Movement Disorders
CLINICAL PRACTICE
CASE REPORT

Biallelic Variants in *COQ4* Cause Childhood-Onset Pure Hereditary Spastic Paraplegia

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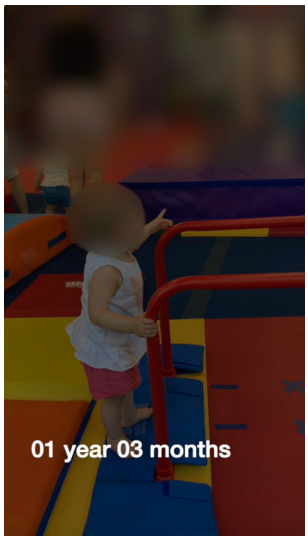
Childhood-onset hereditary spastic paraplegia (HSP) is a clinically and genetically diverse condition, ranging from "pure" forms characterized by lower limb spasticity and weakness to more complex forms that include additional central or peripheral nervous system manifestations such as developmental delay, intellectual disability, extrapyramidal movement disorders, neuropathy, or epilepsy.[1,2] Although over 80 genes are associated with HSP, about 30–40% of children with a clinical diagnosis do not receive confirmation through standard genetic testing.[3,4] Biallelic variants in the gene encoding coenzyme Q4 (*COQ4*) have been reported to cause primary coenzyme Q10 deficiency type 7 (OMIM #616276), spastic ataxia type 10 (OMIM #620666), and hereditary spastic paraplegia in cohorts from China.[5,6] We expand the genotypic and phenotypic spectrum of *COQ4*-associated HSP through a detailed report of a childhood-onset form of pure hereditary spastic paraplegia in the first patient of European ancestry.

Case Report

A 6-year-old female was referred to our Movement Disorders Program for progressive lower limb spasticity and delayed motor development. Born full-term to non-consanguineous parents of mixed European ancestry, her perinatal history was unremarkable. She reached early developmental milestones appropriately, and independent walking was achieved at 15 months, characterized by frequent falls, toe walking, and distal lower limb spasticity (Video 1). MR imaging of the brain and spine at 30 months was normal. She received early intervention with physical and occupational therapy. At 30 months, she started wearing ankle-foot orthoses and underwent serial casting of her ankles. By age 4, she required a posterior walker for longer distances. Her fine motor skills remained delayed, while speech and cognitive development were normal. There was no



Video 1. Videos taken between 1 and 5.5 years of age demonstrate progressive lower limb spasticity and weakness. Initially, the patient is seen walking with the support of handrails. There is bilateral toe-walking with mild scissoring of the legs and proximal leg weakness. Over time, her spastic paraparesis progresses, requiring bilateral ankle-foot orthoses (AFOs) to aid with walking. The patient continues to walk independently but exhibits increasing leg scissoring, a stiff gait, hyperlordosis, and balance difficulties.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14226

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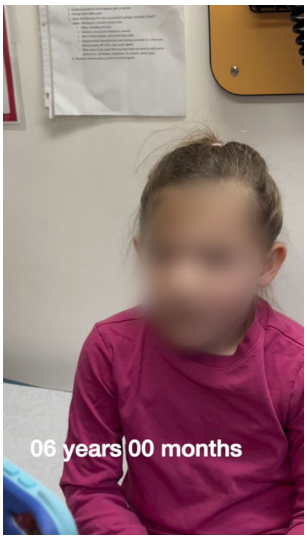

Video 2. Video taken at 6 years of age. On neurological examination, there are no cerebellar signs on finger-to-nose testing. Patellar reflexes are exaggerated. There are contractures of the ankles. Toes are upgoing bilaterally. Gait assessment with one-person assist demonstrates marked spasticity with a crouched gait pattern. There is also toe-walking, leg scissoring, balance difficulties, slower and more effortful steps, and reduced stride length.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14226

history of developmental regression. A visual assessment conducted at age 5 showed no significant abnormalities. Routine biochemical testing was within normal limits. Examination at age 6 (Video 2) revealed significant lower limb spasticity with Modified Ashworth Scale scores, bilaterally: 1 in quadriceps, 2 in hamstrings, and 3 in gastrocnemii, and solei; and a Spastic Paraplegia Rating Scale score of 22/52. These were accompanied by hyperreflexia and bilateral Babinski sign (Video 1). Her gait was crouched with significant crossing of the legs and need for 1-person assist, consistent with a gross motor function classification system (GMFCS) level 3. Notably absent were cerebellar deficits and ataxia. Cognitive assessment indicated age-appropriate skills. Clinical genetic testing, including an HSP gene panel in 2020, whole exome sequencing (WES) in 2021, and whole genome sequencing (WGS) in 2022, were negative.

