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Original article

Genetic modifiers of Hb F: The role of regulatory SNPs in β-Thalassemia phenotypic variability

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Abstract *Background and aim:* Gene modifiers affecting β-thalassemia are important for the patient's phenotype. Primary modifiers are the location of mutations in β gene regions Secondary modifiers are coexistence α-globin chains, and third modifiers are single nucletotide polymorphisms (SNPs) on the effect of Hb F. The aim of this study is to investigate the effect of five important SNPs in modifier genes affecting Hb F level. *Material and methods:* A total of twenty-five cases, aged between 1-44 years (Mean±SD: 14.52±30.40), as four TDT, eighteen with NTDT and three with S+beta thalassemia were included in study. Five SNPs in beta modifier genes: HBG2:g-158(C>T), BCL11A: rs1427407 (G>T), BCL11A: rs10189857 (A>G), HBS1L-MYB : rs28384513 (A>C) and HBS1L-MYB: rs9399137 (T>C) were examined and compared effect on HbF. *Results:* A total of 50 SNPs were detected in 25 cases, found as 41 heterozygous and 9 homozygous polymorphisms The distribution of polymorphisms according to the cases, 4 polymorphisms (8%) were detected in S+Beta thalassemia, 5 polymorphisms (10%) in TDT, and 41 polymorphisms (82%) in NTDT. While the Hb F average of 13 cases (52%) with α and β coexistence was 78.2+28.9, the Hb F average of 12 cases (48%) without α and β coexistence was 44.4+57.2. *Conclusion:* It may contribute to the molecular mechanisms of HbF regulation. For this purpose, it is recommended to make a detailed molecular diagnosis of each patient with β-thalassemia, and to examine the modifier genes affecting the beta gene, as well as alpha and beta gene analyses. (www.actabiomedica.it)

Key words: beta-thalassemia, hemoglobin f, genetic polymorphism, single nucleotide polymorphism, modifier genes, genetic modifiers, fetal hemoglobin, SNP

Background and Aim

Thalassemia syndromes occur when the insufficient synthesis rate of the globin chains (α, β, γ, δ) that form hemoglobins is significantly reduced. This results in unbalanced chain synthesis, which causes ineffective erythropoiesis by damaging erythrocyte precursors, or hemolytic anemia by damaging mature erythrocytes, or both (1). Alpha thalassemia syndromes are caused by three groups of mutation types: approximately 200 deletions and point mutations, and rare large deletion mutations. Deletional mutations are the most common type of mutation. In recent years, it has been reported that point mutations are as common as deletion mutations. Large deletional mutations; There are also rare variants such as ATR-16 and FIL (2). More than 350 mutations have been identified in Beta thalassemia syndromes, the majority of which are point mutations. There are also rare large gene deletions, dominant β-thalassemia mutations, and unusual conditions of β-thalassemia. These include mutations in the transcription factor, basal transcription, and DNA repair that cause the trichothiodystrophy associated with the β-thalassemia phenotype (3). Gene modifiers affecting β-thalassemia are important for the patient's phenotype. Primary modifiers: the location of mutations

(β++, β+ and β0) in different gene regions determine the associated phenotypic severity. Secondary modifiers: It is the amount and stability of α-globin chains that changes the α/β globin balance. Third modifiers are single nucletotide polymorphisms (SNPs) involved in HBG2, HBS1L-MYB, BCL11A on the effect of hemoglobin F (Hb F) gene.Fourth modifiers; gene variations such as VDR and HFE affect the complications of patients with β-thalassemia (4). Fetal hemoglobin (HbF) is the main modulator of the phenotype of hemoglobinopathies. HbF is produced in the fetus from approximately six weeks of pregnancy and accounts for 98% of the total hemoglobin content until birth. HbF consists of 2 alpha and 2 gamma globins and is divided into two types by gamma globulin chains consisting of Glycine and Alanine. Increased HbF levels due to reactivation or overexpression of the Hemoglobin Gamma (HBG) gene alleviates the severity of anemia in thalassemia (5). Patients with β- thalassemia are defined as transfusion-dependent thalassemias (TDT) and non-transfusion-dependent thalassemias (NTDT) according to their modifier gene structures and Hb F status. Important associations have been published between molecular regulators of HbF production and Hb F-inducing drugs such as Hydroxyurea (5,6).

The three most important loci in the expression of HbF are HBG2 at 11p15.4, BCL11A at 2p16.1, and HBS1L-MYB intergenic region at 6q23.3 are very important. Single nucleotide polymorphisms (SNPs) at these loci affect HbF production (6). All gene profiles of patients should be determined in order to benefit from HbF inducers and developed treatments. The aim of this study carried out to investigate whether the patients would not be transfusion dependent and whether they would benefit from HbF-inducing treatments by studying five important SNPs in HBG2, BCL11A and HBS1L-MYB, as well as the alpha and beta genes, of the patients with β-thalassemia.

