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BRIEF REPORT

Bi-Allelic *COQ4* Variants Cause Adult-Onset Ataxia-Spasticity Spectrum Disease

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ABSTRACT: Background: *COQ4* codes for a mitochondrial protein required for coenzyme Q_{10} (CoQ_{10}) biosynthesis. Autosomal recessive *COQ4*-associated CoQ_{10} deficiency leads to an early-onset mitochondrial multi-organ disorder.

Methods: In-house exome and genome datasets ($n = 14{,}303$) were screened for patients with bi-allelic variants in *COQ4.* Work-up included clinical characterization and functional studies in patient-derived cell lines.

Results: Six different *COQ4* variants, three of them novel, were identified in six adult patients from four different families. Three patients had a phenotype of hereditary spastic paraparesis, two sisters showed a predominant cerebellar ataxia, and one patient had mild signs of both. Studies in patient-derived fibroblast lines revealed significantly reduced amounts of COQ4 protein, decreased CoQ_{10} concentrations, and elevated levels of the metabolic intermediate 6-demethoxyubiquinone.

Conclusion: We report bi-allelic variants in *COQ4* causing an adult-onset ataxia-spasticity spectrum phenotype and a disease course much milder than previously reported. © 2022 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: coenzyme Q_{10} deficiency; hereditary spastic paraplegia; cerebellar ataxia; mitochondriopathy

Introduction

Coenzyme Q_{10} (CoQ_{10}) is an essential component of the mitochondrial electron transport chain. Primary CoQ_{10} deficiencies are rare, clinically and genetically heterogeneous disorders caused by variants in 11 distinct genes encoding proteins of CoQ_{10} biosynthesis.[1-3] *COQ4* encodes a ubiquitously expressed protein involved in organizing a multi-enzyme complex required for CoQ_{10} biosynthesis.[4] Bi-allelic variants in *COQ4* have been reported in patients with a neonatal lethal encephalopathy[5,6] infantile mitochondrial multi-organ disorder,[7,8] as well as childhood-onset ataxia, sometimes with stroke-like episodes.[9,10]

Here, we show that CoQ_{10} deficiency due to *COQ4* variants causes adult-onset spastic paraparesis and/or cerebellar ataxia, thereby expanding the *COQ4*-associated phenotypic spectrum.

Methods

Genetic, Clinical, and Laboratory Investigations

Genetic testing and re-analysis of genetic data was performed according to the Declaration of Helsinki and approved by the ethical committee of the University of Tübingen (project no. 066/2021BO2). All patients agreed to the publication and written informed consent was obtained from all subjects.

After having identified an index case with unexplained hereditary spastic paraparesis (HSP) and putative pathogenic bi-allelic *COQ4* variants (patient 1), exome and genome datasets (n = 14,303; Institute of Medical Genetics and Applied Genomics of the University of Tübingen) were screened for bi-allelic variants in *COQ4*. At the time of the analysis, the database contained patients of all ages and various disease groups as well as healthy individuals. A total of 912 patients have been assigned to the HPO term spastic paraplegia and 1206 individuals to ataxia (or cerebellar atrophy). Subsequently, the analysis was extended to the other 10 genes involved in CoQ$_{10}$ biosynthesis. The pathogenicity of the identified variants was determined according to the American College of Medical Genetics and Genomics guidelines.[11] Variant confirmation and carrier testing on available family members to confirm segregation were conducted by Sanger sequencing. Primers and polymerase chain reaction (PCR) conditions are provided on request.

In all patients, an in-depth clinical examination was performed including common scores (Table 1). Standard laboratory values and neurofilament protein levels were analyzed in blood and cerebrospinal fluid (CSF). A lactate exercise test was conducted in selected patients as described.[12] Brain magnetic resonance imaging (MRI) was performed as part of the diagnostic work-up. In one patient, a muscle biopsy was taken and investigated histologically according to standard procedures. Muscular CoQ$_{10}$ was determined via high-performance liquid chromatography in an external laboratory unrelated to this study.

Biochemical and Functional Studies

Fibroblast cell lines were cultured according to standard protocols. Immunoblotting of cell lysates was performed as described previously.[13] Levels of CoQ$_{10}$ and intermediate 6-demethoxyubiquinone (6-DMQ) were measured using ultra-performance liquid chromatography-electrospray ionization tandem mass spectrometry (UPLC-ESI-MS/MS) analysis.[13] Enzyme activities of the oxidative phosphorylation system (OXPHOS) complexes I–V and citrate synthase were determined in isolated mitochondria from skin fibroblasts by spectrophotometry as reported previously.[14] Control samples were healthy pediatric and adult individuals including one male (control 1) and two females (control 2, 3).

