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Molecular characterization of hemoglobinopathies and thalassemias in Northern Guangdong Province, China

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Abstract

To detect the molecular characterization of hemoglobinopathies and thalassemias in Northern Guangdong Province of China.

We recruited 10,285 subjects who were screened for hemoglobin (Hb) variants and thalassaemia genotypes in the outpatient department of Yuebei People's Hospital from January 2018 to December 2020. The subjects collected venous blood samples for blood cell parameter analysis and Hb electrophoresis analysis. When the average red blood cell volume is <82 fL, or the average red blood cell Hb is <27 pg, or $HbA_2 > 3.5\%$, or $HbA_2 < 2.5\%$, or $HbF > 2.0\%$, the screening is positive if one of them is satisfied. All subjects who were screened positive were tested for the thalassaemia gene by gap-polymerase chain reaction, PCR-based reverse dot blot, and DNA sequencing.

Among all subjects screened, the overall prevalence of hemoglobinopathies and thalassemias were 0.46% (47/10,285) and 21.02% (2162/10,285) in Northern Guangdong Province. We found that Hb Q-Thailand is the most common, and other types of hemoglobinopathies are followed by Hb E, Hb New York, Hb G-Chinese, Hb G-Coushatta, Hb J-Bangkok, Hb J-Broussais, Hb Ottawa, and Hb G-Taipei. We identified 1340 cases (13.03%) of α-thalassemia, mainly includes $-^{SEA}$ deletion (71.64%), $-\alpha^{3.7}$ deletion (12.01%), $-\alpha^{4.2}$ deletion (4.78%). And identified 652 cases (6.34%) of β-thalassemia, the most prevalent being CD 41/42 (-TTCT) (35.89%), IVS-II-654 (C > T) (33.44%), CD 17 (A > T) (10.28%) and −28(A > G) (9.66%). Furthermore, there are 170 cases (1.65%) of α combined β thalassaemia. In addition, we found a rare case with −80 (T > A) of β-thalassemia. The results of this study found a high prevalence of hemoglobinopathies and thalassemias in Northern Guangdong Province, China. There were some differences molecular characterizations of thalassemia in different areas of China.

Our results enriched the related information of hemoglobinopathies and thalassemias in the region, which provided valuable references for the prevention and control of thalassemia.

Abbreviation: Hb = hemoglobin.

Keywords: genotype, hemoglobinopathy, molecular characterization, thalassemia

1. Introduction

Hemoglobinopathy and thalassemia are genetic disorders caused by aberrant hemoglobin (Hb). Hemoglobinopathy is caused by an alteration of the globin peptide chain conformation, whereas thalassemia is caused by reduced synthesis of globin peptide chains.[1] More than 600 hemoglobinopathy and 470 thalassemia mutations have been reported and recorded in databases (http://globin.bx.psu.edu/hbvar) until now.[2] Worldwide, thalassemia mainly occurs in malaria-prone parts of the world including Far East Africa, the Mediterranean, the Middle East, the Indian subcontinent, and Southeast Asia. In China, this inherited blood disorder is highly prevalent in Guangxi, Guangdong, and Yunnan provinces.[3] Globally, more than 1.0% of couples are at risk of having children with severe hemoglobinopathy, with more than 330,000 affected babies born each year. It constitutes a major health problem in areas with high carrier frequency, most of which occur in developing countries.[4–7]

Guangdong province, which is located in the southern part of China, has a high prevalence of thalassemia. Shaoguan, a northern city in Guangdong province, is the border area between Guangdong, Hunan, and Jiangxi provinces of China. It is also an important gateway to the north and south of China. The Hakka people account for about 70% of the 3 million residents in Shaoguan. A previous survey showed that Hakka populations living in Guangxi,[8] Guangdong,[9] and Jiangxi provinces had a higher

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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incidence of hemoglobinopathies and thalassemias, thalassemia major is a fatal and disabling single-gene genetic disease, leading to serious public health problems in these areas.[10] Currently, detection of carriers and prenatal diagnosis are the only effective interventions to prevent the birth of babies with thalassemia major, due to lack of effective treatments for thalassemia. However, the scarcity of studies on thalassemia genotypes and hemoglobinopathy in Northern Guangdong Province greatly influences genetic counseling and prenatal diagnosis in this area. This is the first study that seeks to identify the hemoglobinopathy and thalassemia gene mutations in Northern Guangdong Province, which will contribute to find out the cause of anemia, treat it symptomatically and provide a scientific basis for genetic counseling and prenatal diagnosis, so as to prevent the birth of babies with thalassemia major and improve the quality of the birth population.

