Chapter

Interaction of Thalassemia and Hb Variants in Southeast Asia: Genotype-Phenotype Relationship

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Abstract

Thalassemia and hemoglobinopathies are characterized by globin gene mutations affecting the production of quantitative and structural defects of the globin chain. α-Thalassemia, β-thalassemia, hemoglobin E (Hb E), and hemoglobin Constant Spring (Hb CS) are very common in Southeast Asian countries. Complex interactions of thalassemia and Hb variants are also common and affect the thalassemia diagnosis with several techniques including Hb typing and DNA analysis. A family study (family pedigree) is required in the proband with a complex interaction of several globin gene defects with rare types. Homozygous β-thalassemia, Hb E/β-thalassemia, and Hb Bart's hydrops fetalis are severe thalassemia and these diseases have been concerned and included in the prevention and control program in several countries. Understanding the genotype-phenotype could help with the proper laboratory tests, genetic counseling, and effective treatment for the patients.

Keywords: thalassemia, Hb variants, southeast Asian countries, thalassemia interaction, genotype-phenotype, DNA analysis

1. Introduction

Southeast Asia (SEA) is composed of 11 countries such as Burma (Myanmar), Laos, Thailand, Cambodia, Vietnam, Malaysia, Singapore, Brunei, Indonesia, the Philippines, and Timor-Leste (**Figure 1**). As of 2021, around 676 million people live in the region [2]. The ethnic origins of people living in SEA countries are very heterogeneous according to religion, culture, and history. This chapter focused on the genotype-phenotype relationship between thalassemia and hemoglobinopathies in the Southeast Asian population. Both common and rare types of thalassemia and Hb variant are demonstrated in homozygous, double heterozygous, and compound heterozygous states for clinical and red blood cell phenotypes.

Figure 1.
The map of southeast Asian countries [1].

2. Globin gene cluster, functional globin genes, and normal adult hemoglobin

In humans, two globin gene clusters are responsible for hemoglobin synthesis in all developmental stages, including embryonic, fetal, and adult stages (**Figure 2**). The α-like gene cluster contains three functional genes, including the ζ2, α2, and α1 globin genes in chromosome 16 (16p13.3), and encoded to form the ζ- and α-globin chains which consist of 141 amino acids. In addition, the β -like gene cluster contains 5 functional genes including the ε, $^{G}\gamma$, $^{A}\gamma$, δ, and β-globin genes, in chromosome 11 (11p15.5), and encoded to form the ε, γ, δ, and β-globin chains which consist of 146 amino acids. During normal humans, each globin gene from 2 globin gene clusters is activated and expressed according to the specific developmental stage such as the embryonic stage (Hb Portland, Hb Gower I, and Hb Gower II), fetal stage (Hb F or fetal hemoglobin), and adult stage (Hb A and Hb A_2) [3, 4].

Hemoglobin (Hb), an iron-containing protein in erythrocytes (red blood cells), is responsible for transporting oxygen (O_2) from the lungs to tissues and to transporting carbon dioxide (CO_2) from tissues. In adult life, Hb A ($\alpha_2\beta_2$), or adult hemoglobin is the major component of normal adult hemoglobin (more than 95% of the total hemoglobin). Hb A_2 ($\alpha_2\delta_2$) is the second component about less than 3.5% in normal adults. Hb F ($\alpha_2\gamma_2$) or fetal hemoglobin with 1–2% is found in normal individuals [5].

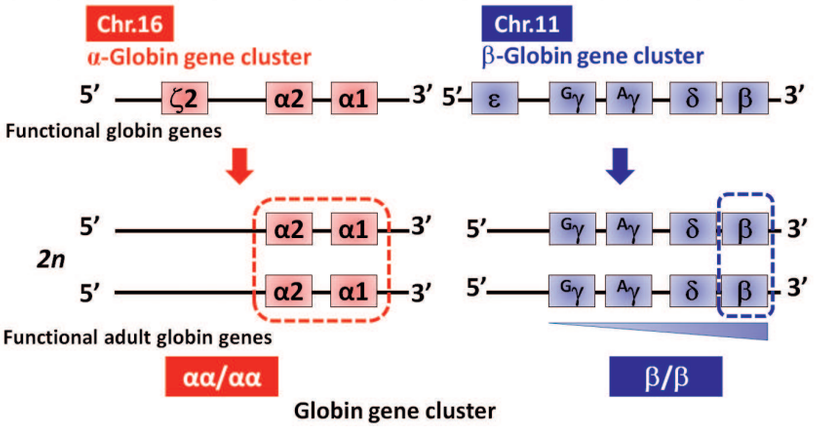

Figure 2.
Schematic representation of the globin gene cluster.

