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Case report

Clinical whole-exome sequencing reveals a common pathogenic variant in patients with CoQ_{10} deficiency: An underdiagnosed cause of mitochondriopathy

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ABSTRACT

Background: Primary CoQ deficiency occurs because of the defective biosynthesis of coenzyme Q, one of the key components of the mitochondrial electron transport chain. Patients with this disease present with a myriad of non-specific symptoms and signs, posing a diagnostic challenge. Whole-exome sequencing is vital in the diagnosis of these cases.

Case: Three unrelated cases presenting as either encephalopathy or cardiomyopathy have been diagnosed to harbor a common pathogenic variant c.370G > A in *COQ4*. *COQ4* encodes a key structural component for stabilizing the multienzymatic CoQ biosynthesis complex. This variant is detected only among East and South Asian populations.

Conclusions: Based on the population data and our case series, *COQ4*-related mitochondriopathy is likely an underrecognized condition. We recommend including the *COQ4* c.370G > A variant as a part of the screening process for mitochondriopathy in Chinese populations.

1. Introduction

Coenzyme Q, also known as CoQ or CoQ10 in humans, is a redox-active non-protein-bound lipidic component of the mitochondrial electron transport chain (mETC), transferring electrons from complexes I and II to complex III for the generation of energy in the form of ATP by the OXPHOS system. Its role in the mETC is particularly vital for high energy-dependent organs, such as the brain, heart, kidney, or liver. CoQ is also an important antioxidant and electron acceptor for other cellular dehydrogenases such as dihydroorotate dehydrogenase or mitochondrial glycerol-3-phosphate dehydrogenase, among others [1].

The CoQ biosynthetic pathway is complex and most of the information regarding this pathway is derived from studies performed in yeast, in which the products of at least 11 genes are necessary. Although information about the human CoQ biosynthetic pathway is limited, it has been reported to involve the products of at least the *PDSS1*, *PDSS2*, *COQ2*, *COQ3*, *COQ4*, *COQ5*, *COQ6*, *COQ7*, *COQ8A*, *COQ8B*, *COQ9*, and *COQ10* genes [1–4]. Any genetic defects of these genes will result in a CoQ deficiency, a rare autosomal recessive disease. Clinical manifestations of primary CoQ deficiency are highly heterogeneous, but they often involve the neurological system, causing seizures, encephalopathy, infantile spasm, cerebellar atrophy, intellectual disability, cerebellar ataxia, or dystonia/hypotonia [1,5–12]. In addition, some patients may further present with cardiomyopathy, respiratory distress, and lactate acidosis [1]. Other systems may also be affected, and the condition may manifest as myopathy, sensorineural hearing loss, retinopathy, and steroid-resistant nephrotic syndrome [13–15]. Nevertheless, the clinical and biochemical features are very non-specific, and hence, many of the cases are potentially underdiagnosed or misdiagnosed. Given the variety of the observed symptoms, a genotype-phenotype correlation for this condition has been difficult to establish [1]. An early diagnosis for patients with CoQ

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deficiency is clinically beneficial since these patients may potentially benefit from high-dose CoQ supplementation [15–19].

In this work, we identified three unrelated cases of primary CoQ10 deficiencies, and a recurring *COQ4* mutation was identified. *COQ4* encodes a potentially non-enzymatic protein that participates in CoQ10 biosynthesis; this protein has been proposed to participate in stabilizing the multienzymatic biosynthetic complex [4]. *COQ4*-related CoQ10 deficiency has been known to cause seizures, fatal neonatal encephalopathy, and hypertrophic cardiomyopathy without any clear, observable genotype-phenotype correlation [1]. Till date, at least 12 families with CoQ10 deficiency due to *COQ4* mutations, mostly from European countries or Northern America, have been reported [1,10,11]. Therefore, it is likely that many of the cases are underdiagnosed, and we recommend including the *COQ4* c.370G > A variant as part of the screening process for mitochondriopathy or suspected CoQ10 deficiency in the Chinese population.

