Targeted gene correction minimally impacts whole-genome mutational load in human-disease-specific induced pluripotent stem cell clones.

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Authors: Keiichiro Suzuki, Chang Yu, Jing Qu, Mo Li, Xiaotian Yao, Tingting Yuan, April Goebl, Senwei Tang, Ruotong Ren, Emi Aizawa, Fan Zhang, Xiuling Xu, Rupa Devi Soligalla, Feng Chen, Jessica Kim, Na Young Kim, Hsin-Kai Liao, Chris Benner, Concepcion Rodriguez Esteban, Yabin Jin, Guang-Hui Liu, Yingrui Li, Juan Carlos Izpisua Belmonte

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Public Summary:
The utility of genome editing technologies for disease modeling and developing cellular therapies has been extensively documented, but the impact of these technologies on mutational load at the whole-genome level remains unclear. We performed whole-genome sequencing to evaluate the mutational load at single-base resolution in individual gene-corrected human induced pluripotent stem cell (hiPSC) clones in three different disease models. In single-cell clones, gene correction by helper-dependent adenoviral vector (HDAdV) or Transcription Activator-Like Effector Nuclease (TALEN) exhibited few off-target effects and a low level of sequence variation, comparable to that accumulated in routine hiPSC culture. The sequence variants were randomly distributed and unique to individual clones. We also combined both technologies and developed a TALEN-HDAdV hybrid vector, which significantly increased gene-correction efficiency in hiPSCs. Therefore, with careful monitoring via whole-genome sequencing it is possible to apply genome editing to human pluripotent cells with minimal impact on genomic mutational load.

Scientific Abstract:
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