Material and methods

Patients who applied to our center for genetic analysis in the last five years were included in the study.Informed consent was obtained from all patients and families. A total of twenty-five cases, (twelve males and thirteen females) aged between 1-44 years (Mean±SD: 14.52±30.40), were included in the study. Four of the cases were diagnosed with TDT, eighteen with NTDT, and three with S+ β thalassemia. After obtaining informed consent forms from the patients, 5 cc EDTA blood samples were taken from each patient for complete blood count, High Performance Liguid Chromatography (HPLC) for hemglobin F levels, alpha, beta gene analysis and beta modifier genes. After DNA isolation, Alpha genes were examined using with Alpha Strip analysis (Vienna Lab), beta gene sequence analysis (Sanger method) and SNPs were examined with Beta Thal Modifier Strip Assay (Vienna Lab) method. SNPs examined in beta modifier genes: HBG2:g-158(C>T), BCL11A: rs1427407 (G>T), BCL11A: rs10189857 (A>G), HBS1L-MYB : rs28384513 (A>C) and HBS1L-MYB: rs9399137 (T>C).

Results

Demographic features, Hb F levels, molecular and clinical diagnosis and Hb F modifier polymorhisms of patients are shown in Table 1.

In the β gene analysis results, the first frequency was IVS 1.110 G>A in 11 cases (44'%), the second frequency was IVS II-1 G>A in 10 cases. Of a total of 25 patients, 13 (52%) had β^0 and 12 (48%) β^+ mutations. Alpha and beta gene association was detected in 13 cases (52%), 11 of the alpha genes were α α / α α $^{3.7}$ (44%) and two were α α / α α $^{20.5}$ mutations (8%). While the Hb F average of 13 cases (52%) with α and β coexistence was 78.2+28.9, the Hb F average of 12 cases (48%) without α and β coexistence was 44.4+57.2. A total of 50 SNPs were detected in 25 cases, found as41 heterozygous and 9 homozygous polymorphisms.

The distribution of polymorphisms; BCL11A: rs10189857A>G polymorphism, 6 Homozygous (12%) 7 heterozygous (14%), BCL11A:rs1427407 G>T polymorphism 0 homozygous (0%), 12 heterozygous (24%), HBS1L-MYB:rs28384513A>C polymorphism, 2 homozygotes (4%), 5 heterozygotes (10%), HBS1L-MYB:rs9399137 T>C polymorphism

Table 1. Demographic features, Hb F levels, molecular and clinical diagnosis and Hb F modifier polymorhisms of patients.

