The Prevalence and Molecular Spectrum of $\alpha$- and $\beta$-Globin Gene Mutations in 14,332 Families of Guangdong Province, China

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Abstract

Objective: To reveal the familial prevalence and molecular variation of $\alpha$- and $\beta$-globin gene mutations in Guangdong Province.

Methods: A total of 40,808 blood samples from 14,332 families were obtained and analyzed for both hematological and molecular parameters.

Results: A high prevalence of $\alpha$- and $\beta$-globin gene mutations was found. Overall, 17.70% of pregnant women, 15.94% of their husbands, 16.03% of neonates, and 16.83% of couples (pregnant women and their husbands) were heterozygous carriers of $\alpha$- or $\beta$-thalassemia. The regions with the highest prevalence were the mountainous and western regions, followed by the Pearl River Delta; the region with the lowest prevalence was Chaoshan. The total familial carrier rate (both spouses were $\alpha$- or $\beta$-thalassemia carriers) was 1.87%, and the individual carrier rates of $\alpha$- and $\beta$-thalassemia were 1.68% and 0.20%, respectively. The total rate of moderate-to-severe fetal thalassemia was 12.78% among couples in which both parents were carriers.

Conclusions: There was a high prevalence of $\alpha$- and $\beta$-thalassemia in Guangdong Province. This study will contribute to the development of thalassemia prevention and control strategies in Guangdong Province.

Introduction

Thalassemia is an autosomal recessive heritable blood disorder resulting from hemoglobin-production deficiency [1,2]. It is one of the most common monogenic disorders in the world and is mainly endemic in some areas of the tropics and subtropics, including southern China [3]. There are two types of thalassemia, $\alpha$- and $\beta$-thalassemia. Most patients with severe $\alpha$-thalassemia may die in utero or shortly after birth as a result of serious intrauterine anemia, and most patients with severe $\beta$-thalassemia may develop serious anemia in early childhood if untreated. Thalassemia is an important public health problem in many countries, and its prevention is mainly dependent on prenatal diagnosis and genetic counseling.

In China, thalassemia is widely distributed on the southern bank of the Yangtze River [4], particularly in southern China, in the Guangdong, Guangxi and Hainan Provinces [5,6,7,8,9]. Previous studies have reported an estimated carrier rate of 3.16–11.72% for $\alpha$-thalassemia and 1.96–3.87% for $\beta$-thalassemia in some regions of Guangdong Province [9,10]; however, these studies may not reveal the true prevalence of thalassemia in Guangdong province because of a limited sampling area and sample size. Furthermore, the main aim of a thalassemia prevention and control program is to prevent the birth of infants with moderate-to-severe thalassemia, so pregnant women and their husbands are critical targets of
such programs. Pregnant women, their fetuses and their husbands
were enrolled in the study, and a large-scale familial investigation
was conducted in 21 regions of Guangdong Province to reveal the
familial prevalence of thalassemia and provide scientific basis for
thalassemia prevention and control in the province.

Materials and Methods

Study design and subjects
A two-stage cluster-sampling method was employed in the
study, and the sampling area covered all 21 regions of Guangdong Province. In the first stage, we randomly sampled one county in
each of the twenty-one regions of Guangdong Province. In the
second stage, we sampled one or several hospitals with qualified
midwives on staff in each county; in all, 91 hospitals were included in
our study. Among 91 sampling hospitals with qualified midwives, 58.2% (53/91) of them are located in urban areas
and 41.8% (38/91) are located in rural areas; and for grade of
sampling hospitals, 2.2% (2/91), 13.2% (12/91), 42.9% (39/91)
and 41.8% (38/91) of them are respectively provincial, municipal,
county, town and community level (Table 1, Table S1). From each
hospital, we selected pregnant women who were going to deliver
between May and August 2012 and their husbands. The inclusion
criteria were that one or both of the spouses were of Guangdong ancestry. After obtaining written informed consent from all
subjects, we collected peripheral venous blood from the pregnant
women and their husbands as well as umbilical blood samples. In
total, 14,332 families were initially contacted to participate in this
study. Among all the couples, the people who were not
Guangdong ancestry and the unqualified samples were excluded
for this study. After selected, 40,808 blood samples (13,386
pregnant women, 13,148 husbands and 14,274 umbilical blood
samples) were included in the final statistical analysis.

