

Haemoglobin H disease and outcomes in Singapore

Dear Editor,

Haemoglobin H (HbH) disease is a haemoglobinopathy affecting 3 of 4 α -globin genes on chromosome 16. It results from the deletion of 2 linked α -globin genes (α^0 -thalassaemia) on one chromosome and either a single α -globin gene deletion ($--/\alpha$) or non-deletional gene mutation ($--/\alpha^T\alpha$) on the other chromosome. The disease is common in East Asia with increasing numbers noted in Western countries due to migration. The prevalence of HbH in Hong Kong is 6 in 10,000 while the incidence in Thailand is 7 in 1,000 live births.^{1,2}

In α -thalassaemia, the deficiency of α -globin chain results in an imbalance of excess β chains to form tetramers that are unstable. Individuals with 1 or 2 α -globin genes affected are usually asymptomatic, while patients with 3 affected α -globin genes show HbH with varied clinical presentations. Severity depends on the genetic heterogeneity and the subtype of HbH, namely deletional or non-deletional.¹ Deletional mutation involves removing 2 α -globin genes on one chromosome, e.g. Southeast Asian (SEA) and Thai (THAI) deletional mutations, and a single α -globin gene on the other chromosome, e.g. $-\alpha^{3.7}$ and $-\alpha^{4.2}$. In the non-deletional subtype, both α -globin genes on one chromosome are deleted, but the other α -globin gene has a non-deletional mutation, e.g. Hb Constant Spring (CS) or Hb Quong Sze (QS) non-deletional mutations. Patients with non-deletional HbH usually have more severe anaemia requiring transfusions.³

Couples at high risk of producing offspring who might be transfusion dependent may be counselled to undergo invasive diagnostic tests such as chorionic villus sampling or amniocentesis to confirm the diagnosis and to consider termination.^{4,5} This study is the first in Singapore to characterise the severity of HbH in our population and aims to provide a rational basis for prenatal counselling.

The National Thalassaemia Registry (NTR) was set up in 1992 to register all Singapore citizens and permanent residents with the thalassaemia gene. It offers counselling and subsidised screening to spouse and first-degree relatives of registrants.⁶ Screening includes full blood count, Hb electrophoresis, HbH inclusion bodies tests, DNA analyses and high-performance liquid chromatography. The NTR receives notifications of thalassaemia cases from other medical institutions and is based in KK Women's and Children's Hospital (KKH), Singapore.

This is a retrospective descriptive study looking at the genotype and clinical characteristics of HbH in KKH

patients only. Clinical parameters are obtained from hospital electronic records and clinical notes. Diagnosis of HbH is confirmed by the presence of HbH inclusion bodies or DNA analysis.⁵ Hb level is the Hb at diagnosis or lowest Hb recorded. Hepatomegaly and splenomegaly are considered if the measurement is at least 1cm below the costal margin. The last recorded height is used for analysis, and a height percentile is obtained from the World Health Organization Child Growth Standards for 0–24 months and the US Centers for Disease Control and Prevention from 2 years onwards.^{7,8} Deletional and non-deletional groups are compared and statistical evaluation is carried out with chi-square test using SPSS Statistics software (IBM Corp, Armonk, US). This study is approved by the Institutional Ethics Review Board in KKH.

Results. Of a total of 45,092 registrants in the NTR from February 1992 to December 2017, 678 HbH (1.5%) were recorded (Fig. 1). The incidence of deletional and non-deletional HbH in Singapore are 0.6% and 0.058%, respectively. Clinical data for 166 patients are analysed and 87 patients with genotype data are sub-analysed (Table 1).

