International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2013): 6.14 | Impact Factor (2013): 4.438

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

Lipika Chaliha[1], S K Sharma[2]

Regional Medical Research Centre, N E Region, (Indian Council of Medical Research), Post Box # 105, Dibrugarh- 786001, Assam, India

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-RNAin 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 intergenicregion on chromosome 6q23 and variation of rs11886868(T→C) in the BCL11A geneon chromosome 2p16 has account for relatively large proportion (20-50%) of the phenotypic variation in HbF levels.HbF levels in HbE/β-thalassemia, and otherβ 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, HemoglobinE (HbE, $\beta^{26\ GAG\text{-}AAG}$) is the most common β-thalassemichemoglobinopathy 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: nonα).[7]TheHbE 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-thalassemiagenotype 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 fromseverely 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 synthesisin the α-thalassemias and of β-globin synthesis in the β-thalassemia's 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 thalassemicerythroid 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-RNAin 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(α_2¥$_2$) 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.

Some genotypic factors have been reported to affect the synthesis of γ-chain, such as 3'HS1 (+179 C→T)

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 levelsin HbE/β-thalassemia,and otherβ-thalassemia syndromes, results from increased erythropoietin levels leading to bone marrow expansion, and possibly increased F-cell production, combined with ineffective erythropoiesisgiving a survival advantage to F cells.[33]

Baruah et al(2014)reported that the HbF level in HbE/β-thalassemia patients (HbF30.7±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 theHbE/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. Erythropoetin correlation was also observed in the level of haemoglobin F and the XmnI +/+ genotype at position -158 of the $^{G}\gamma$gene (HβG2)(p=0.005).[35]Erythropoetin is a circulating hormone, a glycoprotein with a molecular weight of about 34,000. Ninty 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 erythropoetin 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 aresult of decreased erythropoietin production.[36,45]

In the study of an Iranian-American family by Chen etal.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 Gγ globin gene is one of the gene polymorphism thatinfluenceHbF production.Xmn-I which is a typeII restriction endonuclease with a novel site specificity, isolated from Xanthomonasmanihotis 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.

References

[1] Bashyam M.D., Bashyam L., Savithri G.R., Gopikrishna M.,SangalV.,Devi A.R.R. Molecular genetic analyses of β-thalasseamia in South India reveals rare mutations in the β-globin gene. J Hum Genet. 2004, 49:408-413.
[2] Kraft, A. and C. Breymann. Haemoglobinopathy in pregnancy: Diagnosis and treatment. Curr. Med.Chem.2004, 11:2903-2909.
[3] Panja A., Ghosh T.K., Basu A. Genetics of Thalassaemia in Indian Population. Journal of community Nutrition & Health. 2012,1(1).
[4] Deka, R., B. Gogoi, J. Hundrieser and G. Flatz.Haemoglobinopathies in Northeast India. Hemoglobin.1987, 11: 531-538.
[5] Lukens, J.N., Richard Lee, G.J.Foerster, F.Paraskevas, J.P.Greer and G.M.Rodgers. The abnormal Hemoglobin's: General Principles. In: Wintrobe's Clinical Haematology. (Eds.). Williams and Wilkins, USA., ISBN: 0683182420pp: 1329-1345.
[6] Sharma S.K., Mahanta J., Prevalence of Haemoglobin Variants in Malaria Endemic Northeast India. Journal of Biological Sciences. 2009, 9(3): 288-291.
[7] M Sengupta. *Thalassemia among the tribal communities of India*. The Internet Journal of Biological Anthropology. 2007, 1(2).
[8] Weatherall DJ, CleggJB. The Thalassaemia Syndromes. (4thed).Oxford:Blackwell Science Ltd; 2001.
[9] Mujawar Q., Ukkali S., MalagiNN.,Thobbi AN. Hemoglobin Eβ+-Thalassaemia. A case report from Bijapur, South India. Al Ameen J Med Sci. 2009, 2(1): 82-84.
[10] Panigrahi I., Agarwal S., Gupta T., SinghalP.,andPradhan M. Hemoglobin E-beta Thalassemia: 7t6n Factors Affecting Phenotype. Indian Pediatrics. 2005,42.
[11] De Silva. S.*et al*. Thalassaemia in Sri Lanka: implications for the future health burden of Asian populations. *Lancet* . 2000, 355. 786-791.
[12] Schechter AN. Hemoglobin research and the origins of molecular medicine. Blood.2008,112(10):3927-3938.