2. Case series

2.1. Case 1

Patient (case 1) was born full term to non-consanguineous Chinese parents; his elder brother was reported to suffer from cerebral degeneration (Fig. 1A) and passed away at the age of 2. The family ignored the diagnosis of the older brother. The index patient initially presented with seizure at the age of 1 month after several episodes of vomiting. He developed convulsions shortly after admission; fluttering eye movements, with the occasional uprolling of the eyeballs lasting 5 s, were observed Two further episodes involving similar movements were noted despite the administration of two doses of phenobarbital. The patient's elder sister was suffering from upper respiratory tract infection around this time. Physical examination of the patient showed no dysmorphism or neurocutaneous stigmata. Muscle power and muscle tone were observed to be normal. Examination of other systems was unremarkable. Although he was afebrile without any other localizing signs, he was treated initially for a central nervous system (CNS) infection with empirical antibiotics and antivirals; the patient was taken off these medications following negative results for the CNS microbiological investigations. He was later diagnosed as having norovirus gastroenteritis. His lactate level was slightly elevated on admission (4.1 mmol/L; RI: < 3.4 mmol/L) but was normalized to 0.9 mmol/L after one day. The pyruvate level was 0.147 mmol/L (RI: 0.057–0.154 μmol/L). Extensive biochemical workup was performed for seizures, with the following normal findings: blood ammonia, liver/renal function, blood urate, blood pH, CSF:blood glucose ratio (2.5 mmol/L and 4.5 mmol/L, respectively; ratio = 56%; repeated on another occasion with a result of 73%), plasma amino acids, plasma very long-chain fatty acids, plasma acylcarnitine, urine organic acids, and CSF neurotransmitters. Lysosomal enzyme studies performed overseas revealed normal results. He subsequently developed intractable epilepsy, global developmental delay (GDD), and progressive cerebral atrophy since he was six months old. Controlling the epileptic seizures was difficult and required the administration of multiple antiepileptics. Magnetic resonance imaging (MRI) at the age of four months showed cerebral atrophy. The auditory brainstem response test showed features of conduction delay in the central auditory pathway. The nerve conduction study showed features of early demyelinating motor neuropathy. The exact cause of these findings remained unknown, and progressive neurodegeneration and frequent breakthrough seizures were observed. Follow-up MRI at the age of two years showed rapid progression of bifrontal cerebral atrophy, with the involvement of bifrontal cortical grey matter and white matter. The patient required prolonged hospitalization since he was five years old due to an episode of aspiration pneumonia. He was referred to the undiagnosed disease program (UDP) at the University of Hong Kong with central apnea due to neurodegeneration when he was six years old. Unfortunately, he succumbed to recurrent apnea and pneumonia a few months after the diagnosis.

2.2. Case 2

Patient (case 2) was born full term as the first child of a non-consanguineous Chinese couple (Fig. 2A). Newborn screening with dried blood spots revealed normal findings. The antenatal and perinatal periods were unremarkable until the age of six months. Her father observed that she showed reduced eye contact. On examination, she was found to be hypotonic with head lag, plagiocephalic, and relatively microcephalic, without other dysmorphisms. There were no neurocutaneous stigmata. She developed an episode of infantile spasms a few days after the initial presentation. She was given a course of high doses of steroids. Extensive biochemical analysis failed to identify the specific causes; normal levels of plasma creatine kinase, urate, ammonia, very long-chain fatty acids, acylcarnitines, homocysteine, and transferrin isoform were observed. Paired plasma and urine creatine and guanidinoacetate levels were normal. Analysis of the plasma amino acids showed mildly elevated alanine 487 levels (RI: 143–439) with mildly elevated blood lactate levels (2.3 mmol/L; ref. < 2.2 mmol/L). Electroencephalogram (EEG) showed potential epileptogenic discharge in the background, which was normalized after one month. MRI of the brain showed prominent subarachnoid and sulcal spaces of the cerebral hemispheres, which are consistent with microcephaly. Brain magnetic resonance spectroscopy (MRS) revealed a lactate peak signal of uncertain significance. After the initial episode of infantile spasms, the patient developed two episodes of status epilepticus at the age of two and three years. The first status epilepticus was precipitated by urinary tract infection, while the other was ascribed to poor anti-epileptic drug compliance. The seizures were otherwise well controlled with levetiracetam. Subsequently, the patient was found to show GDD with minimal progress, generalized dystonia with admixed spasticity, and bilateral visual impairment.

