CASE REPORT

Primary coenzyme Q10 deficiency-7: expanded phenotypic spectrum and a founder mutation in southern Chinese

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Primary coenzyme Q10 deficiency-7 (COQ10D7) is a rare mitochondrial disease caused by biallelic mutations in COQ4. Here we report the largest cohort of COQ10D7 to date, with 11 southern Chinese patients confirmed with biallelic COQ4 mutations. Five of them have the classical neonatal-onset encephalo-cardiomyopathy, while the others have infantile onset with more heterogeneous clinical presentations. We also identify a founder mutation COQ4 (NM_016035.5): c.370G>A, p.(Gly124Ser) for COQ10D7, suggesting a higher chance of occurrence in the southern Chinese. This study helps improve understanding of the clinical spectrum of this disorder.

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INTRODUCTION

Coenzyme Q10 (CoQ), also known as ubiquinone, is crucial for the function of mitochondrial respiratory chain complexes. Currently, the pathway of CoQ biosynthesis is known to involve at least 18 proteins. Primary CoQ deficiencies in humans involve genetic mutations in COQ2, PDSS1, PDSS2, COQ8A, COQ9, COQ6, COQ4, or COQ7.1

The primary COQ10 deficiency-7 (COQ10D7, MIM: 616276) is caused by autosomal-recessive mutations in COQ4. COQ4 is hypothesized to take part in stabilizing the CoQ complex.2 To date, biallelic COQ4 mutations have been described in 16 patients from 11 unrelated families. They were reported in two case series (with five to six cases each) and three case reports. The patients described had common features of cardiomyopathy, encephalopathy, lactic acidosis often with a neonatal onset, and death in the neonatal or infantile period.3–5 Two siblings of childhood onset presenting with spinocerebellar ataxia and stroke-like episodes5 and two Chinese siblings with neonatal onset of dystonia, seizures, lactic acidosis, and cerebellar atrophy were described in recent case reports.5

In this report, we have 11 patients (4 males and 7 females) from 9 unrelated families who were managed by the Medical Genetics division of the Department of Paediatrics and Adolescent Medicine at the University of Hong Kong and the Department of Medical Genetics and Pediatrics at the National Taiwan University Hospital in the period of 2014–2018. They presented with two overlapping phenotypes: the classical neonatal-onset encephalo-cardiomyopathy and infantile-onset encephalopathy without cardiomyopathy. They were diagnosed as COQ10D7 due to homozygous or compound heterozygous COQ4 mutations. All genetic diagnoses were made by whole-exome sequencing (WES) except Patient 4, Patient 5, and Patient 11 due to their known family history and recognizable features of COQ10D7. More importantly, we have identified a Chinese-specific COQ4 founder mutation in 10 subjects, 5 of whom are homozygous for that mutation.

CASE REPORTS

The study was approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW12-211) and the National Taiwan University Hospital (201703073RINB). Written informed consent was obtained from subjects or their parents. A summary of the clinical, biochemical, and radiological characteristics of the 11 patients with COQ4 mutations identified is presented in Table 1. Patients 1–5 had the classical neonatal-onset phenotype described by Brea-Calvo et al. and Chung et al., whereas Patients 6–11 had later onset and more heterogeneous features. The frequency of distinct phenotypes compared with previous studies is summarized in Table 2. The corresponding MRI (magnetic resonance imaging) images are presented in Fig. 1. The pedigrees of the nine families are presented in Fig. 2.

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| Subject | Family 1 | Family 2 | Family 3 |
|---------|---------|---------|---------|
| Sex     | Male    | Male    | Female  |
| Age at presentation | Neonatal | Neonatal | Neonatal |
| Last follow-up | Passed away at 8 months (redirection of care) | Passed away at 2.5 days (unknown cause) | Neonatal 6 months |
| CoQ4 mutation | c.370G>A/c.402+1G>C | Homozygous c.370G>A | Homozygous c.433C>G |
| Hypotonia | ✓ | ✓ | ✓ |
| Seizures | ✓ | ✓ | ✓ |
| Cardiomyopathy | ✓ | ✓ | ✓ |
| Other presented problems | Severe GDD, cortical visual impairment, bilateral severe to profound hearing impairment, myopathy | Apnea | Severe GDD, poor oromotor function |

| Timing of MRI or other imaging | 3 weeks and 3 months | — | 7 weeks |
| MRI brain or other imaging findings | Symmetrical T1 and T2 hyperintensity with restricted diffusion at bilateral lentiform nuclei, subsequently infarcts with cystic changes, Foci of restricted diffusion also at bilateral frontal white matter | — | Mild cerebellar hypoplasia, mild thinning of corpus callosum |

