One potential hotspot SLC25A20 gene variants in Chinese patients with carnitine-acylcarnitine translocase deficiency

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Background: Carnitine-acylcarnitine translocase deficiency (CACT deficiency) is a rare and life-threatening autosomal recessive disorder of mitochondrial fatty acid oxidation caused by variant of SLC25A20 gene. The most prevalent missense variant in the SLC25A20 gene in Asia was c.199–10T > G. Due to the c.199–10T > G variant, CACT deficiency is a severe phenotype.

Materials and Methods: Herein, we present a neonatal case with c.199–10T > G variant in China and analyze the clinical, biochemical, and genetic aspects of 78 patients previously identified with CACT deficiency.

Results: The patient presented with a series of severe metabolic crises that rapidly deteriorated and eventually died 3 days after delivery. The sequencing of the patient’s genome indicated that he was homozygous for the c.199–10T > G variant. 30 patients were found to have the c.199–10T > G mutation, of which 23 were Chinese and 22 were afflicted by the c.199–10T > G splicing variation. In China, c.199–10T > G allele frequency was 82.6%.

Conclusion: In CACT deficiency, prompt recognition and treatment are critical. Our data suggested that c.199–10T > G may be a potential hotspot SLC25A20 gene mutation in the Chinese population. Detection of single nucleotide polymorphism is possible for high-risk patients and parents in China.

KEYWORDS
CACT deficiency, SLC25A20 gene, c.199–10T > G, hotspot mutation, single nucleotide polymorphism detection

Introduction

Carnitine-acylcarnitine translocase deficiency (CACT deficiency, OMIM # 212138) was first described by Stanley CA et al. in 1992 (1). It is a rare and life-threatening autosomal recessive disorder with an incidence of 1:60,000 in Hongkong and 1:1,017,593 in Zhejiang province China (2, 3). CACT deficiency, encoded by the SLC25A20 gene on chromosome 3p21.31, is the cause of this condition (4). To shuttle long-chain fatty acids through the inner mitochondrial membrane and into the mitochondrial matrix, where mitochondrial β-oxidation takes place, CACT is an essential part of the carnitine cycle (5). Mitochondrial β-oxidation serves as the primary energy source for cardiac and skeletal muscles, while ketogenesis in the liver fuels brains tissue during prolonged fasting and exercise (1, 6, 7). CACT deficiency is characterized by a wide spectrum of clinical manifestations including hypoketotic
hypoglycemia, hyperammonemia, liver dysfunction, cardiomyopathy, severe neurologic impairment and progressive myopathy (8).

There are nine exons in the SLC25A20 gene, which produces a 301-amino-acid protein (9). At least 42 pathogenic variants have been detected in mutation databases like the HGMD around the world (Human Gene Mutation Database, www.hgmd.org). There are 20 missenses, 10 small deletions, 2 small insertions, 1 small indel, 4 large deletions, and 5 splicing mutations in the mutation spectrum (10). SLC25A20 gene missense variation c.199→10T > G was the most frequent in Asia. In our study, approximately 37.5% of pathogenic variants fall within this umbrella.

Though the spectrum of CACT deficiency is wide and continuous, there are two distinct clinical subtypes: a neonatal-onset severe form and an infancy-onset milder form (11). Severe classic presentation occurs at birth and has an extremely poor prognosis, with severe illness and debilitating symptoms. Moderate myopathy and hepatomegaly are seen in milder cases with more accessible residual transporter protein. Metabolic decompensation can be prevented and the prognosis improved with early detection and medicinal intervention (12).

In the present study, we described a patient with CACT deficiency which was failed to diagnosed and treated promptly and then led to rapid illness progression and eventual death. Furthermore, Patients previously diagnosed with CACT deficiency was reviewed systematically by describing the clinical, biochemical, and genetic characteristics and treatment to improve our understanding of this rare disorder.

**Materials and methods**

**Case report**

The patient was born at full term through a cesarean section. At 1 and 5 min, the baby’s Apgar score was 10. The parents were healthy and had no history of consanguineous marriage. The mother’s first child died at two days old from asphyxia, arrhythmia, and cardiac arrest. The baby seemed fine until he was 28 h old when he became very sleepy and showed no interest in breastfeeding. The patient was taken to the neonatal intensive care unit (NICU) for a checkup. During a physical exam, the baby showed no interest in breastfeeding. The patient was taken to the neonatal intensive care unit (NICU) for a checkup.

