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ORIGINAL ARTICLE

Genetic mutations of Transfusion Dependent Thalassaemia (TDT) in paediatric patients

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Abstract

Introduction: Thalassaemia comprises inherited disorders characterised by impaired synthesis of globin chains, leading to varying phenotypes from mild to severe anaemia, transfusion-dependent. The Malaysian Thalassaemia Registry reports that 57.69% of patients are classified as Transfusion-Dependant Thalassaemia (TDT). Despite diagnostic advancements, local data linking genetic mutations with clinical and laboratory features of TDT remain limited. This study aims to address this gap by evaluating paediatric TDT patients at Hospital Tuanku Azizah (HTA), Kuala Lumpur, Malaysia. *Materials and Methods*: A single-centre, cross-sectional study involving TDT patients at HTA from January to December 2022. *Results*: The cohort included 95 patients (52.6% male, 47.4% female), predominantly Malay (88.4%). Twenty-seven distinct genetic mutations were identified across alpha and beta globin genes, the most common being β^E. All patients had at least two mutations, with the most prevalent combination being HbE beta thalassaemia (45.3%), followed by beta thalassaemia major (32.6%), HbH disease (15.8%), and co-inheritance of alpha and beta thalassaemia (6.3%). Beta thalassaemia major shows the most severe phenotype: mean age at diagnosis is 12 months, mean haemoglobin at diagnosis of 5.2 g/dL, and mean age of regular transfusion is 16 months. Mean serum ferritin is highest in co-inheritance of alpha and beta thalassaemia (2616µg/L). The One-Way ANOVA test confirms the statistically significant differences in the median age of diagnosis (p=0.006), median age of starting regular transfusion (p=0.001), and median haemoglobin level at diagnosis (p=0.002) among different DNA combinations. *Conclusion*: This study demonstrates that genetic mutations significantly influence the phenotypes of TDT patients and are essential in guiding management and prognosis.

Keywords: Genetic mutation, Transfusion Dependent Thalassaemia

INTRODUCTION

Thalassaemia is a heterogeneous group of genetic disorders with defective synthesis of one or more globin chains involving both α and β globin chains.[1] The World Health Organization (WHO) has identified thalassaemia as a major public health concern and accurate information regarding its health burden in countries with a high prevalence of thalassaemia is needed.[3] The Malaysian Thalassaemia Registry reported in its Annual Report 2020 a total of 8,767 thalassaemia patients, of whom 4,901 are classified as transfusion-dependent thalassaemia (TDT) patients. The most common diagnosis in the registry is HbE beta thalassaemia (35.6%), followed by beta thalassaemia major (30.8%), Hb H disease (21.9%), and beta thalassaemia intermedia (9.1%).[2]

TDT patients require regular blood transfusions, typically every 3-4 weeks; however, regular blood transfusion is defined as receiving blood transfusion at least every 12 weeks.[2] Regular blood transfusion is crucial as it alleviates anaemia symptoms, suppresses

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ineffective erythropoiesis, reduces iron loading from increased gastrointestinal absorption, enhances growth and development, and improves survival rate.[4]

However, patients with post-transfusion iron overload are at risk of long-term complications such as hepatic dysfunction and failure, endocrinopathies, and cardiac dysfunction, with mortality rates of 9.3 per 1,000 TDT patients.[2] These patients will require iron chelation therapy to help decrease the iron burden and prevent long-term complications. Continuous iron status monitoring is feasible via serum ferritin level, although liver and cardiac MRI T2* are more sensitive and specific.