| MRI brain or other imaging findings | Neonatal stage: symmetrical T1 hyperintensity at bilateral basal ganglia, mild cerebellar hypoplasia, later with generalized progressive cerebellar and cerebral atrophy with diffuse white matter loss, thinning of |

| USG brain at birth | USG brain at birth | USG brain: cerebellar hypoplasia |

| MR at age 12 years: bilateral increased signal intensity in FLAIR and T2W sequencing in both occipital cortical and juxtaglomeral areas MRI at age 17 years cerebellar atrophy, widened ventricular space, scars from cortical necrotic | — | — | — | — |

### Notes
- **Family 1**: Subject 1, Subject 2, Subject 3, Subject 4, Subject 5
- **Family 2**: Subject S1, Subject S2, Subject S3, Subject S4, Subject S5
- **Family 3**: Subject S1, Subject S2, Subject S3, Subject S4, Subject S5
## Table 1 continued

| Phenotype group | Neonatal-onset encephalo-cardiomyopathy |
|-----------------|----------------------------------------|
| **Reference**   | This study                              |
| **Family 1**    | **Family 3**                            |
| **Subject**     | 1 2 3 4 5  S1  S2  S3  S4  S5           |
| MRS: raised lactate peaks at bilateral basal ganglia and cerebral white matter. Mild cerebellar hypoplasia | corpus callosum. Cystic changes within cerebral white matter, bilateral basal ganglia, thalami. MRS: raised lactate peaks at bilateral basal ganglia | lesions in both occipital areas |
| Lactic acidosis | √  √  √  √  √  ×  √  √  ×               |
| Effect of CoQ10 supplement | No significant improvement No significant improvement Cardiac function stable No significant improvement Not used Not used Not used Not used Not used |

| Phenotype group | Neonatal-onset encephalo-cardiomyopathy |
|-----------------|----------------------------------------|
| **Reference**   | Chung et al.3 | Sondheimer et al.4 | Bosch et al.5 | Lu et al.6 |
| **Family 1**    | Family 3      | Family 1           | Family 1      | Family 1   |
| **Subject**     | Proband 1     | Proband 3          | Proband 4     | Patient    |
| **Proband 2**   | Sibling of Proband 1 | Proband 3          | Sibling of Proband 3 | Patient II-1 |
| **Proband 3**   | Proband 4     | Patient            | Patient 2     | Patient II-2 |
| **Proband 4**   | Patient       | Patient I-2        | Patient II-2  |
| **Sex**         | Female        | Female             | Female        | Female     |
| **Age at presentation** | Neonatal | Neonatal | Neonatal | Neonatal |
| **CoQ4 mutation** | c.245T>A/c.473G>A | Homozygous c.718C>T | Homozygous c.197_198delGCinsAA/c.202G>C | Homozygous c.718C>T |
| **CoQ4 mutation** | c.197_198delGCinsAA/c.202G>C | Homozygous c.23_33del11/c.356C>T/c.331G>T/c.356C>T | Homozygous c.230C>T/c.507G>T/c.402+1G>A | Homozygous c.370G>A |
| **Hypotonia**   | √             | —                 | —             | —          |
| **Seizures**    | √ (Suspected) | ×                 | ×             | —          |
| **Cardiomyopathy** | √            | √                 | ×             | —          |
| **Other presented problems** | — | IUGR | IUGR | IUGR |
|**Moderate cerebellar hypoplasia** | Moderate cerebellar hypoplasia | Feeding difficulties, GDD, microcephaly | Feeding difficulties, left hip dysplasia | Gastroesophageal reflux requiring fundoplication, delayed visual maturation without structural abnormality of the eyes, bilateral hearing loss, and absence of development |
|**Delayed speech** | Tremor since age 4 years | Progressive motor deterioration; wheelchair bound by age 12 years, then dysarthria | Spastic tetraplegia | Delayed speech; Tremor since age 10 years |
|**Hearing impairment** | Feeding difficulty | Feeding difficulties | Feeding difficulties | Feeding difficulty; Progressive motor deterioration |
|**Nystagmus**    | —             | —                 | —             | —          |
|**Rearrangement** | (cardiomegaly on chest X ray) | —                 | —             | —          |
Table 1 continued

