HbE/β-thalassemia is the most common severe form of thalassemia particularly in SEA region including Malaysia and globally, it comprised of a significant severe form of β-thalassemia disorder. It has various clinical manifestations ranging from very mild anemia to severe manifestation similar to beta thalassemia major. Many different syndromes are observed in HbE/β-thalassemia. Several genetic modifiers have been reported to play important role in contributing to phenotypic variability. The true reasons underlying this phenotypic variability remain unknown. The most reliable predictive factor of the disease phenotype is the nature of the beta globin gene mutation itself. However, the degree of severity is also believed to be affected by other genetic modifiers. For instance, high HbF level ameliorates the clinical severity of β thalassemia patients. Therefore, identification of these genetic modifiers is very important. The association of severe clinical manifestation and the specific β-globin gene mutation has been known. But the wide scope and other potential predictors have been only recently appreciated. This review therefore aimed to reveal the potential genetic modifiers of HbE/β-thalassemia patients based on the previous reported studies. A better understanding on the mechanisms underlying the variety of phenotypes of this disease may lead to the direction for a better future management plans. This also promotes “personalized medicine” in patient care.

**Keyword:** Thalassemia, Genotype, Phenotype

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Genotype-phenotype Association Of HbE/β Thalassemia Disease And The Role Of Genetic Modifiers

Genetic basis of thalassemia

Thalassemia is characterized by reduced or complete absence of globin chain production and is classified according to the respective affected globin chain. There are mainly 2 types of thalassemias; alpha (α) and beta (β) thalassemias which affects the production of α and β globin chains, respectively. These 2 types of thalassemia also interact each other and influence the clinical presentation. Alpha thalassemia is caused by defective α globin genes (HBA1; haemoglobin subunit alpha 1 and HBA2; haemoglobin subunit alpha 2). HBA1 and HBA2 are arranged in pairs on chromosome 16p. Each of the α globin gene encodes for 1 alpha globin chain in the HbA (α2β2), HbA2 (α2δ2) and HbF (α2γ2) formations [1]. In a normal individual, there are 4 alpha globin genes present (aa/aa).

Majority of α thalassemia is caused by gene deletions and very rarely caused by point mutations. An individual with the loss of one α gene (αα/α-) is almost silent and is called a silent carrier. Loss of 2 genes (-α/-α or aa/-α) produces mild symptoms, α thalassemia trait. Homozygous for α0 (α-/α- or αα/αα) have a lethal condition with intrauterine haemolytic anaemia called Hb Bart’s hydropfetalis. This is due to the total lack of α globin chain leading to excessive delta (γ) globin chains which forms Hb Bart (γ4) in the foetus and this Hb Bart is incompatible with life [2]. Meanwhile, an interaction of α+ with α0 causes HbH disease (-α/-α or αα/αα). In HbH disease, some amount of α-globin chains can still be produced. Thus, it produces an intermediate phenotype and the formation of HbH which consists of 4 beta globin chains (β4) in adult life. Both Hb Bart and HbH have very high oxygen affinity, thus their production is physiologically useless and their precipitations in the red cells cause red cell haemolysis [3].

Beta thalassemia on the other hand, are commonly caused by point mutations and small insertions or deletions of one or two bases on the beta globin gene (HBB; haemoglobin subunit beta) and only a small group of beta thalassemia is caused by gene deletion. Two beta globin chains with 2 alpha globin chains makes HbA (α2β2), which comprises 95% to 97% of haemoglobin in the adult red cell. There are more than 300 mutations of the HBB that had been described, but only a limited few that accounts for the majority of the world wide beta thalassemia mutations. HBB mutations result in quantitative reduction in the output of beta globin chain leading to reduced or complete absence of HbA production which causes thalassemia syndrome. HBB mutations that cause reduced amount of beta globin is called β+ and β++ (milder than β+) thalassemia while mutation that completely inactivates the β globin gene is called β0 thalassemia. Usually normal HBB is assigned as ‘β’ without superscript. An individual with β0/β0 mutation is a beta thalassemia major and typically have severe clinical manifestations. While β/β+ or β+/β+ are thalassemia intermedia and usually these patients have a diverse clinical severity. Patients with β/β0 or β/β+ are thalassemia minor or trait patients and usually are silent carriers [4].

