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Response of patients with transfusion-dependent β-thalassemia (TDT) to betibeglogene autotemcel (beti-cel; LentiGlobin for β-thalassemia) gene therapy based on *HBB* genotype and disease genetic modifiers

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Disclosure

Place video here

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Consultancy: Editas, AllCells, Inc, Veevo Biomedicine

Beti-cel gene therapy response by *HBB* genotype

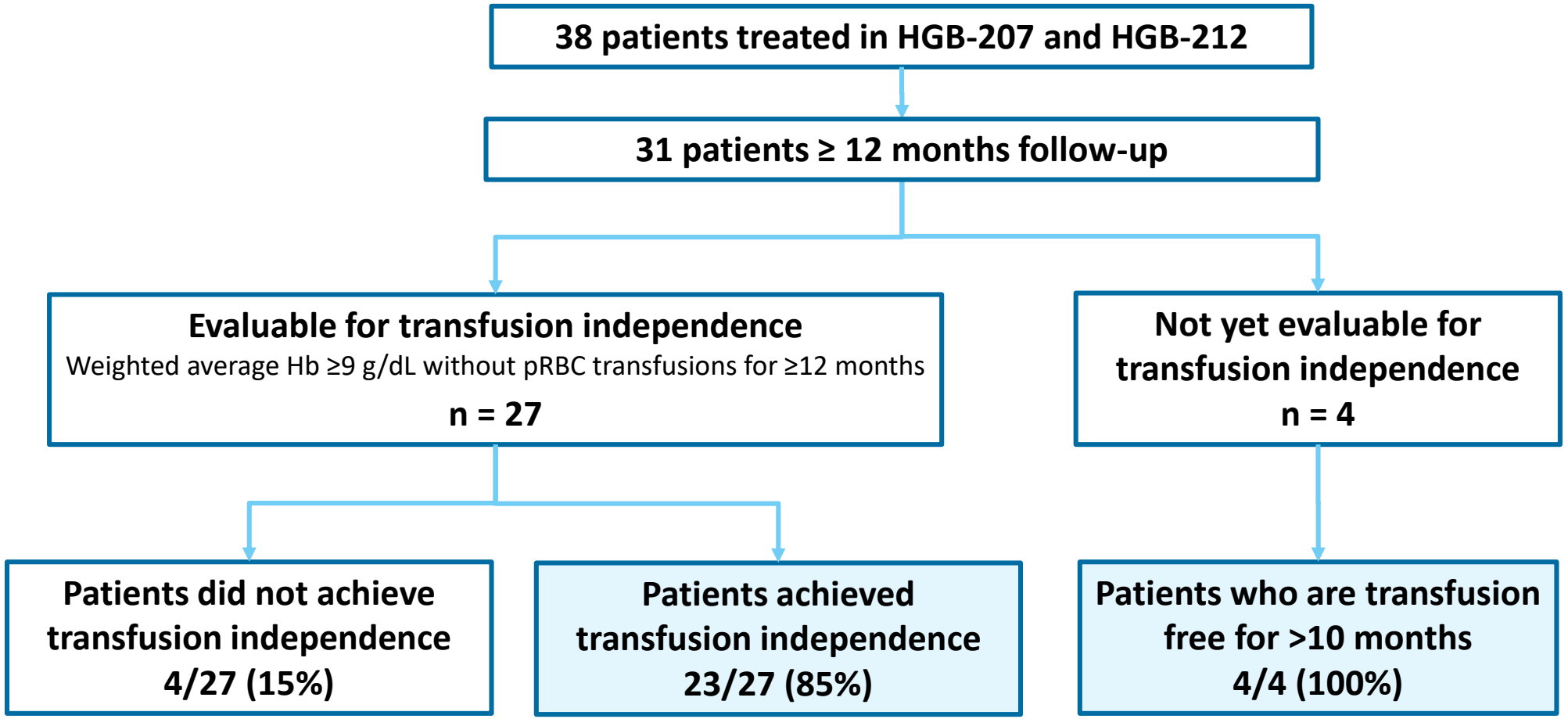
- We evaluated *HBB* genotype and disease genetic modifiers in patients with TDT to assess impact on clinical response following treatment with beti-cel in two ongoing Phase 3 studies, HGB-207 (NCT02906202) and HGB-212 (NCT03207009)

