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Spectrum of Genetic Mutation in Beta Globin Gene in Various Types of Thalassaemia in Bangladesh

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ABSTRACT

Background: *Thalassaemia is a common congenital haemoglobin disorder which is resulted from reduced rate of production of the globin chain of haemoglobin. It is an inherited autosomal recessive disease caused mainly by mutations in the alpha and beta globin gene clusters on chromosome 16 and 11 respectively. Beta gene mutation is very commonly found in Bangladesh.* ***Objective:*** *The aim of the study was to identify the beta globin gene mutation in various types of thalassaemia in Bangladesh.* ***Method:*** *A total of 41 diagnosed thalassaemia patients and carriers presenting as Beta thalassaemia major, Hb E/Beta thalassaemia and Beta thalassaemia trait were included in this cross-sectional study conducted in Department of Haematology, Bangabandhu Sheikh Mujib Medical University Dhaka. The study duration was from May 2019 to July 2020 according to the selection criteria. There were 82 beta alleles present in 41 study subjects. Genetic analysis was done to identify beta gene mutation for each beta allele by Sanger sequencing.* ***Results:*** *In this observational study, we found 15 different types of Beta gene mutations from 82 beta alleles of 41 thalassaemia patients & carriers. Among them Intervening sequence (IVS) 1-5 (G>C) was the most common mutation.* ***Conclusion:*** *Genetic mutation is the confirmatory diagnosis for thalassaemia as well as one of the main factors for clinical expression. Mutation patterns also vary according to the geographical distribution. So, this study shows the frequently found beta gene mutation in Bangladesh which will guide to point out phenotypic expression. Finally, it will help in genetic counselling.*

Key words: *Beta thalassaemia major, Hb E/Beta thalassaemia, Beta thalassaemia trait, Beta gene, Allele, Genetic mutation, Phenotype, Gene sequencing, Sanger sequencing.*

Introduction

Thalassaemia is an inherited disorder characterized by reduced synthesis of one or more of the globin chains. Beta thalassaemia major, Hb E/Beta thalassaemia and beta thalassaemia trait are the common variants of thalassaemia in South East Asia.[1] Mutation is the permanent alteration of the nucleotide sequence of the genome which is the main pathophysiology of beta thalassaemia. The

differences in the splicing sites in Beta globin chain resulting from mutation are responsible for different genetic pattern and also for the phenotype.[2] As there is limited data regarding the genetic pattern and the most frequent mutation of Beta thalassaemia in Bangladesh, so this study was carried out to identify the different beta globin gene mutation of thalassaemia and to recognize the most frequent variant in our country.

Materials and Methods

This study was an out-patient-department-based, cross-sectional study, conducted in the Department of Haematology, Bangabandhu Sheikh Mujib Medical University, Dhaka. The study was approved by the local ethical committee and all patients gave their informed consent to take part in this investigation. The duration of the study was 15 months and included a total 41 thalassaemia patients & carriers attending the Haematology department. Though the duration of the study was sufficient to add more patients and carriers but as the mutational study was very much expensive, most of the patients and traits were unable to do the investigation for their financial constraint. We included patients and carriers meeting the inclusion criteria which was–1) Diagnosed case of Beta thalassaemia major[2], Hb E/Beta thalassaemia and Beta thalassaemia trait (diagnosis was confirmed by capillary Hb electrophoresis) who were interested and financially capable to do the mutational study, and also those who fulfilled the exclusion criteria which was-1) Any chronic disease that interfere Haemoglobin level like Systemic Lupus Erythematosus, Rheumatoid arthritis, Aplastic anaemia, pregnancy etc. Complete history and physical examination of all patients and carriers were undertaken. The information regarding Hb level, requirements of blood transfusion, splenomegaly, growth retardation etc. and all the documents necessary to confirm the diagnosis were collected. Then from each patient 5 ml blood was taken (15-20 days apart from blood transfusion) for assessment of Complete Blood Count (CBC) and gene sequencing. Mutational analysis was done from a recognized and reliable laboratory DNA Solution by Genetic analyser machine. Quality assurance measurements were recorded with a semi structured questionnaire. All data were checked after collection and entered into computer software. Statistical analysis was done using Statistical Packages for Social Science (SPSS-24).

Results

In this observational study, we tested 82 beta alleles of 41 thalassaemia patients & carriers. The diagnoses of the 41 patients are shown in Table I.

