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Compound Heterozygosity of β-Thalassemia Traits of HBB Gene in a Family: A Case Report

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ABSTRACT A report in a Gujarati family in Western India consisting of rare co-inheritance of β-thalassemia (β^0/β^+) in a proband, son was identified. The trio samples, parents and son, of extracted DNA from blood were subjected to gene sequence analysis, electrophoretic pattern of Hb levels and blood indices. The proband (son) showed altered levels of Hb types with higher levels of HbF (90%) and low values of mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) supporting β-thalassemia major. This case also possessed a compound heretozygotic condition c.92+5 G>C and c.47 G>A (β^0/β^+). Based on these markers, the proband was suggested blood transfusion by the clinician. Hence, it is suggested that this family must undergo prenatal diagnosis for the next pregnancy to avoid such risky condition.

INTRODUCTION

The Beta (β) thalassemia is a recessive autosomal genetic disorder related to chromosome 11. It leads to reduced and non-production of β-globin chain synthesis. The β-gene is known to have about 200 mutations worldwide (Weatherall and Clegg 2008; Shah et al. 2017a, b). Moreover, 60,000 children are affected annually in India (Higgs et al. 2011; Rao et al. 2015). It ranges from asymptomatic (carrier) to high severity state requiring blood transfusion depending upon genotype that is minor, intermediate and major thalassemia written as β^+/β, β^0/β; β^+/β^+/ $\beta^0\beta^+$; β^0/β^0 respectively. Genotype β^0/β^0 is severe and no β-globin synthesis takes place. β^+/β^0 is less severe than β^0/β^0 and more severe than β^+/β^+ genotype. Latter two types require blood transfusion depending upon haemo-phenotypic indices, like Hb levels and red cell indices (Weatherall and Clegg 2008; Dhawan et al. 2016). Co-inheritance of β-thalassemia trait with HbE and HbD may also lead to such condition of compound heterozygosity in addition to homozygosity (Shah et al. 2017 c,d; Agarwal et al. 2010;Vichinsky et al. 2005; Dhawan et al. 2016). Genetic testing of such affected carriers need to be done for the status of thalassemia in the family/society. Sometimes prenatal screening of the fetus from amniotic fluid (AF)/Chorionic villus sampling (CVS) and maternal blood are suggested. This knowledge improves understanding the effect of combined genotypes on phenotypic characters in populations. Moreover, therapeutic regimes may also be upgraded for better management of parents in future. Hence, the researchers report such rare case in a family of Gujarat analyzing blood markers and DNA sequence of trio samples (Father, Mother, Son) for co-inheritance of β^0/β^+ mutations in HBB gene.

METHODOLOGY

In this report, a family was affected by β-thalassemia traits. They had a son, having β-thalassemia major. Hence, it was suggested to check β-thalassemia mutations and haematological indices at Supratech Micropath Research Institute, Ahmedabad in these trio samples. DNA was extracted and used for Sanger DNA Sequencing technique after RBC markers and electrophoretic pattern of Hb levels were done.

RESULTS

Case Report

The results detected the father with β-thalassemia minor (c.47G>A; β^0mutation) and mother also with β-thalassemia minor (c.92+5 G>C;β^+ mutation). This condition is substantiated by partially altered Hb levels and red cell indices as

compared to son. But son consisted of both mutation that is,c. 47 G>A (â⁰) and c. 92+5 G>C (â⁺) from parents. Thus altered haematological indices, Hb levels and compound heterozygous state of the proband confirmed â-thalassemia major (â⁰/â⁺) as obtained from DNA sequence analysis. Further, the data of RBC indices with altered Hb levels (HbF-90%) indicated blood transfusion to the proband. It was also suggested by the clinician (Table 1, Fig. 1).