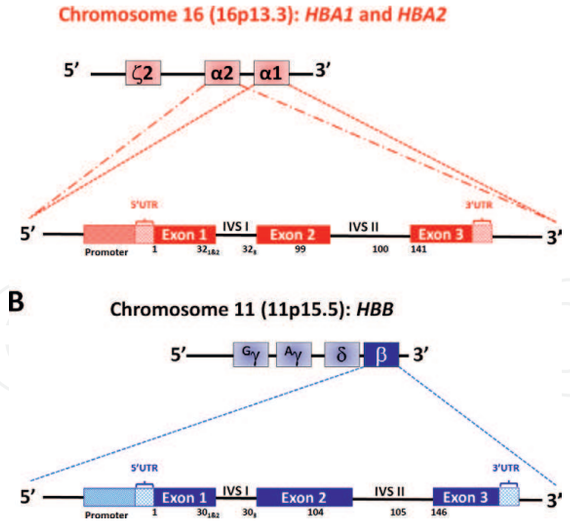

Figure 3.
General structure functional α -globin genes (A)and the β-globin gene (B).

According to Hb A ($\alpha_2\beta_2$) is the major component of total hemoglobin and contributes to gas transport in the human body. In the adult stage, α and β-globin genes are the two most important for globin chain synthesis and build up to form the tetramerization of 2 α-globin chains and 2 β-globin chains and each globin chain bound heme group (an iron atom bound within a protoporphyrin IX ring) [6]. Therefore, α and β-globin gene mutations were the most considered condition in the adult for thalassemia or Hb variants. An approximate 50 bp of the 5′ untranslated region (5'UTR) and codons for amino acid sequences 1–31 in the *HBA1*(or *HBA2*) and 1–30 in the *HBB* genes are represented as the first exon. The second exon encodes amino acids 32–99 and 31–104, respectively. The third exon encodes amino acids 101–141 for the α-globin gene and 105–146 for the β-globin gene, together with about 100 bp of 3′UTR (**Figure 3**) [3].

3. Genotype-phenotype relationship

In the human globin gene clusters, the α-globin gene cluster is located at the short arm of chromosome 16 (two copies of the α-globin gene per chromatid, *HBA2*, and *HBA1* genes) whereas the β-globin gene cluster is located at the short arm of chromosome 11 (one copy of each β-globin gene per chromatid, *HBB* gene). Both chromosomes 11 and 16 are autosomal chromosomes (*2n*, diploid cell). Therefore, a total of four genes per diploid cell of the α-globin genotype (αα/αα) and a total of two genes per diploid cell for the β -globin genotype (β^A/β^A). The mutations of the human globin gene can inherit from the parent ranging from 1 allele to 4 alleles of α- and β-globin genes and resulting in various forms of the carrier or thalassemia disease. α- and β-Globin genotyping can be characterized by several PCR-based methods [7]. In the context of globin gene defects, phenotype refers to the observable hematological (red blood cell morphology, osmotic fragility test, abnormal Hb screening, and Hb analysis) or clinical characteristics of the carriers or patients. Recently, the clinical classification of thalassemia is divided into two phenotypes according to the patient's clinical severity and transfusion requirements such as non-transfusion-dependent thalassemia (NTDT) and transfusion-dependent thalassemia (TDT) [8]. Therefore,

genotype-phenotype correlation is a relationship between specific globin mutations and hematological profiles or clinical symptoms. The red blood cell phenotypes and other related screening methods are the primary results for predicting a possible type of thalassemia carrier or disease [9, 10]. However, globin genotyping is required for a definitive and precise diagnosis of thalassemia for proper management and treatment [11].

