A new genome editing method brings the possibility of gene therapies closer to reality

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Researchers from Salk Institute for Biological Studies, BGI, and other institutes for the first time evaluated the safety and reliability of the existing targeted gene correction technologies, and successfully developed a new method, TALEN-HDAdV, which could significantly increased gene-correction efficiency in human induced pluripotent stem cell (hiPSC). This study published online in *Cell Stell Cell* provides an important theoretical foundation for stem cell-based gene therapy.

The combination of stem cells and targeted genome editing technology provides a powerful tool to model human diseases and develop potential cell replacement therapy. Although the utility of genome editing has been extensively documented, but the impact of these technologies on mutational load at the whole-genome level remains unclear.

In the study, researchers performed whole-genome sequencing to evaluate the mutational load at single-base resolution in individual gene-corrected hiPSC clones in three different disease models, including Hutchinson-Gilford progeria syndrome (HGPS), sickle cell disease (SCD), and Parkinson's disease (PD).

They evaluated the efficiencies of gene-targeting and gene-correction at the haemoglobin gene HBB locus with TALEN, HDAdV, CRISPR/CAS9 nuclease, and found the TALENs, HDAdVs and CRISPR/CAS9 mediated gene-correction methods have a similar efficiency at the gene HBB locus. In addition, the results of deep whole-genome sequencing indicated that TALEN and HDAdV could keep the patient's genome integrated at a maximum level, proving the safety and reliability of these methods.

Through integrating the advantages of TALEN- and HDAdV-mediated genome editing, researchers developed a new TALEN-HDAdV hybrid vector (talHDAdV), which can significantly increase the gene-correction efficiency in hiPSCs. Almost all the genetic mutations at the gene HBB locus can be detected by telHDAdV, which allows this new developed technology can be applied into the gene repair of different kinds of hemoglobin diseases such as SCD and Thalassemia.

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