

## Perspective

## Can genome editing help transitioning to agroecology?

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## SUMMARY

**Meeting the challenges of agroecological transition in a context of climate change requires the use of various strategies such as biological regulations, adapted animal and plant genotypes, diversified production systems, and digital technologies. Seeds and plants, through plant breeding, play a crucial role in driving these changes. The emergence of genome editing presents a new opportunity in plant breeding practices. However, like any technological revolution involving living organisms, it is essential to assess its potential contributions, limits, risks, socio-economic implications, and the associated controversies. This article aims to provide a comprehensive review of scientific knowledge on genome editing for agroecological transition, drawing on multidisciplinary approaches encompassing biological, agronomic, economic, and social sciences.**

## INTRODUCTION

Tackling the major challenges of the agroecological transition (AET) of agricultural production systems in a context of climate change requires the mobilization of a diversity of levers such as interactions between organisms, adapted animal and plant genotypes, diversification of production and production systems, and mobilization of digital technologies. These levers can be mobilized by different models of agriculture that coexist and contribute to improving the sustainability of agricultural and food systems. As the first link in the agricultural and food value chain, seeds and seedlings, through crop breeding and the development of new varieties, are positioned as a major lever for driving and supporting these changes. In this context, genome editing technologies are not only powerful tools for research but also represent new opportunities in the plant breeding tool box. As for all techno-scientific revolutions, and particularly those involving living organisms, it is essential to analyze the potential contributions, promises, limits, uses, risks, socio-economic issues, and associated controversies. This article reflects on a recent report,<sup>1</sup> from the National Research Institute for Agriculture, Food and the Environment (INRAE), on the potential of genome editing technology for AET and adaptation to climate change. This report, by a group of experts in different fields, reviews the scientific knowledge on genome editing technology for AET, based on the international literature, using a multidisciplinary approach combining biological, agronomic, economic, and social sciences.

## New breeding targets to support AET

Agroecology<sup>2</sup> is based on the knowledge of ecological interactions between living organisms, leading to a greater use of intra- and multi-species diversity and less use of chemical inputs. This provides multiple ecosystem services, including mineral nutrient supply to crops, pollination, natural pest control, stabilization of soil structure ... For example, including more legumes (as sole or intercrops, as main or cover crops) in the agroecosystem brings a natural source of nitrogen. The knowledge and exploitation of plant/plant and plant/microorganism interactions are at the core of this form of agriculture (Figure 1A). As different levers have to be combined to develop agroecological solutions, a key feature in research is to implement a broad, inter-disciplinary approach to design such novel agricultural systems, bringing together the skills of geneticists, agronomists, soil scientists, ecologists, economists, and sociologists.

With regard to the genetic lever, the transition to agroecology in the frame of climate change requires to broaden the breeding targets and reconsider the nature and hierarchy of morphological, physiological, and phenological traits to be combined in order to build varieties in phase with the expected agronomic, socio-economic, and environmental contexts.

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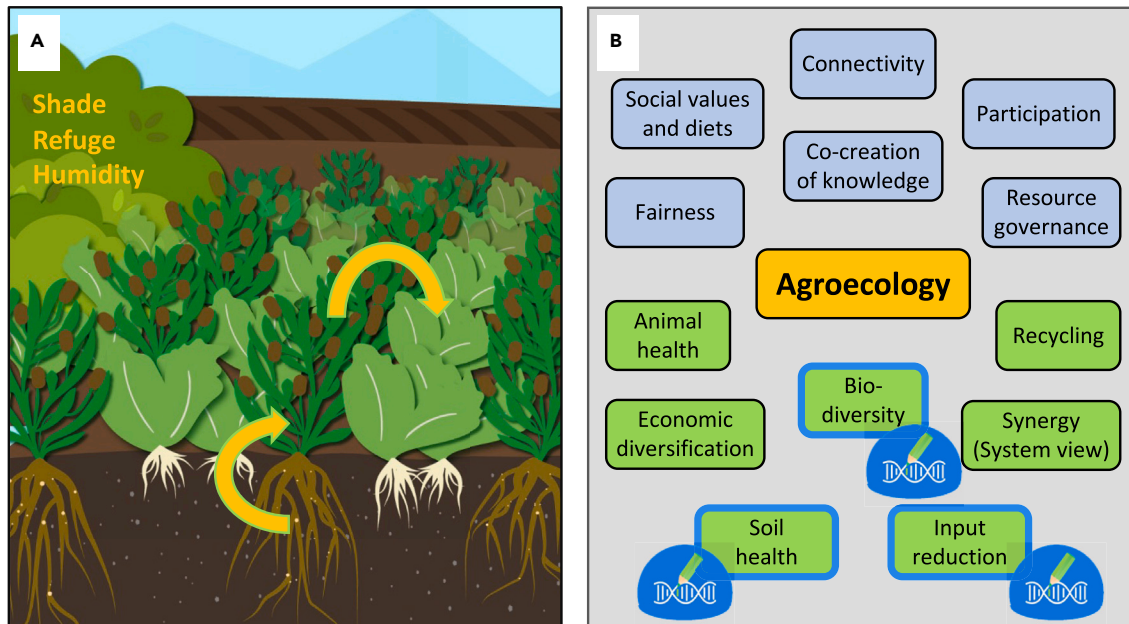
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**Figure 1. Agroecological system**