4. Thalassemia and hemoglobinopathy

Thalassemia, a quantitative defect of globin chain synthesis, is caused by globin gene mutation and characterized by the absence (designed with a "0" superscript) or reduced (designed with a "+" superscript) synthesis of one or more of the normal globin chains. The α- and β-thalassemia are major types during the adult stage. In contrast, hemoglobinopathy is characterized by a qualitative or structural defect of globin chain synthesis. Thalassemic hemoglobinopathy is the combination of quantitative and qualitative features of globin chain synthesis such as Hb Constant Spring (Hb CS, α^+-thalassemia-like effect) and hemoglobin E (Hb E, β^+-thalassemia) [12]. Hereditary persistence of fetal hemoglobin (HPFH) and δβ-thalassemia are characterized by elevated fetal hemoglobin (Hb F) levels in adult life. There are no morphological changes to the red blood cells and red cell indices in HPFH whereas more abnormal red blood cells are observed in δβ-thalassemia [13]. In Southeast Asia α-thalassemia, β-thalassemia, Hb E, and Hb CS are prevalent and the gene frequencies vary in different countries. In Thailand, the carrier frequencies of 10–30% for α-thalassemia, 3–9% for β-thalassemia, and 10–53% for Hb E [14, 15]. The combinations of different globin gene mutations lead to over 60 different thalassemia syndromes and the most complex thalassemia genotypes were found among Southeast Asians [15]. According to common globin gene mutations found in the Southeast Asian population, the four major thalassemia diseases are Hb Bart's hydrops fetalis (−−/−−), homozygous β-thalassemia (β^*/β^*), Hb E/β-thalassemia (β^E/β^*), and Hb H diseases (deletional Hb H disease, −−/−α; non-deletional Hb H disease, −−/$\alpha^T\alpha$) [15–17]. Only the first three thalassemia diseases were concerned with prevention and control programs for severe thalassemia in Thailand and other Southeast Asian countries [18–21]. Clinical manifestations of thalassemia range from asymptomatic with mild microcytic hypochromic red blood cells to the totally lethal Hb Bart's hydrops fetalis [16, 22]. Moreover, the interaction of the thalassemias and hemoglobin variants from multiple globin gene mutations may not be uncommon in Southeast Asians. The hematological and complex hemoglobin profile has been reported in several publications and DNA analysis is required to characterize disease-causing mutation [7, 21]. Therefore, understanding the genotype-phenotype relationship is very useful for precise diagnosis with proper laboratory tests and economic benefits [23]. In Southeast Asia α-Thalassemia is associated with variable numbers of α-globin gene deletions by combining 2 alleles such as $-\alpha^{3.7}$, $-\alpha^{4.2}$, $-(\alpha)^{-20}$, $--^{SEA}$, $--^{THAI}$, $--^{FIL}$, and $--^{CR}$ with other alleles such as normal (αα) or α-globin chain variants ($\alpha^T\alpha$ or $\alpha\alpha^T$) [15, 24–27]. The clinical phenotype of α-thalassemia relates to the number of affected α-globin genes ranging from no clinical symptom (hypochromic and microcytic red cells without anemia) to lethal thalassemia disease [16, 28]. β-Thalassemias are very heterogenous and various β-globin gene mutations have been characterized. β-Thalassemia mutations could be classified as β^{++}, β^+, or β^0 thalassemia phenotypes according to different molecular mechanisms [11, 29–31]. In addition, several Hb chain variants of α-globin genes

(*HBA1* and *HBA2*), β-globin gene (*HBB*), and δ-globin gene (*HBD*) have been found among the Southeast Asian population which are summarized in **Table 1**.

5. Interaction of common thalassemia and hemoglobin variants

α- and β-globin genes can be inherited independently by the next generation. There are 4 possible genotypes of the α-globin gene and 4 possible genotypes of the β -globin gene. Therefore, the maximum genotypes of α- and β-globin genes are 16 possible genotypes. This model is useful for the prediction of severe thalassemia for the child in preconception counseling or prenatal diagnosis (PND) process (**Figure 4**).

