Prevalence and genetic analysis of thalassemia in childbearing age population of Hainan, The Free Trade Island in Southern China

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Abstract
Background: Hainan has one of the high incidences of thalassemia in China, but the epidemiological data in the whole province has not been reported yet. The objective of our study was to reveal the true prevalence and molecular mutation spectrum of thalassemia in the population of Hainan who are of childbearing age.

Methods: We screened 166,936 individuals from 19 cities and counties in Hainan by hematological parameters analysis, and further conducted genetic analysis for individuals whose MCV was less than 82fL.

Results: In total, 21,619 (12.95%) subjects were diagnosed as thalassemia carriers or patients. The overall prevalence of α-thalassemia, β-thalassemia, and α+β-thalassemia were 10.39%, 1.38%, and 1.18%, respectively. Eleven α-thalassemia mutations and sixteen β-thalassemia mutations were identified. The high-frequency genotypes of α-thalassemia were -α3.7/αα (19.70%), -α4.2/αα (19.39%), αα/-SEA (15.60%), αWSα/αα (9.24%), and -α3.7/-α4.2 (8.90%), and those of β-thalassemia were βCD41/42(−TTCT)/βN (58.92%), β28(A>G)/βN (16.05%), βIVS-II−654(C>T)/βN (8.42%), βCD71/72(+A)/βN (6.03%), βCD17(A>T)/βN (5.47%), and βCD26(AG>AAG)/βN (2.69%). In addition, the frequencies and hematological profiles of many rare mutations of α- [Fusion, HKαα, ααanti4.2, IVS-II−55 (T>G), IVS-II−119 (−G,+CTCGGCCC)] and β-globin genes [−50 (G>A), IVS-II−81 (C>T)] in Hainan were reported for the first time.

Conclusion: Our study revealed the high prevalence and extensive molecular spectrum of thalassemia in childbearing age population of Hainan, suggesting thalassemia in Hainan ranks second in prevalence among all regions in China. The findings will be useful for genetic counseling and prevention of thalassemia.

KEYWORDS
childbearing age, molecular spectrum, prevalence, thalassemia
1 | INTRODUCTION

Thalassemia is a group of hereditary hemolytic disorders caused by globin gene deficiency. According to the type of globin involved, thalassemia can be divided into several forms. The two most common forms in clinic are α-thalassemia and β-thalassemia. At the molecular level, depending on whether one or both of the linked α-globin genes are deleted or reduced in activity by mutation, α-globin gene defects can be categorized as a+ and a0. The severity of α-thalassemia is generally well correlated with the number of nonfunctional copies of α-globin genes. Patients with α-thalassemia major (a0/a0) usually die in the uterus or shortly after birth, while patients with HbH disease (a0/a+) can develop mild-to-moderate anemia as they age and may require blood transfusion. β-globin gene defects include point mutations and deletions, where point mutations are most common. Currently, over 200 mutations in β-globin genes have been identified, ranging from mild mutations that cause a relative reduction in β-globin chain synthesis (β0) to severe mutations that result in complete no β-globin chain synthesis (β0). β-Thalassemia major and some β-thalassemia intermedia patients (β+ or β+β) rely on transfusion to sustain their life. The birth of children with severe thalassemia (especially β-thalassemia major patients and some HbH disease or β-thalassemia intermedia patients) will bring serious mental and economic burden to their families and society. Therefore, it is particularly important to conduct prenatal screening and genetic counseling for couples of childbearing age in high-risk areas. People of childbearing age refers to individuals who can have children, usually between the age of 15 to 50 for women and 16 to 65 for men. In order to prevent and control severe thalassemia, the Hainan provincial government has implemented the Hainan Thalassemia Screening Project in Pregnancy program since 2019, providing free thalassemia gene diagnosis for pregnant women and their partners. In this study, people of childbearing age who visited local medical institutions for prenatal health examinations were included, and we used the data obtained from this project to characterize the prevalence and molecular spectrum of thalassemia in Hainan.