| Phenotype group | Neonatal-onset encephalo-cardiomyopathy | Infante-onset encephalo-cardiomyopathy |
|----------------|----------------------------------------|---------------------------------------|
| Reference       | Chung et al. 2                         | This study                            |
| Subject         | Family 1                               | Family 2                              |
| Proband 1       | Sibling of Proband 1                   | Subject 6                             |
| Proband 2       | Proband 3                              | Subject 7                             |
| Proband 3       | Sibling of Proband 3                   | Subject 8                             |
| Proband 4       | Patient                                | Subject 9                             |
|                   | Patient II-1                           | Family 10                             |
|                  | Patient II-2                           |                                      |
| Timing of MRI or other imaging | Early neonatal period | Day 1 | Fetal MRI at 30 weeks and Day 2 | Unknown | First week and tenth week | 10 years | 2 months | 1 month, 4 months and 3 years and 8 months |
| MRI brain or other imaging findings | Small cerebellar size and diffuse T2 white matter hyperintensity | Autopsy: Cerebellar and brainstem hypoplasia and microdysgenesis | MRI normal intracranial anatomy, transverse cerebellar diameter 10–15th percentile | MRI on Day 2: decreased cerebellar hemisphere volume | Normal | First week: focal regions of cortical increased T1 signal and magnetic resonance spectroscopy identified enlarged lactate peaks | 10 years | 13 years | 2 months | 1 month, 4 months and 3 years and 8 months |
| Lactic acidosis | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Effect of CoQ10 supplement | Improvement after 2 weeks of age but recurrent episode of metabolic and hemodynamic decompensation | Not used | Not used | Not used | Not used | Not used | Not used | No significant improvement | Not used | — | Walk test stable over the period of a year | Walk test stable over the period of a year | No significant improvement | Improved seizure control but no improvement in dystonia and motor development |

Phenotype group: Neonatal-onset encephalo-cardiomyopathy
- Subject: Family 1
  - Proband 1: Sibling of Proband 1
  - Proband 2: Proband 3
  - Proband 3: Sibling of Proband 3
  - Proband 4: Patient

Phenotype group: Infantile-onset encephalo-cardiomyopathy
- Subject: This study
  - 6
  - 7
  - 8
  - 9
  - 10
  - 11

| Reference       | Sondheimer et al. 3 | Bosch et al. 4 | Lu et al. 5 |
|-----------------|---------------------|----------------|-------------|
| Family 1        | Family 1            | Family 1       | Family 1    |
| Subject         | Family 1            | Family 1       | Family 1    |
| Proband 1       | Sibling of Proband 1| Proband 2      | Proband 3   |
| Proband 2       | Proband 3           | Sibling of Proband 3 | Proband 4 |
| Proband 3       | Sibling of Proband 3| Proband 4      | Patient     |
| Proband 4       | Patient             | Patient II-1   | Patient II-2 |

| Timing of MRI or other imaging | Early neonatal period | Day 1 | Fetal MRI at 30 weeks and Day 2 | Unknown | First week and tenth week | 10 years | 2 months | 1 month, 4 months and 3 years and 8 months |
| MRI brain or other imaging findings | Small cerebellar size and diffuse T2 white matter hyperintensity | Autopsy: Cerebellar and brainstem hypoplasia and microdysgenesis | MRI normal intracranial anatomy, transverse cerebellar diameter 10–15th percentile | MRI on Day 2: decreased cerebellar hemisphere volume | Normal | First week: focal regions of cortical increased T1 signal and magnetic resonance spectroscopy identified enlarged lactate peaks | 10 years | 13 years | 2 months | 1 month, 4 months and 3 years and 8 months |
| Lactic acidosis | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Effect of CoQ10 supplement | Improvement after 2 weeks of age but recurrent episode of metabolic and hemodynamic decompensation | Not used | Not used | Not used | Not used | Not used | Not used | No significant improvement | Not used | — | Walk test stable over the period of a year | Walk test stable over the period of a year | No significant improvement | Improved seizure control but no improvement in dystonia and motor development |
| Subject | 6 | 7 | 8 | 9 | 10 | 11 |
|---------|---|---|---|---|----|----|
| Cardiomyopathy | × | × | × | × | ✓ | ✓ |
| Other presented problems | Severe GDD, generalized dystonia, cortical visual impairment, impaired oromotor function | Severe GDD, generalized dystonia and spasticity, cortical visual impairment, impaired oromotor function | Severe GDD, generalized dystonia and spasticity, cortical visual impairment | DD | Severe DD, bilateral cortical blindness | DD, intermittent spasticity, impaired oromotor function |
| Timing of MRI or other imaging | Day 21, Day 40, and 1 year 4 months | 6 months | 6, 7, and 35 months | 32 months | 14 months | 1 year 2 months |
| MRI brain or other imaging findings | Mild cerebral atrophy with bilateral frontal predominance | Severe cerebral atrophy | Mild cerebral and cerebellar hypoplasia. Small focus of T2 and FLAIR hyperintensity at the left lentiform nucleus at 35 months. MRS: raised lactate peaks at bilateral basal ganglia and frontal white matter at 6 months, normalized by 7 months | Moderate cerebellar atrophy without isolated vermian hypoplasia, cerebral atrophy, symmetrical loss of cerebral white matter particularly in bilateral frontal and anterior temporal regions. Corpus callosum was thinned, basal ganglia and pons unremarkable | Mild thinning of corpus callosum | Mild cerebellar atrophy and cerebral atrophy, white matter cystic changes with bilateral frontal and anterior temporal predominance. Corpus callosum thinning, preserved basal ganglia and brainstem |
| Lactic acidosis | ✓ | ✓ | ✓ | ✓ | ✓ | × |
| Effect of CoQ10 supplement | No significant improvement | No significant improvement | Subjective improvement in response | Stable condition | Some improvement in seizure control and development | Not used |