2.3. Case 3

The patient was born preterm at a gestational age of 33 weeks and 4 days with maternal pre-eclampsia and intrauterine growth retardation. He was born flaccid and cyanotic, requiring intubation. After the assisted ventilation was withdrawn, he developed apnea of prematurity, which improved initially with caffeine treatment. Initially, the blood lactate level (3.6 mmol/L) was mildly elevated. The ammonia levels were normal. Sudden deterioration was noted on day 26, with bradycardia. The echocardiogram showed a structurally normal heart, but with a grossly dilated left ventricle and atrium. Grossly impaired left ventricular function was accompanied with a largely non-contracting anterior wall, apex, and basal and posterior walls. The patient succumbed despite maximal support on day 28. The autopsy showed a hypertrophy of the left ventricle, with electron micrographs of cardiac muscle showing swollen mitochondria with the loss of cristae. Occasionally, the cristae of the mitochondria appeared semi-circular (Supplementary Fig. 1A, B, and C).

Cases 1 to 3 were subsequently referred to this laboratory for further genetic analyses for the undiagnosed disease.

3. Materials and methods

3.1. Whole-exome sequencing (WES) analysis and Sanger sequencing analysis

Blood samples were collected from the patients (cases 1 and 2) and their family members. An archived tissue sample was retrieved for case 3. Informed consent was obtained from all the families. Details of genomic DNA extraction and subsequent WES analysis have been described previously [20,21]. DNA extraction from paraffin sections of the