In Southeast Asian countries, the complex interaction of thalassemia and the Hb variant is common. The dihybrid cross with the mutations in both α- and β-globin genes from the father (CS EA Bart's disease) and mother (double heterozygosity for β^0-thalassemia and α^0-thalassemia) is used to give an example for the reader. All globin genotypes obtained from the parent are essential information for evaluating the risk ratio of being severe thalassemia. The list of possible α-globin genotypes are 4 distinct genotypes as follows; $\alpha^{CS}\alpha/\alpha\alpha$ (Hb Constant Spring heterozygote), $--^{SEA}/\alpha\alpha$ (α^0-thalassemia heterozygote), $--^{SEA}/\alpha^{CS}\alpha$ (Hb H-Constant Spring), and $--^{SEA}/--^{SEA}$ (Hb Bart's hydrops fetalis or homozygous α^0-thalassemia). In addition, the list of possible β-globin genotypes are 4 distinct genotypes as follows; β^A/β^A (normal genotype), β^A/β^0 (β^0-thalassemia heterozygote), β^E/β^A (Hb E heterozygote), and β^E/β^0 (Hb E/β^0-thalassemia). According to 4 possible α- and 4 possible β-globin genotypes, 16 distinct combinations are obtained. In this case, Hb Bart's hydrops fetalis and Hb E/β^0-thalassemia are concerned and 7 combined genotypes (1, 2, 3, 4, 7, 11, and 15) are risk genotypes and this couple is a true risk couple with 7/16 (43.75%) for being severe thalassemia in the child (**Figure 5**).

Because of the high frequency of thalassemias and Hb variants, the interactions of thalassemias and Hb variants especially in two major globin chains (α- and β-globin) were observed in the Southeast Asian population. Hb E and Hb CS are the two most common Hb variants represented for β- and α-globin genes. Commonly, interactions of Hb E with other thalassemias or Hb variants resulting in Hb E-related syndromes such as Hb E/β-thalassemia with or without α-thalassemia interaction, AE Bart's disease, EF Bart's disease, etc. (**Table 2**). In an area where Hb E, β-thalassemia, and α-thalassemia are prevalent, the interaction of Hb E with several types of thalassemia is frequently observed. Among Hb E heterozygotes, a proportion of Hb A_2/E lower than 25% has been used for suspecting α-thalassemia interaction and confirmed by DNA analysis [9]. Various forms of α-thalassemia are common and interaction of thalassemia with heterozygous Hb E can result in a reduced Hb A_2/E level and hematological changes [35]. In contrast, the interaction of homozygous Hb E with α-thalassemia could not be differentially diagnosed by red cell indices and Hb-HPLC analysis [36]. Hb analysis by capillary electrophoresis can separate Hb A_2 from Hb E and Hb A_2 could be reported in the presence of Hb E [37, 38]. Interestingly, an increased Hb A_2 level is a useful biomarker for differentiation of Hb E homozygote with or without α^0-thalassemia [39]. The combination of heterozygous Hb E and Hb H disease or Hb H-Constant Spring disease has a marked decrease of Hb E (13–15%) with thalassemia intermedia, which is called AE Bart's disease [22]. Co-inheritance of Hb H disease with homozygous Hb E resulted in EF Bart's disease with mild anemia and increased Hb F levels and Hb