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### Literature search

All patients previously genetically diagnosed with CACT deficiency were reviewed in the study. The literature search for “Carnitine-acylcarnitine translocase deficiency,”

### Table 1 Summary of the patient with CACT deficiency biochemistry, ECG and Echo

| Age at detection | 28 h (at admission) | 47 h | 51 h |
|------------------|---------------------|------|------|
| ALT (U/L)        | 20                  | 26   | –    |
| AST (U/L)        | 74                  | 74   | 87   |
| HLD (U/L)        | 461                 | 592  | 784  |
| Lactate (mmol/L) | 6.0                 | 7.2  | –    |
| Ammonia (µmol/L) | 128                 | 355  | 433  |
| CK (U/L)         | 384                 | 418  | 596  |
| CKMB (U/L)       | 66                  | 136  | 168  |
| Ca++ (mmol/L)    | 2.2                 | 1.49 | 1.83 |
| K+ (mmol/L)      | 5.98                | 6.52 | 6.59 |
| TNI (µg/L)       | –                   | 0.03 | –    |
| Glucose (mmol/L) | 1.9                 | 1.49 | 1.3  |
| ECG              | –                   | VT/  | Bradycardia/VF/ |
|                 |                     | CRBBB/ | Unusually broad |
|                 |                     | II-AVB| changing QRS wave |
|                 | Left ventricular wall | complex |
|                 | motion incoordination| (EF55%) |
|                 | (EF30%)             |
| Echo             | Left ventricular wall | Left ventricular wall |
|                 | motion incoordination| motion incoordination |
|                 | (EF30%)             | (EF55%) |

**Cutoff value:** ALT(salanine transaminase):9–50 U/L; AST(aspartate transaminase):15–40 U/L; HLD(lactate dehydrogenase):97–350 U/L; Lactate:1.5–2.5 mmol/L; Ammonia:18–72 µmol/L; CK(creatine kinase): 24–195 U/L; CK-MB(creatinine kinase-MB):0–24 U/L; Ca++2.0–2.6 mmol/L;
“Carnitine-acylcarnitine translocase,” “SLC25A20 gene,” “CACTD,” as keywords on PubMed, Elsevier and Medline from 1992 to June 2022. (Table 2).

Results

Individual case reports are available for all cases as online.

Case for CACT deficiency

Over 30 years, 81 children with CACT deficiency were identified, 3 of which lacked genetic testing to determine the mutation sites. Therefore, in addition to the newly identified patient with CACT deficiency, we included 78 previously diagnosed patients in our sample.

Genetic findings

Patients harbored either homozygous or heterozygous SLC25A20 mutations. 42 different variations have been discovered. The most prevalent splicing variant was homozygous c.199–10T > G (23/79). Heterozygous c.199–10T > G splicing variation (7/79) and homozygous c.82G > T splicing variation (7/79) were quite prevalent variations. Each of the forty remaining variants was detected one to three times. The c.199–10T > G variant was identified in thirty patients (38.0%), of whom 73.3% (22/30) were Chinese. 29.1% (23/79) of the patients were Chinese, and 95.7% (22/23) were affected by the
TABLE 2 Presenting features of patients with CDCT deficiency (1, 3, 5, 8–10, 13–32).  