Ethical declaration
The authors declare that the experiments comply with the
current laws of China and gain informed consent of all the subjects
before joining the study which had the approval by Medical Ethics
Committee of Guangdong Women and Children Hospital.

Hematological analysis
The blood samples were collected consecutively from 14,332
families between May and August 2012 in the sampled hospitals
in twenty-one regions of Guangdong Province. The blood samples
(3 ml) from all subjects were collected in EDTA tubes; routine
blood tests were performed, and the samples were transported on
ice to Guangdong Women and Children’s Hospital for further
analysis. Automatic capillary electrophoresis (Sebia, France) was
used to assess the concentration of the hemoglobins A, A2 and F as
well as any abnormal hemoglobin variants, including Hb Bart’s,
Hb Constant Spring and Hb J.

Molecular analysis
Genomic DNA was extracted from all peripheral venous blood
and umbilical blood samples using an automation system Lab-Aid
820 (Zee San Biotech Company, Fujian, China). Twenty-three
mutations, including three deletions associated with α-thalassemia,
three non-deletional mutations associated with α-thalassemia,
and seventeen point mutations associated with β-thalassemia,
were identified using a suspension-array system developed by our lab,
the sensitivity and specificity of which has been verified for various
types of gene mutation; this system has been patented in the
People’s Republic of China (Pub. No.: WO/2012/136070). The method is based on the Luminex xMAP system, which was
successfully applied to the genotyping of human papillomavirus
(HPV) [11]. The procedure involved probe design, multiplex
PCR, the attachment of probes to microspheres, hybridization and
analysis. A single operator can complete the entire procedure in
five hours. This system can accurately diagnose the genotype
associated with thalassemia with high throughput. The 23
mutations we tested were most common and high incidence in
Southern China which has been validated by several research-
ces[9,11,12], including deletional α-globin mutations (the South-
east-Asian deletion (–SEA), the rightward deletion (–α3.7) and
the leftward deletion (–α4.2+), point mutations associated with α-
thalassemia (Hb Constant Spring, Hb Quong Sze and Hb
Westmead) and the seventeen point mutations associated with β-
thalassemia (codon 41/42 (–TCTT), 654, −29 (A>G), −28
(A>G), codon 71/72 (+A), codon 17 (A>T), codon 43 (G>T), Hb
E. [B26/B8]Glu→Lys, GAG>AAG or codon 26 (G>A),
codon 27/28 (+C), codon 31 (–C), −32 (C>A), −30 (T>C),
codon 14/15 (+G), IVS-1-1 (G>T), IVS-1-5 (G>T), Int and Cap). The
results of the molecular analysis with the suspension-array system
were verified using a Gap-PCR kit (Shenzhen Yaneng Bio) for
deletion mutations associated with α-thalassemia and direct
genomic sequencing for non-deletional mutations associated with
α-thalassemia and point mutations associated with β-thalassemia.

Statistical analysis
Statistical analysis was conducted using the SPSS software (Ver.
13, SPSS Inc., Chicago, USA). The prevalence of familial
thalassemia was evaluated by descriptive statistics. Bootstrap
method was used to estimate the sampling error for the
prevalences of thalassemia mutations.

Table 1. The situation of category of sampling hospitals with qualified midwives.

| Category                   | The number of sampling hospitals with qualified midwives | Percentage (%) |
|----------------------------|--------------------------------------------------------|----------------|
| Urban or rural             |                                                        |                |
| urban                      | 53                                                     | 58.2           |
| Rural                      | 38                                                     | 41.8           |
| Grade of sampling hospitals|                                                        |                |
| Provincial level           | 2                                                      | 2.2            |
| Municipal level            | 12                                                     | 13.2           |
| County level               | 39                                                     | 42.9           |
| Town and community level   | 38                                                     | 41.8           |

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Results

The prevalences of α- and β-globin gene mutations among the pregnant women, their husbands and neonates

