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Population Genomics of Herbicide Resistance: Adaptation via Evolutionary Rescue

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Abstract

The evolution of herbicide resistance in weed populations is a highly replicated example of adaptation surmounting the race against extinction, but the factors determining its rate and nature remain poorly understood. Here, we explore theory and empirical evidence for the importance of population genetic parameters—including effective population size, dominance, mutational target size, and gene flow—in influencing the probability and mode of herbicide resistance adaptation and its variation across species. We compiled data on the number of resistance mutations across populations for 79 herbicide-resistant species. Our findings are consistent with theoretical predictions that self-fertilization reduces resistance adaptation from standing variation within populations, but increases independent adaptation across populations. Furthermore, we provide evidence for a ploidy–mating system interaction that may reflect trade-offs in polyploids between increased effective population size and greater masking of beneficial mutations. We highlight the power of population genomic approaches to provide insights into the evolutionary dynamics of herbicide resistance with important implications for understanding the limits of adaptation.

Contents

HERBICIDE RESISTANCE AS A MODEL SYSTEM TO STUDY ADAPTATION

The evolution of resistant weed populations in response to herbicide applications is a striking example of convergent adaptation across species, but this highly replicated evolutionary experiment is also increasingly becoming a problem for agricultural management. Contemporary agricultural regimes that rely heavily on crop monocultures are susceptible to competition from weed species and thus depend on the use of herbicides to minimize interspecific competition and maximize yields (158). Overreliance on herbicides since they were introduced in the 1950s has led repeatedly to the evolution of weed species resistant to these once-lethal chemicals (12, 42). Observations of resistance phenotypes in natural weed populations are astounding in the extent of their widespread geographic and taxonomic distribution and in their response to a range of herbicides. Herbicide resistance has arisen across 69 countries, and 251 weed species are resistant to 162 different herbicides and to 23 of the 26 herbicide sites of action, for a total of at least 469 unique cases of herbicide resistance (73). With the growing spread of resistance across species and herbicide modes of action, reactive strategies to combat resistance are becoming increasingly ineffective, underlying the need to understand the key factors driving resistance evolution (119). The assurance of global food security via agricultural yields is thus in need of a highly integrative management approach, in which population geneticists, evolutionary biologists, and weed scientists investigate the nature of resistance adaptation and the factors that affect it to both predict and prevent the evolution of herbicide-resistant weeds.

Weed–herbicide systems are governed by the same forces as traditional examples of adaptation but are extreme in that they experience exceptionally severe selective pressures. These systems provide researchers with the unparalleled opportunity to study adaptive processes in plants in real time. Despite the fundamental—and applied, in the case of herbicide resistance—importance of adaptation, key questions about the underlying genetic processes remain. In particular, our empirical knowledge of the effect size and dynamics of beneficial mutations has remained incomplete largely owing to their rarity (124), although from observations of the incidence of resistant weeds, it is evident that beneficial mutations have arisen repeatedly across species in response to selection

from herbicides. It remains unclear however, how often resistance adaptation occurs via de novo mutation or standing genetic variation, whether mutations arise independently across populations or spread through gene flow, and what key population- and species-level factors control the rate and nature of resistance evolution. Addressing these questions will not only inform us about how weeds persist under strict agricultural regimes, but also provide invaluable insight into the population genomics of adaptation.

Models of evolutionary rescue have been used to understand adaptation predominantly in unicellular and fast-growing multicellular systems (e.g., 16, 91, 134), but they are also particularly useful for considering the population genetics of herbicide resistance adaptation. Under an environmental change in which previously fit genotypes are no longer suited to their environment, evolutionary rescue that prevents extinction and restores positive population growth requires the presence of adaptive variants (15, 23, 56, 66, 78, 127). In the context of herbicide resistance adaptation, the adaptive mutants that lead to evolutionary rescue come in two forms: target site resistance (TSR) (43) and nontarget site resistance (NTSR) (39, 41, 172) mutations. These two types of resistance mechanisms may result in different patterns of adaptation yet are influenced by the same fundamental population genetic parameters.

Most broadly, a key question of both basic and applied importance concerns the factors limiting the rate of adaptation and influencing the probability of evolutionary rescue in populations. Here, we review the theoretical expectations and empirical evidence to date for the factors expected to influence the rate and probability of resistance evolution in weed populations. Consideration of these factors leads to important testable predictions about which species and populations are more likely or less likely to evolve resistance, which can be investigated in both experimental and agricultural populations. Because the varying nature of adaptation to herbicide resistance can leave important signals in patterns of genomic variation, we outline the potential for population genomic approaches to provide key insights into these questions over the next decade.

FACTORS THAT INFLUENCE RESISTANCE ADAPTATION

Population genetic theory predicts that several parameters are key to determining the likelihood of adaptation by natural selection: effective population size (N_e), mutation rate (μ), strength of selection (s), and dominance (h). Here, we discuss how much these factors vary across genetic mechanisms of resistance and populations, and their role in determining the probability of resistance adaptation. However, the evolve-or-perish nature of resistance adaptation also suggests that models of evolutionary rescue at the intersection of ecology and evolution are directly relevant (57). The emphasis of evolutionary rescue models on the U-shaped dynamics of population decline and growth, rescuing mutations, absolute fitness and census population size, and influences from external factors such as migration (21, 27, 160) necessitates the discussion of ecological factors in addition to those mentioned above. Therefore, we also expand our discussion to include demographic factors, as well as the source of rescuing adaptive variation, including new mutation, standing genetic variation within populations, and gene flow from other populations.

New Mutation Versus Standing Genetic Variation

One key factor influencing the rate and probability of adaptation is whether adaptive variation preexists in populations or requires new mutations (11). After an environmental change, if adaptive mutations are segregating at significant population frequencies, adaptation will proceed rapidly, whereas a waiting time for new mutations can slow adaptation and impact the demographic recovery of adapting populations (127). Adaptive variants may have preexisted in the population as either neutral or deleterious mutations. For previously neutral mutations, their frequency prior

Standing genetic variation: preexisting neutral or deleterious mutations that persist in the face of selection, but upon an environmental perturbation take on novel beneficial effects

Evolutionary rescue: the rapid decline and recovery of populations following an environmental change, where a rescuing mutation restores positive population growth before extinction occurs

Target site resistance (TSR): resistance caused by mutations that arise in the targeted protein, preventing conformational binding of the inhibiting herbicide

Nontarget site resistance (NTSR): metabolic, transport, penetrative, or protective mechanisms that reduce the exposure of the target enzyme to herbicides

Effective population size (N_e): the size of an ideal population (N) that would experience an equivalent effect of genetic drift as the structured population of interest

Gene stacking: the gradual process of recombining adaptive variants onto the same background

to environmental change depends on mutation rates and the effective population size; for previously deleterious mutations, their initial frequency depends on the strength of purifying selection and the deleterious mutation rate (125, 127). Under a model of evolutionary rescue in which an environmental shift leads to a population decline, the rate at which wild-type individuals are lost directly limits how many new mutations can arise (126). In turn, the probability that adaptation proceeds from standing genetic variation or new mutation depends on the balance between the frequency of standing genetic variants and the rate at which new mutants arise in the declining population (125, 127). The relative importance of these two sources of adaptive variation in rescuing populations from extinction remains a key question in understanding adaptation (11) but can be addressed through population genetic approaches.

Studies of herbicide resistance provide a tractable system to investigate whether adaptation proceeds predominantly from standing genetic variation or from mutations that arise de novo. Given that in many cases the initial frequency of a new mutation ($\frac{1}{2N}$) may be much smaller than the frequency of variants under mutation-selection balance ($\frac{u}{s}$) (11, 74), standing genetic variation may often be involved in resistance adaptation when costs due to the absence of herbicides are not overwhelming.

Several reports of standing genetic variation for herbicide resistance in untreated populations have been documented. For example, TSR to acetyl-CoA carboxylase (ACCase) herbicides has been documented in herbarium specimens of the grass *Alopecurus myosuroides*, collected in 1781, long predating the introduction of herbicides to agricultural practices (40). Investigations of the segregating frequency of herbicide resistance mutations in untreated populations also provide insight into the prevalence of standing genetic variation if gene flow from resistant populations did not occur. The frequency of target site acetolactate synthase (ALS)-resistant individuals in three untreated populations of *Lolium rigidum* was between 1×10^{-5} and 1.2×10^{-4} (120, 138), which is considerably higher than estimates of the spontaneous mutation rate of resistance alleles (between 10^{-8} and 10^{-9}, based on mutation accumulation experiments in *Arabidopsis* and *Nicotiana tabacum*; 67, 69). These results suggest that selection against known, large-effect TSR mutations in the absence of herbicide may often not be sufficiently severe to completely remove resistance alleles; thus, selection from standing genetic variation may be important for this evolutionary process.

Small-effect variants across the genome that confer resistance may be segregating at higher frequencies than large-effect TSR mutations, assuming their costs correspond to their beneficial effect sizes. Indeed, it is thought that NTSR arises gradually over generations by the recombination of small-effect mutations across genes onto the same genetic background (gene stacking) (39), and the coordinated actions of these genes have been identified as conferring resistance in populations of *A. myosuroides* and *Raphanus raphanistrum* (6, 96). The role of standing variation from small-effect mutations depends on the strength of selection; individuals with small-effect mutations are more likely to survive and persist under low doses of herbicide than under high doses. Consistent with this finding, an examination of the effect of low- and high-dose treatment in *Lolium perenne* found the frequency of putative NTSR individuals to be 4×10^{-4} for low dose and between 0 and 3×10^{-5} for high dose (106). Moreover, an initially susceptible population of just 100 individuals of *L. rigidum* was reported as cross-resistant to chemically unrelated herbicides after just three generations of selection from very-low-dose diclofop-methyl (ACCase) (25), implying rapid selection for NTSR from readily available variation. Standing genetic variants may therefore have a direct role in the evolution of NTSR populations, in which their effect size determines their importance for evolutionary rescue of susceptible populations. Persisting small-effect resistance mutations may slow the rate of population decline, increasing the probability that a large-effect de novo mutation may arise and restore positive population growth (119).

The genomic patterns associated with the fixation of standing genetic variants differ from those associated with fixation of a new mutation, as recombination has had time to shuffle standing genetic variants onto different genetic backgrounds (84, 140, 156). These patterns respectively correspond with the processes of fixation called soft and hard selective sweeps (74, 113). The traditional population genetic view of adaptation in eukaryotes sees populations as mutation limited, and therefore adaptation proceeds via hard selective sweeps. In contrast, in populations not limited by mutational input such as those with high levels of standing genetic variation or recurrent mutation, adaptation can occur via soft selective sweeps (74). Because soft selective sweeps draw from multiple adaptive haplotypes, the loss of genetic diversity is much less extreme than under hard sweeps. The extent to which populations are mutation limited ultimately determines the roles of new mutation and standing genetic variation and thus hard and soft sweeps in adaptive evolution (74). As we discuss further below, population genomic approaches can thus help distinguish the relative role of new mutation and standing genetic variation.

Hard sweeps: the signal of selection on a single, newly arisen mutation, whereby neutral genetic variation is lost surrounding the site under selection since one haplotype constitutes the population

Soft sweeps: the signal of selection on multiple variants or allele copies segregating at a single site or at nearby sites within a gene, whereby multiple adaptive haplotypes constitute the population

Population Size

Both census size and the effective size of populations have important effects on the probability of evolutionary rescue. On the one hand, effective population size before the application of herbicides is a key determinant of the strength of drift on neutral and nearly neutral mutations, which subsequently influence the probability of rescue from standing genetic diversity. On the other hand, if resistance adaptation proceeds primarily from new mutation, the rate of resistance adaptation is determined primarily by the rate of new mutations, their beneficial effect, and the effective population size. If their beneficial effect is larger than the rate of population decline ($s > r$), new resistance mutations can contribute to evolutionary rescue with the probability $2(s - r)$ (127). The census population size is also a key parameter for determining the minimum threshold at which rescue can occur, under which extinction from demographic stochasticity is likely (56, 77). Generally, populations with a larger N_e have increased standing genetic variation from previously neutral mutations and an increased number of individuals contributing to the next generation, which should in turn increase the probability of evolutionary rescue under novel environmental conditions (27, 56, 93, 104).