Thalassaemia is classically diagnosed using High-Performance Liquid chromatography (HPLC) and supplemented by a second method, either via Capillary Electrophoresis (CE) or gel electrophoresis. These techniques quantify HbA, HbA2, HbF, and variant haemoglobin. The diagnosis is confirmed by DNA tests, where genetic mutations are detected via Polymerase Chain Reaction (PCR).[4]

TDT patients have a combination of at least two genetic mutations, either in homozygous, compound heterozygous, or co-inherited ways. HbE beta thalassaemia is the most common form of beta thalassaemia syndrome in Southeast Asia, and its clinical presentation is heterogeneous.[8,9,10] The beta thalassaemia syndromes are more diverse because of the diversity of mutations in the beta globin genes.[7] Hb H disease includes the deletional type (3 alpha gene deletions), non-deletional type (Hb H Constant Spring or Hb H Adana), and Hb H phenotype (Hb Constant Spring coinheritance with Hb Adana).[5]

The purpose of this study is to explore the various combinations of genetic mutations and examine their correlation with patient's phenotypes, including clinical presentations, laboratory findings, and transfusion-related complications. Through this analysis, we aim to better characterise each group of thalassaemia, with the ultimate goal of enhancing the management and prognosis of both current and future patients.

MATERIALS AND METHODS

This single-centre, descriptive, cross-sectional study utilised secondary data from paediatric patients in Hospital Tuanku Azizah (HTA) and characterised these patients according to their genetic mutation. The criteria analysed include clinical phenotype (age at diagnosis and age of starting regular blood transfusion), laboratory parameters (haemoglobin level at diagnosis), and transfusion-related complications (serum ferritin level, serum ALT level, and whether patients were started on iron chelation therapy).

This study includes all TDT patients registered in Thalassaemia Daycare, Paediatric Department, HTA, with TDT patients defined as patients who require regular blood transfusions (less and equal to 12 weeks interval), patients aged less and equal to 18 years old, and patients with available data on genetic mutations. The exclusion criteria are non-Malaysian citizen patients.

Demographic data of all TDT patients in HTA from January 2022 to December 2022 were obtained from the master list at the Thalassaemia Daycare. The genetic mutations, sociodemographic data, laboratory data, and clinical information of these patients were extracted from the Hospital Information System (HIS) and the patients' clinic folders. The sociodemographic and clinical data include age at diagnosis, age of starting regular blood transfusion, either starting as a TDT patient or transitioning from Non-Transfusion Dependant Thalassaemia (NTDT) to TDT, and iron chelation status. The laboratory data includes haemoglobin level at diagnosis, the latest serum ferritin level, and the latest liver function test (ALT - Alanine aminotransferase) level. Individual data was recorded in a proforma and entered into an Excel sheet for analysis.

Descriptive analysis is presented using mean, standard deviation, frequency, and percentage. Comparison between groups was done using the One-Way ANOVA test and post hoc pairwise comparison with Bonferroni correction via the latest version of the SPSS application. The mean difference is significant at the p-value <0.05 level.

This study was approved by the UiTM Research Ethics Committee (Reference: 100 - FPR (PT.9/19) (FERC-07-23-01)) and the Medical Research and Ethics Committee (MREC Ref. No: NMRR ID-23-03338-7OQ). All patients' data were kept anonymous and stored securely to maintain confidentiality.

RESULTS

This study involved all TDT patients in HTA from January 2022 to December 2022. The initial total number of patients was 112, with 17 excluded, making a total of 95 patients included in this study. The 17 excluded cases were one non-Malaysian patient, four patients were still

NTDT till the point of data collection, and 12 patients were without DNA analysis results.