Table 1

Prevalence of hemoglobinopathy in Northern Guangdong Province (n = 10,285).

Hemoglobin variant	No. patients detected	Constituent ratio (%)	Prevalence ratio (%)
Hb Q-Thailand (HBA1: c.223 G > C)	17	36.17	0.17
Hb E (HBB: c.79 G > A)	7	14.89	0.07
Hb New York (HBB: c.341 T > A)	6	12.77	0.06
Hb G-Chinese (HBA2: c.91 G > C)	6	12.77	0.06
Hb G-Coushatta (HBB: c.68 A > C)	4	8.51	0.04
Hb J-Bangkok (HBB: c.170 G > A)	3	6.38	0.03
Hb J-Broussais (HBA1:c.273G > C)	2	4.26	0.02
Hb Ottawa (HBA1: c.46 G > C)	1	2.13	0.01
Hb G-Taipei (HBB:c.68A > G)	1	2.13	0.01
Total	47	100.00	0.46

2. Methods

We recruited 10,285 subjects that were screened for Hb variants and thalassemia genotype at the Outpatient Department of Yuebei People's Hospital from January 2018 to December 2020. The subjects had a mean age of 32 years (range, 7 months-83 years). The Ethics Committee of Yuebei People's Hospital reviewed and approved this study. Signed informed consent was obtained from all participants. All experiments were performed in accordance with relevant guidelines and regulations.

2.1. Hemoglobinopathy analysis

Venous blood samples were collected from each subject and anticoagulated with ethylenediaminetetraacetic acid-K2. Approximately 2 mL of the anticoagulated blood samples were used for analysis of blood cell parameters on Sysmex XT-2000i instrument (Japan East Asia Medical Electronics Co., Ltd.), and the Hb components were analyzed with Capillary electrophoresis system (Sebia Electrophoresis System, France). Positive thalassemia screening was defined as a mean corpuscular volume < 82 fL, or mean corpuscular Hb < 27 pg, or $HbA_2 > 3.5\%$, or $HbA_2 < 2.5\%$, $HbF > 2.0\%$. All patients positive for thalassemia screening were subjected to genetic testing.

2.2. Analysis of thalassemias

Genomic DNA was extracted from venous blood samples using a genomic DNA extraction kit (Qiagen, Germany). The 3 common deletional α-thalassemias were detected by gap-polymerase chain reaction; detection of the 3 non-deletional α-thalassemia and 17 genotypes of β-thalassemia were done using reverse dot-blot hybridization with the thalassemia gene detection kit (Shenzhen Yaneng Biotechnology Co., Ltd. China). The assay was carried out following the manufacturer's instructions.

For suspected rare types of hemoglobinopathy, the full-length α1-, α2- and β-globin genes were amplified using PCR assay. The purified PCR products were sequenced by ABI 3700 Sequencer (Applied Bio systems, USA).

2.3. Statistical analysis

Statistical analysis was conducted with SPSS 22.0 software (IBM SPSS22.0). Data were reported with the descriptive statistics method and showed as the means ± SD. The chi-square test was used to compare the distribution of various alleles of Hb variation in Shaoguan and other areas of China. A value of $P < .05$ was considered as statistically significant.

