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Genetic Markers of Quantitative Trait Loci for Phenotypic Manifestation of Thalassemia Major Disease

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ABSTRACT

The genetic predisposition of fetal hemoglobin and modifier genes responsible for regulating the balance of alpha/beta globin chains required to improve the phenotype of beta thalassemia. This condition can prevent the severe phenotype of the disease to occur. Subsequently, β-thalassemia patients presented with diverse clinical manifestation ranging from the severe form of transfusion-dependent thalassemia major to non-transfusion dependent form of asymptomatic thalassemia disease. It was already acknowledged that TM patients represented with higher levels of fetal hemoglobin [HbF] are those patients in which less severe disease phenotype were noted. Currently, the main attention is on secondary & tertiary genetic modifiers factors that can prove to show betterment in the clinical phenotype of β-thalassemia syndromes. The most common quantitative trait loci (QTLs) known for HbF are variations on genes like: B-cell lymphoma/leukemia 11A (BCL11A), HBS1L-MYB intergenic region and Krueppel-like factor 1 (KLF1). To understand the phenotypic variations in thalassemia it is necessary to be looked into the responsible genes and their genetic modifiers factors regulating the balance of the alpha –beta globin gene clusters.

Introduction

Beta thalassemia (BT) is an inherited, autosomal recessive, monogenic genetic disorder, BT mainly caused by a reduced or absent synthesis of one or more of the alpha or beta globin chains. Mainly two forms of thalassemia are well-known i.e., alpha and beta thalassemias which are mainly caused by either reduction or complete absence of the synthesis of either alpha or beta globin chains respectively. The severe complications of iron overload, together with the sequels of the anemia and ineffective erythropoiesis, and the chelation therapy are major reasons of morbidity and mortality in patients of transfusion dependent β-thalassemias. It is mostly prevalent in populations of regions the Mediterranean, Middle East, Transcaucasus, Central Asia, Indian subcontinent, and Far East. Beta thalassemia (β-thal) disease is caused by mutation heamoglobin (HBB) gene, till date more than 400-point mutations are reported that ultimately results in various clinical conditions of Thalassemia [1].

Potential genetic factors that influence the severity of anemia in thalassemia patients probably will be inherited or non-inherited genetic factors. The most commonly known inherited genetic factors considered for the different forms of β-thalassemia are coinheritance of alpha thalassemia (α thalassemia) with mutation in HBB gene and other genetic factors outside of beta globin gene that stimulate and play important role in production of fetal hemoglobin (HbF). [2, 3].

HbF is the dominant hemoglobin found especially high in the fetus. After birth, HbF is nearly or totally replaced or switch over by HbA and finally the "adult" levels of HbA are nearly attained by the age of 6 months. In some cases of the β hemoglobinopathies, in patients at the age of 5 years stable adult levels of HbA are not still produced. The molecular mechanism of switching from HbF to HbA comprises repression of *HBG2* and *HBG1* followed by an up-regulation of *HBB* expression [4, 6]. This process of switch over is never totally ceases the production of HBF and some clones of erythroid precursors are still continuing to make progeny that are enough for expression of the HbF genes. Usually less than 1 % HBF; a very less amounts of HbF still express in normal adults [3].

HbF gene expression includes interaction and binding of many different proteins on promoter of gene, which includes the transcription factors (TF) KLF1 (Krueppel-like factor 1) and BCL11A (B-cell lymphoma/leukemia 11A), and the hematopoietic regulatory factor MYB and other co-repressor complexes that implicate chromatin-modeling and epigenetic modifiers [4]. As *KLF1* is a known transcription regulator of *BCL11A* and globin switching, polymorphisms in these genes might be associated with HbF levels [17]. In beta-thalassemia, patients who have higher levels of fetal hemoglobin have shown to observe less severe disease.