Gene	HGVS nomenclature	Mutation
α-Globin chain variants		
Hb Q-India	*HBA1*:c.193G>C	alpha1 64(E13) Asp>His
Hb Q-Thailand	*HBA1*:c.223G>C	alpha1 74(EF3) Asp>His
Hb Grey Lynn (Hb Vientiane)	*HBA1*:c.274C>T	alpha1 91(FG3) Leu>Phe
Hb St. Luke's-Thailand	*HBA1*:c.287C>G	alpha1 95(G2) Pro>Arg
Hb O-Indonesia	*HBA1*:c.349G>A	alpha1 116(GH4) Glu>Lys
Hb Phnom Penh	*HBA1*:p.Phe118_Thr119insI	I- inserted between codons 117(GH5) and 118(H1) of alpha1
Hb Dunn	*HBA2*:c.19G>A (or *HBA1*)	alpha2 or alpha1 6(A4) Asp>Asn
Hb J-Wenchang-Wuming	*HBA2*:c.34A>C (or *HBA1*)	alpha2 or alpha1 11(A9) Lys>Gln
Hb Siam (Hb Ottawa)	*HBA2*:c.46G>C (or *HBA1*)	alpha2 or alpha1 15(A13) Gly>Arg
Hb I	*HBA2*:c.49A>G	alpha2 16(A14) Lys>Glu
Hb Beijing	*HBA2*:c.[51G>C (or *HBA1*) or 51G>T (or HBA1)]	alpha2 or alpha1 16(A14) Lys>Asn
Hb Shenyang	*HBA2*:c.80C>A (or *HBA1*)	alpha2 or alpha1 26(B7) Ala>Glu
Hb Hekinan	*HBA2*:c.84G>C	alpha2 27(B8) Glu>Asp
Hb G-Honolulu	*HBA2*:c.91G>C (or *HBA1*)	alpha2 or alpha1 30(B11) Glu>Gln
Hb Prato	*HBA2*:c.[96G>C (or *HBA1*) or 96G>T (or *HBA1*)]	alpha2 or alpha1 31(B12) Arg>Ser
Hb Queens	*HBA2*:c.104T>G (or *HBA1*)	alpha2 or alpha1 34(B15) Leu>Arg
Hb Wiangpapao	*HBA1*:c.133C>T	alpha1 44(CE2) Pro>Ser
Hb Kawachi	*HBA2*:c.134C>G (or *HBA1*)	alpha2 or alpha1 44(CE2) Pro>Arg
Hb Thailand	*HBA2*:c.170A>C (or *HBA1*)	alpha2 or alpha1 56(E5) Lys>Thr
Hb J-Norfolk	*HBA2*:c.173G>A (or *HBA1*)	alpha2 or alpha1 57(E6) Gly>Asp
Hb Adana	*HBA2*:c.179G>A (or *HBA1*)	alpha2 or alpha1 59(E8) Gly>Asp
Hb Nakhon Ratchasima	*HBA2*:c.191C>T	alpha2 63(E12) Ala>Val
Hb Westmead	*HBA2*:c.369C>G	alpha2 122(H5) His>Gln
Hb Quong Sze	*HBA2*:c.377T>C	alpha2 125(H8) Leu>Pro
Hb Constant Spring (Hb CS)	*HBA2*:c.427T>C	alpha2 142, Stop>Gln; modified C-terminal sequence: (142)Gln-Ala-Gly-Ala-Ser-Val-Ala-Val-Pro-Pro-Ala- Arg-Trp-Ala-Ser-Gln-Arg-Ala-Leu-Leu-Pro- Ser-Leu-His-Arg-Pro-Phe-Leu-Val-Phe-(172) Glu-COOH
Hb Pakse	*HBA2*:c.429A>T	alpha2 142, Stop>Tyr; modified C-terminal sequence: (142)Tyr-Ala-Gly-Ala-Ser-Val-Ala-Val-Pro-Pro-Ala- Arg-Trp-Ala-Ser-Gln-Arg-Ala-Leu-Leu-Pro- Ser-Leu-His-Arg-Pro-Phe-Leu-Val-Phe-(172) Glu-COOH

Gene	HGVS nomenclature	Mutation
β-Globin chain variants		
Hb Raleigh	*HBB*:c.5T>C	beta 1(NA1) Val>Ala
Hb C	*HBB*:c.19G>A	beta 6(A3) Glu>Lys
Hb G-Makassar	*HBB*:c.20A>C	beta 6(A3) Glu>Ala
Hb S	*HBB*:c.20A>T	beta 6(A3) Glu>Val
Hb G-Siriraj	*HBB*:c.22G>A	beta 7(A4) Glu>Lys
Hb Malay	*HBB*:c.59A>G	beta 19(B1) Asn>Ser
Hb E-Saskatoon	*HBB*:c.67G>A	beta 22(B4) Glu>Lys
Hb E	*HBB*:c.79G>A	beta 26(B8) Glu>Lys
Hb Henri Mondor	*HBB*:c.80A>T	beta 26(B8) Glu>Val
Hb Athens-Georgia	*HBB*:c.122G>A	beta 40(C6) Arg>Lys
Hb J-Bangkok	*HBB*:c.170G>A	beta 56(D7) Gly>Asp
Hb Dhofar	*HBB*:c.176C>G	beta 58(E2) Pro>Arg
Hb J-Kaohsiung	*HBB*:c.179A>C	beta 59(E3) Lys>Thr
Hb Phimai	*HBB*:c.218G>C	beta 72(E16) Ser>Thr
Hb Korle Bu (Hb G-Accra)	*HBB*:c.220G>A	beta 73(E17) Asp>Asn
Hb Pyrgos	*HBB*:c.251G>A	beta 83(EF7) Gly>Asp
Hb D-Punjab (Hb D-Los Angeles)	*HBB*:c.364G>C	beta 121(GH4) Glu>Gln
Hb Tende	*HBB*:c.374C>T	beta 124(H2) Pro>Leu
Hb Dhonburi	*HBB*:c.380T>G	beta 126(H4) Val>Gly
Hb Cook	*HBB*:c.398A>C	beta 132(H10) Lys>Thr
Hb Hope	*HBB*:c.410G>A	beta 136(H14) Gly>Asp
Hb Tak	*HBB*:c.441_442insAC	beta 147(+AC); modified C-terminal sequence: (147)Thr-Lys-Leu- Ala-Phe-Leu-Leu-Ser-Asn-Phe-(157)Tyr-COOH
δ-Globin chain variants		
Hb A_2-Melbourne	*HBD*:c.130G>A	delta 43(CD2) Glu>Lys
Hb A_2-Lampang	*HBD*:c.142G>A	delta 47(CD6) Asp>Asn
Hb A_2-Walsgrave	*HBD*:c.157G>C	delta 52 (D3) Asp>His
Hemoglobin A_2-Mae Phrik	*HBD*:c.158A > G	delta 52(D3) Asp > Gly
Hb A_2-Kiriwong	*HBD*:c.233A>G	delta 77(EF1) His>Arg
Hb Lepore-Hollandia	NG_000007.3:g.63290_70702del	delta-beta hybrid (delta through 22; beta from 50)
Hb Lepore-Washington-Boston	NG_000007.3:g.63632_71046del	delta-beta hybrid (delta through 87; beta from 116)