Region of interest	β-thalassemia implications	Methods
• *HBA* deletions and triplications	α-globin gene triplications may worsen anemia; α-globin gene deletions may attenuate anemia[1,2]	Gap-polymerase chain reaction (PCR)
• Promoters of *HBG1* and *HBG2* including rs7482144 (XmnI site) • *KLF1* including c.115 A>C, c.892 G>C	Increases HbF, may attenuate anemia[3-4]	Nucleotide sequencing
HbF QTL SNPs • *BCL11A* rs1427407, rs10189857 • HMIP rs66650371	Increases HbF, may attenuate anemia[5-6]	Multiplex amplification refractory mutation system (ARMS)

1. Ma et al. Int J Mol Med. 2001. 2. Farashi et al. Hemoglobin. 2015. 3. Wang, Thein. Nature Genetics 2018. 4. Perkins, et al. Blood. 2016. 5. Sherva et al. MC Med Genet. 2010. 6. Al-Allawi, et al. Int J Hematol. 2019.

Hb, hemoglobin; TDT, transfusion-dependent β-thalassemia; TI, transfusion independence

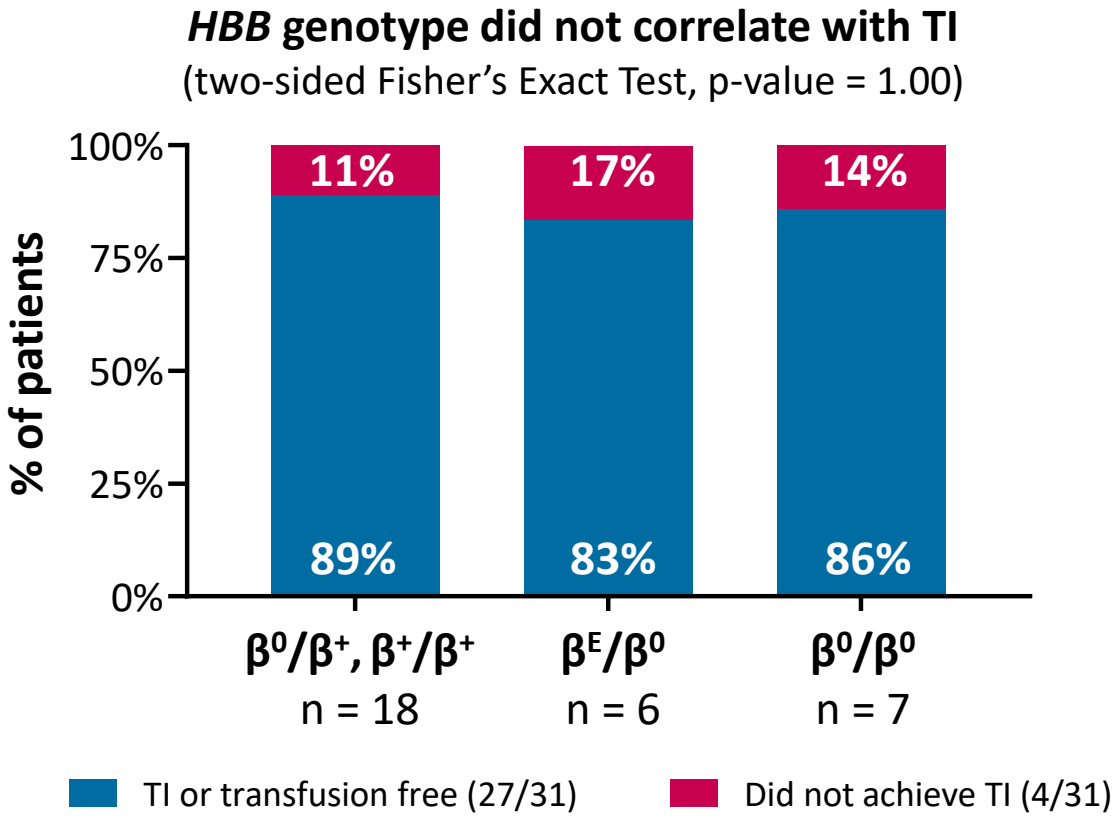
87% (27/31) of patients with ≥ 12 months follow-up are transfusion independent or transfusion free

