

The spectrum of α - and β -thalassemia mutations of the Li people in Hainan Province of China



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ABSTRACT

This study examines the frequency and spectrum of α - and β -thalassemia (thal) mutations of the Li people in Hainan Province of China. We have analyzed by genotyping a sample of 8600 subjects of the Li people and found that 53.45% subjects have only α -thal mutations with high frequencies of $-\alpha^{4.2}$ and $-\alpha^{3.7}$, but fewer $-\alpha^{SEA}$ mutation; 3.83% have β -thal mutations all identified to be 41/42 ($-\text{TCTT}$); whereas 7.99% carry both α -thal and β -thal mutations. We also examined 9800 subjects of the Han people, and the result showed 12.16% subjects have only α -thal mutations with $-\alpha^{SEA}$ and $-\alpha^{3.7}$ the most frequent mutation types, 6.11% have only β -thal mutations of 7 types, whereas 4.85% carry both α -thal and β -thal mutations. Our study demonstrated that the Li people in Hainan province have a high incidence of $-\alpha^{4.2}$ and $-\alpha^{3.7}$ thalassemia, low frequencies of α -thal $-\alpha^{SEA}$, and a novel β mutation, 41/42 ($-\text{TCTT}$). We provide the complete spectrum of α -thal and β -thal mutations and a strategy for accurate molecular diagnostic testing in the Li people in Hainan Province of Southern China.

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Introduction

The thalassemias (thal) are a group of inherited blood disorders resulting from mutation in globin genes, leading to down-regulation of the output of one of the globin chains [1]. Thalassemias can be divided into α -, β -, or δ -thal, with α - and β -thal most widely distributed. The majority of the mutations that cause α -thal are deletional, whereas those that cause β -thal are generally point mutations [2]. The heterozygous globin gene mutation carriers or mild thal patients may not have symptoms of anemia. In contrast, β -thal major and some β -thal intermedia patients depend on blood transfusion to sustain their life, which is a burden to their families and society; the most severe form of α -thal, i.e. hydrops fetalis, is generally incompatible with life and contributes to morbidity and sometimes mortality of the pregnant mother. Therefore, application of the epidemiological method to diagnose the thal could effectively prevent the delivery of the newborns with β -thal major and hydrops fetalis [3–6].

Thal has a highly specific molecular pathology and regional and racial/ethnic characteristics [7]. Thal occurs at high frequencies primarily in Southeast Asian, Middle Eastern, African, and Mediterranean populations of the world. Southern China (Fig. 1) including

Yunnan, Guizhou, Guangxi, and Guangdong Provinces have been reported to have a high incidence of thals, and the spectrum of the mutations has been examined previously [8–12].

The Li people are a minority ethnic group, the majority of whom live off the coast of southern China on Hainan Island [13], where they are the only minority ethnic group. The Li are descendants of the ancient Yue tribes of China, who settled on the island thousands of years ago. DNA analysis on the modern Li population suggests a close relationship with populations in Guangxi province of Southern China [14]. Data suggested that the Li people in Hainan have a high prevalence of thal, yet the detailed spectrum of the types of mutations has not yet been fully characterized [15]. This study is the first comprehensive study using epidemiological and molecular biology methods to investigate the frequency and spectrum of α - and β -thal mutations of the Li people in Hainan Province and compare these findings with the Han people. Our study will provide background for genetic counseling, public education, and the government policies to deliver genetic services and appropriate health measures to prevent severe types of thal.

Materials and methods

Subjects

During the period from March 2010 to June 2012, we screened 8600 individuals of the Li people who sought genetic counseling, premarital

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Fig. 1. The map of southeast of China.

medical checkups, prenatal diagnosis, health examination in healthcare centers or hospitals in Baoting, Baisha, Qiongzong, Tunchang, Dongfang, and Wuzhishan in the Hainan province of China. The age distribution ranged from 1 to 86 years. We also screened 9800 individuals of the Han people in the same area, and their age distribution ranged from 2 to 78 years. Informed consent was obtained from all subjects.

Thalassemia screening

Three ml of blood was collected from each individual into an EDTA anticoagulant tube, and an analysis was performed with the XE-2100 Blood Analyzer (Sysmex Corp. Kobe, Japan) and frozen for further molecular analysis.

Genotype analysis

Genomic DNA was extracted from all the blood samples using whole blood genomic DNA extraction kit (Takara, Dalian, China).

A thal gene diagnostic kit (Chaozhou Hybribio Limited Corporation, Guangdong, China) combining GAP-PCR and hybridization technology was used to test 16 known mutations of β -thal, including codons 41/42(–TCTT), IVS-II-654(C/T), 71/72(+A), –28(A>G), 17(A>T),

26(G>A), –29(A>G), 31(–C), 43(G>T), –29(A>G), 27/28(+C), 14/15(+G), Cap + 40 to +43(–AAAC), initiation codon (T>G), IVS-I-1(G>T) and IVS-I-5(G>C).

