Different regional distribution of SLC25A13 mutations in Chinese patients with neonatal intrahepatic cholestasis

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Abstract

AIM: To investigate the differences in the mutation spectra of the SLC25A13 gene mutations from specific regions of China.

METHODS: Genetic analyses of SLC25A13 mutations were performed in 535 patients with neonatal intrahepatic cholestasis from our center over eight years. Unrelated infants with at least one mutant allele were enrolled to calculate the proportion of SLC25A13 mutations in different regions of China. The boundary between northern and southern China was drawn at the historical border of the Yangtze River.

RESULTS: A total of 63 unrelated patients (about 11% of cases with intrahepatic cholestasis) from 16 provinces or municipalities in China had mutations in the SLC25A13 gene, of these 16 (25%) were homozygotes, 28 (44%) were compound heterozygotes and 19 (30%) were heterozygotes. In addition to four well described common mutations (c.851_854del, c.1638_1660dup23, c.615+5G>A and c.1750+72_1751-4dup17insNM_138459.3:2667 also known as IVS16ins3kb), 13 other mutation types were identified, including three novel mutations: c.985_986insT, c.287T>C and c.1349A>G. According to the geographical division criteria, 60 mutant alleles were identified in patients from the southern areas of China, 43 alleles were identified in patients from the border, and 4 alleles were identified in patients from the northern areas of China. The proportion of four common mutations was higher in south region (56/60, 93%) than that in the border region (34/43, 79%, \( \chi^2 = 4.621, P = 0.032 \)) and the northern region (2/4, 50%, \( \chi^2 = 8.288, P = 0.041 \)).

CONCLUSION: The SLC25A13 mutation spectra among the three regions of China were different, providing a basis for the improvement of diagnostic strategies and interpretation of genetic diagnosis.

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Key words: Citrin deficiency; Mutation spectrum; Intrahepatic cholestasis; SLC25A13

Core tip: Genetic testing of SLC25A13 gene was performed in individuals from southern, border and northern regions of China. The proportion of four common mutations was significant higher in southern region than in the border region and the northern region, so mutation screening for the common 4 mutations an appropriate test in the southern region. In the border and northern region, DNA sequencing is probably more practical.
INTRODUCTION

Citrin deficiency is estimated to be the most common urea cycle disorder in the world. It is an autosomal recessive disorder which includes adult-onset type II citrullinemia (CTLN2; OMIM #60347) [3,4] and neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD; OMIM #605814) [5,6]. Most NICCD patients show symptoms which ameliorate by 1 year of age [6], but some patients may progress to liver failure and even require liver transplantation during infancy [7-10]. Others may develop CTLN2 more than a decade later [11,12]. Dietary treatment has shown to ameliorate symptoms and may prevent the need for transplantation [13,14]. Therefore, prompt diagnosis and appropriate management are important for achieving a favorable long term prognosis for this disease.

Citrin deficiency is caused by mutations in the SLC25A13 gene [15,16]. The protein product of the SLC25A13 gene is citrin, a polypeptide of 675 amino acid residues with a molecular weight of 74 kDa. Citrin contains four EF-hand domains and six mitochondrial transmembrane (TM)-spanning domains, and resides in the mitochondrial inner membrane [15]. Citrin is expressed in the liver and functions as calcium (Ca2+)-stimulated aspartate-glutamate carrier (AGC) for cytosolic glutamate and protons [16]. Over 60 different functional proved mutations in the human SLC25A13 gene have been identified. These show significant differences in their racial distribution [13,17-20]. In China, the carrier frequency of 4 most common known mutations shows significant regional difference [18,20]. The estimated carries in population are 1/48 in south of the Yangtze River and 1/940 are carries of the river in the North [19].

Currently common mutation screening is used for rapid molecular diagnosis [21]. However, the appropriateness of use in specific populations needs to be established in that population. Therefore, we undertook the present study to investigate the regional distribution of SLC25A13 mutations spectrum in Chinese patients with neonatal intrahepatic cholestasis. Our results will facilitate the design of appropriate screening strategies for this disorder in different regions.