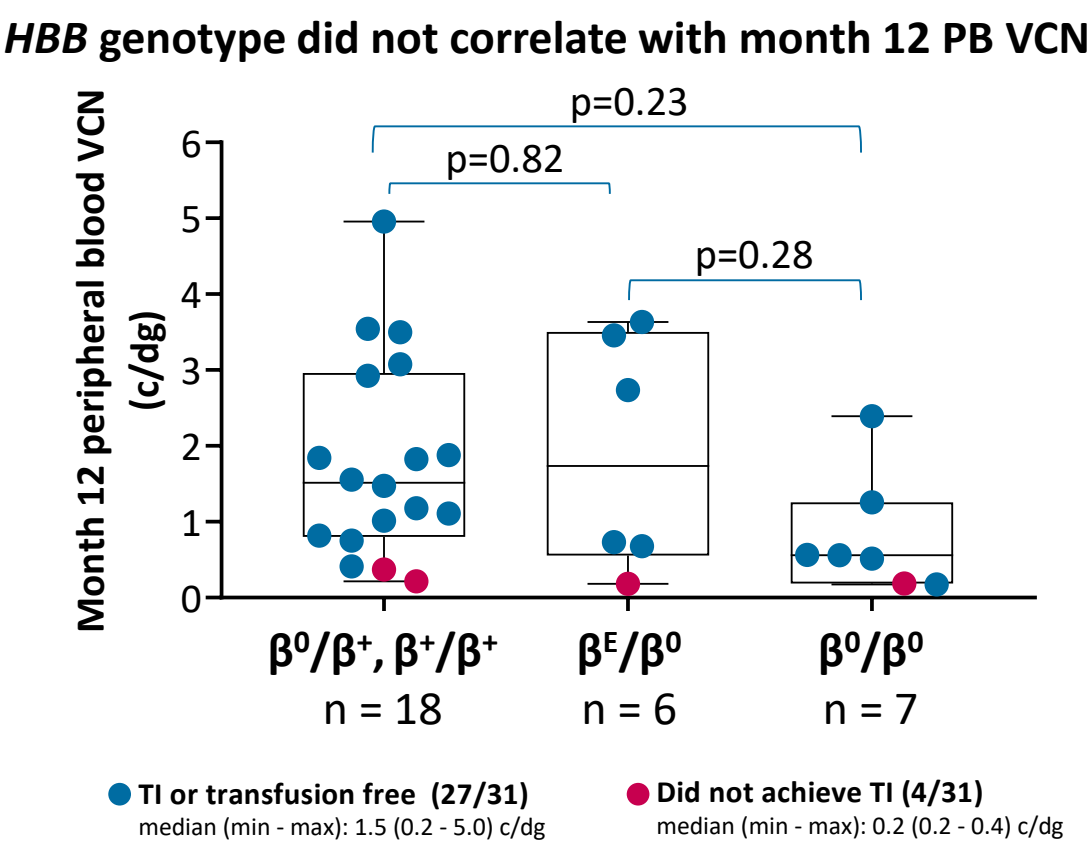


Transfusion independent (TI) patients were those who had a weighted average Hb ≥9 g/dL without pRBC transfusions for ≥12 month; TI period begins when patients have Hb ≥9 g/dL with no transfusions in the preceding 60 days. Patients not yet evaluable for TI but had ≥12 months and stopped transfusions for >10 months were considered transfusion free and grouped with transfusion independent patients for the purposes of these analyses.

