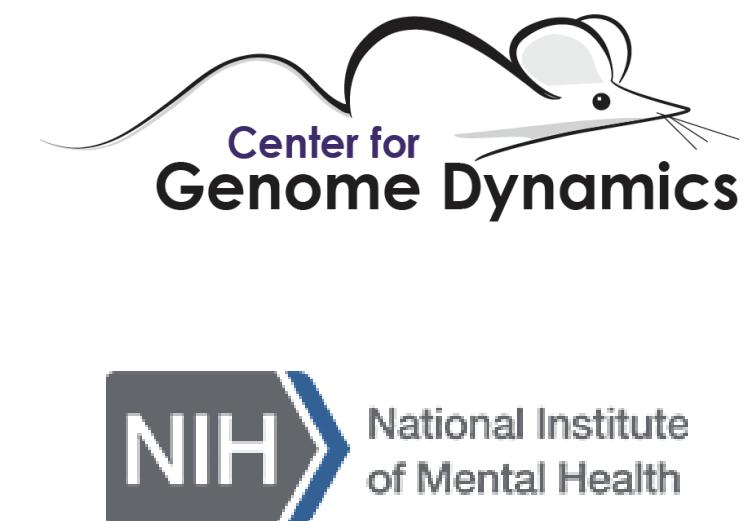




R2d2 drives “selfish sweeps” in mice

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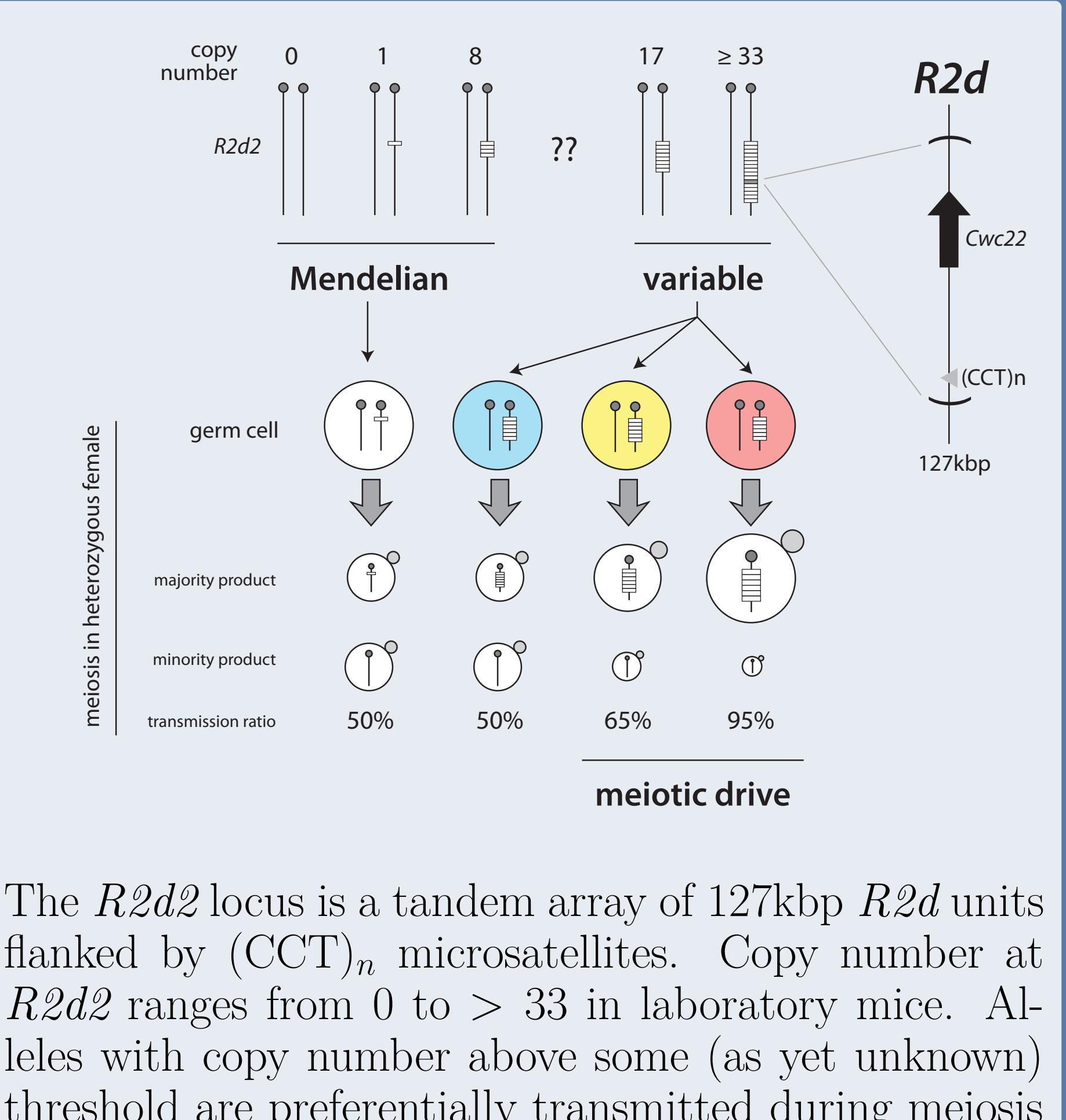
Background