MATERIALS AND METHODS

Subjects

Between June 2003 and December 2011, patients with cholestasis who were referred to the pediatric liver center of Children’s Hospital of Fudan University for conjugated hyperbilirubinemia were enrolled. The inclusion criteria included the onset of conjugated jaundice before 6 mo of age; serum total bilirubin < 5 mg/dL and conjugated bilirubin > 1 mg/dL, or total bilirubin > 5 mg/dL and conjugated bilirubin > 20% [22]. We excluded other diseases that may affect the extrahepatic biliary system, such as biliary atresia, choledochal cyst, tumor, inspissated bile, or hemangioma, by imaging the hepatobiliary system. The imaging procedures included ultrasound scanning and hepatobiliary iminodiacetic acid (HIDA) scintigraphy in each case and laparotomic cholangiography in selected cases. Cases (n = 535) met the inclusion criteria and written informed consent was obtained from their parents.

The study protocol conforms to the ethical guidelines of the Declaration of the Helsinki of 1975 and was approved by the Ethics Committee on human research of the Children’s Hospital of Fudan University.

Mutation identification

DNA was extracted from peripheral blood samples, which were obtained from each participant and his or her parents using the Tiangen Blood Genomic DNA Isolation Kit according to the manufacturer’s instructions (Tiangen Biotech, Shanghai, China). Four common mutations (c.851_854del, c.1638_1660dup23, c.615+5G>A and c.1750+72_1751-4dup17)insNM_138459.3:2667 also known as IVS16ins3kb [19,20] were screened in all subjects. In patients for whom only one mutation was identified by the above screening or who had hyperaminoacidemia were subject to DNA sequencing as described previously [24]. Selection process of patients with mutant allele for analysis is given in Figure 1. The mutation alleles were verified in their parents by the target sequencing to establish segregation. Genomic sequences were obtained at the National Center for Biotechnology Information with RefSeq NM_014251.2 as SLC25A13 reference. Nomenclature of SLC25A13 variants was assigned following the guidelines of Human Genome Variation Society (http://www.hgvs.org/mutnomen) [25].

Geographical division

The population boundary between northern and southern China is drawn at the historical border of the Yangtze River during early Neolithic times (3000-7000 years ago) [26]. According to this criteria, Zhejiang, Jiangxi, Fujian, Guangdong, Hunan, Guizhou, Taiwan are classified as southern areas as they are south of Yangtze River; the provinces of Jiangsu, Shanghai, Anhui, Hubei and Chongqing are classified as border areas as they are in the basin of the Yangtze River; and the provinces of Henan, Liaoning, Shanxi, Jilin, Shandong, Hebei and Ningxia are classified as northern areas as they are in north of Yangtze River (Figure 2).

Patients with at least one mutated SLC25A13 allele were selected. To calculate the mutation spectra, the mutations observed in the related family members were counted only once. If the patient was a heterozygote or a compound heterozygote and the parents were from
different regions, the parent’s sample was tested to determine the origin of the allele(s). Except for two patients who were born from consanguineous parents, all other infants were to our knowledge unrelated.

Homology and structural predictions

The homology between the mutated Citrin protein and the human reference, as well as Citrin from other species, were surveyed using Clustal X software (European Bioinformatics Institute, Hinxton, Saffron Walden, United kingdom). PolyPhen-2 (Polymorphism Phenotyping version2.2.2), which is available at http://genetics.bwh.harvard.edu/pph2/, was used to predict the possible impact of an amino acid substitution on the structure and function of the Citrin protein. MutationTaster was used to evaluate the disease-causing potential of sequence alterations, at http://mutationtaster.org/MutationTaster/index.html. A P value close to 1 indicates a high ‘security’ of the prediction. MutationTaster employs a Bayes classifier to eventually predict the potential of an alteration causing disease. The Bayes classifier is fed with the outcome of all tests and the features of the alterations and calculates probabilities for the alteration to be either disease causing or not.