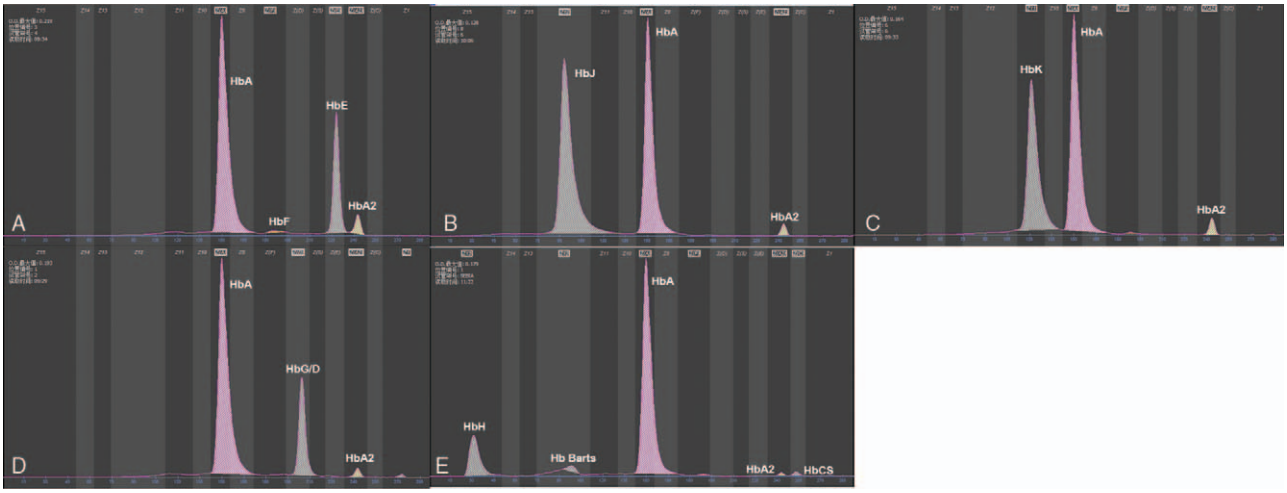

Figure 1. Hemoglobinopathy electrophoresis. (A) Hb E. (B) Hb J. (C) Hb K. (D) HbG/D. (E) Hb H, Hb Barts, Hb CS.

Table 2

Prevalence of α-thalassemia in Northern Guangdong Province (n = 10,285).

Genotypes	Phenotype	Case number	Constituent ratio (%)	Prevalence ratio (%)
$-^{SEA}/\alpha\alpha$	α^0/α	960	71.64	9.33
$-\alpha^{3.7}/\alpha\alpha$	α^+/α	161	12.01	1.57
$-\alpha^{4.2}/\alpha\alpha$	α^+/α	64	4.78	0.62
$-\alpha^{3.7}/-^{SEA}$	α^+/α^0	52	3.88	0.51
$\alpha^{CS}\alpha/\alpha\alpha$	α^+/α	34	2.54	0.33
$\alpha^{WS}\alpha/\alpha\alpha$	α^+/α	25	1.87	0.24
$-\alpha^{4.2}/-^{SEA}$	α^+/α^0	16	1.19	0.16
$\alpha^{QS}\alpha/\alpha\alpha$	α^+/α	10	0.75	0.10
$\alpha^{CS}\alpha/-^{SEA}$	α^+/α^0	9	0.67	0.09
$\alpha^{QS}\alpha/-^{SEA}$	α^+/α^0	4	0.30	0.04
$\alpha^{WS}\alpha/-^{SEA}$	α^+/α^0	3	0.22	0.03
$-\alpha^{3.7}/-\alpha^{4.2}$	α^+/α^+	2	0.15	0.02
Total		1340	100.00	13.03

Table 3

Prevalence of β-thalassemia in Northern Guangdong Province (n = 10,285).