For statistical analyses, RStudio (1.4.1103) was used. Mann–Whitney *U* test was performed to compare results between patients and controls.

Results

Genetic Analysis

Bi-allelic variants in *COQ4* (NM_016035.5) were identified in six affected individuals of four unrelated families. Carrier testing showed full co-segregation of the identified variants with the clinical status (Fig. 1A). No further adult patients with bi-allelic variants in the other genes involved in CoQ$_{10}$ biosynthesis were identified, apart from the previously published cases with variants in *HPDL*.[15]

Patient 1 and his sister harbored the previously reported variant c.473G>A (p.Arg158Gln)[6] in a compound heterozygous state with c.305G>A (p.Arg102His), which has been reported once in a 19-year-old girl.[16] Patient 3 carried c.437 T>G (p.Phe146Cys), which has been detected in a homozygous state in young infants with early-onset motor deterioration and epileptic encephalopathy.[17,18] The second, previously unreported variant in patient 3, c.434G>A (p.Arg145His), was located within close proximity on the same exon in trans. Of note, a different missense change affecting the same amino acid position (p.Arg145Gly) has been determined to be pathogenic.[5] Patient 4 harbored c.473G>A (p.Arg158Gln) in trans with the novel variant c.376G>A (p.Glu126Lys). Patient 5 and her sister both carried a novel homozygous splice variant (c.202+4A>C, p.?) in intron 2.

All variants detected in our patients were either rare or absent as well as not in homozygous state in gnomAD and predicted to be deleterious in silico (Supplementary Table S1). None of the patients carried additional relevant variants in genes associated with neurological phenotypes.

Clinical Phenotypes (Table 1)

Videos of patients 1, 3, and 4 are available online as Supporting Data. Patients 1, 3, and 4 were diagnosed with HSP. No additional sings, such as optic atrophy, polyneuropathy, or hearing impairment were present. Echocardiography did not show any signs of cardiomyopathy. Patients 5 and 6 had the initial diagnosis of hereditary cerebellar ataxia.

Overall, clinical impairment was mild, with only one patient showing more pronounced lower limb spasticity. In all individuals, the disease was slowly progressive over the years. Oral CoQ$_{10}$ supplementation (ubiquinol 400–1200 mg/d) was recently initiated in patients 1, 3, and 4.

TABLE 1 *Genetic and clinical findings in individuals with bi-allelic* COQ4 *variants*

	Patient 1 (F1:II.4)	Patient 2 (F1:II:1)	Patient 3 (F2:II:3)	Patient 4 (F3:II:3)	Patient 5 (F4:II:2)	Patient 6 (F4:II:1)
Variant carrier status						
cDNA change	c.305G>A; c.473G>A	c.305G>A; c.473G>A	c.434G>A; c.437T>G	c.376G>A; c.473G>A	c.202+4A>C; c.202+4A>C	c.202+4A>C; c.202+4A>C
Protein change	p.Arg102His; p.Arg158Gln	p.Arg102His; p.Arg158Gln	p.Arg145His; p.Phe146Cys	p.Glu126Lys; p.Arg158Gln	p.?; ?	p.?; ?
ACMG criteria						
Evidence of pathogenicity[a]	PS1, PS3, PM2, PM3, PP2, PP3; PS1, PS3, PM2, PM3, PP2, PP3	PS1, PS3, PM2, PM3, PP2, PP3; PS1, PS3, PM2, PM3, PP2, PP3	PS3, PM2, PM3, PM5, PP2, PP3; PS1, PS3, PM2, PM3, PP2, PP3	PS3, PM2, PM3, PP2, PP3; PS1, PS3, PM2, PM3, PP2, PP3	PS3, PM2, PP4; PS3, PM2, PP4	PS3, PM2, PP4; PS3, PM2, PP4
Classification	Pathogenic; Pathogenic	Pathogenic; Pathogenic	Pathogenic; Pathogenic	Pathogenic; Pathogenic	Likely Pathogenic; Likely Pathogenic	Likely Pathogenic; Likely Pathogenic
Demographics						
Gender	Male	Female	Male	Male	Female	Female
Age at onset/at examination (y)	15/19	-/30	16/28	24/31	32/49	34/52
Country of origin	Germany	Germany	Iraq	Germany	Germany	Germany
Pyramidal signs/motor function						
Spasticity, upper/lower extremity	−/+	−/−	−/+	−/+	−/−	−/−
Hyperreflexia, upper/lower extremity	−/+	−/+	+/+	−/+	−/−	−/−
Babinski sign	−	−	+	−	−	−
SPRS score (0–52 points)	6	n/a	26	3	6 (because of ataxia)	5 (because of ataxia)
Pareses	−	−	Severe (hip flexion, knee flexion, foot dorsiflexion)	Mild (foot dorsiflexion)	−	−
Walking/running possible	+/−	+/+	+(severely impaired)/−	+/+	+/+	+/+
6-MWT (m)	539	n/a	n/a	614	504	569
Cerebellar syndrome						
Saccadic eye movement	+ (mild)	−	+ (mild)	−	+	+
Ataxia, gait/limb	+ (mild)/+	+ (mild)/−	−/+	−/−	+/+	+/+
Dysarthria	+ (mild)	−	−	−	+	+
SARA score (0–40 points)	5	3	15 (mostly due to spasticity)	0	11	10