DISCUSSION

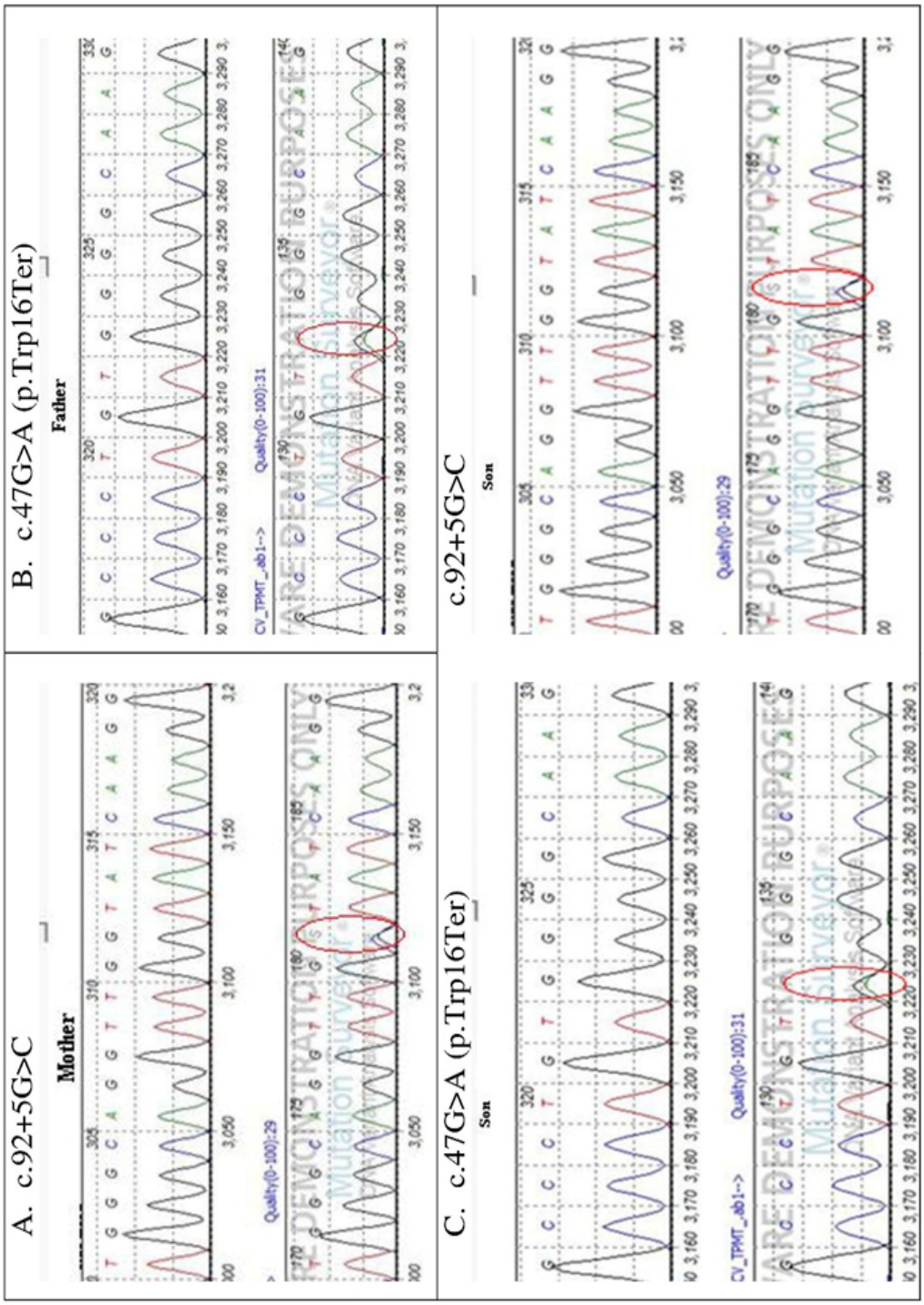
This family of Gujarat consisted of father, mother and son. Upon clinical advice, father and mother were declared â-thalassemia carriers with asymptomatic anemic conditions. But their son had compound heterozygous of two mutations that is, c. 47 G>A (â⁰) and c. 92+5 G>C (â⁺) passed from parents and had altered electrophoretic pattern of Hb levels leading to â-thalassemia major (â⁰/ â⁺) and clinicians suggested transfusions. It is supported by higher amount of HbF (90%) at age of 1 year and altered RBC parameters that is HbA, HbA_2 (4.90g/dL; 3.3%), MCH (19.2pg) and MCV (72.1fL) values (Table 1). Such double mutations are rarely reported in India. Agarwal et al. (2010) reported that one Indian Muslim boy of 3 years had compound heterozygosity who inherited each one mutation from father and mother (c.93-2 A>C and c.92+5 G>C of HBB gene) respectively with altered phenotypic markers. In Gujarat, Chaudhary et al. (2016) identified a family consisting of 3 probands. One of the 2 daughters had compound heterozygosity with c.92+5 G>A and c.92+5 G>C, the other had â-thalassemia minor, whereas the third proband (AF sample) was detected major (c.92+5 G>C+c.92 G>C) condition, passed from father and mother to support the researchers' results. From the researchers' data and that of Chaudhary et al. (2016) and Agarwal et al. (2010), it is evident that the mutation, that is, c. 92+5 G>C is inherited from mother to the respective probands, which is to be noted and needs to be stressed regarding its transmission from maternal side only in all these cases. Further, in the researchers' Gujarati family, the mutation transmitted from father was c. 47 G>A. But in report of Chaudhary et al. (2016) it was HBB: 92 G>C and that of Agarwal et al. (2010) was of HBB; c. 93-2 A>C, which differ. It thus seems that transmission of mutation from the male parent varies from female leading to sex difference. The pedigree chart depicts the autosomal recessive inheritance pattern of â-thalassemia traits in this family and the structural details of HBB gene mutations detected (c.47 G>A and c.92+5 G>C) in the researchers' study are at 47th base of exon 1 and 5th base of intron 1 in the gene (Figs. 2 and 3).