*MRS* magnetic resonance spectroscopy, *MRI* magnetic resonance imaging, *FLAIR* fluid-attenuated inversion recovery, *GDD* global developmental delay, *DD* developmental delay, *IUGR* intrauterine growth restriction, *USG* ultrasound
Frontal white matter (Fig. 1a). Foci of restricted diffusion were also detected at bilateral ventricular tachycardia, and respiratory failure requiring intubation and intrauterine growth restriction (IUGR). He was born at 39 weeks with an antenatal history of IUGR. She developed respiratory distress shortly after birth. On day 22 of life, she had cardiogenic shock. Echocardiogram showed poor contractility with a left ventricular ejection fraction of 20% and a moderate pericardial effusion. There was associated lactic acidemia (24 mmol/L; reference range 0.5–2.2) and hyperammonemia (139 µmol/L; reference range <100). She was empirically given CoQ10 supplementation and intravenous immunoglobulin. Her cardiac function improved gradually and normalized by day 32 of life. She developed seizures at 4 months of age requiring multiple anticonvulsants. She is severely delayed developmentally. WES revealed a homozygous COQ4 mutation c.370G>A, p.(Gly124Ser).

Patient 4 and Patient 5
Patient 4 was the younger sister of Patient 5. She had antenatal history of IUGR and was born at 38 weeks. Immediately postnatal, she developed respiratory distress with intermittent apnea and lactic acidemia (up to 10 mmol/L; reference range 0.5–2.2). MRI brain showed symmetrical T1 and T2 hyperintensity with restricted diffusion at bilateral lentiform nuclei. Foci of restricted diffusion were also detected at bilateral frontal white matter (Fig. 1a–c). Magnetic resonance spectroscopy (MRS) showed raised lactate peaks at bilateral basal ganglia and cerebral white matter. Subsequent follow-up MRI showed established infarcts with cystic changes at bilateral lentiform nuclei (Fig. 1d). Mild cerebellar hypoplasia was also noted. Serial echocardiography in the following months showed progressive septal and ventricular myocardial hypertrophy. WES identified compound heterozygous mutations in COQ4, a missense c.370G>A, p.(Gly124Ser) and a splicing mutation c.402+1G>C. Functional analysis of the skin fibroblasts showed ETC complex II deficiency due to low CoQ concentration. At 5 months of age, CoQ10 supplementation up to 40 mg/kg/day. At 8 months, in view of poor neurological prognosis and poor response to CoQ10 treatment, he was diverted to comfort care and extubated. He passed away shortly from respiratory failure.

Patient 5
Patient 5 was the elder sister of Patient 4. She was born at 39 weeks with an antenatal history of IUGR. She developed seizures from 2 months of age with associated lactic acidosis and respiratory failure requiring home ventilation. Chest radiograph showed cardiomegaly. CoQ10 supplementation was tried at 1 year of age but passed way from respiratory failure 1 month after. After the genetic diagnosis of her younger sister, Sanger sequencing was performed retrospectively and revealed the same compound heterozygous COQ4 mutation: c.370G>A, p.(Gly124Ser) and c.402+1G>C. CoQ10 supplementation has been started since age of 4 years 5 months.

