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Original Research Article

Molecular screening of β-thalassemia mutations among anaemic children and the influence of consanguinity: a hospital-based cross-sectional study from South India

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ABSTRACT

Background: β-thalassemia is the most common inherited haemoglobin in India, affecting 3-4% of the population. Mutations in the β-globin gene cause defective haemoglobin synthesis and chronic anaemia. Consanguineous marriage increases the risk of homozygosity for autosomal recessive disorders. Early molecular diagnosis is essential for differentiating inherited haemoglobinopathies from nutritional anaemia and for implementing preventive strategies. This study aimed to detect β-thalassemia mutations among anaemic children and evaluate the association between parental consanguinity and mutation positivity.
Methods: A hospital-based cross-sectional study was conducted between September 2021 and October 2022 among 40 children with severe anaemia, haemoglobin <8 g/dL. Demographic and clinical information, including parental consanguinity, was collected. Molecular screening for β-thalassemia mutations was performed using Real-Time PCR with the SNP Biotech Beta Thalassemia Kit on the 7500 AB systems. Statistical analyses included Chi-square test, odds ratio (OR), relative risk (RR), and 95% confidence intervals (CI).
Results: Of 40 children, 13 (32.5%) tested positive for β-thalassemia mutations. Mutation positivity was 33.3% among consanguineous families and 31.2% among non-consanguineous families. Statistical analysis showed no significant association between consanguinity and mutation positivity (χ^2=0.019, p=0.890). Odds ratio analysis indicated slightly higher odds among consanguineous families (OR=1.10; 95% CI: 0.28-4.27).
Conclusions: β-thalassemia mutations were identified in a substantial proportion of severely anaemic children. Although prevalence was marginally higher in consanguineous families, comparable rates in non-consanguineous families highlight the widespread carrier burden. Molecular screening is valuable for early diagnosis, family screening, genetic counselling, and prevention of severe β-thalassemia.

Keywords: β-thalassemia, Anaemia, Mutation screening, Consanguinity, Molecular diagnosis, Paediatric haematology

INTRODUCTION

β-thalassemia is a major inherited haemoglobin disorder worldwide, with significant clinical and public health impact due to defective β-globin synthesis and chronic anaemia.[1] The global epidemiology of haemoglobin disorders shows shifting patterns, with β-thalassemia remaining highly prevalent in many regions, particularly in Asia and the Mediterranean.[2] Globally, haemoglobin disorders remain a major public health challenge, with

β-thalassemia contributing substantially to the burden in high-prevalence regions such as South Asia.[3] β-thalassemia is an autosomal recessive hereditary blood disorder caused by defective synthesis of the β-globin chain of haemoglobin.[4] The disease results from mutations in the β-globin gene located on chromosome 11, leading to ineffective and chronic haemolytic anaemia.[5] Depending on the severity of β-globin chain deficiency, β-thalassemia is clinically categorised into major, intermediate, and minor forms.[6] Clinical manifestations range from asymptomatic carrier states to severe transfusion-dependent anaemia associated with growth retardation, skeletal deformities, hepatosplenomegaly, and iron overload complications.[7]

Globally, β-thalassemia is highly prevalent in the Mediterranean region, the Middle East, Southeast Asia, and the Indian subcontinent.[2,8] India contributes significantly to the global disease burden, with approximately 3-4% of the population carrying β-thalassemia mutations.[9] Nearly 10,000-12,000 children with β-thalassemia major are born annually in India.[10] Most Indian β-thalassemia cases are caused by a limited number of mutations, including IVS1-5 G>C, Codon 41/42-TCTT, Codon 8/9 +G, Codon 16-C, and 619 bp deletion.[11]

The disease imposes substantial clinical and economic burdens, particularly in developing countries where regular blood transfusion and iron chelation therapy may be limited.[12] Therefore, early detection of carriers and affected individuals is essential to reduce disease burden and improve quality of life.

Consanguinity is an important risk factor for autosomal recessive disorders because it increases the likelihood of homozygosity for defective genes.[13] In South India, especially in Tamil Nadu, consanguineous marriages remain culturally accepted in several communities.[14] However, due to the high baseline prevalence of β-thalassemia carriers in the Indian population, mutation-positive children may also occur frequently in non-consanguineous families.[15]

Children presenting with severe anaemia are often managed empirically as nutritional anaemia without evaluation for underlying inherited haemoglobin disorders. Molecular diagnostic techniques such as Real-Time PCR provide accurate and rapid identification of β-thalassemia mutations and facilitate differentiation from iron deficiency anaemia.[16] This study aimed to detect β-thalassemia mutations among anaemic children using molecular diagnostic techniques and to evaluate the influence of parental consanguinity on mutation positivity.