Following informed consent (IRB-P00039630), trio short-read whole genome sequencing was performed showing compound-heterozygous variants in *COQ4* (NM_016035.5): a maternally inherited missense variant reported in ClinVar as likely pathogenic (c.718C > T, p.Arg240Cys) and a paternally inherited splice variant (c.202 + 4A > C, p.?), previously reported in ClinVar as a variant of uncertain significance. Based on current evidence, we classified variant c.202 + 4A > C/p.? as likely pathogenic and variant c.718C > T/p.Arg240Cys as pathogenic (Table 1), and confirmed through CLIA-certified testing.

TABLE 1 *Classification of the bi-allelic variants identified in* COQ4 *(NM_016035.5) in the proband according to ACMG criteria*

COQ4 variant	ACMG criterion	Detail	Source
c.202 + 4A > C p.?	PS3	Functional studies in patient-derived fibroblasts demonstrated reduced *COQ4* transcript levels[7] and COQ10 levels.[5,7]	Wei et al 2024[5] Cordts et al 2022[7]
	PM2	Max allele frequency 3.688e-5 (Admixed American)	gnomAD 4.1.0
		Overall allele count: 87/1,583,758	
		Number of homozygous individuals: 0	
	PM3	Proband Allele Count (AC); Depth (DP): 14; 29	Patient blood-derived WGS data processed using DRAGEN (see Methods).
		Mother AC:DP: 0; 44	
		Father AC:DP: 24; 34	
	PP3	CADD: 23.1	gnomAD 4.1.0 Emedgene
		MutationTaster: D	
		DANN: 0	
		phyloP: 1.83	
		SiPhy 29 Mammals: 12.725	
		GERP RS: 2.26	

(Continues)

TABLE 1 *Continued*

COQ4 variant	ACMG criterion	Detail	Source
		phastCons 100 vertebrate: 1	
		SNV Rf Score: 0.89	
		SNV Ada Score: 1	
		SpliceAI: 0.12	
		Pangolin: −0.110	
	PP4	Prior associations of COQ4 deficiency and HSP consist of five distinct variants in three Chinese families, two with pure HSP.	Wei et al 2024[5]
c.718C > T p.Arg240Cys	PS	ClinVar Variation ID: 189201	ClinVar
	PS3	Functional studies in patient-derived fibroblasts demonstrated COQ10 levels.[5]	Wei et al 2024[5]
	PM2	Max allele frequency: 2.948e-3 (Ashkenazi Jewish)	gnomAD 4.1.0
		Overall allele count: 148/1,610,312	
		Number of homozygous individuals: 0	
	PM3	Open the VCF to check	Patient blood-derived WGS data processed using DRAGEN (see Methods).
		Proband AC:DP: 24; 63	
		Mother AC:DP: 17; 48	
		Father AC:DP: 0; 57	
	PM5	ClinVar Variation ID: 2686021	ClinVar
	PP3	CADD: 29.3	gnomAD 4.1.0 Emedgene
		REVEL: 0.792	
		PolyPhen (max): 0.999	
		Polyphen2 HDIV: D	
		Polyphen2 HVAR: D	
		SIFT: D	
		MutationTaster: D	
		LRT: D	
		DANN: 0	
		phyloP: 8.86	
		SiPhy 29 Mammals: 18.4386	
		GERP RS: 2.11	
		phastCons 100 vertebrate: 1	
		SpliceAI: 0	
		Pangolin: −0.0500	
	PP4	Prior associations of COQ4 deficiency and HSP consist of five distinct variants in three Chinese families, two with pure HSP.	Wei et al 2024[5]

