif, GQα5, to represent a hotspot for disease-causing variants in *COQ8B*; although its exact role remains unknown, it may be speculated that due its external localization, it is involved in allosteric signaling or specific, yet uncharacterized protein–protein interactions within the CoQ10 biosynthesis machinery. The most frequent variant in this location, *c.748G>C (p.Asp250His)*, common in China, conveys increased risk for early-onset disease.

In summary, our comprehensive analysis of 251 cases of primary CoQ10 deficiency caused by disease-causing variants

in *COQ2*, *COQ6*, or *COQ8B* demonstrated remarkable heterogeneity in manifestation age, renal and nonrenal manifestations, and natural history of this mitochondrial disorder. The phenotypic variability was in part explained by genotype, but family analysis suggested substantial roles of genetic and nongenetic modifiers. Given the large clinical variability, the disorders may conceivably be frequently diagnosed late, or missed; many of the patients with the most severe *COQ2* disease may die before diagnosis. In view of the availability of oral CoQ10 supplementation as a likely effective therapy,[22–24] we suggest that all patients with glomerular proteinuria and CKD of unknown origin be tested for primary CoQ10 deficiency.

APPENDIX

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DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Overview of 251 patients with *COQ2*, *COQ6*, and *COQ8B*(*ADCK4*) enrolled in the study: genotype and phenotype characteristics.

Table S2. Variant reporting. Annotations (current reference sequence *COQ2*: NM_015697.8, NP_001345850.1; *COQ6*: NM_182476.3, NP_872282.1, and *COQ8B*: NM_024876.4, NP_079152.3.); American College of Medical Genetics and Genomics (ACMG) classification, population frequency, and references. Number of cases among our study population.

Table S3A. Genotype–phenotype correlations in subgroups of patients carrying common *COQ2* variants (homozygous state in at least 5 individuals or reported in at least 5 different families). Numbers represent percentage (number of affected patients/informative number of patients) and median (interquartile range), as appropriate. *P* values of Fisher's exact test are italicized.

Table S3B. Genotype–phenotype correlations in subgroups of patients carrying common *COQ6* variants (homozygous state in at least 5 individuals or reported in at least 5 different families). Numbers represent percentage (number of affected patients/informative number of patients) and median (interquartile range), as appropriate. *P* values of Fisher's exact test are italicized.

Table S3C. Genotype–phenotype correlations in subgroups of patients carrying common *COQ8B* variants (homozygous state in at least 5 individuals or reported in at least 5 different families). Numbers represent percentage (number of affected patients/informative number of patients) and median (interquartile range), as appropriate. *P* values of Fisher's exact test are italicized.

Table S4. Comparison of the subjects with *COQ8B* disease due to biallelic truncating variants (biallelic null alleles) to the rest of the *COQ8B* cohort. *P* values of Fisher's exact test are italicized.

Figure S1. Intrafamilial and interfamilial phenotypic variability in homozygous individuals (variants carried by at least 2 members of 2 different families). Synopsis of clinical disease course (panel A-B-C). Families with disease-causing variants in *COQ2* gene (panel A), *COQ6* gene (panel B), and *COQ8B* gene (panel C). Families with the same variant are grouped with a dotted outline; family members are grouped with brace. The black line denotes the time before the first clinical disease manifestation; the yellow bars denote the period with proteinuria/chronic kidney disease (CKD); the red bars show dialysis periods; and the blue bars show transplantation periods. The symbols denote the time of sensorineural deafness diagnosis (asterisk) and patients with neurologic symptoms (star).

Supplementary Material S1. Structural aspects of the COQ8B protein. Sequence alignment between COQ8A and COQ8B proteins; comparison of COQ8A and COA8B structure models; structural aspects of the selected *COQ8B* recurrent pathogenic missense variants and visualization of their localization within the COQ8B catalytic domain structure.

Supplementary File (Video)

Movie S1. Comparison of the COQ8B homology model and COQ8A fragment crystal structure.

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