(Continues)

TABLE 1 *Continued*

	Patient 1 (F1:II.4)	Patient 2 (F1:II:1)	Patient 3 (F2:II:3)	Patient 4 (F3:II:3)	Patient 5 (F4:II:2)	Patient 6 (F4:II:1)
Additional symptoms/signs						
Cognitive function						
Subjective cognitive impairment	+ (mild)	–	–	–	+	+
MoCA score (0–30 points)	28	n/a	26[b]	27	28	24
Tremor						
Postural tremor (hands)	–	–	+	+	–	–

[a] Based on ACMG standards and guidelines.[11]

[b] Language barrier has to be considered.

Abbreviations: ACMG, American College of Medical Genetics and Genomics; PS, pathogenic strong; PM, pathogenic moderate; PP, pathogenic supporting, SPRS, Spastic Paraplegia Rating Scale; n/a, not available; 6MWT, 6-minute walk test; SARA, Scale for the assessment and rating of ataxia, MoCA, Montreal Cognitive Assessment.

Patients 1 and 2

Patient 1, a 19-year-old male, started to have walking difficulties at the age of 15. Neurological examination revealed moderate lower limb spasticity (Supplementary Video S1). He had mild ataxia and a slight scanning dysarthria. Neuropsychological assessment revealed mild cognitive dysfunction with impaired memory and frontal-executive deficits including attention and concentration. Brain MRI was unremarkable, particularly, showed no signs of cerebellar atrophy. Patient 2, the 30-year-old sister, consulted our outpatient clinic for clinical examination and genetic counseling because of her affected brother and did not complain of any symptoms; especially walking or running difficulties were denied. However, neurological examination revealed brisk deep tendon reflexes of the lower limbs as well as mild upper limb ataxia with dysmetria and slightly irregular fast alternating hand movements. Tandem gait was impaired.

Patient 3

Patient 3, a 28-year-old male, first noticed gait disturbances at the age of 16. Neurological examination revealed pronounced lower limb spasticity with hyperreflexia as well as a postural tremor of his hands (Supplementary Video S2). Cerebellar signs were discrete. He could only walk a few steps with much support and used a wheelchair for longer distances. There was no cognitive impairment. Brain MRI and spectroscopy were normal.

Patient 4

Patient 4, a 31-year-old male, started to experience frequent falls and difficulties walking at the age of 24. Four years later, he had two generalized tonic–clonic epileptic seizures. Examination showed mild lower limb spasticity (Supplementary Video S3) and a mild postural hand tremor. There were no signs of ataxia or cognitive deficits. Brain MRI and spectroscopy were unremarkable.

Patients 5 and 6

Patint 5, the younger daughter of healthy parents, being first-degree cousins, first noted an unsteady gait, a slurred speech, and changes in handwriting at the age of 32. Neurological examination revealed a moderate pan-cerebellar syndrome. On last examination (49 years), she was ambulatory without medical aids; however, falls did occur. The patient reported problems with short-term memory and attention. A neuropsychological assessment revealed short-term and working memory impairments. Brain MRI showed pronounced cerebellar vermian atrophy and mild cerebellar hemispheric atrophy. (Fig. 1B). Patient 6, the older sister, had a cerebellar syndrome of about the same extent as in her sister. She also had a mild cognitive impairment. Brain MRI revealed cerebellar atrophy, again, affecting the vermis more markedly than the hemispheres.

