A new CRISPR-driven technology for gene drive in plants

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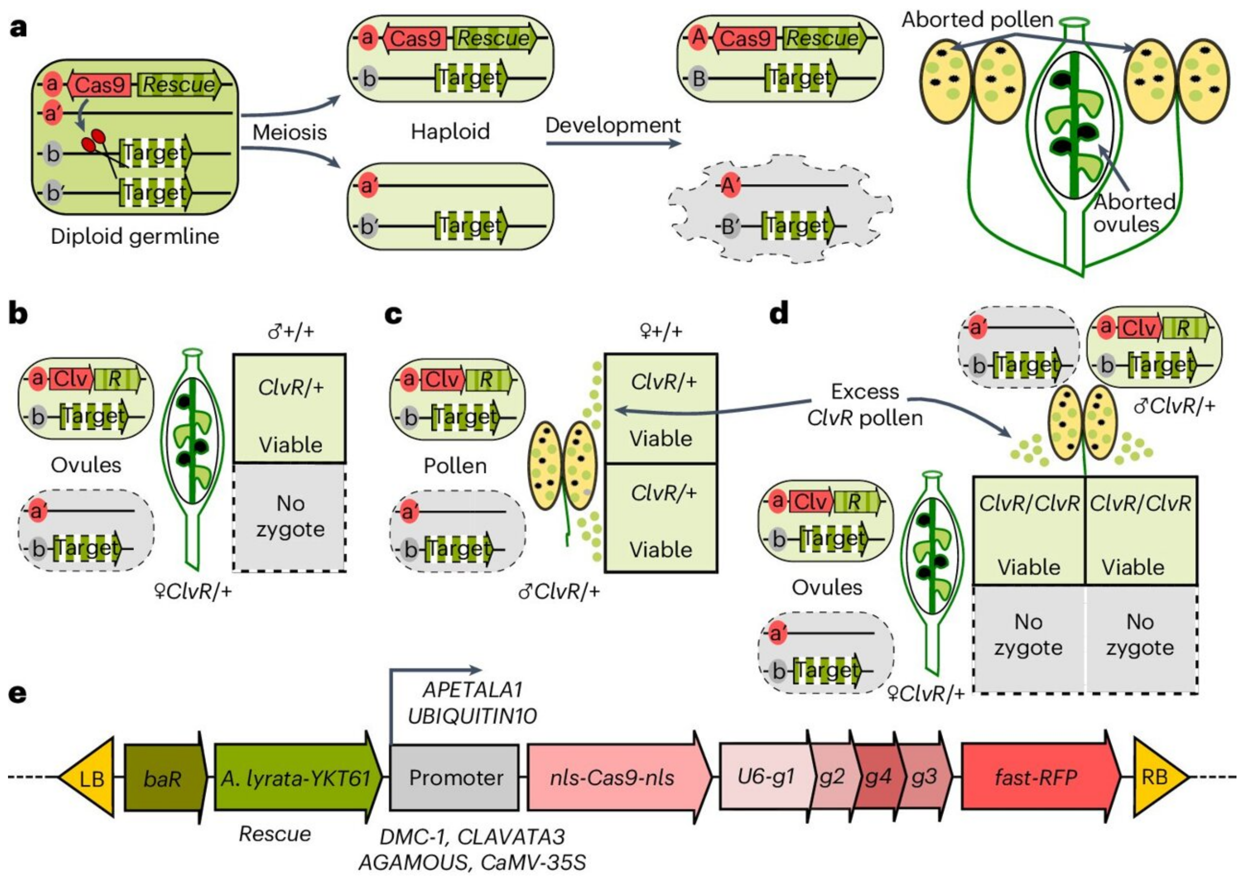

ClvR behavior in a diploid plant and construct design. Credit: *Nature Plants* (2024). DOI: 10.1038/s41477-024-01701-3

Weeds are a pesky irritant for most home gardeners, but in large agricultural settings, weeds can pose an especially deadly problem. For example, Amaranthus palmeri, known as Palmer's pigweed, has evolved in many areas to be completely resistant to modern herbicides, enabling it to take over fields of corn, soybeans, and other important crops. To make pigweed susceptible to herbicides again, you would need to change its genetics.

