

Unprecedented control of genome editing in flies promises insight into human development, disease

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In an era of widespread genetic sequencing, the ability to edit and alter an organism's DNA is a powerful way to explore the information within and how it guides biological function.

A paper from the University of Wisconsin–Madison in the August issue of the journal *Genetics* takes genome editing to a new level in fruit flies, demonstrating a remarkable level of fine control and, importantly, the transmission of those engineered genetic changes across generations.

Both features are key for driving the utility and spread of an approach that promises to give researchers new insights into the basic workings of biological systems, including [embryonic development](#), nervous system function, and the understanding of human disease.

"Genome engineering allows you to change gene function in a very targeted way, so you can probe function at a level of detail" that wasn't previously possible, says Melissa Harrison, an assistant professor of biomolecular chemistry in the UW–Madison School of Medicine and Public Health and one of the three senior authors of the new study.

Disrupting individual genes has long been used as a way to study their roles in [biological function](#) and disease. The new approach, based on molecules that drive a type of bacterial immune response, provides a technical advance that allows scientists to readily engineer genetic sequences in very detailed ways, including adding or removing short bits of DNA in chosen locations, introducing specific mutations, adding trackable tags, or changing the sequences that regulate when or where a gene is active.

The approach used in the new study, called the

CRISPR RNA/Cas9 system, has developed unusually fast. First reported just one year ago by scientists at the Howard Hughes Medical Institute and University of California, Berkeley, it has already been applied to most traditional [biological model](#) systems, including yeast, zebrafish, mice, the nematode *C. elegans*, and [human cells](#). The Wisconsin paper was the first to describe it in fruit flies and to show that the resulting [genetic changes](#) could be passed from one generation to the next.

"There was a need in the community to have a technique that you could use to generate targeted mutations," says Jill Wildonger, a UW–Madison assistant professor of biochemistry and another senior author of the paper. "The need was there and this was the technical advance that everyone had been waiting for."

"The reason this has progressed so quickly is that many researchers—us included—were working on other, more complicated, approaches to do exactly the same thing when this came out," adds genetics assistant professor Kate O'Connor-Giles, the third senior author. "This is invaluable for anyone wanting to study gene function in any organism and it is also likely to be transferable to the clinical realm and gene therapy."

The CRISPR RNA/Cas9 system directs a DNA-clipping enzyme called Cas9 to snip the DNA at a targeted sequence. This cut then stimulates the cell's existing DNA repair machinery to fill in the break while integrating the desired genetic tweaks. The process can be tailored to edit down to the level of a single base pair—the rough equivalent of changing a single letter in a document with a word processor.

The broad applicability of the system is aided by a relatively simple design that can be customized

through creation of a short RNA sequence to target a specific sequence in the genome to generate the desired changes. Previous genome editing methods have relied on making custom proteins, which is costly and slow.

"This is so readily transferable that it's highly likely to enable gene knockout and other genome modifications in any organism," including those that have not previously been used for laboratory work, says O'Connor-Giles. "It's going to turn non-model organisms into genetic model organisms."

That ease may also pay off in the clinic. "It can be very difficult and time-consuming to generate models to study all the gene variants associated with human diseases," says Wildonger. "With this genome editing approach, if we work in collaboration with a clinician to find [clinically relevant] mutations, we can rapidly translate these into a fruit fly model to see what's happening at the cellular and molecular level."

The work, led by genetics graduate student Scott Gratz, was the joint effort of three UW–Madison labs—particularly notable, Harrison says, that each is in a different department and headed by a female assistant professor. "This has been an amazing collaboration," she says. "It wouldn't have worked if any one of us had tried it on our own."

They have already seen tremendous interest in the work: the study, which was posted online in May, quickly became one of the most-viewed papers of the month and the researchers have fielded requests for materials and information from dozens of countries around the world.

Provided by University of Wisconsin-Madison

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