The pathophysiology of beta thalassemia syndrome is mainly caused by excessive α-globin chains in the red blood cells. When only the β globin chain production is affected, there will be excessive amount of alpha globin chains production because they are still normally synthesized. These excessive alpha chains are highly unstable and can precipitate in red cell precursors,
forming intracellular inclusions and also found to associate with the membrane skeletal structure [5]. It has been observed that these beta thalassemic cells have abnormally enhanced cellular oxidant stress due to the production of reactive oxygen species caused by the presence of excessive alpha chains which render the red cells unstable [6,7]. Degradation products of alpha globin chain such as haem and iron also are toxic to the cells. They have shown to directly inhibit a number of cytoplasmic enzymes, further disrupting normal cellular homeostasis which have deleterious effects by binding to the cell membrane proteins and lipids. It is manifested as membrane abnormality and red cell rigidity. Red cell maturation is interrupted and abnormal cells are prematurely destroyed in the bone marrow; a process called ‘ineffective erythropoiesis’. Those red cells which are able to mature enter the peripheral circulation containing these membrane-associated globins which result in reduced deformability of the red cells. Subsequently their passages through the microcirculation in the spleen are interfered resulting in haemolysis [3,5]. Thus, the anaemia in beta thalassemia is due to the combination of ineffective erythropoiesis and haemolysis of red blood cells.

**Molecular pathology of HbE/β thalassemia**

Due to population migration across continents, the inheritance of hemoglobin disorder has spread worldwide. This phenomenon directly leads to the appearance of diverse type of globin disorders. It is not rare if an individual inherited one mutation from alpha or beta globin allele from one parent, and one mutation is inherited from the other parents that comprised mutated allele from hemoglobin variant. Hemoglobin variants are abnormal forms of hemoglobin produced from the mutation in HBB gene and consequently, leads to the hemoglobin structural defect. Reduced production rate and hemoglobin instability are among the effects of the Hb variant production. These genetic changes will contribute to various pathological effect such as unstable hemoglobin, increase or decrease oxygen affinity, structural change (sickle cell disease) and methaemoglobinemia [3].

Numerous interactions between hemoglobin variants and thalassemia have been reported before. However, only three forms are found to be common which are HbE/β thalassemia, HbS/β thalassemia and HbC/β thalassemia. HbE/β thalassemia is the most frequent compound heterozygous that highly is distributed in Southeast Asia. In 1954, Minnich and colleges reported about this disease where they found the disease in 32 patients of Thailand population [8]. In Malaysia, the disease was firstly reported by Lehman and Singh in 1956 [9].

HbE is a beta-chain hemoglobin variant with mild phenotype of beta-thalassemia. Individuals who have homozygous form of HbE are clinically normal. However, individuals with compound heterozygous of HbE/β+ or HbE/β0 thalassemia may have severe clinical manifestation [10]. The pathophysiology of HbE affects the production rate of hemoglobin E. Defects on the beta globin gene dramatically decreased production of beta-E-globin mRNA and beta-E-globin chain. This condition arises due to a single base substitution of G to A base at codon 26 which is located in exon 1, resulting in the alteration of Glutamic acid to Lysine. Figure 1 showed correctly and aberrantly spliced beta-E globin mRNA analysis [11]. The alteration of this amino acid activates a cryptic splice site at codon 25.
thus lowering $\beta^E$ globin chain expression [12]. Therefore, the phenotype for HbE is regarded as $\beta^+$. HbE in the form of heterozygous and homozygous genotype is typically asymptomatic with hypochromic microcytic red cells with mild anemia.

It was believed that, the imbalances of $\alpha/\beta$-globin chain are contributed by several factors. In HbE heterozygous, the decreasing synthesis of $\beta^E$-globin chain leads to the imbalance of $\alpha/\beta$-globin chain synthesis of 1.2 to 2.1, and affecting on the tertiary conformational HbE molecule. It is also associated with reduction synthesis of $\beta^E$-globin chain. Under oxidative stress condition, HbE is partly unstable and it will be precipitated. Besides that, lower percentage of HbE synthesis is also another factor contributing to the imbalance of accumulation of $\alpha$ and $\beta^E$-globin gene production. Hence, the pathophysiology of the disease is very complicated [13,14].