Laboratory Findings and Biochemical Changes in COQ4 Deficiency

Investigations of biomaterials were performed in patients 1, 3, 4, 5, and 6. Standard laboratory exams of CSF and blood, including creatine kinase and lactate, were normal. Lactate exercise showed no pathological increase of serum lactate in patients 1 and 4. Neurofilament levels of blood or CSF, analyzed in patients 1, 3, and 4, were normal. In patient 1, CoQ_{10} levels and CoQ_{10}/citrate synthase ratio determined from muscle were normal; furthermore, histological examination and biochemistry were unremarkable.

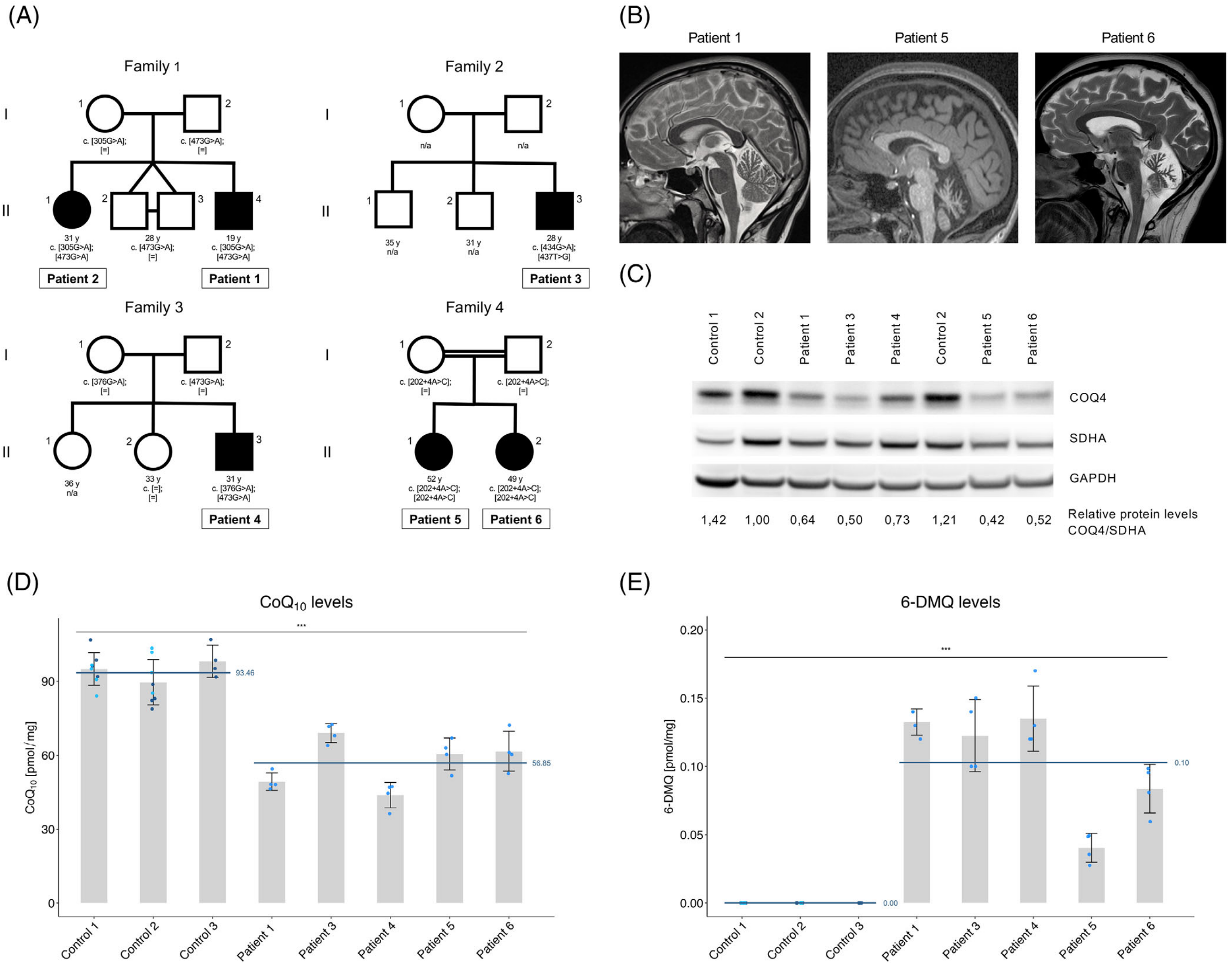

FIG. 1. (**A**) Pedigrees of four families with variants in *COQ4* illustrating the variant carrier status of affected (closed black symbols) and healthy (open symbols) family members. n/a = not available for testing. (**B**) Brain MRI was normal in patient 1 and revealed moderate cerebellar atrophy (pronounced vermian atrophy and mild hemispheric atrophy) in patients 5 and 6. Patient 1 (F1:II:4) midsagittal T2-weighted image; patient 5 (F4:II:2) midsagittal T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) image; patient 6 (F4:II:1), midsagittal T2-weighted image. (**C**) Immunoblot analysis of COQ4 in control and patient-derived fibroblast lines demonstrating reduced COQ4 protein amounts in all patient-derived cell lines. Relative protein levels normalized to succinate dehydrogenase complex subunit A (SDHA). (**D**) Quantification of cellular CoQ_{10} levels using UPLC-ESI-MS/MS analysis showed a significant reduction of CoQ_{10} levels. (**E**) The intermediate 6-DMQ was undetectable in control cell lines, but levels were significantly increased in all cell lines with COQ4 deficiency. (**D,E**) Each bar is presented as mean ± standard deviation (bar and whiskers) with dots representing single values from different experiments. In patients 1, 3, 4, 5, and 6 as well as control 3, four independent experiments, whereas in controls 1 and 2, eight experiments from two different runs (light vs. dark blue dots) were used for mean value calculation. Horizontal line indicates mean values of patients and controls, respectively; $^{***}P < 0.001$ significantly different comparing each patient with pooled controls on Mann–Whitney *U* test. [Color figure can be viewed at wileyonlinelibrary.com]