The southern part of the Yangtze River in China is a high-risk area for thalassemia, including Hainan, Guangdong, Guangxi, Jiangxi, and so on. Hainan province, a region located in the southernmost part of China, has 19 cities and counties, covering an area of approximately 35,400 km². Hainan Island is also a multi-ethnic settlement that comprises mainly groups from Han and Li ethnicities, as well as other smaller groups (Miao, Zhuang, Hui, and so on). The estimated population in this region was around 10 million, of which about 83.33% are Han ethnic group, 14.73% are Li ethnic group, and other ethnic groups account for only 1.94% of the whole population (http://stats.hainan.gov.cn/tjj/). Apart from Hainan, the molecular epidemiological characteristics of thalassemia in other China provinces had been reported in a large number of studies. However, Hainan does not have the epidemiological surveillance data in the whole province at present, only few small studies have reported single region or small datasets, and the overall frequency ranged from 13% to 70%, which were not enough to reflect the true prevalence of thalassemia genetic profiles in Hainan Island. In this study, we aimed to reveal the prevalence and molecular mutation spectrum of thalassemia from a large samples study to provide clinical support for the lasting prevention and control of thalassemia in Hainan Island.

2 | MATERIALS AND METHODS

2.1 | Participants

All subjects were recruited from the medical institutions within 19 cities and counties in Hainan Province between July 2019 and May 2021. This included Haikou, Sanya, Sansha, Danzhou, Wuzhishan, Wenchang, Qionghai, Wanning, Dongfang, Ding’an, Chengmai, Tunchang, Lingao, Baisha, Changjiang, Ledong, Lingshui, Baoting, and Qiongzhou. All couples who visited local medical institutions for prenatal health examinations were included in this study after signing the informed consent. All subjects in this study were tested for routine hematological parameters, and thalassemia genetic analysis was conducted for individuals with microcytosis [mean corpuscular volume (MCV) values <82 fl and/or mean cell hemoglobin (MCH) <27 pg]. All participants voluntarily joined this study with informed consents and all studies were approved by the Ethics Committee for Clinical Investigation of Hainan Women and Children’ Medical Center.

2.2 | Hematological parameters analysis and genotyping of thalassemia

Peripheral venous blood samples of 2 ml volume were taken from all subjects and collected into an EDTA anti-coagulated tube. The hematology phenotypic indicators were determined and analyzed by the antenatal care agency using the hemocyte analyzer. Subjects with red blood cell MCV values of less than 82 fl were considered possible thalassemia carriers. Then, the peripheral venous blood of the participants was transported to our center by cold chain immediately for thalassemia genotyping. The gap polymerase chain reaction was used to identify three common Chinese α-globin gene deletion mutations (–α3.7, –α4.2, and –α4.2SEA) and rare deletion mutations. Reverse dot-blot hybridization was used to identify three common nondeletional mutations of α-thalassemia (Hb CS, Hb QS, and Hb WS) and 17 common β-globin gene mutations in China (Yaneng Biosciences, Shenzhen, China). DNA sequence was used to detect unknown and rare thalassemia gene mutations.

2.3 | Statistics

Graphpad Prism 8 (GraphPad Software) was used for statistical analyses.
3 | RESULTS

In this study, 166,936 subjects from 19 cities and counties in Hainan were screened by hematological parameters analysis, and genetic analysis was conducted for individuals whose MCV was less than 82fL. Totally, 21,619 (12.95%) subjects were diagnosed as carriers or patients of thalassemia. Among them, 17,338 (10.39%) subjects were diagnosed as α-thalassemia, 2305 (1.38%) subjects as β-thalassemia, and 1976 (1.18%) as αβ-thalassemia. Among them, 17,338 (10.39%) as αβ-thalassemia carriers or patients of thalassemia.

TABLE 1

Distribution of α-thalassemia genotypes in population of childbearing age in Hainan Island