(A) Agroecological culture system characterized by the coculture of two crops next to a hedge. Plant/plant and plant/microbe interactions are symbolized by orange arrows.

(B) The 13 principles of agroecology for agroecosystems (green background) and food systems (blue background) based on<sup>2</sup>. The three principles that could benefit from plant genome editing are framed in blue and marked by a pen and a double helix.

In terms of research and breeding avenues, this requires the following:

- (1) Expanding the range of target species (minor species, service plants, new food crops) while maintaining enough varietal diversity available to farmers in main crops (e.g., for composing intra- and inter-specific mixtures);
- (2) Intensifying research on tolerant, resistant, or resource-efficient varieties, alone or in mixtures, to cope with multiple and uncertain biotic and abiotic stresses (e.g., by exploring the genetic diversity offered by wild relatives) and develop breeding programs for these traits;
- (3) Breeding for new traits related to the multiple functions of service plants, the composition of new food crops, and also the suitability of varieties for intercropping (e.g., agroforestry, cereal-legume mixtures);
- (4) Developing varieties adapted to changes in crop practices (e.g., shifting of sowing dates, non-chemical weed control, mulching) and environments (e.g., shifting of crops to higher latitudes).

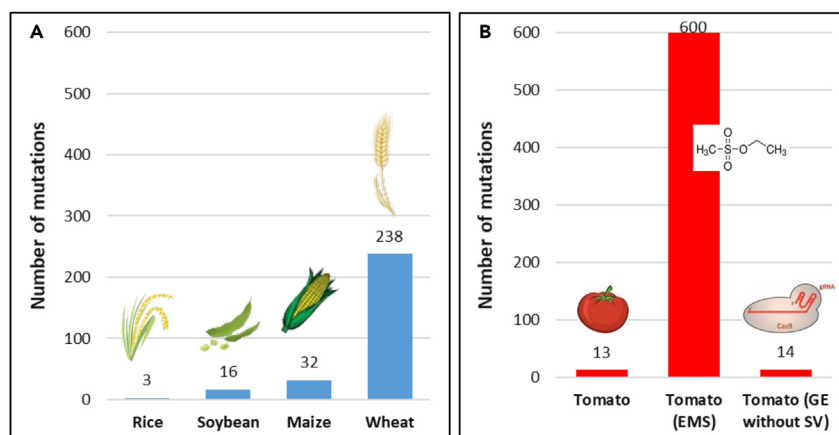
Among the 13 principles of agroecology shown in Figure 1B, maintaining and enhancing biodiversity, preserving and improving soil health, and reducing chemical inputs could potentially benefit from plant breeding, including innovations in plant genome editing.