Statistical analysis

Statistical tests on the distribution of mutant genotypes in the three areas of China were assessed by performing a $2 \times 2 \chi^2$ test with the SPSS version 17.0 software (University of Chicago, Chicago, IL, United States) package. A P value < 0.05 was considered to be statistically significant. When there are small expected values in the $2 \times 2$ table, the result of Fisher’s exact test was used.

RESULTS

General information

Among the 535 patients, 183 originated from the southern area, 291 were from the border area and 61 were from the northern area. Sixty-nine patients with at least one SLC25A13 gene mutation were found, including 6 sibling pairs. These sixty-three unrelated patients, including 25 females and 38 males, were further analyzed. Sixteen (25%) were found to be homozygotes for one mutation, 28 (44%) were compound heterozygotes and 19 (30%) heterozygotes for only one mutation. The distribution of carriers according to the state of origin is depicted in Figure 2.

Mutation types

A total of 17 mutations, including 14 mutations that had been previously reported by us and others (c.851_854del, c.615+5G>A, c.1750+72_1751-4dup17insNM_138459.3:2667, c.1019_1177del, c.1080G>A, c.550C>T, c.955C>T, c.1754G>A, c.775C>T, c.1092_5delT, c.615+1G>A, c.254T>G) [17,20,24,27-30] and 3 novel mutations (c.985_986insT, c.287T>C, c.1349A>G), were observed in the present investigation (Table 1).

Analysis of 3 previously unreported variants

The c.287T>C mutation in exon 4 is predicted to result in the substitute of phenylalanine to serine at position 96 (p.F96S). This mutation was found in a compound heterozygote state with the mutations c.851_854del. p.F96S is located between the second and third EF-hand domain, which is highly conserved in different species (Table 2). The Polymorphism Phenotyping for the variant amino acid p.F96S from Polyphen 2 is 1.000, indicating that the missense mutation has a high chance of affecting protein function. The P value from MutationTaster is 0.997, suggesting that is most likely a disease-causing mutation.

Mutations c.985_986insT and c.1349A>G were found in compound heterozygote state in a patient. The mutation c.985_986insT was found to be derived from this patient’s paternal allele and predicted to result in a frame shift and the introduction of a premature stop codon at position 372. Mutation c.1349A>G (p.E450G) was derived from the patient’s maternal allele, which is located in the loop between the TM3 and TM4 spanning regions. Conservation analysis in different species indicated that the amino acid in this position is highly conserved (Table 2). The Polymorphism Phenotyping for the variant amino acid p.E450G from Polyphen 2 is 1.000, indicating that the missense mutation has a high chance of affecting protein function. The P value from MutationTaster is 0.997, suggesting that is most likely a disease-causing mutation.

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Acid p.E450G was 1.000, indicating a high chance of affecting protein function. The P value from MutationTaster is more than 0.999, suggesting that the mutation might affect the protein’s features.

**Distribution of SLC25A13 gene mutations**

The distribution of SLC25A13 mutations in carriers originating from different regions of China is given in Figure 1. Sixty (56%) mutant alleles originated from the southern region with Zhejiang, Jiangxi, Fujian, Guangdong, Hunan, Guizhou, and Taiwan accounting for 27, 15, 9, 1, 4, 3 and 1 mutant allele, respectively. Forty-three mutant alleles (40%) originated from the border region, with Jiangsu, Shanghai, Anhui, Hubei, Sichuan, and

| Mutation       | South   | Border  | North   | Nucleotide change        | Protein change        | Ref.        |
|----------------|---------|---------|---------|--------------------------|-----------------------|------------|
| Common         | 56 (93) | 34 (79) | 2 (50)  | c.851_854del              | p.M285fsX286          | Kobayashi et al[1] |
| 851delE        | 41 (69) | 22 (51) | 2 (50)  | c.1638_1660dup23         | p.A554X570            | Kobayashi et al[1] |
| 1638ins23      | 9 (15)  | 4 (9)   |         | c.615 + 5G>A             | -                     | Saheki et al[2] |
| IVS5+5G>A      | 2 (3)   | 4 (9)   |         | c.1750+72_1751-4dup17ins | NM_138459.3:2667      | Tabata et al[5] |
| IVS16ins3kb    | 4 (7)   | 4 (9)   |         |                          |                       |            |

