EVOLUTION

Sex decreases the pleiotropic costs of local adaptation by purging hitchhiking load

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Understanding the evolutionary mechanisms that maintain sex despite its direct costs is a long-standing challenge. Previous work has shown that sexual recombination can accelerate adaptation, in part by separating beneficial mutations from deleterious hitchhikers. However, earlier studies focused on effects of sex in a constant environment. We show that recombination provides an advantage during changing conditions in promoting the evolution of generalist phenotypes by reducing pleiotropic costs caused by local adaptation. Using laboratory evolution in *Saccharomyces cerevisiae*, we show that hitchhiking load leads to pleiotropic costs and hence specialization in response to local adaptation in asexual but not sexual lineages. This provides evidence that sex can be maintained over long evolutionary timescales because it enables lineages to persist in the face of environmental change.

Explaining why sex is pervasive across eukaryotes, despite its substantial direct costs, is a longstanding question in evolutionary biology. Prior theoretical and experimental work has highlighted mechanisms by which sex can speed adaptive evolution—for example, by bringing together beneficial mutations that occur in different genetic backgrounds or by purging any hitchhiking deleterious genetic load (*1*–*6*). However, most past work focused on how sex speeds adaptation in a single environment [but see (*7*)]. In this work, we analyzed a potential benefit of sex when environmental conditions change intermittently across time or space: Recombination can promote generalism by alleviating the pleiotropic costs of local adaptation. Specifically, sex can decouple locally adaptive mutations from other hitchhiking variation, which may have negative effects in other environments. This increases robustness to environmental change and hence provides a potential evolutionary advantage over longer timescales.

This potential advantage of sex is related to the "Red Queen" hypothesis, which posits that recombination accelerates adaptation in the face of the changing selection pressures of arms-race dynamics—for example, in host-pathogen coevolution (*8*–*10*). However, the Red Queen hypothesis focuses on how sex accelerates adaptation to a rapidly changing target. We analyzed the role of sex in mitigating the negative trade-offs that occur when environmental conditions change slowly or episodically. We expected the strength of this effect to depend on the genetic architecture of pleiotropy. If neutral or mildly deleterious hitchhiking variation tends to be more costly in other conditions (hitchhiking pleiotropy), purging this variation by means of recombination will mitigate the tendency of local adaptation to lead to specialization. On the other hand, if specialization results from the direct effects of locally adaptive alleles (antagonistic pleiotropy), then sex will not have this effect because it cannot decouple locally beneficial mutations from their costs in other conditions (Fig. 1A).

To test for the potential effect of sex in promoting generalism, we describe a comparison of the pleiotropic costs of adaptation in sexual versus asexual populations, using laboratory evolution in the budding yeast *Saccharomyces cerevisiae* as a model system. We evolved both sexual and asexual populations in rich laboratory media and measured the effect of regular bouts of recombination on the rate and pleiotropic consequences of adaptation. By comparing both molecular and phenotypic evolution in sexual versus asexual populations, we analyzed how recombination could mitigate the costs of local adaptation and promote the evolution of generalism.

Results

We established 17 replicate sexual and 18 replicate asexual *S. cerevisiae* populations from a single laboratory strain and propagated them independently for 960 generations of laboratory evolution in rich media [yeast extract, peptone, and dextrose (YPD)] using a standard batch culture protocol with effective population size ~10^5. Using a system we established in earlier work that ensured that sexual and asexual populations are otherwise maintained as identically as possible, sexual populations were propagated by interspersing asexual mitotic growth with regular bouts of recombination every 120 generations. Otherwise, sexual and asexual populations were maintained as identically as possible (fig. S1) (*5*, *11*).

Sex increased the rate of adaptation and decreased its pleiotropic costs

After 960 generations of adaptation, we measured the competitive fitness of each population relative to a reference strain in the "home" environment (the environment in which they evolved: rich laboratory media, YPD at an optimal temperature, 30°C). We found that sexual populations increased in fitness by 8% over the ancestor in this home environment, compared with 5.7% in asexual populations. Thus, consistent with previous work, our work showed sex accelerated adaptation (generalized Wilcoxon test, $P < 0.001$) (Fig. 1A).