Spreading a specific genetic trait through a population, even if that trait does not benefit those who carry it, is the purpose of a "gene drive." Gene drives can be used for many different applications. These are divided into two broad categories: population modification and population suppression.

Population modification can make mosquitos immune to, and therefore unable to spread, malaria, or make a crop more heat-tolerant in anticipation of climate change. Population suppression can be used to bring about local reduction or elimination of a weed or invasive species.

But any gene editing program needs to have strict built-in controls to keep the modifications localized to a specific area and to prevent other species from accidentally inheriting modified genes.

Now, Caltech researchers have developed a new gene drive technology, called ClvR (pronounced "cleaver"), that can be specifically customized to plant species, preventing accidental gene editing in cross-pollination situations.

Crucially, the technology can be designed to be self-limiting, only spreading the desired genes for a limited number of generations, thereby limiting their spread in time and space. The work is the first engineered gene drive in plants and the first to enable species-specific modification as well as the first to act at the level of plant sex cells.

A paper describing the new study was published in the journal *Nature Plants* on June 17. The research was conducted in the laboratory of Bruce Hay, professor of biology and biological engineering.

How do you genetically engineer a plant so that its offspring definitely will have a certain gene of interest? When breeding plants and animals, one of the two copies of a gene present in a parent is randomly inherited by a progeny.

Gene drive tips the inheritance scales in favor of one of these copies: the one on which the DNA responsible for bringing about gene drive is located. This results in its spread to high frequency in the population over time.

ClvR ensures that the genes of interest are passed on by affecting a plant's sex cells, or gametes. The ClvRsystem uses CRISPR/Cas9 gene editing technology to ensure that if a gamete does not contain the desired gene, it will not survive. In this way, any future offspring will come from gametes with the desired gene.

The system works by using a so-called "toxin/antidote" paradigm. Cas9 (the "toxin") is programmed to destroy, in the adult stage, a gene required for gamete survival, essentially ensuring its death. But the catch is, gametes carrying ClvR are also provided with an undamaged version of the same target gene (the "Rescue" or "antidote"), which functions like an antidote to a poison, leading to the survival of ClvR-bearing gametes.

That Rescue—the key to the gamete's survival—is also linked to a cargo gene, the gene of interest that a researcher wants to spread into the plant population. In other words, the cargo gene hitchhikes along with the Rescue gene. This ensures that only the gametes that contain both will survive—essentially forcing the cargo gene into the population.

"There are two ways to win a race: Be better than all the other competitors or trip all of the other racers up," says Hay. In this case, the ClvR system trips up all other competing chromosomes that could be inherited by progeny by ensuring that only sex cells with the desired cargo survive.

Importantly, the ClvR system is customizable for different circumstances. The toxin and antidote genes can be chosen to be specific for the desired plant species, so that if the genetic information gets passed into another species, nothing will happen.

Additionally, the "cargo" gene can be designed for various purposes—for example, this gene could re-sensitize pigweed to herbicide or make an endangered plant more heat tolerant or disease resistant—a form of evolutionary rescue.

Finally, the ClvR system can also be engineered to bring about local suppression or elimination of a weed or invasive species through the creation of a high frequency of sterile females, which leads to a population collapse.

"The ClvR system provides a general species-specific tool for altering the genetics of plant populations in ways that can contribute to global challenges such as food security and resilience in endangered native species and ecologies threatened by invasive species and climate change," says Hay. "We are excited to collaborate with others on these problems."

More information: Georg Oberhofer et al, Cleave and Rescue gamete killers create conditions for gene drive in plants, *Nature Plants* (2024). DOI: 10.1038/s41477-024-01701-3

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