GENETIC TECHNOLOGIES

POLICY FORUM

Genomics, Genetic Engineering, and Domestication of Crops

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Genomic sequencing projects are rapidly revealing the content and organization of crop genomes (*1*). By isolating a gene from its background and deliberately modifying its expression, genetic engineering allows the impacts of all genes on their biochemical networks and organismal phenotypes to be discerned, regardless of their level of natural polymorphism. This greatly increases the ability to determine gene function and, thus, to identify new options for crop domestication (*2*). The organismal functions of the large majority of genes in genomic databases are unknown.

At the same time, however, government regulatory regimes are making field studies of genetically engineered (GE) plants needed to understand gene function in the context of normal plant development increasingly difficult. These regimes have been created largely because of biosafety issues raised by genes imported from distant species. However, they have been applied to asexually introduced genes whose source and effects resemble those of traditional breeding. This imposes large costs that impede the delivery of public benefits from genomics research.

The first wave of widely planted transgenic crops expressed traits that were encoded by exogenous (bacterial or viral), gain-of-function genes such as those for herbicide or pest resistance. Their action depended on the solitary effects of single proteins that were virtually independent of plant metabolism. By transferring functions between phylogenetically divergent organisms, these genes imparted traits that could not be readily obtained from traditional breeding. This created transgenic plants with very high agronomic and environmental value but also raised difficult questions because of their ecological and evolutionary novelty (*3*).

In contrast, genomics-guided transgenes (GGT) will increasingly be based on native or homologous genes from related species. Such genes will often modify metabolism in a manner similar to that of natural or induced mutations, but it should be possible to create desired phenotypes with greater precision and efficiency. Dominant alleles important to agricultural goals, but poorly represented in breeding populations because they are rare or deleterious to wild progenitors, can be created and inserted into varied kinds of germplasm. Traits that have already been genetically engineered in this manner include diverse modifications to plant reproduction, stature, and lipid and lignocellulose chemistry. The improvements achieved via GGTs should be comparable to or of greater value than those obtained via traditional breeding approaches that have achieved wide public acceptance, and have been free of calls for government regulation.

Field trials are important for identifying useful GGTs and provide several biosafety mechanisms. GGT modifications will generally be achieved by altering the function or expression of key regulatory molecules that influence plant development, including enzymes, transcription factors, and signal transducers. Organismal regulatory systems are expected to be under strong stabilizing selection due to natural selection and their high degree of internal complexity (*4*). Strong modifications to such systems are therefore likely to be deleterious to fitness in wild environments.

The limited scale of release from small field trials provides a large safety buffer for transgenes that produce deleterious, neutral, or even mildly beneficial changes in fitness. For a recombinant gene from a field trial to invade and therefore have a significant environmental consequence, it must overcome the huge numerical obstacle that is normally provided by extant wild and domesticated gene pools. Despite the great diversity of genes that can comprise GGTs, many of the modified traits are familiar, having a long history of domestication and consequent reduced fitness through artificial selection. Male sterility, seedless fruits, delayed spoilage, and dwarf stature are familiar examples.

GGTs that improve abiotic stress tolerance of crops, including tolerance of cold, heat, salt, and drought, would appear to pose a higher risk of spread in the environment than domestication traits. However, physiological considerations and breeding experience suggest this might not be the case. Alterations of regulatory genes that control pathways related to tolerance of abiotic stresses often have complex antagonistic effects on other dimensions of fitness (*5*). Natural adaptations to highly stressful environments, including the C_4 pathway of carbon fixation, often involve multiple physiological mechanisms controlled by sets of elaborately regulated genes [e.g., (*6*, *7*)]. Manipulations of one or a few genes to promote stress-tolerance in agronomic environments may therefore not significantly elevate fitness in wild plants and could even do the opposite.

Despite intensive direct and indirect breeding for abiotic and biotic stress-tolerance in annual crops, where populations or species adapted to highly diverse ecological conditions are hybridized, inbred, and effectively cloned, there appear to be no known cases where populations that are substantially more invasive in the wild were generated as a consequence (*8*). It appears that wild plants achieve stress resistance differently from crops bred for high yield under agricultural conditions.