We measured the pleiotropic effects of this adaptation on the fitness of each evolved population in five "away" environments [synthetic complete media (SC), at 30°C, and SC with one of the following perturbations that create additional stress: +0.2 M sodium chloride (NaCl), buffered pH 7.3, phosphate limitation, and high temperature of 37°C], which the populations had not previously encountered during evolution (Fig. 1). We found that sex also mitigates the costs (and in some cases enhances the benefits) of local adaptation to the home environment: Sexual lines exhibit an average fitness advantage of between 2 and 5.6% over asexual populations in each of the five away conditions (generalized Wilcoxon test with Benjamini-Hochberg correction, all $P < 0.001$) (Fig. 1B). In asexual populations, adaptation to YPD often results in fitness declines in the away environments (Fig. 1B), indicating specialization relative to the ancestor (in which specialization is defined as a loss of fitness in some nonhome environments) (*12*). By contrast, the pleiotropic fitness effects of adaptation are very rarely deleterious for sexual lines (Fig. 1B), even though sexual lines adapted more rapidly to the home environment. Consistent with this, we also found that in both sexuals and asexuals, populations that are more fit at home are also more fit away (permutation test of pairwise Spearman correlations, mean $\rho = 0.476$ for asexual populations and 0.386 for sexual populations, both $P < 0.001$) (fig. S2), suggesting that antagonistic pleiotropy is not the major cause of specialization.

A corollary theoretical prediction is that sex should narrow the range of evolutionary outcomes seen among independent lines evolving in the same environment because recombination alleviates stochastic effects of clonal interference among beneficial lineages and reduces the effect of genetic draft that would otherwise carry neutral and mildly deleterious mutations to high frequencies. However, prior experimental

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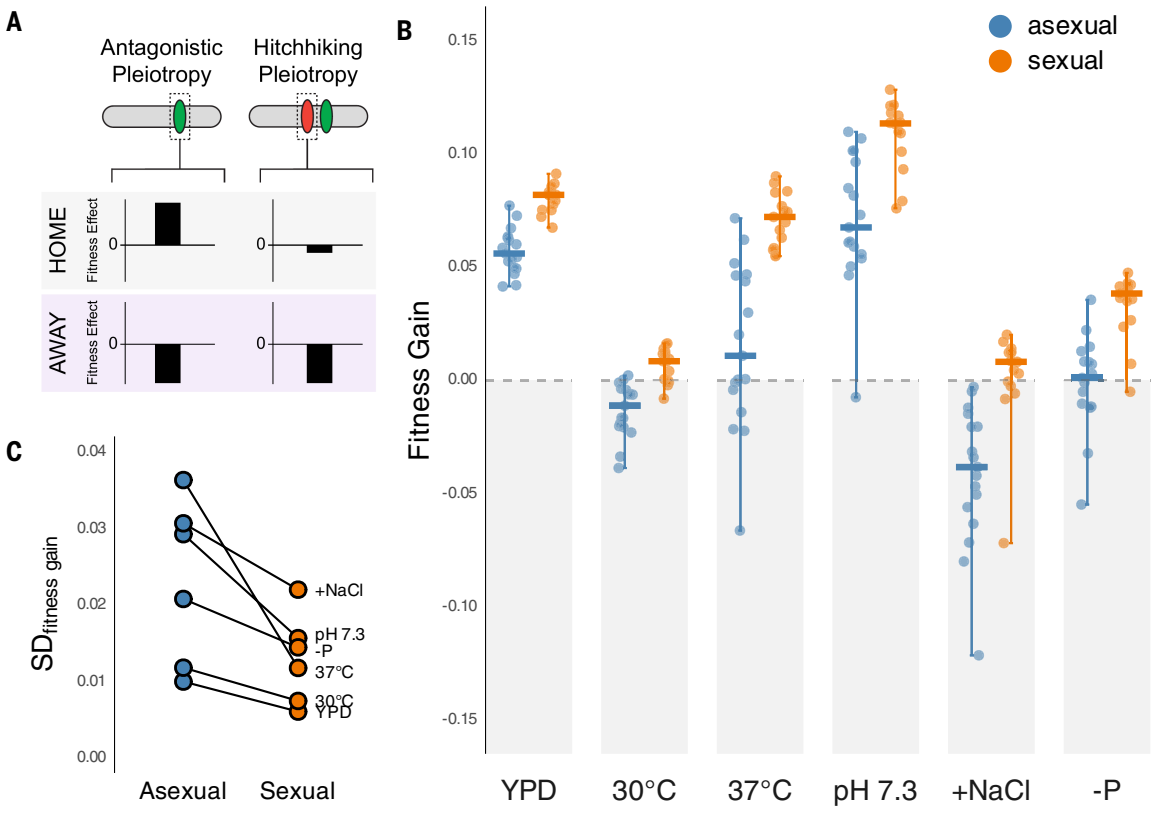

