

Factors Associated in Production of Raised Gama Globin Chain in HbE/ β -Thalassemia – A Review

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Abstract: HbE/ β -thalassaemia genotype represent approximately 50% of all severe β -thalassemia worldwide and is the commonest form of thalassemia in many Asian countries, predominantly prevalent in North-Eastern region exhibiting phenotypes that range from severely symptomatic and transfusion-dependent anaemia in early life to a asymptomatic and clinically 'silent' condition that is ascertained by chance in middle age. Assay of m-RNA in cell free system clearly shows a deficiency of m-RNA in heterozygous β -thalassemic bone marrow. Compensation for defective β - chain synthesis by the β - chain locus on the unaffected chromosome in β -thalassemia heterozygous have been reported. Some genotypic factors have been reported to affect the synthesis of γ -chain, such as 3'HS1 (+179 C→T) polymorphism, the (AT)xNy(AT)z motif in the 5'HS2 site, the (AT)x(AT) motif in the -540 region of the β -globin gene, GATA-1 (26), and heme-regulated initiation factor 2 alpha kinase (HRI). Also genetic variation at three major loci - XmnI-HBG2, HBS1L-MYB intergenic region on chromosome 6q23 and variation of rs11886868(T→C) in the BCL11A gene on chromosome 2p16 has account for relatively large proportion (20-50%) of the phenotypic variation in HbF levels. HbF levels in HbE/ β -thalassemia, and other β thalassemia syndromes, results from increased erythropoietin levels leading to bone marrow expansion, and possibly increased F-cell production, combined with ineffective erythropoiesis giving a survival advantage to F cells. Among the known genetic factors XmnI, DNA sequence variation (C→T) at position -158 upstream of the G γ globin gene is one of the gene polymorphism that influence HbF production.

Keywords: Gama Globin, HbF, Xmn-I, HbE, Thalassemia

1. Introduction

Hereditary hemoglobinopathies and thalassemia are the worldwide prevalent heterogenous group of autosomal recessive disorders.^(1,2) Amongst the variant structural haemoglobin, Hemoglobin E (HbE, β^{26} GAG-AAG) is the most common β -thalassemic hemoglobinopathy in Southeast Asian population.^(3,4,5,6) Similarly, thalassemia arises due to transcriptional failure of globin synthesis with a corresponding decrease or absence in the amount of functionally active protein resulting in an abnormal Hb ratio (α : non α).⁽⁷⁾ The HbE gene can interact with β -thalassemic gene and result in double heterozygous state which may exhibit phenotypic manifestations of β -thalassemia major or β -thalassemia trait.⁽⁸⁾

HbE/ β -thalassemia genotype represent approximately 50% of all severe β -thalassemia worldwide and is the commonest form of thalassemia in many Asian countries, predominantly prevalent in North-Eastern region^(5,6,9,10,36) of India imposing a major genetic health problem. The affected individual may have phenotypes that range from severely symptomatic and transfusion-dependent anaemia in early life to a asymptomatic and clinically 'silent' condition that is ascertained by chance in middle age^(36,11). Manifestations of HbE/ β -thalassemia include refractory anaemia, splenomegaly and bony deformities, sometimes unexplained jaundice, variable degree of iron overload, depending on severity of anemia and transfusion requirement, hypercoagulable states (post-splenectomy), pulmonary hypertension and cardiopulmonary disease.^(9,10)

The genetic mechanisms causing reduction of α -globin synthesis in the α -thalassemias and of β -globin synthesis in the β -thalassemias have been models for the study of other genetic diseases.⁽¹²⁾ Weatherall (1981) hypothesized that the hallmark of β -thalassemia is defective β -globin synthesis,

which leads to imbalanced globin chain production and an excess of α -chains which aggregate in red-cell precursors, and cause abnormal cell maturation and their premature destruction in the bone marrow.⁽¹³⁾ Pathophysiology due to chain imbalances within the thalassaemic erythroid precursors resulting in ineffective erythropoiesis and medullary as well as intravascular hemolysis, perhaps as a result of oxidative processes and resulting apoptosis-like events during erythroid development was explained by Schrier (1994).⁽¹⁴⁾

Assay of m-RNA in cell free system clearly shows a deficiency of m-RNA in heterozygous β -thalassemic bone marrow.⁽¹⁵⁾ It has been proposed that in β -thalassemia heterozygous there is compensation for defective β - chain synthesis by the β - chain locus on the unaffected chromosome^(16,17). It has also been suggested that there is a compensatory reduction in α chain synthesis or that possibly both this mechanism may be operative.⁽¹⁸⁾

In a recent study it has been shown that a highly expressed protein called Alpha Hemoglobin Stabilizing Protein (AHSP) can act as a chaperone for free α -chains and prevent their precipitation^(19,20) as it is highly expressed in hemoglobin-synthesizing erythroid precursors.^(21,22) AHSP acts as a secondary compensatory mechanism to balance the excess α -globin chain in β -thalassemia after the formation of HbF. Thus it can be said that AHSP is a modifier for phenotypic severity in HbE/ β -thalassemia patients.