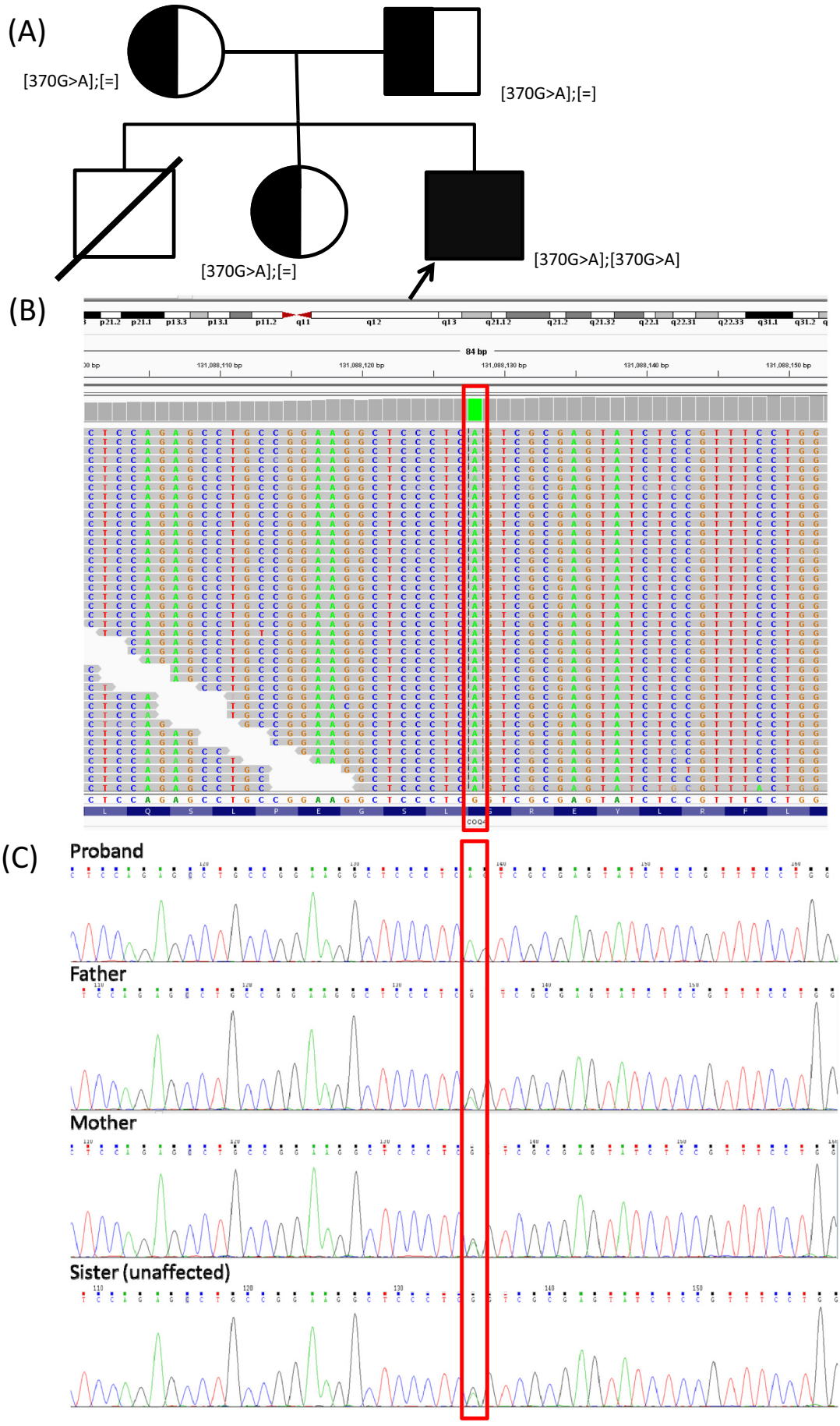

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Fig. 1. (A) Family tree for case 1. (B) Sequencing reads from the WES data are shown using IGV. The position for *COQ4* c.370G > A (p.Gly124Ser) is shown in the red box. (C) Corresponding electropherograms from Sanger sequencing showed that the same pathogenic variant existed in the family. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

cardiac sample was performed according to an in-house protocol. Target enrichment was performed using the SureSelect Target Enrichment System Human All Exon V4 target kit (Agilent Technologies). Sequencing analysis was performed on an Illumina HiSeq 2000 sequencer with the 100-bp paired-end module (Illumina). WES data analysis was performed using VariantStudio (version 2.2.1, Illumina) and an in-house bioinformatics pipeline.

3.2. Mutational analysis of the COQ4 gene

Protocols for polymerase chain reaction (PCR) and Sanger sequencing have been described in our previous work. The PCR conditions and primer sequences for *COQ4* are available upon request. The sequencing results were compared with the National Center for Biotechnology Information (NCBI) reference sequences and the reference sequences NM_016035.3 and NP_05719.2.

3.3. CoQ extraction and HPLC analysis from plasma samples

The lipid fractions from the plasma samples were extracted and analyzed by HPLC. First, 100 µl of plasma was mixed with 1% SDS in the presence of 35 pmol of CoQ6, which was used as the internal standard. The lipids were then dispersed by adding 3 volumes of ethanol:2-propanol (95:5). Hexane-based extraction of lipids (sample:-hexane, 3:5, v:v) was performed in triplicate. All three hexane fractions were subsequently mixed, dried under vacuum, and reconstituted in ethanol prior to HPLC injection. The total lipid extracts were injected into a reverse-phase Beckman 166 HPLC system, equipped with a C18 column (5 µm, 150 × 4.6 mm) and a column oven set at 40 °C. Mobile phase, flow rate, and gradient settings were determined as described in a previous study (Rodríguez-Aguilera et al., 2017). CoQ detection was performed using a Coulochem III ESA electrochemical detector (ECD) linked to the HPLC system.