Genetic mutation

There are 27 genetic mutations found in this group of patients, and they can be divided into 6 groups, which are alpha gene deletion, alpha gene point mutation, alpha triplication, delta/beta gene deletion, beta gene deletion, and beta gene mutation (Table 1). For alpha gene deletion, they are comprised of Southeast Asian deletion (4.1%), 3.7 deletion (1.5%), and GB deletion (0.5%). For alpha gene mutation, they are comprised of Hb Constant Spring (6.7%), Hb Adana (3.6%), Hb Pakse (0.5%), and Hb Quong Sze (0.5%). Alpha triplication accounts for 1.0% of all mutations. There are two delta beta thalassaemia deletions which are Gγ $(A\gamma\delta\beta)^0$-thal, Siriraj ~118 Kb deletion (2.1%), and Hb Lepore Washington-Boston deletion (0.5%), both were later included in the beta thalassaemia major group. For beta gene deletion, they are comprised of 45 kb Filipino deletion (5.1%), 619 bp deletion (1.0%), and 3.5 kb deletion (0.5%). For beta gene mutation, they are comprised of Codon 26 [GAG>AAG] HbE (β^E) mutation (22.7%), IVS I-5 [G>C] (β^+) mutations (16.5%), Codons 41/42 (-TTCT) (β^0) mutations (11.3%), IVS I-1 [G>T] (β^0) mutation (5.7%), IVS II-654 [C>T] (β^+) mutation (4.1%), Codon 35 (β^0) mutation (2.6%), Cap+1 5'UTR [A>C] (β^+) mutations (2.6%), Codon 123/124/125 Hb Khon Kaen mutation

Table 1: Genetic mutation results

Category	Type of mutations	n (%)
Alpha deletion	Alpha SEA deletion	8 (4.1)
	Alpha 3.7 deletion	3 (1.5)
	Alpha GB deletion	1 (0.5)
Alpha point mutation	Termination codon mutation (TAA>CAA) Hb Constant Spring	13 (6.7)
	Codon 59 mutation (GGC>GAC) Hb Adana	7 (3.6)
	Codon 125 mutation (CTG>CCG) Hb Quong Sze	1 (0.5)
	Codon 142 mutation (TAA>TAT) Hb Pakse	1 (0.5)
Alpha triplication	Alpha 3.7 triplication	2 (1.0)
Delta beta deletion	$G\gamma(A\gamma\delta\beta)^0$-thal, Siriraj 118kb deletion	4 (2.1)
	Delta87/Beta IVS II-8 deletion, Hb Lepore-Washington-Boston	1 (0.5)
Beta deletion	Beta zero 45kb deletion (Filipino deletion)	10 (5.1)
	Beta zero 619bp deletion	2 (1.0)
	Beta zero 3.5kb deletion	1 (0.5)
Beta point mutation	Codon 26 (GAG>AAG) mutation, HbE	44 (22.7)
	IVS-I-5 (G>C) mutation	32 (16.5)
	Codon 41/42 (-TTCT) mutation	22 (11.3)
	IVS-I-1 (G>T) mutation	11 (5.7)
	IVS-II-654 (C>T) mutation	8 (4.1)
	Codon 35 (-C) mutation	5 (2.6)
	Cap+1 5'UTR (A>C) mutation	5 (2.6)
	Codon 123/124/125 (-8bp) mutation, Hb Khon Khaen	4 (2.1)
	IVS-I-2 (T>C) mutation	2 (1.0)
	Codon 17 (AAG>TAG) mutation	2 (1.0)
	PolyA (AATAAA>AATAGA) mutation	2 (1.0)
	Codon 8/9 (+G) mutation	1 (0.5)
	Codon 19 (A>G) mutation, Hb Malay	1 (0.5)
	-28 (A>G) mutation	1 (0.5)
TOTAL		194 (100)

Notes: *The total number of mutations identified n is 194 instead of 95 as every patient has at least 2 mutations, either in homozygous, compound heterozygous, or co-inherited ways.*

(2.1%), Codon 17 [AAG>TAG] (β^0) mutation (1.0%), IVS I-2 [T>C] (β^0) mutations (1.0%), Poly A [AATAAA>AATAGA] (β^+) mutation (1.0%), Codon 8/9 [+G](β^0) mutation (0.5%), Codon 19 Hb Malay (β^+) mutation (0.5%), and -28 (A>G) (β^+) mutation (0.5%).

