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A homozygous *KLF1* gene mutation presenting as mild Thalassemia Intermedia unraveled by targeted Next Generation Sequencing

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Abstract

The krupple-like factor 1 (KLF1) is a crucial transcription factor that is responsible for the proper maturation of the erythroid cells. Recent studies have demonstrated that mutations in *KLF1* gene may lead to increased fetal hemoglobin (HbF) and reduced or borderline hemoglobin A2 (HbA2) levels. Increased HbF levels and concomitant α-thalassemia are two main modifiers that can ameliorate the clinical and hematological severity of β-thalassemia. Mutations in *KLF1* have been found in association with β thalassemia. DNA was extracted with QIAmp DNA Blood kit and quantified spectrophotometrically. Gap PCR was used to screen common HPFH deletions and Sanger's sequencing was done to screen β-globin (*HBB*) mutations. Libraries were prepared using TruSight One sequencing panel and sequenced on MiSeq Sequencing System. MiSeq Reporter and Variant Studio were used for data analysis. A 56 years male presented with splenomegaly and unconjugated hyperbilirubinemia with normal hematological indices. Hemoglobin high performance liquid chromatography revealed 72.3% HbF, 0.5% HbA_2 and 25.2% HbA_0. Patient was found to be clinically consistent with mild TI. No mutation/s in *HBB* was found by Sangers sequencing. Hereditary Persistence of Fetal Hemoglobin (HPFH) deletions [HPFH1, HPFH2, HPFH3, Chinese $^{G}\gamma$ deletion, Asian-Indian inversion-deletion] were also found to be negative. Targeted resequencing revealed a novel homozygous probably causative mutation in *KLF1* [c. 943C>T (p.Arg301Cys)]. This mutation was found to be probably damaging via PolyPhen2 and SIFT. The patient's son showed 5% HbF with heterozygous mutation. This is the first report from India where a homozygous mutation in *KLF1* gene is implicated with high HbF in a patient with TI. Thus, mutations which affect the activity of *KLF1* gene may lead to high level of fetal hemoglobin in patients presenting as TI with no *HBB* mutations.

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