METHODS

A hospital based cross-sectional study was conducted between September 2021 and October 2022 at the Institute of Child Health and Hospital for Children, Egmore -. A total of 40 children presenting with severe anaemia haemoglobin <8 g/dL were enrolled after obtaining informed consent from their parents or guardians. Children with previously confirmed sickle cell disease, aplastic anaemia, or haematological malignancies were excluded from the study.

Detailed demographic and clinical information, including age, sex, family history of anaemia, history of blood transfusion, and parental consanguinity, as well as pedigree details, were collected using a structured questionnaire and clinical examination. Approximately 2 mL of venous blood was collected from each participant in EDTA tubes for laboratory investigations.

Complete blood count CBC, peripheral smear examination, and serum ferritin estimation were performed for all participants. Genomic DNA was extracted using the QIAGEN QIA amp DNA Blood Kit according to the manufacturer's protocol. Molecular screening for β-thalassemia mutations was performed using the SNP Biotech Beta Thalassemia Real-Time PCR Kit (AB 7500 Systems), which identifies common Indian β-thalassemia mutations, including IVS 1.1 G>A, IVS 2.1 G>A, IVS 1.110 G>A, IVS 2.745 C>G, IVS 1.5 G>C, IVS 1.6 T>C, -30 T>A, Codon 5-CT, Codon 29 C>T, Codon 39 C>T, and Codon 44-C 11,16.

Data were entered and analysed using statistical software. Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were presented as frequencies and percentages. The association between parental consanguinity and β-thalassemia mutation positivity was analysed using the chi-square test. Odds ratio OR, relative risk RR, risk difference, and 95% confidence interval CI were calculated to assess the strength of association. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 40 children presenting with severe anaemia haemoglobin <8 g/dL were included in the present study. The mean age of the participants was 9.8±3.6 years, indicating that most children belonged to the late childhood age group. The mean haemoglobin concentration among the study population was 6.9±0.7 g/dL, confirming the severe degree of anaemia among enrolled participants. Female children accounted for 55% (n=22) of the study population, whereas male children accounted for 45% (n=18), yielding a female-to-male ratio of 1.22:1 (Table 1).

Among the 40 children evaluated, 24 (60%) belonged to consanguineous families, while 16 (40%) were from non-consanguineous families. Molecular analysis using real-time PCR identified β-thalassemia mutations in 13 children, resulting in an overall mutation prevalence of 32.5%.

Table 1: Demographic details.

Variable	Category	Mean±SD/ N (%)
Age (years)	Mean ± SD	9.8±3.6
Sex	Male	18 (45)
	Female	22 (55)
Female:Male ratio	-	1.22:1
Haemoglobin (g/dL)	Mean±SD	6.9±0.7

Of the 13 mutation-positive children, 8 (61.5%) were born to consanguineous parents, whereas 5 (38.5%) belonged to non-consanguineous families. The mutation positivity rate among children from consanguineous marriages was 33.3%, compared to 31.2% among children from non-consanguineous families.

The overall distribution of β-thalassemia mutation positivity among severely anaemic children showed that 27 children (67.5%) were mutation negative, while 13 children (32.5%) were mutation positive. These findings indicate that inherited hemoglobinopathies contribute significantly to the burden of paediatric anaemia encountered in tertiary healthcare settings (Table 2 and 3).

Table 2: Frequency distribution of parental background and the mutation positivity rate.

Parental background	Total children, N (%)	Mutation positive, N (%)	Mutation negative, N (%)	Mutation positivity rate, %
Consanguineous	24 (60)	8 (20)	16 (40)	33.3
Non-consanguineous	16 (40)	5 (12.5)	11 (27.5)	31.2
Total	40 (100)	13 (32.5)	27 (67.5)	32.5

Table 3: Association between the parental background and mutation.

Parental marriage category	Mutation positive, N (%)	Mutation negative, N (%)	Odds ratio (OR)	95% CI	χ^2	df	P value
Consanguineous (n=24)	8 (33.3)	16 (66.7)	1.10	0.28-4.27	0.019	1	0.890
Non-consanguineous (n=16)	5 (31.2)	11 (68.8)					

Further statistical analysis was performed to determine the association between parental consanguinity and β-thalassemia mutation positivity. Chi-square analysis revealed no statistically significant association between parental consanguinity and mutation positivity χ^2=0.019, df=1, p=0.890. Odds ratio analysis demonstrated that children born to consanguineous parents had marginally increased odds of mutation positivity compared to those from non-consanguineous families OR=1.10; 95% CI: 0.28-4.27. However, the confidence interval crossed unity, indicating that the association was not statistically significant.