Genotypes	Phenotype	Case number	Constituent ratio (%)	Prevalence ratio (%)
CD 41/42 (–TTCT)/N	β^0/β^N	234	35.89	2.28
IVS-II-654 (C > T)/N	β^+/β^N	218	33.44	2.12
CD 17 (A > T)/N	β^0/β^N	67	10.28	0.65
–28 (A > G)/N	β^+/β^N	63	9.66	0.61
CD 71/72 (+A)/N	β^0/β^N	24	3.68	0.23
CD 27/28 (+C)/N	β^0/β^N	14	2.15	0.14
βE(G > A)/N	β^+/β^N	13	1.99	0.13
CD 14/15 (+G)/N	β^0/β^N	5	0.77	0.05
–29 (A > G)/N	β^+/β^N	4	0.61	0.04
CAP +1 (A > C)/N	β^+/β^N	4	0.61	0.04
IVS-I-1 (G > T/A)/N	β^0/β^N	3	0.46	0.03
CD43 (G > T)/N	β^0/β^N	2	0.31	0.02
–80 (T > A)/N*	β^+/β^N	1	0.15	0.01
Total		652	100.00	6.34

* A rare case with –80(T > A) homozygous mutation of β-thalassemia by Sanger sequencing.

3. Results

3.1. Hemoglobinopathy results

Among the 10,285 subjects screened for hemoglobinopathy, there were 47 cases positive, include 26 cases α-globin gene mutations and 21 cases β-globin mutations, the prevalence of hemoglobinopathy was 0.46%. Nine different Hb variants were identified, Hb Q-Thailand (*HBA1*: c.223 G > C) (17/47) was the main Hb variant, followed by Hb E (*HBB*: c.79 G > A) (7/47), Hb New York (*HBB*: c.341 T > A) (6/47), Hb G-Chinese (*HBA2*: c.91 G > C) (6/47), Hb G-Coushatta (*HBB*: c.68 A > C) (4/47), Hb J-Bangkok (*HBB*: c.170 G > A) (3/47), Hb J-Broussais (*HBA1*:c.273G > C) (2/47), Hb Ottawa (*HBA1*: c.46 G > C) (1/47), and Hb G-Taipei (HBB:c.68A > G) (1/47) (Table 1 and Fig. 1).

3.2. Thalassemia results

Of the 10,285 cases who were screened for thalassemia, 1340 cases were diagnosed as α-thalassemia, the prevalence of α-thalassemia was 13.03% (1340/10,285). The most frequent mutations were seen in the genotype $-^{SEA}/\alpha\alpha$ (71.64%), followed by $-\alpha^{3.7}/\alpha\alpha$ (12.01%), and $-\alpha^{4.2}/\alpha\alpha$ (4.78%), and the 3 most frequent non-deletional mutation detected were $\alpha^{CS}\alpha/\alpha\alpha$ (2.54%), $\alpha^{WS}\alpha/\alpha\alpha$ (1.87%), and $\alpha^{QS}\alpha/\alpha\alpha$ (0.75%) (Table 2).

Furthermore, 652 cases were diagnosed as β-thalassemia. The prevalence of β-thalassemia was 6.34% (652/10,285). The 4 most common mutation genotypes were $\beta^{CD41-42(-TCTT)}/\beta^N$ (35.89%), $\beta^{IVS\text{-}II\text{-}654(C>T)}/\beta^N$ (33.44%), $\beta^{CD17(A>T)}/\beta^N$ (10.28%) and $\beta^{-28(A>G)}/\beta^N$ (9.66%) (Table 3). Finally, there are 170 cases of α combined β thalassaemia (Table 4). In addition, A case of rare type with -80(T > A) homozygous mutation of β-thalassemia was found (Fig. 2).

4. Discussion

Epidemiological data have shown that thalassemia is highly prevalent in Guangdong province of China,[11] however; there are no studies on the hemoglobinopathy and thalassemia genotypes in Northern Guangdong Province until now. The present study detected for the first time, a prevalence 0.46% of hemoglobinopathy, and 19.37% overall prevalence of thalassemia in Northern Guangdong Province. Our findings confirm that hemoglobinopathy and thalassemia are highly prevalent in Guangdong province, and suggest that screening of thalassemia should be performed to prevent the birth of babies with thalassemia major.

The prevalence of hemoglobinopathy was similar to that of the neighboring Meizhou (0.47%). There was no significant statistical difference between the 2 regions ($P = .13$). However, the frequency is higher than that of the average level of Guangdong province (0.36%, $P < .05$), that of the average level of the 7 provinces in southern region of the Yangtze River

Table 4

Prevalence of α+β-thalassemia in Northern Guangdong Province (n = 10,285).