Foetal haemoglobin, HbF ($\alpha_2\gamma_2$) is one of the major Hb during the foetal life and gradually in diminishing trend, and finally reported in the adult Hb comprising up <2%. HbF level is considered to be one of the major diagnostic criteria in detection of HbE/ β -thalassemia.

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polymorphism⁽²³⁾, the (AT)_xNy(AT)_z motif in the 5'HS2 site⁽²⁴⁾, the (AT)_x(AT) motif in the -540 region of the β -globin gene⁽²⁵⁾, GATA-1 (26), and heme-regulated initiation factor 2 alpha kinase (HRI)⁽²⁷⁾. Also genetic variation at three major loci - XmnI-HBG2^(27,28), HBS1L-MYB intergenic region on chromosome 6q23 and variation of rs11886868(T→C) in the BCL11A gene^(29,30,31) on chromosome 2p16 has account for relatively large proportion (20-50%) of the phenotypic variation in HbF levels.⁽³²⁾

HbF levels in HbE/ β -thalassemia, and other β -thalassemia syndromes, results from increased erythropoietin levels leading to bone marrow expansion, and possibly increased F-cell production, combined with ineffective erythropoiesis giving a survival advantage to F cells.⁽³³⁾

Baruah et al (2014) reported that the HbF level in HbE/ β -thalassemia patients (HbF 30.7±10.1) was found to be statistically significant when compared to HbF levels of HbE homozygous (HbF=4.6±3.1) and subjects with normal hemoglobin pattern (HbF=0.5±0.7)⁽³⁴⁾

Study by Premawardhena et al in the HbE/ β -thalassemia patients in the Sri Lankan patients noted a significant correlation within a narrow range of haemoglobin values between the steady state hemoglobin and the absolute level of haemoglobin F (r=0.7, p=0.001). Relation between concentration of erythropoietin and haemoglobin (r=0.66, p=0.0001) and a decline in erythropoietin response with age (r=0.56, p=0.0001) was found to be statistically significant in the HbE/ β -thalassemic patient. Erythropoietin correlation was also observed in the level of haemoglobin F and the XmnI +/+ genotype at position -158 of the γ gene (HBG2) (p=0.005).⁽³⁵⁾ Erythropoietin is a circulating hormone, a glycoprotein with a molecular weight of about 34,000. Ninety per cent of all erythropoietin is formed in the kidneys of a normal person and the lingering is formed mainly in the liver. Hypoxia causes marked increase in erythropoietin production in its functional state, and the erythropoietin in turn enhances red cell production until hypoxia is released. People with kidney problem or who have been placed in hemodialysis, develops anemia as a result of decreased erythropoietin production.^(36,45)

In the study of an Iranian-American family by Chen et al. 2008, a novel T-to-G SNP at nt-567 upstream of the HGB2 promoter was found in the father and son who had moderately elevated HbF levels. This mutation alters a GATA-1 binding motif to GAGA sequence. Also this GATA motif is likely to play a significant role in the silencing of γ -globin gene expression. The mutation of GATA to GAGA disrupts its silencing effect and is associated with increased γ -globin gene expression in affected adults.⁽³⁹⁾

Among the known genetic factors XmnI, DNA sequence variation (C→T) at position -158 upstream of the γ globin gene is one of the gene polymorphism that influence HbF production. Xmn-I which is a type II restriction endonuclease with a novel site specificity, isolated from *Xanthomonas manihoti* is present in all population groups at a frequency of 0.32 to 0.35^(43,44). Wong et al (2006) reported

10.3% heterozygosity for (+/-) genotype and 0% for (++) genotype in Chinese β -thalassemia patients where as in Malays β -thalassemia patients heterozygosity (+/-) was reported in 63.3% and homozygosity (++) in 3.7% of patients which shows marked ethnic variations.⁽⁴⁰⁾ In India Sharma et al 2014 reported the XmnIG γ heterozygous state (+/-) in 26.1% and 6.9% homozygous state (++) in β -thalassemia major patients.⁽⁴¹⁾ Kosaryan et al (2009) in observed 76% of Iranian β -thalassemia patients had either (+/-) or (++) for XmnI gene polymorphism.⁽⁴²⁾

Studies conducted reveal that heterozygous state of XmnI polymorphism is more common and is responsible for raised fetal hemoglobin HbF in HbE/ β -thalassemia individuals. Increased level of γ -globin chain reduces the globin chain imbalance due to markedly decreased or absent β -globin protein levels. As a consequence, augmented γ -globin gene expression or HbF production can ameliorate the clinical severity of these common hereditary disorders.

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