### Table 2. Phenotypic comparison between patients in this study and previously reported cases

| Feature               | This study | Chung et al. | Brea-Calvo et al. | Sondheimer et al. | Bosch et al. | Lu et al. |
|-----------------------|------------|--------------|------------------|------------------|--------------|-----------|
| Number of subjects    | 11         | 6            | 5                | 1                | 2            | 2         |
| Female-to-male ratio  | 7:4        | 6:0          | 3:2              | 0:1              | 1:1          | 1:1       |
| Age of presentation   | Birth to 8 months | Birth to day 1 | Birth to 6 h | 1 day | 4–9 years | 1–2 months |
| Neonatal onset        | 5/11 (45%) | 6/6 (100%)   | 4/5 (80%)        | 1/1 (100%)       | 0/2 (0%)     | 2/2 (100%) |
| Infantile onset       | 6/11 (54%) | 0/6 (0%)     | 1/5 (20%)        | 0/1 (0%)         | 0/2 (0%)     | 0/2 (0%)  |
| Childhood onset       | 0/11 (0%)  | 0/6 (0%)     | 0/5 (0%)         | 0/1 (0%)         | 2/2 (100%)   | 0/2 (0%)  |
| Respiratory distress  | 5/11 (45%) | 6/6 (100%)   | 4/4/100%         | 1/1 (100%)       | —            | 2/2 (100%) |
| Cardiomyopathy        | 6/11 (54%) | 5/6 (83%)    | 2/5 (40%)        | 1/1 (100%)       | 1/2 (50%)    |           |
| Hypotonia             | 7/11 (64%) | 4/5 (100%)   | 2/5 (40%)        | 1/1 (100%)       | —            |           |
| Dystonia              | 2/11 (18%) | —            | —                | —                | 2/2 (100%)   |           |
| Seizures              | 8/11 (73%) | 3/6 (50%)    | 3/5 (60%)        | 1/1 (100%)       | 2/2 (100%)   | 2/2 (100%) |
| Lactic acidosis       | 10/11 (91%)| 4/6 (67%)    | 4/5 (80%)        | 1/1 (100%)       | —            | 2/2 (100%) |
| Cerebellar atrophy    | 6/11 (54%) | 4/5 (80%)    | 3/5 (60%)        | —                | 2/2 (100%)   |           |
| Basal ganglia         | 5/11 (45%) | —            | —                | —                | 1/2 (50%)    |           |

*Lacking information from one patient
Patient 6
Patient 6 presented at 8 months of life with severe global developmental delay, microcephaly, generalized dystonia, cortical visual impairment, and oromotor dysfunction. Metabolic workup revealed lactic acidemia of 2.5–5.9 mmol/L and hyperalanemia (626 µmol/L; reference range 143–439). WES revealed compound heterozygous mutations in the \( \text{COQ4} \) gene: \( \text{c.550T>C, p.} \text{(Trp184Arg)} \) and \( \text{c.402} + 1\text{G>A} \). Functional analysis of the skin fibroblasts showed ETC complex II+III deficiency with low CoQ concentration. There was no further follow-up because of overseas adoption.

Patient 7
Patient 7 was a girl, born full term. She had bilateral cortical visual impairment since birth and progressive oromotor dysfunction requiring gastrostomy feeding. She had severe global developmental delay. She developed generalized dystonia and spasticity around 5 months of age. Lactic acidemia of 2.4–3.2 mmol/L was present. WES revealed a homozygous variant in the \( \text{COQ4} \) gene: \( \text{c.370G>A, p.(Gly124Ser)} \). Functional analysis of the skin fibroblasts showed ETC complex II+III deficiency and low CoQ concentration. She had been on CoQ10 supplement since 2 years old. There was no clinical improvement and the patient died at 3 years and 6 months of age.

Patient 8
Patient 8 is a girl, born full term. She developed infantile spasms at 6 months of age. Metabolic workup showed lactic acidemia at 2.2–4.2 mmol/L and hyperalanemia (487 µmol/L; reference range 143–439). WES revealed compound heterozygous variants of the \( \text{COQ4} \) gene: \( \text{c.371G>T, p.(Gly124Val)} \) inherited from the mother and \( \text{c.370G>A, p.(Gly124Ser)} \) inherited from the father. Interestingly, respiratory chain enzymology of the skeletal muscle activities was normal but skin fibroblast functional analysis showed ETC complex II+III deficiency and low CoQ10 concentration. CoQ10 supplement has been given since 9 months of age.

