RESEARCH LETTER

Genetic Profile of Beta-Thalassemia and Sickle Cell Disease in Eastern Uttar Pradesh

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ABSTRACT

We report the prevalence of different mutations in the hemoglobin subunit beta (HBB) gene of 133 children with beta-thalassemia and 23 children with sickle cell disease (SCD), most of them belonging to the states of Uttar Pradesh (UP), Jharkhand, Chhattisgarh and Bihar. IVS 1-5 was the most common mutation (n = 42) followed by CD41/42 (n = 4) and CD8/9 (n = 4). Notably, some mutations like c.47G>A, c.51del and c.123delT not previously reported from UP were found.

Keywords: *Genetic counselling, Hemoglobinopathy, Mutation, Prenatal testing*

Published online: Sep 10, 2024; ***PII***: S097475591600693

India has an estimated 30-40 million carriers and 8,000 to 10,000 children born with thalassemiaevery year [1]. In contrast to a global frequency of 1.5%, the carrier rate for beta-thalassemia in India is 3.3% [2]. The clinical phenotype varies with the type of beta(â)globin mutation and number of â alleles affected. Approximately, 300 â-thalassemia mutations have been reported with a variable geographic distribution. These mutations cause either reduction in the number or a structural change in the â globin chain resulting in various structurally abnormal hemoglobins e.g., hemoglobin E (HbE), hemoglobin D (HbD) and hemoglobin S (HbS). However, the pattern of mutations in the hemoglobin subunit beta (HBB) gene from eastern part of India have been only sparsely reported. This study aimed to identify the mutations in thalassemiaat a tertiary care public hospital that caters to population from the states of Uttar Pradesh (UP), Bihar, Chhattisgarh and Jharkhand.

This was a retrospective cross-sectional observational study. Children with transfusion dependent thalassemia (TDT) and non-transfusion dependent thalassemia (NTDT) or sickle cell disease (SCD) registered in the thalassemia unit over a period of 10 years (January 2012 to December 2022)were enrolled in the study with their family members including both parents and siblings. Patient data were collected from hospital records regarding the age, type of hemoglobinopathy, severity of blood transfusion, age at first blood transfusion, religion, caste, and place of residence. Records were also analyzed regarding the mutation in the HBB gene of the index child as well as their family members.

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Received: May 24, 2024; Initial review: Jul 02, 2024;
Accept: Sep 6, 2024

The children with TDT (group I) were classified based on the age at first blood transfusion i.e. ≤ 2 years which corresponds to thalassemia major phenotype (group IA), and > 2 years which corresponds to thalassemia intermedia phenotype (group IB). Children with NTDT or SCD comprised group II. Data were analysed using SPSS software version 24. Student t test was used to compare continuous data and Chi square test was used to compare categorical data. P value <0.05 was considered significant.

A total of 156 children (age range 8months to 25years) with their respective family members (n = 377) were enrolled. The patients hailed from the states of Uttar Pradesh (n = 128), Bihar (n = 17), Jharkhand (n = 7), Madhya Pradesh (n = 3) and Rajasthan (n = 1). Among them, 116 children belonged to Hindu community; 42 belonged to the general caste; 38 to other backward castes (OBC), and 36 belonged to scheduled castes (SC) or scheduled tribes (ST) as defined by the Indian constitution. Forty patients belonged to the Muslim community.

The distribution of children in group I (n = 133), comprised of β-thalassemia (n = 98), Eβ-thalassemia (n =