| Patient ID | Ethnicity | Age at onset | Current age/age of death | Hypoglycemia | Hyperammonemia | CK | ALT | Arhythmias | Cardiac hypertrophy | Cardiac arrest | Hepatomegaly | Seizures | Poor response/Hypotonia | Dyspnea | Other futures | SLC25A20 genotype |
|------------|-----------|--------------|--------------------------|--------------|----------------|----|-----|-----------|------------------|----------------|--------------|----------|----------------------------|---------|---------------|-------------------|
| 1          | Malaysia  | 24 h         | 2.5 months              | 1            | 1              | NA | NA | NA        | NA               | NA             | NA           | NA       | NA                          | NA      | (C16 + C18:1)/C21 > G | Homozygous c.199-10T |
| 2          | Malaysia  | 24 h         | 5 days                  | 1            | 1              | NA | ↑   | AVB/VT/VF/bradycardia | NA             | NA            | NA           | NA       | NA                          | NA      | (C16 + C18:1)/C21 > G | Homozygous c.199-10T |
| 3          | Chinese   | 24 h         | 3 years                 | 1            | 1              | ↑   | NA | RBBB/AVB | LV hypertrophy    | 1              | NA           | 1           | NA       | NA                          | NA      | Homozygous c.199-10T > G |
| 4          | Vietnamese| 28 h         | 6 months                | 1            | 1              | ↑   | NA | Broad complex VT | NA             | NA           | NA           | NA       | NA                          | NA      | Homozygous c.199-10T > G |
| 5          | Chinese   | 14.5 h       | 4 years lived           | 1            | 1              | ↑   | NA | Bradycardia | Cardiomyopathy with thickened LV/RV and septum | 1              | NA           | 1           | NA       | NA                          | NA      | Homozygous c.199-10T > G |
| 6          | Chinese   | 8 days       | 14 months lived         | 1            | 1              | ↑   | ↑   | Bradycardia | Hypertrophic cardiomyopathy | NA             | NA           | NA        | NA       | NA                          | 1       | Rhabdomyolysis C16, C18 † | Homozygous c.199-10T > G |
| 7          | Vietnamese| 12 h         | 5 months lived          | 1            | 1              | ↑   | NA | VT | NA               | 1              | NA           | 1           | NA       | NA                          | NA      | Homozygous c.199-10T > G |
| 8          | Chinese   | 25 min       | 71 h                    | 1            | 1              | ↑   | NA | NA        | NA               | 1              | NA           | 1           | NA       | NA                          | NA      | (C16 + C18:1)/C21 > G | Homozygous c.199-10T |
| 9          | Chinese   | 24 h         | 48 h                    | 1            | 1              | ↑   | NA | AVB/VT | NA               | NA             | NA           | 1           | 1       | 1                          | C16, C18 † | Homozygous c.199-10T > G |
| 10         | Thailand  | 2 h          | 2 years and 8 months    | 1            | 1              | ↑   | ↑   | NA        | Hypertrophic cardiomyopathy | 1              | 1            | NA        | NA       | 1                          | NA      | C16, C18 † | Homozygous c.199-10T > G |
| 11         | Thailand  | 10 h         | 2 years and 8 months    | 1            | 1              | ↑   | ↑   | NA        | Hypertrophic cardiomyopathy | 1              | 1            | NA        | 1       | 1                          | NA      | C16, C18 † | Homozygous c.199-10T > G |
| 12         | Chinese   | Early Neonatal| 2 months               | 1            | NA             | ↑   | NA | VT | Cardiac hypertrophy | 1              | NA           | NA        | 1       | 1                          | C16, C18 † | Homozygous c.199-10T > G |
| 13         | Chinese   | 21 day       | 3 days                  | NA           | NA             | NA | NA | 1        | Cardiac hypertrophy | 1              | NA           | 1           | NA       | NA                          | NA      | Homozygous c.199-10T > G |
| 14         | Chinese   | Treated from birth | 19 months lived       | NA           | NA             | NA | NA | VT | NA               | NA             | NA           | NA        | NA       | NA                          | NA      | C16, C18 † | Homozygous c.199-10T > G |
| 15         | Chinese   | 2 days       | 2 days                  | 1            | 1              | NA | NA | NA        | Cardiac hypertrophy | 1              | NA           | NA        | NA       | NA                          | NA      | Homozygous c.199-10T > G |
| 16         | Chinese   | 41 h         | 41 h                    | NA           | NA             | NA | NA | NA        | NA               | NA             | NA           | NA        | NA       | NA                          | NA      | Homozygous c.199-10T > G |
| Patient ID | Ethnicity | Age at onset | Current age/age of death | Hypoglycemia | Hyperammonemia | CK ALT | Arhythmias | Cardiac hypertrophy | Cardiac arrest | Hepatomegaly | Seizures | Poor response/ Hypotonia | dyspnea | Other futures | SLC25A20 genotype |
|------------|-----------|--------------|--------------------------|--------------|-----------------|--------|------------|-------------------|----------------|-------------|----------|------------------------|---------|---------------|-------------------|
| 17         | Chinese   | 32 h         | 32 months                | 1            | 1               | NA     | NA         | Hypertrophic cardiomyopathy | NA            | NA          | NA       | NA                     | NA      | NA            | Homozygous c.199-T > G |
| 18         | Chinese   | 28 h         | 38 h                     | NA           | NA              | NA     | NA         | VT/Bradycardia                | NA            | 1           | NA       | NA                     | NA      | NA            | Homozygous c.199-T > G |
| 19         | Chinese   | 61 days      | 62 days                  | 1            | NA              | ↑↑     | NA         | NA                              | NA            | NA          | NA       | 1                      | NA      | NA            | Homozygous c.199-T > G |
| 20         | Chinese   | In 7 days    | In 7 days                | 1            | 1               | NA     | NA         | Hypertrophic cardiomyopathy   | 1             | 1           | NA       | NA                     | NA      | NA            | Homozygous c.199-T > G |
| 21         | Chinese   | In 7 days    | In 7 days                | 1            | 1               | NA     | NA         | NA                              | NA            | 1           | NA       | 1                      | NA      | NA            | Homozygous c.199-T > G |
| 22         | -         | 1 day        | 4 years lived            | 1            | 1               | NA     | NA         | symptomatic tachyarrhythmia   | cardiac hypertrophy | NA          | NA       | NA                     | NA      | NA            | Homozygous c.199-T > G |
| 23         | Chinese   | 2 days       | 3 days                   | 1            | 1               | ↑↑     | ↑↑         | VT/IRBBB Bradycardia          | NA            | 1           | NA       | 1                      | NA      | NA            | Homozygous c.199-T > G |
| 24         | Chinese   | 24 h         | 9 years lived            | 1            | 1               | ↑↑     | ↑↑         | Broad complex tachyarrhythmia atrial flutter | biventricular hypertrophy | NA          | NA       | 1                      | NA      | NA            | c.199-T > G |
| 25         | Chinese   | 24 h         | 71 h                     | 1            | 1               | ↑↑     | ↑↑         | 1                              | NA            | NA          | NA       | 1                      | 1       | NA            | c.199-T > G |
| 26         | Chinese   | 24 h         | 6 days                   | 1            | 1               | ↑↑     | ↑↑         | NA                              | NA            | NA          | NA       | NA                     | 1       | NA            | c.199-T > G |
| 27         | Chinese   | -            | 1 year and 3 months      | 1            | 1               | ↑↑     | NA         | NA                              | NA            | NA          | NA       | NA                     | NA      | NA            | c.199-T > G |
| 28         | Japanese  | 48 h         | 2 years and 9 months     | 1            | NA              | NA     | ↑↑         | NA                              | NA            | NA          | NA       | 1                      | 1       | C14, C16, C18 |
| 29         | Chinese   | 2 days       | 3 days                   | 1            | 1               | ↑↑     | ↑↑         | 1                              | cardiac hypertrophy | 1           | NA       | NA                     | 1       | 1            | C161, C18 |
| 30         | Chinese   | 4 days       | 8 days                   | 1            | 1               | ↑↑     | ↑↑         | 1                              | NA            | NA          | NA       | 1                      | 1       | 1            | C161, C18 |
| 31         | Pakistani | 1 month lived| -                        | NA           | NA              | NA     | NA         | NA                              | NA            | NA          | NA       | NA                     | NA      | NA            | Homozygous c.82G > T |