No	Age	Gender	HPLC (HbF%)	Molecular diagnosis	Clinic diagnosis	Hb F modifier polymorhisms
1	44	M	36.1	β: c.20A>T / IVS-I-110 G>A (β^{+}) α : α α / α α	S+B	BCL11A:rs10189857 A>G Homozygous
2	34	F	15.5	β: IVS-I-110 G>A / IVS-I-110 G>A(β^{+}) α : α α / α α	NTDT	HBS1L-MYB:rs28384513 A>C Heterozygous
3	33	M	67,7	β: IVS-I-110 G>A / IVS-I-110 G>A (β^{+}) α: α α / α α $^{3.7}$	NTDT	BCL11A:rs10189857 A>G Heterozygous HBS1L-MYB:rs28384513 A>C Heterozygous HBS1L-MYB:rs9399137 T>C Heterozygous
4	29	F	71.1	β: IVS-I-110 G>A / IVS-I-110 G>A (β^{+}) α: α α / α α $^{3.7}$	NTDT	BCL11A:rs10189857 A>G Heterozygous
5	4	M	56.6	β IVS-I-6 T >C / IVS-I-6 T >C(β^{+}) α: α: α α / α α $^{20.5}$	NTDT	BCL11A:rs1427407 G>T Heterozygous
6	1	F	63	β: IVS-I-110 G>A / IVS-I-110 G>A (β^{+}) α: α α / α α $^{20.5}$	NTDT	BCL11A:rs1427407 G>T Heterozygous BCL11A:rs10189857 A>G Heterozygous HBS1L-MYB:rs9399137 T>C Heterozygous
7	1	M	97,9	β: IVS-II-1 G>A / IVS-II-1 G>A(β^{0}) α: α α / α α $^{3.7}$	NTDT	HBG2:g.-158 C>T Homozygous BCL11A:rs1427407 G>T Heterozygous BCL11A:rs10189857 A>G Heterozygous HBS1L-MYB:rs9399137 T>C Heterozygous
8	4	M	62	β: c.20A>T / IVS-I-110 G>A (β^{+}) α : α α / α α	S+B	BCL11A:rs1427407 G>T Heterozygous BCL11A:rs10189857 A>G Heterozygous HBS1L-MYB:rs28384513 A>C) Heterozygous
9	1	F	53.2	β: IVS-I-6 T >C / IVS-II-1 G>A (β^{0}) α : α α / α α	TDT	BCL11A:rs10189857 A>G Heterozygous
10	9	M	7.1	β: 25_26DELAA / 25_26DELAA (β^{0}) α : α α / α α	TDT	BCL11A:rs1427407 G>T Heterozygous HBG2:g.-158 C>T Heterozygous
11	31	M	27.6	β: IVS-I-110 G>A / IVS-I-110 G>A (β^{+}) α : α α / α α	NTDT	BCL11A:rs1427407 G>T Heterozygous HBG2:g.-158 C>T Heterozygous
12	30	M	27.7	β: 25_26DELAA / IVS II-1.G>A(β^{0}) α : α α / α α	NTDT	BCL11A:rs1427407 G>T Heterozygous HBG2:g.-158 C>T Heterozygous
13	3	M	28.8	β: 25_26DELAA / IVS II-1.G>A(β^{0}) α : α α / α α	NTDT	BCL11A: rs10189857 [A>G] Homozygous
14	32	M	48.2	β: 20A>T / IVS-I-110 G>A (β^{+}) α : α α / α α	S+B	BCL11A: rs1427407 [G>T] Heterozygous
15	5	F	52	β: IVS-I-6 T >C / IVS-II-1 G>A (β^{0}) α : α α / α α	NTDT	HBG2: g.-158 [C>T] Heterozygous BCL11A: rs10189857 [A>G] Homozygous

Table 1 (*Continued*)

No	Age	Gender	HPLC (HbF%)	Molecular diagnosis	Clinic diagnosis	Hb F modifier polymorhisms
16	6	F	56	β: 126-129del CTTT /126-129del CTTT(β^0) α: α α / α α $^{3.7}$	NTDT	BCL11A: rs10189857 [A>G] Homozygous HBS1L-MYB: rs28384513 [A>C] Heterozygous
17	7	M	63	β: IVS-II-1 G>A / IVS-II-1 G>A(β^0) α: α α / α α $^{3.7}$	NTDT	HBG2: g.-158 [C>T] Heterozygous HBS1L-MYB: rs28384513 [A>C] Heterozygous HBS1L-MYB: rs9399137 [T>C] Heterozygous
18	1	M	97	β: IVS-II-1 G>A / IVS-II-1 G>A(β^0) α: α α / α α $^{3.7}$	NTDT	HBG2: g.-158 [C>T], XMN-1 G-Gamma Homozygous BCL11A: rs1427407 [G>T] Heterozygous BCL11A:rs10189857 [A>G] Heterozygous HBS1L-MYB: rs9399137 [T>C] Heterozygous
19	7	F	86	β: 126-129del CTTT /126-129del CTTT (β^0) α: α α / α α $^{3.7}$	NTDT	HBG2: g.-158 [C>T] Homozygous BCL11A: rs1427407 [G>T] Heterozygous HBS1L-MYB: rs28384513 [A>C] Homozygous HBS1L-MYB: rs9399137 [T>C] Heterozygous
20	7	F	82	β: IVS-II-1 G>A /: IVS-II-1 G>A(β^0) α: α α / α α $^{3.7}$	NTDT	HBG2: g.-158 [C>T] Homozygous BCL11A: rs1427407 [G>T] Heterozygous HBS1L-MYB: rs28384513 [A>C] Homozygous HBS1L-MYB: rs9399137 [T>C] Hete Heterozygous
21	5	F	96	β: IVS-II-1 G>A / IVS-II-1 G>A(β^0) α: α α / α α $^{3.7}$	NTDT	BCL11A : rs10189857 [A>G] Heterozygous HBS1L-MYB : rs28384513 [A>C] Heterozygous
22	5	M	87	β: 25_26DELAA / IVS II-1.G>A(β^0) α : α α / α α	TDT	BCL11A: rs1427407 [G>T] : Heterozygous BCL11A:rs10189857 [A>G] : Heterozygous
23	9	F	88	β: IVS-I-110 G>A / IVS-I-110 G>A(β^+) α : α α / α α	TDT	BCL11A:rs10189857 [A>G]: Homozygous
24	7	F	94	β: IVS-I-110 G>A / IVS-I-110 G>A(β^+) α: α α / α α $^{3.7}$	NTDT	HBG2 : g.-158 [C>T] Homozygous BCL11A : rs10189857 [A>G] Homozygous HBS1L-MYB : rs28384513 [A>C] Homozygous
25	48	F	92	β: IVS-I-110 G>A / IVS-I-110 G>A(β^+) α: α α / α α $^{3.7}$	NTDT	HBG2 : g.-158 [C>T] : Heterozygous BCL11A:rs10189857 [A>G] : Homozygous