Studies of the influence of N_e relevant to evolutionary rescue have examined its genomic influences on the type of selective sweep. Notably, pesticide adaptation in *Drosophila* occurs by soft selective sweeps in parallel across populations worldwide, as a remarkably large contemporary N_e (112) means that adaptation is not mutation limited, in contrast to expectations from the historical N_e (85). Similarly, a study of the impact of N_e on reductions in diversity in primates concluded that the number of experienced selective sweeps over time increases with population size, but that adaptation was likely mutation limited in apes (116). No empirical study of plant populations thus far has investigated the relationship between effective population size, mode of selection, and probability of evolutionary rescue, and more basically, only a couple of studies have investigated the genomic consequences of the spread of resistance (50, 90; see the section titled Toward a Research Program in the Population Genomics of Herbicide Resistance). Nevertheless, some of the most resistant weeds are those with large populations (e.g., *Amaranthus* spp., *Avena fatua*, and *Conyza canadensis*) (72), consistent with the prediction that rates of adaptation should be highest in such species.

Mutational Target Size

Another key factor that may limit or aid in the evolution of herbicide resistance adaptation is the mutational target size. Resistance mutations may arise through new mutation after the addition

of herbicide pressure or through standing genetic variation; both cases depend on the product of the per-base mutation rate and the number of sites in which a nucleotide substitution is adaptive (33). The probability of a susceptible population surviving herbicide treatment via evolutionary rescue increases linearly with the number of targets across the genome that can contribute to the resistance phenotype (126). In the context of herbicide resistance, variation in mutational target size manifests in many forms and at multiple levels: the number of binding sites in target proteins across herbicides, the number of genes involved, the length of those genes, and the number of whole genome copies.

Mutational target size: the number of sites or regions that can contribute to any given phenotype

Transition state enzyme: the chemical analog in a reaction with the highest energy and lowest stability; thought to be the most effective and tightly binding target for inhibition

Gene amplification: the repeated duplication of genes within a cell cycle

The repeated evolution of herbicide resistance in natural weed populations has been increasingly documented since herbicides were first introduced. Despite a wealth of distinct resistance mutations, parallel convergence of the underlying molecular basis of resistance phenotypes—down to the gene, amino acid, or nucleotide—is by no means the exception. For example, several ALS TSR mutations occur recurrently across species; Trp_{574}-to-Leu and Pro_{197}-to-Ser amino acid substitutions are present across 36 and 25 species, respectively, more than twice as many species as any of the other 26 unique TSR mutations (73). Similar patterns are present for NTSR; a few gene families are repeatedly implicated in resistance adaptation across a range of species (39). These patterns of molecular convergence at the levels of the single nucleotide polymorphism and the gene imply evolutionary constraint in the form of a limited mutational target size.

Between herbicides, target proteins differ in the number of amino acids that influence conformational binding and thus in the number of sites in which a mutation may confer resistance. The rate of emergence of TSR thus varies between herbicides, with the prediction that herbicides with a larger mutational repertoire for resistance experience faster rates of resistance adaptation. These expectations can thus inform risk assessments on whether certain herbicides may be more likely than others to lead to resistance adaptation. For example, glyphosate herbicides that target the 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) enzyme were thought to be at low risk for leading to the evolution of resistance: Glyphosate mimics the transition state enzyme and thus leads to strong inhibition (147), a lack of active plant transporters were known (22), and target site mutations were few and could not be produced from mutagenesis experiments (69, 80). In fact, a comparative mutagenesis study of glyphosate and ALS herbicides in two biotype replications of 125,000 *Arabidopsis* lines found no glyphosate-resistant mutants arose, whereas the spontaneous frequency of ALS resistance individuals was 3.2×10^{-5} (80). Indeed, TSR to glyphosate in weed populations has been identified in just one amino acid residue, Pro106, which is not directly involved in binding but rather slightly alters the protein structure owing to the large fitness costs in the form of kinetic activity from other resistance mutations that arise directly within binding residues (71). However, although the emergence of resistance to glyphosate was slower than that for other herbicides, resistance is now widespread. The apparent reason for the discrepancy between the predicted risk of resistance evolution and the increasing number of glyphosate-resistant species goes beyond point mutations conferring TSR; NTSR and gene amplification (see the sidebar titled A Case Study of Gene Amplification in *Amaranthus*) are thought to have a particularly important role in the evolution of resistance to glyphosate herbicides (147).

In contrast to large-effect mutations from alterations to the target site, another possibility is that resistance initially evolves through many small-effect mutations across the genome. This would be possible through NTSR. The idea of gene stacking emphasizes the polygenic nature of NTSR (136), yet it remains unclear how much NTSR is quantitative; within a single individual or population, is NTSR controlled by many small-effect genes or a few large-effect genes? If NTSR is highly polygenic, this can have an important effect on the mutational target size and the probability of evolutionary rescue. In particular, the waiting time for TSR mutations to arise in a limited mutational target window (127) is expected to be longer than that for NTSR mutations,

A CASE STUDY OF GENE AMPLIFICATION IN *AMARANTHUS*

Glyphosate resistance via amplification of the target EPSPS gene is best known in *Amaranthus palmeri* and *A. tuberculatus*, in which this novel mode of resistance was first described (53, 99) but has since been reported in five other species (32, 108, 117, 146, 165). The distribution of target gene copy number differs drastically between *A. palmeri* and *A. tuberculatus*. In *A. palmeri*, EPSPS copy number ranges from 40 to the hundreds and is distributed across chromosomes in the genome (53), whereas in *A. tuberculatus*, EPSPS copy number is constrained to lower values, typically less than 10, and occurs in tandem repeats (30, 31). The dichotomy in gene copy number across these species likely traces back to the mechanistic process by which amplification occurs; in *A. palmeri*, mobile genetic elements are thought to mediate EPSPS gene amplification and insertion across the genome (52), whereas in *A. tuberculatus*, tandem gene amplification is thought to result from unequal recombination (44). Herbicide resistance by gene amplification has been reported primarily in response to glyphosate applications, although other isolated instances exist (e.g., amplification in response to glutamine synthetase-inhibiting herbicides in *Medicago sativa*; 45). How much these adaptive responses are determined by the particular species or herbicide investigated, and the situations in which gene duplication is likely to relieve evolutionary constraint, remains unclear.

which can occur at many different positions across the genome. Thus, a larger mutational target size for NTSR mutations may further increase the probability of evolutionary rescue. Despite the traditional emphasis on TSR, the robust nature of NTSR mechanisms in conferring cross-resistance to many different herbicides, particularly early on following herbicide application, perhaps suggests a foremost way by which weed populations respond to herbicide applications. In fact, the powerful nature of NTSR—constitutive or induced—is now recognized as a predominant mode of resistance adaptation to not only glyphosate but also ACCase herbicides and in grasses in response to ALS herbicides (39). A number of gene families have an important and predictable role in conferring NTSR (172). More work remains to be done on the magnitude of resistance these individual genes can confer, and on how well represented these gene families are across populations and species for providing insight into the likelihood of NTSR evolution (172).

Dominance of Beneficial Mutations

Most of our empirical knowledge of dominance comes from imperfect estimates of its distribution from deleterious mutations in fast-growing model systems (1), leaving much that eludes evolutionary biologists. Robust conclusions about dominance are difficult to find, in part because it is highly dependent on both the selective and the molecular environments. What determines the dominance of a mutation is also thought to depend on the type of enzyme and its position in a network of interfunctioning enzymes (metabolic control theory of dominance) (83; reviewed in 86). When mutations are deleterious, large-effect segregating mutations will most often be recessive because highly deleterious dominant mutations will be immediately removed by selection (66). The same thinking applies to how selection sees beneficial mutations and forms the basis of Haldane's sieve; for sexual outcrossing species, most beneficial mutations that fix should be dominant, because rare and heterozygous recessive mutations will be hidden by selection (65). In selfing species with high levels of homozygosity, Haldane's sieve does not apply because recessive mutations can be seen by selection (29).

For the evolution of herbicide resistance, dominance matters in two ways. Most intuitively, the probability of adaptation in outcrossing species depends on dominance coefficients by directly

Metabolic control theory: a nonlinear relationship between the output of a metabolic network and the extent that this depends on the expression or activity of each individual component of the network

Haldane's sieve: the tendency for beneficial mutations that contribute to adaptation to be dominant, as recessive mutations are likely to be hidden from selection

determining whether the benefit is expressed and therefore seen by selection. The literature largely suggests that known herbicide resistance mutations are partially or completely dominant (100, 114, 121, 131, 132, 144, 145, 150, 152, 154, 159). This may be because de novo resistance mutations tend to be dominant, but it could also be due to the action of Haldane's sieve.

Furthermore, dominance is a property of phenotypes, and so the expression of alleles varies with the genetic, selective, and abiotic environments (49). The relative absence of recessive mutational effect estimates may be due to the strength of the selection imposed and the type of herbicide used; low-rate herbicides may result in reduced mortality (loss of only homozygous susceptibles) and the appearance of dominance, whereas higher rates remove more individuals (homozygous and heterozygous susceptibles) and may lead to the interpretation of recessivity (145). Aside from findings by Roux et al. (145), who identify a distribution of dominance ranging from completely recessive to overdominant, quantitative evaluations of dominance with variable herbicide types, rates, and TSR mutations are largely absent (but see 68, 94). The apparent scarcity of recessive TSR mutations may thus also be due to the lack of quantitative estimates. Disentangling Haldane's sieve, environmental effects, and the inherent dominance of resistance mutations will require mutagenesis experiments and additional estimates of dominance through quantitative approaches.

The dominance of the cost of resistance influences the frequency of resistance alleles in the population prior to herbicide application, which in turn determines the probability of adaptation from standing genetic variation. In *A. myosuroides*, the dominance of the cost of resistance for the Gly-2078 ACCase mutation was investigated and its consequences for vegetative biomass, seed production, and plant height were partially recessive (111). In the selfer *Arabidopsis thaliana*, the dominance of the cost of resistance to eight different herbicides spanned the continuum from recessive to dominant and did not predict the dominance of the resistance benefit (144). Furthermore, Paris et al. (131) found the cost of resistance (s) varies with genetic background more than the dominance of cost (h) does. Further investigations of the dominance of costs and benefits of resistance will be important for understanding the variation in resistance adaptation across herbicides and species.

Fluctuating Selection

Whether a single herbicide is applied recurrently or whether multiple herbicides are cycled within and between seasons has important implications for the rate and process of resistance adaptation. Because of the extreme strength of selection from herbicides, whether a herbicide is present or absent drastically shifts the selective environment in which weed populations exist. The cadence of herbicide regimes varies widely across agricultural landscapes and is highly dependent on crop rotation. Rotating crops from year to year is the traditional and recommended approach of managing soil fertility, pests, and ultimately yield (10, 70, 97), though many farmers forego rotation in favor of a single crop–herbicide system. Although herbicide dose is the primary determinant of the strength of selection on weed populations, the consistent use of a single mode of action should lead to a long-term trajectory of fixed herbicide resistance (81). In contrast, with rotating crop and herbicide regimes, selection should change in direction between applications, with levels of resistance fluctuating across seasons (although dependent on costs) (61, 62, 81, 92). The amount of time a population spends in each selective environment (with or without herbicides) and the fitness difference between resistance and susceptible alleles in these environments thus determine the magnitude and direction of net selection over time and the evolutionary trajectory of populations toward or away from resistance (81).

