

# Three cases of Hb Q-H disease found in a Cantonese family

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Received September 30, 2010; Accepted December 22, 2010

DOI: 10.3892/mmr.2011.419

**Abstract.** Hemoglobin (Hb) Q-Thailand, also known as G-Taichung, Mahidol, Kurashiki-I and Asabara, is an  $\alpha$ -globin chain variant that results from a point mutation (GAC→CAC; Asp→His) at codon 74 of the  $\alpha 1$ -globin gene on chromosome 16p with a leftward single  $\alpha$ -globin gene deletion ( $-\alpha^{4.2}$ ). Co-inheritance of Hb Q-Thailand with  $\alpha$ -thalassemia (mainly  $--^{SEA}$ ) results in thalassemia intermedia, termed Hb Q-H disease. The aim of the present study was to identify Hb Q-H disease in a Cantonese family. The presence of the Hb variant was confirmed by cellulose acetate electrophoresis. DNA analysis, based on polymerase chain reaction and sequencing, was developed to identify the  $\alpha^{Q-Thailand}$  mutation and common  $\alpha$ -thalassemia gene deletions. Three cases of Hb Q-H disease and two Hb Q-Thailand carriers were found in the family. The 3-day-old proband with Hb Q-H disease did not show anemia (Hb 144g/l), having 25.47% Hb F<sup>Q</sup> ( $\alpha^Q_2\gamma_2$ ) in the total Hb; the other two cases of Hb Q-H disease manifested mild-to-moderate anemia. None required regular transfusions.

## Introduction

Hemoglobin (Hb) Q-Thailand, also known as G-Taichung, Mahidol, Kurashiki-I and Asabara, is often found in Thai, Chinese, and Japanese individuals (1). The hemoglobin (Hb) Q-Thailand mutation is an  $\alpha$ -globin chain variant that results from a point mutation (GAC→CAC; Asp→His) at codon 74 of the  $\alpha 1$ -globin gene on chromosome 16p (2,3). Individuals heterozygous for Hb Q-Thailand usually show slight red cell microcytosis, since the mutation is invariably linked to ( $-\alpha^{4.2}$ ) (1). Hb Q-H disease is caused by the co-inheritance of Hb Q-Thailand and  $\alpha^0$ -thalassemia (mainly  $--^{SEA}$ ), and presents with marked microcytosis, chronic hemolytic anemia associated with jaundice and hepatosplenomegaly (4). Affected individuals show a thalassemic blood shape similar to that observed in Hb

H disease, but Hb analysis reveals the absence of Hb A, with Hb Q-Thailand being the predominant fraction (4).

Hb Q-H is a rarely occurring disease; to date, all identified individuals have been Chinese or of Chinese origin. Here, we reported three cases of this disorder in a Cantonese family.

## Materials and methods

**Subjects and hematological analysis.** The proband was a 3-day newborn who presented for thalassemia screening at the Guangzhou Kingmed Center for Clinical Laboratory. According to the specific results of hematological analysis, the proband was diagnosed as a homozygous Hb H with an unknown Hb variant. Blood samples with EDTA were collected from the proband and his family members and immediately sent at 4°C to the Hematology and Molecular Laboratory for further analysis. Hematological data were collected on an automated blood cell counter (AC-T™ 5diff; Beckman Coulter, USA). Electrophoresis of hemoglobins was carried out in agar using a Spife 3000 electrophoresis system (Helena Laboratories, USA).

**DNA analysis.** Genomic DNA was extracted from peripheral blood leukocytes with the Genomic DNA Mini-Prep kit (Decipher Bioscience Shenzhen Ltd., China) as previously described (5).  $\alpha$ -thalassemia-1 (SEA type) and  $\alpha$ -thalassemia-2 ( $-\alpha^{3.7}$  and  $-\alpha^{4.2}$ ) were identified by gap-PCR with the  $\alpha$ -thalassemia genotype detection kit (Decipher Bioscience Shenzhen Ltd.) in a KP-TC48 DNA Thermal Cycler (Chaozhou HybriBio Biotechnology, China). Polymerase chain reaction (PCR) was performed under the following conditions: DNA was denatured at 96°C for 15 min, followed by 35 cycles at 98°C for 45 sec, annealing at 60°C for 90 sec, extension at 72°C for 150 sec and a final extension step for 5 min. The PCR products were separated by electrophoresis on 2.0% agarose gel.