[13] Weatherall, Clegg JB. The Thalasaemia Syndromes. 4th ed. Oxford:BlackwellScientific Publication;1981.
[14] SchrierSL.Thalassaemia:pathophysiology of red cell changes. Annual Rev Med. 1994,45;211-8.
[15] Natta,C., Banks J., Niazi,G., Marks, P.A. &Bank,A Decreased beta globin m-RNA activity in bome marrow cells in homozygous and heterozygous beta thalasaemia. Nature New Biol. 1973; 244: 280-281.
[16] Kan,Y.W., Nathan D.G. &Lodish, H.F. Equal synthesis of -and- globin chains in erythroid precursors in heterozygous-thalassemia. J.Clin. Invest. 1972; 51: 1906-1909.
[17] Gill, F.M. & Schwartz, E. Free α-Globin Pool in Human Bone Marrow. J.Clin.Invest.1973; 52, 709-714.
[18] NathanD.J. Thalassemia. N.Eng.J.Med. 1972; 286, 583-594.
[19] KihmAJ, Kong Y, Hong W, et al. An abundant erythroid protein that stabilizes free alpha-haemoglobin. Nature. 2002;417:758-763.
[20] Gell D, Kong Y, EatonSA, Weiss MJ, MackayJP. Biophysical characterization of the alpha-globin binding protein alpha-hemoglobin stabilizing protein. J Biol Chem. 2002;277: 40602-40609.
[21] Rund D., Rachemilewitz E. β-thalassaemia. N Eng J Med.2005, 353;11.
[22] Lai MI, JiangJ, Silver N, Menzel S, Miijovic A, Colella S, Ragoussis J, Garner C, Weiss MJ, Thein SL: Alpha-haemoglobin stabilizing protein is a quantitative trait gene that modifies the phenotype of beta –thalassaemia. 2006, 133:675-682.
[23] Papachatzopolou A, Kaimakis P, Poufarzard F,Menounos PG, Evangelakou P, Kollia P, Grosveld FG, Patrinos GP: Increased gamma-globin gene expression in beta-thalasseamiaintermedia patients correlates with a mutation in 3'HS1. *Am J Hematol* 2007, 82:1005-1009.
[24] Papachatzopolou A, Kourakli A, Makropolou P, Kakagianne T, Sgourou A, Papadakis M, Athanassiadou A: Genotypic heterogeneity and correlation to intergenic haplotype within high HbF beta-thalassaemiaintermedia. *Eur J Hematol* 2006, 76: 322-330.
[25] Guida V, Cappabianca MP, Colosimo A, Rafanelli F, Amato A, Dallapiccola B: Influence of Ggamma-158C→and beta-(AT)x(T)y globin gene polymorphisms on HbF levels in Italian beta –thalassaemia carriers and wild type subjects. *Haematologica* 2006, 91: 1275-1276.
[26] Yu C, Niakan KK, Matsushita M, Stamatoyannopoulos G, Orkin SH, raskindWH:X-linkedthrompbocytopenia with thalassemia from a mutation in the amino finger of GATA-1 affecting DNA binding rather than FOG-1 interaction. *Blood* 2002, 100: 2040-2045.
[27] Han AP, Fleming MD, Chen JJ: Heme –regulated elF2alpha kinase modifies the phenotypic severity of murine models of erythropoieticprotoporphyria and beta-thalassemia. *J Clin Invest* 2005, 115: 1562-1570.
[28] NThein,S.L., Wainscoat, J.S., Sampietro, M., Old, J.M., Cappellini, D., Fiorelli, G., Modell, B. and Weatherall, D.J. Association of thalassaemiaintermedia with a beta globin gene haplotype. *Br.J. Haematol.*,1987, 65, 367-373.
[29] Labie, D., Dunda- Belkhodja, O., Rouabhi, F., Pagnier, J., Ragusa, A. and Nagel, R.L. The -158 site 5' to the $^{G}\gamma$ gene and $^{G}\gamma$ expression. Blood, 66, 1463-1465.
[30] Uda M, Galanello R, Sanna S, Lettre G, Sankarn VJ, Chen W, Usala G, Busonero F, Maschio A, Albai G, Piras MG, Sestu N, Lai S, Dei M, Mula A, Crisponi L, Natiza S, Asunis I, Deiana M, Nagaraja R, Perseu L, satta S, Cipollina MD, Sollaino C, Moi P, Hirschhorn JN, Orkin SH, Abecasis GR, Schlessinger D, Cao A: Genome wide association studies shows BCL11A associated with persistent fetalhemoglobin and amelioration of the phenotype of beta –thalassaemia. *ProcNatlAcadSci USA* 2008, 105: 1620-1625.