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**Fig. 1** Cerebral magnetic resonance (MR) findings. a Axial T1W, b axial FLAIR, c DWI from Patient 1 at neonatal stage, and d axial T2W at follow-up; e axial T1W and f MR spectroscopy (MRS) at basal ganglia at neonate and g axial T1W at infant stages from Patient 4; h coronal T2W, i sagittal T1W, j axial T2W, k axial T1W from Patient 11. MR features include cerebellar atrophy (white arrows) (h, i) with progression (e, g); cerebral atrophy with frontal and anterior temporal lobar predominance (i–k); thinning of the corpus callosum (i); white matter loss and cystic change with frontal predominance (asterisks) (j, k); basal ganglia involvement with restricted diffusion and cystic change on follow-up (curved arrows) (a–d); lactate peak at around 1.3 ppm on MRS (arrowheads) (f).
with subjective improvement in responsiveness. She is alive and has achieved fair seizure control with levetiracetam and global developmental delay.

**Patient 9**
Patient 9 is a boy, born full term at 40 weeks. He presented with infantile spasms at 2 months of age. CoQ10 supplementation started at 7 years of age and has remained stable. WES revealed a homozygous \( \text{COQ4} \) mutation, c.370G>A, p.(Gly124Ser). Skin fibroblast functional analysis showed ETC complex II+III deficiency and low CoQ concentration.

**Patient 10 and Patient 11**
Patient 10 is the younger sister of Patient 11. She was born at 36 weeks. She developed transient respiratory distress after birth. She was asymptomatic until 2 months of age when she developed progressive hypotonia, cortical visual impairment, severe developmental delay, and seizures requiring multiple anticonvulsants. Her echocardiogram showed progressive dilated cardiomyopathy.

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**Fig. 2** Pedigrees of 9 families with 11 subjects described in our study
and mitral regurgitation. WES revealed a homozygous COQ4 mutation: c.370G>A, p.(Gly124Ser). CoQ10 supplement at 30 mg/kg/day was started at 11 months of age, and her seizure control improved.

Patient 11 is the elder sister of Patient 10. She was born full term. At 4 months of age, she presented with seizures, hypotonia, spasticity, oromotor dysfunction, and severe developmental delay. She also developed an episode of acute myocarditis during which her echocardiogram showed diastolic dysfunction. Brain MRI at 14 months showed mild cerebellar atrophy and cerebral atrophy, white matter cysts with bilateral frontal and anterior temporal predominance, and thinning of the corona callosum. Basal ganglia and brainstem appeared preserved (Fig. 1h–k). No lactic acidosis was detected. Owing to the exome findings of her sister, Sanger sequencing was performed and revealed a homozygous COQ4 mutation: c.370G>A, p.(Gly124Ser). She was not on CoQ10 supplement and passed away at 20 months due to an episode of sepsis.

**RESULTS**

Pathogenicity of the COQ4 variants

We analyzed the COQ4 variants identified in our cohort by previously reported literatures, ClinVar, population frequency in gnomAD,7 conversation score by Combined Annotation-Dependent Depletion, in silico prediction by Rare Exome Variant Ensemble Learner,9 and protein stability change prediction by STRUM10 (Table 3). All variants demonstrated a deleterious effect. Together with the reduced level of CoQ10 of the patients, the pathogenicity of these variants is strongly supported by the biochemical findings of the patients.

Founder mutation analysis

Among these 11 patients, we identified the same missense mutation c.370G>A, p.(Gly124Ser) in 10 of them. This missense mutation is a rare variant with a population frequency of 0.001118 and it is exclusively found in South East Asians in the gnomAD database.7 Further analysis of the DNA of the five homozygous patients using Infinium OmniZhongHua-8 Bead Chip SNP array showed a common haplotype of 0.464 of nearest heterozygous single-nucleotide polymorphism. The length of the haplotype for each subject is at the right panel. The maximum shared length is approximately 577 kb. This has been described predominantly with a neonatal onset, with only two cases of childhood onset.5,18 In this study, we have expanded the phenotypic spectrum of primary COQ10D7 from neonatal to infantile onset.

We have five patients exhibiting the well-described neonatal presentation of COQ10D7 as in the literature, characterized by respiratory distress, encephalopathy, seizures, hypotonia, and cardiomyopathy. Previously, it was believed that phenotypes from affected males with COQ4 mutation would be more severe and highly likely lethal.3,6 However, in our study the male-to-female death ratio was 2:3. We have six patients with infantile-onset phenotypes. Unlike those of neonatal onset, MRI brain for those infantile-onset patients did not show characteristic basal ganglia lesions. Dystonia was observed in two out of the six patients with infantile-onset presentation in our cohort, and it was also observed in the two neonatal-onset cases reported by Lu et al.5 but not reported in non-Chinese patient.