Genotypes	Case number	Constituent ratio (%)	Prevalence ratio (%)
$-^{SEA}/\alpha\alpha$; CD 41/42 (–TTCT)/N	40	23.53	0.39
$-^{SEA}/\alpha\alpha$; IVS-II-654 (C > T)/N	33	19.41	0.32
$-^{SEA}/\alpha\alpha$; –28 (A > G)/N	18	10.59	0.18
$-^{SEA}/\alpha\alpha$; CD 17 (A > T)/N	4	2.35	0.04
$-^{SEA}/\alpha\alpha$; CD 71/72 (+A)/N	3	1.76	0.03
$-^{SEA}/\alpha\alpha$; βE(G > A)/N	3	1.76	0.03
$-^{SEA}/\alpha\alpha$; CD 41/42 (–TTCT)/–28 (A > G)	3	1.76	0.03
$-^{SEA}/\alpha\alpha$; IVS-II-654 (C > T)/–28 (A > G)	3	1.76	0.03
$-^{SEA}/\alpha\alpha$; –28 (A > G)/CD 17 (A > T)	1	0.59	0.01
$-\alpha^{3.7}/\alpha\alpha$; CD 41/42 (–TTCT)/N	22	12.94	0.21
$-\alpha^{3.7}/\alpha\alpha$; IVS-II-654 (C > T)/N	15	8.82	0.15
$-\alpha^{3.7}/\alpha\alpha$; –28 (A > G)/N	4	2.35	0.04
$-\alpha^{3.7}/\alpha\alpha$; CD 27/28 (+C)/N	1	0.59	0.01
$-\alpha^{3.7}/\alpha\alpha$; CD 41/42 (–TTCT)/–28 (A > G)	2	1.18	0.02
$-\alpha^{4.2}/\alpha\alpha$; CD 17 (A > T)/N	1	0.59	0.01
$-\alpha^{4.2}/\alpha\alpha$; βE(G > A)/N	1	0.59	0.01
$-\alpha^{3.7}/-^{SEA}$; CD 41/42 (–TTCT)/N	2	1.18	0.02
$-\alpha^{3.7}/-^{SEA}$; IVS-II-654 (C > T)/N	2	1.18	0.02
$-\alpha^{4.2}/-^{SEA}$; CD 41/42 (–TTCT)/N	10	5.88	0.10
$\alpha^{QS}\alpha/-^{SEA}$; IVS-II-654 (C > T)/N	1	0.59	0.01
$\alpha^{CS}\alpha/\alpha\alpha$; IVS-II-654 (C > T)/N	1	0.59	0.01
Total	170	100.00	1.65