Table 1.
Hb variants in southeast Asian countries [32–34].

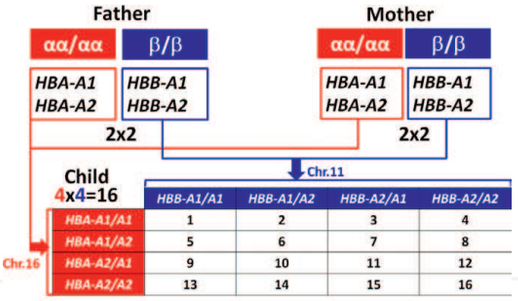

Figure 4.
The model of the dihybrid cross of α- and β-globin genotypes.

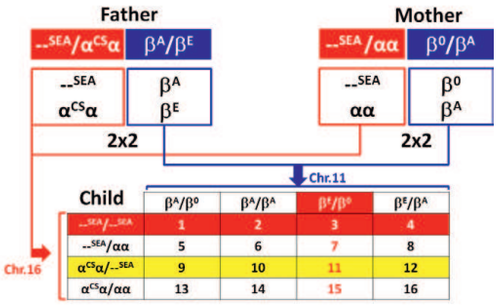

Figure 5.
The model of dihybrid cross of CS EA Bart's disease and double heterozygosity for β^0-thalassemia and α^0-thalassemia.

Bart's [22]. The compound heterozygous state for β-thalassemia and Hb E namely Hb E-β-thalassemia is variable disease severity ranging from transfusion-dependent thalassemia to thalassemia intermedia. An ameliorating effect of α-thalassemia interactions and high Hb F determinants has been well studied [40–42]. Moreover, the interaction of thalassemia and Hb variants has been reported in several publications in the Thai population such as compound heterozygosity for Hb Korle-Bu and Hb E with α^+-thalassemia, complex interactions between Hb Lepore-Hollandia and Hb E with α^+-thalassemia and interaction between Hb E and Hb Yala resulting in Hb E/β^0-thalassemia, double heterozygosity of Hb Hope and α^0-thalassemia and compound heterozygotes for Hb Hope and β^0-thalassemia [43–46]. Hereditary persistence (HPFH) and δβ-thalassemia are characterized by elevated fetal hemoglobin levels in adult life. There are several mutations reported in the Thai population such as $^{G}\gamma^{A}\gamma$ $(\delta\beta)^0$-thalassemia, deletional HPFH-6, and deletion-inversion $^{G}\gamma(^{A}\gamma\delta\beta)^0$-thalassemia [47–49].