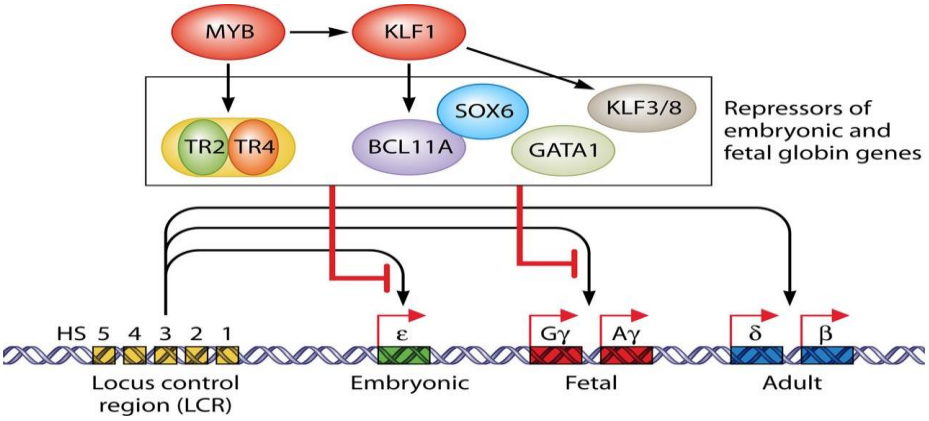

Figure1- *Gene regulating Hb switching*.

The most important QTLs (quantitative trait loci) (modifier genes) for HbF and F-cells that have been widely researched and studied are shown in Figure1 and mostly reported to be found in three loci, one is *in-cis* with the β-globin gene cluster and two are i*n-trans* with the β-globin gene cluster, the others include *HBS1L-MYB* intergenic region and *BCL11A* gene. Any deletions in BCL11A-binding motifs were believed to be associated with increased HbF levels as BCL11A plays an important role in heamoglobin switching [5, 7]. BCL11A mainly binds to the upstream locus control region (LCR), γ-globin and the intergenic regions present between β-globin and γ- globin genes, working together with SOX6 gene that is well known for reconfiguration of the β-globin cluster by selectively modulating chromosomal loop formation, which ultimately leads to transcriptional silencing of the γ-globin genes [16]. Numerous studies have verified that patients presented with sequence variations in the BCL11A or HSB1L-MYB genes have higher levels of fetal heamoglobin and less severe beta-thalassemia [8].

To better understand the clinical or molecular interactions, it is essential to know or investigate any factor which play important role in of reducing the alpha/non alpha globin chain imbalance and may show an ameliorating effect on the clinical picture of the disease [9]. Also, some of the reported mutations present within the β-globin promoter region are observed to be associated with increased γ-globin chain expression. These are mainly known as primary modifiers. Presently, the more focus shifts towards the research on other genetic variants that modulate HbF levels, but located outside of the HBB genes (known as Secondary modifiers) have also been reported to play center role. These modifiers commonly called as secondary modifiers; they primarily act directly to modify the known pathophysiology of the disease [10].

Secondary modifiers comprise of alterations in the genes affecting α/β globin chain balance such results in α/γ-globin genes expression, besides this more research is required on those genes which are involved in the γ-globin gene expression (*HBS1MYB*, *BCL11A*,) [11]. In the upcoming years, there has been significant advancement in the fields research on secondary genetic modifiers that were found to ameliorate the clinical phenotype of β-thalassemia disease. Absolutely, any increase in the production of fetal hemoglobin (HbF) throughout adulthood period could ameliorate the severity of β-thalassemia phenotype; as γ-globin polypeptide chains pay off the role in place of the functional β-globin polypeptide chains [10, 12]. Therefore, γ-globin genes, together with other secondary modifiers, signified as the most common targets for current developmental therapeutic strategies. Individually, *BCL11A* loci account for approximately 50% of the HbF level variation, indicative of fact that other factors are also involved [9].

In northern Europeans countries it was reported that presence of variants within *HBS1LMYB* intragenic region, located on chromosome 6q23, reason for more than 20% of the increased HbF level [13]. Hematopoiesis is up-regulated by MYB gene and accountable for modulation in HbF expression indirectly through modification of the kinetics of erythroid differentiation; also, directly via activation of KLF1 and other repressors. On inducing reduction in MYB levels erythroid differentiation is enhanced leading to release of early erythroid progenitor cells that are still synthesizing predominantly HbF [14, 15].