Fig. 1. Recombination increases fitness gain and repeatability and decreases pleiotropic costs of adaptation. (**A**) Schematic of fitness effects of mutations in home and away environments underlying antagonistic pleiotropy and hitchhiking pleiotropy. (**B**) Distribution of fitness changes relative to the ancestor across home (YPD) and away environments (SC 30°C, 37°C, pH 7.3, +NaCl, −phosphate), with each independent asexual ($n = 17$) or sexual ($n = 18$) population indicated with a dot. Horizontal bars indicate median and vertical lines indicate range. (**C**) Standard deviation (SD) in fitness across replicate populations in asexual compared with sexual populations in home and each away environment.

work found mixed support for this effect (*5*, *7*, *11*, *13*). In this study, consistent with the theoretical expectation, we found that the range of fitness outcomes was consistently more variable among asexual populations than among sexual populations for both home and away environments (paired t test of σ values, $t = 3.19$, $P = 0.02$) (Fig. 1C).

Sex narrows the outcomes of molecular evolution

Greater fitness variation in asexual versus sexual populations suggests an underlying model in which asexual populations genetically diverge more rapidly and more stochastically than sexual populations. To evaluate this claim, we compared the number and spectrum of de novo mutations in sexual and asexual populations by sequencing adapted clones from generation 960 in each population. We first isolated two clones from each replicate population and assayed the fitness of each clone in both home and all away environments and found that the fitness measurements of the clones recapitulated the population-wide results (fig. S3). We then conducted whole-genome sequencing of each clone at ~20× depth and used a standard bioinformatics pipeline to identify mutations. Library preparation failed in three clones, and we excluded six clones owing to suspected whole-genome duplications in three populations that made mutation identification unreliable, leaving us with a total of 65 sequenced clones (for consistency, the three populations with genome duplications were excluded from both fitness and sequence analysis). We defined a mutation as putatively fixed in a population if it was identified in both clones isolated from that population, and as nonfixed if it was identified in one of the two clones.

We found that asexual populations fixed sevenfold as many mutations as that of sexuals and contained twice as many nonfixed mutations (generalized Wilcoxon test with Benjamini-Hochberg correction, both $P < 0.001$) (Fig. 2A and fig. S4). To analyze the potential functional consequences of these mutations, we classified each mutation within a coding region as synonymous, nonsense, missense, or indel and referred to mutations in the latter three classes as "putatively functional" (although we noted that the effect of these putatively functional mutations may often arise from disrupting rather than improving gene function). We found that asexual populations contained threefold as many putatively functional mutations as sexuals contained (Welch's t test, $t = 10.20$, $P < 0.001$) (Fig. 2, A and B). Thus, the average degree of genetic divergence of evolved clones from their ancestors was elevated in asexual compared with sexual lines, and this effect was stronger among putatively functional mutations.

We aimed to analyze how much of the genetic variation observed in asexual versus sexual populations was potentially adaptive. To do so, we reasoned that functional mutations that were present in only a single population were less likely to be targets of adaptation than genes mutated in multiple replicate lines. We therefore classified a gene as "multi-hit" if we identified a fixed or nonfixed functional mutation in that gene in multiple replicate populations, and as "single-hit" otherwise. Because it is unlikely (although not impossible) for multiple independent hits to happen by chance, multi-hit genes are putative targets of adaptation. We found that both sexual and asexual lines contained mutations in many of these multi-hit genes (Fig. 2A, inset), indicating that these putative targets of adaptation were similarly available to populations regardless of recombination regime. Mutations in multi-hit genes represent a substantially larger proportion of all mutations in sexual compared with asexual clones (Welch's t test, $t = -3.24$,