The  $\alpha 1$ -globin gene was amplified with previously described primers (6). The 50- $\mu$ l PCR reaction mixture contained 0.1  $\mu$ g DNA, 25 pmol primers, 200  $\mu$ mol dNTPs and 2.5 units *Taq* DNA polymerase (Shanghai Sangon Biological Engineering Technology & Services Co., Ltd., China) in 10 mmol/l Tris-HCl (pH 8.0), 50 mmol/l KCl and 3 mmol/l MgCl<sub>2</sub>. The amplification reaction was carried out at 95°C for 3 min, 59°C for 1 min and 72°C for 1 min for 30 cycles in the KP-TC48 DNA Thermal Cycler. The PCR products were analyzed on the ABI 377 DNA Sequencer (Applied Biosystems, CA, USA).

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**Key words:** hemoglobin variant, hemoglobin Q-H disease

Table I. Hematological findings for the family members.

Parameter	1	2	3	4	5	6
Gender	Male	Female	Female	Female	Male	Male
Age	47 years	45 years	16 years	13 years	11 years	3 days
RBC (10 <sup>12</sup> /l)	5.69	2.84	4.51	4.72	5.38	6.30
Hb (g/dl)	155.00	64.00	85.00	126.00	105.00	144.00
MCV (fl)	79.00	71.00	63.00	77.00	65.00	75.00
MCH (pg)	27.20	22.60	18.90	26.70	19.50	22.90
HCT (%)	0.45	0.20	0.286	0.365	0.348	0.471
RDW(%)	13.30	14.90	17.90	12.30	17.00	19.80
Hb A <sub>2</sub> (%)	1.86	2.57	0.47	1.81	0.33	0.13
Hb A (%)	65.54	97.43	1.18	66.34	3.81	3.83
Hb Q-Thailand (%)	32.60	0.00	81.58	31.85	80.81	32.50 ( $\alpha^Q_2\beta_2$ ) 25.47 ( $\alpha^Q_2\gamma_2$ )
Hb H + H Bart's (%)	0.00	0.00	16.77	0.00	15.05	37.97
Genotype	$\alpha\alpha/\alpha^{4.2-Q}$	$\alpha\alpha/--^{SEA}$	$--^{SEA}/\alpha^{4.2-Q}$	$\alpha\alpha/\alpha^{4.2-Q}$	$--^{SEA}/\alpha^{4.2-Q}$	$--^{SEA}/\alpha^{4.2-Q}$

1, father; 2, mother; 3, elder brother; 4, young sister; 5, elder sister; 6, the proband (newborn); RBC, red blood cell count; Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; HCT, hematocrit; RDW, red blood cell distribution width.

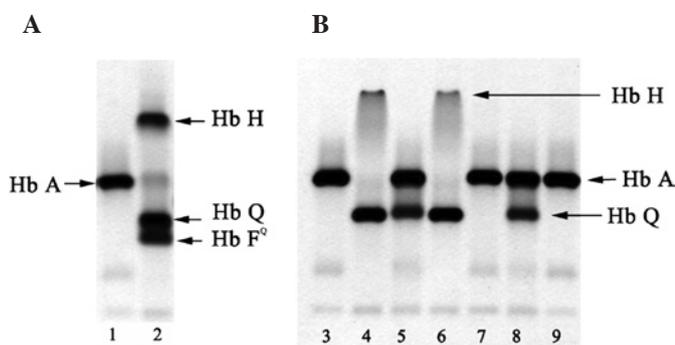


Figure 1. Hemoglobin analysis of the proband and family members with agarose electrophoresis. (A) 1, Normal control; 2, the proband (3-day newborn); (B) 3, Normal control; 4, elder brother; 5, young sister; 6, elder sister; 7, mother; 8, father; 9, normal control.