Immunoblot analysis of COQ4 in control and patient-derived fibroblast lines demonstrated significantly reduced COQ4 protein amounts in patients ($P < 0.01$) (Fig. 1C). Quantification of cellular CoQ_{10} levels by UPLC-ESI-MS/MS showed a significant reduction of CoQ_{10} levels in all patient-derived fibroblast lines ($P < 0.001$) (Fig. 1D). The metabolic intermediate 6-DMQ was undetectable in control cells, but levels were increased in all cell lines with COQ4 deficiency ($P < 0.001$) (Fig. 1E). Respiratory chain enzyme activities in mitochondria isolated from patients' fibroblasts were normal in two individuals (patients 4 and 5) and mildly reduced in patient 1 (Supplementary Table S2).

Discussion

COQ4-associated CoQ_{10} deficiency typically causes severe early-onset multi-organ phenotypes. Cerebellar degeneration has been previously reported in infants with bi-allelic variants in *COQ4*[5] and other genes involved in CoQ_{10} biosynthesis.[19] Only five patients with childhood-onset ataxia have been published, the latest onset being 9 years.[9,10,16] The reported patients had a cerebellar syndrome often with wheelchair-dependency in late childhood, cognitive impairment, and seizures. Thus far, an adult-onset of symptoms has never been described for COQ4 deficiency. However, other CoQ_{10} deficiencies, e.g., due to *COQ8A*-variants have been associated with late-onset ataxia).[20,21] Furthermore, it cannot be excluded that cerebellar atrophy was present years before the first clinical symptoms appeared.

The slowly progressive spastic paraparesis led to the diagnosis of HSP in three patients, whereas two sisters had a cerebellar syndrome with mild cognitive impairment and were diagnosed with hereditary cerebellar ataxia. The substantial overlap between hereditary ataxias (spinocerebellar ataxia [SCA] or autosomal-recessive cerebellar ataxia [ARCA]) and HSP is well known. First, ataxia and spasticity frequently co-occur in patients. Second, various genes have been identified to cause both hereditary ataxias and HSP.[22,23] Therefore, the distinction between "HSP vs. ataxia genes" should probably be softened and various genes, including *COQ4*, have to be considered as being associated with ataxia and spastic paraparesis, representing two ends of the ataxia-spasticity spectrum (ASS).[23] Following the previously recommended classification of genetic movement disorders that combines the main phenotype and the causative gene,[24] the disease described here can be referred to as ASS-*COQ4*.