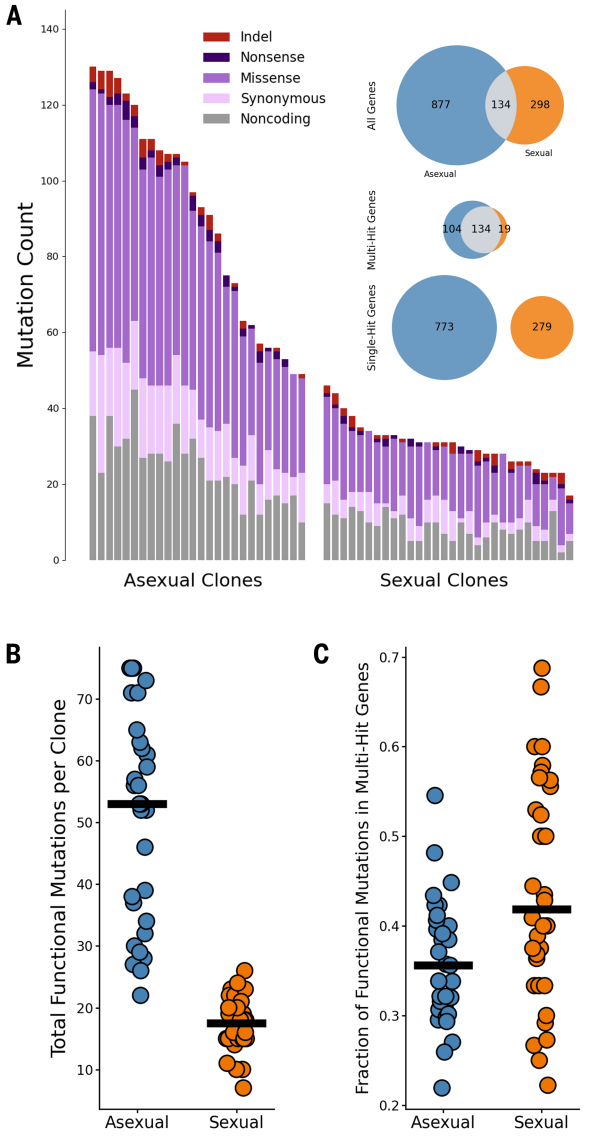

Fig. 2. Recombination decreases the rate of genetic divergence and narrows the spectrum of mutational targets. (**A**) Number of mutations is lower among sexual compared with asexual clones. (Inset) Number of mutational targets (genes) with putatively functional mutations in sexual and asexual clones, broken down into multi-hit targets and single-hit targets. Genes are classified as multi-hit if they contain functional mutations in multiple replicate populations, and otherwise classified single-hit. (**B**) Distribution of total putatively functional mutations (nonsynonymous single-nucleotide polymorphisms + genic insertions and deletions) per clone, showing higher tendency and greater spread for asexual versus sexual clones. (**C**) Fraction of all putatively functional mutations per clone found in multi-hit genes. Horizontal black bars indicate medians.

$P = 0.002$) (Fig. 2C); hence, molecular evolution in sexual populations involves accumulation of a higher proportion of putatively adaptive mutations than that in asexual populations.

Hitchhiking genetic load leads to pleiotropic fitness costs in asexual lineages

Together, our fitness and mutation data support a model in which genetic linkage increases rates of genetic divergence in asexual populations through the stochastic accumulation of nontarget mutations. Such linked mutations constitute a genetic load that could potentially suppress fitness both in home and away environments and reduce the genotypic (and thus phenotypic) repeatability of local adaptation. This pleiotropic load may result from mutations that are either neutral or mildly deleterious in the home environment but are more deleterious in at least some of the away environments. To further explore this hypothesis, we sought to examine the relationship between fitness and the number of nontarget mutations. Given that nondriver mutations (potential load) tend to outnumber beneficial driver mutations in mutational cohorts that segregate during adaptation (*14*), we predicted that clones with more overall putatively functional mutations should exhibit stronger direct and pleiotropic fitness liabilities.

We found that asexual clones with relatively more putatively functional mutations had relatively lower fitness, and thus more genetic load, across both home and away environments (Fig. 3A). Using a linear model, we found that the relative fitness of asexually evolved clones, in home and away environments, was negatively correlated with the number of mutations harbored by such clones [linear regression, coefficient of determination (R^2) = 0.52, $F_{1,27} = 29.19$, $P < 0.001$] (Fig. 3). No such correlation was evident for sexually evolved clones (linear regression, $R^2 = 0.0005$, $F_{1,26} = 0.01$, $P = 0.91$) (Fig. 3). This pattern is strongest among single-hit mutations, which are likely enriched for nontargets, and weaker among multi-hit mutations, likely because they contain a smaller fraction of nontargets (asexual single-hit, $R^2 = 0.53$, $F_{1,27} = 31.23$, $P < 0.001$; asexual multi-hit, $R^2 = 0.31$, $F_{1,27} = 12.13$, $P = 0.002$) (fig. S5).

