

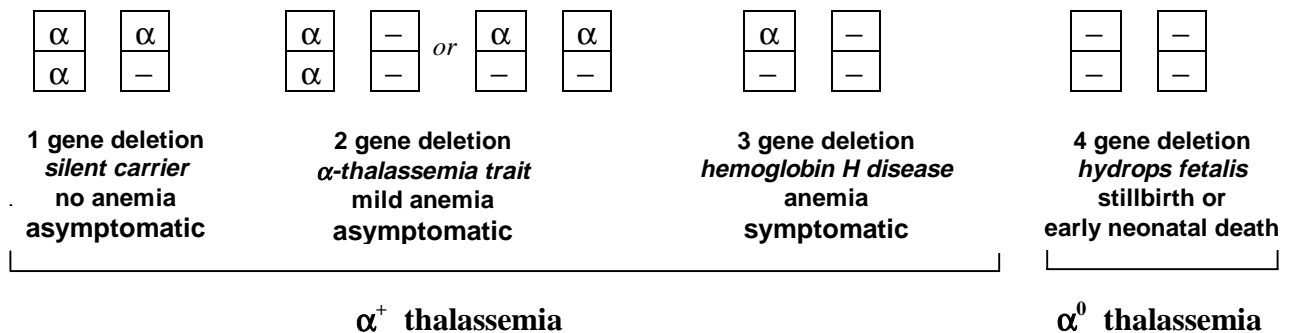
## ALPHA-THALASSEMIA AND HEMOGLOBIN E

The thalassemias are the most common single gene disorders in the world. The most common and clinically most important forms are  $\alpha$ ,  $\beta$ , and  $\delta\beta$  thalassemia. In many populations the thalassemias coexist with a variety of different abnormal hemoglobins.

Hemoglobin E (Hb E) is the most common hemoglobin variant in the world. It results from a substitution of glutamic acid by lysine at position 26 in the  $\beta$  chain. It is found mainly in Asians and reaches its highest frequency in Thailand and Laos.

### $\alpha$ thalassemia

There are two loci for the  $\alpha$  globin chain of hemoglobin, and therefore there are 4 possible  $\alpha$  thalassemia genotypes due to  $\alpha$  gene deletions.



### Clinical Phenotypes and Genotypes of $\alpha$ Thalassemia <sup>1</sup>

Phenotype	Number of functional $\alpha$ genes	Level of Hb Bart's* at birth, %	% Hb H inclusion bodies	MCV (fl)	$\alpha/\beta$ -globin chain synthetic ratio	Most frequently encountered genotypes
Normal	4	0**	0 (none)	85-100	1.0	$\alpha\alpha/\alpha\alpha$
$\alpha$ Thalassemia minor	3	0-2	0 (rare)	75-85	~0.8	$-\alpha/\alpha\alpha$
$\alpha$ Thalassemia minor	2	2-8	0 (occasional)	65-75	~0.6	$--/\alpha\alpha$ or $-\alpha/-\alpha$
Hemoglobin H disease	1	10-40	2-4 (many)	55-65	~0.3	$--/-\alpha$
Hydrops fetalis	0	~80	Present	110-120	0.0	$--/--$

\* Hb Bart's ( $\gamma_4$ ) is formed because of the lack of  $\alpha$  chains to pair with the  $\gamma$  chains to form fetal hemoglobin ( $\alpha_2\gamma_2$ ). Hb Bart's gradually disappears from peripheral blood in the 3 to 6 months following birth.

\*\* Very small amounts of Hb Bart's have been detected in normal infants at birth.

### Hemoglobin E

The *heterozygous* state for hemoglobin E (A/E) is asymptomatic. The red cells show a slight but significant reduction in MCH and MCV. The blood film is usually normal. Hemoglobin electrophoresis will show 2 bands: hemoglobin A and E. (Hb E will be about 27%.) The *homozygous* state for hemoglobin E (E/E) has a mild degree of anemia with slightly reduced red-cell survival. A significant reduction in MCH and MCV is seen and target cells are visible on a blood film.

**The interaction of Hb E and  $\alpha$  thalassemia** results in a variety of genotypes (see table below). The presence of  $\alpha$  thalassemia reduces the amount of Hb E usually found in Hb E heterozygotes.

**Some interactions of hemoglobin E with  $\alpha$  thalassemia <sup>2</sup>**

Genotype	Clinical findings	Hemoglobin
$\alpha\alpha/\alpha\alpha \beta^A\beta^E$	Normal Red cells slightly hypochromic	A + E Hb E 25-30%
$-\alpha/\alpha\alpha \beta^A\beta^E$	Normal Hypochromic red cells	A + E Hb E 20-25%
$---/\alpha\alpha \beta^A\beta^E$	Normal Hypochromic red cells	A + E Hb E 17-20%
$---/-\alpha\alpha \beta^A\beta^E$	Hb E/Hb H disease (see below)	A + E + Bart's Hb E about 14%
$-\alpha/\alpha\alpha \beta^E\beta^E$	As for homozygous Hb E (mild anemia)	E + trace Bart's
$---/-\alpha \beta^E\beta^E$	Severe thalassemia intermedia	E + F + Bart's Hb E 80%, HbF 13%

**HbE/HbH disease <sup>3</sup>** is one of the more serious hemoglobinopathies involving both HbE and  $\alpha$  thalassemia. Its characteristics include:

- Mean hemoglobin value = 7.3 g/dl
- RBC morphology similar to hemoglobin H disease but with fewer red cell inclusion bodies
- Hemoglobin pattern = A, E, Bart's or F (occasionally a small amount of hemoglobin H)
- Hemoglobin Barts usually present in adults\*\* (8% of total hemoglobin)
- Hemoglobin E averages 14% of total hemoglobin
- Hemoglobin F is 1-2% total hemoglobin

*\*\* Why do adults with HbE/HbH disease produce hemoglobin Barts ( $\gamma_4$ ) rather than hemoglobin H ( $\beta_4$ )? Since the  $\gamma$  chain genes remain active there are therefore  $\gamma$ ,  $\beta^A$  and  $\beta^E$  chains competing for a reduced amount of  $\alpha$  chains. The  $\alpha$  chains have an increased affinity for the  $\beta^A$  chains as compared to the  $\beta^E$  chains leaving an excess of  $\beta^E$  and  $\gamma$  chains. The excess  $\gamma$  chains form the tetramer  $\gamma_4$ , Bart's.  $\beta^E$  chains do not form stable tetramers.*

A **newborn** identified to have Hbs F, A, and E who has a fast-moving hemoglobin has 1, 2, or 3  $\alpha$  gene deletions. If no fast-moving hemoglobin is present, no more than one  $\alpha$  gene is deleted.

References:

1. Scriver CR, Beaudet AL, Sly WS, Valle D (eds). The Metabolic Basis of Inherited Disease. Seventh Edition. New York, McGraw-Hill, 1995, p 3347.
2. Weatherall DJ and Clegg JB. The Thalassemia Syndromes. Third Edition. Oxford, Blackwell Scientific Publications, 1981, p 639.
3. Ibid p. 640.