The same kit was also used to detected the three common α -globin gene deletions(–^{SEA}, – $\alpha^{3.7}$, – $\alpha^{4.2}$), and three nondeletional α -thal mutations: hemoglobin (Hb) Constant Spring (HbCS) or α^{142} , Term → Gln, TAA>CAA(α^2), Hb Quong Sze (HbQS) or α^{109} (H8)Leu → Pro, CTG>CCG(α^2), Hb Westmead or α^{122} (H8) His → Gln, CAC>CAG(α^2).

The thals were classified as silent α -thal (α/α^+), mild α -thal (α^0/α and α^+/ α^+), more severe hemoglobin H disease syndrome of α -thal (α^0/α^+), minor β -thal (β^+/ β , β^0/β), and intermedia and major β -thal (β^0/β^0 , β^0/β^+). Risk evaluations were carried out with these genotypes.

Results

We utilized a thal gene diagnostic kit combining GAP-PCR and hybridization technology to test thal genotypes. The full spectrum of mutation that could be detected by the kit (Fig. 2A) and several representative results (Fig. 2B) are shown.

A high proportion (65.27%) of the 8600 Li subjects carried thal mutations (Table 1), and among them, 4597 carried only α -globin mutation (53.45%); 329 carried only β globin mutation (3.83%); 687 carried both α and β -globin mutation (7.99%).

Four types of mutations were found in the 4597 cases of α -thal in 12 α globin genotypes, including 3367 cases (73.24%) with heterozygous mutations and 1230 cases (26.76%) with compound heterozygous or homozygous mutations. Overall, – $\alpha^{4.2}/\alpha\alpha$ and – $\alpha^{3.7}/\alpha\alpha$ are the most frequent α -thal types among the Li people, accounting for 18.23% and 17.55% respectively of the total 8600 screened people. Surprisingly, the 329 cases (3.83%) of all screened people with β -thal mutation had 41/42 (–TCTT). β -thal patients among the Li people were dormant mutation carriers or mild thalassemia. 687 cases carried both α and β -globin gene mutations and, among them, the 4 most frequent types were – $\alpha^{4.2}/\alpha\alpha$, – $\alpha^{3.7}/\alpha\alpha$, and – $\alpha^{4.2}/\alpha^{3.7}$, all accompanied by 41/42 (–TCTT), respectively accounting for 2.88%, 2.31%, and 1.08% of all the subjects.

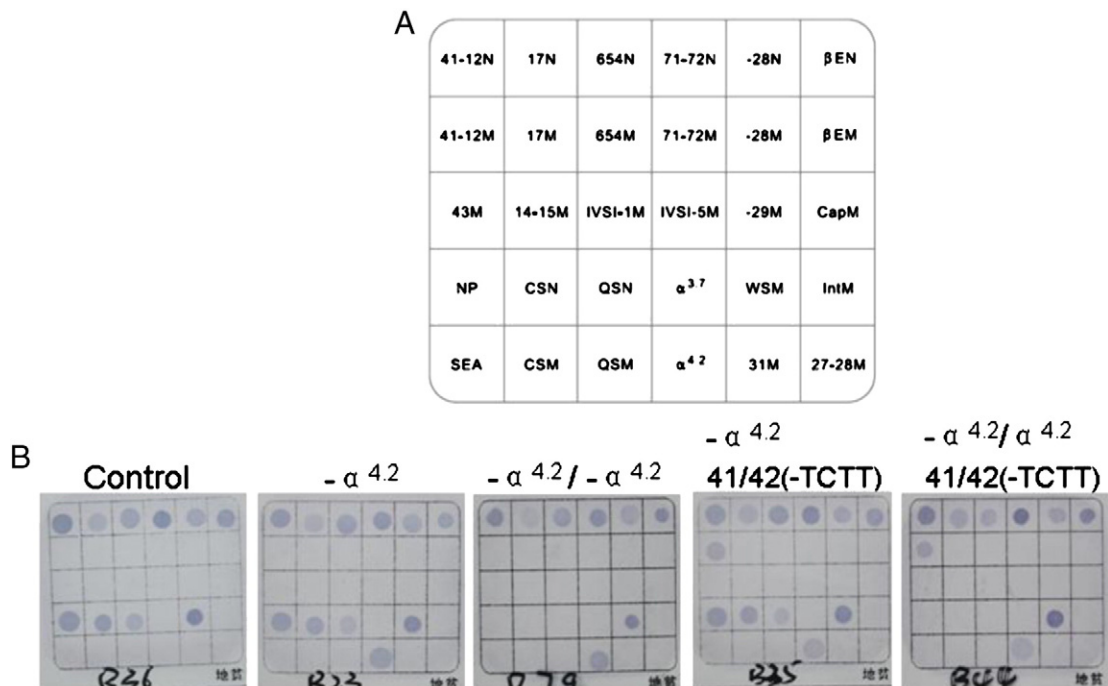


Fig. 2. The spectrum in Thalassaemia Gene Diagnostic kit (A), and representative results of mutations detected (B).

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