Sex purges load underlying pleiotropic costs of adaptation

To more directly test whether asexual lines harbor more load-causing mutations, we sought to separate load-causing from beneficial mutations by back-crossing adapted clones to an ancestral genotype (Fig. 4A). We predicted that parental genotypes with more genetic load would be more likely to produce back-crossed F_1 offspring with higher fitness than that of their adapted parent, as compared with parental genotypes with less genetic load. After isolating at least 60 F_1 offspring from each of 19 back-crosses, we found that offspring of asexual parents were on average more fit than their parent in 6 of 10 crosses, whereas offspring of sexual parents were on average more fit than their parent in 2 of 9 cases (Fig. 4, B and C). However, this difference is not statistically significant (Fisher's exact test, $P = 0.17$).

We used randomly selected subsets of our back-crossed F_1 pools (six asexual and six sexual) to test the hypothesis that genetic load in the home environment underlies pleiotropic fitness costs in away environments. To do so, we assayed the fitness of individual F_1 offspring from back-crosses with adapted parents across a subset of our away environments (+0.2 M NaCl, pH 7.3, and 37°C). Offspring fitness was positively correlated across all environments (Fig. 4D); offspring with lower pleiotropic fitness also had lower fitness in the home environment, whereas relatively more fit offspring enjoyed this benefit across all away environments. Averaged across away environments, the relative fitness rank of an F_1 genotype within its cohort was tightly positively correlated with its fitness rank in the home environment (Spearman correlation $\rho = 0.53$ to 0.76 for sexual populations and $\rho = 0.62$ to 0.91 for asexual populations, all $P < 0.01$ with Benjamini-Hochberg correction) (fig. S6). This result reveals that genotypes with higher load in the home environment show similar extents of load in alternate environments, whereas more fit genotypes retain their advantage overall. This is consistent with off-target hitchhiking mutations (which are neutral or possibly slightly deleterious in the home environment but more strongly deleterious in other conditions) rather than antagonistic pleiotropy driving the pleiotropic costs of local adaptation.

Discussion

The evolution of fitness trade-offs across environments or ecological niches is central to local adaptation, ecological specialization, and eventually speciation (*12*). Reciprocal transplant experiments between natural populations of plants and animals from different environments