pRBC, packed red blood cells

HBB genotype did not correlate with transfusion independence or peripheral blood VCN





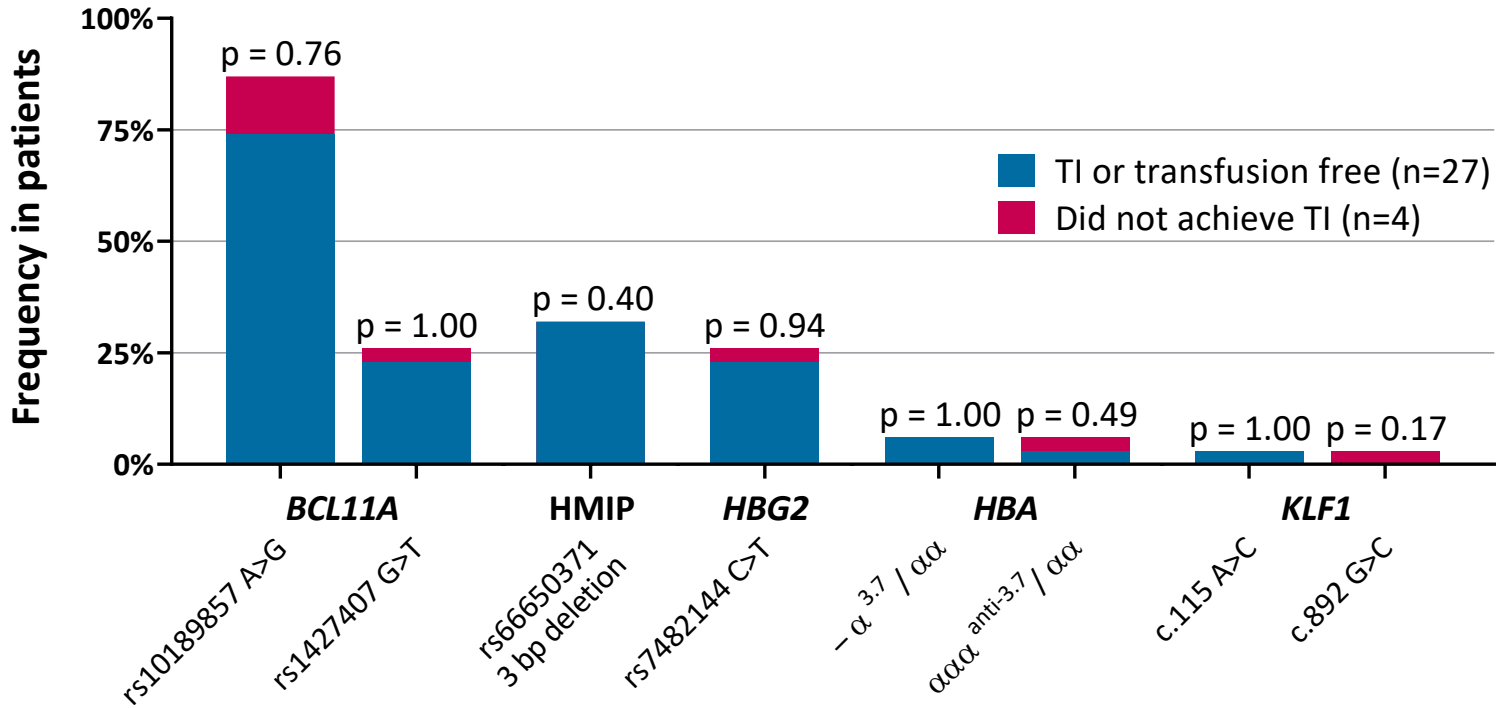
- Data do not suggest a difference in safety based on genotype