A summary of the predominant phenotypes in the spectrum of neonatal, infantile, and childhood onset of COQ10D7 is shown in Fig. 4. The varied symptoms and disease onsets explain the frequent delay of diagnoses of COQ10D7. This also highlights the importance of the complementarity of biochemical screening for children with unexplained neurological disturbances and the prompt application of WES in order to reach a genetic diagnosis that has an impact on patient management.

Functional analysis to demonstrate the deficiency of CoQ should be carefully examined because mitochondrial enzmyology can be tissue specific. In this study, among the five patients (Patients 1, 6, 7, 8, 9) with ETC chain analysis in the skin fibroblast, all of them showed a reduced level of succinate-UKO oxidoreductase c oxidoredactase (complex II+III). Measurement of CoQ level was also found significantly decreased. For Patients 7 and 8, complex II+III analysis and CoQ level measurement were also performed in the muscle. Interestingly, the CoQ level from the muscle is normal but that from skin fibroblasts was reduced. From the Genotype-Tissue Expression (GTEx) data, the COQ4 median expression in the muscle is 7.58 transcripts per million (TPM) while in the skin it is 44.14 TPM, demonstrating a 6-fold lower expression in the muscle.

**DISCUSSION**

To our knowledge, this is the largest case series of primary COQ10D7 reported. In the literature, primary COQ10D7 cases have been described predominantly with a neonatal onset, with only two cases of childhood onset.5,18 In this study, we have expanded the phenotypic spectrum of primary COQ10D7 from neonatal to infantile onset.

We have five patients exhibiting the well-described neonatal presentation of COQ10D7 as in the literature, characterized by respiratory distress, encephalopathy, seizures, hypotonia, and cardiomyopathy. Previously, it was believed that phenotypes from affected males with COQ4 mutation would be more severe and highly likely lethal.3,6 However, in our study the male-to-female death ratio was 2:3. We have six patients with infantile-onset phenotypes. Unlike those of neonatal onset, MRI brain for those infantile-onset patients did not show characteristic basal ganglia lesions. Dystonia was observed in two out of the six patients with infantile-onset presentation in our cohort, and it was also observed in the two neonatal-onset cases reported by Lu et al.5 but not reported in non-Chinese patient.

A summary of the predominant phenotypes in the spectrum of neonatal, infantile, and childhood onset of COQ10D7 is shown in Fig. 4. The varied symptoms and disease onsets explain the frequent delay of diagnoses of COQ10D7. This also highlights the importance of the complementarity of biochemical screening for children with unexplained neurological disturbances and the prompt application of WES in order to reach a genetic diagnosis that has an impact on patient management.

Functional analysis to demonstrate the deficiency of CoQ should be carefully examined because mitochondrial enzmyology can be tissue specific. In this study, among the five patients (Patients 1, 6, 7, 8, 9) with ETC chain analysis in the skin fibroblast, all of them showed a reduced level of succinate-UKO oxidoreductase c oxidoredactase (complex II+III). Measurement of CoQ level was also found significantly decreased. For Patients 7 and 8, complex II+III analysis and CoQ level measurement were also performed in the muscle. Interestingly, the CoQ level from the muscle is normal but that from skin fibroblasts was reduced. From the Genotype-Tissue Expression (GTEx) data, the COQ4 median expression in the muscle is 7.58 transcripts per million (TPM) while in the skin it is 44.14 TPM, demonstrating a 6-fold lower expression in the muscle.

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**Table 3. Analysis of the four variants identified in our cohort**

| Variant       | gnomAD population frequency | Reported to be disease causing? | CADD | REVEL | ddG |
|---------------|-----------------------------|---------------------------------|------|-------|-----|
| c.370G>A, p.(Gly124Ser) | 1.13e−04                    | Yes (Lu et al.)5                 | 24.8 | 0.817 | −1.19 |
| c.402+1G>C    | 2.79e−05                    | Yes (ClinVar)                    | 28.8 | N/A   | N/A  |
| c.371G>T, p.(Gly124Val) | 3.98e−06                   | No                              | 24.6 | 0.753 | −1.53 |
| c.550T>C, p.(Trp184Arg) | 0                           | No                              | 26.7 | 0.538 | −0.62 |

*CADD Combined Annotation-Dependent Depletion, REVEL Rare Exome Variant Ensemble Learner, N/A not available.*