Compound heterozygosity of â⁺/â⁰ mutation of HBB gene leads to â-thalassemia major in the proband, transmitted from parents and is of autosomal recessive inheritance type and such case

Table 1: Haematological indices of a Gujarati family

Sample	*Haemoglobin indices*	*Units*	*Normal range*	*Mutations*	*Genotype*	*Inference/ Clinical report*
Mother (27)	HbA	89.5%	96.8-97.8%	c.92+5G>C		
	HbA2	5.90%	1.5 to 3.5 %			Thalassemia
	MCV	70.9fL	80 to 96		β^+/β	minor
	MCH	20.6pg	33 to 36			
Father (30)	HbA	96.00%	96.8-97.8%			
	HbA2	4.00%	1.5 to 3.5	c.47G>A (p.Trp		β–Thalassemia
	MCV	64.9fL	80 to 96 fL	16 Ter)	β^0/β	minor
	MCH	21.2pg	33 to 36 pg			
Proband/Son (1)	HbA	6.70	96.8-97.8%			
	HbA2	3.30%	1.5 to 3.5	c.47G>A (p.Trp	β^0/β^+	β–Thalassemia
	HbF	90.00%	<2% (Age Dependent)	16 Ter) and c.92+5G>C		major
	MCV	72.1fL	80 to 96 fL			
	MCH	19.2pg	33 to 36 pg			

Figures in parenthesis indicate age in years. HbA= Hemoglobin A, HbF- Fetal Hb, MCV= Mean Corpuscular Volume, MCH= Mean Corpuscular Hemoglobin.



A. Mother with c.92+5G>CB. Father with c. 47G>A (p.Trp 16Ter). C. Proband (Son) had c.47G>A (p.Trp6Ter) and c.92+5G>C

Fig. 1. DNA sequence analysis of a Gujarati family

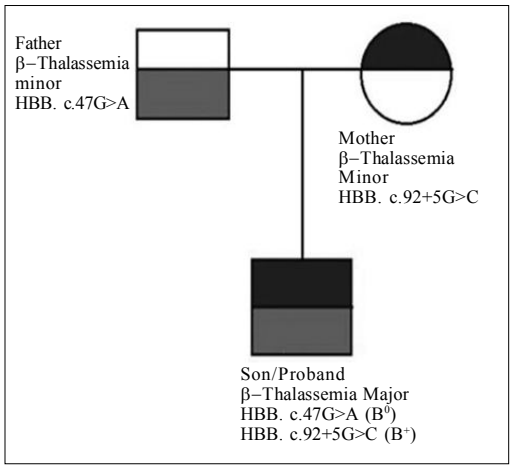


Fig. 2. Pedigree chart depicting autosomal recessive inheritance pattern of gene mutation transmission in a family

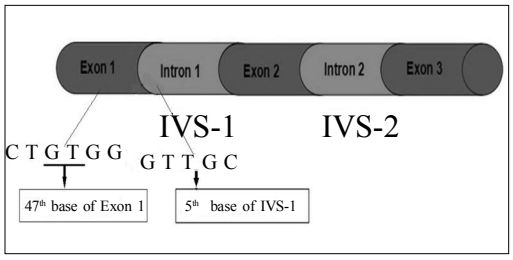


Fig. 3. Structure of HBB gene with mutation location

is rare as only two reports are available from Western India (Gujarat). The mutation in HBB gene, c. 92+5 G>C is common, inherited from mother only and HBB gene c.47 G>A transmitted is from father variable from case to case. Hence, it is strongly recommended that genetic screening is necessary to avoid such conditions in affected families through latest genetic diagnostic technologies and discourage marriages taking place between such carriers.

CONCLUSION

A rare co-inheritance of β-thalassemia (β^0/β^+) proband in a family of Gujarat is reported which requires blood transfusion. Such family traits need counseling and genetic testing in future to avoid such cases.

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