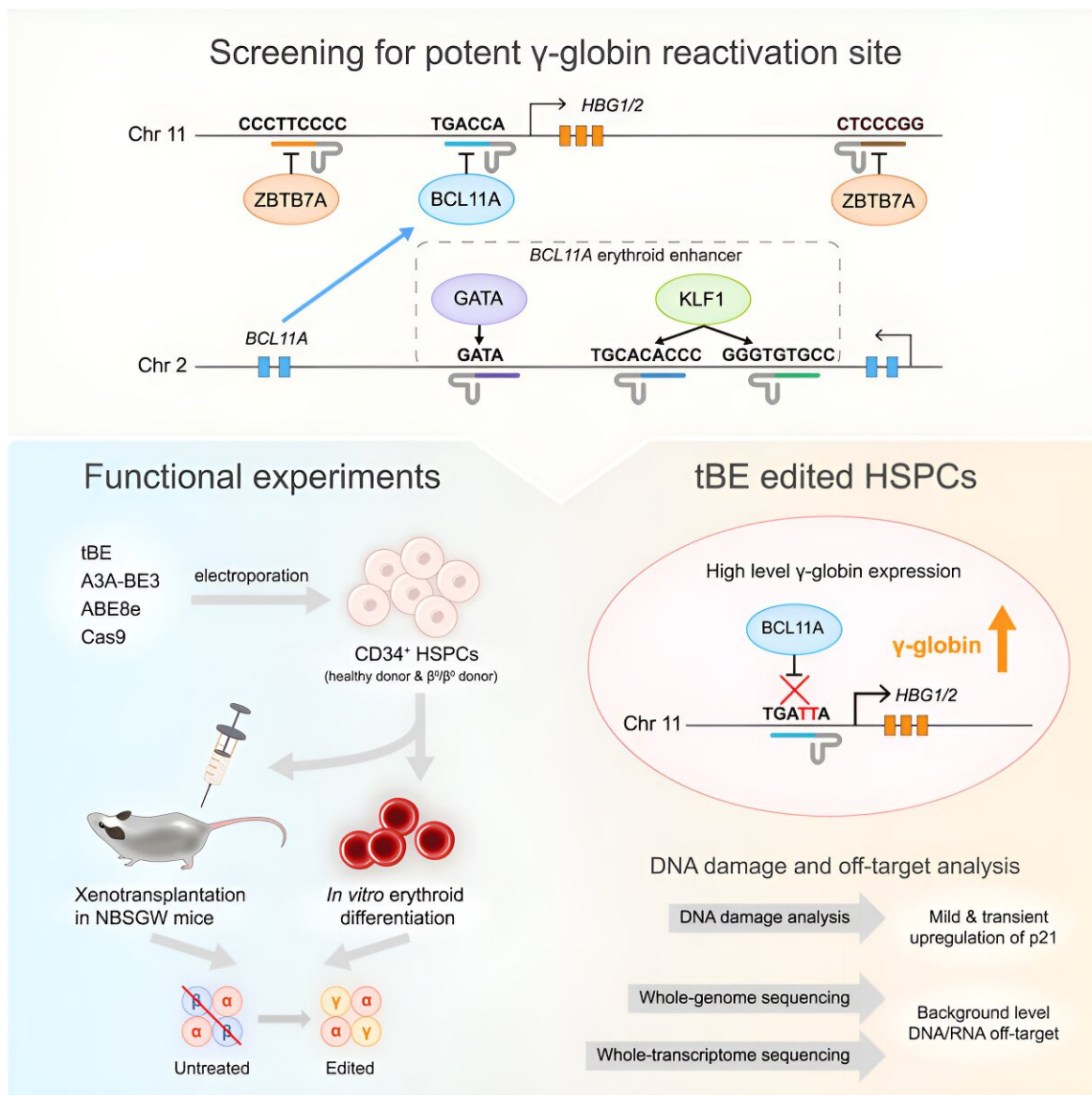


# Reactivating silenced fetal hemoglobin genes could counter sickle cell–related diseases

November 24 2023, by Justin Jackson



Credit: *Cell Stem Cell* (2023). DOI: 10.1016/j.stem.2023.10.007

Researchers from multiple institutions in China have found a way to use gene editing to reactivate dormant fetal oxygen-transporting proteins in adult blood cells to potentially reverse a wide range of blood disorders.

In a paper, "Base editing of the HBG promoter induces potent [fetal hemoglobin](#) expression with no detectable off-target mutations in human HSCs," [published](#) in *Cell Stem Cell*, the team compares gene editing techniques while formulating a method that could have important clinical applications.

Fetal gamma ( $\gamma$ ) globin is normally replaced by adult ( $\beta$ ) hemoglobin during development. In an odd quirk of evolution, only humans and a few types of monkeys are known to switch from  $\gamma$  to  $\beta$  gene expression.

The [genes](#) producing the fetal hemoglobin become silenced and dormant after the [genetic switch](#) by repressors such as BCL11A and ZBTB7A, whose binding motifs have been identified as targets for reactivation.

$\beta$ -hemoglobinopathies, including  $\beta$ -thalassemia and [sickle cell disease](#), result from mutations in the HBB gene, leading to impaired  $\beta$ -globin production and resulting in anemia, impaired oxygen delivery to tissues and possible multi-organ tissue damage.

The researchers experimentally discovered that reactivating  $\gamma$ -globin expression could be developed into a universal therapeutic strategy for these conditions.

Six regulatory motifs (BCL11A enhancer and HBG1/2 promoter regions) were targeted using a recently developed cytosine base

editor—transformer base editor (tBE). The team compared tBE with other base editors and Cas9 nuclease for efficiency and off-target effects.

In the study, tBE exhibited comparable or higher editing efficiency than other editors across the targeted motifs. Comprehensive analysis revealed no detectable off-target mutations in tBE-edited cells, indicating the potential of tBE as a safer and more potent treatment strategy for  $\beta$ -hemoglobinopathies.

Experiments conducted with patient-derived [cells](#) highlighted that disrupting the BCL11A binding sites within the HBG1/2 promoters led to the highest levels of  $\gamma$ -globin expression. Xenotransplantation in mice showed persistent editing in HSCs and their progenies, maintaining engraftment potential and differentiation ability.

The increased  $\gamma$ -globin expression observed due to tBE-mediated editing signifies a promising therapeutic avenue for  $\beta$ -hemoglobinopathies.

While editing methods and not direct [clinical outcomes](#) were the focus of the study, the substantial enhancement in  $\gamma$ -globin expression levels strongly suggests potential clinical benefits, including symptom alleviation and improved disease management for individuals affected by  $\beta$ -hemoglobinopathies.

**More information:** Wenyan Han et al, Base editing of the HBG promoter induces potent fetal hemoglobin expression with no detectable off-target mutations in human HSCs, *Cell Stem Cell* (2023). [DOI: 10.1016/j.stem.2023.10.007](https://doi.org/10.1016/j.stem.2023.10.007)

Citation: Reactivating silenced fetal hemoglobin genes could counter sickle cell–related diseases (2023, November 24) retrieved 9 May 2024 from <https://medicalxpress.com/news/2023-11-reactivating-silenced-fetal-hemoglobin-genes.html>

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