GENETICS

# Hitting the mark

**Genome-editing technologies generally stay on target, but researchers should remain vigilant for variants acquired during experimental manipulation.**

Even the most devastating genetic disorders are often traceable to relatively small defects in the genome. Fortunately, scientists now have a plethora of options for attempting the precise editing of DNA typos, including synthetic transcription activator–like effector nucleases (TALENs) or the bacterially derived clustered, regularly interspaced, short palindromic repeat (CRISPR)-Cas9 system.

No biological process is 100% precise, however—and the consequences of an editing error could be just as dire as the initial mutation. A trio of recent reports largely lay these concerns to rest; their authors used whole-genome sequencing to profile single-nucleotide variants (SNVs) along with insertions and deletions (indels) in cell lines subjected to genomic editing via various techniques.

Researchers led by Linzhao Cheng and Zhaohui Ye of the Johns Hopkins University Medical School used both TALENs and CRISPR-Cas9 to introduce the gene encoding GFP into four different induced pluripotent stem cell (iPSC) lines (Smith *et al.*, 2014), whereas Kiran Musunuru's team at the Harvard Stem Cell Institute used the same two editing strategies to target the *SORT1* gene in human embryonic stem cells (Veres *et al.*, 2014). Finally, Guang-Hui Liu of the Chinese Academy of Sciences, Yingrui Li of the Beijing Genomics Institute and Juan Carlos Izpisua Belmonte of the Salk Institute for Biological Studies used four different editing approaches to correct disease-related alterations in iPSC lines derived from patients with a variety of genetic disorders (Suzuki *et al.*, 2014).

True or likely off-target editing events proved rare in all three studies, although Suzuki *et al.* did observe evidence that existing predictive strategies may overlook a subset of TALEN-associated off-target events. Instead, the majority of SNVs and indels appear to accumulate randomly during stem cell cultivation and expansion. These results indicate that existing genome-editing strategies achieve sufficient specificity for the use of edited lines in disease modeling.

**Michael Eisenstein**


RESEARCH PAPERS

Smith, C. *et al.* Whole-genome sequencing analysis reveals high specificity of CRISPR/Cas9 and TALEN-based genome editing in human iPSCs. *Cell Stem Cell* **15**, 12–13 (2014).

Suzuki, K. *et al.* Targeted gene correction minimally impacts whole-genome mutational load in human-disease-specific induced pluripotent stem cell clones. *Cell Stem Cell* **15**, 31–36 (2014).

Veres, A. *et al.* Low incidence of off-target mutations in individual CRISPR-Cas9 and TALEN targeted human stem cell clones detected by whole-genome sequencing. *Cell Stem Cell* **15**, 27–30 (2014).