4. Results

4.1. Mutational analysis identified a common pathogenic variant in COQ4 in three unrelated Chinese families

Case 1 – Whole-exome sequencing (WES) identified a homozygous COQ4 missense variant at c.370G > A leading to p.Gly124Ser (Fig. 1B). Segregation studies showed that both parents were heterozygous for the mutation. Further Sanger sequencing was performed for the asymptomatic sister, which confirmed her carrier status (Fig. 1C).

Case 2 – WES identified two heterozygous variants in COQ4, c.370G > A and c.371G > T (p.Gly124Val). The NGS data also support that the two variants are in trans (Fig. 2B), and the phasing is further substantiated by the Sanger sequencing results of samples from the parents (Fig. 2C); c.370G > A was shown to be inherited from the father and the c.371G > T, from the mother. The two variants (c.370G > A and c.371G > T) are just 1 bp apart; this allows their phasing during sequencing via the synthesis of individual reads (Fig. 2C).

Case 3 – This case was reviewed by our Undiagnosed Disease Program (UDP), and COQ4 deficiency was suspected by the pathologist due to the resemblance of the mitochondrial morphology of this case with that of a published case of COQ4 mutation [12]. For this reason, a targeted genetic analysis instead of WES was performed on the COQ4 gene, using an archived cardiac sample from the autopsy. Sanger sequencing analysis of the DNA extracted from the archived sample showed two heterozygous mutations of COQ4 at c.370G > A and c.533G > A (Supplementary Fig. 1D and E, respectively). Unfortunately, parental samples were not available for further analysis.

A summary of the clinical features and genetic findings is shown in Table 1.

4.2. Functional analysis of COQ activities

Detailed functional analysis of skin fibroblasts and muscle biopsy was available only for case 2. This was not performed for cases 1 and 3 as both patients had already succumbed. In case 2, the plasma CoQ10 level was significantly lower than that of the control subject (Fig. 2D). The same finding was observed in the skin fibroblast analysis (report provided by the family and the test was performed at the Radboud University Medical Center at Nijmegen; raw data not available). However, muscle biopsy, performed at the Newcastle Upon Tyne Mitochondrial Centre, showed normal histology, normal respiratory chain, and immunohistochemical staining for CoQ10 (report provided by the family).

4.3. Outcome after CoQ10 supplementation

Case 1 – CoQ10 supplementation was started at a dose of 200 mg, 3 times a day (TDS) at the age of six. A subjective improvement of the patient's awareness to the surroundings was the major observation. The patient succumbed two months later due to recurrent central apnea, aspiration pneumonia, and respiratory failure, and no further clinical improvement was reported. Case 2 – Supplementation was commenced when the patient was nine months old at a dose of 250 mg per day; then, the dose was increased to 400 mg per day. Intriguingly, the parents reported an increase in the alertness of the child after CoQ10 supplementation. After a year on ubiquinol, the regimen was switched to liquid liposomal ubiquinol at a dose of 100 mg per day. No further seizures were documented after the second episode of status epilepticus at the age of three years. Case 3 – CoQ10 supplementation was not initiated for this patient.

