SCIPOD

////Title: Assessing the Relevance of Off-Target Changes in Gene Edited Crops

////Standfirst:

Humans have a long history of developing crops with improved characteristics, benefitting consumers, and farmers alike. Selective breeding, inducing genetic mutations, and, more recently, gene editing, are all tools that are used to produce plants with beneficial traits. As with any breeding technique, gene editing can lead to unintended genetic changes, but how does the prevalence of these off-target changes compare with those arising from other breeding practices? Plant scientists from the University of Minnesota and collaborating organizations reviewed the rate of unintended changes arising from gene editing with those from other plant development techniques. The researchers conclude that off-target edits in crops present no new safety concerns compared to unintended genetic changes that occur using other breeding techniques.

////Main text:

Genetic differences between individuals are the basis for adaptation to a changing environment. Genetic mutations are changes in DNA sequences that arise spontaneously over many generations, forming the foundation for evolution. Humans have been taking advantage of this fundamental aspect of life for thousands of years by selecting plants and animals with desirable mutations to breed successive generations. This process of selective breeding has given rise to the vast array of crop varieties cultivated today. Modern crop varieties are more disease resistant, tolerate environmental stress better, and have higher yields compared to older varieties.

As our understanding of genetics has improved, researchers and plant breeders have developed more efficient methods of harnessing the diversity in plants to develop new varieties. Conventional selective breeding relies on natural variation within a plant species and spontaneous DNA mutations. Promoting higher rates of genetic mutation – or 'induced mutagenesis' (mute-ah-JEN-uh-siss) – using radiation or chemical agents, effectively speeds up the process that produces novel characteristics. To date, over 3,200 plant varieties developed through induced mutagenesis have been grown commercially.

However, not all genetic mutations lead to desirable traits. Plant breeders remove undesirable traits from the crop through repeated crossbreeding, field trials, and selection over multiple generations. This process is the foundation of plant breeding, regardless of how genetic variation is introduced in a crop. By the time a plant variety reaches the market, about 99% of the lines evaluated will have been discarded during the breeding process, meaning that only the most elite genetics, with the best combination of characteristics, make it into farmers' fields and onto consumers' tables.

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Recent advancements in genetic technologies have provided researchers with powerful new tools to develop better crops. Of these, targeted gene editing using a group of enzymes called 'site-directed nucleases' (NEW-klee-ay-zuhs) offers unprecedented precision in altering genes. These nucleases can be directed to specific genes for editing, by matching a DNA sequence in their structure with a sequence within the plant's genes.

As with selective breeding and induced mutagenesis, targeted gene editing can sometimes produce unintended changes in the plant's genome – or full DNA sequence. Such unintended changes, referred to as 'off-target edits', may sometimes arise when another region of the plant's genome has a similar sequence to the targeted gene and is 'recognized' by the site-directed nuclease.

Off-target edits in human therapeutic applications of gene editing may pose health risks to patients and have therefore been an essential consideration in the use of the technology in this field. However, plants differ from animals in substantive ways. In plants, unintended genetic changes have little consequence beyond increasing the workload for the plant breeders tasked with identifying and eliminating these 'off-type' plants. Therefore, off-target edits in crops present far fewer safety concerns than those that could arise with therapeutic applications of gene editing.

Evaluating the potential impact of unintended mutations and off-target edits first requires an understanding of how these compare to mutation rates associated with other approaches commonly used in plant breeding. Plant scientists and geneticists from the University of Minnesota and collaborating organizations aimed to provide this context by synthesizing the current knowledge into a comprehensive new review. In their paper, entitled 'Plant genome editing and the relevance of off-target changes', they highlight the accuracy of gene editing compared to other plant breeding methods and provide a basis for understanding the contributions of gene editing to genetic variation.

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As explained in the team's paper, the rate of spontaneous DNA mutations, from a change in a single DNA building block – called a 'nucleotide base' – to large rearrangements and deletions, has become clearer as genetic sequencing technologies have advanced. Scientists have been able to quantify the baseline level of natural variation in plant species and found roughly one new mutation for every 100 million nucleotide base pairs every generation. To put that in context, every corn plant in a field will have approximately 50 new mutations relative to its parents. This means that in a one-acre field of corn, you would find 1.5 million new spontaneous single-nucleotide mutations. Larger genetic changes, such as insertions or deletions of short DNA sequences, genes moved from one location to another, and duplicated genes, arise at lower natural frequencies.

When using induced mutagenesis techniques, such as applying radiation and chemical agents, the mutation rates and types of mutations are significantly increased relative to background rates of spontaneous mutation. For example, the team's paper describes research that found that mutagenized rice had on average of 61,150, and 3,323 mutations per plant, depending on the agent used to induce these genetic changes.

Spontaneous and induced mutations can occur across the plant genome. In contrast, gene editing offers a level of control not possible with conventional breeding and induced mutagenic techniques. Although plants developed using gene editing still have the potential to have off-target changes in addition to targeted gene edits, the rate at which off-target edits arise is no higher than the background spontaneous mutation rates that occur naturally.

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While the researchers state that off-target edits are not of concern in plants, several approaches to further optimize and improve the specificity of gene editing methods are being pursued. Modern DNA sequencing methods have made it easier and cheaper to sequence a wider range of plant species and crop varieties. As more 'reference genomes' have been produced, powerful computing technology has facilitated the development of better predictive tools for designing the gene-editing components. With these tools, researchers can identify DNA sequences similar to the targeted sequence elsewhere in the plant genome, and thus further reduce the potential for off-target edits and increasing the efficiency of the process. Furthermore, as a variety of site-directed nucleases are available and more are in development, scientists can optimise editing specificity and efficiency by selecting the most appropriate nuclease for their target gene. In many cases, the potential for off-target edits can be reduced to almost zero using the currently available technology. Varieties developed through gene editing will be subjected to the same screening and selection practices used for plant varieties developed in other ways.

Importantly, the accuracy and lower potential for unintended genetic changes offered by gene editing technology offers a more cost-effective and faster process for developing new crop varieties. With the ongoing threats to crop production posed by climate change, the ability to rapidly adapt to new environmental stressors by producing more resilient crop varieties may be vital to our future food security.

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This SciPod is a summary of the paper 'Plant genome editing and the relevance of off-target changes', from *Plant Physiology*. https://doi.org/10.1104/pp.19.01194

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