Among 13,386 pregnant women and 13,148 of their husbands of Guangdong ancestry, the total number of α- and β-globin gene mutations was 4,732 (17.83%); there were 3,531 α-globin gene mutations (13.31%), with mutation rates of 6.85% for the α-SEA deletion, 3.68% for the −α3.7 deletion, and 1.27% for the −α5.2 deletion; the remaining 1201 mutations were in the β-globin gene (4.53%), with mutation rates of 1.78% for the 41/42 (-CTTT) mutation and 1.18% for the IVS-II-654 (C→T) mutation. The prevalence of α- and β-globin gene mutations among the pregnant women, their husbands and the 14,274 neonates of Guangdong ancestry was similar proportionately to that observed in the total population of pregnant women and husbands of Guangdong ancestry (Table 2).

In all, 4,725 deletion mutations associated with α-thalassemia were verified by direct genomic sequencing, and 341 samples randomly selected from 34,054 sequenced, and 341 samples randomly selected from 34,054 samples with negative results were also confirmed by corresponding above-mentioned methods.

The rates of α- and β-thalassemia carrier status among the pregnant women, their husbands and neonates

Among the statistical samples, there were 4,465 thalassemia carriers (16.83%); of these, 3,268 (12.32%) were carriers of α-thalassemia alone, 1,027(3.87%) were carriers of β-thalassemia alone and 170 (0.64%) were carriers of both α- and β-thalassemia. The prevalence of the α- and β-thalassemia carrier status among the pregnant women and their husbands of Guangdong ancestry and the 14,274 neonates with one or both parents of Guangdong ancestry were proportionally similar to that observed in the total population of pregnant women and husbands of Guangdong ancestry (Table 3).

The rates of α- and β-thalassemia carrier status among the pregnant women and their husbands in the 21 regions of Guangdong Province

Among the 21 regions of Guangdong Province, the rate of α-thalassemia carrier status in the 13386 pregnant women (ancestry data were missing for 799 subjects) and 13,148 husbands (ancestry data were missing for 1195 subjects) of Guangdong ancestry varied between 6.03 and 18.13. The rate is higher in mountainous

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Table 2. The prevalences of α- and β-globin gene mutations among the pregnant women, their husbands and neonates in Guangdong Province, China.

| Mutation          | Pregnant women | Husbands | Neonates | Pregnant women + Husbands |
|-------------------|----------------|----------|----------|---------------------------|
|                   | n   | %    | n   | %    | n   | %    | n   | %    |
| α-Thalassemia     |     |      |     |      |     |      |     |      |
| α-SEA             | 992 | 7.41 | 825 | 6.27 | 931 | 6.52 | 1817 | 6.85 |
| α-3.7             | 501 | 3.74 | 475 | 3.61 | 487 | 3.41 | 976  | 3.68 |
| α-4.2            | 192 | 1.43 | 145 | 1.10 | 177 | 1.24 | 337  | 1.27 |
| α-6.1            | 53  | 0.40 | 44  | 0.33 | 45  | 0.32 | 90   | 0.37 |
| α-6.5            | 30  | 0.22 | 22  | 0.17 | 25  | 0.18 | 52   | 0.20 |
| α-6.7            | 134 | 1.00 | 118 | 0.90 | 138 | 0.97 | 252  | 0.95 |
| α-Thalassemia Total | 1902 | 14.21 | 1629 | 12.39 | 1803 | 12.63 | 3531 | 13.31 |
| β-Thalassemia     |     |      |     |      |     |      |     |      |
| Codons 41/42 (-CTTT) | 243 | 1.82 | 228 | 1.73 | 258 | 1.81 | 471  | 1.78 |
| IVS-II-654 (C→T)  | 171 | 1.28 | 141 | 1.07 | 156 | 1.09 | 312  | 1.18 |
| -29 (A→G)         | 10  | 0.07 | 9   | 0.07 | 9   | 0.06 | 19   | 0.07 |
| -28 (A→G)         | 95  | 0.71 | 75  | 0.57 | 86  | 0.60 | 170  | 0.64 |
| Condons 71/72 (+A) | 15  | 0.11 | 14  | 0.11 | 12  | 0.08 | 29   | 0.11 |
| Condon 17, A>T     | 53  | 0.40 | 45  | 0.34 | 46  | 0.32 | 98   | 0.37 |
| Condon 43 (G→T)    | 3   | 0.02 | 2   | 0.02 | 3   | 0.02 | 5    | 0.02 |
| E                 | 15  | 0.11 | 16  | 0.12 | 15  | 0.11 | 31   | 0.12 |
| Codons 27/28 (+C)  | 9   | 0.07 | 10  | 0.08 | 11  | 0.08 | 19   | 0.07 |
| 14-15             | 6   | 0.04 | 6   | 0.04 | 6   | 0.04 | 10   | 0.04 |
| IVS-I+1 (G→T)     | 4   | 0.03 | 4   | 0.03 | 7   | 0.05 | 8    | 0.03 |
| IVS-II-5 (G→C)    | 2   | 0.01 | 1   | 0.01 | 1   | 0.01 | 2    | 0.01 |
| Int               | 0   | 0.00 | 1   | 0.01 | 0   | 0.00 | 1    | 0.00 |
| Cap               | 10  | 0.07 | 15  | 0.11 | 13  | 0.09 | 25   | 0.09 |
| β-Thalassemia Total | 636 | 4.75 | 565 | 4.34 | 619 | 4.34 | 1201 | 4.53 |
| Total             | 2538| 18.96| 2194| 16.69| 2422| 16.97| 4732 | 17.83 |