5. Discussion

Three unrelated cases of *COQ4*-related primary CoQ10 deficiency were presented. They all harbored the same missense variant, c.370G > A (p.Gly124Ser). According to the Genome Aggregation Database (gnomAD) [22], this particular variant was detected only in East Asian and South Asian populations, at an allele frequency of 0.1504% and 0.006533% respectively. Probably, the c.370G > A is a founder mutation in the Chinese population. This is a missense putative pathogenic variant causing the substitution of the highly conserved glycine at position 124 to serine. Multiple in silico analyses (SIFT, MutationTaster, and PolyPhen-2) have predicted this variant to be deleterious, disease-causing, and probably damaging, respectively. In this case series, the pathogenic significance of this variant is further substantiated. Firstly, no other disease-causing variant was identified in case 1 through WES; secondly, the biochemical phenotype was further substantiated by the decreased levels of CoQ10 in the skin fibroblasts of case 2, and thirdly, post-mortem EM in case 3 showed features that were consistent with those described in a previously published case of *COQ4* mutation (Supplementary Fig. 1A, B, and C). In accordance with the American College of Genetics and Genomics (ACMG) guidelines, this variant may be classified as “likely pathogenic” (Table 2). On the other hand, EM findings, which reported swollen mitochondria with loss of cristae and semi-circular arrangements of cristae, may raise the suspicion of *COQ4* mutations.