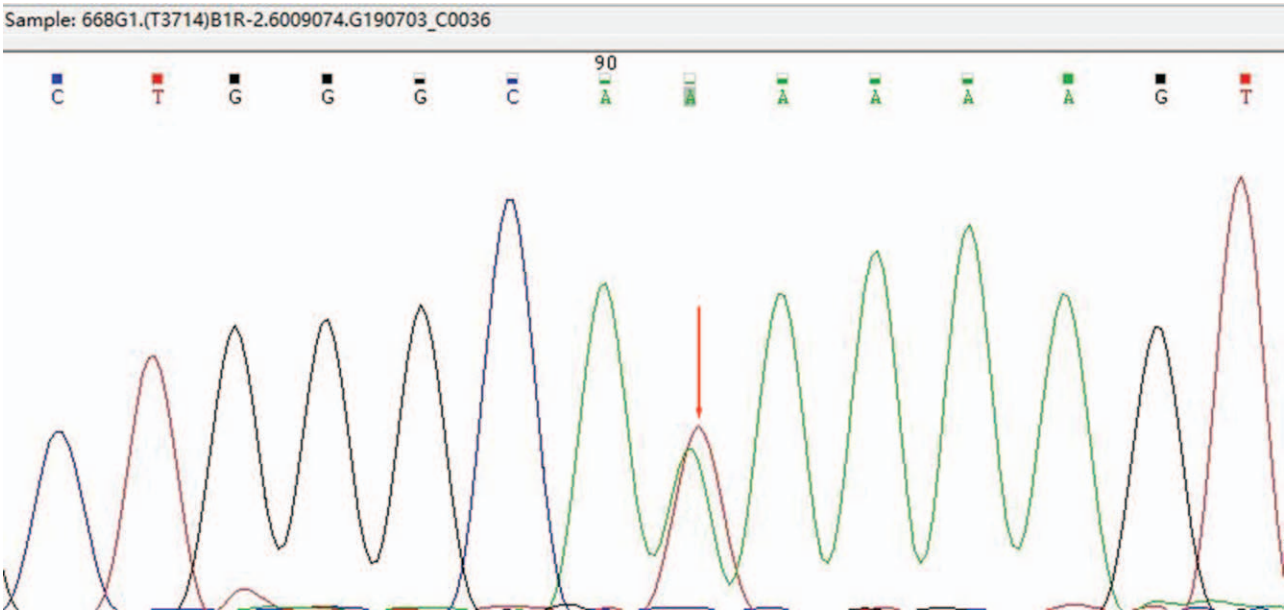

Figure 2. A case with –80(T > A) homozygous mutation of β-thalassemia by Sanger sequencing.

(0.33%, $P < .05$), and that of the average level of the 7 provinces in northern region of the Yangtze River (0.17%, $P < .05$).[11]

In this study, Hb Q-Thailand (*HBA1*: c.223 G > C) was the most frequent Hb variant (0.17%, 17/10,285) in Shaoguan. All Hb Q-Thailand cases were associated with $-\alpha^{4.2}$ thalassemia and showed slight microcytosis. Although this structural Hb variant was initially identified from a Chinese family, data on its origin and spread remains to be elucidated.[12] Previous studies have shown that Hb Q-Thailand is mainly distributed in the Hakka population of Meizhou, Guangdong province.[9] It is also widely distributed in Southeast Asia, with the Hakka migration model, which has led to populations in Taiwan, Thailand, and Singapore.[13,14] Our data supports previous speculations about Hb Q-Thailand originating from Chinese Hakkas.

In the present study, we detected α-thalassemias genotypes, including 93.66% deletional mutations and 6.34% non-deletional mutations. The most common deletional mutations were $-^{SEA}/\alpha\alpha$ (71.64%), $-\alpha^{3.7}/\alpha\alpha$ (12.01%) and $-\alpha^{4.2}/\alpha\alpha$ (4.78%). The prevalence of β-thalassemias was 6.34%, and the most common genotypes were $\beta^{CD41-42(-TCTT)}/\beta^{N}$ (35.89%), followed by $\beta^{IVS-II-654(C>T)}/\beta^{N}$ (33.44%), $\beta^{CD17(A>T)}/\beta^{N}$ (10.28%), $\beta^{-28(A>G)}/\beta^{N}$ (9.66%) and these 4 genotypes consisted 89.27% of all β-thalassemias. Our data are consistent with the report of Guangdong,[15] Hainan,[16] Hunan,[17] and Jiangxi.[18] Our findings differ from that of the report in Guangxi and Chongqing,[19,20] where $\beta^{CD17(A>T)}/\beta^{N}$ was the most common genotype in these areas, indicating region-specific prevalence of thalassemia genotypes. It is important to first obtain reliable epidemiological data on indigenous populations in order to propose effective public health strategies for prevention and control of hemoglobinopathies. Therefore, special attention should be paid to screening for hemoglobinopathies and thalassemia.[21]

The present study confirmed the high prevalence of hemoglobinopathies and thalassemias in Northern Guangdong Province of China. There were some differences molecular characterizations of thalassemia in different areas of China. Our results enriched the related information of hemoglobinopathies and thalassemias in the region, which provided valuable references for the prevention and control of thalassemia.

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Author contributions

Conceptualization: Zhanzhong Ma.
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