Oxidative damage, apoptosis, and ineffective erythropoiesis are the main constituents of this disease in which it shortened the life span of the red blood cells. According to Gibbons et al (2001), the association of E hemoglobin variant with $\beta$-thalassemia alleles is the primary basis that contribute to pathophysiologic changes [15]. The mutations caused the imbalance of globin chain to interact resulting in phenotypic variability. However, among the family member with similar mutation, different clinical severity may be displayed [16]. Thus, the true reason for phenotypic variability is still unknown and other genetic modifiers play the role in the clinical variability of HbE/$\beta$ thalassemia.

**Figure 1. Simplified representation of aberrant splicing of $\beta^E$-globin mRNA**

$\beta^E$-globin Pre-mRNA

<table>
<thead>
<tr>
<th></th>
<th>Exon 1</th>
<th>Intron 1</th>
<th>Exon 2</th>
<th>Intron 2</th>
<th>Exon 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>5’</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3’</td>
</tr>
</tbody>
</table>

Correctly spliced $\beta^E$–mRNA

Aberrantly spliced $\beta^E$–mRNA

*Black box represents 16 nucleotides at the 3’ end of exon 1 deleted by aberrant splicing
The diversity of HbE/beta thalassemia phenotype and classification

In general, β thalassemia patients can be classified into 3 phenotypes which are; thalassemia major, thalassemia intermedia and thalassemia minor. Patients with β/β₀ or β/β⁺ are classified as thalassemia minor or trait. Apart from being anemic during stressful metabolic events, the natural history of patients with thalassemia minor are typically symptomless. Thalassemia major patients are patients who inherited β₀/β₀ mutations and are highly transfusion dependent, hence they are also called as transfusion-dependent thalassemia. These children present clinically during the first year of life, as early as 4 to 8 months old, during which the switch from fetal Hb (HbF) to adult Hb (HbA and HbA2) is taking place. The Hb level can be 7g/dl or lower at presentation [17]. There may be evidence of marked erythroid hyperplasia with the typical ‘thalassemic facies’ due to bone marrow expansion of the skull bault and maxillary bones. They usually required blood transfusion in average of 4 weeks or in the range from every 2 to 6 weeks to maintain a steady Hb level of 12 to 12.5g/dl [18].

Thalassemia intermedia patients are compound heterozygotes or homozygous with β₀/β⁺ or β⁺/β⁻ mutations. Typically, this group of patients have much severe symptoms than thalassemia minor, but not as severe as thalassemia major. Thus, thalassemia intermedia have a wide spectrum of phenotypes. They usually present at later age than thalassemia major at more than 1 year of age or they even present in late teenager or adulthood. The haemoglobin level at presentation usually ranges from 8g/dl to 10g/dl [18]. On the severe side of the disease spectrum, some may need regular transfusions, developed splenomegaly, signs of marrow expansion and showing growth retardation [19].

The compound heterozygous state of β⁺ thalassemia and HbE mutation causes both qualitative and quantitative changes to the haemoglobin and HbE/β⁺ thalassemia patients are classified as thalassemia intermedia. HbE/β⁺ thalassemia is said to have a ‘modified natural history’ as the patients have a wide range of clinical severity from being asymptomatic with normal growth and development to severely anaemia who are transfusion-dependent [20]. However, most of them have been inaccurately converted to transfusion dependent β thalassemia major. This is because patients first presented with severe anaemia in early childhood. In fact, the anaemia is made worse by a concomitant illness usually secondary to infection. The presenting haemoglobin is usually less than 7g/dl which is similar presentation with beta thalassemia major. They then start receiving transfusion resulting for their life time [21].

But studies have shown that there are HbE/β thalassemia patients who did not require transfusion at all, while some required transfusion only in childhood and still had normal growth and maturity until adulthood [20,22]. Due to this heterogenous and changing phenotype, it has been difficult to develop a straight forward guideline for better management and predict the clinical behavior of these patients control of the disease.