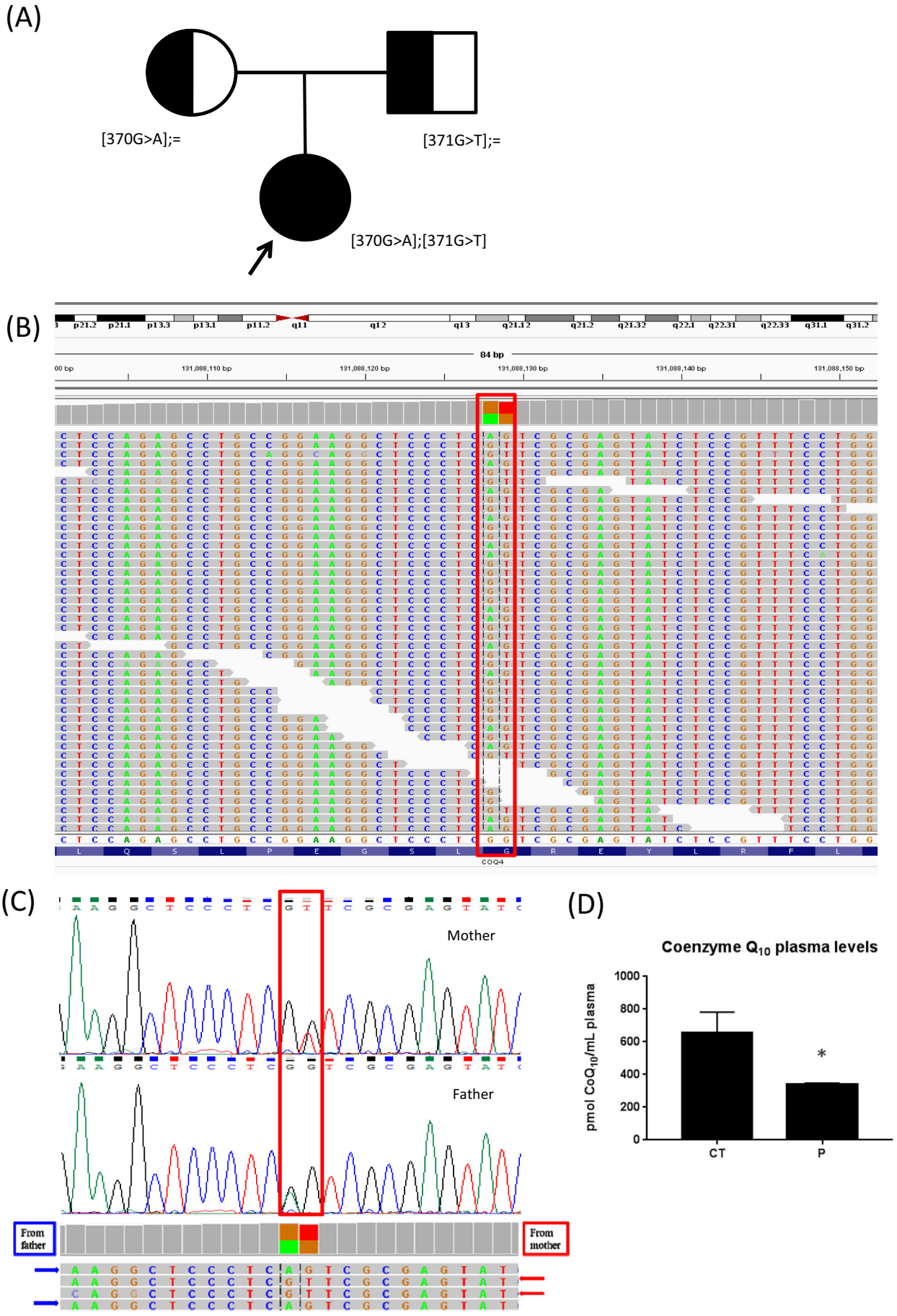

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Fig. 2. (A) Family tree for case 2. (B) Sequencing reads from the WES data are shown using IGV. Heterozygous mutations of *COQ4*, i.e., c.370G > A (p.Gly124Ser) and c.371G > T (p.Gly124Val), are shown in the red box. The NGS data also conveniently phase the two variants, c.370G > A and c.371G > T, as those that are *in trans*. (C) Sanger sequencing data of the mother and father, illustrating that c.370G > A was inherited from the father, while c.371G > T was inherited from the mother. An enlarged view of Fig. 2B has been shown to better illustrate the phasing from the proband's NGS data. The paternal and maternal alleles are shown by the blue and red arrows, respectively. Because the two variants (c.370G > A and c.371G > T) are just 1 bp apart, this special situation allows phasing during sequencing via the synthesis of individual reads. (D) The plasma CoQ10 level in this patient was significantly lower than that in the control samples. Three lipid extractions from both the control and patient samples were performed. Each replicate was analyzed twice by HPLC. Statistical analysis performed using the Mann-Whitney Test; *p*-value = .0022. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Summary of three unrelated cases of primary CoQ10 deficiency due to *COQ4* mutation. c.370G > A (p.Gly124Ser) is a common pathogenic variant.

Case	Presenting symptoms	Zygosity	Mutation in COQ4	Protein change	Onset age	Age at the start of CoQ supplementation	Remarks
1	Epilepsy	Homozygous	c.370G > A	Gly124Ser	1 m	6 y	Succumbed at the age of 7 y
2	Infantile spasm	Heterozygous	c.370G > A	Gly124Ser	6 m	9 m	Alive with GDD since the age of 3 y
		Heterozygous	c.371G > T	Gly124Val			
3	Fatal neonatal hypertrophic cardiomyopathy	Heterozygous	c.370G > A	Gly124Ser	D0	N/A	Succumbed on day 28
		Heterozygous	c.533G > A	Gly178Glu			

Table 2
Classification and in silico prediction of the three variants.

Variant	Protein changes	Detected in case	Align GVGD	SIFT	Mutation-Taster	PolyPhen-2	ACMG classification	Remarks
c.370G > A	Gly124Ser	All	GV: 0.00 GD: 55.27	Deleterious	Disease-causing	Probably damaging	Likely pathogenic	PS3, PM2, PP1, PP3
c.371G > T	Gly124Val	2	GV: 0.00 GD: 109.55	Deleterious	Disease causing	Probably damaging	Likely pathogenic	PS3, PM2, PP1, PP3
c.533G > A	Gly178Glu	3	GV: 0.00 GD: 97.85	Deleterious	Disease causing	Probably damaging	Likely pathogenic	PM2, PM3, PP1, PP3

According to the gnomAD browser [22], no homozygous cases for the variant c.370G > A have been reported. Based on the allele frequency from the gnomAD browser and Hardy-Weinberg equilibrium, the expected frequencies for the carriers and cases in the Chinese population are 0.0030 (about 1 in 333) and 2.3e-06 (about 1 in 435,000), respectively. The population in this location is about 7.4 million (end of 2017), and therefore, we expect many other patients to be likely undiagnosed or enrolled in other studies.