The theory of natural selection posits that the fate of a new mutation depends on its effect on reproductive fitness: beneficial mutations will rise to fixation and deleterious alleles will be purged. However, so-called *selfish elements* subvert their host to promote their own transmission despite being neutral or deleterious with respect to host fitness.

As a beneficial new mutation rises in frequency it crowds out other alleles, leading to a local loss of genetic diversity known as a *selective sweep*. By contrast, little evidence exists for complete sweeps in favor of selfish alleles.

R2d2 is a multiallelic copy-number variant on mouse chromosome 2 which promotes its own transmission via meiotic drive [1]. We show that *R2d2* alleles with high copy number (*R2d2*^{HC}) have driven rapidly to high frequency (and, in several cases, have fixed) in multiple wild and laboratory populations despite being associated with reduced fitness.

The *R2d2* system



The *R2d2* locus is a tandem array of 127kbp *R2d* units flanked by (CCT)_n microsatellites. Copy number at *R2d2* ranges from 0 to > 33 in laboratory mice. Alleles with copy number above some (as yet unknown) threshold are preferentially transmitted during meiosis in heterozygous females. The extent of this *transmission ratio distortion* (TRD) depends on multiple loci in the genetic background [1].

Acknowledgements

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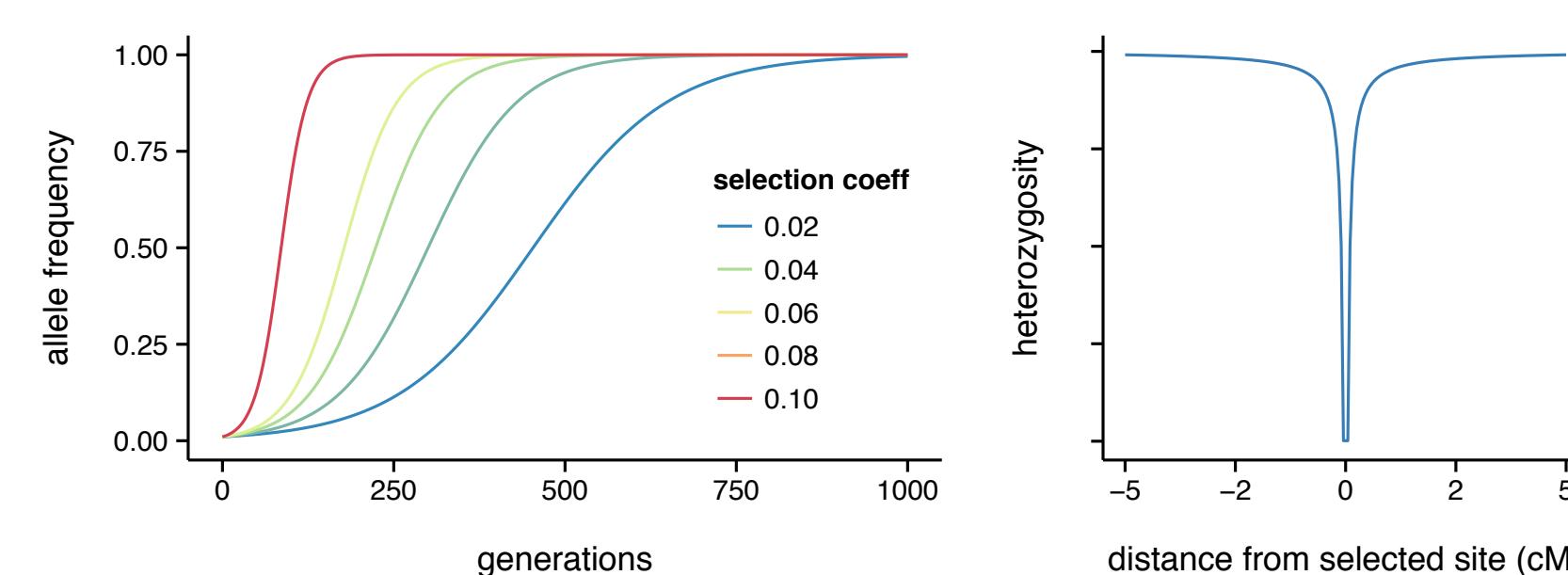
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Future work