(continued)
| Patient ID | Ethnicity       | Age at onset | Current age/age of death | Hypoglycemia | Hyperammonemia | CK ALT | Arhythmias | Cardiac hypertrophy | Cardiac arrest | Hepatomegaly | Seizures | Poor response/ Hypotonia | dyspnea | Other futures | SLC25A20 genotype |
|------------|----------------|--------------|--------------------------|--------------|----------------|--------|------------|---------------------|----------------|--------------|----------|----------------------------|---------|---------------|-------------------|
| 32         | Pakistani descent | 2 months   | lived | 1 | NA | NA | NA | NA | LVH, Impaired contractility | NA | NA | NA | NA | NA | NA | C16† | Homozygous c.82G > T |
| 33         | Pakistani descent | – | lived | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | Homozygous c.82G > T |
| 34         | Pakistani descent | 9 days     | lived | 1 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | C16† | Homozygous c.82G > T |
| 35         | Pakistani descent | – | lived | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | Homozygous c.82G > T |
| 36         | Pakistani descent | 1 month   | lived | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | Homozygous c.82G > T |
| 37         | Pakistani descent | 4 months | lived | 1 | NA | NA | NA | NA | Mild left ventricular hypertrophy | NA | NA | NA | NA | NA | Homozygous c.82G > T |
| 38         | Malaysia        | 33 h       | 33 h | 1 | NA | NA | NA | NA | NA | NA | NA | NA | NA | Homozygous c.109C > T c.706C > T |
| 39         | Indian          | 12 h       | 7 days | 1 | NA | NA | NA | Bradycardic arrest (rosc after 10 min) | NA | 1 | 1 | NA | NA | NA | c.82G > T c.706C > T |
| 40         | Caucasian       | 10 h       | 3 days | 1 | 1 | NA | NA | VT | NA | 1 | NA | NA | NA | NA | NA | Homozygous c.646G > T |
| 41         | Iranian         | 24 h       | 11 years lived | 1 | 1 | † | NA | SVT | NA | 1 | NA | 1 | NA | NA | NA | Homozygous c.67G > T |
| 42         | Guiana          | 15 h       | 3 years lived | 1 | 1 | NA | † | NA | NA | NA | NA | NA | 1 | NA | NA | Homozygous c.110G > C |
| 43         | Caucasian       | 2 days     | 10 years lived | 1 | 1 | † | NA | NA | NA | NA | NA | 1 | NA | NA | NA | c.50G > C c.326 + 1 delG |
| 44         | Iranian         | Treated from birth | 19 months lived | NA | 1 | NA | NA | AVT/VT | NA | NA | NA | NA | NA | NA | NA | Homozygous c.417 + 1G > A |
| 45         | Irish           | 32 h       | 16 months lived | 1 | 1 | † | NA | AV | NA | 1 | NA | NA | NA | NA | NA | Mild coagulation disorder c.326 + 1delG (Splice donor); c.691G > C |
| 46         | New Zealanders  | 36 h       | 12 months lived | 1 | 1 | † | NA | NA | echogenic myocardium | NA | NA | NA | NA | NA | NA | c.804delG |
| 47         | Iranian         | 5 months   | – | 1 | NA | NA | NA | NA | Hypertrophic cardiomyopathy | NA | NA | NA | NA | NA | NA | Homozygous c.67G > T |
| 48         | Caucasian       | 2 months   | – | 1 | NA | NA | † | NA | NA | NA | NA | NA | NA | NA | Hypokalemia c.379C > T deletion c.779_781delAAG |