Table I: Types of Thalassaemia Patients That Was Included In This Study (n=41)

Types of thalassaemia	No of patients
Beta thalassaemia major	11 (26.82%)
Hb e/beta thalassaemia	28 (68.29%)
Beta thalassaemia trait	02 (04.87%)

Among the 82 alleles of 41 patients, we found 15 different types of Beta gene. The types and their frequency among the 82 alleles are shown in Figure 1.

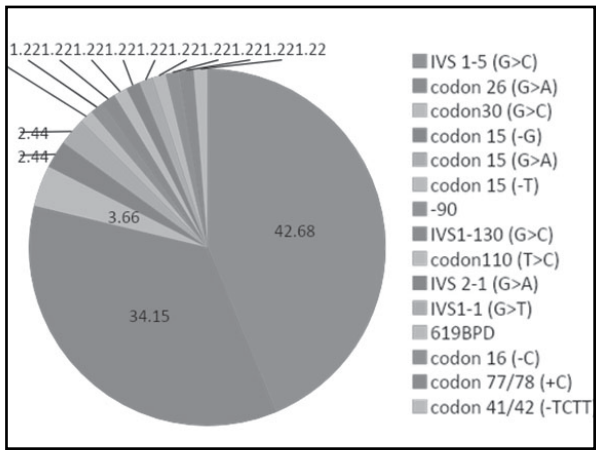

Figure 1: Pie chart showing the β gene mutations found in 82 allele (n = 82)

Discussion

This cross-sectional study was performed to identify the genetic mutation of Beta thalassaemia major, Hb E/Beta thalassaemia and Beta thalassaemia trait in Bangladesh. In our study we included 11 Beta thalassaemia major patients, 28 Hb E/Beta thalassaemia patients and 2 Beta thalassaemia traits for their genetic study who were already diagnosed by capillary Hb electrophoresis and could bear the cost of genetic studies. Total 41 patients and carriers have 82 allele, 2 of the alleles were normal from 2 carriers. Another 80 beta alleles showed different types of beta globin gene mutations. In our study, we found 15 different types of beta gene mutation. A study published on December, 2020 showed the researchers found 9 different types of beta gene mutation in Bangladesh.[3] Another study found a total of 8 different Beta thalassaemia mutations in Bangladesh.[4] A study conducted in Vietnam in the year of 2017 also identified 9 different beta thalassaemia mutations.5 In our study the most frequently identified beta gene mutation was IVS 1-5 (G>C). We found a total of 35 (42.68%) beta alleles of this mutation. The second most common mutation we found was codon 26 (G>A), we found 28 alleles (34.15%) of this mutation. The next common mutations were codon 30(G>C), total 3 alleles (3.66%) were found. We also found 2 alleles of Codon 15 (-G) (2.44%) and 2 alleles of Codon 15 (G>A) (2.44%). The other 10 mutations we found were -90 (C>T), IVS 1-130 (G>C), IVS 1-1 (G>T), codon 110 (T>C), IVS 2-1 (G>A), 619 base pair deletion, codon 16 (-C), codon 77/78 (+C), codon 41/42 (-TTCT), and codon 15 (-T). We found single allele (1.22%) of each of these mutations. A study published in 2020 showed codon 26 (G>A) that is C.79 G>A was the most frequently found beta gene mutation in Bangladesh.[3] Another study showed IVS 1-5 (G>C) was the most frequently found (55.5%) mutation in Bangladesh, codon 26 (G>A) is the second most occurred mutation (25%).4 A study held in Vietnam represented that codon 26 (G>A) was the mostly occurring mutation (29.2%) in Vietnam and the second most was codon 17 (A>T) (25.0%).5Another study performed in Yunnan province found codon 17 (A>T) as the mostly found (29.51%) beta gene mutation in their geographical area.[6] In Thailand ,the most common beta gene mutation was codon 41/42 (-TCTT) (48.6%).[7] In Bangladesh, an attempt to see the mutational pattern of beta thalassaemia trait revealed that IVS 1-5 (G>C) is the most frequently occurred (63.0%) beta gene mutation.[8] So, we can see the geographical similarity and variation as well and we can achieve a conception about the mostly found beta gene mutation in our country.

Conclusion

It can be concluded that 15 beta globin gene mutations were detected in our study. The most frequently found mutation was IVS 1-5 (G>C). So, this study showed the spectrum of beta gene mutation and its pattern in thalassaemia which will also guide us towards proper genetic counselling. The study could have been more accurate with a higher number of samples and samples from only one tertiary care hospital might not be representative to the whole country. Nationwide community-based study, or if it is not possible, at least a multicentre study is strongly recommended.

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