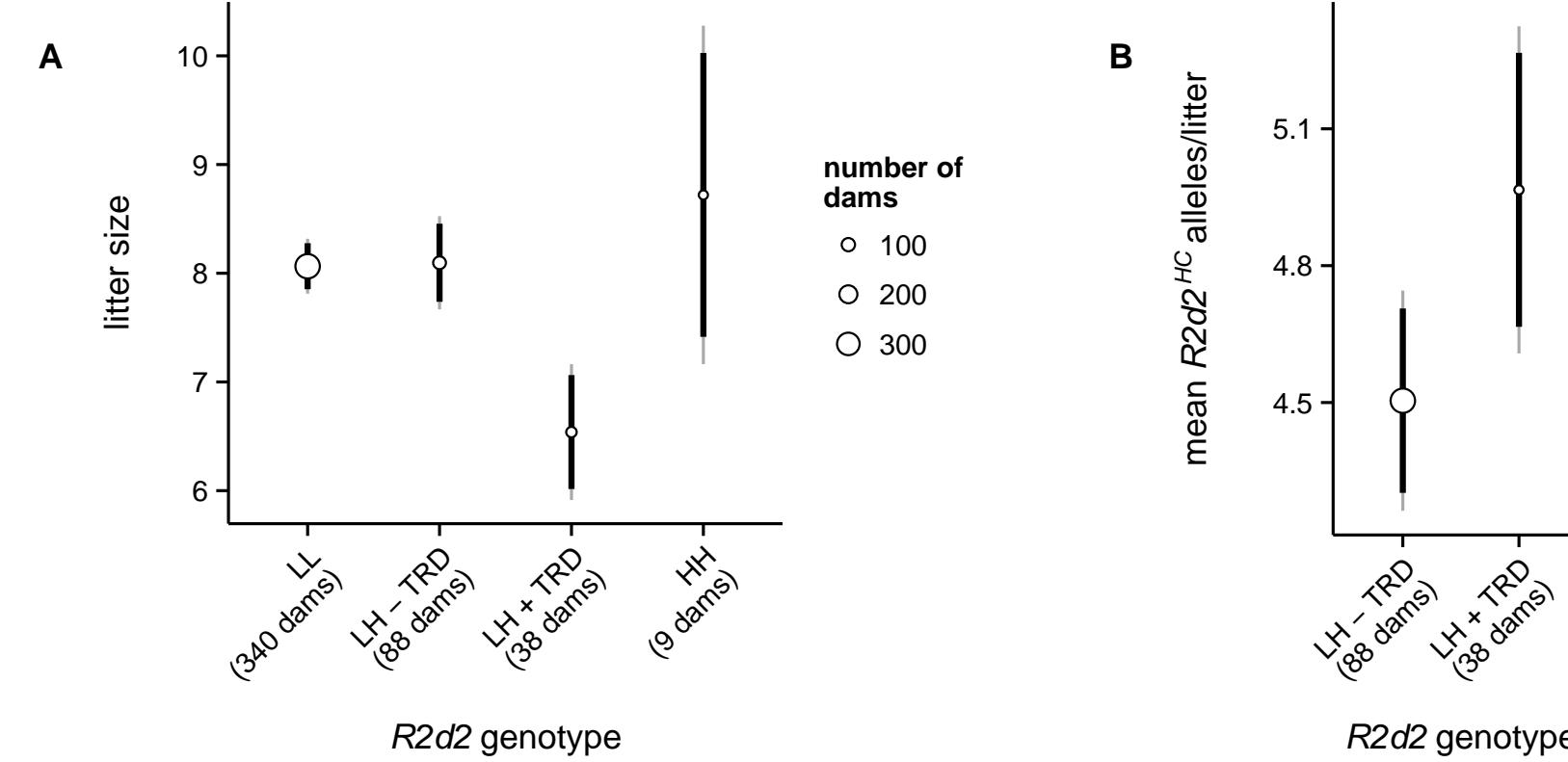
- What is the effect of *R2d2*^{HC} on fitness in natural populations?
- What is the mechanism of meiotic drive at *R2d2*?
- What is the genetic architecture of meiotic drive at *R2d2*? How are selfish sweeps at constrained by number and frequency of modifier loci?
- How common are selfish sweeps, in general?