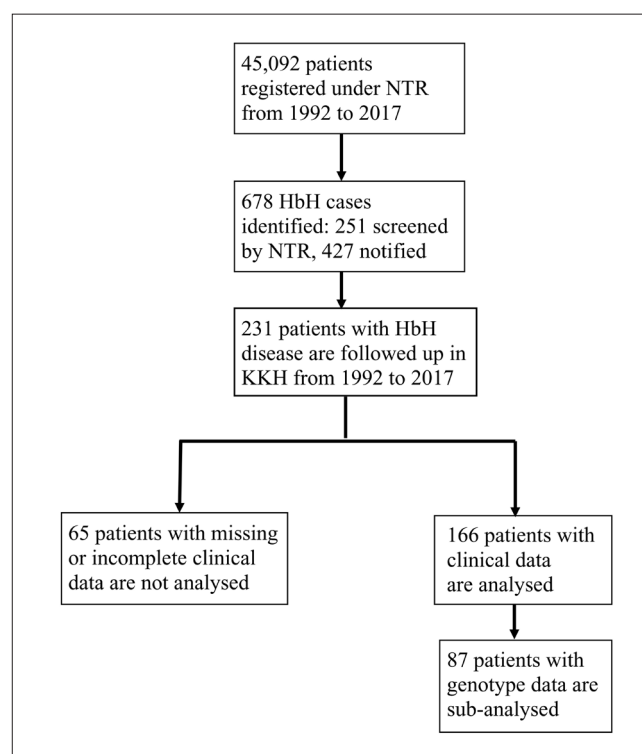


Fig. 1. Flow diagram of patients included in study. HbH: haemoglobin H; KKH: KK Women's and Children's Hospital; NTR: National Thalassaemia Registry

Table 1. Clinical characteristics of patients with haemoglobin H (HbH) disease

Clinical characteristics	Total number of patients, N=166 No. (%)	Number of patients with molecularly confirmed deletional HbH disease, n=77 No. (%)	Number of patients with molecularly confirmed non-deletional HbH disease, n=10 No. (%)	P value ^a
Sex				
Male	39 (23.5)	22 (28.6)	2 (20)	0.568
Female	127 (76.5)	55 (71.4)	8 (80)	
Ethnicity				
Chinese	141 (84.9)	66 (85.7)	9 (90)	0.620
Malay	16 (9.6)	7 (9.1)	0 (0)	
Indian	2 (1.2)	1 (1.3)	0 (0)	
Others	7 (4.2)	3 (3.9)	1 (10)	
Age at diagnosis				
<12 years old	120 (72.3)	69 (89.6)	9 (90)	0.505
12–21 years old	15 (9.0)	5 (6.5)	0 (0)	
>21 years old	31 (18.7)	3 (3.9)	1 (10)	
Genotype^b				
Deletional HbH disease	-	77 (46.4)	-	-
SEA deletion/3.7kb deletion ($-\text{SEA}/\alpha^{3.7}$)		58 (34.9)		
SEA deletion/4.2kb deletion ($-\text{SEA}/\alpha^{4.2}$)		17 (10.2)		
SEA deletion/4.2kb deletion with Q mutation ($-\text{SEA}/\alpha^{4.2}(\text{Q}_{\text{THAI}})$)		1 (0.6)		
THAI deletion/4.2kb deletion ($-\text{THAI}/\alpha^{4.2}$)		1 (0.6)		
Non-deletional HbH disease	-	-	10 (6.0)	-
SEA deletion/CS ($-\text{SEA}/\alpha^{\text{CS}}\alpha$)			8 (4.8)	
SEA deletion/QS ($-\text{SEA}/\alpha^{\text{QS}}\alpha$)			2 (1.2)	
Haemoglobin level, g/dL				
<8.0	21 (12.7)	6 (7.8)	3 (30)	0.003
8.0 to <10.0	128 (77.1)	60 (77.9)	7 (70)	
≥10.0	17 (10.2)	11 (14.3)	0 (0)	
No. of transfusion episodes				
0	142 (85.5)	77 (100)	2 (20)	<0.001
1	10 (6.0)	0 (0)	4 (40)	
2–3	4 (2.4)	0 (0)	1 (10)	
>4	10 (3.0)	0 (0)	3 (30)	
Complications of disease				
Hepatomegaly (>1cm)	25 (15.1)	13 (16.9)	7 (70)	<0.001
Splenomegaly (>1cm)	19 (11.5)	6 (7.8)	5 (50)	<0.001
Splenectomy	4 (2.4)	0 (0)	0 (0)	-
Cholecystectomy	0 (0)	0 (0)	0 (0)	-
Hypothyroidism	2 (0.1)	1 (1.3)	0 (0)	0.876
Hypoparathyroidism	0 (0)	0 (0)	0 (0)	-
Other marker of severity				
Height <3rd percentile ^c	20 (13.3)	7 (9.9)	1 (12.5)	0.856

^a P value applies to the comparison between the deletional and non-deletional groups^b Genotypic data are not available for 79 patients (47.9%)^c Denominator taken as 150 in the full cohort, 71 in the deletional group and 8 in the non-deletional group due to missing height data

SEA: Southeast Asian; THAI: Thai

The higher percentage of female patients (76.5%) is attributed to the study being conducted in a women's and children's hospital. Median age of diagnosis is 5.7 (2–12.9) years, with most patients (72.3%) diagnosed before 12 years old. Median Hb is 8.7 (8.2–9.3) g/dL with most patients (85.5%) not requiring any transfusion. Ten patients (6.0%) have higher transfusion requirements (>4); of these, 3 had genetic studies done and all belong to the SEA deletion/Constant Spring (--^{SEA}/α^{CS}α) non-deletional subtype.