For beta gene deletion, all of them were classified as β^0 based on the quantity of beta globin production. At the same time, the beta gene point mutation can be divided into β^0, β^+, and β variants. β^+ itself can be further subclassified into a spectrum ranging from β^+s (severe beta plus), which behaves like β^0, β^+ (behaves like beta trait), and β^{++} (very mild beta trait) (Table 2). From this study, beta gene point mutations that belong to the β^0 category are Codon 35 mutation, IVS I-1 [G>T] mutation, Codons 41/42 (-TTCT) mutations, Codon 17 [AAG>TAG] mutation, IVS I-2 [T>C] mutations, and Codon 8/9 [+G] mutation. IVS I-5 [G>C] mutations and IVS II-654 [C>T] mutations belong to the category of β^+s. For the β^+ category, the mutations are -28 (A>G) mutation and Codon 19 Hb Malay mutation. For the β^{++} category, the mutations are Poly A [AATAAA>AATAGA] mutation and Cap+1 5'UTR [A>C] mutation. For the beta variant category, they are Codon 26 [GAG>AAG] HbE (β^E) mutation and Codon 123/124/125 Hb Khon Kaen mutation.

All our TDT patients have a combination of at least 2 genetic mutations. The most common combination is HbE beta thalassaemia (45.3%), followed by beta thalassaemia major (32.6%), followed by non-deletional HbH disease (15.8%), and co-inheritance of alpha and beta thalassaemia (6.3%) (Table 3). HbE Beta thalassaemia can be further divided into (β^E/β^0) and (β^E/β^+). Beta thalassaemia major can also be further divided into (β^0/β^0), (β^0/β^+), and (β^+/β^+). Non-deletional HbH disease either comprises a combination of two gene deletions (alpha zero) with alpha mutation, or a combination of Hb Adana with alpha mutation, or a single gene deletion (alpha plus). Co-inheritance of alpha and beta thalassaemia comprises a combination of either beta thalassaemia major or HbE beta thalassaemia with alpha point mutation or alpha plus deletion. Only one patient from this group comprises a combination of β^0 and alpha mutation, which generally would not produce a TDT phenotype, and is supposed to ameliorate the effect. However, a concomitant Southeast Asian Ovalocytosis might be the reason behind this severe phenotype.

Patient characteristics

A total of 95 patients were included in our study, including 43 HbE beta thalassaemia patients (21 males and 22 females), 31 beta thalassaemia major patients (15 males and 16 females), 15 HbH disease patients (10 males and 5 females), and 6 co-inheritance alpha and beta thalassaemia

Table 2: The spectrum of beta thalassaemia mutations

Category	Type of mutations
β^0	β^0-thal 45kb deletion/ Filipino deletion
	β^0-thal 3.5kb deletion
	β^0-thal 619bp deletion
	IVS I-1 [G>T] (β^0) mutation
	IVS I-2 [T>C] (β^0) mutation
	Codon 8/9 [+G] (β^0) mutation
	Codon 17 [AAG>TAG] (β^0) mutation
	Codon 35 [-C] (β^0) mutation
	Codon 41/42 [-TTCT] (β^0) mutation
β^+s	IVS I-5 [G>C] (β^+) mutation
	IVS II-654 [C>T] (β^+) mutation
β^+	[-28 (A>G)] (β^+) mutation
	Codon 19 [A>G] (β^+) mutation, Hb Malay
β^{++}	Poly A [AATAAA>AATAGA] (β^+) mutation
	Cap+1 5'UTR [A>C] (β^+) mutation
βV	Codon 26 [GAG>AAG] HbE (β^E) mutation
	Codon 123/124/125 Hb Khon Kaen mutation

Notes: *β^0 – Beta zero, β^+s – Severe beta plus, β^+ – Beta plus, β^{++} – mild beta plus, βV – Beta variant.*