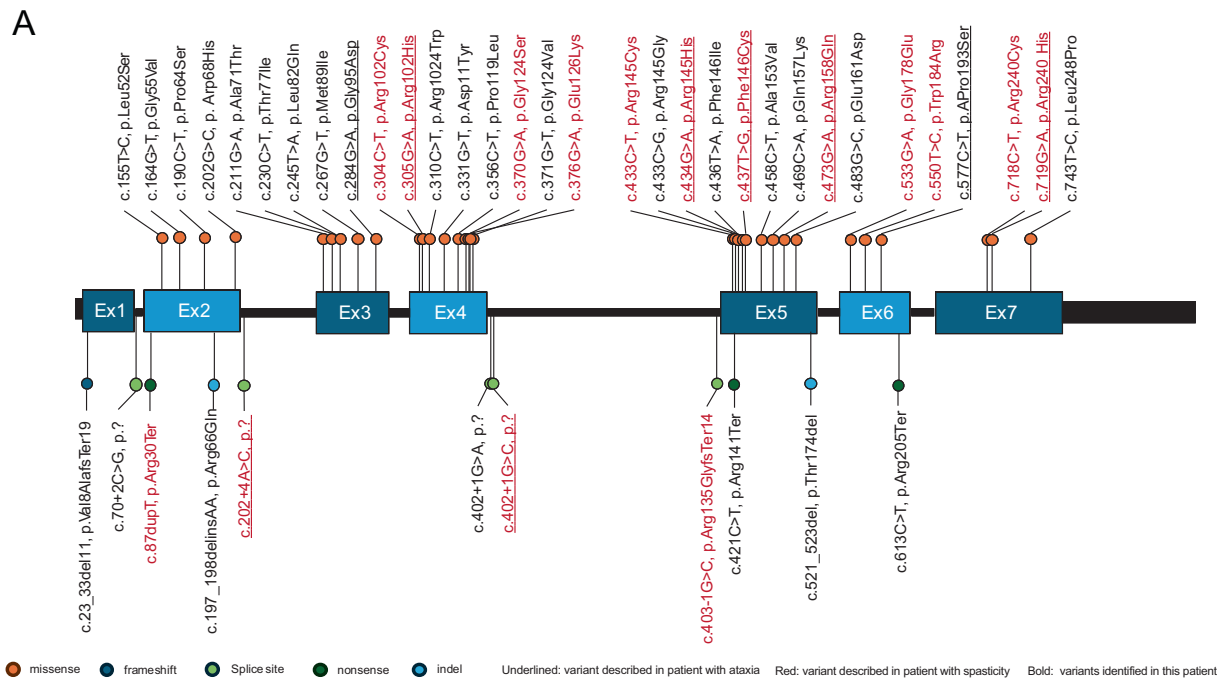

Figure 1. (**A**) Schematic of the molecular spectrum of variants in *COQ4*. Schematic of *COQ4*. Variants are annotated to NM_016035.5. Coding impacts are color coded and missense variants are annotated above the gene structure, while all other variants are depicted below. Variants described to cause spasticity are labeled in red, variants reported to cause ataxia are underlined. Variants described in our patient are marked in bold letters. (**B**) Pedigree of the proband's family.

Discussion

This case describes the first patient of European ancestry with an early childhood-onset pure form of HSP caused by biallelic variants in *COQ4*. Each variant identified in our patient have been previously reported with different phenotypes. The c.202 + 4A > C variant has been reported by Cordts et al in two sisters with predominant cerebellar ataxia and cerebellar atrophy with onset in the third decade of life.[7] The variant c.718C > T, p.-Arg240Cys has been reported in individuals with hypotonia, seizures, abnormal brain morphology, cardiomyopathy, and respiratory failure, leading to demise in the first weeks of life in some cases[7–10] (Fig. 1).

Prior associations of COQ4 deficiency and HSP consist of five distinct variants in three Chinese families, two with pure HSP and one with additional epilepsy and vision impairment. The age at onset varied between 6 and 17 years. Functional studies in patient-derived fibroblasts demonstrated reduced CoQ10 levels.[5] Lin et al recently described an additional six Chinese families, four with pure HSP and two families with cerebellar ataxia and epilepsy. Age at onset ranged between 1 and 55 years, with a median age at onset of 10 years[6] (Fig. 1). The phenotypic spectrum of COQ4 deficiency is likely still expanding, and the cause of the significant inter- and intrafamilial variability, as well as the natural history of this rare disease, remains to be established. It has been speculated that combinations of different mutant

COQ4 alleles are associated with varying degrees of CoQ10 deficiency, which determine disease severity.[6]

This case highlights the importance of reanalyzing WES/WGS data based on the most recent evidence. Given that prior publications reported CoQ10 deficiency in fibroblasts with COQ4 deficiency, this finding has potential therapeutic implications, as CoQ10 can be supplemented to potentially ameliorate deficits.[7] Consequently, our patient was started on CoQ10 supplementation (200 mg three times daily) with subjective improvement of gait after 8-weeks of therapy, and cardiomyopathy was ruled out via echocardiogram, underscoring the immediate clinical implications of this genetic diagnosis.

Author Roles

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

L.S.: 1A, 1B, 1C, 2A, 2B, 2C, 3A
V.Q.: 1A, 1B, 1C, 2A, 2B, 2C, 3B
A.T.: 1A, 1B, 1C, 2A, 2B, 2C, 3B
U.Z.: 1A, 1B, 1C, 2A, 2B, 2C, 3B
L.T.: 1C, 3B
R.S.: 1C, 3B
K.Y.: 1A, 1B, 1C, 3B
D.E.-F.: 1A, 1B, 1C, 2A, 2B, 2C, 3B

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Disclosures

Ethical Compliance Statement: This patient was identified through the HSP Genomic Sequencing Initiative (NCT05354622), part of the Children's Rare Disease Cohorts at Boston Children's Hospital (IRB-P00039630). Written consent was obtained. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. ■

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