In weed systems that experience heterogeneity in selection from herbicides, constraint on proteins to maintain original function while allowing for resistance adaptation may lead to trade-offs,

often at the cost of the original kinetic activity of the target protein or pleiotropic phenotypes (46, 110, 161, 162). Given that a number of known genetically engineered mutations that confer herbicide resistance in the lab are not found in nature (171), significant costs may explain their marked absence in natural settings. For documented ALS TSR mutations (171), 16 of the 24 possible amino acid residues (66%) and 103 of 130 unique mutations (amino acid by position) (79%) have been confirmed in artificial experiments but are not observed in the wild, indeed implying costs as the key factor limiting their success. Costs are also a limiting factor in the number of TSR glyphosate mutations seen in nature (71), although evidence for the cost of resistance is by no means ubiquitous. Because the factors influencing the costs of herbicide resistance have been thoroughly reviewed elsewhere (18, 141, 162), we do not consider this further except to note that they depend on the mutation, environment, genetic background (131), and presence of modifiers (37, 131). As we highlight further below, costs of resistance that may be of important evolutionary relevance may still be difficult to detect from fitness assays in experimental populations.

Fluctuating herbicide use also has important implications for the diversity of populations and the likelihood of resistance mutations fixing. Examples of short-term adaptations fluctuating with the direction of selection have been accumulating (e.g., 14, 20, 87), perhaps coinciding with a shift in thinking by population geneticists toward acknowledging the contribution of adaptation at ecological timescales to long-term evolutionary patterns (112). The diversity of populations in fluctuating environments should be increased relative to that of populations in environments with persistent herbicide use; selection occurring in opposing directions can manifest over time as balancing selection and thus maintain variants at intermediate levels (14, 20). In addition to increased standing genetic variation after a herbicide-off season, the absence of treatment allows for a population recovery, increasing the number of backgrounds on which new beneficial mutations can arise (133). So far, no work has investigated this possibility of an association between temporal allele-frequency fluctuations and variation in herbicide use.

Extent of Gene Flow

Because of its tremendous repeatability, resistance adaptation has become a textbook example of convergent evolution in response to human-mediated selection in nature. However, the relative importance of gene flow, as opposed to the independent adaptation in populations, in facilitating the spread of herbicide resistance across a range remains unclear. Anecdotally, cases in which highly problematic resistant weeds become more widespread across a range are often attributed to human-mediated gene flow via seed dispersal, such as for glyphosate-resistant *Amaranthus palmeri* across the United States (28) or the introduction of *Amaranthus tuberculatus* into Ontario, Canada (35). Similarly, three 20-kg Japanese imports of wheat from the United States, Canada, and Australia contained between 2,931 and 4,673 seeds of *Lolium* spp., with frequencies of ALS resistance ranging from 28.6% to 84.6% encoded by seven unique TSR substitutions (155). Anecdotal cases such as this suggest that the spread of genetic variation for resistance via seed dispersal may be of primary importance for long-range establishment of resistance.

Pollen-mediated gene flow (PGF), however, should occur at much smaller geographic scales than seed dispersal. One of the longest reports of gene-flow-mediated spread of resistance is for the wind-pollinated outcrosser *Agrostis stolonifera*, for which dispersal ranged up to 21 km (164). In contrast, under ideal conditions, the contribution of PGF in the wind-pollinated, dioecious *A. tuberculatus* var. *rudis* was halved at just less than 3 m from the pollen source (148). PGF is of even less importance in predominately selfing species, which have reduced investment in pollen as compared to ovules (36), and is estimated to be extremely low (0.5% and 3%) for resistance

transfer in *Chenopodium album* and *Echinochloa crus-galli*, even at a close distance of 2 m from the pollen donor (7, 168). Taken together, there is much evidence that both seed and pollen dispersal are important for the spread of herbicide resistance, although likely at different geographic scales, with their relative importance dependent on the reproductive biology of weed species.

Mating system: type of sexual reproductive strategy, ranging from obligately self-fertilizing (mating within genets) to outcrossing (mating between genets)

Less explored is the relative importance of gene flow compared with independent adaptation in populations for the spread of resistance across a range. Only Kuester et al. (88) have directly examined this question, by pairing investigations of neutral variation and isolation by distance with glyphosate resistance levels across the Southeastern and Midwestern United States. The authors found that populations of *Ipomoea purpurea* evolved herbicide resistance independently in hotspots across the range. However, without causal resistance haplotypes, the authors were constrained in their ability to detect gene flow; different demographic origins do not necessarily equal different adaptive allelic origins, as migrant alleles are likely to be retained only in genomic regions with the causal variants. Further understanding of the spatial scale of resistance adaptation and gene flow will be important for integrative weed management, because it affects whether prevention should be focused on local farm-based management or on regional prevention of pollen and seed dispersal.

CHARACTERISTICS OF POPULATIONS AND SPECIES

In this section, we consider how the parameters discussed above vary across species and thus influence differences in the rate and nature of resistance adaptation. We focus on important differences in mating system and ploidy and their implications for predicting herbicide resistance adaptation, as summarized in **Figure 1**. We do not discuss the effect of life history and generation time, as it has been well explored elsewhere (60, 76).

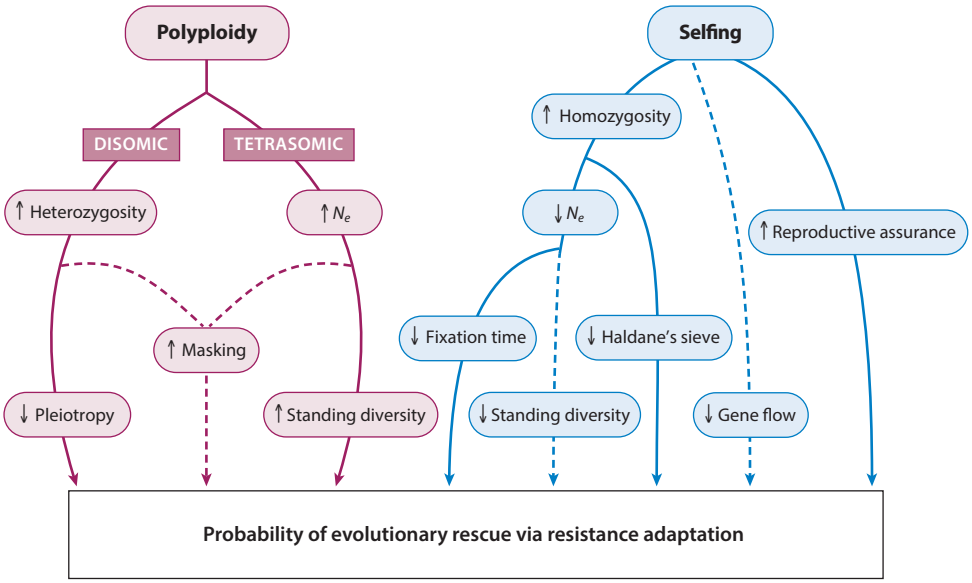

Figure 1

Summary of how polyploidy and selfing influence the population genomic and demographic parameters important for the probability of evolutionary rescue via resistance adaptation. Solid lines represent a positive influence on the probability of adaptation, whereas dashed lines indicate a negative influence.

Mating Systems

Outcrossing plant populations maintain high levels of heterozygosity and a large effective rate of recombination and thus often a large N_e. In contrast, highly selfing populations that are largely homozygous have a smaller N_e (122). Because of this difference, outcrossers typically have higher levels of standing neutral genetic variation (13, 19, 98, 105, 149) and are consequently more likely to maintain and recover genetic diversity after demographic bottlenecks (important for lineage persistence) (166). On the one hand, because most annual, competitive weed species are selfers (157), N_e may often be small. At the very least, N_e in most weeds is presumably nowhere near that of the estimated 10^8 for current N_e in *Drosophila* (85). On the other hand, many agronomically important weeds are outcrossing (e.g., *A. palmeri* in the United States, *Sinapis arvensis* in Canada), with a large N_e and likely high levels of standing genetic variation. Variation in N_e along the axis of mating systems in resistant weeds thus leads to an important testable prediction: Relative to the selfing species, the elevated N_e in outcrossing populations should lead to an increased probability of evolutionary rescue from standing genetic variation. In a comparison of artificial selection experiments for very-low-dose ACCase resistance in the outcrossing *L. rigidum* and the highly selfing *Avena fatua*, resistance evolution from standing genetic variation was reduced in the selfer in comparison with the outcrosser (24, 25), thus supporting this prediction.

If many adaptive mutations are recessive, however, higher homozygosity in selfing species may lead to higher rates of adaptation because Haldane's sieve is minimized (29). That is, the distribution of the dominance of fixed mutations in selfing species should reflect that of all de novo mutations, not just those that pass through selection's sieve (29). Moreover, given that a beneficial mutation is present, fixation should take longer in outcrossers than in selfers, under most conditions, regardless of whether the source is standing genetic variation or new mutation (55). However, Haldane's sieve in outcrossing populations can break down for adaptation from standing genetic variation; recessive standing variants can be important for adaptation in outcrossers because they are sheltered from selection and can therefore persist at intermediate frequencies, whereas higher homozygosity in selfers purge recessive deleterious mutations, reducing inbreeding depression (125, 143). As yet, the only test of Haldane's sieve across mating systems (143), which used 14 studies of domestication quantitative trait loci, confirmed these predictions; recessive and partially recessive mutations contributed to adaptation in highly selfing species, and dominant or partially dominant mutations contributed to adaptation in outcrossing species. However, a significant proportion of recessive mutations still contributed to adaptation in outcrossing species, likely because those mutations persisted across the environmental change as standing variants (125, 143).

Despite the complex interaction between mating system, N_e, dominance, and mutational age, we can make several basic predictions about how herbicide resistance adaptation proceeds in selfers versus outcrossers. Outcrossing populations may have a higher number of independent mutations contributing to resistance owing to increased N_e and standing genetic variation and thus an increased likelihood of soft selective sweeps. Conversely, we might expect that when selfing species evolve herbicide resistance, adaptation involves selection on a lower number of mutations owing to reduced N_e and standing genetic variation and thus an increased likelihood of hard selective sweeps. Furthermore, reduced rates of PGF in selfing populations may increase the probability of independent adaptations across populations. Well-documented agricultural weed populations that experience similar environmental conditions and vary in mating systems provide a unique system for investigating the predominance of soft or hard selective sweeps across variable effective population sizes and levels of standing genetic diversity.

We took advantage of the extensive literature on the molecular basis of herbicide resistance within and between populations to examine how mating systems influence whether adaptation

occurs from selection on single or multiple mutations. We identified 118 studies across 71 species for which the molecular basis of herbicide resistance was confirmed and we could characterize the mating system as predominantly selfing or predominantly outcrossing (**Supplemental Table 1**). Because the number of populations analyzed (from 1 to 297) varied tremendously between studies, we took two approaches: We tested whether mating system influences (*a*) the average number of unique amino acid mutations conferring resistance per population and (*b*) the total number of unique mutations across populations.

