Research team finds new way to identify 'safe harbor' for gene therapies

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A schematic representation of the overall genomic safe harbor identification strategy. a Selection of common pMEIs from healthy individuals with AF > 0.1. b Removing pMEIs significantly associated with gene expression (FDR less than 0.1 in eQTL mapping). c Removing pMEIs showing spatial proximity with oncogenes, tumor suppressor genes, and dosage-sensitive genes based on TADs and chromatin interaction mapping. d Removing pMEIs overlapping repressive chromatin regions. Credit: Dewan Shrestha et al, *Genome Biology* (2022). DOI: 10.1186/s13059-022-02770-3

Scientists at St. Jude Children's Research Hospital have created a tool that can find safe places to introduce genes into human DNA. The tool is

an early step in the process to improve the safety and efficacy of gene and cell therapies. The work appears today in *Genome Biology*.

"We've created the Google Maps of editing the genome," said co-corresponding author Yong Cheng, Ph.D., St. Jude Department of Hematology. "With this tool, we provide a new approach to identify places to safely integrate a gene cassette. We created step-by-step directions, so you can follow the steps and easily find safe harbor sites in specific tissues."

Gene therapy, where a patient is given a functional copy of a dysfunctional gene, has shown success in curing certain genetic disorders. However, the field has encountered safety issues, including the inadvertent activation of an oncogene that led to cancer in some patients. In response, the field has searched for "safe harbor sites"—places in the genome where a gene can be inserted without causing cancer or other problems. The scientists created a pipeline that uses genomic and epigenetic information from specific tissue, such as blood cells, to find safe harbor sites.

A novel way to find safe harbor sites

The tool compares the DNA sequences that are highly variable between healthy people, using data from the 1000 Genomes Project. If a region of DNA is often deleted or inserted in healthy people, the researchers reasoned that it could likely also be altered safely by a gene therapy.

"Our method is a new way to identify genomic safe harbor sites in a tissue-specific manner," Cheng said. "Nobody has tried it from this angle. Our first step was to find the genomic loci that show a high frequency of insertion or deletion among healthy individuals."

If DNA in a single cell were a string, it would be two meters long. But in

addition to the linear sequence, DNA can loop into complex 3D structures using chromatin, the proteins associated with DNA, to fit within a cell. Just like a string, DNA can have loops that affect its function. The St. Jude tool considers the presence of these loops and other structures when searching for accessible safe harbor sites.

"Our tool assesses the 3D structure of DNA, because human DNA is not a one-dimensional linear structure, it's actually 3D," Chen said. "So, parts of DNA may be far away in the linear sequence of DNA but may physically be next to each other because of the looping of the 3D structure. In that case, the 3D proximity is more important than the linear distance."

Balancing safety and therapeutic gene expression

"Safe gene therapy requires two things," said Cheng. "Number one, maintaining high expression of the new gene. And number two, the integration needs to have minimal effects on the normal human genome, which is a major concern for people performing gene therapy."

The scientists found that the genes placed in safe harbor sites identified by their tool maintained their expression over time. The researchers also showed that if they put a gene into one of the safe harbor sites identified by their tool, it affected nearby genes less than a classic safe harbor site.

The tool, Genomics and Epigenetic Guided Safe Harbor mapper (GEG-SH mapper), is freely available on Github.

More information: Dewan Shrestha et al, Genomics and epigenetics guided identification of tissue-specific genomic safe harbors, *Genome Biology* (2022). DOI: 10.1186/s13059-022-02770-3

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