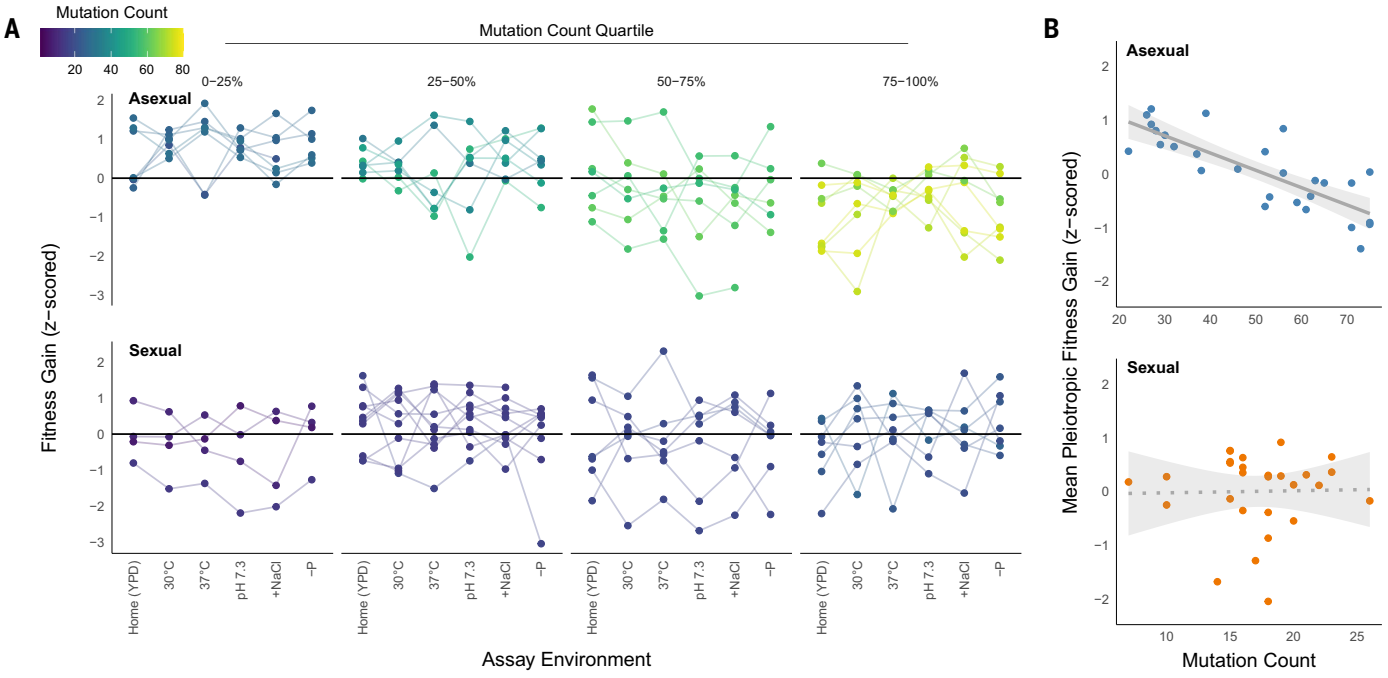

Fig. 3. Asexual clones with more mutations show decreased pleiotropic fitness. (**A**) Fitness (scaled) across home and each away environments for clones binned by quartiles of total putatively functional mutations reveals that asexual clones with more mutations are relatively less fit across all environments. (**B**) Asexual clones with more putatively functional mutations show lower relative mean fitness gain across away environments (pleiotropic fitness gain), whereas sexual clones show no such pattern.

have shown that local adaptation is widespread in the wild but that the magnitude of specialization is low (*15*). However, the factors underlying the speed, magnitude, and genetic basis of the evolution of specialization are not fully understood. Potentially, the evolution of specialization in natural populations of sexual organisms differs from the asexual laboratory microbial populations often used to probe this question. Our results showed that specialization proceeds more rapidly and erratically in asexual lines, in which genetic hitchhiking promotes specialization by increasing genetic load across environments. By contrast, in sexual populations, local adaptation leads to fewer pleiotropic fitness costs and hence enables lower cost generalism to evolve.

A longstanding challenge in evolutionary biology is to understand how sex is maintained in almost all eukaryotes despite its clear costs to survival, including the costs of mating, increased risks of predation or parasitism, and disruption of coadapted gene complexes (*1*–*4*, *6*). Our work lends further support to earlier studies showing that recombination speeds adaptation by rescuing beneficial mutations from deleterious backgrounds (*5*). Additionally, we have shown that this genetic load is responsible for pleiotropic fitness trade-offs in asexual populations, which are largely alleviated by recombination. In other words, sex not only speeds local adaptation but also reduces its pleiotropic costs. This effect of reducing the costs of generalism or niche expansion provides a previously unknown potential advantage for recombination when conditions vary across environments encountered sequentially, which may help explain why sex is prevalent over longer evolutionary histories. Our results are focused on slow or episodic environmental change; they do not address rapid alternation between environments but instead inform expectations when environments change more slowly than the time required for hitchhiking load to accumulate.

This advantage of sex depends on the genetic basis of the pleiotropic costs of adaptation, which has traditionally been studied in the context of distinguishing antagonistic pleiotropy (*16*) from mutation accumulation (*17*–*21*). Earlier work has produced mixed evidence for both of these effects across many field and experimental studies (*22*–*36*). Our results are consistent with mutation accumulation being dominant over antagonistic pleiotropy because recombination purges accumulated mutational load and alleviates pleiotropic fitness costs. If antagonistic pleiotropy were strong, we would expect sexual lines to have lower fitness than that of the ancestor in away environments, which they did not. Moreover, we saw no antagonistic pleiotropy even among asexual populations after a single bout of sex, with fitness in the home and away environments positively correlated. This indicated that at least in our system, direct biochemical or physiological trade-offs were less important than hitchhiking deleterious load in driving specialization. Whenever this is true, we expect that sex can provide a benefit in mitigating the pleiotropic costs of local adaptation.

Although our study has focused on recombination in eukaryotes, the advantage of sex may also extend to prokaryotes, which reproduce asexually but engage in frequent homologous recombination by means of horizontal gene transfer (HGT) through transformation, conjugation, and transduction (*37*). Such prokaryotic forms of sexual exchange have previously been shown to accelerate adaptation to new or stressful environments (*38*–*41*), although the evidence remains inconclusive (*42*). Testing for the role of sex in alleviating pleiotropic trade-offs as a putative benefit of HGT could help understanding the advantages of generalism during changing conditions—for example, soil bacteria during environmental perturbations and clinically relevant pathogenic bacteria in host transitions.