**Table 1 Regional distribution of mutant SLC25A13 alleles and frequencies in China n (%)**

| Mutation       | South   | Border  | North   | Nucleotide change        | Protein change        | Ref.        |
|----------------|---------|---------|---------|--------------------------|-----------------------|------------|
| Other          | 4 (7)   | 9 (21)  | 2 (50)  | c.1019_1177del           | -                     | Kobayashi et al[5] |
| IVS1+1G>A      | 1 (2)   | 1 (2)   |         | c.1801G>A                | p.E601K               | Yamaguchi et al[5] |
| E601K          | 1       |         |         | c.558C>T                 | p.R184X               | Lu et al[10] |
| R184X          | 1       |         |         | c.1078C>T                | p.R360X               | Tabata et al[5] |
| R360X          | 1       |         |         | c.955G>T                 | p.R319X               |            |
| R319X          | 1 (2)   | 1 (2)   |         | c.615+1G>A               | -                     | Fu et al[12] |
| IVS6+1G>A      | 2 (5)   |         |         | c.2547C                  | p.L85P                | Fu et al[12] |
| L85P           | 1 (2)   |         |         | c.1754G>A                | p.R585H               | Song et al[13] |
| R585H          | 1 (2)   |         |         | c.1092_5delT             | p.R319X               |            |
| 1092_5delT     | 1 (2)   |         |         | c.775C>T                 | p.Q529X               | Wen et al[14] |
| Q259X          | 1 (2)   |         |         | c.985_986insT            | p.A3296X372           | Present study |
| 986insT        | 1 (2)   |         |         | c.287T>C                 | p.P46S                | Present study |
| P965           | 1 (2)   |         |         | c.1349A>G                | p.E450G               | Present study |
| E450G          | 1 (2)   |         |         | c.1349A>G                |                       |            |

Allele counts for the mutations are given together with their relative frequencies expressed as percentage value (in brackets). Novel mutations found in this study are indicated by bold letters. Variation in allele proportion (counts) between the three regions: $\chi^2 = 4.621$, $P = 0.032$, common mutation in south vs in border; $\chi^2 = 8.288$, $P = 0.041$, common mutation in south vs in north. GenBank reference sequences were NT_079595 and NM_014251.2.

As shown in the map, the provinces were separated into three parts by the Yangtze River. The numbers in parentheses are the number of mutation c.851_854del/c.1638_1660dup23/c.615+5G>A/c.1750+72_1751-4dup17ins NM_138459.3:2667/other alleles.

Figure 2 Distribution of mutant alleles enrolled in this study. As shown in the map, the provinces were separated into three parts by the Yangtze River. The numbers in parentheses are the number of mutation c.851_854del/c.1638_1660dup23/c.615+5G>A/c.1750+72_1751-4dup17ins NM_138459.3:2667/other alleles.
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Table 2  Conservation analysis of SLC25A13 gene mutations F96S and E450G among different species