Abbreviations: NTDT: Non-Transfusion Dependent Thalassemia, TDT: Transfusion Dependent Thalassemia. S+B: S+Beta Thalassemia; HPLC: High Performance Liquid Chromatogrphy.

0 homozygotes (0%), 7 heterozygotes (14%), HBG2:g.-158 C>T polynorphism, 5 homozygotes (10%), 6 were heterozygous (12%) (Table 2). The distribution of polymorphisms according to the cases, 4 polymorphisms (8%) were detected in S+ β thalassemia, 5 polymorphisms (10%) in TDT, and 41 polymorphisms (82%) in NTDT (Table 2)

The Hb F levels and polymorphism numbers of the in 25 cases were compared, of the four cases (20%) in which four polymorphisms were detected were NTDT, Hb F distribution was: 97.9-82%, mean±SD:88.33±11.24. Of the 6 cases (24%) in which three polymorphisms were detected, one was S+Beta thalassemia, five were NTDT, Hb F distribution was 94.0-62.0%, mean±SD:69.94±21.99. Of the 7 cases (28%) in which two polymorphisms were detected, two were TDT and five were NTDT, Hb F distribution was 92.0-52, mean±SD: 75.5±28.28. Of

Table 2. Distribution polymorphisms in patients (n:50).

Polymorhysims	S+Beta (n) %	TDT (n) %	NTDT (n) %	Total (n) %
BCL11A:rs10189857A>G Homozygous	1	1	4	6 12
BCL11A:rs10189857A>G Heterozygous	1	1	5	7 14
BCL11A:rs1427407 G>T Homozygous	0	0	0	0 0
BCL11A:rs1427407 G>T Heterozygous	1	2	9	12 24
HBS1L-MYB:rs28384513A>C Homozygous	0	0	2	2 4
HBS1L-MYB:rs28384513A>C Heterozygous	1	0	4	5 10
HBS1L-MYB:rs9399137 T>C Homozygous	0	0	0	0 0
HBS1L-MYB:rs9399137 T>C Heterozygous	0	0	7	7 14
HBG2:g.-158 C>T Homozygous	0	0	5	5 10
HBG2:g.-158 C>T Heterozygous	0	1	5	6 12
Total	**(4) 8**	**(5) 10**	**(41) 82**	**(50) 100**

Abbreviations: NTDT: Non-Transfusion Dependent Thalassemia TDT: Transfusion Dependent Thalassemia, S+B: S+Beta Thalassemia.

Table 3. Relationship between Hb F level and polymorphism in patients (n:25).

The number of Polymorhisms positive	Hb F (%) Ort+SD	Hb F (%) Distribution	S+Beta n (%)	TDT n (%)	NTDT n (%)	Total n (%)
Four Polymorhisms	88,33±11.24	97,9-82	-	-	4	4 16
Three Polymorhisms	69,94±21.99	94.0-62.0	1 4		5 20	6 24
Two Polymorhisms	75,5±28,28	92.0-52.0	-	2 8	5 20	7 28
One Polymorhisms	45,28±51,26	88.0-15,5	2 8	2 8	4 16	8 32
Total			**3 12**	**4 16**	**18 72**	**25 100**

Abbreviations: NTDT: Non-Transfusion Dependent Thalassemia TDT: Transfusion Dependent Thalassemia, S+B: S+Beta Thalassemia.

the 8 cases (32%) in which a polymorphism was detected, two were S+Beta, two were TDT and four were NTDT, and the Hb F distribution was 88.0-15.5%, mean±SD:45.28±51.26 (Table 3).