Selective sweeps and diversity



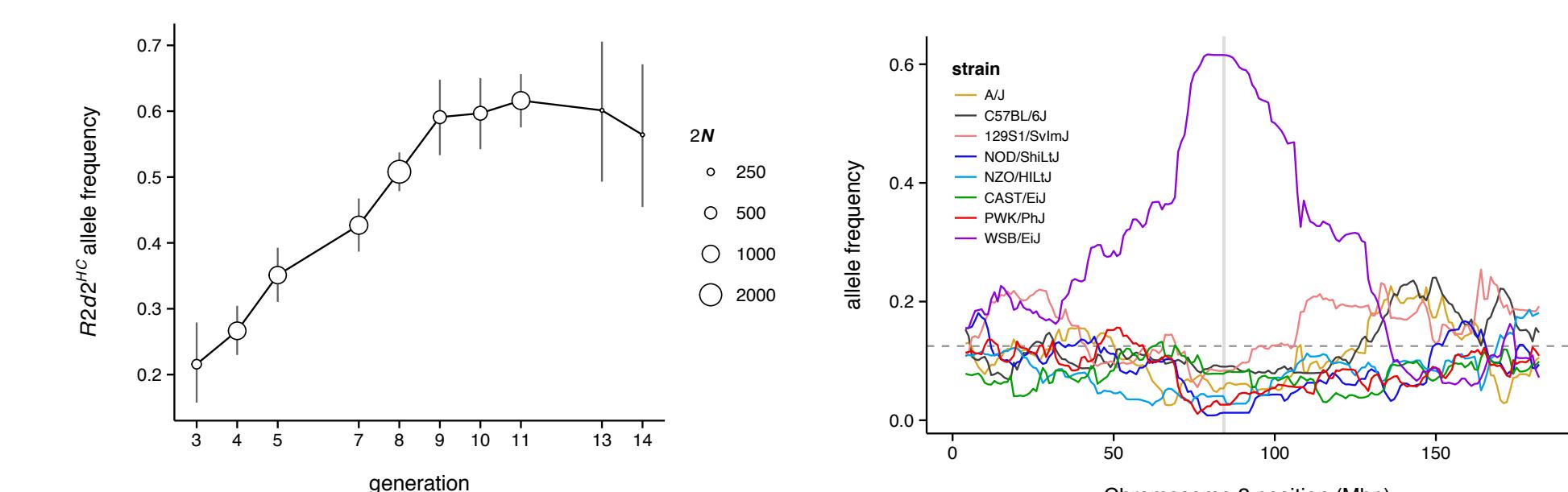
In an idealized population, a beneficial new mutation will rise from initial frequency $1/2N$ to 1 at a rate determined by its selection coefficient (s). Fixation of the mutation is accompanied by a loss of diversity around the selected site (genetic hitchhiking [2]). Recombination between the derived and ancestral haplotypes restores diversity.