Reproductive assurance: in the context of selfing populations, the ability to produce offspring despite strong mate or pollinator limitation

Apomixis: asexual seed production

We found a clear influence of mating system on the log average number of mutations per population ($\lambda = 0.61$, $F_{(1,68)} = 5.56$, $p = 0.021$; **Supplemental Table 2**), even when controlling for phylogenetic relatedness using a phylogenetic least squares (PGLS) [gls function in the nlme package (137) in *R* and a trimmed version of the angiosperm tree (173)]. As predicted, this test indicated that selfing species have a smaller average number of resistance mutations per population than outcrossing species do (**Figure 2*a***). For the analysis of the number of unique resistance mutations by population number and mating system, we found a significant effect of mating system ($F_{(1,36)} = 5.98$, $p = 0.019$) and of number of populations ($F_{(1,36)} = 13.45$, $p = 0.008$), and a highly significant interaction between mating system and population number ($F_{(1,36)} = 18.34$, $p = 0.0001$) (**Figure 2*b***) (**Supplemental Table 2**). In this second analysis, we used a simple linear mixed model, with a random effect of species nested within genus nested within herbicide, but we did not correct for relatedness because of the absence of a phylogenetic signal in the data ($\lambda = -0.01$). Differences among species explained 27% of the variation in the model, orders of magnitude greater than the effect of herbicides or genera, consistent with an important influence of variation in population genetic parameters between species. These data further indicate that selfing species have a significantly lower number of unique mutations within populations than outcrossing species do. Moreover, the number of unique resistance mutations by the number of populations is highly dependent on mating system, with selfing species having a much greater positive relationship than outcrossing species do (**Figure 2*b***). The interaction between mating system and population number suggests that reduced rates of gene flow among selfing populations may lead to higher rates of independent adaptation, whereas in outcrossing species reduced mutation limitation, increased gene flow, or both contribute to a convergent genetic basis of herbicide resistance. These findings are consistent with the theoretical prediction that mutation-limited, smaller N_e selfing populations should adapt predominantly through selection on a single mutation, whereas adaptation from standing genetic variation or the successive fixation of new mutations is more likely to occur in outcrossers. Because the probability of soft sweeps is also correlated with the probability of adaptation (166), these results may also suggest that outcrossing species experience a higher rate of adaptation to herbicide resistance.

In addition to population genetic consequences, differences in mating system will also have important effects on ecology and demography, which can influence resistance adaptation (89). With these considerations in mind, selfing strategies can be favored in the evolution of resistance; increased reproductive assurance (8, 9, 58, 129) is particularly relevant for evolutionary rescue via herbicide resistance adaptation in mate-limited populations (89). Similarly, facultatively sexual modes of reproduction such as apomixis provide reproductive assurance in populations constrained to small sizes owing to strong selective pressures. Moreover, because they do not mate with dissimilar individuals that are potentially susceptible, resistant selfing and facultatively sexual species may prevent recombination with and gene flow from maladapted individuals and populations (4, 5).

A recent test of these predictions in the mixed-mating *Ipomoea purpurea* found the level of glyphosate resistance across populations to correlate positively with the level of inbreeding (89), implying that once a resistance mutation arises, increased rates of selfing may be more likely to

Supplemental Material

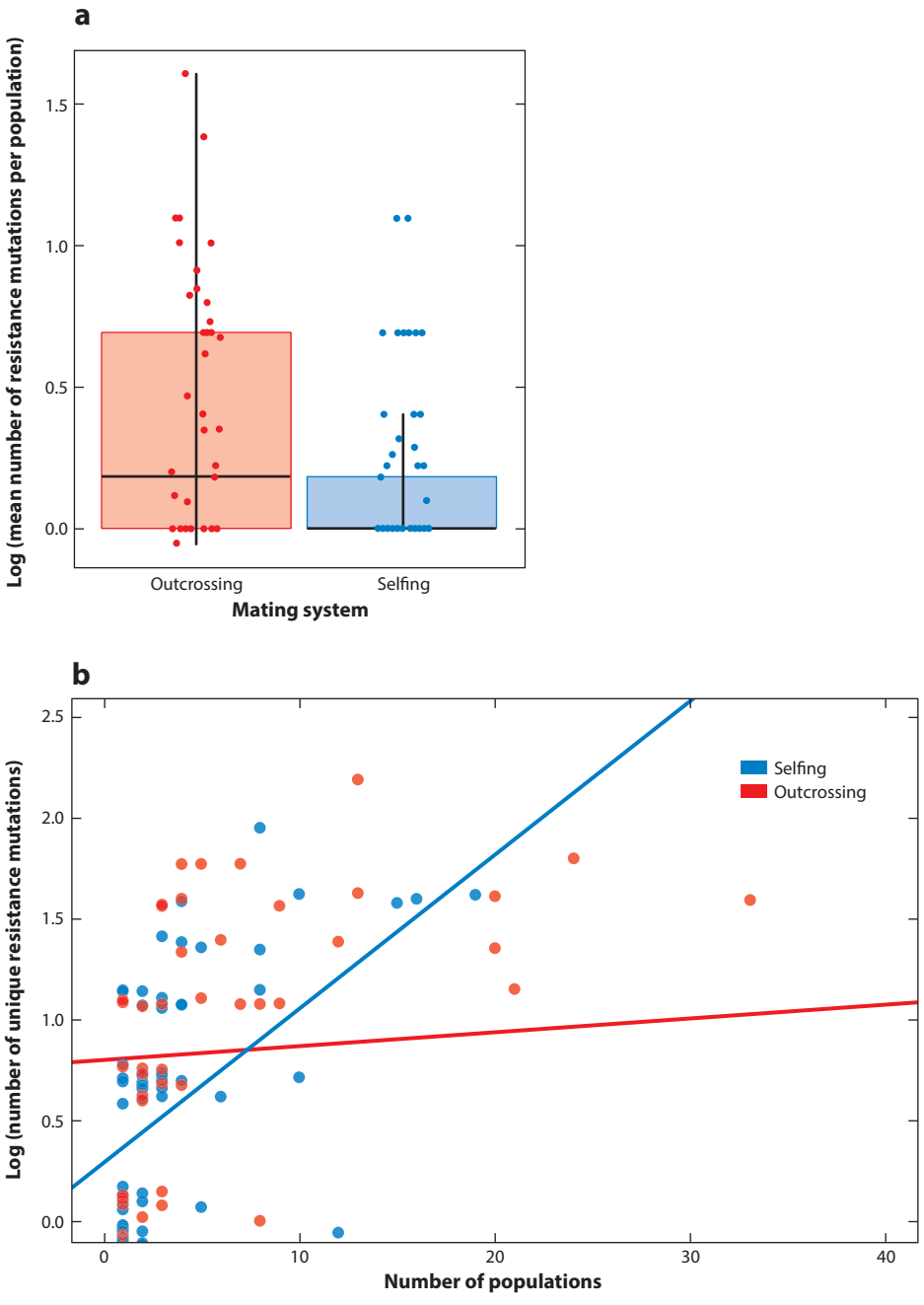

Figure 2

(*a*) Box plot overlaid with raw data of the log-transformed distribution of the average number of mutations per population, before phylogenetic correction. (*b*) Log-transformed number of unique amino acid mutations conferring resistance across populations by mating system. Regression lines represent the slope coefficients of a linear mixed model for each mating system. Each point represents a single study; points scattered along the *y*-axis for clarity.

lead to fixation and restore positive population growth. Along these lines, facultative apomixis in *Amaranthus palmeri* is hypothesized to play a role in the persistence of the resistant phenotype in the absence of reproductive partners (142). Importantly, reproductive assurance in these selfing and facultatively sexual species leads to a lower minimum population size at which evolutionary rescue can occur.

Taken together, it is difficult to predict whether resistance adaptation is more likely in selfing or outcrossing populations, and the outcome will be heavily parameter dependent. Reproductive assurance in partially selfing populations should increase the probability that newly resistant individuals contribute to the rebound of the population, but this is dependent on whether the resistance mutation is already present. However, gene flow may be a source of rescuing mutations for susceptible populations rather than just an impediment to resistant populations, in which case outcrossing populations may be at an advantage. Furthermore, given the strong selection for resistance mutations, the influx of susceptible alleles via gene flow should have minimal effect on the probability of evolutionary rescue (81). As discussed above, the relative importance of new mutation versus standing genetic variation, dominance, and population size will all contribute to determining how resistance adaptation proceeds across mating systems. Broadly, the demographic and ecological assurance of selfing and facultatively sexual species implies that they may be most suitable for withstanding the challenge of population crashes and perhaps evolutionary rescue given a resistance mutation occurs. However, theoretical and empirical evidence outlined above predicts that when population sizes are less limited, such as at the onset of herbicide applications, outcrossing species may be more likely to have the genetic innovation necessary—in the form of diversity and gene flow from resistant populations—to allow for evolutionary rescue.

Autopolyploids: polyploids formed within a single species

Tetrasomic inheritance: for a polyploid during meiosis, the lack of discrimination in pairing between homologous chromosomes and formation of either bi- or quadrivalents

Allopolyploids: polyploids formed before or after hybridization of two species

Disomic inheritance: for a polyploid during meiosis, the separate pairing of ancestral homologous chromosomes and formation of bivalents

Polyploidy

Given that polyploids account for a significant portion of current angiosperm diversity (estimated between 10% and 40%) (128, 167), understanding how genome duplication influences the probability that beneficial mutations are seen by selection is a key question in plant evolution. Aside from differences in mutational target size between target site and nontarget site genetic architectures of resistance, mutational target size may differ between organisms owing to increased genome copy number (i.e., polyploidy). The increased mutational target size alone results in established polyploids harboring more polymorphism, with a larger expected collection of beneficial mutations from which adaptation can occur (130) but also a higher deleterious mutational load (with load scaling by $\mu \times$ ploidy level) (128). The presence of multiple gene copies dampens the effect of both increased beneficial mutations and mutational load when variants are partially recessive; however, at equilibrium, polyploids still have a higher mutational load and number of beneficial mutations (128). If adaptation is mutation limited in diploids (as it is under conditions of small population size), polyploids should adapt faster than diploids when mutations are partially dominant because of their increased mutational input (128). These predictions have only begun to be tested and have been limited to yeast owing to their cycling through haploid and diploid stages; higher ploidies adapt faster, but only when population size and mutational input are limiting factors (3, 153, 174).

These patterns are also expected to differ between auto- and allopolyploids, in which only N_e and dominance effects are changed in autopolyploids with tetrasomic inheritance, in contrast to the more complex joint effects of hybridization and whole genome duplication in allopolyploids. Typical disomic inheritance in allopolyploids prevents the breakdown of fixed heterozygosity between subgenomes (128). Moreover, the lack of recombination between subgenomes in allopolyploids allows for their independent evolution to the extent that redundancy in their function may release

pleiotropic constraints and allow for neo- or subfunctionalization (51, 103) and degeneration via gene silencing and deletion (109, 123, 163).

The importance of polyploidy in facilitating adaptation to stressful environments has long been debated (38, 59, 63, 64, 101, 102, 107, 115, 157), and there is currently no evidence that this effect for herbicide resistance adaptation is widespread. Despite experimental evidence in yeast that polyploidy facilitates rapid adaptation (153), anecdotal evidence from a study of ACCase resistance in the hexaploid wheat, *A. fatua*, points to a limiting effect of polyploidy on resistance adaptation; the effect size of the same TSR mutation was much smaller in the hexaploid wheat than in a previously observed diploid grass (170). This finding suggests that greater masking of beneficial mutations may limit adaptation in polyploids, although much more should be investigated to test this.