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The frequencies of carrying genes for the same type of thalassemia. In total, 266 of the 14,332 couples included two carriers of the same thalassemia genotype (genotype data were missing for 132 individuals). The total familial carrying rate was 1.68%, and the familial carrying rates of α- and β-thalassemia were 1.87% and 0.20%, respectively (Table 6).

Distributions of the α- and β-globin genotypes and the frequencies of α- and β-thalassemia.

Among the 13,386 pregnant women of Guangdong ancestry, 1,837 were carriers of α-thalassemia, and —SEA/αα was the most common mutation, accounting for more than half of all α-thalassemia genotypes (51.71%). Other high-prevalence genotypes were α3.7/αα, —α2.2/α2 or αW52/αα. Overall, these four genotypes accounted for 92.43% of all α-thalassemia genotypes. The rates of carrier status among the 13,148 husbands of Guangdong ancestry and 14,274 neonates with one or both parents of Guangdong ancestry were 94.56% and 93.68%, respectively (Table 4). The results displayed that 635 pregnant women were carriers of β-thalassemia, and B41-42/BA was the most common mutation, accounting for almost 40% of all β-thalassemia genotypes (38.27%). Most of the remaining genotypes were β654/BA, β-28/BA or β117/BA. Overall, these four genotypes accounted for 55.19% of all β-thalassemia genotypes. The rates of carrier status among the husbands and the 14,274 neonates were 86.48% and 88.19% of all β-thalassemia genotypes.

The probabilities of moderate-to-severe fetal thalassemia.

The standard strategy of laboratory diagnosis used for moderate-to-severe fetal thalassemia was combined by phenotypic screening and genotyping. The screening for α- and β-thalassemia was carried out when the mean corpuscular volume (MCV) was <82fL and/or mean corpuscular Hb (MCH) was <27pg which indicate hypochromic microcytic anemia. Meanwhile, the serum iron and ferritin were measured for exclusion of iron deficiency anemia. In combination with the Hb A2 level that Hb A2 <3.0% indicate α-thalassemia trait and Hb A2 >3.5% indicate β-thalassemia trait. Then all such positive samples were further characterized by genotyping. Among the 266 couples carrying mutant genes for the same type of thalassemia, 34 had produced fetuses with moderate-to-severe thalassemia. The total rate moderate-to-severe fetal thalassemia was thus 12.78% (34/266) among the couples with the same type of thalassemia, and the rates of moderate-to-severe fetal α- and β-thalassemia were 12.61% (30/238) and 14.29% (4/28), respectively.