Discussion

Increasing HbF results in a reduction of clinical symptoms in beta-hemoglobinopathies. Various transcription factors, as well as drugs such as hydroxyurea, can help red blood cells produce more HbF. HbF expression is increased by downregulation of three major quantitative trait loci, namely XMN1-HBG2, HBS1L-MYB and BCL11A genes. These genes contain SNPs that differentially modulate HbF expression in various populations The clinical and hematological features of beta thalassemia are determined by various factors leading to a wide range of severity (7). In Italy, a multicenter conducted representative cohort study of 890 β-thalassemia patients, 54 genetic variants in five loci were analyzed by disease severity. They used Cox proportional hazard analysis on a training set, evaluated the effect of these loci on the patient's age at starting regular transfusion, created a thalassemia severity score, and published that it is an important factor in determining whether patients will become transfusion dependent (7). In our study, we compared

the polymorphisms according to the transfusion status of the patients. We found 4 polymorphisms (8%) in S+ β thalassemia, 5 polymorphisms (10%) in TDT, and 41 polymorphisms (82%) in NTDT. As the number of polymorphisms increases, transfusion dependence decreases. In a cohort study conducted in Pakistan; in order to evaluate the effect of genetic modifiers on fetal hemoglobin levels in patients with TDT and NTDT. A total of 116 patients, 52 (45%) with NTDT and 64 (55%) with TDT, were included in the study. While fetal hemoglobin levels were affected by SNPs in the HBG2 (rs7482144) and BCL11A (rs766432) genes, it was found that the HBS1L-MYB (rs9399137) SNP was not significant (p>0.05). While rs7482144 SNP affected fetal hemoglobin levels in 8.3% of the patients, rs766432 was found to affect 5%. It has been published that there is a clear relationship between fetal hemoglobin level and SNPs in the HBG2 (rs7482144) and BCL11A (rs766432) genes (8).

A study was conducted in China to investigate the relationship between HBS1L-MYB and BCL11A SNPs and Hb F levels in 96 patients with NTDT. A total of 13 SNPs were confirmed to be significantly associated with Hb F levels in this population. Six SNP high-risk genotypes, rs9376090, rs7776054, rs9399137, rs939137, rs9402685, rs1899898, were detected in the HBS1L-MYB intergenic region, while one was detected significantly at rs18998860 in the BCL 11 A locus (9). In our study, BCL11A:rs10189857A>G polymorphism was found in 26% of the total patients, BCL11A:rs1427407 in 24%, HBS1L-MYB:rs28384513A>C polymorphism was found positive in 14%, and HBS1L-MYB:rs9399137 T>C polymorphism was found positive in 14%. Two polymorphisms in BCL11A were found to be 50% effective, and two polymorphisms in HBS1L-MYB were found to be 28% effective in total. In Indonesia, a study conducted in 189 patients with β-thal and HbE/β-thal, minor allele distributions at the XmnI locus, rs11886868, rs766432 and rs9399137 were found to be 14%, 22%, 19% and 18%, respectively (10). In Turkey, XmnI polymorphism was investigated in a total of 84 patients including 58 TDT and 26 NTDT While 18.9% of TDT patients were positive, 80.8% of NTDT patients were positive (11). In 25 patients participating in our study, HBG2:g.-158 C>T polynorphism was found to be positive in a total of 22%, 5 patients being homozygous (10%) and 6 patients being heterozygous (12%). In another study, a total of 200 patients (100 β-thalassemia, 100 Sickle Cell Anemia) and 50 healthy controls were recruited to evaluate the role of genetic modifiers leading to HbF production, together with the cumulative effect of the modifiers on disease severity. γ-globin gene promoter [- 158 C → T, + 25 G → A], BCL11A rs1427407 G → T, - 3 bp HBS1L-MYB rs66650371 and rs9399137 T → C polymorphisms were associated with higher HbF and lower disease severity score was found to be significant (P < 0.00001) (12). In our study, Hb F levels and positive polymorphism numbers of the cases were compared. Hb F mean±SD:88.33±11.24 in four NTDT cases (20%) in which four polymorphisms were detected. Of the 6 cases (24%) in which three polymorphisms were detected, one was S+Beta thalassemia, five were NTDT, Hb F mean±SD:69.94±21.99. Of the 7 cases (28%) in which two polymorphisms were detected, two were TDT and five were NTDT, Hb F mean±SD: 75.5±28.28. Of the 8 cases in which a polymorphism was detected, two were S+Beta, two were TDT and four were NTDT, Hb F mean±SD:45.28±51.26. As the number of positive polymorphisms increases, the HbF level increases, the clinical picture becomes better, and the transfusion requirement becomes less. In conclusion, defining the clinical phenotype of thalassemia patients at an early stage is important for the effective management of the disease. It may contribute to the molecular mechanisms of HbF regulation. For this purpose, it is recommended to make a detailed molecular diagnosis of each patient with β-thalassemia, and to examine the modifier genes affecting the beta gene, as well as alpha and beta gene analyses.

Limitation of Study: This study is the low number of patients.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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