### Genetic diversity, the cornerstone of plant breeding

Genetic diversity is defined as the variation of heritable traits within a population or species. Among the mechanisms underlying genetic diversity, spontaneous mutations (point mutations, deletions, or insertions) occur at a relatively constant frequency between organisms.<sup>3</sup> Thus, the number of spontaneous mutations between generations is proportional to the size of the genome (Figure 2A). Plant breeding is based on genetic diversity because it consists, by crossing and selection, in recombining in the same genotype the favorable alleles for one or several selected traits. This also holds for traits necessary for AET. These traits can either be identified in existing germplasm and selected by simple phenotypic evaluation, use of molecular markers, and/or genomic selection or created *de novo* by knowledge-based enlargement of the gene pool via genome editing.

### Genome editing, a tool for breeders to fully leverage genetic diversity

Induced mutagenesis is a way to artificially increase genetic diversity. From the 1950s, chemical or physical mutagens have been used to induce mutations, which thus occur at a much higher level than spontaneous mutations. Although this has proven to be effective in creating useful genetic diversity,<sup>7</sup> induced mutations occur randomly and simultaneously impact a large number of loci. Therefore, the major drawback of randomly induced mutagenesis is the need for screening thousands of mutated plants to find desired mutations. The recent development



**Figure 2. Number of spontaneous versus induced mutations in selected crop plants**

(A) Estimation of the number of spontaneous mutations per generation in the indicated crop plants by extrapolation of the spontaneous mutation rate of  $7.1 \times 10^{-9}$  measured in *Arabidopsis thaliana*,<sup>3</sup> knowing that a higher mutation rate of  $5.4 \times 10^{-8}$  has been calculated in rice.<sup>4</sup>

(B) Estimation of the number of mutations per generation in sexually propagated, chemically mutagenized, and genome-edited (GE) tomato. The estimate of the number of ethyl methanesulfonate (EMS)-induced mutations in tomato is based on<sup>5</sup>. The estimate of the number of mutations in the edited tomato is based on a case where no or very few off-target mutations would be detected<sup>6</sup> and does not take into account somaclonal variation (SV) induced to various degrees by tissue culture.

of genome editing makes it possible to overcome this issue by targeting mutations at specifically chosen loci. Thanks to site-directed nucleases (SDNs), genome editing can modify/edit the genetic material of an organism. There are three modalities of SDNs, SDN1 (targeted but random modification), SDN2 (targeted and predicted modification), and SDN3 (targeted transgene integration). We will focus here on the first two modalities that result in modifications that cannot be distinguished from spontaneous mutations, making their detection a challenge.

Since 2012, the CRISPR-Cas system has been the preferred nuclease for editing plant genomes.<sup>8</sup> It consists of a Cas nuclease, which, once associated with a guide RNA, precisely cuts a target DNA sequence, which is repaired either identically or with errors, depending on the plant cell's repair mechanism involved. Recent developments in CRISPR-Cas technology, such as base or prime editors,<sup>9</sup> blur the boundaries between SDN1 and SDN2. Genome editing can produce precise modifications of a given gene, thereby introducing key polymorphisms identified in related species, which may not be crossed through traditional breeding (see for example<sup>10</sup>). Genome editing can also reduce the time required for introgression of desired alleles from distant species while limiting the risk of introgressing unwanted genetic material.<sup>11</sup>