R2d2^{HC} is selfish



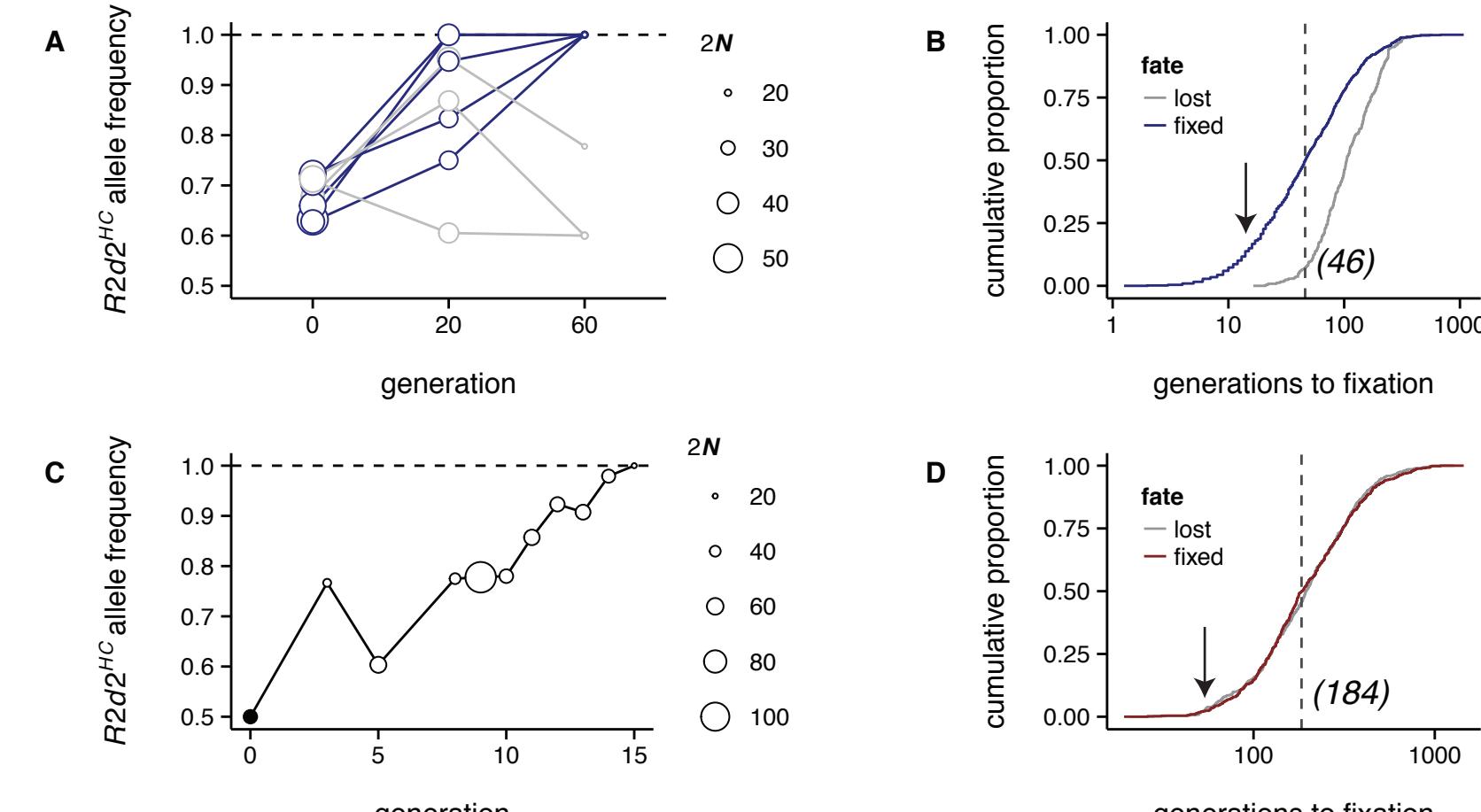
DO females heterozygous for *R2d2*^{HC} and with meiotic drive have significantly smaller litters than either homozygous genotype (panel A). However, despite having smaller litters, these females transmit a higher absolute number of *R2d2*^{HC} alleles (panel B). *R2d2*^{HC} is therefore a selfish allele with an underdominant effect on fitness.