| α-Thalassemia genotype | Type       | Number of cases (n) | Constituent ratio (%) |
|------------------------|------------|---------------------|-----------------------|
| αα−/−SEa               | α²/α       | 2705                | 15.60                 |
| αa²−/α²−SEa            | α¹a⁰       | 145                 | 0.84                  |
| αa²−/α²−SEa            | α²/α⁰      | 772                 | 4.45                  |
| α−α³−/α³−β             | α³/α⁰      | 1543                | 8.90                  |
| α−α³−/α³−β             | α³/α⁰      | 3415                | 19.70                 |
| α−α³−/α³−β             | α³/α⁰      | 161                 | 0.93                  |
| α−α³−/α³−β             | α³/α⁰      | 731                 | 4.22                  |
| α−α³−/α³−β             | α³/α⁰      | 3361                | 19.39                 |
| α−α³−/α³−β             | α³/α⁰      | 17                  | 0.10                  |
| α−α³−/α³−β             | α³/α⁰      | 34                  | 0.20                  |
| α−α³−/α³−β             | α³/α⁰      | 37                  | 0.21                  |
| α−α³−/α³−β             | α³/α⁰      | 79                  | 0.46                  |
| α−α³−/α³−β             | α³/α⁰      | 10                  | 0.06                  |
| α−α³−/α³−β             | α³/α⁰      | 128                 | 0.74                  |
| α−α³−/α³−β             | α³/α⁰      | 95                  | 0.55                  |
| α−α³−/α³−β             | α³/α⁰      | 547                 | 3.15                  |
| α−α³−/α³−β             | α³/α⁰      | 107                 | 0.62                  |
| α−α³−/α³−β             | α³/α⁰      | 826                 | 4.76                  |
| α−α³−/α³−β             | α³/α⁰      | 703                 | 4.05                  |
| α−α³−/α³−β             | α³/α⁰      | 1602                | 9.24                  |
| α−α³−/α³−β             | α³/α⁰      | 4                   | 0.02                  |
| α−α³−/α³−β             | α³/α⁰      | 59                  | 0.34                  |
| α−α³−/α³−β             | α³/α⁰      | 6                   | 0.03                  |
| α−α³−/α³−β             | α³/α⁰      | 218                 | 1.26                  |
| α−α³−/α³−β             | α³/α⁰      | 9                   | 0.05                  |
| α−α³−/α³−β             | α³/α⁰      | 11                  | 0.06                  |
| α−α³−/α³−β             | α³/α⁰      | 6                   | 0.03                  |
| α−α³−/α³−β             | α³/α⁰      | 3                   | 0.02                  |
| α−α³−/α³−β             | α³/α⁰      | 2                   | 0.01                  |
| α−α³−/α³−β             | α³/α⁰      | 1                   | 0.01                  |
| α−α³−/α³−β             | α³/α⁰      | 1                   | 0.01                  |
| α−α³−/α³−β             | α³/α⁰      | 17338               | 100.00                |
genotypes accounted for 97.57% of all β-thalassemia genotypes in Hainan. One patient with rare genotype of $\alpha^{\text{IVS-I-1} (G>T)} / \beta^{\text{IVS-II-81} (C>T)}$ and another with $\beta^{5' \text{UTR} + 40-43 (A>C)} / \beta^{\text{IVS-II-81} (C>T)}$ were also identified (Table 2). A total of 1976 subjects were diagnosed as α+β-thalassemia, and among them, the high-frequency genotypes were $-\alpha^3.7/\alpha^a$ combined with $\beta^{CD41/42 (TTCT)} / \beta^N$, $-\alpha^{4.2}/\alpha^a$ combined with $\beta^{CD41/42 (TTCT)} / \beta^N$, and $\alpha^{WS/\alpha^a}$ combined with $\beta^{CD41/42 (TTCT)} / \beta^N$, accounting for 20.19%, 18.72%, and 12.65% of all α+β-thalassemia genotypes, respectively. Furthermore, $-50 (G>A)$ is a rare β-globin gene mutation in China and two cases with $\beta^{-50 (G>A)} / \beta^N$ were identified in all α+β-thalassemia genotypes (Table S1).

We also calculated the frequency of a specific type of mutation in all α (or β) mutant chromosomes (allele frequency) in Hainan Island. Eleven α-thalassemia gene mutations and sixteen β-thalassemia gene mutations were found. Of α-globin mutant chromosomes, the five top frequent types were $-\alpha^3.7$, $-\alpha^{4.2}$, $-\text{SEA}$, $\alpha^{WS}$, and $\alpha^{Q5}$, with the allele frequencies of 33.59%, 32.26%, 12.86%, 16.83%, and 3.60% of all α mutant chromosomes, respectively. Other mutations with frequencies less than 1% included $\alpha^{50}$, Fusion, HKκa, $\alpha\alpha\alpha\alpha\alpha$, $\text{IVS-II-55 (T>G)}$, and $\text{IVS-II-119 (G+C;TCGCCC)}$ (Table 3). Of β-globin mutant chromosomes, the data showed the highest allele frequency of CD41/42 (73.15%), followed by $-28 (A>G)$ (10.62%), IVS-II-654 (C>T) (5.25%), CD71/72 (+A) (4.27%), CD17 (A>T) (3.38%), and CD26 (GAG>AGG) (1.59%). Other mutations with frequencies less than 1% included CD14/15 (+G), CD27/28 (+C), $-29 (A>G)$, CD43 (G>T), 5'UTR;+40-43 (A>C), initiation codon (ATG>AGG), IVS-I-1 (G>T), IVS-I-5 (G>C), $-50 (G>A)$, and IVS-II-81 (C>T) (Table 4).