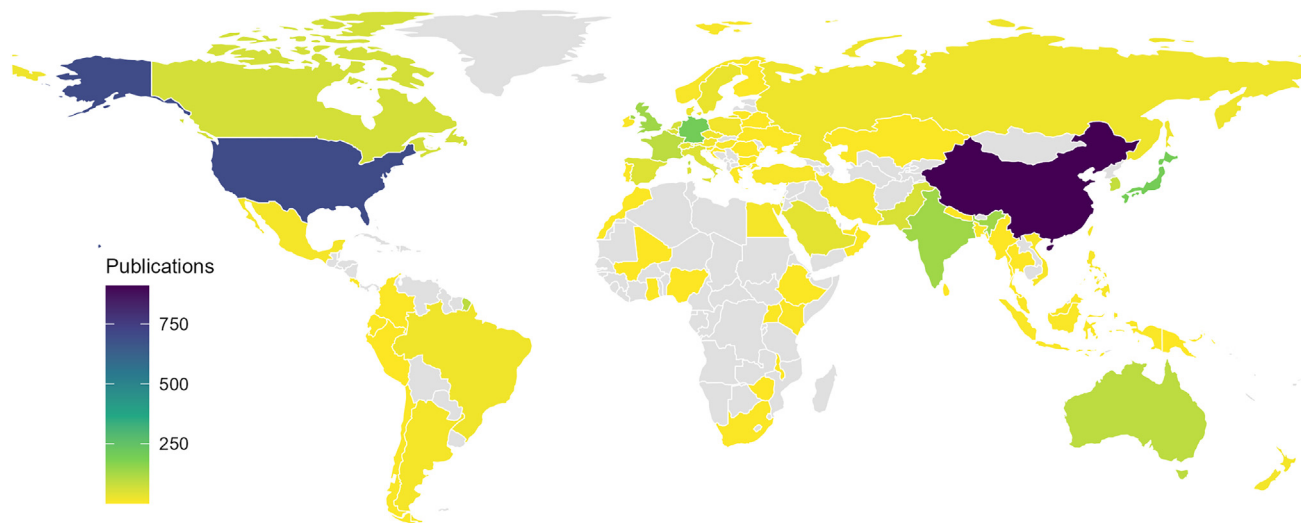
From a technical point of view, two major factors are currently limiting the application of genome editing. Firstly, for many traits, the knowledge of the genes to be modified to change the phenotype is limited. This is particularly true for novel traits needed for AET. Secondly, if introducing the CRISPR-Cas tool needed for genome editing into plant cells is relatively easy, regenerating plants from these cells is challenging for many crops. Concerning the second point, a promising solution is the use of genes promoting cell proliferation, either by the temporary introduction of classical transgenes<sup>12</sup> or by innovatively activating endogenous genes with the CRISPR-Combo technique.<sup>13</sup>

Regarding the technology itself, the impact of genome editing tools and plant regeneration processes on the plant genome outside the target site is still a matter of debate, but recent studies suggest that off-target modifications caused by the gene editing tool itself are likely rare.<sup>14</sup> However, the tissue culture techniques necessary in most species for the regeneration of edited plants or the transfection process itself are known to cause genome modifications, generally referred to as somaclonal variations (SVs). Whole genome sequencing of edited plants allowed to measure these modifications in rice,<sup>4</sup> tomato,<sup>15</sup> and the model plant *Physcomitrium*.<sup>16</sup> From a regulatory point of view, it has to be recalled that somaclonal variations are considered to have a history of safe use in conventional plant breeding, just like random mutagenesis, which induces a lot more mutations in the rest of the genome than genome editing (Figure 2B). Despite these challenges, genome editing can become a new plant breeding tool for AET once these limitations are overcome.

### Which species and traits for genome editing? Which countries? Which potential for AET?

To answer these questions, a literature survey was performed<sup>1</sup> using the Web of Science (SCIE, SSCI, and A&HCI databases) for the document types Article, Review, Editorial material, and Letter for the last 30 years. The equation combined terms related to genome editing with terms related to plants. It was applied to the Title, Author keywords, and Abstract fields. Starting with an initial corpus of 2,415 publications, several subsets were extracted by queries using terms related to traits or agroecology or other farming systems and manually curated to answer specific questions.

The analysis clearly identified CRISPR/Cas9 technology as a game changer among the genome editing technologies. The advent of CRISPR/Cas9 technology in 2012 not only marked the transition from a flat curve alimented by publications on earlier, less performing genome editing tools to a curve of exponential growth. It also provoked a shift from purely technology-centered publications to an ever-increasing proportion of trait-related publications starting in 2015. Looking at the countries that are active in the field (Figure 3), we can



**Figure 3. Distribution of the number of publications on plant genome editing by country**

All the country affiliations in the corpus of publications have been taken into account in drawing up this map. The corpus of 2,415 publications, retrieved by a search on terms related to genome editing and plants over the last 30 years, corresponds to 3,391 country affiliations, showing the cooperation between countries on the subject.

see that 74 countries have published work related to plant genome editing. China accounts for more than quarter of the publications (27%). The USA (21%) clearly holds second place.