A sweep in an outbred population



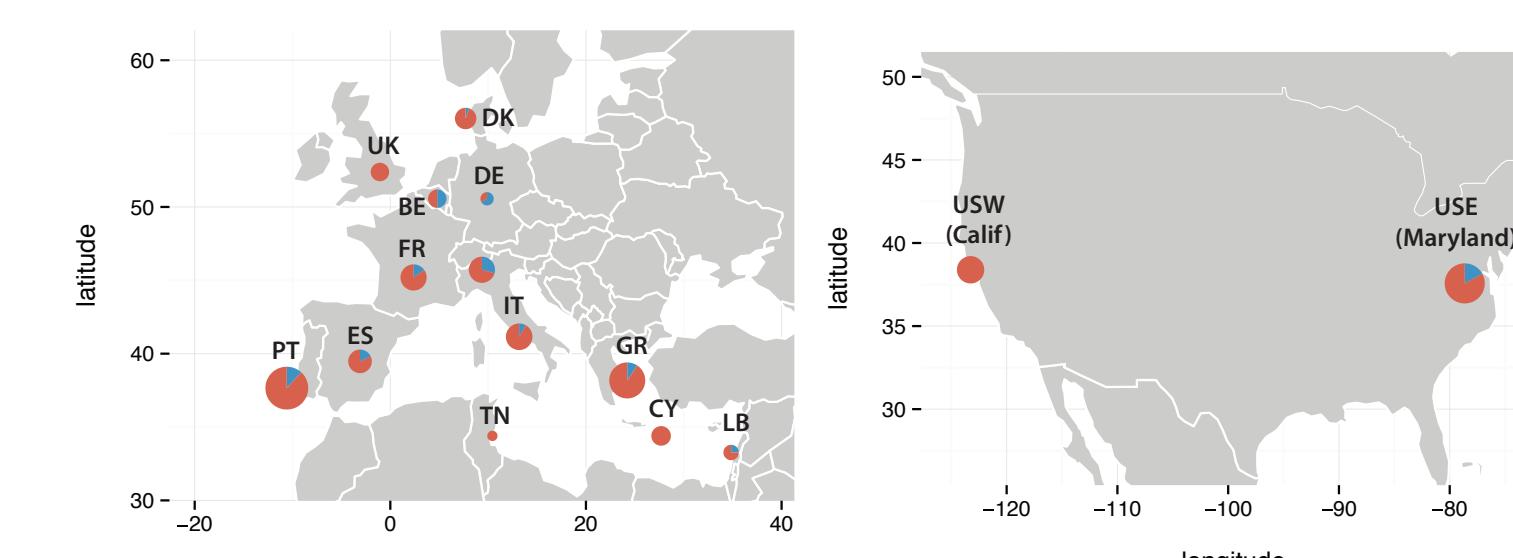
The Diversity Outbred (DO) is an outbred stock derived from eight inbred founder strains with $N_e = 350$. The *R2d2*^{HC} allele from the WSB/EiJ strain rose from initial frequency 0.125 to 0.62 in only 11 generations (left) vs a maximum of 0.26 in 1000 neutral simulations [3]. This resulted in a loss of diversity across a ~ 50 cM region of chromosome 2. Efforts to purge the allele were undertaken after generation 11.

Sweeps in other laboratory populations



In a long-term selection experiment [4], *R2d2*^{HC} alleles were fixed in 5 of 8 breeding lines ($N_e \approx 20$ each) within 20 – 60 generations (panel A), more rapidly than in neutral simulations (panel B). In an advanced intercross line ($N_e \approx 30$), *R2d2*^{HC} fixed in 15 generations (panel C), again faster than in neutral simulations (panel D).

Selfish sweeps in the wild



R2d2^{HC} is present at intermediate frequencies in wild mouse populations in Europe and the United States (above). Consistent with recent positive selection, identity-by-descent (IBD) between unrelated individuals is increased around *R2d2* (panel A at right). Haplotype homozygosity is increased on *R2d2*^{HC} vs *R2d2*^{LC} haplotypes (panels B,C).

Theory

Let $0.5 + m$ be the transmission ratio of a meiotic drive allele ($0 \leq m \leq 0.5$) and s the selection coefficient against the heterozygote ($0 \leq s \leq 1$). If f_t is the frequency of the driving allele in generation t , its frequency is at generation $t+1$ is:

$$f_{t+1} = \frac{(1-s)(1+2m)(1-f_t)f_t + 2f_t^2}{2[1-2sf_t(1-f_t)]} \quad (1)$$

In a large population, the fate of the driving allele is determined by the quantity q :

$$q = \frac{1}{2}(1-s)(1+2m) \quad (2)$$

When $q > 1$, the driving allele will rise to fixation (black region in panel A at right); while for $q \ll 1$, the driving allele will be lost (grey region in panel A at right). For $q \approx 1$, f tends to an unstable equilibrium which depends on m and s [5].

Should a selfish allele fix?

Simulations show that a new underdominant selfish allele, which arises with frequency $1/2N$, is not likely to fix unless s is small, m is large, or the population (N) is quite small. This is true especially when meiotic drive is dependent on modifier loci.