Fetal hemoglobin (HbF) is regulated by multigenic traits or factors. The presence of HBS1L-MYB intergenic polymorphism (HMIP) on chromosome 6q23 and the polymorphism on BCL11 A gene located on chromosome 2p16.5 that can modify HbF expression and ameliorate disease severity in β-thalassemia, sickle cell anemia. Among different populations the relative contributions of these polymorphisms to HbF regulation changes variably. Genetic heterogeneity related to fetal

hemoglobin (HbF) production has been reported as an influencing phenotypic factor of β-thalassemia (β-thal) so it is current demand to do more research in this direction.

References

1. Thein SL , Pathophysiology of beta thalassemia-a guide to molecular therapies. Hematology Am Soc Hematol Educ Program. 2005:31-7 DOI: 10.1182/ash education-2005.1.31 PMID: 16304356.
2. Cardoso GL, Diniz IG, Silva AN, Cunha DA, Silva Junior JS, Uchôa CT, Santos SE, Trindade SM, Cardoso Mdo S, Guerreiro JF. DNA polymorphisms at BCL11A, HBS1L-MYB and Xmn1-HBG2 site loci associated with fetal hemoglobin levels in sickle cell anemia patients from Northern Brazil. Blood Cells Mol Dis. 2014 Dec; 53(4):176-9. doi: 10.1016/j.bcmd.2014.07.006. Epub 2014 Jul 30.
3. Cyrus C, Vatte C, Borgio JF, Al-Rubaish A, Chathoth S, Nasserullah ZA, Jarrash SA, Sulaiman A, Qutub H, Alsaleem H, Alzahrani AJ, Steinberg MH, Ali AK. Existence of HbF Enhancer Haplotypes at HBS1LMYB Intergenic Region in Transfusion-Dependent Saudi β-Thalassemia Patients. Biomed Res Int. 2017; 2017:1972429. doi: 10.1155/2017/1972429. Epub 2017 Feb 9.
4. Wonkam A, Ngo Bitoungui VJ, Vorster AA, Ramesar R, Cooper RS, Tayo B, Lettre G, NgogangJ.Association of variants at BCL11A and HBS1LMYB with hemoglobin F and hospitalization rates among sickle cell patients in Cameroon. PLoS One. 2014 Mar 25; 9(3):e92506. doi: 10.1371/journal.pone.0092506. eCollection 2014.
5. Galarneau G, Palmer CD, Sankaran VG, Orkin SH, Hirschhorn JN, Lettre G Fine-mapping at three loci known to affect fetal hemoglobin levels explains additional geneticvariation. Nat Genet. 2010 Dec; 42(12):1049-51. doi: 10.1038/ng.707. Epub 2010 Nov 7.
6. Perrine SP, Pace BS, Faller DV.Targeted fetal hemoglobin induction for treatment of beta hemoglobinopathies. Hematol Oncol Clin North Am. 2014 Apr; 28(2):233-48. doi: 10.1016/j.hoc.2013.11.009.
7. Ngo DA, Steinberg MH, Genomic approaches to identifying targets for treating β hemoglobinopathies. BMC Med Genomics. 2015 Jul 29; 8:44. doi: 10.1186/s12920-015-0120-2.
8. Sedgewick AE, Timofeev N, Sebastiani P, So JC, Ma ES, Chan LC, Fucharoen G, Fucharoen S, Barbosa CG, Vardarajan BN, Farrer LA, Baldwin CT, Steinberg MH, Chui DH. BCL11A is a major HbF quantitative trait locus in three different populations with be hemoglobinopathies. Blood Cells Mol Dis. 2008 Nov-Dec; 41(3):255-8. doi: 10.1016/j.bcmd.2008.06.007. Epub 2008 Aug 8.
9. Sebastiani P, Farrell JJ, Alsultan A, Wang S, Edward HL, Shappell H, Bae H, Milton JN, Baldwin CT, Al-Rubaish AM, Naserullah Z, Al-Muhanna F, Alsuliman A, Patra PK, Farrer LA, Ngo D, Vathipadiekal V, Chui DH, Al-Ali AK, Steinberg MH, BCL11A enhancer haplotypes and fetal hemoglobin in sickle cell anemia. Blood Cells Mol Dis. 2015 Mar ;54(3):224-30. doi: 10.1016/j.bcmd.2015.01.001. Epub 2015 Jan 30.
10. Pereira C, Relvas L, Bento C, Abade A, Ribeiro ML, Manco L. Polymorphic variations influencing fetal hemoglobin levels: association study in beta-thalassemia carriers and in normal individuals of Portuguese origin. Blood Cells Mol Dis. 2015 Apr; 54(4):315-20. doi: 10.1016/j.bcmd.2015.02.001. Epub 2015 Feb 21.PMID: 25842369

