Compositions And Methods For Allelic Gene Drive Systems And Lethal Mosaicism

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BACKGROUND

Efficient super-Mendelian inheritance of transgenic insertional elements has been demonstrated in flies, mosquitoes, yeast, and mice. While numerous potentially impactful applications of such so-called gene-drive systems have been proposed they are currently limited to copying relatively large DNA cargo sequences (~1-10 Kb). Many desired genetic traits (e.g., drought tolerance in plants, crop yield, pest-resistance, or insecticide sensitivity), however, result from allelic variants altering only one or a few base pairs. An efficient system for super-Mendelian inheritance of such subtle genetic variants would accelerate a wide array of efforts to disseminate favorable traits throughout populations, or to assemble complex genotypes consisting of point-mutant alleles in combination with insertional transgenes for a multitude of research and applied purposes.

TECHNOLOGY DESCRIPTION

Researchers at UC San Diego designed new allelic-drive systems that permit the efficient Super-Mendelian transmission (>>50%) of a desired allelic variant of a gene of interest to progeny. These allelic-drive systems build on CRISPR-based active genetic systems that we have previously developed in flies , mosquitoes and, most recently, in mice in which gene-drive cassettes are copied efficiently from one chromosome to another in the germline. Here we adapt these active genetic methods to preferentially transmit allelic variants (allelic-drive) resulting from only a single or a few nucleotide substitutions. We demonstrate allelic drive in two configurations: one, copy-cutting, in which a non-preferred allele is selectively targeted for Cas9/guide RNA (gRNA) cleavage, and a more general approach, copy-grafting, that permits selective inheritance of a desired allele located at some distance from the gRNA cut site .

We also characterize a phenomenon we refer to as lethal-mosaicism, that dominantly eliminates NHEJ-induced mutations and favors inheritance of functional cleavage-resistant alleles. The basis for lethal mosaicism is that mutant alleles produced by non-homologous end-joining (NHEJ) in an essential gene become dominantly lethal during the drive process. In contrast, a protected non-cleavable functional allele of the gene, remains immune to such lethal mosaicism. Thus, lethal mosaicism results in selective elimination of un-desired alleles generated by NHEJ.

APPLICATIONS

Expand the gene-drive tool kit to include biased Super-Mendelian inheritance of beneficial allelic variants (e.g., pesticide sensitivity, or alleles conferring resistance to pathogens in vector species) along with a gene-drive element, as well as deleterious mutations for population suppression strategies. Generate more efficient gene-drive systems that eliminate drive-resistant mutant alleles during the drive process.

ADVANTAGES

Lethal mosaicism offers the only current solution to the major “drive resistance” concern. Next-generation drive systems thus may include a recoded functional portion of a gene inserted in-frame into the endogenous copy of that gene, resulting in a functional chimeric gene immune to Cas9-mediated cleavage. Progeny inheriting such a gene-drive including a protected copy of the gene would then be immune to lethal mosaicism, while those inheriting NHEJ-induced non-functional mutations would all die. This strategy represents a major advance in the field of gene-drive, since transmission of drive-resistant NHEJ alleles represent a prominent obstacle in all prior experiments and models.

STATE OF DEVELOPMENT

The invention is at the proof-of-concept stage.

INTELLECTUAL PROPERTY INFO

The invention is patent-pending and is available for licensing and collaborations.

RELATED MATERIALS

▶ López Del Amo V, Bishop AL, Sánchez C HM, Bennett JB, Feng X, Marshall JM, Bier E, Gantz VM. A transcomplementing gene drive provides a flexible platform for laboratory investigation and potential field deployment. Nat Commun. 2020 Jan 17;11(1):352. doi: 10.1038/s41467-019-13977-7 - 01/17/2020

PATENT STATUS

Patent Pending

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OTHER INFORMATION

KEYWORDS

Allelic Gene Drive, Genetic engineering, CRISPR-Cas9 genome editing, Population genetics, pathogen resistance

CATEGORIZED AS

- ▶ **Agriculture & Animal Science**
  - ▶ Animal Science
- ▶ **Biotechnology**
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RELATED CASES

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