This unique phenotypic diversity of HbE/β thalassemia patients are well-known and have been reported in many populations. Researchers are trying to define the phenotypic variations by classifying them into different severity groups according to their clinical symptoms, signs and
transfusion needs. This approach will provide precise care for patients with different level of disease severity to avoid unnecessary treatment. One of the most comprehensive observational studies was conducted by Premawardhena et al in 2005 to define the phenotypic variability of HbE/β thalassemia patients in Sri Lanka. One hundred and nine (109) patients were followed closely for 5 years and they were classified into 5 groups. Group 1 patients had the most mild symptoms where they present at later age (mean 9.9 years), required no to minimal transfusion, sexually mature in adulthood and had normal growth velocity. Group 2 patients are the same as Group 1 but they required more transfusion than the previous group. Group 3 patients are patients who had splenectomy with better growth and development post splenectomy. Group 4 and 5 patients are on the severe spectrum of the disease where they are transfusion-dependent and had retarded growth and sexual maturity. It is important to note that the mean Hb between the severe and mild groups were only marginally lower with 5.5g/dl and 6.3g/dl (p-value=0.0001) respectively. In short, Premawardhena et al stated that Hb is a very poor indicator of the likely course of HbE/beta thalassemia. They also highlighted that there were lacking of information on the indications for regular transfusion in these patients [20].

Sripichai et al also had developed a scoring system for HbE/βthalassemia patients published in 2008. It was based on 6 independent parameters which are steady Hb state, age at receiving first blood transfusion, requirements for blood transfusion, size of spleen, age at thalassemia presentation and patients’ growth and development. Steady state Hb is the average of Hb levels from previous records before receiving blood transfusion. Requirements for blood transfusion was defined as frequency of transfusion to maintain patient quality of life with rare as being none or once in several years, occasional is every 4 months to once a year and regular is transfusion every 3 weeks to 3 months. Age at thalassemia presentation is the age at which thalassemia symptoms e.g. anaemia, jaundice or splenomegaly appeared in an individual. Growth and development percentile of patients were based on weight and height measurements plotted on a standard Thai growth chart. The first 4 parameters are given scores from a range between 0 to 2 while the last 2 parameters are scored from 0 to 1, giving a potential total score of 10. Patient who scores 0 to 3.5 is considered to have mild disease, 4 to 7 as moderate and 7.5 to 10 as severe. This new scoring system for HbE/β thalassemia disease severity was tested in 950 Thai/Chinese HbE/β thalassemia patients. They found that these 6 parameters were the best combination model where they were all independently associated with disease severity with p-value of less than 0.001 in all parameters [23]. Unfortunately to date, there is no standard classification system that has been applied in clinical practice for management HbE/β thalassemia patients in Malaysia.

**Genetic modifiers of HbE/β-thalassemia**

The diverse of clinical phenotypes of HbE/β thalassemia are believed to be predominantly determined by few factors such as genetic modifiers, access to healthcare facilities and environmental factors. Genetic modifiers are the main factors that play a major role in contributing to the remarkable variable phenotype of the disease [24, 25]. Pertaining to this factor, many studies were conducted to reveal the role of genetic modifiers in determining the
severity of the disease. Among the first few studies, HBB was the candidate gene investigated in the past. From the studies, most researchers found their own unique spectrum mutations that correlated to this disease. However, mutations may not be the only molecular alteration that caused different patterns of gene expression. Then, the studies were continued to association with family linkage analysis. Finally, a robust technique known as Genome wide association study (GWAS) was applied to the predict phenotypes from genotypes with certainty. The genetic modifiers of HbE/β thalassemia can be classified as following groups: Primary, β-globin gene mutations in those with underlying β-thalassemia; secondary, loci that involved in globin synthesis and tertiary, loci that are not involved in globin synthesis but might modify the severity of the disease [26].

i) Primary modifier

It has been noted that primary modifier is the most important factor leading to the phenotype variability in β-thalassemia disorder. Primary modifier is the genetic defect or nature of mutation underlying β-globin gene itself [21]. To date, more than 200 of β-globin gene mutations have been reported (http://globin.cse.psu.edu). Most of the mutations are point mutation, small insertion or deletion of 1 or 2 bases along the gene. These diverse mutations are located in several regions of the gene such as promoter, exon, intron, intron-exon boundaries and polyadenylation site [27]. The different locations of the mutations give the different effect on the severity of the phenotype. For instance, mutations that occurred in promoter region influence the mRNA transcription process, resulting in mild phenotype [28].