Discussion

Previous studies have examined the prevalence and molecular spectrum of α- and β-globin gene mutations in Guangdong Province, but they were limited in sampling area and sample size; there is not a large-scale, large-sample and province-wide study conducted in Guangdong Province. Therefore, previous studies were of limited representative value and may not reveal the true prevalence of thalassemia in Guangdong Province. Our study had considerable financial support, and it has three key features. The first is the large scale, random sampling of one county in each of the twenty-one regions of Guangdong Province. The second is the family-based sampling; because the main aim of thalassemia intervention is to prevent the birth of infants with moderate-to-severe thalassemia, pregnancy is a critical period, and pregnant women and their husbands are critical subjects of intervention. Therefore, we selected pregnant women, their husbands and their fetuses as the subjects of our study. The third advantage is the large random sample. By scientific design and random sampling, we obtained a large random familial sample, including 14,332 families and 40,808 blood samples (13,386 peripheral venous blood samples from pregnant women, 13,148 peripheral venous blood samples from husbands, 14,274 umbilical blood samples). Therefore, our study could reveal the prevalence and molecular variation of α- and β-globin gene mutations in Guangdong Province.

We found a high prevalence of α- and β-globin gene mutations. Overall, the frequencies of α- and β-globin gene mutations are 18.96%, 16.69%, 16.97% and 17.83% among pregnant women,
husbands, neonates and “pregnant women and husbands”,
respectively. We also found a high prevalence of α- and
β-thalassemia carrier status. The frequencies of carrier status for
α-thalassemia alone were 12.96% of pregnant women, 11.66% of
husbands, 11.73% of neonates, and 12.32% of pregnant women
and husbands. The frequencies for β-thalassemia alone were
3.98% of pregnant women, 3.76% of husbands, 3.73% of
neonates, and 3.87% of pregnant women and husbands. Finally,
the frequencies for α- and β-thalassemia together were 0.76% of
pregnant women, 0.52% of husbands, 0.57% of neonates, and
0.64% of pregnant women and husbands. Overall, 17.70% of
pregnant women, 15.94% of husbands, 16.03% of neonates, and
16.83% of pregnant women and husbands in Guangdong
Province were heterozygous carriers of α- and/or β-thalassemia.
Comparing with other countries, the frequency of α-thalassemia
reported in our study are lower than that reported in the north of
Thailand and Laos (30%–40%) and higher than that reported in
Malaysia (4.5%) and Filipine (5%) [13], and the frequency of
β-thalassemia reported in our study are lower than that reported in
Cyprus (14%) and Sardinia (10.3%) [14]. And comparing with
previous studies in China, these rates are higher than those
reported in previous studies in Guangdong Province and other
provinces in southern China [9,10,15,16,17,18,19] but are lower
than those reported in several studies in Guangxi, Yunnan and
Guizhou Provinces [11,20,21,22]. The potential reasons for these
differences may include differences in the study population,
sampling area and method of gene detection.

The prevalences of α- and β-thalassemia carrier status varied
among the twenty-one regions of Guangdong Province. The
regions with the highest prevalence were the mountainous region
(including Yunfu, Qingyuan, Meizhou, Heyuan and Shaoguan)
and the western region (including Yangjiang, Maoming and
Zhanjiang), followed by the Pearl River Delta (including
Guangzhou, Shenzhen, Foshan, Zhongshan, Dongguan, Zhuhai,
Jiangmen, Zhaoqing and Huizhou). The lowest prevalence was
found in Chaoshan (including Jieyang, Chaozhou, Shanwei and Shantou). The three regions with the highest prevalence of \(\alpha\)-thalassemia carrier status were Yangjiang, Yunfu and Qingyuan; the three regions with the lowest prevalence were Shantou, Chaozhou and Shanwei. The three regions with the highest prevalence of thalassemia and low accessibility of thalassemia prenatal diagnosis and induced labor. Because of the high prevalence of thalassemia and low accessibility of thalassemia intervention, thalassemia remains a severe public health problem in Guangdong Province. The emphasis in thalassemia prevention and control should be placed on public health education, training doctors, establishing networks and the wide implementation of effectual thalassemia intervention, including prenatal screening, prenatal diagnosis and induced labor. Because of the high prevalence of thalassemia and low accessibility of thalassemia intervention, thalassemia remains a severe public health problem in Guangdong Province. The emphasis in thalassemia prevention and control should be placed on public health education, training doctors, establishing networks and the wide implementation of