TABLE 2 Distribution of β-thalassemia genotypes in population of childbearing age in Hainan Island

| β-Thalassemia genotype | Type | Number of cases (n) | Constituent ratio (%) |
|------------------------|------|---------------------|-----------------------|
| $\beta^{CD41/42 (TTCT)} / \beta^N$ | $\beta^0/\beta$ | 1 | 0.04 |
| $\beta^{CD17 (A>T)} / \beta^N$ | $\beta^0/\beta$ | 126 | 5.47 |
| $\beta^{CD27/28 (+C)} / \beta^N$ | $\beta^0/\beta$ | 10 | 0.43 |
| $\beta^{CD41/42 (+C)} / \beta^N$ | $\beta^0/\beta$ | 370 | 16.05 |
| $\beta^{CD43 (G>T)} / \beta^N$ | $\beta^0/\beta$ | 1358 | 58.92 |
| $\alpha^{IVS-II-55 (T>G)} / \beta^N$ | $\beta^0/\beta$ | 5 | 0.22 |
| $\beta^{CD71/72 (+A)} / \beta^N$ | $\beta^0/\beta$ | 194 | 8.42 |
| $\alpha^{IVS-I-1 (G>T)} / \beta^N$ | $\beta^0/\beta$ | 139 | 6.03 |
| $\alpha^{IVS-I-5 (G>C)} / \beta^N$ | $\beta^0/\beta$ | 11 | 0.48 |
| $\beta^{CD26 (GAG>AGG)} / \beta^N$ | $\beta^0/\beta$ | 13 | 0.56 |
| $\beta^{CD17 (A>T)} / \beta^N$ | $\beta^0/\beta$ | 2 | 0.09 |
| $\beta^{CD41/42 (TTCT)} / \beta^N$ | $\beta^0/\beta$ | 62 | 2.69 |
| $\beta^{CD71/72 (+A)} / \beta^N$ | $\beta^0/\beta$ | 1 | 0.44 |
| $\beta^{IVS-I-1 (G>T)} / \beta^{IVS-II-81 (C>T)}$ | $\beta^0/\beta^+$ | 1 | 0.04 |
| Total | | 2305 | 100.00 |

4 | DISCUSSION

In this study, we investigated 166,936 subjects of childbearing age population from 19 cities and counties in Hainan Island and reported the prevalence and mutation spectrum of thalassemia at molecular level in the whole province for the first time. A total of 21,619 (12.95%) subjects were diagnosed with thalassemia, and the frequencies of α-thalassemia, β-thalassemia, and α+β-thalassemia of the childbearing age population in Hainan were 10.39%, 1.38%, and 1.18%, respectively. These data showed the high prevalence...
of thalassemia in Hainan. The overall frequency of thalassemia obtained from this study was higher than the data reported recently in Guangdong (11.90%) but lower than that of Guangxi (19.10%), the two provinces with highest prevalence in China. When compared to the previous small-scale studies in a single region of Hainan, in which the prevalence of thalassemia ranged from 13% to 70%, our data always showed a lower frequency of specific genotypes, the reason may be the small sample size or different selection criteria for study subjects included in the former studies.  