Subfunctionalization: functional outcome of gene duplication characterized by neutral drift and a division of labor, as opposed to adaptation and novel function (neofunctionalization)

Similar to the manifestation of Haldane's theory in outcrossing species, adaptation from new mutations should favor dominant mutations in polyploids, as recessive mutations will mostly be masked from selection by other genome copies (128). Specifically, for sexual organisms with a higher ploidy to adapt faster than lower ploidy species, the dominance of an autopolyploid must be greater than half that of the diploid (128). For allopolyploids, the product of the dominance of each parental subgenome must be greater than half that of the diploid in order for them to adapt faster (128). However, standing genetic variation may be much more important to adaptation in polyploids than in diploids if slightly deleterious standing variants are partially recessive and can be masked by other genome copies. The masking effect of polyploids may thus allow for mutations to persist, whereas in a diploid they would have been selected out (128). This may be important particularly if the cost of resistance differs from the benefit in dominance (as in 144); resistance mutations may persist longer in the absence of herbicides if polyploids can mask their recessive costs while expressing their dominant benefit. In diploid yeast cells, adaptation to the antibiotic fluconazole proceeds from exclusively dominant mutations, whereas haploids undergo adaptation from both dominant and recessive mutations at near equal rates, with higher concentrations favoring recessive mutations (2, 3). Systematic tests of the interaction between dominance and polyploid are absent for most other systems, but will be fundamental to understanding the effectiveness and process of adaptation in polyploids.

Using the same phylogenetic approach as above, we looked to the weed–herbicide literature to see whether the increased mutational target size of higher ploidy species led to a higher number of unique resistance mutations on average (**Supplemental Table 2**). Interestingly, although we did not find that ploidy alone had an effect on the average number of resistance mutations per population, there was a marked interaction between ploidy and mating system (**Figure 3**) ($\lambda = 0.65$, $F_{(1,63)} = 14.9$, $p = 0.0003$). In selfing species, as ploidy increases, so too does the average number of resistance mutations per population. In contrast, the ploidy of outcrossing species negatively relates to the average number of resistance mutations per population. This interaction may be the result of the beneficial effect of ploidy on standing genetic variation when populations are small; in selfing populations where N_e is constrained to low values, polyploidy will increase the number of standing variants in the population by increasing N_e and facilitating masking. In contrast, in large outcrossing populations, the number of copies of the previously deleterious or neutral variant may be sufficient enough that a higher ploidy will no longer facilitate increased standing genetic variation, but rather, will slow the rate of fixation due to a decreased efficacy of selection. The interaction between mating system and ploidy on adaptive potential has yet to be explored theoretically or empirically, even though the effects of ploidy are highly dependent on heterozygosity and dominance, factors that vary considerably across mating systems.

Supplemental Material

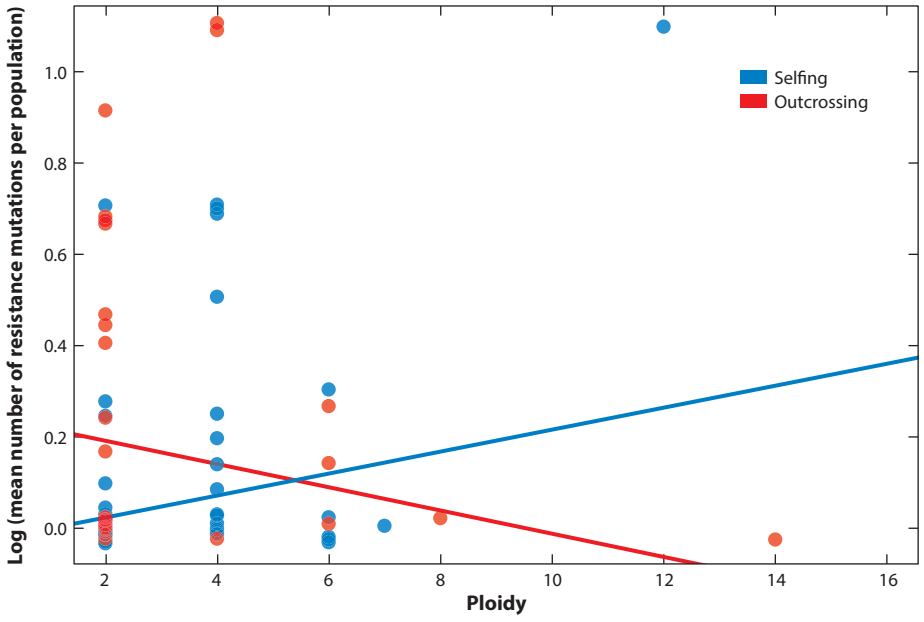

Figure 3

Log-transformed average number of resistance mutations per population by ploidy, showing the interaction between mating systems. Regression lines represent slopes of phylogenetic generalized least squares regression for selfing and outcrossing species, with each point representing a single species (scattered along the *y*-axis for clarity).

TOWARD A RESEARCH PROGRAM IN THE POPULATION GENOMICS OF HERBICIDE RESISTANCE

Now that it is feasible to study genome-wide diversity in any organism, population genomics provides key opportunities to investigate the underlying evolutionary mechanisms responsible for herbicide resistance adaptation, with potentially important implications for management. Tools such as genome-wide association studies (GWAS) (17) and selective scans [e.g., using F_{ST}, the differentiation of sub-populations in the total population (118), and the population branch statistic (PBS) (169)] that rely on the ability to relate phenotype to fine-scale changes in allele frequencies between populations will allow us to identify many more loci contributing to resistance, including alleles contributing to highly polygenic traits such as NTSR. Traditionally, population genetic approaches were inadequate for detecting fine-scale changes in allele frequencies that should accompany polygenic adaptation from standing genetic variation (139). However, with the increasing influx of genomic data, empirical approaches for studying polygenic adaptation are growing. One such method is Bayenv (34), a Bayesian approach that looks to detect covariance in allele frequencies across the genome between populations in select environments. These approaches will likely enable researchers to identify many more candidate resistance alleles beyond the well-known large-effect TSR mutations.

However, while these population genomic and GWAS approaches offer promise for identifying many additional candidate loci, it is important to remember that such studies can be prone to statistical limitations and the identification of false positives or negatives (26). For example, patterns of linkage disequilibrium have important consequences on the power to detect causal loci and their resolution: Self-fertilization in plants increases linkage disequilibrium, which up to a certain

extent can increase power by combining the signal of multiple small-effect loci, however linkage disequilibrium will interfere with ability to resolve causal loci within the tract (79). Furthermore, the probability of false negatives in GWAS approaches increases if underpowered due to an insufficient number of individuals sampled, and/or if causal variants tend to be at low frequencies, whereas the number of false positives increases with reduced representation sequencing or strong population structure (see box 1 in Reference 82 for a thorough discussion of the statistical and genetic biases of GWAS). Therefore, GWAS-like methods should be conducted (*a*) with these biases in mind and, importantly, (*b*) in combination with the functional validation of candidate genes through transgenic gain-of-function and loss-of-function lines, fine-scale genetic mapping, and other experimental approaches in order to pinpoint the causal mechanism(s) of NTSR.

By examining haplotype data and linkage around selected sites, we can also make important inferences about the strength of selection, the source(s) of adaptive variation, and how much adaptation is independent or shared across populations. For example, a recent composite likelihood-based approach can not only identify loci across the genome involved in convergent evolution across populations, but also distinguish between shared ancestry, independent origins, and convergence through gene flow (95). Analyses of the number of unique resistant haplotypes within and across populations will provide a powerful approach for inferring the extent of independent resistance evolution on multiple spatial scales.

Furthermore, subtle costs of herbicide resistance on the order of 1% or less may be important for the adaptive dynamics of resistance alleles but would be difficult to measure in field experiments estimating relative fitness in a finite number of individuals. A population genomics approach would track resistance allele frequencies over the course of herbicide-on and herbicide-off periods, along with the magnitude of reduction in diversity around the selected site, to decompose the opposing strengths and fitness consequences according to the timing of selection. This could easily be done for TSR mutations, and integration with other functional approaches would be necessary for identifying loci involved in NTSR and possibly pleiotropic trade-offs.

Given that a weed population adapts to herbicides, a phenotypic shift toward resistance may occur via an extreme bottleneck, the extent of which depends on the type of selective sweep that occurred. Theory predicts that when rescue is likely (e.g., with low-dose herbicide applications), adaptation should occur predominantly through soft sweeps (166). This is because when selection is strong, the longer waiting time associated multiple beneficial mutations arising in soft sweeps decreases the probability of evolutionary rescue. Empirical tests of this prediction in HIV-infected cells indeed show that more effective drug treatments are associated with adaptation via hard sweeps and an increased reduction in diversity, whereas less effective treatments are associated with adaptation via soft sweeps (47). In parallel with these findings, higher doses of herbicide should increase the severity of the genetic bottleneck, the probability of extinction, and the likelihood that adaptation proceeds through hard selective sweeps. In highly selfing species, these effects will be exacerbated by low effective rates of recombination, possibly driving genome-wide diversity loss. Two notable studies that examine the dynamics of herbicide resistance adaptation found an associated nonnegligible reduction in genomic diversity: The spread of a triazine resistance mutation in the chloroplast of *Arabidopsis thaliana* resulted in the hitchhiking of the entire nuclear genome along British railways (50), and increased resistance of the same populations of *Ipomoea purpurea* after nine years was associated with reductions in most measures of genomic diversity (90). Aside from these exceptions, the genomic consequences for diversity and the prevalence of hard or soft sweeps in herbicide resistance adaptation have been rarely investigated.

Currently, much work is under way to address the relative importance of hard and soft selective sweeps in adaptation and to develop methods for distinguishing between the two with genomic data (see 75 for a recent and thorough review). Each type of selective sweep leaves

behind distinctive genomic and coalescent patterns. Hard-swept beneficial mutations share a recent common ancestor and no haplotypic diversity. Soft-swept single-origin standing variants recombine onto multiple backgrounds, thus extending their coalescent history and shortening the length of diversity-depleted haplotypes, whereas soft sweeps from multiple independent mutations leave behind extended haplotypes corresponding to each origin (75). Methods have been developed on the basis of these defining characteristics to tease apart the mutational origins of adaptation (48, 54, 135, 151; but for caveats, see 75) and will be pivotal for evaluating the role of new mutational input versus standing genetic variation in adaptation, as well as for elaborating integrative management strategies for preventing resistance. Comparisons of the sweep signals of resistance across species with contrasting population sizes, mating systems, and ploidy levels will enable key tests of the factors driving the rate and nature of adaptation.

In the field of herbicide resistance much progress has been made in documenting the parallel molecular mechanisms underlying resistance phenotypes across species, yet we are only beginning to understand the genomic and population-level processes by which adaptation to herbicides occur and the repeatability of these processes across the range. Outstanding questions can be elegantly addressed through population genomic approaches: How many loci or distinct mutations are typically involved in resistance phenotypes? What is the relative representation of TSR and NTSR within populations and across the range? Does this representation depend on the herbicide or species? What are the dynamics of adaptive resistance mutations and their genomic consequences? With the decrease in cost and increase in throughput of whole genome sequencing, answering these questions, among others, from studies of herbicide resistance both within and across populations is becoming increasingly tractable. In our current global climate, a highly integrative evolutionary genomic approach is sorely needed not only for the practical management of herbicide-resistant weeds, but also for answering questions related to the future of environmental, health, and agricultural security.