Earlier work has argued that the evolution of evolvability, often defined as the ability to generate adaptive variation, is an important response to changing environmental conditions (*43*, *44*). However, empirical demonstrations of this effect have primarily been limited to asexual microbes (*45*, *46*). By contrast, in sexual populations, recombination is predicted to constrain the evolution of evolvability by separating loci that increase evolvability from the adaptive variation they generate (*47*, *48*). Our results here offer a simpler explanation for how sexual populations can adapt in the face of new or changing environments.

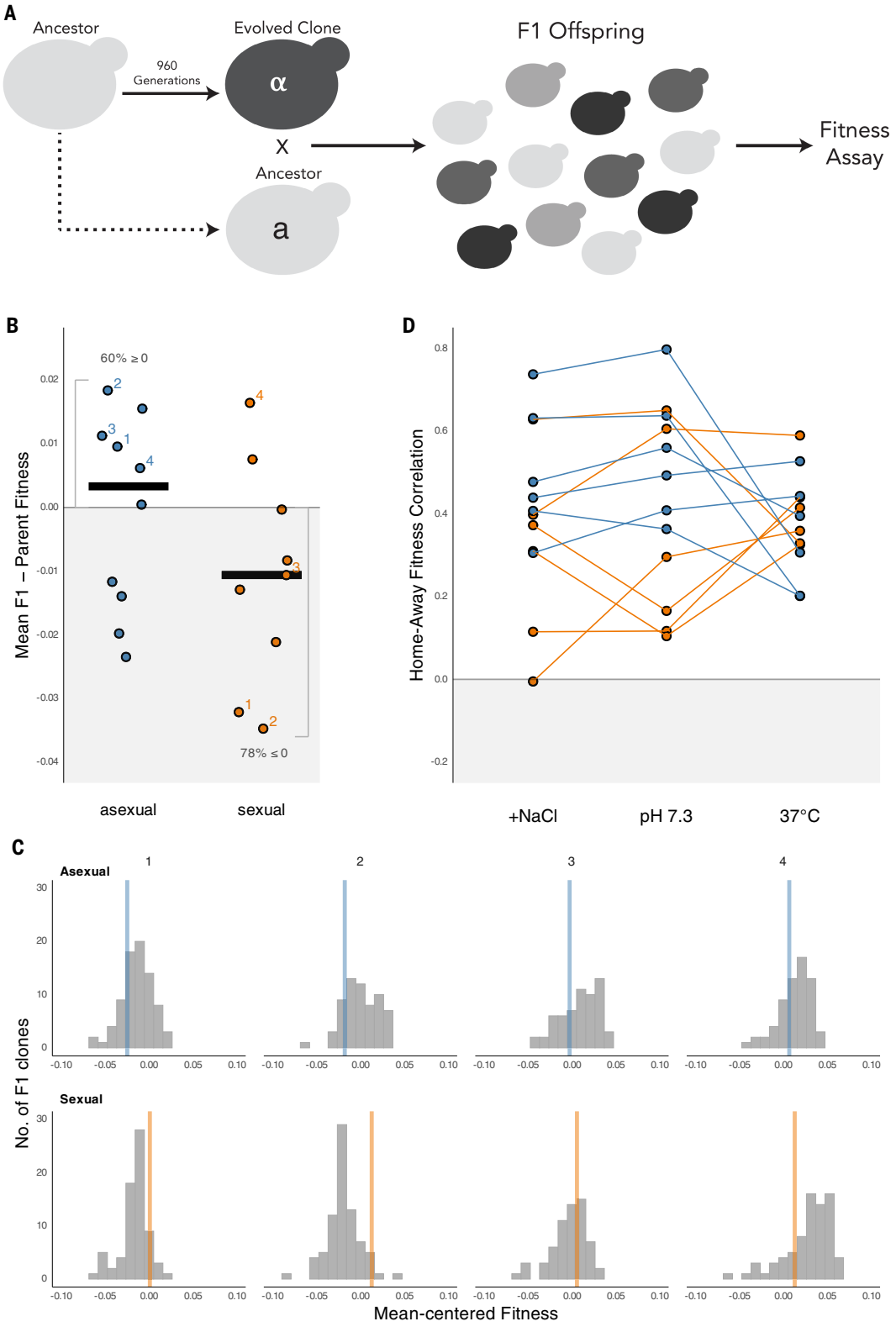

Fig. 4. Ancestral back-crossing purges genetic load from adapted asexual parents in home and away environments. (**A**) Schematic of ancestral back-cross. Evolved MATα clones at generation 960 are crossed with the MATa ancestor to generate a pool of F_1 offspring, whose fitness is then measured with competitive fitness assays as earlier. (**B**) Mean fitness difference in home environment (YPD) between parent and back-crossed offspring for sexually and asexually evolved parents ($n \geq 60$ F_1 clones assayed per cross). Horizontal lines indicate medians. Populations shown in (C) are indicated with numbers. (**C**) Examples of back-crossed F_1 fitness distributions from (top) four sexual and (bottom) four asexual parents indicated in (B), with parental fitness of each strain indicated with a vertical bar. Fitness of parents and F_1 offspring are displayed mean-centered relative to mean of all parental strains ($n = 19$). Fitness values between −0.1 and +0.1 are shown for clarity, and these account for >99% datapoints. (**D**) Fitness correlation of back-crossed offspring across home and a subset of away environments (+NaCl, pH 7.3, 37°C). Almost all correlations are positive.

We found that recombination increases the robustness of the evolutionary response to shifting conditions, despite (and indeed because of) observing that these populations generate less genetic variation than that of asexual populations.

We emphasize that although our results show that sexual populations have higher fitness than that of asexual populations in away conditions because recombination purges hitchhiking pleiotropic load, in this study we did not directly conduct evolution in changing conditions. We expect the detailed temporal dynamics of any such environmental changes, along with other population genetic parameters (such as population size and mutation rate) to play an important role. Future theoretical and computational work will be required to quantify precisely how we expect the strength of this advantage of recombination to depend on these factors. In particular, theory should be developed to analyze the effect of the timing of environmental shifts and to consider how rapidly fluctuating environments may behave differently. Direct experimental confirmation of these predictions would then require conducting evolution in appropriately