The mutant alleles can either reduce the synthesis of β-globin chain (β+) or result in complete absence of β-globin chain (β0), thus no HbA production at all [29]. Majority of β0 allele are single base substitution and small insertion or deletion. Defects from the single base substitution in coding sequence of the β polypeptide will produced premature stop codon while, effects of small insertion and deletion lead to the alteration in mRNA reading frame. Similarly, in β+ allele the defect is typically also causes by single base substitution where the new splice site is created [27]. Lists of specific mutations or location for mild β+ and silent mutations were presented in Table 1. In Malaysian Malay population, IVS 1-5(G-C) and IVS 1-1 (G-T) are the most frequent β-globin gene mutation whereas in Chinese population the most common mutations are CD41/42 (-TCTT), IVS 2-654(C-D), CD71/72(+A), CD 17 (A-T) and -28 (A-G). All those mutations appeared to cause completely absence of β-globin chain, except for IVS 1-5(G-C) and -28 (A-G) which belongs to have β+ phenotype [30, 31]. Figure 2 showed some mutations with specific location in exonics and intronics regions [32].

The interaction of two β+ globin allel which are IVS 1-5(G-C) and -28 (A-G), caused mild phenotype. Same with a cohort study from Thailand, showing that patients with HbE/β thalassemia have mild clinical symptom. However, co-inheritance of β0 allele with HbE results in widely clinical phenotype, since βE-globin gene mutation leads to alternative splicing of βE-globin mRNA which plays a major role in clinical variability. Hence, severity of the disease can’t be predicted by the β-globin gene mutations alone since, few studies reported that HbE/β0-thalassemia and β0-thalassemia intermedia patients also appear to have mild
phenotype. All those patients showed the variability in HbF level and this factor may ameliorate the severity of patients with β-thalassemia [22,33].

Table 1. List of HBB gene mutations

<table>
<thead>
<tr>
<th>Mutation type or location</th>
<th>Mild β⁺</th>
<th>Silent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcriptional mutants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In the proximal CACC box</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-90 (C-T)</td>
<td>-101 (C-T)</td>
<td></td>
</tr>
<tr>
<td>-88 (C-T)</td>
<td>-92 (C-T)</td>
<td></td>
</tr>
<tr>
<td>-87 (C-A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-87 (C-G)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-87 (C-T)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-87 (C-A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-86 (C-T)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-86 (C-G)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TATA box</td>
<td>-31 (A-G)</td>
<td></td>
</tr>
<tr>
<td>-30 (T-A)</td>
<td>-29 (A-G)</td>
<td></td>
</tr>
<tr>
<td>5’ UTR</td>
<td>+22 (G-A)</td>
<td></td>
</tr>
<tr>
<td>+10 (−T)</td>
<td>+33 (C-G)</td>
<td></td>
</tr>
<tr>
<td>+1 (A-C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative splicing</td>
<td>CD 19 (A-C), Malay CD 27 (G-T), Hb Knossos</td>
<td></td>
</tr>
<tr>
<td>Consensus splicing</td>
<td>IVS 1-6 (T-C)</td>
<td></td>
</tr>
<tr>
<td>Intron</td>
<td>IVS 2-844 (C-G)</td>
<td></td>
</tr>
<tr>
<td>3’ UTR</td>
<td>+6 (C-G)</td>
<td></td>
</tr>
<tr>
<td>Poly-A site</td>
<td>AACAAA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AATGAA</td>
<td></td>
</tr>
<tr>
<td>Mild β°-frameshift</td>
<td>CD 6 (-AA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD 8 (−AA)</td>
<td></td>
</tr>
</tbody>
</table>
Non-functional mRNA

a. Nonsense mutants
   CD 43 (G-T)
   CD 35 (C-A)
   CD 15 (A-G)

b. Frame shift mutants
   CD 8/9 (+G)
   CD 15 (-T)

ii. RNA processing mutations
   CD 41/42 (-TTCT)
   a. Splice junction changes
      CD 27/28 (+C)
      CD 14/15 (+G)
      CD 71/72 (+T)
      CD 17 (A-T)
      CD 95 (+A)
      CD 41 (-C)
      CD 26 (G-T)
      IVS 1-1 (G-T)
      IVS 1-1 (G-A)

iii. Deletion
   619bp del
   3.5kb del
   12.5kb del
   45kb del
   105bp del

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Figure 2. Simplified representation of some HBB mutations
ii) Secondary modifier

As previously described, the pathophysiologic changes in patients with HbE/β-thalassemia are also determined by the excess number of α-globin chain production. In 1960s, in vitro technique proved that the pathophysiology of the disease is influenced by the globin chain imbalance and the excessive of α-globin chain synthesis [34]. Therefore, it was granted that the secondary modifying factors are controlled by the excess of α-globin chain assembly and degree of globin chain imbalance either through co-inheritance of α-globin gene or via genetic variants that regulated the expression of HbF production [35].