SUMMARY POINTS

1. A tremendous literature on herbicide resistance in weeds points to highly convergent phenotypic and genetic mechanisms, yet the evolutionary process itself is variable and context dependent. Models of evolutionary rescue can help us understand the implications of this variability for the nature of adaptation.
2. Population genetic theory can assist in predicting how much populations respond to extreme selection pressure. Empirical examples from the weed–herbicide literature provide an important test of this theory.
3. Species characteristics such as selfing and polyploidy that dramatically alter population genetic parameters offer an axis of variation to investigate rates of adaptation and elucidate its limiting factors.
4. Paired with this conceptual framework, the decreasing costs of sequencing and increasingly sophisticated population genomic approaches integrated with functional validation provide unparalleled power to dissect the nature, rate, and extent of resistance adaptation across populations and species.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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LITERATURE CITED

1. Agrawal AF, Whitlock MC. 2011. Inferences about the distribution of dominance drawn from yeast gene knockout data. *Genetics* 187:553–66
2. Anderson JB, Sirjusingh C, Parsons AB, Boone C, Wickens C, et al. 2003. Mode of selection and experimental evolution of antifungal drug resistance in *Saccharomyces cerevisiae*. *Genetics* 163:1287–98
3. Anderson JB, Sirjusingh C, Ricker N. 2004. Haploidy, diploidy and evolution of antifungal drug resistance in *Saccharomyces cerevisiae*. *Genetics* 168:1915–23
4. Antonovics J. 1968. Evolution in closely adjacent plant populations V. Evolution of self-fertility. *Heredity* 23:219–38
5. Antonovics J, Bradshaw AD, Turner RG. 1971. Heavy metal tolerance in plants. *Adv. Ecol. Res.* 7:1–85
6. Ashworth MB, Walsh MJ, Flower KC, Powles SB. 2016. Recurrent selection with reduced 2,4-D amine doses results in the rapid evolution of 2,4-D herbicide resistance in wild radish (*Raphanus raphanistrum* L.). *Pest Manag. Sci.* 72:2091–98
7. Bagavathiannan MV, Norsworthy JK. 2014. Pollen-mediated transfer of herbicide resistance in *Echinochloa crus-galli*. *Pest Manag. Sci*. 70:1425–31
8. Baker HG. 1955. Self-compatibility and establishment after long-distance dispersal. *Evolution* 9:347–49
9. Baker HG. 1974. The evolution of weeds. *Annu. Rev. Ecol. Syst.* 5:1–24
10. Ball DA. 1992. Weed seedbank response to tillage, herbicides, and crop rotation sequence. *Weed Sci*. 40:654–59
11. Barrett RDH, Schluter D. 2008. Adaptation from standing genetic variation. *Trends Ecol. Evol.* 23:38–44
12. Baucom RS. 2016. The remarkable repeated evolution of herbicide resistance. *Am. J. Bot.* 103:181–83
13. Baudry E, Kerdelhué C, Innan H, Stephan W. 2001. Species and recombination effects on DNA variability in the tomato genus. *Genetics* 158:1725–35
14. Behrman EL, Watson SS, O'Brien KR, Heschel MS, Schmidt PS. 2015. Seasonal variation in life history traits in two *Drosophila* species. *J. Evol. Biol.* 28:1691–704
15. Bell G, Gonzalez A. 2009. Evolutionary rescue can prevent extinction following environmental change. *Ecol. Lett.* 12:942–48
16. Bell G, Gonzalez A. 2011. Adaptation and evolutionary rescue in metapopulations experiencing environmental deterioration. *Science* 332:1327–30
17. Berg JJ, Coop G. 2014. A population genetic signal of polygenic adaptation. *PLOS Genet*. 10:e1004412
18. Bergelson J, Purrington CB. 1996. Surveying patterns in the cost of resistance in plants. *Am. Nat.* 148:536–58
19. Bergelson J, Stahl E, Dudek S, Kreitman M. 1998. Genetic variation within and among populations of *Arabidopsis thaliana*. *Genetics* 148:1311–23
20. Bergland AO, Behrman EL, O'Brien KR, Schmidt PS, Petrov DA. 2014. Genomic evidence of rapid and stable adaptive oscillations over seasonal time scales in *Drosophila*. *PLOS Genet*. 10:e1004775
21. Bourne EC, Bocedi G, Travis JMJ, Pakeman RJ, Brooker RW, Schiffers K. 2014. Between migration load and evolutionary rescue: dispersal, adaptation and the response of spatially structured populations to environmental change. *Proc. R. Soc. Lond. B* 281:20132795
22. Bradshaw LD, Padgette SR, Kimball SL, Wells BH. 1997. Perspectives on glyphosate resistance. *Weed Technol*. 11:189–98
23. Burger R, Lynch M. 1995. Evolution and extinction in a changing environment: a quantitative-genetic analysis. *Evolution* 49:151–63
24. Busi R, Girotto M, Powles SB. 2016. Response to low-dose herbicide selection in self-pollinated *Avena fatua*. *Pest Manag. Sci.* 72:603–8
25. Busi R, Neve P, Powles S. 2013. Evolved polygenic herbicide resistance in *Lolium rigidum* by low-dose herbicide selection within standing genetic variation. *Evol. Appl.* 6:231–42

26. Brachi B, Morris GP, Borevitz JO. 2011. Genome-wide association studies in plants: the missing heritability is in the field. *Genome Biol.* 12:232
27. Carlson SM, Cunningham CJ, Westley PAH. 2014. Evolutionary rescue in a changing world. *Trends Ecol. Evol.* 29:521–30
28. Chahal PS, Aulakh JS, Jugulam M, Jhala AJ. 2015. Herbicide-resistant Palmer amaranth (*Amaranthus palmeri* S. Wats.) in the United States—mechanisms of resistance, impact, and management. In *Herbicides, Agronomic Crops and Weed Biology*, ed. AJ Price, JA Kelton, L Sarunaite, pp. 1–30. London: InTech
29. Charlesworth B. 1992. Evolutionary rates in partially self-fertilizing species. *Am. Nat.* 140:126–48
30. Chatham LA, Bradley KW, Kruger GR, Martin JR, Owen MDK, et al. 2015. A multistate study of the association between glyphosate resistance and EPSPS gene amplification in waterhemp (*Amaranthus tuberculatus*). *Weed Sci.* 63:569–77
31. Chatham LA, Wu C, Riggins CW, Hager AG, Young BG, et al. 2015. EPSPS gene amplification is present in the majority of glyphosate-resistant Illinois waterhemp (*Amaranthus tuberculatus*) populations. *Weed Technol.* 29:48–55
32. Chen J, Huang H, Zhang C, Wei S, Huang Z, et al. 2015. Mutations and amplification of EPSPS gene confer resistance to glyphosate in goosegrass (*Eleusine indica*). *Planta* 242:859–68
33. Concepcion D, Seburn KL, Wen G, Frankel WN, Hamilton BA. 2004. Mutation rate and predicted phenotypic target sizes in ethylnitrosourea-treated mice. *Genetics* 168:953–59
34. Coop G, Witonsky D, Di Rienzo A, Pritchard JK. 2010. Using environmental correlations to identify loci underlying local adaptation. *Genetics* 185:1411–23
35. Costea M, Weaver SE, Tardif FJ. 2005. The biology of invasive alien plants in Canada. 3. *Amaranthus tuberculatus* (Moq.) Sauer var. *rudis* (Sauer) Costea & Tardif. *Can. J. Plant Sci.* 85:507–22
36. Cruden RW. 1977. Pollen-ovule ratios: a conservative indicator of breeding systems in flowering plants. *Evolution* 31:32–46
37. Darmency H, Menchari Y, Le Corre V, Délye C. 2015. Fitness cost due to herbicide resistance may trigger genetic background evolution. *Evolution* 69:271–78
38. de Wet JMJ. 1971. Polyploidy and evolution in plants. *Taxon* 20:29–35
39. Délye C. 2013. Unravelling the genetic bases of non-target-site-based resistance (NTSR) to herbicides: a major challenge for weed science in the forthcoming decade. *Pest Manag. Sci.* 69:176–87
40. Délye C, Deulvot C, Chauvel B. 2013. DNA analysis of herbarium specimens of the grass weed *Alopecurus myosuroides* reveals herbicide resistance pre-dated herbicides. *PLOS ONE* 8:e75117
41. Délye C, Gardin J, Boucansaud K, Chauvel B, Petit C. 2011. Non-target-site-based resistance should be the centre of attention for herbicide resistance research: *Alopecurus myosuroides* as an illustration. *Weed Res.* 51:433–37
42. Délye C, Jasieniuk M, Le Corre V. 2013. Deciphering the evolution of herbicide resistance in weeds. *Trends Genet.* 29:649–58
43. Devine MD, Shukla A. 2000. Altered target sites as a mechanism of herbicide resistance. *Crop Prot.* 19:881–89
44. Dillon A, Varanasi VK, Danilova TV, Koo D-H, Nakka S, et al. 2017. Physical mapping of amplified copies of the 5-enolpyruvylshikimate-3-phosphate synthase gene in glyphosate-resistant *Amaranthus tuberculatus*. *Plant Physiol.* 173:1226–34
45. Donn G, Tischer E, Smith JA, Goodman HM. 1984. Herbicide-resistant alfalfa cells: an example of gene amplification in plants. *J. Mol. Appl. Genet.* 2:621–35
46. Duggleby RG, McCourt JA, Guddat LW. 2008. Structure and mechanism of inhibition of plant acetohydroxyacid synthase. *Plant Physiol. Biochem.* 46:309–24
47. Feder AF, Rhee S-Y, Holmes SP, Shafer RW, Petrov DA, Pennings PS. 2016. More effective drugs lead to harder selective sweeps in the evolution of drug resistance in HIV-1. *eLife* 5:e10670
48. Ferrer-Admetlla A, Liang M, Korneliussen T, Nielsen R. 2014. On detecting incomplete soft or hard selective sweeps using haplotype structure. *Mol. Biol. Evol.* 31:1275–91
49. Fisher RA. 1930. *The Genetical Theory of Natural Selection: A Complete Variorum Edition*. Oxford, UK: Oxford Univ. Press. 318 pp.
50. Flood PJ, van Heerwaarden J, Becker F, de Snoo CB, Harbinson J, Aarts MGM. 2016. Whole-genome hitchhiking on an organelle mutation. *Curr. Biol.* 26:1306–11