Ten patients have hepatosplenomegaly (6.0%), 15 (9.0%) have isolated hepatomegaly and 9 (5.4%) have isolated splenomegaly. Only 4 required (2.4%) splenectomy and have higher transfusion requirements, although their genetic profiles are unknown. No cholecystectomy or hypoparathyroidism are reported. Two patients have hypothyroidism; one with a history of Turner syndrome and congenital hypothyroidism, and the other has subclinical hypothyroidism. Twenty patients (13.3%) are below the third percentile for height.

Among the 87 patients with genotyping, there is a higher percentage of deletional HbH (88.5%). Median age of diagnosis is 4.1 (1.8–7.5) compared to 3.5 (0.7–6.4) years in non-deletional group. Patients in the non-deletional group have significantly lower Hb, higher rate of hepatomegaly and splenomegaly, and higher transfusion rate (80%) compared to the deletional group.

Discussion. The percentage of non-deletional HbH in Singapore is 7% according to NTR, compared to 43.5% in Thailand, 24–30% in Hong Kong and 28.9% in Taiwan.^{2,9,10} This corresponds to a lower rate of transfusion (14.5%) in our study compared to the Thai study (44.2%) involving patients of similar age distribution. There is also a lower rate of hepatomegaly (15.1% versus 54.4%), splenomegaly (11.5% vs 49%), splenectomies (2.4% vs 5%), cholecystectomies (0% vs 3.4%) and growth deficiency (13.3% vs 20%) in Singapore compared to Thailand.

The most common non-deletional variant is Hb CS followed by Hb QS in Singapore, Taiwan and Hong Kong compared to Hb CS followed by Hb-Paksé and Hb QS in Thailand. The 2-gene deletional variants (--^{SEA}, --^{THAI}) and single gene deletional variants (α^{3.7} and α^{4.2}) were similar in incidence among the countries. Presence of any non-deletional mutations portends a worse outcome rather than the different molecular basis of the deletional mutations.^{2,9,10}

Our data suggest that most HbH in Singapore belongs to the deletional subtype with mild phenotype. Most patients have a good outcome with low rate of transfusion and complications, hence routine prenatal diagnosis is not necessary. This is in accordance with the European

Molecular Genetics Quality Network Best Practice Guideline, which recommends prenatal diagnosis only in cases where severe phenotypes are expected.¹¹ As this is not a population-based study, a multicentre study involving all institutions treating HbH patients would give a more comprehensive picture of HbH in Singapore.

REFERENCES

1. Chen FE, Ooi C, Ha SY, et al. Genetic and clinical features of hemoglobin H disease in Chinese patients. *N Engl J Med* 2000;343:544-50.
2. Laosombat V, Viprakasit V, Chotsampancharoen T, et al. Clinical features and molecular analysis in Thai patients with HbH disease. *Ann Hematol* 2009;88:1185-92.
3. Chui DH, Fucharoen S, Chan V. Hemoglobin H disease: not necessarily a benign disorder. *Blood* 2003;101:791-800.
4. Li J, Li R, Zhou JY, et al. Prenatal control of nondeletional α-thalassaemia: first experience in mainland China. *Prenat Diagn* 2013;33:869-72.
5. Harteveld CL, Higgs DR. Alpha-thalassaemia. *Orphanet J Rare Dis* 2010;5:13.
6. Ng I, Law HY. Challenges in screening and prevention of Thalassaemia in Singapore. *Asian-Oceanian Journal of Pediatrics and Child Health* 2003;2:29-38.
7. World Health Organization. WHO Child Growth Standards. Available at: <http://www.who.int/tools/child-growth-standards>. Accessed on 11 April 2022.
8. US Centers for Disease Control and Prevention (CDC) Growth chart. Available at: <http://www.cdc.gov/growthcharts>. Accessed on 11 April 2022.
9. Lau YL, Chan LC, Chan YY, et al. Prevalence and genotypes of alpha- and beta-thalassemia carriers in Hong Kong -- implications for population screening. *N Engl J Med* 1997;336:1298-301.
10. Chao YH, Wu KH, Wu HP, et al. Clinical features and molecular analysis of Hb H disease in Taiwan. *Biomed Res Int* 2014;271070.
11. Traeger-Synodinos J, Harteveld CL, Old JM, et al. EMQN Best Practice Guidelines for molecular and haematology methods for carrier identification and prenatal diagnosis of the haemoglobinopathies. *Eur J Hum Genet* 2015;23:426-37.

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