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Update in the genetics of thalassemia: What clinicians need to know

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Thalassemia is a significant health problem worldwide. Prenatal diagnosis is the only effective way to prevent the birth of a fetus with severe thalassemias, which include hemoglobin Bart's hydrops fetalis and thalassemia major. However, accurate prenatal diagnosis depends on the comprehensive consideration of the molecular basis of thalassemias. To make a correct decision, the obstetrician should have a certain understanding of the genetics of thalassemias. Here we present a brief introduction of some fundamental genetic knowledge of thalassemias, including the production of hemoglobin, structure and location of globin genes, hemoglobin switch, epidemiology, clinical classification, molecular and cellular pathology, genotype–phenotype correlation, and genetic modifiers. Furthermore, some unusual clinical cases that cannot be explained by Mendel's laws are described. On the basis of a thorough understanding of the above information, clinicians should have the ability to precisely diagnose thalassemia patients and provide applicable genetic counselling to the affected families.

Introduction

Inherited hemoglobin (Hb) disorders are the most common inherited blood disorders globally and account for approximately 3.4% of deaths in children under 5 years of age [1]. This group of diseases is

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caused by mutations in human globin genes, which are classified into two categories: those that produce structurally abnormal globin (Hb variants) and those with impaired globin synthesis (thalassemia). Thalassemia is characterized by the absence or decreased accumulation of one of the globin subunits. The most common forms are α-thalassemia (OMIM: #604131) and β-thalassemia (OMIM: #613985), which affect the synthesis of α- and β-globin subunits, respectively.

Thalassemias are prevalent in tropical and subtropical areas where malaria was and still is epidemic. The high frequency may be due to carriers of hemoglobinopathies who have a survival advantage in malarial endemic areas [2]. People carrying thalassemia variants are concentrated in Southeast Asia, the Mediterranean area, the Indian subcontinent, the Middle East, and Africa [3,4]. Moreover, it is noteworthy that as a consequence of recent massive population migrations, thalassemia is not restricted to traditional high-incidence regions and is now a relatively common clinical problem in North America, North Europe, and Australia [2]. The clinical management of thalassemia, such as its diagnosis and treatment, has challenged the local health system. For example, screening for Hb H disease (one form of α-thalassemia) has been added for newborns in California [5]. An analysis of 86 Hb H disease patients performed by Lal's group supported the usefulness of universal newborn screening and suggested that the screening should be extended to other populations [6].

The inheritance mode of thalassemias is autosomal recessive (AR). Carriers of thalassemia mutations are clinically normal. However, when both parents are carriers, for every pregnancy, there is a 25% chance that the child will be a thalassemia patient, a 50% chance that the child will be a thalassemia carrier, and a 25% chance that the child will be normal. To date, prenatal diagnosis is the only way to prevent the birth of an affected child. Therefore, in highly prevalent regions, an ideal and effective strategy to decrease the birth rate of thalassemia patients is to identify high-risk couples, who are both carriers, before pregnancy by screening (or carrier testing) and then perform a prenatal diagnosis during pregnancy.

Basic genetic structures of Hemoglobin gene clusters

All normal human Hbs are tetramers of two pairs of globin chains: one pair of α-like globins and one pair of β-like globins. At the molecular level, Hb synthesis is controlled by two multigene clusters (Fig. 1A). The α-cluster contains an embryonic gene (ζ2), two fetal/adult α genes (α2 and α1), two pseudo genes (Ψζ1 and Ψα1), and two minor globin-like genes (Ψα2 and θ), which are all arranged in the following order: 5′-ζ2–Ψζ1–Ψα2–Ψα1–α2–α1–θ-3′. HS-40 is the major regulatory element of the α-globin locus. The β-cluster contains an embryonic gene (ε), two fetal genes ($^{G}\gamma$ and $^{A}\gamma$), one pseudo gene (Ψβ), and two adult genes (δ and β), which are arranged in the following order: 5′-ε–$^{G}\gamma$–$^{A}\gamma$–Ψβ–δ–β–3′. Locus control region (LCR) is the important upstream regulatory region.

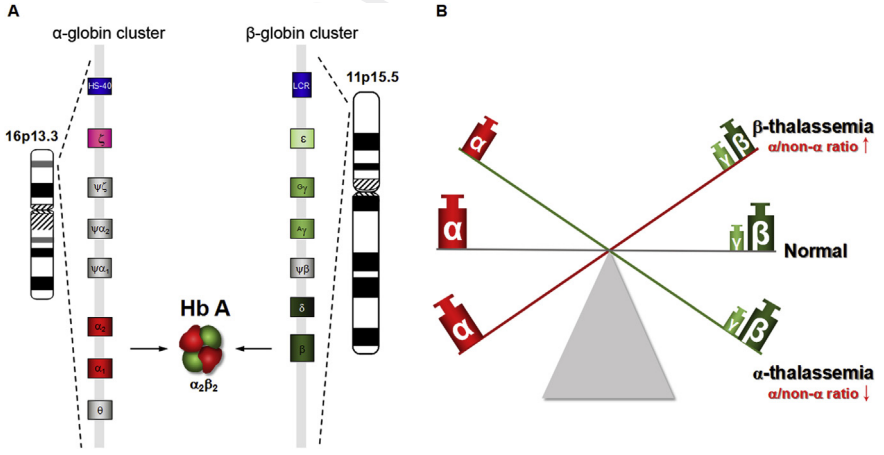

Fig. 1. Structure of the α- and β-globin gene cluster (A) and the pathophysiology of thalassemia (B).

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