11. Nguyen TK, Joly P, Bardel C, Moulsma M, Bonello-Palot N, Francina A. The XmnI (G)gamma polymorphism influences hemoglobin F synthesis contrary to BCL11A and HBS1L-MYB SNPs in a cohort of 57 beta-thalassemia intermedia patients.Blood Cells Mol Dis. 2010 Aug 15; 45(2):124-7. doi: 10.1016/j.bcmd.2010.04.002. Epub 2010 May 15. PMID:2047247
12. Chaouch L, Moumni I, Ouragini H, Darragi I, Kalai M, Chaouachi D, Boudrigua I, Hafsia R, Abbes S. rs11886868 and rs4671393 of BCL11A associated with HbF level variation and modulate clinical events among sickle cell anemia patients.Hematology. 2016 Aug; 21(7):425-9. doi: 10.1080/10245332.2015.1107275. Epub 2016 Jan 22. PMID:27077760
13. Lai Y, Chen Y, Chen B, Zheng H, Yi S, Li G, Wei H, He S, Zheng C. Genetic Variants at BCL11A and HBS1L-MYB loci Influence Hb F Levels in Chinese Zhuang β-Thalassemia Intermedia Patients. Hemoglobin. 2016 Nov; 40(6):405-410. doi: 10.1080/03630269.2016.1253586.PMID:28361591
14. Chan NC, Lau KM, Cheng KC, Chan NP, Ng MH.A Multi-locus Approach to Characterization of Major Quantitative Trait Loci Influencing Hb F Regulation in Chinese β-thalassemia Carriers. Hemoglobin. 2016 Nov; 40(6):400-404. doi: 10.1080/03630269.2016.1245198. Epub 2016 Nov 14. PMID:27707011
15. Farrell JJ, Sherva RM, Chen ZY, Luo HY, Chu BF, Ha SY, Li CK, Lee AC, Li RC, Li CK, Yuen HL, So JC, Ma ES, Chan LC, Chan V, Sebastiani P, Farrer LA, Baldwin CT, Steinberg MH, Chui DH. A 3-bp deletion in the HBS1L-MYB intergenic region on chromosome 6q23 is associated with HbF expression. Blood. 2011 May 5; 117(18):4935-45. doi: 10.1182/blood-2010-11-317081. Epub 2011 Mar 8.
16. Sankaran VG, Xu J, Orkin SHTranscriptional silencing of fetal hemoglobin by BCL11A, Ann N Y Acad Sci. 2010 Aug; 1202:64-8. doi: 10.1111/j.1749-6632.2010.05574.x.
17. Duyen Ngo, Harold Bae, Martin H. Steinberg, Paola Sebastiani, Nadia Solovieff, Clinton T. Baldwin, Efthymia Melista, Surinder Safaya, Lindsay A. Farrar, Ahmed M. Suliman, Waleed H. Albuali, Muneer H. Al Bagshi, Idowu Akinsheye, Patrick Gallagher, Hongyuan Luo, David H.K. Chui, John J. Farrell, Amein K. AlAli, and Abdulrahman Alsultan Fetal Hemoglobin in Sickle Cell Anemia: Genetic Studies of the ArabIndian Haplotype Blood Cells Mol Dis. 2013 June; 51(1): 22–26. doi: 10.1016/j.bcmd.2012.12.005 PMCID: PMC3647015