Table 3: DNA combinations

DNA combinations		n=95, (%)
HbE beta thalassaemia	(β^E/β^0)	21 (22.1)
	(β^E/β^+)	22 (23.2)
	Subtotal	**43 (45.3)**
Beta thalassaemia major	(β^0/β^0)	9 (9.5)
	(β^0/β^+)	14 (14.7)
	(β^+/β^+)	8 (8.4)
	Subtotal	**31 (32.6)**
HbH disease - non-deletional	($--^{SEA}/\alpha\alpha^{CS}$)	7 (7.4)
	($--^{SEA}/\alpha\alpha^{Pakse}$)	1 (1.1)
	($--^{GB}/\alpha\alpha^{CS}$)	1 (1.1)
	($\alpha\alpha^{CS}/\alpha\alpha^{Adana}$)	4 (4.2)
	($\alpha-^{3.7}/\alpha\alpha^{Adana}$)	2 (2.1)
	Subtotal	**15 (15.8)**
Co-inheritance of alpha and beta thalassaemia	($\alpha\alpha/\alpha\alpha^{CS}$) ($\beta/\beta^0$)	1 (1.1)
	($\alpha\alpha/\alpha\alpha^{Adana}$) ($\beta^E/\beta^+$s)	1 (1.1)
	($\alpha\alpha/\alpha-^{3.7}$) ($\beta^+/\beta^+$s)	1 (1.1)
	($\alpha\alpha/\alpha-^{anti3.7}$) ($\beta^0/\beta^0$)	2 (2.1)
	($\alpha\alpha/\alpha\alpha^{QZ}$) ($\beta^E/\beta^0$)	1 (1.1)
	Subtotal	**6 (6.3)**

patients (4 males and 2 females). As for racial distribution, Malay predominates in all groups. Specific distributions are as follows: HbE beta thalassaemia (41 Malay, 1 Chinese, and 1 Dusun). Beta thalassaemia major (25 Malay, 4 Chinese, and 2 Dusun). HbH disease (13 Malay, and 2 Chinese). Co-inheritance of alpha and beta thalassaemia (5 Malay and 1 Indian).

For age at diagnosis, the earliest mean age is seen in beta thalassaemia major at 12±8 months, followed by HbH disease at 18±15 months, co-inheritance of alpha and beta thalassaemia at 22±35 months, and lastly by HbE beta thalassaemia at 29±25 months. For haemoglobin level at diagnosis, the lowest mean is seen in beta thalassaemia major with a haemoglobin level of 5.2±1.3g/dL, followed by co-inheritance of alpha and beta thalassaemia with a haemoglobin level of 6.4±1.0g/dL, HbE beta thalassaemia with a haemoglobin level of 6.5±1.4g/dL, and HbH disease with a haemoglobin level of 6.9±2.1g/dL. For the age of starting regular blood transfusion, the earliest mean age is also seen in beta thalassaemia major at 16±18 months, followed by co-inheritance of alpha and beta thalassaemia at 34±57 months, HbE beta thalassaemia at 44±32 months, and lastly by HbH disease at 51±46 months. Next, they are further classified into either starting directly as TDT after diagnosis or starting as NTDT first and later becoming TDT. By percentage, 87.1% of beta thalassaemia major patients started directly as TDT after diagnosis, followed by co-inheritance of alpha and beta thalassaemia (66.7%), HbE beta thalassaemia (46.5%), and HbH disease (13.3%).

For transfusion-related complications, we describe the level of serum ferritin, the level of serum Alanine aminotransferase (ALT), and the percentage of patients started on iron chelation therapy. For serum ferritin, the highest mean is seen in co-inheritance of alpha and beta thalassaemia of 2616±1093 µg/L, followed by HbH disease of 2334±1700 µg/L, beta thalassaemia major of 2296±1435 µg/L, and HbE beta thalassaemia of 1743±1304 µg/L. A similar trend is observed in serum ALT, with the highest mean seen in co-inheritance of alpha and beta thalassaemia of 41.2±57.5, followed by HbH disease of 35.5±27.4, beta thalassaemia major of 31.8±41.0, and HbE beta thalassaemia of 23.7±25.5. For iron chelation therapy, the highest percentage is seen in HbH

disease (100%), followed by beta thalassaemia major (93.5%), co-inheritance of alpha and beta thalassaemia (83.3%), and lastly HbE beta thalassaemia (81.4%). The summary of the patient's characteristics is presented in Table 4 below.

