following the manufacturer's instructions. **Results:** Our findings reveal that the variant genotypes of rs4671393, rs1427407, rs11886868, and rs9399137 were significantly associated with higher HbF levels. Linear regression models revealed that all minor alleles of the four polymorphisms were associated with increased HbF levels. Among the BCL11A variants, rs1427407 exhibited the strongest effect ($p < 0.001$) and explained 7.7% of the variance in HbF levels. However, the HBS1L-MYB variant rs9399137 demonstrated the most substantial effect ($p < 0.001$), accounting for 14.9% of HbF variance, indicating a stronger regulatory influence on HbF levels. A genetic risk score (GRS) was constructed by summing the number of risk alleles (low HbF levels) present across the four SNPs evaluated. A multiple linear regression model including age and gender as covariates was statistically significant ($p < 0.001$), explaining approximately 11.5% of the variance in HbF levels. The GRS was significantly associated with HbF levels, indicating that a higher GRS was associated with lower HbF levels. These findings suggest that the cumulative effect of risk variants contributes to reduced HbF levels and may increase the risk of clinical complications. **Discussion and conclusion:** BCL11A and HBS1L-MYB polymorphisms are well-established modulators of HbF levels, and the variants analyzed here are located in regulatory regions, which likely explain their influence on HbF expression. The GRS may serve as a valuable tool for risk stratification, potentially guiding early interventions for patients lacking HbF-boosting alleles. Overall, this study underscores the clinical significance of HbF-related genetic variants for personalized management in SCA.

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A NOVEL BASE-EDITING STRATEGY FOR THERAPEUTIC FETAL HEMOGLOBIN REACTIVATION IN SICKLE CELL DISEASE

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Introduction: Sickle cell disease (SCD) is a common monogenic disorder caused by a point mutation in the HBB gene, leading to the formation of sickle hemoglobin (HbS). Under low oxygen, HbS polymerizes, distorting red blood cells and triggering hemolysis, inflammation, and vaso-occlusion. Although allogeneic hematopoietic stem cell transplantation offers a cure, its use is limited by donor compatibility and transplant risks. Gene editing strategies that reactivate fetal hemoglobin (HbF) have emerged as promising alternatives. Among them, adenine base editors (ABEs) enable precise A-to-G conversions without inducing double-stranded breaks, lowering genotoxic risks. **Objectives:** This project focuses on developing an ex vivo ABE-based approach to upregulate HbF in human hematopoietic stem and progenitor cells (HSPCs), mimicking naturally occurring non-deletional hereditary persistence of fetal hemoglobin (HPFH). **Material and methods:** Target sites include the HBG1/2 promoter region (−113 to −198) and the +55 and +58 erythroid enhancers of BCL11A. **Results:** We have identified HBG-123 and HBG-175 as top candidates, based on editing efficiency and HbF induction (via NGS and F-cell analysis) in $CD34^+$ HSPCs. Editing efficiencies averaged 66.8% and 49.4%, resulting in HbF levels of 23.3% and 41.2%, respectively, with maintained erythroid differentiation and minimal indel formation (<1%). Further optimizations—adjusting gRNA:ABE ratios, electroporation timing, and using engineered Cas9/TadA with custom UTRs—boosted editing efficiency and HbF expression without impairing HSPC clonogenicity. Functional evaluation in single- cell colony assays with stromal co-culture, which enhances erythroid output and hemoglobinization compared to methylcellulose, enabled parallel assessment of editing and HbF expression by HPLC. Results showed strong correlation between A-to-G conversion and HbF for HBG-175 ($r = 0.9$), while HBG-123 clones, though highly edited (~90%), showed more variability and lower HbF. **Discussion and conclusion:** Together, these findings establish a scalable and efficient base editing platform for HbF induction in HSPCs. We are currently performing in vivo validation and already started the development of a GMP-compliant production process. Implementing this technology in Brazil, where SCD is highly prevalent, will support local capacity-building and broaden access to advanced gene-editing therapies.

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ACIDENTE VASCULAR CEREBRAL ISQUÊMICO E DÉFICIT COGNITIVO NA DOENÇA FALCIFORME

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Introdução: O declínio cognitivo (DC) tem sido relatado em pacientes com doença falciforme (DF) em crianças e adultos. A elevada frequência de manifestações cerebrovasculares na DF é considerada, em parte, como causa do DC. No entanto, ainda existe pouca informação sobre DC em adultos, embora ele comprometa as funções diárias e a aderência ao tratamento. **Objetivos:** Avaliar adultos com DF e antecedente de acidente vascular cerebral isquêmico (AVC) e sua possível correlação com o DC. **Material e métodos:** Trata-se de estudo observacional e transversal, onde foram incluídos pacientes com idade 18 anos que concordaram em participar da pesquisa. Os dados demográficos e clínicos foram coletados a partir da análise dos prontuários. Avaliação do DC foi realizada por método subjetivo. Para testar a associação entre variáveis categóricas foi utilizado o Teste Exato de Fisher e na comparação de variáveis contínuas o Teste de Wilcoxon-