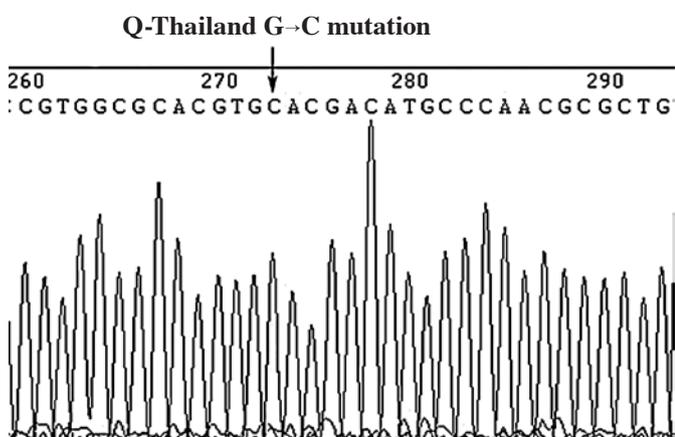


Figure 2. DNA sequence analysis of amplified  $\alpha 1$ -globin gene from the proband and his family members. The downward arrow indicates the G-C substitution at codon 74 of the  $\alpha 1$ -globin gene.

## Results

Three cases of Hb Q-H disease and two Hb Q-Thailand carriers were found in the family. The hematological data for the family are summarized in Table I. The Hb, mean corpuscular volume and mean corpuscular hemoglobin values of the family members with Hb Q-H were lower than normal, except in the 3-day-old newborn, which is consistent with previous reports (2,3,7). The proband had Hb Q ( $\alpha^Q_2\beta_2$ ) and Hb F<sup>Q</sup> ( $\alpha^Q_2\gamma_2$ ) bands as revealed by agar electrophoresis (Fig. 1A), but no anemia (Hb, 144g/l), with a 25.47% Hb F<sup>Q</sup> ( $\alpha^Q_2\gamma_2$ ) in the total Hb. The results of electrophoresis of samples from the family members are shown in Fig. 1B. Gap-PCR studies for  $\alpha$ -thalassemia indicated that the proband, his elder brother and elder sister were  $-\alpha^{4.2}/--^{SEA}$ , his young sister and father were  $\alpha\alpha/\alpha^{4.2}$ , and his mother was  $\alpha\alpha/--^{SEA}$ . DNA sequence analysis of the amplified  $\alpha 1$ -globin gene indicated that all family members, except for the mother, had a point mutation (GAC→CAC; Asp→His) at codon 74 of the  $\alpha 1$ -globin gene and were carriers of Hb Q-Thailand (Fig. 2). The proband, his elder brother and elder sister had Hb Q-H disease ( $-\alpha^{4.2-Q}/--^{SEA}$ ).

## Discussion

Hb Q-Thailand ( $\alpha 74\text{Asp}\rightarrow\text{His}$ ) is an abnormal Hb variant that was first identified in a Chinese family (8). All carriers of the Hb Q-Thailand gene in previous reports are Chinese or of Chinese origin (2,3,7). Patients heterozygous for the Hb Q-Thailand mutation possess a 4.2-kb deletion at chromosome 16p of the  $\alpha$ -globin gene, and have mild red cell microcytosis (2,3,7). It is well known that the high incidence area of Hb Q-Thailand is also the high incidence area of thalassemia, and co-inheritance of Hb Q-Thailand with  $\alpha$ -thalassemia (mainly  $--^{SEA}$ ) results in thalassemia intermedia, termed Hb Q-H disease.

In the present study, we identified three cases of Hb Q-H disease in a family from the Canton Province of China. The father of the family carried the Q-Thailand mutation and had  $-\alpha^{4.2}$   $\alpha$ -thalassemia with slightly altered hematological parameters and no clinical symptoms (Hb, 15.5g/l; MCV, 79fl). The Hb Q-Thailand variant was stable and had normal oxygen affinity. The mother had  $--^{SEA}$  thalassemia.

Clinically, patients with Hb Q-H disease are categorized as having deletional Hb H disease, and genetic counseling for Hb Q-H disease is similar to that for deletional Hb H (9). Three of the four children in the present study – the proband, his elder brother and elder sister – had Hb Q-H disease. The 3-day-old proband did not have anemia (Hb, 144g/l), since there was 25.47% Hb F<sup>Q</sup> ( $\alpha^Q_2\gamma_2$ ) in the total Hb. The other two cases of Hb Q-H disease manifested mild-to-moderate anemia (elder brother, 105 g/l; elder sister, 85 g/l). None of the three family members affected by Hb Q-H disease required regular transfusions.

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