The risk difference between the two groups was 2.1%, indicating a minimal increase in mutation positivity among children born to consanguineous parents. Despite the absence of statistical significance, the slightly higher mutation positivity among consanguineous families supports the established role of consanguinity in increasing the likelihood of autosomal recessive disorders.

DISCUSSION

The present study demonstrated that nearly one-third 32.5% of children with severe anaemia carried β-thalassemia mutations, underscoring the importance of considering inherited haemoglobinopathies in the evaluation of paediatric anaemia.[17] The findings indicate that severe anaemia in children may not always be attributable to nutritional deficiencies alone and that molecular screening can play a crucial role in accurate diagnosis. Also, this indicates that anaemic children had an underlying inherited haemoglobin disorder rather than nutritional anaemia alone, highlighting the importance of molecular evaluation in paediatric anaemia screening.[11,15]

The prevalence observed in this study is consistent with previous Indian studies reporting a high burden of β-thalassemia carriers among high-risk and anaemic populations.[9,18] A systematic review and meta-analysis by Sumedha and Anita reported a pooled β-thalassemia carrier prevalence of approximately 3.7% in the Indian population, with significantly higher prevalence among individuals with anaemia and suspected hemoglobinopathies.[19]

In the present study, mutation positivity among children from consanguineous families (33.3%) was marginally higher than that among children from non-consanguineous families (31.2%). Although the association was not statistically significant, consanguinity remains an established risk factor for autosomal recessive disorders because it increases homozygosity for defective genes.[13,20] Although the prevalence was slightly higher among children born to consanguineous parents, mutation positivity was also notably high among non-consanguineous families, suggesting a substantial carrier burden within the general population.[9,19]

Interestingly, the comparable mutation prevalence observed in non-consanguineous families highlights the widespread distribution of β-thalassemia mutations within the Indian population. This finding suggests that screening strategies should not be limited only to high-risk consanguineous groups but should also include the broader community.[21]

The use of Real-Time PCR enabled rapid and reliable detection of common β-thalassemia mutations prevalent in the Indian population. Molecular diagnostic techniques are particularly valuable in differentiating inherited haemoglobin disorders from iron deficiency anaemia, thereby preventing misdiagnosis and inappropriate treatment.[16,22]

Early diagnosis of β-thalassemia mutations provides opportunities for genetic counselling, family screening, premarital counselling, and prenatal diagnosis.[23] These preventive approaches are essential for reducing the incidence of severe β-thalassemia and improving long-term clinical outcomes.[24,25]

The comparison of mutation positivity rates between consanguineous and non-consanguineous families demonstrated relatively similar prevalence between the two groups. This observation emphasises that β-thalassemia mutations are widely distributed within the community and are not exclusively restricted to consanguineous marriages. Therefore, population-wide carrier screening and genetic counselling programs may be more beneficial than restricting screening only to high-risk consanguineous families.[21,22]

Overall, the present findings support previous Indian epidemiological studies reporting a substantial prevalence of β-thalassemia carriers among high-risk and anaemic populations.[9,15,19] The study further highlights the importance of molecular screening among children presenting with severe anaemia to facilitate early diagnosis, appropriate management, family screening, genetic counselling, and the implementation of preventive strategies to reduce the burden of β-thalassemia.[16,23]

The study had certain limitations. The sample size was relatively small due to the cost factor, which may have reduced the statistical power to detect significant associations. The study was conducted at a single tertiary care centre, limiting the generalizability of the findings. In addition, only common Indian β-thalassemia mutations were screened, and rare mutations may have gone undetected.

CONCLUSION

β-thalassemia mutations were identified in a substantial proportion of severely anaemic children. Although mutation positivity was slightly higher among children born to consanguineous parents, a comparable prevalence was also observed among non-consanguineous families, indicating the widespread carrier burden within the general population.

The findings highlight the importance of incorporating molecular screening into the routine evaluation of paediatric anaemia. Early identification of β-thalassemia mutations facilitates appropriate clinical management, family screening, genetic counselling, and preventive strategies to reduce disease burden.

Recommendations

It is recommended to implement population-based carrier screening programs in high-prevalence regions, strengthen premarital and prenatal genetic counselling services, and introduce newborn screening for hemoglobinopathies, particularly among anaemic newborns. Public awareness regarding β-thalassemia and the risks associated with consanguinity should be enhanced. Additionally, molecular diagnostic facilities should be made affordable and accessible in government healthcare institutions, and large multicentric studies should be conducted to better understand regional mutation patterns and disease epidemiology.

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