Because one of the agroecological principles is species diversity, we inquired the question how broadly genome editing has been successfully implemented in the plant kingdom. Among the 145 species mentioned in the initial corpus, genes related to specific traits have been mutated for only 69 of them. These numbers are in agreement with the conclusions of earlier reports<sup>17</sup> and suggest that wild relatives of crops (e.g., wild tomatoes), orphan species (e.g., cassava), or service plants (e.g., camelina or alfalfa) are amenable to genome editing. Indeed, the possible limitations for species with agroecological interest are not linked to their present “non-crop status” but to the rather unpredictable difficulty to introduce CRISPR/Cas9 tool and/or the regeneration of mutated plants from edited explants for certain species.

With regard to the improvement of agronomic traits, this study revealed that proofs of concept in confined and less frequently in field conditions have been achieved by genomic editing for a large variety of traits. They include complex traits such as yield, addressed in 9.5% of the publications, thereby corroborating an earlier study.<sup>6</sup> A focus on traits with potential contributions to the AET showed that traits already considered in the past for durable but not necessarily agroecological systems, such as product quality (27.6%), disease resistance (18.0%), or tolerance to abiotic stress (9.9%), were a lot more frequently subject to publications than novel traits specifically needed for agroecological systems. Examples for the latter are some of the works linked to plant architecture (11.7%), phenology (4.6%), or specific services (3.2%). Among the changes in architecture, the height of the plant, the formation of branches, the stiffness of the stem, or the growth habit of inflorescences represent entry points for improving plant/plant interactions in mixtures or associations, traits sought after in agroecology. This is also true for modulations of phenology, which make it possible to lengthen or shorten the life cycle of a variety to better match it with that of other species in space (associations) or time (rotations) and to expand its cultivation area. Finally, the improvement of plant/microorganism interactions is an important agroecological service successfully achieved by genome editing, both of plant and microbe genomes. For example, nodule number and thereby symbiosis were increased by simultaneous editing of two soybean genes,<sup>18</sup> and the relative frequency of targeted microbial species was modified directly in a community of soil microbes without need for the isolation and pure culture of these species.<sup>19</sup> It is noteworthy that the scarce number of works on traits specifically needed for the AET is not specific to genome editing but also holds for conventional plant breeding methods. This shows that the genetic bases of these novel, often complex and multigenic traits are still insufficiently known to be worked on.

### Genome editing applied to AET: A need to renew the analysis of socio-economic impact

Applications of genome editing share some similarities with the applications of transgenesis that leads to GMOs, because they both lead to genome modification. The negative public perception associated to GMOs have somehow extended to the application of genome editing, and this has been reinforced by the 2018 decision of the European Court of Justice to consider applications made from new mutagenesis techniques as GMOs. This is associated with multiple controversies related to the introduction of new technologies in agriculture<sup>20</sup>: ethical issues related to the modification of living organisms, health and environmental risk associated with the applications of these technologies, the fact that these technologies can reinforce the market power of suppliers of an industrial agriculture, and the information of consumers on the farming practices that lead to the food product they consume. However, one could think that public perception of genome editing

techniques may evolve, at least in part, if the application of these technologies could favor agroecological practices. However, this requires to think of the way public debate should be organized to go beyond the opposition between advocates and opponents to these technologies *per se* and address issues related to the application of these technologies.

The negative public perception of new genomic techniques is consistent with the first experiments in economics showing that consumers' willingness to pay is lower for products developed using genome editing compared with products developed using conventional breeding techniques.<sup>21</sup> One interesting issue would be to test whether this result is also observed in a context where the production is made following agroecological practices.

In accordance with the literature review of the INRAE report,<sup>1</sup> the published literature surveys show that a wide range of genetic traits is currently being worked on using genome editing. However, these analyses do not take into account the alternative ways for developing these traits. It is thus necessary to identify situations where genome editing technologies are critical or offer added value to the development of certain traits or species that can favor agroecology, in the sense that these traits can hardly be developed with alternative research technologies.