| Table 5. \(\beta\)-globin genotypes and \(\beta\)-thalassemia frequencies among pregnant women, their husbands and neonates in Guangdong Province, China. |
|----------------|----------------|----------------|
| Genotype       | Pregnant women | Husbands        |
|                | \(n\) | \(n\%\) | \(n\) | \(n\%\) | \(n\) | \(n\%\) |
| \(\beta^{±}\)-/-\(\beta^{±}\) | 0 | 0.00 | 0 | 0.00 | 1 | 0.16 |
| \(\beta^{±}\)-/\(\beta^{±}\) | 1 | 0.16 | 0 | 0.00 | 0 | 0.00 |
| \(\beta^{±}\)-/\(\alpha\) | 94 | 14.80 | 74 | 13.17 | 82 | 13.36 |
| \(\beta^{±}\)/\(\epsilon\) | 0 | 0.00 | 1 | 0.18 | 0 | 0.00 |
| \(\beta\)-/-\(\alpha\) | 10 | 1.57 | 9 | 1.60 | 9 | 1.47 |
| \(\beta\)-/\(\epsilon\) | 6 | 0.94 | 4 | 0.71 | 2 | 0.33 |
| \(\beta\)-/ME | 0 | 0.00 | 0 | 0.00 | 1 | 0.16 |
| \(\beta\)-/JIA | 52 | 8.19 | 45 | 8.01 | 45 | 7.33 |
| \(\beta\)-/JIA | 9 | 1.42 | 10 | 1.78 | 11 | 1.79 |
| \(\beta\)-/JIA | 0 | 0.00 | 0 | 0.00 | 2 | 0.33 |
| \(\beta\)-/JIA | 243 | 38.27 | 226 | 40.21 | 254 | 41.37 |
| \(\beta\)-/JIA | 0 | 0.00 | 1 | 0.18 | 1 | 0.16 |
| \(\beta\)-/JIA | 3 | 0.47 | 2 | 0.36 | 3 | 0.49 |
| \(\beta\)-/JIA | 171 | 26.93 | 141 | 25.09 | 156 | 25.41 |
| \(\beta\)-/JIA | 15 | 2.36 | 14 | 2.49 | 12 | 1.95 |
| \(\beta\)-/JIA | 0 | 0.00 | 1 | 0.18 | 0 | 0.00 |
| \(\beta\)-/JIA | 15 | 2.36 | 14 | 2.49 | 15 | 2.44 |
| \(\beta\)-/JIA | 0 | 0.00 | 1 | 0.18 | 0 | 0.00 |
| \(\beta\)-/JIA | 4 | 0.63 | 4 | 0.71 | 7 | 1.14 |
| \(\beta\)-/JIA | 2 | 0.31 | 1 | 0.18 | 1 | 0.16 |
| Total         | 635 | 100.00 | 562 | 100.00 | 614 | 100.00 |

| Table 6. The frequencies of carrying genes for the same type of thalassemia among couples in Guangdong Province, China. |
|----------------|----------------|----------------|
| Variable       | The number of couple (N) | Family-based carrying rate (%) |
| Both \(\alpha\)-carriers | 238 | 1.68 |
| Both \(\beta\)-carriers | 28 | 0.20 |
| Both \(\alpha\) and \(\beta\)-carriers | 0 | 0 |
| Total         | 266 | 1.87 |

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premarital and prenatal screening to increase the accessibility of thalassemia intervention and reduce (ultimately, to zero) the number of infants born with moderate-to-severe thalassemia. The government of Guangdong Province has committed to investing thirty-five million yuan for thalassemia prevention and control among pregnant women and their husbands every year. We also suggest the need for further research, especially on the factors influencing the accessibility of thalassemia intervention, to provide a scientific basis for government decision-making.

Supporting Information

Table S1 The situation of sampling.

S1(XLS)

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Author Contributions

Conceived and designed the experiments: XZZ AHY BL QGZ. Performed the experiments: AHY BL QGZ LJX LW YM TTC SG MYL JQL HG DQQ JCY TW YXZ CL. Analyzed the data: XZZ AHY BL QGZ. Contributed reagents/materials/analysis tools: LZ WH WFH QSC SJX. Wrote the paper: XZZ AHY BL QGZ.