The five most common mutations of α-thalassemia in Hainan were α−3.7, α−4.2, SEA, αWS, and αDS, which account for 99.14% of all α-thalassemia carriers. The molecular spectrum of α-thalassemia mutations was different from that previously depicted in southern China, where α−SEA and α−CS always had high frequencies. While in Hainan, 65.85% of α-thalassemia was caused by α−3.7 and α−4.2, and the prevalence of αDS was higher than the incidence of αCS. In addition, some uncommon mutations of α-globin genes in China were identified in our study. Fusion gene is the mutant gene that resulted from a fusion between the α2 and ωα1 genes, which was identified in 22 subjects and with the allele frequency of 0.09% in our study. The HKαα is a rearrangement occurring in the α-globin gene cluster containing both the α−3.7 and αωα2 unequal crossover junctions. It was detected in 11 subjects and with an allele frequency of 0.04%. The αωα2 is a rare mutation found in three subjects with an allele frequency of 0.01%. IVS−II−81 (C>T) was the most frequent α-thalassemia minor. In the present study, we identified the IVS−II−81 (C>T) in 11 subjects and with an allele frequency of 0.09% in our study. The HKαα is a rearrangement occurring in the α-globin gene cluster containing both the α−3.7 and αωα2 unequal crossover junctions. It was detected in 11 subjects and with an allele frequency of 0.04%. The αωα2 is a rare mutation found in three subjects with an allele frequency of 0.01%. IVS−II−81 (C>T) was the most frequent α-thalassemia minor. In the present study, we identified the IVS−II−81 (C>T) in 11 subjects and with an allele frequency of 0.09% in our study. The HKαα is a rearrangement occurring in the α-globin gene cluster containing both the α−3.7 and αωα2 unequal crossover junctions. It was detected in 11 subjects and with an allele frequency of 0.04%. The αωα2 is a rare mutation found in three subjects with an allele frequency of 0.01%. IVS−II−81 (C>T) was the most frequent α-thalassemia minor. In the present study, we identified the IVS−II−81 (C>T) in 11 subjects and with an allele frequency of 0.09% in our study. The HKαα is a rearrangement occurring in the α-globin gene cluster containing both the α−3.7 and αωα2 unequal crossover junctions. It was detected in 11 subjects and with an allele frequency of 0.04%. The αωα2 is a rare mutation found in three subjects with an allele frequency of 0.01%. IVS−II−81 (C>T) was the most frequent α-thalassemia minor. In the present study, we identified the IVS−II−81 (C>T) in 11 subjects and with an allele frequency of 0.09% in our study. The HKαα is a rearrangement occurring in the α-globin gene cluster containing both the α−3.7 and αωα2 unequal crossover junctions. It was detected in 11 subjects and with an allele frequency of 0.04%. The αωα2 is a rare mutation found in three subjects with an allele frequency of 0.01%.

Since β-thalassemia intermediate or major is usually detected in infants and they require lifelong transfusion treatment, most subjects in childbearing age population were carriers with the genotypes of β-thalassemia minor. In the present study, we identified 16 β-thalassemia mutations with 18 genotypes in both β+ and α+β-thalassemia carriers, demonstrating that the molecular spectrum of β-thalassemia mutations in childbearing age population of Hainan was complex. Of β-thalassemia mutations, CD41/42 (−TTCCT) was the most frequent β-thalassemia mutation with the allele frequency of 73.15%. The finding is similar to the former studies in other regions of southern China, but with a higher prevalence. Other common mutations of β-thalassemia were −28 (A>G) (10.62%), IVS−II−654 (C>T) (5.25%), CD71/72 (+A) (4.27%), CD17 (A>T) (3.38%), and CD26 (GAG>AAG) (1.59%). The ranking of the high-frequency genotypes was also different from other regions of southern China.  

Two rare mutations of β-globin genes in China were identified in Hainan. The mutation of −50 (G>A) in the direct repeat element of β-globin gene was first reported in a Chinese family and heterozygotes of carriers had normal hematological parameters. In our study, one subject with the genotype of α−3.7/α−4.2 combined β−50G>A/βK and another with α−3.7/α−4.2 combined β−50G>A/βK were detected, and the hematology indicators of both carriers showed α-thalassemia minor phenotype, which was similar with the former studies. The other rare mutation was IVS−II−81 (C>T), which is located in introns of the β-globin genes, and it is presumably a neutral polymorphism (http://globin.bx.psu.edu/cgi-bin/hbvar/query_vars3). One patient with the genotype of β−IVS−1−1 (G>T)/β−IVS−II−81 (C>T) and another with β−5’UTR:+40−43 (A>C)/β−IVS−II−81 (C>T) were also identified. The hematology indicators of β−IVS−1−1 (G>T)/β−IVS−II−81 (C>T) showed β-thalassemia minor phenotype, but the subject with β−5’UTR:+40−43 (A>C)/β−IVS−II−81 (C>T) had almost normal hematological parameters. This information may be helpful in genetic counseling for couples in high-prevalence areas of thalassemia.

5 | CONCLUSION

In this study, we revealed the high prevalence and extensive molecular spectrum of thalassemia in childbearing age population in Hainan province for the first time. The findings suggest that the prevalence of thalassemia in Hainan ranks second highest among other China provinces. Furthermore, the frequency of many rare mutations in Hainan was first reported in our study. These findings will provide valuable reference to genetic counseling and the prevention of severe thalassemia in this region.

CONFLICTS OF INTEREST

Meifang Xiao received the funding from the Open Foundation of NHC Key Laboratory of Tropical Disease Control, Hainan Medical University, and Hainan Natural Science Foundation. The remaining authors have no relevant conflicts of interest to disclose, and the manuscript is approved by all authors for publication.

DATA AVAILABILITY STATEMENT

All relevant data are included in the manuscript and the supplementary material of this article. The datasets that support the findings of this study are available on request from the corresponding author. The datasets are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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