The technologies used for genome editing are protected by patents as well as most of the innovations developed on their basis. Application in agriculture requires license agreement with patent holders and royalty payment by licensees. Social science analyses show that this system leads to transaction costs, especially with stacked traits, and can reduce the range of application of these techniques.<sup>22</sup> Alternatives to these property right systems using, for instance, open or free licensing are barely considered for the time being. One should also question whether the consolidation of the seed industry observed after the introduction of GMOs could also be reinforced after the development of these new genomic techniques. Agroecology requires a large diversity of seed supply in terms of species and adaptation to production contexts. For the time being, most of the economic analyses on intellectual property rights focus on their impact on the incentive to innovate and the diffusion of innovation for given applications. There is thus a need to broaden the scope of these analyses and address the impact of different intellectual property rights systems on the diversity of genetic innovation supply. More broadly, analyses are required on alternative research funding mechanisms that could favor diversity of supply and, in particular, more funding on minor crops.

Numerous publications address issues related to the regulation of innovations created with genome editing technologies. They raise, in particular, the opposition between a process-based regulatory system that differentiates regulatory requirements based on the process used to make the product and a product-based approach that bases regulatory requirements on the characteristics of the final product, regardless of the process by which it was made. International comparison of regulations shows that this dichotomy is difficult to apply because most of the regulations combine these two types of approaches.<sup>23</sup> Much less analysis has been made on the possibility to integrate a preliminary assessment of socio-economics impact in the regulation. With the perspective of agroecology-related applications, the issue is also to make this assessment in a context that differs from the "business as usual." This perspective also raises issues concerning the adequate way to regulate such innovations. Markets related to agroecology are generally small and emerging, so that regulation cost could create a barrier for developing applications in this direction. If developing agroecological practices is a main objective, regulation should enable experimentation of innovation at the adequate scales for such practices.

## Conclusions

The principle of genome editing is to induce one or more targeted mutations in one or more genes that are at the origin of the variation of a trait of agronomic interest. Compared with the tools currently used, this technology has several advantages: gains in precision and time and possibility of accumulating several mutations simultaneously in several genes, but it also has several limitations:

- (1) It requires knowledge of the genetic basis of the agronomic traits of interest, at minimum a major gene, ideally the structure of each gene involved and its alleles.
- (2) Like other plant breeding techniques, it faces the difficulty of improving polygenic traits, as are often the traits of agroecological interest.
- (3) With current protocols requiring somatic regeneration, it is not possible to perform genome editing on certain plant species (e.g., peas, beans, cowpeas, sunflowers) or certain "elite" lines (e.g., most varieties of rapeseed) of agroecological interest.
- (4) It requires reconsidering the selection schemes that must be optimized for each species according to the trait considered, the known genes, and the ease of implementation.
- (5) It is still at the stage of promises to find a market, particularly in the field of AET. Consumers have a lower propensity to pay for products resulting from these technologies than for conventional products, and it is the subject of controversy linked to the place of Nature and Technology in society.

Overcoming these limitations requires studying the potential of genome editing for AET by identifying the case where it can improve given agroecological traits involved, for example, in plant-microorganism interactions. In particular, improving interactions of the crops with soil bacteria (mycorrhizal or nitrogen-fixing symbioses, beneficial non-symbiotic microbiota) should have significant positive effects on the mineral nutrition of crops. Genome editing also has the potential to accelerate the new era of domestication needed to increase crop diversity, one of the pillars of agroecology. Here again, demonstrating that the tool can be used in a large number of species will be a key step in bringing this technology to future agriculture. In any case, it is essential to get out of the regime of promises surrounding this technology and to recognize that the response to the challenges of transitions toward sustainable agricultural and food systems cannot be based on a single technology, genome editing, or even a single lever, genetic and plant breeding, but rather on a combination of levers within a coherent production

system, the development of which requires the mobilization of biological sciences, agronomic sciences, and social sciences. Finally, development of new crops that would help AET will need a Global Regulatory Harmonization, and the recent proposal<sup>24</sup> of the European Commission, on the regulation of plants obtained by certain new genomic techniques, could be a first step in this direction.

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## AUTHOR CONTRIBUTIONS

Conceptualization, F.N., M.C., P.D., A.D., S.L., G.R., P.R., and C.C.; funding acquisition, F.N.; writing—original draft, F.N., P.R., and C.C.; writing, review, and editing, F.N., M.C., P.D., A.D., S.L., G.R., P.R., and C.C.

## DECLARATION OF INTERESTS

As INRAE experts, the authors were part of the group that produced the report considered in this reflection. The opinions expressed in this reflection are solely those of the authors.

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