(continued)
| Patient ID | Ethnicity | Age at onset | Current age/age of death | Hypoglycemia | Hyperammonemia | CK ALT | Arhythmias | Cardiac hypertrophy | Cardiac arrest | Hepatomegaly | Seizures | Poor response/Hypotonia | dyspnea | Other futures | SLC25A20 genotype |
|------------|-----------|--------------|-------------------------|--------------|----------------|--------|-----------|---------------------|----------------|-------------|---------|----------------------|---------|--------------|------------------|
| 49         | Caucasian | 20 days      | -                       | 1            | 1              | NA     | NA        | NA                  | NA             | NA          | NA      | NA                   | NA      | NA           | c.823C > T is nonsense mutation |
| 50         | Iranian   | 10 months    | -                       | 1            | NA             | ↑↑     | ↑↑        | NA                  | NA             | NA          | 1       | NA                   | NA      | NA           | c.160_163delins4 and c.804delG |
| 51         | -         | 1 month      | -                       | 1            | NA             | NA     | NA        | 1                   | NA             | NA          | NA      | NA                   | NA      | NA           | c.397C > T |
| 52         | -         | 20 days      | -                       | NA           | NA             | NA     | NA        | NA                  | NA             | NA          | NA      | NA                   | NA      | NA           | c.528delT |
| 53         | Turkey    | 24 h         | 10 months               | 1            | 1              | NA     | ↑↑        | NA                  | NA             | NA          | 1       | NA                   | 1       | 1            | c.168delT   |
| 54         | Turkey    | 10 days      | 12 months               | 1            | 1              | NA     | ↑↑        | NA                  | NA             | NA          | 1       | NA                   | 1       | 1            | Homozygous c.408C > A   |
| 55         | Turkey    | 24 h         | 52 days                 | NA           | 1              | NA     | ↑↑        | NA                  | NA             | 1           | NA      | NA                   | 1       | NA           | Homozygous c.270del   |
| 56         | Japanese  | 48 h         | 3 days                  | NA           | NA             | NA     | NA        | NA                  | NA             | 1           | NA      | NA                   | 1       | NA           | C14, C16, C18, C18:11  |
| 57         | Dutch     | Neonatal     | 9 years lived           | 1            | NA             | NA     | NA        | NA                  | NA             | 1           | NA      | NA                   | 1       | NA           | C16, C18↑ |
| 58         | Dutch     | 36 h         | 24 months               | 1            | NA             | NA     | NA        | Hypertrophic cardiomyopathy | NA             | NA          | 1       | NA                   | NA      | NA           | c.241G > A misense mutation |
| 59         | Dutch     | 24 h         | 12 years lived          | 1            | NA             | NA     | ↑↑        | Hypertrophic cardiomyopathy | 1              | 1           | NA      | 1                   | 1       | 1            | c.955insC mutation   |
| 60         | Italian   | 1 month      | 6 months                | 1            | 1              | NA     | ↑↑        | 1                   | NA             | 1           | NA      | 1                   | 1       | 1            | C16, C18↑ |
| 61         | Italian   | 2 days       | 8 months lived          | 1            | NA             | NA     | NA        | Bradycardia and tachycardia | Hypertrophic cardiomyopathy | 1           | 1       | 1                   | 1       | 1            | C16, C18↑ |
| 62         | Spanish   | NA           | 4.5 years lived         | NA           | NA             | NA     | NA        | NA                  | NA             | NA          | 1       | NA                   | NA      | NA           | c.843 + 4_843 + 50del  |
| 63         | Spanish   | 40 h         | 4 months                | 1            | NA             | ↑↑     | ↑↑        | NA                  | NA             | 1           | NA      | NA                   | NA      | NA           | c.532C > T  |
| 64         | Spanish   | 72 h         | 3 years and 5 months    | 1            | 1              | NA     | ↑↑        | NA                  | Malign cardiomegaly | NA          | 1       | NA                   | 1       | 1            | Homozygous c.842C > T |
| 65         | Italian   | 18 h         | 2 years lived           | 1            | 1              | ↑↑     | ↑↑        | NA                  | Hypertrophic cardiomyopathy | NA          | NA      | 1                   | NA      | NA           | c.362delG, c.691G > C |