51. Force A, Lynch M, Pickett FB, Amores A, Yan YL, Postlethwait J. 1999. Preservation of duplicate genes by complementary, degenerative mutations. *Genetics* 151:1531–45
52. Gaines TA, Wright AA, Molin WT, Lorentz L, Riggins CW, et al. 2013. Identification of genetic elements associated with EPSPS gene amplification. *PLOS ONE* 8:e65819
53. Gaines TA, Zhang W, Wang D, Bukun B, Chisholm ST, et al. 2010. Gene amplification confers glyphosate resistance in *Amaranthus palmeri*. *PNAS* 107:1029–34
54. Garud NR, Rosenberg NA. 2015. Enhancing the mathematical properties of new haplotype homozygosity statistics for the detection of selective sweeps. *Theor. Popul. Biol.* 102:94–101
55. Glémin S, Ronfort J. 2013. Adaptation and maladaptation in selfing and outcrossing species: new mutations versus standing variation. *Evolution* 67:225–40
56. Gomulkiewicz R, Holt RD. 1995. When does evolution by natural selection prevent extinction? *Evolution* 49:201–7
57. Gonzalez A, Ronce O, Ferriere R, Hochberg ME. 2013. Evolutionary rescue: an emerging focus at the intersection between ecology and evolution. *Philos. Trans. R. Soc. Lond. B* 368:20120404
58. Goodwillie C, Kalisz S, Eckert CG. 2005. The evolutionary enigma of mixed mating systems in plants: occurrence, theoretical explanations, and empirical evidence. *Annu. Rev. Ecol. Evol. Syst.* 36:47–79
59. Grant V. 1981. *Plant Speciation*. New York: Columbia Univ. Press. 2nd ed.
60. Gressel J, Segel LA. 1978. The paucity of plants evolving genetic resistance to herbicides: possible reasons and implications. *J. Theor. Biol.* 75:349–71
61. Gressel J, Segel LA. 1990. Herbicide rotations and mixtures. *ACS Symp. Ser.* 421:430–58
62. Gressel J, Segel LA. 1990. Modelling the effectiveness of herbicide rotations and mixtures as strategies to delay or preclude resistance. *Weed Technol*. 4:186–98
63. Gustafsson A. 1946. Apomixis in higher plants. *Lunds Univ. Arsskr.* 42:1–67
64. Hagerup O. 1932. Über polyploidie in beziehung zu klima, ökologie und phylogenie. *Hereditas* 16:19–40
65. Haldane JBS. 1927. A mathematical theory of natural and artificial selection, part V: selection and mutation. *Math. Proc. Camb. Philos. Soc.* 23:838–44
66. Haldane JBS. 1937. The effect of variation on fitness. *Am. Nat.* 71:337–49
67. Harms CT, DiMaio JJ. 1991. Primisulfuron herbicide-resistant tobacco cell lines. Application of fluctuation test design to in vitro mutant selection with plant cells. *J. Plant Physiol.* 137:513–19
68. Hart SE, Saunders JW, Penner D. 1993. Semidominant nature of monogenic sulfonylurea herbicide resistance in sugarbeet (*Beta vulgaris*). *Weed Sci*. 41:317–24
69. Haughn G, Somerville CR. 1987. Selection for herbicide resistance at the whole-plant level. *ACS Symp. Ser.* 334:98–107
70. Havlin JL, Kissel DE, Maddux LD, Claassen MM, Long JH. 1990. Crop rotation and tillage effects on soil organic carbon and nitrogen. *Soil Sci. Soc. Am. J.* 54:448–52
71. Healy-Fried ML, Funke T, Priestman MA, Han H, Schönbrunn E. 2007. Structural basis of glyphosate tolerance resulting from mutations of Pro101 in *Escherichia coli* 5-enolpyruvylshikimate-3-phosphate synthase. *J. Biol. Chem.* 282:32949–55
72. Heap I. 2014. Herbicide resistant weeds. In *Integrated Pest Management*, ed. D Pimentel, R Peshin, pp. 281–301. Dordrecht, Neth.: Springer
73. Heap I. 2017. *International Survey of Herbicide Resistant Weeds*. **http://weedscience.org**
74. Hermisson J, Pennings PS. 2005. Soft sweeps: molecular population genetics of adaptation from standing genetic variation. *Genetics* 169:2335–52
75. Hermisson J, Pennings PS. 2017. Soft sweeps and beyond: understanding the patterns and probabilities of selection footprints under rapid adaptation. *Methods Ecol. Evol.* 8:700–16
76. Holt JS, Welles SR, Silvera K, Heap IM, Heredia SM, et al. 2013. Taxonomic and life history bias in herbicide resistant weeds: implications for deployment of resistant crops. *PLOS ONE* 8:e71916
77. Holt RD, Gomulkiewicz R. 1997. The evolution of species' niches: a population dynamic perspective. In *Case Studies in Mathematical Modelling: Ecology, Physiology, and Cell Biology*, eds. HG Othmer, FR Adler, MA Lewis, JC Dalton, pp. 25–50. Upper Saddle River, NJ: Prentice-Hall
78. Holt RD, Gomulkiewicz R. 2004. Conservation implications of niche conservatism and evolution in heterogeneous environments. In *Evolutionary Conservation Biology*, ed. R Ferrière, U Dieckmann, D Couvet, pp. 244–64. Cambridge, UK: Cambridge Univ. Press

55. Outlines the probability of adaptation in selfers versus outcrossers, from new mutation and standing genetic variation.

79. Huang X, Han B. 2014. Natural variations and genome-wide association studies in crop plants. *Annu. Rev. Plant Biol.* 65:531–51
80. Jander G, Baerson SR, Hudak JA, Gonzalez KA, Gruys KJ, Last RL. 2003. Ethylmethanesulfonate saturation mutagenesis in Arabidopsis to determine frequency of herbicide resistance. *Plant Physiol.* 131:139–46
81. Jasieniuk M, Brûlé-Babel AL, Morrison IN. 1996. The evolution and genetics of herbicide resistance in weeds. *Weed Sci.* 44:176–93
82. Josephs EB, Stinchcombe JR, Wright SI. 2017. What can genome-wide association studies tell us about the evolutionary forces maintaining genetic variation for quantitative traits? *New Phytol.* 214:21–33
83. Kacser H, Burns JA. 1981. The molecular basis of dominance. *Genetics* 97:639–66
84. Kaplan NL, Hudson RR, Langley CH. 1989. The "hitchhiking effect" revisited. *Genetics* 123:887–99
85. Karasov T, Messer PW, Petrov DA. 2010. Evidence that adaptation in *Drosophila* is not limited by mutation at single sites. *PLOS Genet.* 6:e1000924
86. Keightley PD. 1996. A metabolic basis for dominance and recessivity. *Genetics* 143:621–25
87. Kubrak OI, Nylin S, Flatt T, Nässel DR, Leimar O. 2017. Adaptation to fluctuating environments in a selection experiment with *Drosophila melanogaster*. *Ecol. Evol.* 7:3796–807
88. Kuester A, Chang S-M, Baucom RS. 2015. The geographic mosaic of herbicide resistance evolution in the common morning glory, *Ipomoea purpurea*: evidence for resistance hotspots and low genetic differentiation across the landscape. *Evol. Appl.* 8:821–33
89. Kuester A, Fall E, Chang S-M, Baucom RS. 2017. Shifts in outcrossing rates and changes to floral traits are associated with the evolution of herbicide resistance in the common morning glory. *Ecol. Lett.* 20:41–49
90. Kuester A, Wilson A, Chang S-M, Baucom RS. 2016. A resurrection experiment finds evidence of both reduced genetic diversity and potential adaptive evolution in the agricultural weed *Ipomoea purpurea*. *Mol. Ecol.* 25:4508–20
91. Lachapelle J, Bell G. 2012. Evolutionary rescue of sexual and asexual populations in a deteriorating environment. *Evolution* 66:3508–18
92. Lagator M, Vogwill T, Colegrave N, Neve P. 2013. Herbicide cycling has diverse effects on evolution of resistance in *Chlamydomonas reinhardtii*. *Evol. Appl.* 6:197–206
93. Lanfear R, Kokko H, Eyre-Walker A. 2014. Population size and the rate of evolution. *Trends Ecol. Evol.* 29:33–41
94. Lavigne C, Millecamps JL, Manac'h H, Cordonnier P, Matejicek A, et al. 1994. Monogenic semidominant sulfonylurea resistance in a line of white chicory. *Plant Breed.* 113:305–11
95. Lee KM, Coop G. 2017. Distinguishing among modes of convergent adaptation using population genomic data. *Genetics* 207:1591–619
96. Letouzé A, Gasquez J. 2003. Enhanced activity of several herbicide-degrading enzymes: a suggested mechanism responsible for multiple resistance in blackgrass (*Alopecurus myosuroides* Huds.). *Agronomie* 23:601–8
97. Liebman M, Dyck E. 1993. Crop rotation and intercropping strategies for weed management. *Ecol. Appl.* 3:92–122
98. Liu F, Zhang L, Charlesworth D. 1998. Genetic diversity in *Leavenworthia* populations with different inbreeding levels. *Proc. R. Soc. B* 265:293–301
99. Lorentz L, Gaines TA, Nissen SJ, Westra P, Strek HJ, et al. 2014. Characterization of glyphosate resistance in *Amaranthus tuberculatus* populations. *J. Agric. Food Chem.* 62:8134–42
100. Lorraine-Colwill DF, Powles SB, Hawkes TR, Preston C. 2001. Inheritance of evolved glyphosate resistance in *Lolium rigidum* (Gaud.). *Theor. Appl. Genet.* 102:545–50
101. Löve A. 1953. Subarctic polyploidy. *Hereditas* 39:113–24
102. Löve A, Löve D. 1949. The geobotanical significance of polyploidy. I. Polyploidy and latitude. *Port. Acta Bio. Ser. A* (Spec. Vol.):273–352
103. Lynch M, Force A. 2000. The probability of duplicate gene preservation by subfunctionalization. *Genetics* 154:459–73

81. Gives the first thorough synthesis of the evolutionary genetics of herbicide resistance; models the dynamics of resistance across key influencing parameters.

85. Provides a remarkable example of parallel soft selective sweeps and refutes the traditional mutation-limited view of adaptation.

89. Provides the first discussion of and evidence for the demographic consequences of selfing in herbicide resistance evolution.

104. Lynch M, Lande R. 1993. Evolution and extinction in response to environmental change. In *Biotic Interactions and Global Change*, ed. P Kareiva, J Kingsolver, R Huey, pp. 234–50. Sunderland, MA: Sinauer
105. Mable BK, Adam A. 2007. Patterns of genetic diversity in outcrossing and selfing populations of *Arabidopsis lyrata*. *Mol. Ecol.* 16:3565–80
106. Mackenzie R, Mortimer AM, Putwain PD, Bryan IB, Hawkes TR. 1997. The potential for the evolution of herbicide resistance: selection, characterisation and polygenic inheritance of resistance to chlorsulfuron in perennial ryegrass. In *Weed and Crop Resistance to Herbicides*, ed. R De Prado, J Jorrín, L García-Torres, pp. 207–13. Dordrecht, Neth.: Springer
107. Madlung A. 2013. Polyploidy and its effect on evolutionary success: old questions revisited with new tools. *Heredity* 110:99–104
108. Malone JM, Morran S, Shirley N, Boutsalis P, Preston C. 2016. EPSPS gene amplification in glyphosate-resistant *Bromus diandrus*. *Pest Manag. Sci.* 72:81–88
109. Ma X-F, Gustafson JP. 2005. Genome evolution of allopolyploids: a process of cytological and genetic diploidization. *Cytogenet. Genome Res.* 109:236–49
110. McCourt JA, Pang SS, King-Scott J, Guddat LW, Duggleby RG. 2006. Herbicide-binding sites revealed in the structure of plant acetohydroxyacid synthase. *PNAS* 103:569–73
111. Menchari Y, Chauvel B, Darmency H, Délye C. 2008. Fitness costs associated with three mutant acetyl-coenzyme A carboxylase alleles endowing herbicide resistance in black-grass *Alopecurus myosuroides*. *J. Appl. Ecol.* 45:939–47
112. Messer PW, Ellner SP, Hairston NG Jr. 2016. Can population genetics adapt to rapid evolution? *Trends Genet.* 32:408–18
113. Messer PW, Petrov DA. 2013. Population genomics of rapid adaptation by soft selective sweeps. *Trends Ecol. Evol.* 28:659–69
114. Miki BL, Labbé H, Hattori J, Ouellet T, Gabard J, et al. 1990. Transformation of *Brassica napus* canola cultivars with *Arabidopsis thaliana* acetohydroxyacid synthase genes and analysis of herbicide resistance. *Theor. Appl. Genet.* 80:449–58
115. Müntzing A. 1936. The evolutionary significance of autopolyploidy. *Hereditas* 21:363–78
116. Nam K, Munch K, Mailund T, Nater A, Greminger MP, et al. 2017. Evidence that the rate of strong selective sweeps increases with population size in the great apes. *PNAS* 114:1613–18
117. Nandula VK, Ray JD, Ribeiro DN, Pan Z, Reddy KN. 2013. Glyphosate resistance in tall waterhemp (*Amaranthus tuberculatus*) from Mississippi is due to both altered target-site and nontarget-site mechanisms. *Weed Sci.* 61:374–83
118. Narum SR, Hess JE. 2011. Comparison of FST outlier tests for SNP loci under selection. *Mol. Ecol. Resour.* 11:184–94
119. Neve P, Busi R, Renton M, Vila-Aiub MM. 2014. Expanding the eco-evolutionary context of herbicide resistance research. *Pest Manag. Sci.* 70:1385–93
120. Neve P, Powles S. 2005. Recurrent selection with reduced herbicide rates results in the rapid evolution of herbicide resistance in *Lolium rigidum*. *Theor. Appl. Genet.* 110:1154–66
121. Newhouse K, Singh B, Shaner D, Stidham M. 1991. Mutations in corn (*Zea mays* L.) conferring resistance to imidazolinone herbicides. *Theor. Appl. Genet.* 83:65–70
122. Nordborg M. 2000. Linkage disequilibrium, gene trees and selfing: an ancestral recombination graph with partial self-fertilization. *Genetics* 154:923–29
123. Ohno S. 1970. *Evolution by Gene Duplication*. Heidelberg, Ger.: Springer
124. Orr HA. 2003. The distribution of fitness effects among beneficial mutations. *Genetics* 163:1519–26
125. Orr HA, Betancourt AJ. 2001. Haldane's sieve and adaptation from the standing genetic variation. *Genetics* 157:875–84
126. Orr HA, Unckless RL. 2008. Population extinction and the genetics of adaptation. *Am. Nat.* 172:160–69
127. Orr HA, Unckless RL. 2014. The population genetics of evolutionary rescue. *PLOS Genet.* 10:e1004551
128. Otto SP, Whitton J. 2000. Polyploid incidence and evolution. *Annu. Rev. Genet.* 34:401–37
129. Pannell JR, Auld JR, Brandvain Y, Burd M, Busch JW, et al. 2015. The scope of Baker's law. *New Phytol.* 208:656–67