changing conditions. We also emphasize that this advantage of sex relies on the structure of pleiotropy—in particular, the presence of hitchhiking neutral or mildly deleterious mutations with larger pleiotropic costs in other conditions. There may be general reasons to expect this to be a common phenomenon, but it could also reflect circumstances that are more particular to our laboratory microbial system. This is ultimately an empirical question, which will require future studies across a variety of organisms and ecological settings.

Further work is needed to fully understand the interplay between sex, pleiotropy, and ecological generalism. A more direct approach to show that pleiotropic fitness costs are caused by costly genetic load would be to reconstruct putative beneficial drivers and deleterious hitchhikers to directly measure their fitness effects. Although technically challenging to conduct at scale, this is now becoming feasible by using CRISPR-based methods. It would also be interesting to analyze adaptation on standing variation and in diploids rather than haploids and to test whether these benefits of sex are diluted or amplified in such scenarios. Population genetics theory and mathematical modeling of sexual recombination in the face of episodically changing environments could complement these empirical findings and stimulate hypotheses to test in natural and laboratory populations. Previous work on antagonistic pleiotropy has focused on life history trait trade-offs, such as between pre- and postreproductive survival, conflict between the sexes, and even between asexual and sexual life cycle phases (*49*, *50*). Future work that considers this richer set of phenotypes; expands our approach to other facultatively sexual species with varying life histories; and integrates these studies with high-throughput phenotyping, genotyping, and genetic manipulation techniques may shed more light on the critical question of why sex is so widespread across biology.

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SUPPLEMENTARY MATERIALS

science.org/doi/10.1126/science.aec9708
Materials and Methods; Figs. S1 to S7; References (*53*–*65*); MDAR Reproducibility Checklist

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Sex decreases the pleiotropic costs of local adaptation by purging hitchhiking load

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Editor's summary

Sexual reproduction is a complex and costly undertaking for eukaryotes such as budding yeast, which can also divide asexually. The great advantage is that sexual recombination accelerates adaptation and leaves behind deleterious mutations. In an attempt to find out how sex is maintained, Pai *et al*. found that for yeast subjected to a changing growth environment, which is the norm for most organisms, recombination promotes the evolution of generalists. Sexual reproduction is thus maintained in the long term because it reduces the pleiotropic costs of local adaptation and permits the persistence of lineages. —Caroline Ash