[31] Sankaran,V.G., Menne,T.F., Xu,J., Akie,T.E., Lettre, G., Van Handel,B., Mikkola, H.K., Hirschhorn, J.N., Cantor,A.B. and Orkin,S.H. Human fetalhemoglobin expression is regulated by the developmental stage-specific repressor BCL11A. Science, 332, 1839-1842.
[32] Menzel, Stephen; Thein, Swee Lay. Genetic architecture of hemoglobin F control. Current Opinion in Hematology: 2009; 16(3): 179-186.
[33] D.C. Rees, J.B. Porter, J.B.Clegg and D.J. Weatherall. Why areHemoglobin F Levels Increased in HbE/beta thalassaemia? Blood. 1999, 94: 3199-3204.
[34] Baruah M.K., Saikia M., Baruah A. Pattern of hemoglobinopathies and thalassemias in upper Assam region of North Eastern India: High performance liquid chromatography studies in 9000 patients. Indian Journal of Pthology and microbiology. 2014,57(2).
[35] Premawardhena A, Fisher CA, Oliveri NF, deSiva S, Arambepola M, Perera W, O'Donnell A, Peto T E A, Viprakasit V, Merson L, Muraca G. Haemoglobin Eβ thalassaemia in Sri Lanka.www.thelancet.com.2005,366
[36] OliveriNancyF., pakbaz Z., V. Elliot. HbE/beta-thalassaemia: a common & clinically diverse disorder.Indian J Med Res.2011, 134;pp 522-531
[37] Khatak I., Khattak ST., Khan J. Heterozygous Beta ThalassaemiaIn Patients Of Children With Beta Thalassemia Major. Gomal Journal of Medical Sciences. 2006,4(2).
[38] Baig S.M., Rabbi F., Hameed U., Qureshi J.A., mahmood Z., Bokhari S.H., Kiani A., Hassan H., Baig J.M., Azhara A., Zaman T. Molecular characterization of mutations causing β-thalassaemia in Faisalabad Pakistan using the amplification refractory mutation system (ARMS-PCR). Indian Journal of Human Genetics.2005,11(2).
[39] Chen Z., Luo HY., Basran RK., Hsu T-H., Mang D W.H., Nantakarn L., Rosenfield C G., Patrinos G P., Hardison R C., Steinberg M H., Chui D H.K. A T-to-G Transversion at Nucleotide-567 Upstream of HBG2 in a GATA-1 Binding Motif Is Associated with Elevated Hemoglobin F. *Molecular and Cellular Biology.* 2008, 28(13): 4386-4393.
[40] Wong YC, George E, tan KL, Yap SF, Chan LL and Tan MA, Molecular characterization and frequency of G_{γ}XmnI polymorphism in Chinese and Malay ?-thalassemia patients in malaysi. Malaysian J Pathol 2006; 28(1):17-21
[41] Sharma N, Das R, Kaur J, Ahluwalia J, Trehan A, Bansal D, Panigrahi I, Marwaha RK. Evaluation of the genetic basis of phenotypic heterogeneity in north

Indian patients with thalassemia major. Eur J Haematol. 2010;84(6):531-537.
[42] Kosaryan M, Vahidshahi K, Karami H, Ehteshami S. Effect of Hydroxyurea on Thalassemia major and thalassemia Intermedia in Iranian patients. pakJ med sci 2009; 25(1):74-78.
[43] Craig JE, Barnetson RA, Prior J, Raven JL, TheinSL,rapid detection of deletions causing δβ thalassemia and hereditary persistence of fetalhemoglobin by enzymatic amplification. Blood.1994; 83(6):1673-82
[44] Panyasai S, Fucharoen S, Surapot S, Fucharoen G, Sanchaisuriya K. Molecular basis and hematologic characterization of δβ thalassemia and hereditary persistence of fetalhemoglobinin Thailand. Haematologica. 2004; 89(7):777-81.
[45] Guyton A C., Hall J E. Textbook of Medical Physiology.(11th Edition) An Imprint of Elseveir.2006