Table I Distribution of Various Mutations inBased on Phenotype

Type of mutation	*Group IA (n = 83)*	*Group IB (n = 50)*	*Group II (n = 23)*
Homozygous mutations			
IVS1-5	35 (42.1)	7 (14)	-
CD8/9	3 (3.6)	1(2)	-
CD41/42	3 (3.6)	1(2)	-
c.20A>C	2 (2.4)	6 (12)	13 (56.5)
c.47G>A	2 (2.4)	1(2)	—
c.92G>C	1 (1.2)	3 (6)	-
c.123delT	1 (1.2)	-	-
c.51del	2 (2.4)	-	-
Compound heterozygous mutations			
IVS1-5/IVS1-1	3 (3.6)	-	-
IVS1-5/CD41/42	3 (3.6)	1 (2)	-
IVS1-5/c.51del	5 (6)	1 (2)	-
IVS1-5/CD8/9	1 (1.2)	-	-
IVS1-5/c.92G>C	8 (9.6)	1 (2)	-
IVS1-5/c.-50A>C	1 (1.2)	2 (4)	-
IVS1-5/c.364G>C	-	1 (2)	2 (8.7)
IVS1-5/CD15	1 (1.2)	-	-
IVS1-5/c.47G>A	3 (3.6)	2 (4)	-
IVS1-5/del HBB (exon1), introns 1 & 2, HBD (exon 3) and HBG1(exons 2 & 3)	1 (1.2)	-	-
IVS1-5/Del spanning HBB (exon1, intron 1&2 upstream), HbD (exan 3) and HbG1 (intron 2 & exon 3)	1 (1.2)	1 (2)	-
c.79G>A*/IVS1-5	2 (2.4)	12 (24)	2 (8.7)
c.79G>A/CD8/9	1 (1.2)	3 (6)	-
c.79G>A/CD41/42	-	2 (4)	-
c.79G>A/CD30	-	1 (2)	1 (4.3)
c.50A>C(cap +1)/c.20A>T	-	1 (2)	1 (4.3)
c.50A>C (cap +1)/c.92G>C	-	1 (2)	-
c.20A>C/IVS1-5	-	1 (2)	-
c.20A>C/CD41/42	1 (1.2)	-	-
c.20A>C/c.92 G>C	-	1 (2)	1 (4.3)
c.20A>T/c.364G>C	-	-	2 (8.7)
619del/IVS1/1	1 (1.2)	-	-
CD30/c.47G>A	1 (1.2)	-	-
c.46delT/c.47G>A	1 (1.2)	-	-
Del HBB(downstream region exon 1&3, introns 1 & 2,upstream region), HBBP (exon 1&3) & ORS1V1(exon1) c.126_129del	-	1 (2)	-
Hetero HbD iran /IVS1-5	-	-	1 (4.3)

Data expressed as n (%); Group IA TDT with onset d+ 2 years, IB TDT with onset > 2 years, II –NTDT or SCD
**c.79G>A represents HbE mutation*

20), Sβ-thalassemia (*n* = 3), sickle cell anemia (*n* = 8), δβ thalassemia (*n* = 2), HbDβ-thalassemia (*n* = 1) and hereditary persistence of fetal hemoglobin (HPFH) (*n* = 1). (**Table I**) Group II (*n* = 23) included children with sickle cell anemia (*n* = 13) HbEβ-thalassemia (*n* = 3), Sβ-thalassemia (*n* = 2), Hb SD (*n* = 2), HbDβ-thalassemia (*n* = 2) and HbD Iran-β thalassemia (*n* = 1). The distribution of different mutations in the study population is shown in **Table I**.

In the respective family members (*n* = 377), 14 types of mutations in the HBB gene were found, the most common being IVS1-5 (*n* = 176) followed by CD30 (*n* = 23), CD41/42 (*n* = 19), CD8/9 (*n* = 15), c.47G>A (*n* = 13) and c.51del (*n* = 9). Mutations causing structural Hb variation (HbE, HbS and HbD) reported were c.20A>C (*n* = 43), c.79G>A (*n* = 25) and c.364G>C (*n* = 3). Only 32

i.e. 8.4% family membershadno affection of disease.

In India, IVS1-5 followed by IVS1-1, CD41/42, CD8/9 and 619bp deletions are responsible to cause â-thalassemia in approximately 90% of cases as reported from Delhi, Gujarat, Punjab and Haryana [3,4]. Similar mutations have been reported from Uttar Pradesh in previous studies [5-7] i.e., IVS 1-5 followed by CD41/42 and CD 8/9 resulting in the most severe clinical phenotype, however, IVS1-1 and 619bp deletion were uncommon [7] as also seen is current study. Furthermore, three mutations that were previously unreported from UP were found; namely, c.51del mutation, c.47G>A and c.123delT.

The patients with HbS mutation in this study belonged to Sonbhadra (UP), Mirzapur (UP), Chhattisgarh or Jharkhand. The presence of sickle cell disease in Sonbhadra and Mirzapur has been described earlier [8]. The detection of HbS in patients from these districts can be associated to geographical contiguity with the tribal regions of Madhya Pradesh [8]. The study also found homozygous c.20A > C (n = 21), to have a variable clinical phenotype which is in accordance with previous studies [8]. The co-occurrence of c.20A > C and c.364G > C, however, resulted in NTDT. The presence of HbD in natives of eastern UP is rare and only reported recently with clinical phenotype varying from mild to severe anemia depending on mutation in other allele [9].

The co-occurrence of IVS1-5 and HbE (n = 16) predicted thalassemia intermedia phenotype in most and thalassemia major in a few. Previous studies have ascribed this variability to either presence of mild β-mutation, or co-inheritance of alpha-thalassemia [10]. However, the presence of alpha mutation was not analysed in this study.

The main limitation of this study is the small sample size limited to a geographical zone. We reiterate the importance of screening and genetic counselling in children with hemoglobinopathy. A multicentric population-based study in future could yield a more representative genomic data to help design a cost-effective targeted mutation panel.

Ethics clearance: Ref no Dean/2022/EC/3589, dated Oct 20, 2022.

Funding: None; *Competing interest*: None stated.

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