Genotype and phenotype correlation

The One-Way ANOVA test and post hoc pairwise comparisons are utilised to compare different parameters among different DNA combination groups of our thalassaemia patients. This non-parametric analysis is appropriate given the non-normal distribution of data and small sample sizes per group. The One-Way ANOVA test confirms statistically significant differences in the median age of diagnosis (p-value 0.006), median age of starting regular transfusion (p-value 0.001), and median haemoglobin level at diagnosis (p-value 0.002) among the DNA combination groups (Table 5).

The post-hoc pairwise comparisons with Bonferroni correction refine this insight (Table 6). A significant difference in age of diagnosis is observed between beta thalassaemia major and HbE beta thalassaemia (p-value 0.003), supporting that beta thalassaemia major is diagnosed at a significantly earlier age. There are also significant differences in the age of starting regular transfusion observed between beta thalassaemia major and HbE beta thalassaemia (p-value 0.003), as well as between beta

Table 4: Patients' characteristics

Patients' characteristics	HbE Beta thalassaemia, n=43 (%)	Beta thalassaemia major, n=31 (%)	HbH disease - non deletional, n=15 (%)	Co-inheritance of alpha and beta thalassaemia, n=6 (%)
Gender				
Male	21 (48.8)	15 (48.4)	10 (66.7)	4 (66.7)
Female	22 (51.2)	16 (51.6)	5 (33.3)	2 (33.3)
Race				
Malay	41 (95.3)	25 (80.6)	13 (86.7)	5 (83.3)
Chinese	1 (2.3)	4 (12.9)	2 (13.3)	0 (0.0)
Indian	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Dusun	1 (2.3)	2 (6.5)	0 (0.0)	0 (0.0)
Age at diagnosis (months)	29±25	12±8	18±15	22±35
Haemoglobin at diagnosis (g/dL)	6.5±1.4	5.2±1.3	6.9±2.1	6.4±1.0
Age of starting regular transfusion (months)	44±32	16±18	51±46	34±57
Started regular transfusion				
as TDT	20 (46.5)	27 (87.1)	2 (13.3)	4 (66.7)
as NTDT*	23 (53.5)	4 (12.9)	13 (86.7)	2 (33.3)
Serum ferritin (µg/L)	1743±1304	2296±1435	2334±1700	2616±1093
Serum ALT (U/L)	23.7±25.5	31.8±41.0	35.5±27.4	41.2±57.5
Started on iron chelation therapy				
Yes	35 (81.4)	29 (93.5)	15 (100)	5 (83.3)
No	8 (18.6)	2 (6.5)	0 (0.0)	1 (16.7)

Notes: *Data shown as mean±SD or number (%). *Start regular transfusion as NTDT first, then later become TDT.*

Table 5: One-Way ANOVA test

Numerical parameters	Df	F	p-value
Age at diagnosis (months)	3	4.437	**0.006**
Age starting of regular transfusion	3	5.713	**0.001**
Hb at diagnosis	3	5.423	**0.002**
Serum ferritin	3	1.521	0.214
Serum ALT	3	0.869	0.460

Notes: *The mean difference is significant at the p-value <0.05 level.*

thalassaemia major and HbH disease (p-value 0.05) supporting that beta thalassaemia major started regular transfusion at a significantly earlier age. Apart from that, a significant difference in haemoglobin level at diagnosis is observed between beta thalassaemia major and HbE beta thalassaemia (p-value 0.007), as well as between beta thalassaemia major and HbH disease (p-value 0.007), supporting that beta thalassaemia major is presented with significantly lower haemoglobin level at diagnosis.

There are a few missing data points apart from data on genetic mutations. This is partly due to the inability to retrieve data as most of the older data were recorded manually, either in hospital old notes or in patients' clinic folders.