Field trials need to be conducted in the

Confinement level	Type 1 field trials (exploratory)	Type 2 field trials (precommercial)	Examples
High	Biological and physical confinement—detailed data		Highly toxic or allergenic pharmaceuticals and proteins
Medium	FSC, basic data	FSC, detailed data	Novel pest-management genes, low toxicity pharmaceuticals and proteins
Stress tolerance	FSC, basic data	FSC, detailed data	Genomics-guided transgenes
Low			
Domesticating	Petition for exemption?	FSC, basic data	

Categories of confinement and monitoring for small- and large-scale transgenic field trials. Biological confinement includes genetic mechanisms to preclude spread and/or reproduction. Physical confinement requires use of geographical isolation or physical barriers. FSC, farm-scale confinement; use of spatial isolation within and between farms and border crops, combined with postharvest monitoring. Detailed data include surveys of gene flow away from the site. Basic data documents establishment of confinement mechanisms.

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early stages of research and development to identify valuable GGTs. The differences in crop physiology in field versus laboratory and greenhouse environments are well known. Anticipated benefits, as well as unexpected pleiotropic effects, may be missed if field trials are avoided at this stage. Because of large variation in plant phenotype as a result of transgene configuration (e.g., promoters), chromosomal site, host variety, soil, climate, and their many complex interactions, studies need to include many insertion events, years, and locations. This is especially true for transgenes that impart complex phenotypes such as abiotic stress resistance. In contrast, the first wave of transgenic traits, largely pest and herbicide resistance, could be evaluated to a high degree of confidence in artificial environments because their expression was little changed by growth environment.

In many parts of the world, however, conducting adequate field tests is extremely difficult. Many European countries stringently limit all but a few kinds of recombinant field trials (i.e., those for major crops and transgenes that have very high economic value to companies). Except for China and a few other countries with sophisticated biotechnology research programs, developing countries generally lack the research infrastructure, or effective regulatory institutions, for extensive field tests. In the United States, U.S. Department of Agriculture (USDA) and Environmental Protection Agency regulations permit many kinds of field tests to be undertaken (*9*), so long as performance standards are followed that provide high levels of confinement (e.g., large crop borders and separation distances), and there is sufficient infrastructure in place to allow regulatory procedures to be monitored. However, the time span and expense of rigorous field studies that conform to regulations often far exceed the resources available to genomics researchers, particularly academic scientists funded by research grants.

The possibility of vandalism and the threat of attacks on personal property associated with publication of field trial notices can be intimidating to researchers and institutions. They may necessitate large investments in security systems and, because of the potential for arson (*10*, *11*), may pose substantial risk for personal and institutional liabilities. Increasing concerns over legal and public perception impacts from low-level contamination of food crops especially by industrial feedstock or pharmaceutical-producing crops (*12*), even if of negligible health or environmental consequence, may require that costly measures are put in place to restrict gene flow from all kinds of GE crop trials, or that field test sites are placed in isolated, difficult-to-reach places.

For transgenes that produce a domestication trait and are in a small-scale trial (see table p. 61, Type 1), the degree of intrinsic environmental safety seems sufficiently high that most trials could, perhaps after an initial USDA Animal and Plant Health Inspection Service (APHIS) notification and review, be exempted from continued regulatory oversight. This exemption assumes that linked transgenic sequences, such as selectable markers or other pieces of transferred DNA, are acceptable (online fig. S1). This would likely be the case in the U.S.A. for an intensively studied gene like *nptII* (resistance to the antibiotic kanamycin), which has been deemed acceptable for food use and entry into the environment on a large scale (*13*).

Where there is a concern about gene movement and possible invasive properties, more detailed data on both extent of confinement and fitness effects could be required, particularly for larger tests. This might be the case where an abiotic stress-resistance gene, under the control of a physiologically appropriate promoter, appears to improve stress resistance substantially and without negative pleiotropic effects in field or laboratory environments. The degree of domestication of the crop, the social value of the GGT, and the characteristics of the test environment (e.g., proximity and weediness of wild relatives), are also important in decisions about regulation and data collection.

