Supplementary Methods

Forward Population Genetic Simulations

We modeled an isolated population of diploid individuals at initial mutation-selection balance using SLiM v3.3.2 (Haller and Messer 2019). We simulated a population of N=50,000 diploid individuals. The genome consisted of two chromosomes of 5 Mb, 1 Mb of which were coding regions where allelic content was simulated. The allelic content of the rest of the chromosome was not simulated to alleviate the computational load, although recombination could occur anywhere. Coding regions, at which all sites could harbor selected mutations, were 100 kb segments, separated from each other by 400 kb of non-coding regions (i.e. areas where allelic content was not simulated).

We chose parameter estimates inspired by *Arabidopsis thaliana* to calibrate our model, because mutation and recombination rates are well characterized in this species. In our model, mutations happened at a rate of μ=7 x 10^{-9} per bp per generation (Weng et al. 2019). All mutations only occurred in coding regions and affected individual fitness multiplicatively. The vast majority of mutations (99.9%) were deleterious and recessive with magnitudes of fitness effects ($|s|$) drawn from a Gamma distribution Γ (α=0.5, mean=0.0025). Beneficial mutations (0.1% of mutations) were co-dominant and drawn from an exponential distribution with a mean of 0.001. Overall recombination rate was set at 5.4 x 10^{-7} per base pair per meiosis following estimates from *A. thaliana* (Wijnker et al. 2013) but corrected for the high rate of selfing (all individuals in our simulations were obligate outcrossers). All simulations started following a burn-in of 500,000 generations to ensure that mutation-selection-drift equilibrium was attained.

Modeling an Insertion

We assumed that an insertion occurred in a random haplotype. The insertion occurred between two given loci on chromosome one and encompassed 0.625%, 1.25%, or 2.5% of the genome, corresponding to 31.25 kb, 62.5 kb or 125 kb prior to scaling (see below). For a given haplotype we modeled a 500-generation "invasion phase" and a subsequent 99,500-generation "evolution phase". We performed 3 replicates of the "evolution phase" per haplotype. During the invasion phase, the insertion occurred in a random haplotype and was given a strong heterozygote advantage s_{HET}=0.0075 or $2Ns_{HET}$=750 to aid invasion. During invasion no recombination occurred in the inserted region, all mutations in the inserted region were dominant, and any insertion homozygote offspring were re-drawn.

After 500 generations of invasion the heterozygote advantage was removed and mating rules were added. We followed the mating rules of the S-locus in *Primula* only allowing for insertion heterozygotes (*S/s*) X standard homozygotes (*s/s*) matings. As in the invasion phase, no recombination occurred in the insertion heterozygotes (*S/s*), all mutations in the inserted region were dominant, and any insertion homozygote (*S/S*) offspring were re-drawn. The simulation ran for a total of 100,000 generations after the burn in. The final population was retained for calculating the distribution of fitness effects for various regions of the genome.

For each size of insertion we ran 3 replicates from 50 haplotypes.

Modeling an Inversion

As in our indel model, recombination in our inversion model was fully suppressed in heterokaryotypes but proceeded normally in homokaryotypes. As before we assumed that the inversion occurred in a random haplotype. The inversion occurred between two given loci on chromosome one and encompassed 1.25% of the genome (i.e. 62.5 kb prior to rescaling, see below). The "invasion phase" and the "evolution phase" were identical to the insertion except that all mutations in the inverted region were recessive.

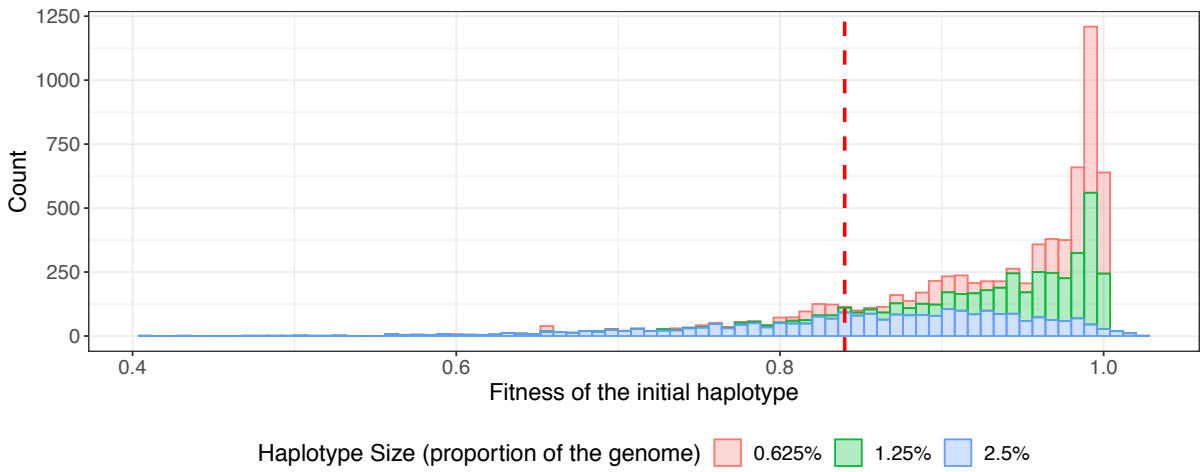
Scaling

Simulation with these parameters was not feasible because of the extremely large computational burden. Instead we used the common practice of rescaling parameters so that evolutionary processes happened at an accelerated rate (see for example Tuttle et al. 2016). We thus downscaled both population size and genome length by a factor 20 and upscaled the remaining parameters so that $2N\mu L$ and $2NrL$ (with L the length of the genome) remained constant.

Supplementary Results

Invasion

Inversions invaded the population much more easily than insertions. This is likely due to mutation masking in the early stages of invasion for inversions when only heterokaryotypes occur. Invasion success for the hemizygous region, where all mutations are dominant, was lower and was strongly affected by the size of the region. This is because larger regions contained more deleterious mutations (Supplementary figure 1).



Supplemental Figure 1. Histogram depicting the fitness of initial S haplotype by size (red - 0.625% of the genome, green - 1.25%, blue - 2.5%). The dashed red line indicates the fitness needed for the haplotype to invade as an indel under our parameters.

Literature Cited

Haller BC, Messer PW. 2019. SLiM 3: Forward genetic simulations beyond the Wright-Fisher model. Mol Biol Evol. 36:632-7.

Tuttle EM et al. 2016. Divergence and functional degradation of a sex chromosome-like supergene. Curr Biol. 26:344-350.

Weng ML et al. 2019. Fine-grained analysis of spontaneous mutation spectrum and frequency in *Arabidopsis thaliana*. Genetics. 211:703-14.
Wijnker E et al. 2013. The genomic landscape of meiotic crossovers and gene conversions in *Arabidopsis thaliana*. elife. 2:e01426.