According to the gnomAD browser, the variant c.371G > T (p.Gly124Val) has been detected only in the East Asian population, with a frequency of 0.0054%, while c.533G > A (p.Gly178Glu) has been detected in the East Asian population, with a frequency of 0.016% [22]. They were also predicted to be deleterious, disease-causing, and probably damaging by SIFT, MutationTaster, and PolyPhen-2, respectively. The two variants were also classified as “likely pathogenic” based on the ACMG guidelines (Table 2).

In case 2, both skin fibroblasts and plasma showed a significantly low CoQ10 content. This functional analysis provided additional evidence of the pathogenicity of the c.370G > A and c.371G > T variants in *COQ4*. Additional functional analysis further substantiated this conclusion with genetic findings. Unfortunately, appropriate samples may not be available in case of all patients, e.g. case 1 and 3. Thus, the CoQ10 level could not be measured for these two cases. Indeed, false negative results have been reported in functional analysis, for example, in the muscle biopsy for the diagnosis of primary CoQ10 deficiency [23]. In Montero's work, two out of five patients with CoQ10 deficiency did not show reduced CoQ10 levels in the muscles, while all cases showed reduced CoQ10 levels in the fibroblasts. In our case, we also observed a similar finding for case 2, for whom the muscle biopsy showed normal histology and further functional analysis showed normal respiratory chain and immunohistochemical staining for CoQ10 (functional analysis performed at the Newcastle Upon Tyne Mitochondrial Centre). A skin fibroblast test may first be considered, given its easier access and the potentially unlimited availability of biological material for further studies. Alternatively, a clinical WES analysis has the added benefit of being able to identify the causative mutation from genes not included in the initial panel [4].

Any patient with suspected CoQ deficiency should be treated with CoQ10 supplementation before any genetic or biochemical confirmation. Importantly, the pharmacology of CoQ10 has been well studied for years, and it has been considered safe in various groups of patients [24–26]. Delay in CoQ supplementation may result in irreversible damage, for example, in case 1, for which CoQ10 supplementation was started at the age of six, and only an improvement in the patient's awareness was observed. The limited clinical improvement is probably due to irreversible neurological damage. Case 2 was diagnosed early, at the age of nine months (three months after symptom onset). It was noted that the seizure condition was controlled, and there was also an improvement in the patient's awareness. The patient had only one further episode of epilepsy at the age of three. Clinically, there was no other major improvement. Early treatment of primary CoQ10 deficiency by oral supplementation with high doses of CoQ10 has been demonstrated to restrict the disease progression, but the preexisting tissue damage cannot be reversed [16].

CoQ supplementation has been used to treat a variety of other clinical conditions [27,28], such as for a case of a Chinese patient with Leigh syndrome who showed obvious improvement of clinical features, as supported by MRI analysis [29], or for different cases of Friedreich's Ataxia [27], among many others. Nevertheless, the therapeutic response could not be predicted from the administered dosage, and therapeutic drug monitoring (TDM) may be necessary for these patients. Blood CoQ quantitation has been proposed to this end, but further experimental work is needed to establish the correlation between blood and tissue CoQ levels, in particular, the CSF CoQ10 levels [30]. This may explain the limited clinical response in case 1.

In conclusion, we encountered three cases of primary CoQ deficiency confirmed by molecular genetic analysis. c.370G > A is a common pathogenic variant in Chinese patients, and we predicted that this condition is under-diagnosed and not well recognized. Hence, we recommend including this variant as a part of the screening process for

mitochondriopathy in the Chinese population.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2019.07.016.

Potential conflicts of interest

No reported conflicts.

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