(continued)
| Patient ID | Ethnicity | Age at onset | Current age/age of death | Hypoglycemia | Hyperammonemia | CK ALT | Arhythmias | Cardiac hypertrophy | Cardiac arrest | Hepatomegaly | Seizures | Poor response | Dyspnea | Other futures | SLC25A20 genotype |
|------------|-----------|--------------|--------------------------|--------------|----------------|--------|------------|-------------------|----------------|---------------|-----------|---------------|---------|---------------|------------------|
| 67         | Australian | 27 h         | After 27 h               | 1            | NA             | NA NA | NA         | NA                | NA             | NA            | NA        | NA           | NA NA  | NA           | C14, C16 and Glu-decarboxylase (adipyl) acylcarnitines↑ |
| 68         | Arabs      | 32 h         | 9 days                   | 1            | 1 ↑ ↑ ↑ ↑ 1    | NA NA | NA         | NA                | NA             | NA NA         | NA        | 1            | C6, C14, C16↑ | Homozygous c.609-3C > G |
| 69         | South Africans | 12 h       | 8 months                 | 1            | 1 NA NA NA     | NA         | Biventricular hypertrophy | NA     | NA NA NA NA NA | NA        | NA           | C12, C16, C18↑ | Homozygous c.59G > A |
| 70         | Spanish    | 8 months     | 4 years lived            | 1            | NA  ↑ ↑ NA     | NA         | NA         | NA                | NA             | 1 1 1 1     | NA        | C14, C18↑    | c.160_163delinsac.536A > G |
| 71         | Moroccan   | 33 h         | 12 months                | 1            | NA NA NA NA    | NA         | NA         | NA                | NA             | NA NA NA NA | NA        | NA           | NA      | NA           | Homozygous c.536A > G |
| 72         | Spanish    | Treated from birth | 16 years lived          | NA           | NA NA NA NA    | NA         | NA         | NA                | NA             | NA NA       | NA        | NA           | NA      | NA           |                         |
| 73         | American   | 5 days       | 3 years                  | 1            | 1 NA NA LBBB/Prolonged QT interval | Hypertrophic cardiomyopathy | NA         | NA         | NA                | NA             | NA NA NA NA | NA        | NA           | NA      | NA           | c.84delT a 506-kb deletion |
| 74         | Chinese    | –            | 2 months                 | 1            | 1 NA ↑ NA      | NA         | Hypertrophic cardiomyopathy | NA     | 1 NA NA NA     | NA        | C12, C14, C16, C18, C16.1, C18.1↑ | c.270delC c.804delG |
| 75         | Italian    | 18 h         | 2 years lived            | 1            | 1 ↑ ↑ ↑ Tachycardia and acute arrhythmias | Biventricular hypertrophy | NA         | 1 NA NA      | NA                | NA             | 1 NA       | C2, C16.0, C18.1, C18.2↑ | Homozygous c.713A > G |
| 76         | Japanese   | 2 days       | 5 years lived            | NA           | 1 NA NA Bradycardia | NA         | NA         | 1 NA                | NA             | NA 1        | 1        | C16, C14-C3, C16 + C18.1/C2↑ | Homozygous c.824G > A |
| 77         | Japanese   | 2 days       | 26 months                | 1            | 1 NA NA VT     | NA         | NA         | 1 NA                | 1 NA            | NA NA 1     | NA        | C16, C14-C3, C16 + C18.1/C2↑ | Homozygous c.824G > A |
| 78         | Japanese   | 30 min       | 5 years lived            | 1            | NA NA NA NA    | NA         | Biventricular hypertrophy | NA     | NA NA NA NA     | NA        | C16, C14-C3, C16 + C18.1/C2↑ | Homozygous c.824G > A |
| 79         | American   | 2 days       | lived                    | 1            | 1 ↑ NA NA      | NA         | Left ventricular septal hypertrophy | NA    | NA NA NA       | 1 1        | C16, C18.1/C2↑ | c.397C > T c.658G > A |