|     | Human | Canis | Bos | Equus | Pan | Mus | Gallus | Xenopus |
|-----|-------|-------|-----|-------|-----|------|--------|---------|
| F96S |       |       |     |       |     |      |        |         |
| L   | C     | A     | P   | D     | A   | L   | F      | M       | V       | A     | F   | Q   | L   | F      | D   | K     | A     | G     | K     | G    | E   | V   |
|     |       |       |     |       |     |      |        |         |         |       |     |     |     |        |     |       |       |       |       |       |     |     |     |     |
| E450G|       |       |     |       |     |      |        |         |         |       |     |     |     |        |     |       |       |       |       |       |     |     |     |     |
| Human| G     | G     | S   | Q     | V   | I   | F     | T      | N       | P       | L   | E   | I   | V   | K     | I   | R     | L     | Q     | V     | A   | G   | E   |
| Canis| G     | G     | S   | Q   | V   | I   | F     | T      | N       | P       | L   | E   | I   | V   | K     | I   | R     | L     | Q     | V     | A   | G   | E   |
| Bos  | G     | G     | S   | Q   | V   | I   | F     | T      | N       | P       | L   | E   | I   | V   | K     | I   | R     | L     | Q     | V     | A   | G   | E   |
| Equus| G     | G     | S   | Q   | V   | I   | F     | T      | N       | P       | L   | E   | I   | V   | K     | I   | R     | L     | Q     | V     | A   | G   | E   |
| Pan  | G     | G     | S   | Q   | V   | I   | F     | T      | N       | P       | L   | E   | I   | V   | K     | I   | R     | L     | Q     | V     | A   | G   | E   |
| Mus  | G     | G     | S   | Q   | V   | I   | F     | T      | N       | P       | L   | E   | I   | V   | K     | I   | R     | L     | Q     | V     | A   | G   | E   |
| Gallus| G   | M     | C   | Q   | V   | I   | F     | T      | N       | P       | L   | E   | I   | V   | K     | I   | R     | L     | Q     | V     | A   | G   | E   |

DISCUSSION

The mutation spectra for the SLC25A13 gene differ within the Asian population[18,30]. A different carrier rate for the common mutations between different parts of China has been reported[19,30]. Here we demonstrate that the mutation spectrum of SLC25A13 gene varies considerably among specific regions of China with common mutations having a higher proportion in the southern region than in the border and northern regions.

In the southern region of China, four common mutations accounted for 93% and c.851_854del is the predominant mutation accounting for 68%. This is consistent with the published data[19,30]. The c.851_854del mutation is a common ancestral mutation, and the frequency difference between various regions of China may be associated with ancient migration.

The explanations for this may be that other common mutations were much greater than that in the southern region (43 vs 60), but the mutation types were very limited. This study is the first paper providing an estimate for the border region and significantly increases the data on the distribution of southern and northern China. Considering the high proportion of uncommon mutations, the previously reported SLC25A13 mutation carrier rate in this region may be underestimated and sequencing may be a perfect method for testing.

Since variants c.287T>C and c.1349A>G have not undergone functional testing, so we analyzed the data without these and statistical significance was reached even when those two variants were removed from the analysis. The proportion of the four common mutations was higher in southern region (95%) than that in the border region (79%, \( \chi^2 = 4.621, P = 0.032 \)) and that in the north (50%, \( \chi^2 = 8.288, P = 0.041 \)) (Table 1).

Among the four common mutations, c.851_854del was the most. Propportion accounts for 68% (41/60) in southern region, 51% (22/43) in the border region and 50% (2/4) in the northern region. The difference of the proportion between the southern and border part of China was marginally significant (\( \chi^2 = 3.109, P = 0.078 \)).
from different parts of China. The previous study evaluated the population frequency for the common mutations and conducted that the carrier frequency in China is 1/79-1/621.[17,19] Conversely only 94% (59/63) of cases with suspected citrin deficiency in our study had the common mutations. This suggests that point mutation testing alone is not sufficient to exclude citrin deficiency even in cases from the southern region but may be a cost effective way of confirming the diagnosis as the first step.

There were limitations of this study. Firstly, only a small number of patients came from the north of the Yangtze River, and only limited cases were reported from that area, so the sampling bias needs to be considered. The current literature has not shown a significant difference between SLC25A13 mutation types and the phenotype observed, so the smaller sample size is not likely to lead to referral bias in favor of null or missense mutations in this study. Secondly, for 19 of the 126 alleles, we could not find any mutations. One possible explanation could be that the patients with one detected mutant allele are carriers and this may be a risk factor for cholestasis or they may have an alternate cause for cholestasis. Alternatively, as previously described,[31,32] they may have a second mutation not detected by Sanger sequencing or the targeted test for the IVS16ins3kb rearrangement such as intronic mutations or large rearrangements.

In conclusion, the mutation spectra of the SLC25A13 gene are significantly different among patients with neonatal intrahepatic cholestasis from different parts of China. These differences should be considered when establishing a molecular diagnostic strategy or interpreting their results.

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