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Clinical phenotype of haemoglobin Q-H disease

K F S Leung, E S K Ma, A Y Y Chan and L C Chan

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Clinical phenotype of haemoglobin Q-H disease
K F S Leung, E S K Ma, A Y Y Chan, L C Chan

Seven patients of Chinese origin who had haemoglobin (Hb) Q-H disease were studied. They were found to have a similar clinical phenotype to that of patients with deletional Hb H disease, who have a near identical genotypic configuration. The complete absence of Hb A in Hb Q-H disease and the similar clinical phenotype to deletional Hb H disease lends support to the observation that Hb Q-Thailand shares similar functional properties with Hb A.

The haemoglobin (Hb) Q-Thailand mutation is an α globin chain variant that results from a point mutation (GAC → CAC; Asp → His) in codon 74 of the α1 globin gene on chromosome 16p with a leftward single α globin gene deletion (−α74). Individuals who are heterozygous for Hb Q-Thailand usually show slight red cell microcytosis because the mutation is invariably linked to (−α74), and this mutation has been reported in subjects of Chinese, Thai and Japanese origin. In contrast, Hb Q-H disease, caused by the co-inheritance of Hb Q-Thailand and α0 thalassaemia, has only been reported in Chinese families. The genotype of Hb Q-H disease is −/−α0. Molecular analysis of Hb Q-H disease commonly shows that the (−/−SEA) α-thalassaemia deletion (SEA deletion) is the α0 thalassaemia determinant. Hb Q-H disease manifests as chronic anaemia associated with jaundice and hepatosplenomegaly. Affected individuals show a thalassaemic blood picture resembling Hb H disease, but Hb analysis shows absence of Hb A, with Hb Q-Thailand being the predominant fraction. We report the clinical phenotype of seven unrelated patients with Hb Q-H disease, the largest series to date of this relatively uncommon phenotype of seven unrelated patients with Hb Q-H disease, who have a near identical genotypic configuration. These seven patients were anaemic with steady state Hb concentrations ranging from 79 g/litre to 109 g/litre (mean, 97 g/litre). None of them required regular transfusions, although three of the seven had a history of infrequent blood transfusions. The other four had never been transfused. Four of the patients had splenomegaly, and splenectomy was performed in two as a result of hypersplenism. Two patients showed hepatomegaly. The six patients with iron studies available showed raised ferritin values, but none was put on iron chelation treatment.

DISCUSSION
Patients with Hb Q-H disease can be categorised under deletional Hb H disease, because genotypically they show deletion of three α globin genes. Therefore, we compared the clinical features of Hb Q-H disease with those of Hb H disease caused by the (−/−SEA) configuration in our archive, because their genetic configurations are almost identical. There appears to be no significant difference between the two groups with respect to clinical phenotype (table 1). Our results are entirely in accordance with the observation that Hb Q-Thailand shows normal oxygen affinity, Bohr effect, and cooperativity. Thus, patients with Hb Q-H disease have similar clinical features to patients with deletional Hb H disease, even though Hb A is absent in the former condition.

ACKNOWLEDGEMENTS
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HAEMATOLOGICAL AND CLINICAL FINDINGS
Table 1 details the clinical and haematological data. All of the study subjects are Hong Kong Chinese, with patient number 7 being of Chinese descent from Thailand. Diagnosis was made on Hb pattern studies in all cases. Archival blood samples were of sufficient quantity for genotype determination in four individuals (patients 3, 4, 5, and 7). Genotyping revealed the Hb Q-Thailand mutation, as confirmed by direct nucleotide sequencing of the α1 globin gene, together with 4.2 kb single α globin gene deletion and SEA deletion, as detected by multiplex polymerase chain reaction. Hb A was absent and Hb Q-Thailand accounted for 93.9–97.9% of the total Hb. There was a high proportion of Hb H inclusion bodies, which were detected in 70–90% of red blood cells in these patients on supravital staining.