1. existence; ↑, increase; VT, ventricular tachycardia; VF, ventricular fibrillation; LBBB, left bundle branch block; RBBB, right bundle branch block; AVB, Atrioventricular block.
c.199–10T > G splicing mutation. The remaining sufferers were scattered in different nations. The frequency of the c.199–10T > G allele was 33.5% in all cases, whereas it was 82.6% in China.

Biochemical and clinical specifications

Twenty of the thirty individuals with the c.199–10T > G variant exhibited clinical symptoms within 48 h (66.7%). There were arrhythmias in 18 patients (60%), cardiomyopathy in 13 patients (43.3%), hepatomegaly in 4 patients (13.3%), seizures in 9 patients (30%), hyperammonemia in 22 patients (73.3%), increase of CKMB and ALT in 17 patients (56.7%) and 12 patients (40%) respectively. 23 of 30 individuals (76.7%) perished due to the variation c.199

42/79 individuals harbored additional SLC25A20 mutations. 25 out of 42 participants exhibited clinical signs within 48 h (59.6%). These patients exhibited associated clinical manifestations: 14/42 (33.3%) had arrhythmias, 15/42 (35.7%) had bouts of cardiomyopathy, 11/42(26.2%) had hepatomegaly, and 7/42(16.7%) had seizures. Ammonia, CK and ALT levels were elevated in 22/42(52.3%), 11/42(26.2%) and 14/42(33.3%) patients, respectively.

Discussion

CACT deficiency appears to be very rare in the general population, except for a small number of ethnic subgroups. This study described the biochemical, clinical and genetic characteristics of patients with CACT deficiency, analyzed the distribution and ethnic specificity of the pathogenic genes, provided a theoretical basis of single nucleotide polymorphism detection, and thus contributed to the body of knowledge for early diagnosis and timely intervention in this rare disorder.

There is a wide variation in the prevalence of CACT deficiency among ethnic groups. About 30 cases of CTCT deficiency have been reported elsewhere, while there have been more than 50 reported in Asia. It is reported that the estimated incidence of CACT deficiency is 1/60,000 in Hongkon, 1/76,894 in Hunan, and at least 1/100,000 in Guangzhou China (2, 10, 15). Caucasian groups had a substantially lower incidence of CACT deficiency, which was reported to be 1:750,000–12,000,000. Indeed, the misleading clinical presentation, poor prognosis and the need to collect blood and urine specimens for metabolic investigation at an appropriate time in relation to the illness frequently limit the recognition of the disorder. For these reasons, the frequency of CACT deficient inborn defects is probably higher than recorded cases.