The U.S. National Research Council and its parent body, the National Academy of Sciences, have issued three major reports that identified traits, rather than the method of production, as the key factor for consideration of risks of GE plants [(*14*) and references therein]. Until recently, this distinction was mostly academic, as there were very few introduced genes, and most were of exotic origin and conferred novel phenotypes. Genomics is changing this significantly. It is allowing breeders to generate similar kinds of traits to those sought conventionally by targeting the underlying genes. These kinds of GGT traits—particularly those that impart obvious domestication phenotypes or utilize native or homologous genes—should require far less oversight by government regulators, especially at the field-testing stage.

Decisions about which traits are sufficiently domesticating or homologous in mechanism to consider suitable for exemption will not always be simple. However, a logical starting point might be to consider the extent of diversity likely to be present in relatives of crop plants. Where novel biochemical pathways or distinct kinds of proteins are added that are unknown within a crop genus, a strong scientific rationale or new experimental data about its domesticating effect and food safety would need to be presented to qualify for exemption. Regardless of exemption at the field-trial stage, it is expected that data on environmental and food safety would need to be presented before commercial release was permitted. By facilitating field trials, however, relaxed regulation of GGTs will help in collection of high-quality safety data.

Regulations that distinguish between classes of recombinant plants may decrease some public condemnation of agricultural GE. If regulatory costs and hurdles were significantly reduced, it might promote GE crop development by small companies and public sector investigators. Given the widespread suspicion of the power and ethics of many large corporations, and the major role that this social skepticism has played in the controversy over GE crops, such "democratization" of biotechnology might be as important as biological advances in promoting public approval of GE in agriculture.

References and Notes

1. J. Bennetzen, *Science* **296**, 60 (2002).
2. "Domesticate—to train or adapt (an animal or plant) to live in a human environment and be of use to humans" from *American Heritage Dictionary* (Houghton Mifflin, New York, 1982).
3. L. L. Wolfenbarger, P. R. Phifer, *Science* **290**, 2088 (2000).
4. M. L. Siegal, A. Bergmann, *Proc. Natl. Acad. Sci. U.S.A.* **99**, 10528 (2002).
5. T. H. Chen, N. Murata, *Curr. Opin. Plant Biol.* **5**, 250 (2002).
6. A. Yeo, *J. Exp. Bot.* **49**, 915 (1998).
7. M. Matsuoka *et al.*, *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **52**, 297 (2001).
8. At a symposium lecture in 2001 D. Duvick (personal communication) reported an informal survey of 20 senior breeders that failed to uncover observations of increased invasiveness or weediness of wild relatives of crops growing in natural populations due to direct breeding efforts for pest resistance (i.e., apart from the importation of the exotic species themselves). Such cases are also unknown by others highly knowledgeable of breeding, biotechnology, and population biology (J. Hancock, N. Ellstrand, personal communications). Although effects may have gone undetected because of insufficient study, these results support the view that selection for stress resistances in agronomic environments has little benefit, or is detrimental, to the fitness of wild relatives.
9. "Field test releases in the USA" (Information Systems for Biotechnology, Virginia Tech, Blacksburg, VA 2003); available at www.isb.vt.edu/cfdocs/fieldtests1.cfm
10. M. Kaufman, *Washington Post*, 24 May 2001, p. A17 .
11. Southern Poverty Law Center, Intelligence Report 107 (2002); available at www.splcenter.org/cgi-bin/goframe.pl?refname=/intelligenceproject/ip-4w3.html
12. *Fed. Regist.* **67** FR 50578 (U.S. Office of Science and Technology Policy, Washington, DC, 2002); available at www.ostp.gov/html/redregbio.html
13. Antibiotic resistance markers may become increasingly unnecessary and undesirable as alternative transformation methods develop and regulations make their use more onerous. However, their use is currently essential for efficient transformation of most crop species.
14. National Research Council, *Environmental Effects of Transgenic Plants: The Scope and Adequacy of Regulation* (National Academy Press, Washington, DC, 2002).

Supporting Online Material

www.sciencemag.org/cgi/content/full/300/5616/62/DC1

Fig. S1