6. Conclusions

The understanding of the genotype-phenotype relationship is essential for proper laboratory testing, genetic counseling, and treatments. The concept of thalassemia interaction could be applied in a country with high frequency and heterogeneity of thalassemia and hemoglobinopathies. DNA analysis is very important for definitive diagnosis, as well as the family study, and could be helped

Type	Genotype	Disease/clinical phenotype	Hb type*
Homozygous conditions			
α^+-thal	−α/−α	No clinical symptoms	A_2A
α^+-thal (Hb variant)	$\alpha^T\alpha/\alpha^T\alpha$ ($\alpha^{CS}\alpha/\alpha^{CS}\alpha$)	Hb H disease	(CS) A_2A Bart's H
α^0-thal	−−/−−	Hb Bart's hydrops fetalis	Bart's
β^0 or severe β^+ thal	β^0/β^0	Thal major (TM) or TDT	A_2F
Mild β^+ or β^{++} thal	β^+/β^+	Thal intermedia (TI) or NTDT	A_2FA
Hb E (β^+ thal)	β^E/β^E	No clinical symptoms	EE or E(F)
Compound heterozygous conditions			
α^0-thal/α^+-thal	−−/−α	Deletional Hb H disease	A_2A Bart's H
α^0-thal/α^+-thal (Hb variants)	−−/$\alpha^T\alpha$ (−−/$\alpha^{CS}\alpha$)	Non-deletional Hb H disease (severe)	(CS) A_2A Bart's H
Severe β^+ thal/β^0 thal	β^+ (severe form)/β^0	Thal major (TM) or TDT	A_2F
Mild β^+/β^0 thal	β^+ (mild form)/β^0	Variable disease severity	A_2FA
Hb E/β^+ thal	β^E/β^+	Thal intermedia (TI)	EFA
Hb E/β^0 or severe β^+ thal	β^E/β^0 or β^E/β^+ (severe)	Variable disease severity	EF
Hb E/Hb C	β^E/β^C	No clinical symptoms (mild anemia)	EC
Hb E/$(\delta\beta)^0$ thal	$\beta^E/(\delta\beta)^0$	Thal intermedia	EF
Hb E/HPFH	β^E/HPFH	Mild thal intermedia	EF
Hb E-related syndromes			
Heterozygous Hb E + α^0-thal heterozygote	β^E/β^A + −−/αα	Double heterozygotes for Hb E and α^0-thal, no clinical symptoms	EA (reduced Hb E levels)
Heterozygous Hb E + α^0-thal/α^+-thal	β^E/β^A + −−/−α	AE Bart's disease, thal intermedia	EA Bart's
Heterozygous Hb E + α^0-thal/α^+-thal (Hb variants)	β^E/β^A + −−/$\alpha^T\alpha$ ($\alpha^T\alpha$ = $\alpha^{CS}\alpha$ or $\alpha^{PS}\alpha$)	CS/PS AE Bart's disease, thal intermedia	(CS) EA Bart's
Homozygous Hb E + α^0-thal/α^+-thal	β^E/β^E + −−/−α	EF Bart's disease, thal intermedia	EF Bart's
Homozygous Hb E + α^0-thal/α^+-thal (Hb variants)	β^E/β^E + −−/$\alpha^T\alpha$ ($\alpha^T\alpha$ = $\alpha^{CS}\alpha$ or $\alpha^{PS}\alpha$)	CS/PS EF Bart's disease, thal intermedia	(CS) EF Bart's
Hb E/β^0 thal+α^0-thal/α^+-thal	β^E/β^0 + −−/−α	EF Bart's disease, thal intermedia	EF Bart's
Hb E/β^0 thal+α^0-thal/α^+-thal (Hb variants)	β^E/β^0 + −−/$\alpha^T\alpha$ ($\alpha^T\alpha$ = $\alpha^{CS}\alpha$ or $\alpha^{PS}\alpha$)	CS EF Bart's disease, thal intermedia	(CS) EF Bart's

*CS, Constant Spring; PS, Pakse; HPFH, hereditary persistence of fetal hemoglobin; NTDT, non-transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia; Thal, Thalassemia; TI, thalassemia intermedia; TM, thalassemia major.*Hb type is based on HPLC technique.*

Table 2.
Phenotypes of thalassemias, Hb variants and interaction of thalassemia and Hb variants in the southeast Asian population.

in complex thalassemia with a rare hemoglobin variant. Characterization of globin gene mutations in the population is important and a globin gene mutation database in each country is required for improving prevention and control program for severe thalassemia.

Conflict of interest

The author declares no conflict of interest.

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