Take home messages
- Seven Chinese patients with haemoglobin (Hb) Q-H disease were found to have a similar clinical phenotype to that of patients with deletional Hb H disease, which has a near identical genotypic configuration
- The complete absence of Hb A in Hb Q-H disease and the similar clinical phenotype to deletional Hb H disease lends support to the observation that Hb Q-Thailand shares similar functional properties with Hb A

Abbreviations: Hb, haemoglobin; SEA deletion, (−SEA) α thalassaemia deletion

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Table 1 Haematological and clinical profiles of patients with Hb Q-H disease

| Patient | Sex | Age (years) | L | S | History of transfusion | Hb | MCV (fl) | MCH (pg) | Hb H (%) | Hb A (%) | Hb A2 (%) | Hb F (%) | Retic (%) | Bilirubin (μmol/l) | Iron (μmol/l) | Ferritin (pmol/l) | Transferrin saturation (%) |
|---------|-----|-------------|---|---|------------------------|----|----------|---------|----------|----------|-----------|----------|----------|---------|----------------|---------------|----------------|-------------------|
| 1       | M   | 58          | N | N | N                      | 96 | 83.4     | 20.0    | 70       | 0.3      | -0.3 97.9 | -        | 39       | 5200               |               |                 |                   |
| 2       | M   | 17          | N | N | N                      | 105| 60.5     | 18.5    | 80       | 0.4      | -0.3 93.9 | -        | -        | -                   |               |                 |                   |
| 3       | M   | 28          | Y | Y | N                      | 100| 63.6     | 18.8    | 90       | 0.2      | -0.3 95.6 | 9.2      | 90       | 32      | 1430               | 77            |               |                   |
| 4       | M   | 23          | N | Y*| Y                      | 105| 59.7     | 18.4    | 89       | 0.2      | -0.3 95.8 | 4.7      | 35       | 20      | 965     | 16               |               |                 |                   |
| 5       | M   | 38          | N | N | N                      | 10.9| 66.6     | 18.1    | 90       | 0.5      | 0.5 94.2 | 3.7      | 30       | 21      | 1530               | 38            |               |                   |
| 6†      | F   | 68          | N | Y*| Y                      | 79 | 70.2     | 18.9    | 70       | 0.2      | -0.3 93.9 | 6.5      | -        | 25      | 467                |               |                 |                   |
| 7†      | F   | 49          | Y | Y | Y                      | 84 | 77.2     | 21.7    | 85       | 0.1      | -0.3 96.9 | 5.0      | 26       | -       | 1907                |               |                 |                   |

HbH disease cases | case | cases* | transfusion independent | – | – | – |

* | 35 | 1 | 4 | – | – | – | – | – |

** | SEA/ | 2 | a | 4 | 2 | 3 | cases, all transfusion independent | – | – | – | – | – | – | – | – |

** | S | 2 | 3 | 4 | 3 | 2 | cases, all transfusion independent | – | – | – | – | – | – | – | – |

*Splenectomy performed; †gallstones present; ‡hepatitis C carrier; liver biopsy showed chronic hepatitis and grade 2 iron overload (modified Scheuer grading); ‡‡mean values quoted for age and laboratory parameters in these 12 patients with deletional HbH disease as a result of –α4.2/a-configuration; *spleenectomy performed in one patient.

Reference ranges: Hb, 130–180 g/l (men), 115–165 g/l (women); MCV, 80–96 fl; MCH, 27–32 pg; HbA2, 2.3–3%; HbF<0.9%; reticulocytes, 0.2–2%; bilirubin, 7–19 μmol/l; iron, 9–33 μmol/l (men), 5–28 μmol/l (women); ferritin, 115–884 pmol/l (men), 15–331 pmol/l (women); transferrin saturation, 15–45%.

Hb, haemoglobin; Hb H, percentage of red cells with HbH inclusions; L, hepatomegaly; MCH, mean cell haemoglobin; MCV, mean cell volume; N, absent; NA, not applicable; Retic, reticulocytes; S, splenomegaly; Y, present; –, data not available.