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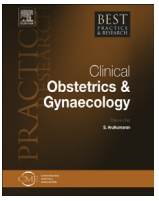

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Thalassaemia screening and confirmation of carriers in parents

Angela N. Barrett, PhD [a, 1, 2], Ramasamy Saminathan, PhD [b, 1, 3], Mahesh Choolani, MBBS, MMED, FRCOG, PhD, Associate Professor [c, *]

[a] Department of Obstetrics & Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, 10 Medical Drive, 117597, Singapore
[b] 11-59, The Choolani Clinic, Mount Elizabeth Novena Hospital, 38 Irrawaddy Road, 329563, Singapore
[c] Department of Obstetrics & Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, Level 12 NUHS Tower Block, 1E Kent Ridge Road, 119228, Singapore

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Haemoglobinopathies are among the most common inherited monogenic disorders worldwide. Thalassaemia screening for carrier status is recommended for adults of reproductive age if suspected of being at risk. Conventional laboratory methods for screening include the assessment of haematological indices, and high-performance liquid chromatography, capillary electrophoresis or isoelectric focusing to measure the levels of HbA_2 and HbF, and to identify haemoglobin variants. Each screening method has its advantages and disadvantages, the main disadvantage being that none can fully resolve all variants. The complex nature of the genetics of haemoglobinopathies necessitates expertise in the interpretation of screening results to evaluate the most likely genotypes, which must then be confirmed using the DNA diagnosis. This review highlights the limits and pitfalls of each screening technique, and outlines a rational combination of different methods to overcome issues in thalassaemia carrier detection.

* Corresponding author. Tel.: +65 67722672; Fax: +65 67794753.
E-mail addresses: obganb@nus.edu.sg (A.N. Barrett), sami@choolani.net (R. Saminathan), mahesh_a_choolani@nuhs.edu.sg (M. Choolani).
[1] Authors contributed equally.
[2] Tel.: +65 67722672; Fax: +65 67794753.
[3] Tel.: +65 6570 2000; Fax: +65 65702212.

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Introduction

Anaemia is a major public health problem, affecting the lives of more than two billion people worldwide, representing approximately 30% of the global population [1]. Women are particularly susceptible, with over 38% of pregnant and almost 30% of non-pregnant women being affected [2]. Iron deficiency is the cause of anaemia in around 50% of cases [3], but iron-deficient anaemia (IDA) is clinically indistinguishable from thalassaemia. It is important to differentiate these conditions to determine the underlying cause of IDA (for example, menstrual complications or cancer) and to avoid unnecessary iron therapy for thalassaemia, with its related haemosiderosis, leading to serious complications, including cardiomyopathy, hepatic fibrosis and endocrine dysfunction [4–6].

Thalassaemia is inherited as an autosomal recessive disorder; therefore, a child of two carrier parents has a 25% chance of being unaffected, a 25% chance of being affected, and a 50% risk of also being a carrier. Haemoglobinopathies contribute nearly 3.4% to overall worldwide mortality of children aged under five years [7]. Clinical presentation for thalassaemia carriers ranges from almost asymptomatic to severe anaemia requiring lifelong blood transfusions [6,8]. Because of this health burden, many countries with high prevalence of thalassaemia are committed to the implementation of control measures, including carrier screening and prenatal diagnosis. Couples with a family history of thalassaemia planning to have children are advised to have haemoglobinopathy screening, followed by appropriate genetic counselling. The risk of passing on a major thalassaemia should be thoroughly explained, and the information provided should be aimed at aiding decisions on reproduction. The severity of disease that the child may potentially inherit depends upon the combination of the parent's genotypes and the number of affected genes co-inherited (Figure 1). Complete DNA testing prior to commencement of any treatment is required to determine prognosis and appropriate therapy.

More than one thousand abnormal haemoglobin (Hb) variants involving the α-, β-, γ-, and δ-globin subunits have been reported to date [10], with varying degrees of co-inheritance [11]. Normal adult Hb consists of 95–98% HbA ($2\alpha2\beta$), 2–3% HbA_2 ($2\alpha2\delta$), and less than 1% HbF (foetal haemoglobin, $2\alpha2\gamma$) [12]. These globin chains are covalently linked to a haem molecule. The reduced synthesis of globin chains can be complete or partial, depending upon the mutations present, and clinical severity depends upon the quantity of globin chains produced, their stability and the ratio of globin chains present in the Hb tetramer [13]. The most common forms of thalassaemia are α- and β-thalassaemias; other types of thalassaemia may occur because of the alterations in other minor globin chains, for example δβ- and εγδβ-thalassaemias, or hereditary persistence of foetal Hb (HPFH) [12]. Because of the high frequencies of haemoglobin mutations in certain regions, children may inherit two thalassaemia

Carriers parents	α^+-Thalassemia	α^0-Thalassemia	Hb S	β-Thalassaemia	δβ-Thalassaemia	Hb Lepore	Hb E	Hb O Arab	Hb C	Hb D Punjab
α^+-Thalassemia	0	2	0	0	0	0	0	0	0	0
α^0-Thalassemia	2	1	0	3	3	3	3	0	0	0
Hb S	0	0	1	1	2	2	0	1	1	1
β-Thalassaemia	0	3	1	1	1	1	1	2	0	0
δβ-Thalassaemia	0	3	2	1	1	1	2	2	0	0
Hb Lepore	0	3	2	1	1	1	2	2	0	0
Hb E	0	3	0	1	2	2	0	0	0	0
Hb O Arab	0	0	1	2	2	2	0	0	0	0
Hb C	0	0	1	0	0	0	0	0	0	0
Hb D Punjab	0	0	1	0	0	0	0	0	0	0

0	NOT KNOWN RISK
1	POSSIBLE SERIOUS RISK
2	LESS SERIOUS RISK
3	POSSIBLE HIDDEN RISK

Figure 1. Potential clinical severity of haemoglobinopathy in affected children from carriers of indicated disorders. Adapted from [9].

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