At least some genotype–phenotype correlation can be stated in COQ4 deficiency; bi-allelic loss-of-function variants have not yet been reported for *COQ4*, presumably resulting in non-viable phenotypes. Furthermore, truncating variants in a compound-heterozygous state with missense variants have only been described in severely affected patients.[5,7] Interestingly, all missense variants in our patients were located in exon 4 or 5 of *COQ4*. Three of our patients harbored the same variant c.473G>A. The second variant in family 1, c.305G>A, has recently been identified in a 19-year-old girl with childhood-onset cognitive impairment and slowly progressive ataxia with spastic paraparesis.[16]

With regard to the wide clinical variability of *COQ4*-related disorders, biochemical proof of a defect of CoQ_{10} synthesis is important. In our patients, lactate levels were normal. A muscular CoQ_{10} deficiency could not be proven in the one patient investigated. Furthermore, biochemical analysis of skin fibroblasts did not disclose clearly abnormal respiratory chain enzyme activities. This is in line with the heterogeneity of data from biochemical characterizations in previous studies. Although reduced CoQ_{10} levels in muscle tissue and fibroblasts have been reported for individual cases with COQ4 deficiency,[5,18] other studies detected normal CoQ_{10} levels in fibroblasts and no abnormalities of skeletal muscle biochemistry.[16,25] Importantly, in other adult patients with defects in CoQ_{10} synthesis (eg, adult-onset cerebellar ataxia because of variants in *COQ8*) biochemical confirmation in muscle tissue[26] or fibroblasts[27] could not be proven. However, normal enzyme activities in fibroblasts or skeletal muscle do not exclude mitochondrial dysfunction in other tissue more affected by the disease, especially because in adult patients with defects in CoQ_{10} synthesis, the central nervous system involvement is the predominant feature. In our study, patient-derived fibroblast lines revealed reduced amounts of COQ4 protein and decreased CoQ_{10} concentrations, however, in some individuals values were only mildly reduced. One could speculate that a milder clinical presentation might be associated with a less prominent reduction of CoQ_{10}, similar to what has already been observed in *COQ7*.[28] However, a correlation between genetic, clinical, and biochemical profiles, could not be identified in COQ4 deficiency so far.[18] Possibly, additional regulatory processes might influence CoQ_{10} biosynthesis. Interestingly, our data confirm that 6-DMQ levels are consistently elevated in COQ4-deficient cell lines, similar to what has been reported recently.[18] Although 6-DMQ indicates a generally impaired CoQ-synthome function rather than being a specific marker for COQ4 deficiency,[13] it might serve as an interesting biomarker candidate for future studies.

Treatment response to CoQ_{10} supplementation in individuals with early-onset COQ4 deficiency has been shown to be at least partially effective,[6,10] although clinical improvement was rare in patients with a slower disease progression.[9,10,16] However, these data are limited by considerable variation in dosages and the lack of clinical or biochemical biomarkers to assess treatment response. Supplementation has recently been initiated in our adult patients and will hopefully provide useful follow-up data in near future.

Identifying the genetic defect in patients with hereditary movement disorders is crucial not only for patient counseling, but also in terms of emerging therapeutic options. *COQ4*, and possibly also other genes involved in CoQ_{10} biosynthesis, expands the list of genetic causes underlying the continuous ataxia-spasticity spectrum. ■

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Data Availability Statement

Additional supporting information may be found in the online version of this article at the publisher's website. Further data that support the findings of this study are available on request from the corresponding author.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

IC planned the study, coordinated the cooperation between the centers involved, interpreted the data, was responsible for local data collection, and wrote the manuscript. LS, JP, JP, ND, LL, SLG, PL, NB, AM, MS, DT, and MD contributed to local data collection. AS, DH, and TN conducted immunoblotting and UPLC-ESI-MS/MS analyses of fibroblasts, supervised by FD. The respiratory chain enzyme activities in mitochondria isolated from fibroblasts were studied by JAM. LS has provided statistical support. TBH was involved in the interpretation of genetic data and coordinated the cooperation between the centers involved. MD and FD were responsible for supervision and interpretation of data. All authors critically revised the manuscript.

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