- Transfusion independent (TI) patients were those who had a weighted average Hb ≥9 g/dL without pRBC transfusions for ≥12 month
- Patients not yet evaluable for TI but had ≥12 months and stopped transfusions for >10 months were considered transfusion free
- Patients who did not achieve TI were those who were evaluable for transfusion independence, but did not meet the necessary criterion

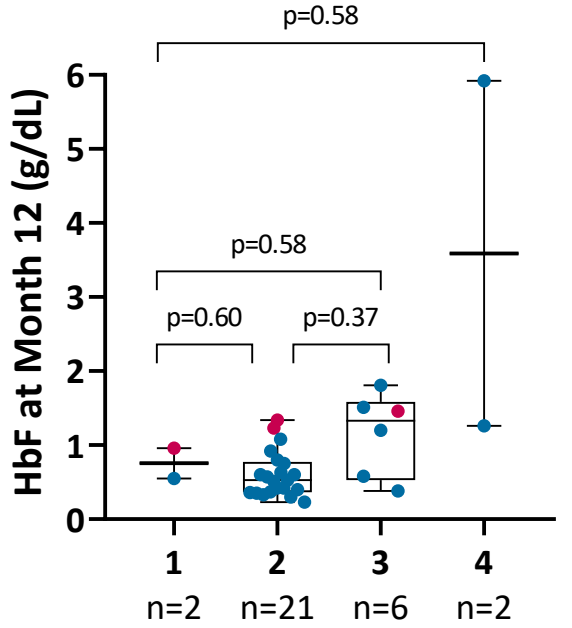
c/dg, copies per diploid genome; PB VCN, peripheral blood vector copy number; pRBC, packed red blood cell; Adjusted p-value (FDR).

No correlation between individual SNPs and transfusion independence

Frequency of SNPs and mutations by transfusion status (N=31)



HbF levels by incidence of minor alleles in HbF QTL sentinel SNPs*



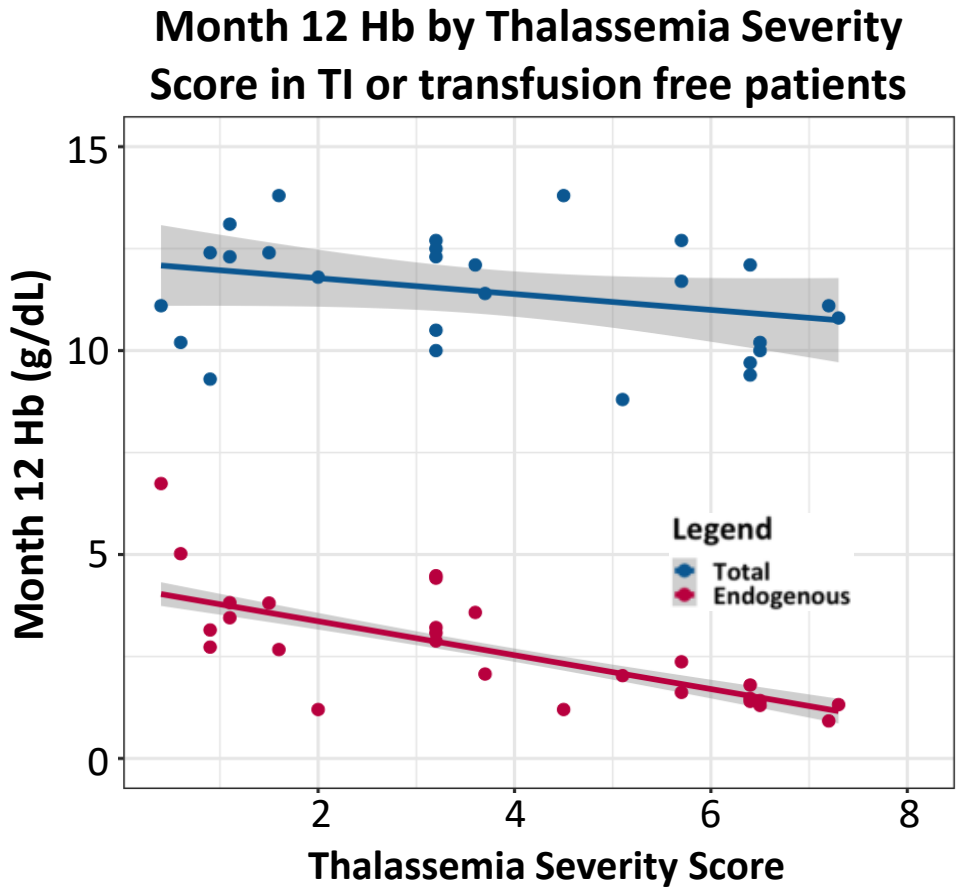
- All patients were heterozygous or homozygous for mutations or SNPs that may modulate disease severity
  - 16/31 patients were homozygous for ≥1 of these mutations or SNPs
  - Tests of association of SNPs/mutations with TI/transfusion free status vs not TI were not significant; no p-value < 0.17 (chi-squared test)
- Evaluation of number of minor alleles in HbF QTL sentinel SNPs did not significantly impact HbF production; no p-value < 0.37
  - The patient with the highest HbF levels was homozygous for T/T at rs7482144 (*HBG2* Xmn1 site) and G/G at rs10189857 (*BCL11A*), and heterozygous for single α-globin gene deletion