Inheritance of α-globin gene mutation with homozygous or heterozygous β-thalassemia reduced the severity of the disease due to less production of α-globin chain, subsequently improved the degree of α or non-α globin chain imbalance [36]. In contrast, individual inherited triplicated α-globin genes tend to have more severe clinical phenotype due to the increasing degree of α or non-α globin chain imbalance [4]. Meanwhile, the inherited of the two additional α-globin genes in triplicated α-globin genes in homozygous triplicated α-globin genes (aaa/aaa) or heterozygous quadruplicated α-globin genes (aaαa/aaα) was found in patients with β-thalassemia minor and was classified as thalassemia intermedia [37, 38].

At the stage of α-globin gene formation, the newly-generated α-globin attach to erythroid protein known as Alpha-Hemoglobin-Stabilizing Protein (AHSP) to stabilized itself, then AHSP fold them to form Hb protein. In the study by Kong et al., 2004, animal phenotype was studied and found that the loss of AHSP in knockout mice showed the higher precipitation of α and β-globin leading to the destruction erythropoiesis and worsened the severity of β-thalassemia [39]. According to Lim et al 2012, the expression of AHSP was significantly associated with MCV, HbF, α/β-globin, and excess α-globin production [40].

HbF is one of the indicators which play an important role in disease modifiers as it able to reimburse the deficiency of β-globin chains and HbA. The expression of HbF level is dominated by three different loci: HBG2:g.-158C>T on 11p15.4, BCL11A on 2p16.1 and HBS1L-MYB intergenic region on 6q23.3. It had been reported that, HbF expression in patients with sickle cell anaemia (SCA) was strongly regulated by SNP rs10128556 located at promoter region of HBG1 gene [41], followed by regulation from BCL11A which account for 7-12% in elevating HbF level [42].

Individuals with Hereditary Persistence of Fetal Hemoglobin (HPFH) have the potential to produced high quantity of HbF. This condition is due to the SNP rs11886868 in the BCL11A region that control the production of HbF. Similar effect by this SNP also was seen in patients with homozygotes β0-thalassemia, making individual with both diseases appeared to have mild phenotype [43]. In patients with thalassemia intermedia, SNP rs11886868 in BCL11A and SNP rs9389268 in intergenic region of HBS1L-MYB showed the lowest effect in expression of HbF level [42]. On
top of that, various SNPs are believed to involve in the regulation of disease severity, however only 3 aforementioned SNPs are reported to show high correlation with remarkable variable phenotype. Further investigation needs to be clarified to search the actual role in modifying the disease severity.

iii) Tertiary modifier

Tertiary modifiers are the genetic factors that are not associated with synthesis of globin chain, but may modify the progression of the disease in a different way [47]. For example, factors that influenced the severity of jaundice, iron loading and bone diseased state. Glucuronosyltransferase 1 (UGT1A1) is believed to affect the levels of bilirubin and responsible for gallstones development, hemolysis and ineffective erythropoiesis [48]. While Hemochromatosis gene (HFE) showed correlated with iron overload [49, 50] and for bone disease, the severity is regulated by 3 other different SNP which are Collagen (COL1A1), Vitamin D receptor (VDR) and transforming growth factor beta 1 (TGFB1) [51].

Conclusion

The phenotypic heterogeneity of HbE/β thalassemia poses difficulty in classifying and managing HbE/β thalassemia patients. The heterogeneity is largely contributed by genetic variations. Genetic constitution has been widely accepted to play as a key role in affecting thalassemia phenotype. Other than the primary mutation causing the disease, genetic variations such as SNPs that affect the HbF has been widely accepted as a major factor ameliorating thalassemia severity. Hence an understanding of how genetic factors contribute to the disease heterogeneity is very important. With the advances in molecular technologies, studies on association between genetic polymorphisms and thalassemia may have potential clinical application by providing markers of risk, diagnosis, prognosis and possibly therapeutic targets. Personalised medicine is the ultimate aim and we suggest that genetic testing to be included in providing structured patient care programme in the management of HbE/β thalasemia patients in the future.

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