119. Gives an ecological-evolutionary synthesis of the key factors influencing resistance adaptation with an emphasis on integrative management approaches.

127. Presents an important extension of evolutionary rescue theory "as a race against extinction" allowing for rescue from new mutation and standing genetic variation.

128. Reviews polyploid population genetics, microevolution, and macroevolution.

130. Paquin C, Adams J. 1983. Frequency of fixation of adaptive mutations is higher in evolving diploid than haploid yeast populations. *Nature* 302:495–500
131. Paris M, Roux F, Bérard A, Reboud X. 2008. The effects of the genetic background on herbicide resistance fitness cost and its associated dominance in *Arabidopsis thaliana*. *Heredity* 101:499–506
132. Parker WB, Marshall LC, Burton JD, Somers DA, Wyse DL, et al. 1990. Dominant mutations causing alterations in acetyl-coenzyme A carboxylase confer tolerance to cyclohexanedione and aryloxyphenoxypropionate herbicides in maize. *PNAS* 87:7175–79
133. Pennings PS. 2012. Standing genetic variation and the evolution of drug resistance in HIV. *PLOS Comput. Biol.* 8:e1002527
134. Perron GG, Gonzalez A, Buckling A. 2007. Source-sink dynamics shape the evolution of antibiotic resistance and its pleiotropic fitness cost. *Proc. R. Soc. B* 274:2351–56
135. Peter BM, Huerta-Sanchez E, Nielsen R. 2012. Distinguishing between selective sweeps from standing variation and from a de novo mutation. *PLOS Genet*. 8:e1003011
136. Petit C, Duhieu B, Boucansaud K, Délye C. 2010. Complex genetic control of non-target-site-based resistance to herbicides inhibiting acetyl-coenzyme A carboxylase and acetolactate-synthase in *Alopecurus myosuroides* Huds. *Plant Sci*. 178:501–9
137. Pinheiro J, Bates D, DebRoy S, Sarkar D, R Core Team. 2017. nlme: linear and nonlinear mixed effects models. *R Package Version* 3.1–131. **https://CRAN.R-project.org/package=nlme**
138. Preston C, Powles SB. 2002. Evolution of herbicide resistance in weeds: initial frequency of target site-based resistance to acetolactate synthase-inhibiting herbicides in *Lolium rigidum*. *Heredity* 88:8–13
139. Pritchard JK, Pickrell JK, Coop G. 2010. The genetics of human adaptation: hard sweeps, soft sweeps, and polygenic adaptation. *Curr. Biol.* 20:R208–15
140. Przeworski M, Coop G, Wall JD. 2005. The signature of positive selection on standing genetic variation. *Evolution* 59:2312–23
141. Purrington CB, Bergelson J. 1999. Exploring the physiological basis of costs of herbicide resistance in *Arabidopsis thaliana*. *Am. Nat*. 154:S82–91
142. Ribeiro DN, Pan Z, Duke SO, Nandula VK, Baldwin BS, et al. 2014. Involvement of facultative apomixis in inheritance of EPSPS gene amplification in glyphosate-resistant *Amaranthus palmeri*. *Planta* 239:199–212
143. Ronfort J, Glemin S. 2013. Mating system, Haldane's sieve, and the domestication process. *Evolution* 67:1518–26

144. Identifies that the dominance of the cost of resistance for pleiotropic traits is not related to the dominance of the resistance benefit.

144. Roux F, Gasquez J, Reboud X. 2004. The dominance of the herbicide resistance cost in several *Arabidopsis thaliana* mutant lines. *Genetics* 166:449–60

145. Roux F, Matéjicek A, Gasquez J, Reboud X. 2005. Dominance variation across six herbicides of the *Arabidopsis thaliana csr1-1* and *csr1-2* resistance alleles. *Pest Manag. Sci.* 61:1089–95
146. Salas RA, Dayan FE, Pan Z, Watson SB, Dickson JW, et al. 2012. EPSPS gene amplification in glyphosate-resistant Italian ryegrass (*Lolium perenne* ssp. *multiflorum*) from Arkansas. *Pest Manag. Sci.* 68:1223–30
147. Sammons RD, Gaines TA. 2014. Glyphosate resistance: state of knowledge. *Pest Manag. Sci.* 70:1367–77
148. Sarangi D, Tyre AJ, Patterson EL, Gaines TA, Irmak S, et al. 2017. Pollen-mediated gene flow from glyphosate-resistant common waterhemp (*Amaranthus rudis* Sauer): consequences for the dispersal of resistance genes. *Sci. Rep.* 7:srep44913
149. Savolainen O, Langley CH, Lazzaro BP, Fr H. 2000. Contrasting patterns of nucleotide polymorphism at the alcohol dehydrogenase locus in the outcrossing *Arabidopsis lyrata* and the selfing *Arabidopsis thaliana*. *Mol. Biol. Evol*. 17:645–55
150. Scarabel L, Panozzo S, Varotto S, Sattin M. 2011. Allelic variation of the ACCase gene and response to ACCase-inhibiting herbicides in pinoxaden-resistant *Lolium* spp. *Pest Manag. Sci.* 67:932–41
151. Schrider DR, Kern AD. 2016. S/HIC: robust identification of soft and hard sweeps using machine learning. *PLOS Genet*. 12:e1005928
152. Sebastian SA, Fader GM, Ulrich JF, Forney DR, Chaleff RS. 1989. Semidominant soybean mutation for resistance to sulfonylurea herbicides. *Crop Sci*. 29:1403–8
153. Selmecki AM, Maruvka YE, Richmond PA, Guillet M, Shoresh N, et al. 2015. Polyploidy can drive rapid adaptation in yeast. *Nature* 519:349–52

154. Shaaltiel Y, Chua NH, Gepstein S, Gressel J. 1988. Dominant pleiotropy controls enzymes co-segregating with paraquat resistance in *Conyza bonariensis*. *Theor. Appl. Genet*. 75:850–56
155. Shimono Y, Shimono A, Oguma H, Konuma A, Tominaga T. 2015. Establishment of *Lolium* species resistant to acetolactate synthase-inhibiting herbicide in and around grain-importation ports in Japan. *Weed Res*. 55:101–11
156. Smith JM, Haigh J. 1974. The hitch-hiking effect of a favourable gene. *Genet. Res.* 23:23–35
157. Stebbins GL. 1950. *Variation and Evolution in Plants*. New York: Columbia Univ. Press. 643 pp.
158. Tilman D. 1999. Global environmental impacts of agricultural expansion: the need for sustainable and efficient practices. *PNAS* 96:5995–6000
159. Tranel J, Wassom J, Jeschke R, Rayburn L. 2002. Transmission of herbicide resistance from a monoecious to a dioecious weedy *Amaranthus* species. *Theor. Appl. Genet*. 105:674–79
160. Uecker H, Otto SP, Hermisson J. 2014. Evolutionary rescue in structured populations. *Am. Nat.* 183:E17–35
161. Vila-Aiub MM, Neve P, Powles SB. 2005. Resistance cost of a cytochrome P450 herbicide metabolism mechanism but not an ACCase target site mutation in a multiple resistant *Lolium rigidum* population. *New Phytol*. 167:787–96
162. Vila-Aiub MM, Neve P, Powles SB. 2009. Fitness costs associated with evolved herbicide resistance alleles in plants. *New Phytol*. 184:751–67
163. Wang X, Shi X, Hao B, Ge S, Luo J. 2005. Duplication and DNA segmental loss in the rice genome: implications for diploidization. *New Phytol*. 165:937–46
164. Watrud LS, Lee EH, Fairbrother A, Burdick C, Reichman JR, et al. 2004. Evidence for landscape-level, pollen-mediated gene flow from genetically modified creeping bentgrass with CP4 EPSPS as a marker. *PNAS* 101:14533–38
165. Wiersma AT, Gaines TA, Preston C, Hamilton JP, Giacomini D, et al. 2015. Gene amplification of 5-enol-pyruvylshikimate-3-phosphate synthase in glyphosate-resistant *Kochia scoparia*. *Planta* 241:463–74
166. Wilson BA, Pennings PS, Petrov DA. 2017. Soft selective sweeps in evolutionary rescue. *Genetics* 205:1573–86
167. Wood TE, Takebayashi N, Barker MS, Mayrose I, Greenspoon PB, Rieseberg LH. 2009. The frequency of polyploid speciation in vascular plants. *PNAS* 106:13875–79
168. Yerka MK, de Leon N, Stoltenberg DE. 2012. Pollen-mediated gene flow in common lambsquarters (*Chenopodium album*). *Weed Sci*. 60:600–6
169. Yi X, Liang Y, Huerta-Sanchez E, Jin X, Cuo ZXP, et al. 2010. Sequencing of 50 human exomes reveals adaptation to high altitude. *Science* 329:75–78
170. Yu Q, Ahmad-Hamdani MS, Han H, Christoffers MJ, Powles SB. 2013. Herbicide resistance-endowing ACCase gene mutations in hexaploid wild oat (*Avena fatua*): insights into resistance evolution in a hexaploid species. *Heredity* 110:220–31
171. Yu Q, Powles SB. 2014. Resistance to AHAS inhibitor herbicides: current understanding. *Pest Manag. Sci.* 70:1340–50
172. Yuan JS, Tranel PJ, Stewart CN Jr. 2007. Non-target-site herbicide resistance: a family business. *Trends Plant Sci*. 12:6–13
173. Zanne AE, Tank DC, Cornwell WK, Eastman JM, Smith SA, et al. 2013. Three keys to the radiation of angiosperms into freezing environments. *Nature* 506:89–92
174. Zeyl C, Vanderford T, Carter M. 2003. An evolutionary advantage of haploidy in large yeast populations. *Science* 299:555–58

166. Models the roles of soft and hard sweeps in evolutionary rescue; finds soft sweeps are more likely to occur when evolutionary rescue is likely.

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Errata

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