DISCUSSION

The study on TDT patients in HTA explores genetic mutations, clinical presentations, and laboratory parameters of this diverse patient population, particularly in Kuala Lumpur, Malaysia. This is crucial given the high prevalence of thalassaemia, particularly beta thalassaemia and HbE beta thalassaemia in Southeast Asia. Globally, there is considerable variability in the types of thalassaemia mutations, which directly influence the clinical severity and management of the patients. This variability underlines the importance of understanding the genetic basis of thalassaemia to tailor clinical management for individual patients, as well as help in perinatal diagnosis and genetic counselling of couples at risk.[16]

One of the major findings of this study is the identification of 27 common genetic mutations in the TDT patient population. These include both alpha and beta gene mutations, with the most frequent being β^E and IVS I-5 (G>C) mutations, particularly among the Malay population. Previous studies have shown that the β^E mutation is common in Southeast Asia and contributes significantly to the clinical presentation of thalassaemia in the region, especially in countries like Malaysia and Thailand.[10,11] In fact, the β^E/β^0 subtype of HbE beta thalassaemia combination, as observed in the current cohort, is one of the most prevalent forms of thalassaemia in Southeast Asia.[12]

The phenotypic presentation in these patients is closely tied to the genotype, as demonstrated in this study, where beta thalassaemia major presents more severely with lower haemoglobin levels at diagnosis and an earlier onset of

Table 6: Post-hoc pairwise comparison with Bonferroni correction

Dependent Variable			p-value
Age of diagnosis - Bonferroni	Beta thalassaemia major	HbE beta thalassaemia	0.003
Age starting of regular transfusion - Bonferroni	Beta thalassaemia major	HbE beta thalassaemia	0.003
	Beta thalassaemia major	HbH disease – non-deletional	0.005
Hb at diagnosis - Bonferroni	Beta thalassaemia major	HbE beta thalassaemia	0.007
	Beta thalassaemia major	HbH disease – non-deletional	0.007

Notes: *The mean difference is significant at the p-value <0.05 level*

diagnosis and transfusion dependency. This is consistent with other studies that show that beta thalassaemia major typically manifests early, and the need for blood transfusions begins in early childhood.[7] Moreover, it was found that the mean age of diagnosis varied across different genetic forms of TDT, with beta thalassaemia major diagnosed the earliest, followed by HbH disease and HbE beta thalassaemia. These differences are consistent with findings in other countries such as India and Egypt, where the early diagnosis of severe forms like beta thalassaemia major is typical.[13] This genetic complexity, reflected in clinical and laboratory parameters, can guide clinicians in diagnosing and tailoring therapeutic approaches for TDT patients.

Another significant aspect is the management of iron overload, which is a common complication in TDT patients who undergo regular blood transfusions. The study's finding that the majority of TDT patients had elevated serum ferritin levels indicates that iron chelation therapy is a critical part of managing these patients to prevent complications such as liver toxicity and cardiac damage.[14] The study notes that the highest mean ferritin levels were seen in patients with HbH disease, beta thalassaemia major, and co-inheritance of alpha and beta thalassaemia, which suggests a higher iron burden in patients with more complex genotypic combinations. This aligns with findings from other studies indicating that iron overload is often more severe in patients with mixed genetic mutations.[15] The study also found that some TDT patients had elevated serum ALT levels, which were consistent with a rise in serum ferritin levels. Elevated serum ALT in TDT patients is mostly directly related to liver iron overload, but it can also be caused by other transfusion-related complications like Transfusion Transmitted Infection.

We hope that this descriptive analysis of genetic mutations in TDT patients and their phenotypic correlation at HTA will serve as a foundation and reference for future perinatal genetic diagnoses and genetic counselling for at-risk couples. Additionally, it will aid in predicting the phenotype of patients or offspring based on the genetic combinations of the parents.

CONCLUSION

This study demonstrates that genetic mutations significantly influence clinical severity and transfusion-related complications in TDT patients. These findings underscore the importance of genetic analysis in guiding clinical management, particularly in optimising transfusion schedules and iron chelation therapy, while also highlighting the role of genetic counselling for at-risk families.

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