**Title: The gene family that cheats Mendel**

**Authors:** J. Dylan Shropshire1 and Antonis Rokas1,2

**Affiliations:**

1Department of Biological Sciences, Vanderbilt University, Nashville, TN 37235, USA

2Department of Biomedical Informatics, Vanderbilt University, Nashville, TN 37235, USA

**ABSTRACT**

**Genes in the *wtf* family of fission yeasts boost their own spread at the expense of their less fortunate *wtf*-less siblings through production of poisons and antidotes.**

**TEXT**

In 1866, Gregor Mendel described his now famous laws of segregation and independent assortment that state that in a diploid organism, half the gametes will carry one allele and half the other; thus, both parental alleles have an equal likelihood of being transferred to their children (Mendel, 1866). However, not all genes’ alleles obey this law; some alleles have evolved ways to kill sibling gametes that carry alleles from the other parent, achieving their transmission to offspring at frequencies much higher than would be expected from equal segregation (Burt & Trivers, 2006). Genes harboring alleles that increase their own propagation have been identified in plants, fungi, and animals, including humans, and come by various names, such as selfish drivers, meiotic drivers, and gamete or spore killers.

Despite the diversity of meiotic drivers described, a full characterization of their mechanisms of action has remained elusive in most cases. Of those described, they are generally classified as either poison-antidote or killer target systems (Fig. 1). In poison-antidote systems, an antidote is produced that neutralizes the effects of the poison. These effects can be produced by the same gene (a single-gene model) as with the *Spok* genes of *Podospora anserina* (Grognet et al., 2014) or by two distinct genes (two-gene model) as in *Neurospora* (Hammond et al., 2012). On the other hand, the segregation distortion (SD) gene in *Drosophila* acts by killing sperm that carry a ‘target’ locus which is typically absent in viable flies (Larracuente & Presgraves, 2012).

Recognizing the necessity for a genetically tractable system to better understand selfish genetic elements, two research groups led by Sarah Zanders at the Stowers Institute for Medical Research in the United States and Li-Lin Du at the National Institute of Biological Sciences in China turned to the fission yeasts *Schizosaccharomyces kambucha* and *S. pombe* (Hu et al., 2017; Nuckolls et al., 2017). These yeast species are genetically nearly identical, so much so that some do not consider them as separate species, but hybrids between the two are often sterile. In fact, spores derived from crosses between different isolates of *S. pombe* are often inviable, suggesting a very recently emerging reproductive barrier. Previous work by the Zanders group suggested that at least three spore killer genes are responsible for this barrier (Zanders et al., 2014). There most recent work sought to uncover the genetic basis of these spore killers.

To narrow their search, Zanders and colleagues conducted introgression studies to isolate a region of the 3rd chromosome that caused meiotic drive. They then knocked out a gene in the *wtf* gene family (*wtf4*), found in the center of this region, and determined that spores that do not inherit the gene are subject to reduced survival whereas spores with *wtf4* survive, but why? They proposed two hypotheses based on previously characterized meiotic drive systems (Fig.1), asking whether their gene killed spores by acting on target locus as in SD or by producing a poison and antidote as in *Podospora.* Upon testing, they found that *wtf4* does not appear to be acting on a target locus (Nuckolls et al., 2017). However, they found that *wtf4* produces both a poison and an antidote through variable translation of the *wtf4* transcript.

But how does the poison, and not the antidote, act on the surrounding spores? They tested this question by creating variants of *wtf4* with green fluorescent protein tags and visualized the protein’s localization in the gamete and its surrounding. They found that the poison can travel through the membrane of the gamete and interact with sibling spores while the antidote protein is stuck within the cell (Nuckolls et al., 2017). These finding illustrates a novel mechanism used by selfish genes to encourage their spread.

Du and colleagues identified two additional genes in the same *wtf* gene family that act as spore killers. They did this through targeted deletion of two *wtf* genes which they named *cw9* and *cw27*, where they noticed a reduction in meiotic drive. They then asked whether the two genes can rescue the other’s spore killing ability. If both parents have one or either of the genes, then viability was normal. However, if one parent had *cw9* and the other had *cw27* then offspring containing either of the two genes suffered from inviability. These findings suggest that they do not rescue each other and act independently to drive (Hu et al., 2017).

In summary, the data provided by the Zanders and Du groups reveal several genes in a unique gene family that are responsible for the targeted killing of sibling spores that do not carry the genes, via a novel mechanism of action involving alternative transcription of the gene. This work, done in the genetically tractable fission yeast, sets the basis for a promising future of genetic drive research that may yield a fuller picture of the mechanisms of the genes that break Gregor Mendel’s acclaimed genetic laws. Future work in this area will not only help us understand the role of selfish elements on speciation but knowing the biomolecular basis of these phenomena may lead to a better appreciation for the role of these kind of mechanisms in infertility in species as diverse as plants, fungi, and animals including humans.

**FIGURES**

**Figure 1. Meiotic drive generally occurs via poison-antidote or killer-target mechanisms.** In a Poison-antidote model, a toxin (skull-and-crossbones) is produced which is neutralized by an antitoxin (pill). These products can be produced by the same gene (boxes) via alternative transcription, as illustrated by the Zanders and Du groups (Nuckolls et al., 2017; Hu et al., 2017). Alternatively, different genes could produce the poison and antidote (Hammond et al., 2012). In a killer-target model, a toxin is still produced but lethality occurs when the toxin interacts with a specific allele (target), if that allele is absent then the gamete survives (Larracuente et al., 2012).

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