CACT deficiency is one of the most severe disorders of the carnitine transport system and mitochondrial fatty acid oxidation. The disorder results in deficient formation of energy-yielding substrates and toxicity of acylcarnitine accumulation which plays a pivotal role in the production of arrhythmias, and then presents a simultaneous dysfunction of the heart, liver, and skeletal muscle, associated with hypoketotic hypoglycemia (33). Severe classic manifestation, the most common, is accompanied by severe hypoketotic hypoglycemia, refractory hyperammonemia, elevated transaminase levels and CK, cardiomyopathy, and abrupt arrhythmias. The prognosis for those with the classic results is exceptionally dismal. Moderate myopathy and hepatomegaly are seen in milder cases, which are less common but do have more accessible residual transporter protein (11, 34, 35). Following an initial metabolic decompensation at birth, the neonate, in our case, developed hypoglycemia, hyperammonemia, and acute and severe arrhythmias before passing away. This may be related to the less residual enzyme activity and the increased accumulation of carnitine-acylcarnitine (33, 34). In our study, CACT deficiency due to the c.199–10T > G variation is a severe phenotype with a significantly higher mortality, arrhythmia, seizures, and hyperammonemia incidence than other variations, while CACT deficiency caused by the c.82G > T mutation is associated with milder phenotype (5). The most frequent mutation was a splicing site variation of c.199–10T > G.

Early recognition and timely treatment are crucial in CACT deficiency. NBS (Newborn screening) plays an important role in early detection of deficiency in enzymes of mitochondrial carnitine-acylcarnitine cycle. Most patients with CACT and CPT2 deficiency had a higher C12–C18:1 level than those without these (3). SLC25A20 gene mutational analysis is required to identify CACT deficiency, but this can be done without CACT activity assessment. Once a CACT deficiency has been diagnosed, the proper treatment must be implemented. To begin, sufficient glucose must be provided to prevent lipolysis from being broken down. Fasting prevention with frequent meals, a diet rich in carbohydrate, restricting long-chain fatty acids, supplementing with medium chain triglycerides (MCT) and essential polysaturated fatty acids are recommended as long-term treatments for CACT deficiency. Administration of carnitine is controversial, on the one hand it exerts to prevent arrhythmias, and on the other hand it causes an increase of acylcarnitines, responsible of arrhythmias (26, 33, 35). Triheptanoin can ameliorate acute cardiomyopathy and increase survival in patients with severe long-chain fatty acid oxidation disorders (26). CACT deficiency can also be treated with skimmed breast milk (30).

There are nine exons in the SLC25A20 gene, which spans more than 903 bp of genomic DNA on chromosome 3p21.31
At least 42 pathogenic variants of SLC25A20 have been discovered so far. In contrast to the majority of pathogenic variations, c.199–10T > G and c.82G > T were shown to be shared in Asian and Pakistani origins, respectively. The founder mutation c.82G > T was detected in people of Pakistani ancestry. Our study’s Chinese patients were found to have a wide range of homology, with seven distinct variants. The most common variant, c.199–10T > G, suggests that c.199–10T > G may be a hotspot of SLC25A20 gene mutation in the Chinese population. c.1A > G was detected only 3 times and was not yet found in other than Chinese populations, so it may be unique to the Chinese individuals. The remaining variant was detected only once or twice.

In conclusion, the biochemical, clinical, and genetic characteristics of Chinese patients with CACT deficiency identified in this investigation may aid early identification and intervention. In addition, it appeared from the data that the Chinese patients have a high degree of homozygosity. The c.199–10T > G variant, which is the most common one in this population, has the potential to be a hotspot SLC25A20 gene mutation. As a result, economical and rapid single nucleotide polymorphism and the genotyping assay can be performed for high-risk patients and their parents in China. In addition, prenatal or presymptomatic diagnosis can be performed in siblings.

Data availability statement

All data, models, and code generated or used during the study appear in the submitted article.

Ethics statement

Written informed consent was obtained from the individual(s), and minor(s)’ legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

JS: contributed significantly to analysis and manuscript preparation. XL: performed the data analyses and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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