



Beyond GM Brief

Gene editing makes the whole genome accessible to changes

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Gene editing promotes itself as a technology of near limitless possibilities. But, in natural systems and in naturally occurring organisms, some limits are innate, necessary and even desirable.

The narrative driving the deregulation of so-called precision bred organisms is, in part, that mutations happen all the time in the natural world and that precision breeding simply speeds up this natural process.

However, a review of the literature shows that gene editing-induced changes are different from changes that occur in natural/traditional breeding (i.e., between sexually compatible organisms) and conventional mutagenesis breeding. This is because gene editing makes the whole genome accessible to changes, whereas in natural breeding, some regions of the genome are protected against mutations.¹

Strategies to overcome what are portrayed as the limits of nature and conventional breeding have been developed using gene editing. But the 'access all areas' approach of gene editing actually raises the risk of creating unintended and serious errors in the genome.

Recent research in plants (not involving gene editing) has underscored the fact that, in natural/traditional breeding, mutations are not random and certain regions of the genome involved in important processes are protected from mutations.²

Further, studies have shown that mutations induced by conventional mutation breeding more often than not occur in areas of the genome that are non-coding and non-regulatory and therefore are unlikely to affect gene function. But with gene editing, mutations are more likely to happen at locations in the genome that directly affect the function of one or more genes.³

¹ Kawall K. New possibilities on the horizon: Genome editing makes the whole genome accessible for changes, *Frontiers in Plant Science*, 2019; 10: 525, <https://www.frontiersin.org/articles/10.3389/fpls.2019.00525/full>. For a review of this and other issues see: Scientists' and policy experts' statement: Gene editing is not "precision breeding" and the term is misleading, Sept 2022, <https://docs.google.com/document/d/1bTWTWZwwDHfReRaiA4Kt25Jfrqab4iNyALLAsEGTPR4/edit>

² Monroe JG et al, Mutation bias reflects natural selection in *Arabidopsis thaliana*, *Nature*, 2022; 602: 101-5, <https://www.nature.com/articles/s41586-021-04269-6>; UC Davies, Study challenges evolutionary theory that DNA mutations are random, *Phys.org*, 12 Jan 2022, <https://phys.org/news/2022-01-evolutionary-theory-dna-mutations-random.html>

³ As demonstrated with *e.g. Barley and Brassicas*: Lawrenson T et al, Induction of targeted, heritable mutations in barley and *Brassica oleracea* using RNA-guided Cas9 nuclease, *Genome Biol*, 2015, (16): 258, <https://pubmed.ncbi.nlm.nih.gov/26616834/>; **Rice**: Endo A et al, Efficient targeted mutagenesis of rice and tobacco genomes using Cpf1 from *Francisella novicida*, *Sci Rep*, 2016, (6): 38169, <https://pubmed.ncbi.nlm.nih.gov/27905529/>; Hua K et al, Simplified adenine base editors improve adenine base editing efficiency in rice, *Plant Biotechnology Journal*, 2020; (18): 770, <https://pubmed.ncbi.nlm.nih.gov/31469505/>; Ren B et al, Cas9-NG Greatly Expands the Targeting Scope of the Genome-Editing Toolkit by Recognizing NG and Other Atypical PAMs in Rice, *Molecular Plant*, 2019, 12 (7): 1015-26, <https://pubmed.ncbi.nlm.nih.gov/30928635/> and **Wheat**: Arndell T et al, GRNA validation for wheat genome editing with the CRISPR-Cas9 system, *BMC Biotechnology*, 2019, 19 (1): 71, <https://pubmed.ncbi.nlm.nih.gov/31684940/>; Zhang Y et al, Efficient and transgene-free genome editing in wheat through transient expression of CRISPR/Cas9 DNA or RNA, *Nat Commun*, 2016, 7 (1): 12617, <https://pubmed.ncbi.nlm.nih.gov/27558837/>.

This can happen for several reasons:

- With gene editing, there is intentional targeting of a gene's coding region or its regulatory elements in order to alter its function. Gene editors will preferentially target sites that are, for instance, relevant for protein production and gene regulation for alterations, since the objective is to change a trait.
- In addition, much of the off-target mutation-causing activity of the gene-editing tool will occur at locations within the genome with a similar DNA sequence to the intended target site. If the intended gene editing target site is a gene's coding region or its regulatory elements, off-target mutations will occur in other genes with a similar DNA sequence.
- Even gene-editing techniques that do not involve the deliberate insertion of foreign genetic material to produce a specific trait (that is SDN-1 and SDN-2 techniques) enable complex alterations of genomes that would be extremely difficult or impossible to achieve with traditional breeding or older style mutation breeding. So-called multiplexing approaches, for example, which subject an organism to multiple edits, allow the simultaneous targeting and alteration of multiple gene variants, which can be members of the same or different gene families.⁴

As a result of these actions, off-target and unintended on-target mutations are likely to affect important protein-coding gene regions and gene regulatory activity.

These outcomes are well known to scientists working in the field and indeed form the knowledge base used to improve the precision and predictability of gene editing.

Relevance to new regulatory proposals in the UK

Defra insists that the products of so-called precision breeding (gene editing) are the same as could have occurred naturally and therefore require no special regulation. This is patently not true and, as a growing body of evidence shows, certainly not scientific.

Gene editing can and is being used to 'break biology' and generate a wide range of novel genetic combinations that have never existed before and cannot readily be achieved using traditional breeding or mutagenesis techniques.

This is a very different picture from first-generation genetic engineering technology, which has predominantly focused on a relatively narrow range of traits such as herbicide and insecticide resistance (and combinations thereof).

We have even less of a baseline for genome-edited farm animals, because to date, there have been no applications to market GM farm animals for food use in the UK or EU and existing risk assessment guidelines (e.g., in the EU) for animals largely focuses on insects and fish.

We have no clear reference points with which to judge the safety of these new novel organisms in the environment or in the food system. The broad spectrum of possible traits created using precision breeding (gene editing) in plants and animals is likely to provide new, and complex issues for risk assessment, potentially requiring more, rather than less regulatory oversight.

⁴ Kawall K et al, Broadening the GMO risk assessment in the EU for genome editing technologies in agriculture, *Environmental Sciences Europe*, 2020; 32(1): 106, <https://enveurope.springeropen.com/articles/10.1186/s12302-020-00361-2>