*4 HbF quantitative trait loci (QTL) sentinel SNPs: *BCL11A* rs10189857, rs1427407; HMIP rs66650371; *HGB2* rs7482144. SNP/mutation figure chi-squared tests; HbF SNPs figure, adjusted p-value (FDR)

SNP, single nucleotide polymorphism; TI, transfusion independent

At month 12, TSS correlated with endogenous Hb but not with total Hb in TI or transfusion-free patients indicating response across TDT severity

- Thalassemia Severity Score (TSS) considers gender, *HBB, HBA* genotypes, and 4 SNPs in HbF QTL to predict clinical severity[1]
  - Based on analyses in 890 patients with β-thalassemia, using age at 1st transfusion as a surrogate of disease severity
  - Scored from 0 (least severe) to 10 (most severe)
- Median TSS in transfusion independent/free patients was 3.2 (min – max: 0.4 – 7.3) (n=27)
- TSS correlated strongly with month 12 endogenous Hb without pRBC transfusion support*
  - Robust correlation coefficient = –0.76; $p < 0.0001$
- TSS did not correlate with month 12 total Hb levels without pRBC transfusion support
  - Robust correlation coefficient = –0.32; $p = 0.10$



1. Danjou et al, Haematologica, 2015. *Endogenous Hb without packed red blood cell (pRBC) transfusion support is defined as HbA + HbA_2 + HbF + HbE without pRBC transfusions for 60 days

Hb, hemoglobin; SNP, single nucleotide polymorphism; QTL, quantitative trait locus

Summary

- After treatment with beti-cel gene therapy, 87% (27/31) of patients with ≥12 months follow-up in ongoing Phase 3 studies have stopped transfusions
- *HBB* genotype did not correlate with TI or transfusion free status
- Genetic characterization revealed diverse SNP/mutation profile that may influence disease severity but not TI outcome
  - No individual loci strongly associate with TI status
  - However, statistical power to detect a small effect was limited (non-TI, n = 4)
- Despite genetic heterogeneity, beti-cel enabled transfusion independence across *HBB* genotypes, TSS, and disease genetic modifiers including *HBA* and HbF QTL SNP genotypes

Thank you to the study participants and their families

QTL, quantitative trait locus; SNP, single nucleotide polymorphism; TI, transfusion independence; TSS, Thalassemia Severity Score.