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**Fig. 3 Founder mutation analysis. Shared haplotypes among homozygous COQ4:c.370G>A. Red square indicates the location of homozygous COQ4:c.370G>A, while black square indicates the nearest heterozygous single-nucleotide polymorphism. The length of the haplotype for each subject is at the right panel. The maximum shared length is approximately 577 kb.**
More significantly, we have identified a common founder pathogenic COQ4 mutation associated with COD10D7. In this study, 10 out of the 11 patients carry the COQ4: c.370G>A, p.(Gly124Ser) allele. This mutation fulfills the criteria of a founder mutation: (1) all patients with the mutant alleles share a haplotype associated with the mutation; (2) the haplotype is shared among affected families with a genetic distance >1 cM; (3) the mutant allele is rare and specific to the population; and (4) all carriers are delineated to the same geographic region. It is likely that this founder mutation causes a relatively higher rate of COQ10D7 in southern Chinese individuals, and that may explain why we can present a larger cohort as compared to past studies in this field.

CoQ10 oral supplementation was previously reported effective in COQ4 mutation cases. Among the 10 patients who received CoQ10 supplement and with continuous follow-up, those shown with stabilized cardiac condition or seizure control are those of genotype of homozygous missense variant c.370G>A (Patients 3, 9, 10). Another patient on CoQ supplement with improved clinical condition is Patient 8 with genotype of compound heterozygous missense variants c.370G>A/c.371G>T. For those without improvement are patients with genotype in the presence of a splicing mutation c.402+1G>A (Patients 1, 2, 4, 5, 6). Among these five patients, three of them (Patients 1, 2, and 5) died from the disease. Retrospectively, Patients 1, 4, and 5 were documented IUGR antenatally. This may suggest that the presence of c.402+1G>A, a loss-of-function mutation, would cause more severe neonatal onset of phenotypes and less responsive to CoQ10 supplement.

In this study, we have expanded the phenotypic spectrum of COQ4 mutation. Now COQ10D7 can range from neonatal, infantile to childhood onset. We have also identified a pathogenic COQ4 founder mutation in the southern Chinese population. The importance of complementarity of biochemical screening and prompt application of WES on patients with unexplained neurological symptoms is highlighted.

**Table 4. COQ level in the skin fibroblasts in patients with COQ4 mutation**

| Patient | Tissue | COQ level | CI | CI+III | CII | CI+III |
|---------|--------|-----------|----|--------|-----|--------|
| 1       | Skin fibroblast | 0.4 pmol/U COX (1.64–3.32) | Normal | Not done | Normal | 130 mU/U COX (269–781) |
| 6       | Skin fibroblast | 0.63 pmol/U CS (1.04–2.92) | Normal | Not done | Normal | 183 mU/U COX (269–781) |
| 7       | Skin fibroblast | 0.4 pmol/UCOX (1.64–3.32) | Not done | Not done | Normal | 183 mU/U COX (269–781) |
| 8       | Muscle | 191 pmol/mg (140–580) | Normal | Not done | Normal | Not done |
| 7       | Skin fibroblast | 0.29 nmol/UCOX (1.64–3.32) | Normal | Not done | Normal | 135 mU/U COX (control 269–781 in the skin) |
| 9       | Skin fibroblast | 16.4 ng/mg prot (46.1±3) | Not done | 64% of CS | 90% of CS | 55% of CS |

Reference values are given in brackets. Experiment performed at the Radboud University Medical Centre, Nijmegen and the National Taiwan University Hospital.

CI complex I, CII complex II, CIII complex III, CV complex IV, CS citrate synthase.
DATA AVAILABILITY
The data that support the findings in this study are available on request from the corresponding authors (N.-C.L., C.-W.F., B.H.-Y.C.). The data are not publicly available as they contain information that could compromise research participant privacy or consent.

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AUTHOR CONTRIBUTIONS
M.H.-C.Y., M.H.-Y.T., S.L., M.S.-P.H. and B.W. drafted the manuscript. D.M.L.T. and W.L. interpreted the MRI images. R.J.T.R. and J.S. provided functional analysis. M.H.-C.Y., M.H.-Y.T., A.K.-Y.K., C.C.-Y.M., K.-S.Y. and J.L.-F.F. performed the data analysis. Y.-Y.C., S.-P.L., C.M.Q., W.-L.H., Y.-H.C., P.-L.K., V.C.-M.C., C.T., S.-C.C., J.H., N.-C.L., C.-W.F. and B.H.-Y.C recruited and managed the patients. N.-C.L., C.-W.F. and B.H.-Y.C. conceived and supervised the study.

ADDITIONAL INFORMATION
Supplementary Information accompanies the paper on the npj Genomic Medicine website (https://doi.org/10.1038/s41525-019-0091-x).

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